Clinical trial results:
A Phase II, Multicenter, Randomized, Observer-blind, Placebo-controlled Study to Evaluate the Immunogenicity, Safety and Tolerability of CSL's 2009 H1N1 Influenza Vaccine (CSL425) in a Healthy Pediatric Population.

Summary

EudraCT number	2015-000176-10
Trial protocol	Outside EU/EEA
Global end of trial date	04 November 2009

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	CSLCT-CAL-09-62

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00958243
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Limited
Sponsor organisation address	43 Poplar Rd, Parkville, Australia, 3052
Public contact	Clinical Program Director, bioCSL, bioCSL PTY LTD, biocsl.clinicaltrials@biocsl.com.au
Scientific contact	Clinical Program Director, bioCSL, bioCSL PTY LTD, biocsl.clinicaltrials@biocsl.com.au

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	16 November 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2009
Global end of trial reached?	Yes
Global end of trial date	04 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the immunogenicity of the 7.5 µg haemagglutinin (HA) and 15 µg HA antigen doses of 2009 H1N1 vaccine (H1N1 vaccine) in two cohorts of healthy children: Cohort A: participants aged 6 months to less than 3 years ; Cohort B: participants aged 3 years to less than 9 years.

Protection of trial subjects:

This study was conducted under a United States (US) Investigational New Drug Application and in accordance with US guidelines and regulations, and in accordance with the World Medical Association Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2009
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	United States: 473
Worldwide total number of subjects	473
EEA total number of subjects	0

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 months)	129
Children (2-11 years)	344
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:

Study Initiation Date: 24 August 2009 (First Participant First Visit)
Active Study Completion Date: 04 November 2009 (Last Participant, Last Visit)
This phase II pediatric study was conducted in 12 sites in the USA.

Pre-assignment

Screening details:

Eligible participants were stratified by age to one of two cohorts (Cohort A: participants aged 6 months to <3 years; Cohort B: participants aged 3 to <9 years). After stratification, participants were randomised, in a 1:4:4 allocation ratio, to either placebo or one of the two HA antigen doses of H1N1 vaccine (7.5 ug or 15 ug).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A (6 months to < 3 years) - placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	thimerosal-free vaccine diluent
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

The placebo comprised thimerosal-free vaccine diluent. The placebo was supplied in pre-filled syringes. Participants in the placebo group received two vaccinations of 0.5mL of placebo, administered 21 days apart. The placebo was administered by intramuscular injection.

Arm title	Cohort A (6 months to < 3 years) - 7.5 mcg dose

Arm description: -

Arm type	Experimental
Investigational medicinal product name	H1N1 vaccine - 7.5 mcg dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

The H1N1 vaccine, a monovalent, inactivated, split-virus vaccine, contains the HA antigen for the influenza strain A/California/7/2009(H1N1)v like virus (2009 H1N1) as recommended by the World Health Organization. The vaccine was supplied as a thimerosal-free suspension in pre-filled syringes. The dose of H1N1 vaccine was 7.5 mcg HA antigen per 0.25 mL dose. Participants received two vaccinations of their assigned dose, administered 21 days apart. Each dose was administered by intramuscular injection.

Arm title	Cohort A (6 months to < 3 years) - 15 mcg dose

Arm description: -

Arm type	Experimental

Investigational medicinal product name	H1N1 vaccine - 15 mcg dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

The H1N1 vaccine, a monovalent, inactivated, split-virus vaccine, contains the HA antigen for the influenza strain A/California/7/2009(H1N1)v like virus (2009 H1N1) as recommended by the World Health Organization. The vaccine was supplied as a thimerosal-free suspension in pre-filled syringes. The dose of H1N1 vaccine was 15 mcg HA antigen per 0.5mL dose. Participants received two vaccinations of their assigned dose, administered 21 days apart. Each dose was administered by intramuscular injection.

Arm title	Cohort B (3 years to <9 years) - placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	thimerosal-free vaccine diluent
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

The placebo comprised thimerosal-free vaccine diluent. The placebo was supplied in pre-filled syringes. Participants in the placebo group received two vaccinations of 0.5mL of placebo, administered 21 days apart. The placebo was administered by intramuscular injection.

Arm title	Cohort B (3 years to < 9 years) - 7.5 mcg dose

Arm description: -

Arm type	Experimental
Investigational medicinal product name	H1N1 vaccine - 7.5 mcg dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

The H1N1 vaccine, a monovalent, inactivated, split-virus vaccine, contains the HA antigen for the influenza strain A/California/7/2009(H1N1)v like virus (2009 H1N1) as recommended by the World Health Organization. The vaccine was supplied as a thimerosal-free suspension in pre-filled syringes. The dose of H1N1 vaccine was 7.5 mcg HA antigen per 0.25 mL dose. Participants received two vaccinations of their assigned dose, administered 21 days apart. Each dose was administered by intramuscular injection.

Arm title	Cohort B (3 years to < 9 years) - 15 mcg dose

Arm description: -

Arm type	Experimental
Investigational medicinal product name	H1N1 vaccine - 15 mcg dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

The H1N1 vaccine, a monovalent, inactivated, split-virus vaccine, contains the HA antigen for the influenza strain A/California/7/2009(H1N1)v like virus (2009 H1N1) as recommended by the World Health Organization. The vaccine was supplied as a thimerosal-free suspension in pre-filled syringes. The dose of H1N1 vaccine was 15 mcg HA antigen per 0.5mL dose. Participants received two vaccinations of their assigned dose, administered 21 days apart. Each dose was administered by intramuscular injection.

Number of subjects in period 1	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose
Started	26	105	96
Completed	24	99	82
Not completed	2	6	14
Consent withdrawn by subject	-	1	3
Lost to follow-up	2	5	11

Number of subjects in period 1	Cohort B (3 years to <9 years) - placebo	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose
Started	28	109	109
Completed	25	100	99
Not completed	3	9	10
Consent withdrawn by subject	1	1	5
Lost to follow-up	2	8	5

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A (6 months to < 3 years) - placebo
Reporting group description: -	
Reporting group title	Cohort A (6 months to < 3 years) - 7.5 mcg dose
Reporting group description: -	
Reporting group title	Cohort A (6 months to < 3 years) - 15 mcg dose
Reporting group description: -	
Reporting group title	Cohort B (3 years to <9 years) - placebo
Reporting group description: -	
Reporting group title	Cohort B (3 years to < 9 years) - 7.5 mcg dose
Reporting group description: -	
Reporting group title	Cohort B (3 years to < 9 years) - 15 mcg dose
Reporting group description: -	

Reporting group values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose
Number of subjects	26	105	96
Age categorical Units: Subjects			
<= 18 years	26	105	96
between 18 and 65 years	0	0	0
>= 65 years	0	0	0
Age continuous Units: years			
arithmetic mean	1.87	1.73	1.85
standard deviation	± 0.77	± 0.72	± 0.66
Gender categorical Units: Subjects			
Female	11	57	44
Male	15	48	52

Reporting group values	Cohort B (3 years to <9 years) - placebo	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose
Number of subjects	28	109	109
Age categorical Units: Subjects			
<= 18 years	28	109	109
between 18 and 65 years	0	0	0
>= 65 years	0	0	0
Age continuous Units: years			
arithmetic mean	5.9	5.94	5.91
standard deviation	± 1.71	± 1.71	± 1.7
Gender categorical Units: Subjects			
Female	13	53	50
Male	15	56	59

Reporting group values	Total		
Number of subjects	473		
Age categorical Units: Subjects			
<= 18 years	473		
between 18 and 65 years	0		
>= 65 years	0		
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	228		
Male	245		

End points

End points reporting groups

Reporting group title	Cohort A (6 months to < 3 years) - placebo
Reporting group description: -	
Reporting group title	Cohort A (6 months to < 3 years) - 7.5 mcg dose
Reporting group description: -	
Reporting group title	Cohort A (6 months to < 3 years) - 15 mcg dose
Reporting group description: -	
Reporting group title	Cohort B (3 years to <9 years) - placebo
Reporting group description: -	
Reporting group title	Cohort B (3 years to < 9 years) - 7.5 mcg dose
Reporting group description: -	
Reporting group title	Cohort B (3 years to < 9 years) - 15 mcg dose
Reporting group description: -	

Primary: Seroconversion Rate 21 Days After First Study Vaccination.

End point title	Seroconversion Rate 21 Days After First Study Vaccination.[1]

End point description:

Seroconversion rate: the percentage of participants achieving seroconversion in HI antibody titer. Seroconversion is defined as participants with a pre-vaccination titer of less than 1:10 achieving a post-vaccination HI antibody titer of 1:40 or more; or participants with a pre-vaccination HI titer of 1:10 or more achieving a four-fold or greater increase in post-vaccination HI titer.
The Evaluable Population (for the first vaccination) comprised all randomized participants who received the first study vaccine; provided both pre- and post-vaccination blood samples; were not excluded from analyses (e.g., the use of a prohibited medication or a laboratory confirmed infection with 2009 H1N1 between Visit 1 and Visit 3).

End point type	Primary

End point timeframe:

21 days after the first study vaccination.

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: Data were analysed using descriptive statistics only.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	Cohort B (3 years to <9 years) - placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	102	89	27
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	4 (0.1 to 20.4)	88.2 (80.4 to 93.8)	83.1 (73.7 to 90.2)	3.7 (0.1 to 19)

End point values	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	102		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	84.6 (76.2 to 90.9)	88.2 (80.4 to 93.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Seroconversion Rate 21 Days After Second Study Vaccination.

End point title	Seroconversion Rate 21 Days After Second Study

End point description:

Seroconversion rate: the percentage of participants achieving seroconversion in HI antibody titer. Seroconversion is defined as participants with a pre-vaccination titer of less than 1:10 achieving a post-vaccination HI antibody titer of 1:40 or more; or participants with a pre-vaccination HI titer of 1:10 or more achieving a four-fold or greater increase in post-vaccination HI titer.
The Evaluable Population (for the second vaccination) comprised all randomized participants who received the second study vaccine; provided both pre- and post-vaccination blood samples; were not excluded from analyses (e.g., the use of a prohibited medication or a laboratory confirmed infection with 2009 H1N1 between Visit 1 and Visit 3).

End point type	Primary

End point timeframe:

Seroconversion Rate 21 Days After Second Study Vaccination.

Notes:

[2] - 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: Data were analysed using descriptive statistics only.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	Cohort B (3 years to <9 years) - placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	90	80	26
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	28.6 (11.3 to 52.2)	98.9 (94 to 100)	100 (95.5 to 100)	15.4 (4.4 to 34.9)

End point values	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	98 (92.8 to 99.8)	99 (94.4 to 100)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Achieving an Hemagglutination Inhibition (HI) Antibody Titer of 1:40 or More 21 Days After First Study Vaccination.

End point title	Percentage of Participants Achieving an Hemagglutination Inhibition (HI) Antibody Titer of 1:40 or More 21 Days After First Study Vaccination.[3]

End point description:

The Evaluable Population (for the first vaccination) comprised all randomized participants who received the first study vaccine; provided both pre- and post-vaccination blood samples; were not excluded from analyses (e.g., the use of a prohibited medication or a laboratory confirmed infection with 2009 H1N1 between Visit 1 and Visit 3).

End point type	Primary

End point timeframe:

21 days after the first study vaccination.

Notes:

[3] - 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: Data were analysed using descriptive statistics only.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	Cohort B (3 years to <9 years) - placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	102	89	27
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	8 (1 to 26)	90.2 (82.7 to 95.2)	84.3 (75 to 91.1)	25.9 (11.1 to 46.3)

End point values	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	102		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	84.6 (76.2 to 90.9)	89.2 (81.5 to 94.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Achieving an Hemagglutination Inhibition (HI) Antibody Titer of 1:40 or More 21 Days After Second Study Vaccination.

End point title	Percentage of Participants Achieving an Hemagglutination Inhibition (HI) Antibody Titer of 1:40 or More 21 Days After Second Study Vaccination.[4]

End point description:

The Evaluable Population (for the second vaccination) comprised all randomized participants who received the second study vaccine; provided both pre- and post-vaccination blood samples; were not excluded from analyses (e.g., the use of a prohibited medication or a laboratory confirmed infection with 2009 H1N1 between Visit 1 and Visit 3).

End point type	Primary

End point timeframe:

21 days after the second study vaccination.

Notes:

[4] - 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: Data were analysed using descriptive statistics only.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	Cohort B (3 years to <9 years) - placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	90	80	26
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	28.6 (11.3 to 52.2)	98.9 (94 to 100)	100 (95.5 to 100)	34.6 (17.2 to 55.7)

End point values	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)	98 (92.8 to 99.8)	100 (96.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency and Intensity of Solicited Adverse Events (AEs) After the First or Second Study Vaccination, Cohort A

End point title	Frequency and Intensity of Solicited Adverse Events (AEs) After the First or Second Study Vaccination, Cohort A[5]

End point description:

Grade 3 solicited AE definitions: Prevented normal daily activities or required medical intervention for systemic AEs; Cried when limb was moved/spontaneously painful (aged < 3 years) for injection site

pain; Size > 30 mm for injection site redness and injection site induration/swelling; Oral temperature > 104.0°F (40.0°C) or axillary temperature > 103.1°F (39.5°C) for fevers.
Safety Population comprised all randomized participants who received at least one dose of study vaccine and had provided follow-up safety data.

End point type	Secondary

End point timeframe:

During the 7 days after each study vaccination.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were analysed using descriptive statistics only.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	105	96	
Units: percentage of participants				
number (not applicable)				
Any local solicited adverse event	42	44	37	
Any pain	35	33	27	
Grade 3 pain	0	0	0	
Any redness	23	27	19	
Grade 3 redness	0	0	0	
Any swelling / induration	8	16	6	
Grade 3 swelling / induration	0	0	0	
Any systemic solicited adverse event	58	70	65	
Any fever	23	25	43	
Grade 3 fever	0	3	4	
Any nausea / vomiting	8	11	15	
Grade 3 nausea / vomiting	0	0	0	
Any diarrhea	39	37	38	
Grade 3 diarrhea	0	1	2	
Any loss of appetite	12	24	22	
Grade 3 loss of appetite	0	0	1	
Any irritability	23	48	34	
Grade 3 irritability	0	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Solicited Adverse Events After the First and Second Study Vaccination, Cohort A

End point title	Duration of Solicited Adverse Events After the First and Second Study Vaccination, Cohort A[6]

End point description:

Safety Population comprised all randomized participants who received at least one dose of study vaccine and had provided follow-up safety data. In Cohort A, Safety Population after the first vaccination are placebo group was n=26, 7.5 mcg group n=105 and 15 mcg group n=96; and n=25, n=101 and n=91 respectively after the second vaccination.

End point type	Secondary

End point timeframe:

During the 7 days after each study vaccination.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were analysed using descriptive statistics only.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	105	96	
Units: days				
arithmetic mean (standard deviation)				
Any pain after first vaccination	1 (± 0)	1.52 (± 0.677)	1.91 (± 1.743)	
Any redness after first vaccination	1.5 (± 0.577)	2.2 (± 1.323)	2.56 (± 1.459)	
Any swelling / induration after first vaccination	1.5 (± 0.707)	1.63 (± 0.957)	2 (± 1.549)	
Any fever after first vaccination	3.33 (± 3.215)	1.32 (± 0.557)	1.29 (± 0.893)	
Any nausea / vomiting after first vaccination	1 (± 0)	1.43 (± 0.535)	1.11 (± 0.333)	
Any diarrhea after first vaccination	1.67 (± 0.707)	2.38 (± 1.996)	3.95 (± 4.248)	
Any loss of appetite after first vaccination	2 (± 0)	3.13 (± 2.5)	2.07 (± 1.486)	
Any irritability after first vaccination	6 (± 7.81)	2.08 (± 1.412)	1.97 (± 1.224)	
Any pain after second vaccination	1.43 (± 0.787)	1.57 (± 0.676)	1.23 (± 0.599)	
Any redness after second vaccination	2.4 (± 2.608)	2 (± 1.24)	1.63 (± 0.916)	
Any swelling / induration after second vaccination	3 (± 0)	3 (± 2.098)	2.5 (± 0.707)	
Any fever after second vaccination	1.4 (± 0.894)	1.4 (± 0.894)	2.19 (± 2.344)	
Any nausea / vomiting after second vaccination	0 (± 0)	1.27 (± 0.647)	1.5 (± 0.837)	
Any diarrhea after second vaccination	8 (± 9.899)	1.92 (± 1.248)	4.33 (± 6.754)	
Any loss of appetite after second vaccination	1.5 (± 0.707)	1.75 (± 1.183)	3.6 (± 5.168)	
Any irritability after second vaccination	1.5 (± 0.577)	1.81 (± 1.001)	2.86 (± 4.597)	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency and Intensity of Solicited Adverse Events After the First or Second Study Vaccination, Cohort B

End point title	Frequency and Intensity of Solicited Adverse Events After the First or Second Study Vaccination, Cohort B[7]

End point description:

Grade 3 solicited AE definitions: Prevented normal daily activities or required medical intervention for systemic AEs; Prevented normal daily activities (aged >= 3 years) for injection site pain; Size > 30 mm for injection site redness and injection site induration/swelling; Oral temperature > 104.0°F (40.0°C) or axillary temperature > 103.1°F (39.5°C) for fevers.
Safety Population comprised all randomized participants who received at least one dose of study vaccine and had provided follow-up safety data.

End point type	Secondary

End point timeframe:

During the 7 days after each study vaccination.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were analysed using descriptive statistics only.

End point values	Cohort B (3 years to <9 years) - placebo	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	107	109	
Units: percentage of participants				
number (not applicable)				
Any local solicited adverse event	43	38	49	
Any pain	29	34	40	
Grade 3 pain	0	0	0	
Any redness	29	18	26	
Grade 3 redness	0	0	0	
Any swelling / induration	11	13	17	
Grade 3 swelling / induration	0	0	0	
Any systemic solicited adverse event	46	44	46	
Any fever	14	19	20	
Grade 3 fever	0	0	0	
Any nausea / vomiting	14	8	13	
Grade 3 nausea / vomiting	0	2	1	
Any diarrhea	21	8	9	
Grade 3 diarrhea	0	1	0	
Any headache	21	17	25	
Grade 3 headache	0	1	0	
Any malaise	21	27	20	
Grade 3 malaise	4	0	0	
Any myalgia	21	14	22	
Grade 3 myalgia	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Solicited Adverse Events After the First and Second Study Vaccination, Cohort B

End point title	Duration of Solicited Adverse Events After the First and Second Study Vaccination, Cohort B[8]

End point description:

Safety Population comprised all randomized participants who received at least one dose of study vaccine and had provided follow-up safety data. In Cohort B, Safety Population after the first vaccination are placebo group n=28, 7.5 mcg group n=107 and 15 mcg group n=109; and n=27, n=105 and n=103 respectively after the second vaccination.

End point type	Secondary

End point timeframe:

During the 7 days after each study vaccination.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data were analysed using descriptive statistics only.

End point values	Cohort B (3 years to <9 years) - placebo	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	107	109	
Units: days				
arithmetic mean (standard deviation)				
Any pain after first vaccination	1.33 (± 0.516)	1.63 (± 1.066)	1.46 (± 0.691)	
Any redness after first vaccination	2.29 (± 1.254)	2.17 (± 1.339)	2.24 (± 1.809)	
Any swelling / induration after first vaccination	2 (± 1.732)	1.8 (± 0.632)	1.79 (± 0.975)	
Any fever after first vaccination	1.2 (± 0.447)	1.12 (± 0.332)	1.56 (± 0.856)	
Any nausea / vomiting after first vaccination	1 (± 0)	1.25 (± 0.5)	1 (± 0)	
Any diarrhea after first vaccination	1.13 (± 0.354)	1 (± 0)	1.22 (± 0.441)	
Any malaise after first vaccination	1.38 (± 0.744)	0.47 (± 0.964)	1.6 (± 0.995)	
Any myalgia after first vaccination	1.6 (± 0.548)	1.42 (± 0.669)	1.56 (± 0.984)	
Any headache after first vaccination	1.4 (± 0.894)	1.15 (± 0.376)	1.25 (± 0.645)	
Any pain after second vaccination	1.25 (± 0.5)	1.56 (± 0.856)	1.33 (± 0.555)	
Any redness after second vaccination	2 (± 0)	1.67 (± 0.516)	1.6 (± 0.699)	
Any swelling / induration after second vaccination	2 (± 0)	1.17 (± 0.408)	1.63 (± 0.744)	
Any fever after second vaccination	1 (± 0)	1.4 (± 0.548)	1.57 (± 1.134)	
Any nausea / vomiting after second vaccination	1 (± 0)	1.25 (± 0.5)	1.17 (± 0.408)	
Any diarrhea after second vaccination	1 (± 0)	1 (± 0)	1 (± 0)	
Any malaise after second vaccination	1.5 (± 0.707)	1.75 (± 0.754)	1.83 (± 1.467)	
Any myalgia after second vaccination	1 (± 0)	1.38 (± 0.518)	1.42 (± 0.669)	
Any headache after second vaccination	1.5 (± 0.707)	1.38 (± 0.518)	1.29 (± 0.488)	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency and Intensity of Unsolicited Adverse Events (UAE) After the First or Second Vaccination

End point title	Frequency and Intensity of Unsolicited Adverse Events (UAE) After the First or Second Vaccination

End point description:

UAE grading:
Grade 1: Symptoms were easily tolerated and did not interfere with daily activities.
Grade 2: Enough discomfort to cause some interference with daily activities. Grade 3: Symptoms that prevented normal, everyday activities.
Safety Population comprised all randomized participants who received at least one dose of study vaccine and had provided follow-up safety data.

End point type	Secondary

End point timeframe:

During the 21 days after each vaccination.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	Cohort B (3 years to <9 years) - placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	105	96	28
Units: percentage of participants				
number (not applicable)				
Proportion of participants with at least one UAE	69	52	55	50
Proportion of participants reported Grade 1 UAE	31	26	22	14
Proportion of participants reported Grade 2 UAE	39	22	27	25
Proportion of participants reported Grade 3 UAE	0	5	6	11

End point values	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	109		
Units: percentage of participants				
number (not applicable)				
Proportion of participants with at least one UAE	49	41		
Proportion of participants reported Grade 1 UAE	23	19		
Proportion of participants reported Grade 2 UAE	21	17		
Proportion of participants reported Grade 3 UAE	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs) and New Onset of Chronic Illness (NOCIs)

End point title	Incidence of Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs) and New Onset of Chronic Illness (NOCIs)

End point description:

A NOCI was defined as the diagnosis of a new medical condition that was chronic in nature, including those potentially controllable by medication (e.g., diabetes, asthma).
Safety Population comprised all randomized participants who received at least one dose of study vaccine and had provided follow-up safety data.

End point type	Secondary

End point timeframe:

Up to 180 days after the last vaccination.

End point values	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose	Cohort B (3 years to <9 years) - placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	105	96	28
Units: percentage of participants				
number (not applicable)				
Proportion of participants with at least one SAE	0	2	3	0
Proportion of participants with related SAE	0	0	0	0
Proportion of participants with at least one AESI	0	0	0	0
Proportion of participants with related AESI	0	0	0	0
Proportion of participants with at least one NOCI	0	0	1	0
Proportion of participants with related NOCI	0	0	0	0

End point values	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	109		
Units: percentage of participants				
number (not applicable)				
Proportion of participants with at least one SAE	0	0		
Proportion of participants with related SAE	0	0		
Proportion of participants with at least one AESI	0	0		
Proportion of participants with related AESI	0	0		
Proportion of participants with at least one NOCI	1	0		
Proportion of participants with related NOCI	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

180 days after the last study vaccination for SAEs. 21 days after each study vaccination for unsolicited adverse events.

Adverse event reporting additional description:

Other adverse events presented are unsolicited adverse events 21 days after either study vaccination by systematic assessment.
SAEs were collected by non-systematic assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Cohort A (6 months to < 3 years) - placebo
Reporting group description: -	
Reporting group title	Cohort A (6 months to < 3 years) - 7.5 mcg dose
Reporting group description: -	
Reporting group title	Cohort A (6 months to < 3 years) - 15 mcg dose
Reporting group description: -	
Reporting group title	Cohort B (3 years to <9 years) - placebo
Reporting group description: -	
Reporting group title	Cohort B (3 years to < 9 years) - 7.5 mcg dose
Reporting group description: -	
Reporting group title	Cohort B (3 years to < 9 years) - 15 mcg dose

Reporting group description: -

Serious adverse events	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	2 / 105 (1.90%)	3 / 96 (3.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Ataxia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 105 (0.95%)	0 / 96 (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
Psychiatric disorders			
Mental status changes			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 26 (0.00%)	0 / 105 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 105 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 105 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 105 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 105 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 105 (0.95%)	0 / 96 (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	Cohort B (3 years to <9 years) - placebo	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Ataxia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (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
Psychiatric disorders			
Mental status changes			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (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
Infections and infestations			
Bronchiolitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (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
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (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
Pneumonia viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (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			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (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
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (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

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort A (6 months to < 3 years) - placebo	Cohort A (6 months to < 3 years) - 7.5 mcg dose	Cohort A (6 months to < 3 years) - 15 mcg dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 26 (96.15%)	58 / 105 (55.24%)	82 / 96 (85.42%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 26 (0.00%)	0 / 105 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 26 (19.23%)	8 / 105 (7.62%)	14 / 96 (14.58%)
occurrences (all)	6	8	15
Irritability			
subjects affected / exposed	0 / 26 (0.00%)	2 / 105 (1.90%)	7 / 96 (7.29%)
occurrences (all)	0	2	7
Malaise			
subjects affected / exposed	1 / 26 (3.85%)	2 / 105 (1.90%)	1 / 96 (1.04%)
occurrences (all)	1	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)	5 / 105 (4.76%)	5 / 96 (5.21%)
occurrences (all)	1	5	7
Teething			

subjects affected / exposed	1 / 26 (3.85%)	5 / 105 (4.76%)	7 / 96 (7.29%)
occurrences (all)	1	7	10
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)	4 / 105 (3.81%)	4 / 96 (4.17%)
occurrences (all)	0	4	5
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	10 / 26 (38.46%)	17 / 105 (16.19%)	14 / 96 (14.58%)
occurrences (all)	13	19	17
Cough			
subjects affected / exposed	4 / 26 (15.38%)	9 / 105 (8.57%)	17 / 96 (17.71%)
occurrences (all)	6	11	21
Nasal congestion			
subjects affected / exposed	1 / 26 (3.85%)	4 / 105 (3.81%)	11 / 96 (11.46%)
occurrences (all)	1	5	12
Infections and infestations			
Ear infection			
subjects affected / exposed	2 / 26 (7.69%)	2 / 105 (1.90%)	1 / 96 (1.04%)
occurrences (all)	2	2	1

Non-serious adverse events	Cohort B (3 years to <9 years) - placebo	Cohort B (3 years to < 9 years) - 7.5 mcg dose	Cohort B (3 years to < 9 years) - 15 mcg dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 28 (78.57%)	70 / 107 (65.42%)	49 / 109 (44.95%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 28 (14.29%)	8 / 107 (7.48%)	4 / 109 (3.67%)
occurrences (all)	5	8	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 28 (21.43%)	15 / 107 (14.02%)	10 / 109 (9.17%)
occurrences (all)	9	17	11
Irritability			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	3 / 109 (2.75%)
occurrences (all)	0	0	5
Malaise			

subjects affected / exposed	2 / 28 (7.14%)	3 / 107 (2.80%)	1 / 109 (0.92%)
occurrences (all)	2	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 28 (0.00%)	7 / 107 (6.54%)	2 / 109 (1.83%)
occurrences (all)	0	7	2
Teething			
subjects affected / exposed	0 / 28 (0.00%)	0 / 107 (0.00%)	0 / 109 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)	7 / 107 (6.54%)	2 / 109 (1.83%)
occurrences (all)	2	7	2
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	3 / 28 (10.71%)	6 / 107 (5.61%)	7 / 109 (6.42%)
occurrences (all)	3	8	7
Cough			
subjects affected / exposed	3 / 28 (10.71%)	21 / 107 (19.63%)	15 / 109 (13.76%)
occurrences (all)	3	22	17
Nasal congestion			
subjects affected / exposed	1 / 28 (3.57%)	3 / 107 (2.80%)	5 / 109 (4.59%)
occurrences (all)	1	3	5
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 107 (0.00%)	0 / 109 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported