



Clinical trial results:

A Phase II, Randomized, Observer-Blind, Multi-Center, Study to Evaluate Safety, Tolerability and Immunogenicity of an Adjuvanted Cell Culture-Derived H5N1 Subunit Influenza Virus Vaccine at Two Different Formulations in Healthy Pediatric Subjects.

Summary

EudraCT number	2021-004813-37
Trial protocol	Outside EU/EEA
Global end of trial date	16 June 2014

Results information

Result version number	v1 (current)
This version publication date	09 July 2022
First version publication date	09 July 2022

Trial information

Trial identification

Sponsor protocol code	V89_11
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01776554
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seqirus Inc. formerly Novartis Vaccines and Diagnostics Inc. Inc.
Sponsor organisation address	475 Green Oaks Parkway, Holly Springs, North Carolina, United States, 27540
Public contact	Clinical Study Disclosure Desk, Seqirus Inc. formerly Novartis Vaccines and Diagnostics Inc., Seqirus.ClinicalTrials@seqirus.com
Scientific contact	Clinical Study Disclosure Desk, Seqirus Inc. formerly Novartis Vaccines and Diagnostics Inc., Seqirus.ClinicalTrials@seqirus.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002869-PIP01-21
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2014
Global end of trial reached?	Yes
Global end of trial date	16 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Immunogenicity Objective:

To select the vaccine (low dose or high dose aH5N1c) to be tested in Phase III based on achievement of CBER criteria 3 weeks after the second vaccine administration as measured by strain-specific hemagglutination inhibition (HI) assays.

Primary Safety Objective:

To evaluate the safety and tolerability of low dose and high dose aH5N1c vaccine in Subjects 6 months to 17 years of age.

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki. Only subjects who met all of the eligibility criteria were enrolled and vaccinated in the study. Potential subjects with allergy to any component of the vaccine or a history of serious vaccine reactions were not included in the study. Vaccinations were performed by trained, qualified healthcare professionals. After vaccination, subjects remained under medical supervision and were monitored for any immediate post-vaccination reactions for at least 30 minutes.

Background therapy:

None

Evidence for comparator:

No comparator

Actual start date of recruitment	31 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 182
Country: Number of subjects enrolled	Thailand: 480
Worldwide total number of subjects	662
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)	126
Children (2-11 years)	409
Adolescents (12-17 years)	127
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 10 centers in the United States and 2 centers in Thailand.

Pre-assignment

Screening details:

A total of 662 subjects were enrolled in the study, of whom 658 subjects received study vaccine.

Period 1

Period 1 title	Period 1 (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

Blinding implementation details:

The study was an observer-blind study. Vaccine administration was shielded from the subject's parent(s)/Legally Acceptable Representative(s) and blinded study personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	aH5N1c low dose

Arm description:

Enrolled subjects who were randomized and received 0.25mL of aH5N1c vaccine containing 3.75µg HA_0.125mL MF59 (low dose)

Arm type	Experimental
Investigational medicinal product name	Adjuvanted cell culture-derived H5N1 subunit influenza virus vaccine
Investigational medicinal product code	aH5N1c
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Each subject randomized to the low dose arm received a 0.25 mL (low dose) IM dose of aH5N1c on Day 1 and Day 22.

Arm title	aH5N1c high dose
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Arm description:

Enrolled subjects who were randomized and received 0.5mL of aH5N1c vaccine containing 7.5µg HA_0.25mL MF59 (high dose)

Arm type	Experimental
Investigational medicinal product name	Adjuvanted cell culture-derived H5N1 subunit influenza virus vaccine
Investigational medicinal product code	aH5N1c
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Each subject randomized to the high dose arm received a 0.5 mL (high dose) IM dose of aH5N1c on Day 1 and Day 22.

Number of subjects in period 1	aH5N1c low dose	aH5N1c high dose
Started	330	332
Completed	307	315
Not completed	23	17
Consent withdrawn by subject	8	3
Adverse event, non-fatal	-	1
Other	1	4
Lost to follow-up	9	6
Administrative reason	5	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	aH5N1c low dose
Reporting group description:	
Enrolled subjects who were randomized and received 0.25mL of aH5N1c vaccine containing 3.75µg HA_0.125mL MF59 (low dose)	
Reporting group title	aH5N1c high dose
Reporting group description:	
Enrolled subjects who were randomized and received 0.5mL of aH5N1c vaccine containing 7.5µg HA_0.25mL MF59 (high dose)	

Reporting group values	aH5N1c low dose	aH5N1c high dose	Total
Number of subjects	330	332	662
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	65	61	126
Children (2-11 years)	204	205	409
Adolescents (12-17 years)	61	66	127
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: months			
arithmetic mean	78.1	78.7	
standard deviation	± 55.6	± 55.9	-
Gender categorical			
Units: Subjects			
Female	164	152	316
Male	166	180	346

End points

End points reporting groups

Reporting group title	aH5N1c low dose
Reporting group description: Enrolled subjects who were randomized and received 0.25mL of aH5N1c vaccine containing 3.75µg HA_0.125mL MF59 (low dose)	
Reporting group title	aH5N1c high dose
Reporting group description: Enrolled subjects who were randomized and received 0.5mL of aH5N1c vaccine containing 7.5µg HA_0.25mL MF59 (high dose)	

Primary: Primary Immunogenicity: Percentage of subjects achieving seroconversion against A/H5N1 strain

End point title	Primary Immunogenicity: Percentage of subjects achieving seroconversion against A/H5N1 strain ^[1]
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End point description:

Immunogenicity was measured in terms of the percentages of subjects achieving seroconversion or significant increase in HI titer against the vaccine strain, three weeks after receiving two injections of low dose or high dose of aH5N1c vaccine according to the CBER criteria.

Seroconversion is defined as the percentages of subjects with a prevaccination HI titer <10, a postvaccination titer ≥40; or in subjects with prevaccination HI titer ≥10, and a minimum four-fold rise in postvaccination HI antibody titer.

CBER criterion is met if the lower limit of the two-sided 95% CI for the percentages of subjects achieving seroconversion for HI antibody titer meets or exceeds 40%.

Dataset used: FAS

End point type	Primary
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End point timeframe:

End point timeframe: Three weeks after 2nd vaccination (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: There is no formal statistical analysis between group comparison. Only individual treatment arm seroconversion compared with CBER criteria.

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	279		
Units: percentage				
number (confidence interval 97.5%)				
day 43	86 (81 to 90)	96 (93 to 98)		

Statistical analyses

No statistical analyses for this end point

Primary: Primary Immunogenicity: Percentage of subjects achieving

hemagglutination inhibition titers $\geq 1:40$ against A/H5N1 strain

End point title	Primary Immunogenicity: Percentage of subjects achieving hemagglutination inhibition titers $\geq 1:40$ against A/H5N1 strain ^[2]
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End point description:

The optimal aH5N1c vaccine formulation was evaluated in terms of percentages of subjects achieving HI titers $\geq 1:40$ against homologous A/H5N1 strain, three weeks after second vaccination with either low dose or high dose of aH5N1c vaccine, according to the Center for Biologics Evaluation and Research (CBER) criterion.

As there is no CBER criteria defined for children, immunogenicity was evaluated using CBER criterion applicable for adults (18-64 years).

CBER criterion is met if the lower limit of the two-sided 95% confidence interval (CI) for the percentages of subjects achieving HI titer $\geq 1:40$ meets or exceeds 70%.

Dataset used: FAS

End point type	Primary
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End point timeframe:

End point timeframe: Three weeks after 2nd vaccination (Day 43).

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: There is no formal statistical analysis between group comparison. Only individual treatment arm hemagglutination inhibition titers $\geq 1:40$ compared with CBER criteria.

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: percentage				
number (confidence interval 97.5%)				
Day 43	86 (81 to 90)	96 (92 to 98)		

Statistical analyses

No statistical analyses for this end point

Primary: Primary Safety: Number of subjects (6 month to <6 years) reporting solicited local and systemic AEs, after each dose and any vaccination

End point title	Primary Safety: Number of subjects (6 month to <6 years) reporting solicited local and systemic AEs, after each dose and any vaccination ^[3]
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End point description:

Safety was assessed using the number of subjects who reported solicited local and systemic adverse events following vaccination with either low or high dose of aH5N1c vaccine.

Dataset used: Analysis was done on the safety dataset, i.e. the subjects in the exposed population who provided postvaccination safety data.

Grades of AE: Grade 0 (< 25 mm), any (10-25mm [Grade 1], 26-50 mm [Grade 2], >50 mm [Grade 3])

End point type	Primary
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End point timeframe:

From Day 1 through Day 7 after each 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: There is no statistical null hypothesis associated with the safety objective, which was analyzed descriptively. All safety analyses were done by vaccine group and by age group.

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	159		
Units: number of subject				
number (not applicable)				
any local solicited event after first vaccination	80	74		
Injection site erythema after first vaccination	2	2		
injection site induration after first vaccination	0	1		
injection site ecchymosis after first vaccination	0	0		
injection site tenderness after first vaccination	79	74		
Any systemic solicited event after 1st vaccination	57	53		
change in eating habits after 1st vaccination	19	21		
Irritability after first vaccination	35	35		
sleepiness after first vaccination	32	27		
fever after first vaccination	10	11		
prevention of pain and/or fever after 1st vaccine	22	16		
treatment of pain and/or fever after 1st vaccine	19	26		
fever ($\geq 40^{\circ}\text{C}$) after first vaccination	0	0		
Any local solicited event after 2nd vaccination	61	68		
Injection site erythema after 2nd vaccination	0	2		
Injection site induration after 2nd vaccination	2	1		
injection site ecchymosis after 2nd vaccination	1	0		
injection site tenderness after 2nd vaccination	60	68		
Any systemic solicited event after 2nd vaccination	31	43		
change in eating habits after 2nd vaccination	6	12		
irritability after 2nd vaccination	26	29		
sleepiness after 2nd vaccination	14	23		
fever after 2nd vaccination	4	16		
prevention of pain and/or fever after 2nd vaccine	5	3		
treatment of pain and/or fever after 2nd vaccine	11	18		
fever ($\geq 40^{\circ}\text{C}$) after 2nd vaccination	0	1		
Any local solicited event after any vaccination	92	89		

Injection site erythema after any vaccination	2	4		
Injection site induration after any vaccination	2	2		
injection site ecchymosis after any vaccination	1	0		
injection site tenderness after any vaccination	91	89		
Any systemic solicited event after any vaccination	65	68		
change in eating habits after any vaccination	20	29		
Irritability after any vaccination	45	47		
sleepiness after any vaccination	40	40		
fever after any vaccination	13	25		
prevention of pain and/or fever after any vaccine	25	18		
treatment of pain and/or fever after any vaccine	26	37		
fever ($\geq 40^{\circ}\text{C}$) after any vaccination	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Primary Safety: Number of subjects (≥ 6 years to 17 years) reporting solicited local and systemic AEs, after any vaccination

End point title	Primary Safety: Number of subjects (≥ 6 years to 17 years) reporting solicited local and systemic AEs, after any vaccination ^[4]
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End point description:

Safety was assessed using the number of subjects who reported solicited local and systemic adverse events following vaccination with either low or high dose of aH5N1c vaccine.

Dataset used: Analysis was done on the safety dataset, i.e. the subjects in the exposed population who provided postvaccination safety data.

Grade of AE: Grade 0 (< 25 mm), any (10-25mm [Grade 1], 26-50 mm [Grade 2], >50 mm [Grade 3])

End point type	Primary
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End point timeframe:

From Day 1 through Day 7 after each 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: There is no statistical null hypothesis associated with the safety objective, which was analyzed descriptively. All safety analyses were done by vaccine group and by age group.

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	163		
Units: Number of subject				
Any local solicited event after 1st vaccination	109	109		
Injection site erythema after 1st vaccination	0	1		

Injection site induration after 1st vaccination	0	3		
Injection site ecchymosis after 1st vaccination	0	0		
Injection site pain after 1st vaccination	109	109		
Any systemic solicited event after 1st vaccination	75	70		
Myalgia after 1st vaccination	36	45		
Arthralgia after 1st vaccination	13	17		
Headache after 1st vaccination	36	28		
Fatigue after 1st vaccination	43	34		
Loss of appetite after 1st vaccination	14	15		
Malaise after 1st vaccination	33	34		
Fever after 1st vaccination	3	5		
Prevention of pain and/or fever after 1st vaccine	8	11		
Treatment of pain and/or fever after 1st vaccine	18	19		
Fever ($\geq 40^{\circ}\text{C}$) after 1st vaccination	0	0		
Nausea after 1st vaccination	22	14		
Any local solicited event after 2nd vaccination	65	61		
Injection site erythema after 2nd vaccination	0	1		
Injection site induration after 2nd vaccination	2	1		
Injection site ecchymosis after 2nd vaccination	0	0		
Injection site pain after 2nd vaccination	65	61		
Any systemic solicited event after 2nd vaccination	42	28		
Myalgia after 2nd vaccination	20	14		
Arthralgia after 2nd vaccination	9	6		
Headache after 2nd vaccination	23	14		
Fatigue after 2nd vaccination	22	19		
Loss of appetite after 2nd vaccination	8	9		
Malaise after 2nd vaccination	13	16		
Fever after 2nd vaccination	2	2		
Prevention of pain and/or fever after 2nd vaccine	3	3		
Treatment of pain and/or fever after 2nd vaccine	9	6		
Fever ($\geq 40^{\circ}\text{C}$) after 2nd vaccination	0	0		
Nausea after 2nd vaccination	9	10		
Any local solicited event after any vaccination	115	111		
Injection site erythema after any vaccination	0	2		
Injection site induration after any vaccination	2	4		
Injection site ecchymosis after any vaccination	0	0		
Injection site pain after any vaccination	115	111		
Any systemic solicited event after any vaccination	82	79		
Myalgia after any vaccination	44	49		
Arthralgia after any vaccination	19	21		

Headache after any vaccination	47	36		
Fatigue after any vaccination	48	43		
Loss of appetite after any vaccination	18	22		
Malaise after any vaccination	38	40		
Fever after any vaccination	5	7		
Prevention of pain and/or fever after any vaccine	10	14		
Treatment of pain and/or fever after any vaccine	23	24		
Fever ($\geq 40^{\circ}\text{C}$) after any vaccination	0	0		
Nausea after any vaccination	26	21		

Statistical analyses

No statistical analyses for this end point

Primary: Primary Safety: Number of subjects reporting unsolicited AEs after any vaccination

End point title	Primary Safety: Number of subjects reporting unsolicited AEs after any vaccination ^[5]
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End point description:

Safety was assessed using the number of subjects who reported any unsolicited adverse events, adverse events possibly or probably related to study vaccine, serious adverse events (SAEs), new onset of chronic diseases (NOCs), medically attended AEs, AEs of special interest (AESIs), AEs leading to withdrawal from study following vaccination with either low or high dose of aH5N1c vaccine.

Dataset used: Analysis was done on the safety dataset, i.e. the subjects in the exposed population who provided postvaccination safety data.

End point type	Primary
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End point timeframe:

Any unsolicited AEs - day 1 through day 22 after any vaccination; SAEs, NOCs, medically attended AEs, AESIs, AEs leading to study withdrawal- day 1 to day 387.

Notes:

[5] - 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: There is no statistical null hypothesis associated with the safety objective, which was analyzed descriptively. All safety analyses were done by vaccine group and by age group.

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329	329		
Units: number of subject				
Any AEs after first vaccination	59	67		
Any AEs after second vaccination	47	36		
Any AEs after any vaccination	96	84		
Any SAEs	11	8		
Deaths	0	0		
Medically attended AEs	113	110		
AEs resulting in premature withdrawal	0	1		
AEs of special interest	0	0		
New onset of chronic disease	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: Geometric Mean HI Titers and Geometric Mean Ratios Against A/H5N1 Strain Following 2-Dose Vaccination Schedule Of Either Low Dose Or High Dose AH5N1c Vaccine

End point title	Secondary Immunogenicity: Geometric Mean HI Titers and Geometric Mean Ratios Against A/H5N1 Strain Following 2-Dose Vaccination Schedule Of Either Low Dose Or High Dose AH5N1c Vaccine
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End point description:

Immunogenicity was measured as the geometric mean HI titers (GMT) and geometric mean ratio (GMR). The ratio of postvaccination to prevaccination HI GMTs, 3 weeks after first vaccination, 3 weeks after second vaccination and 12 months after second vaccination with either low dose or high dose of aH5N1c.

The criterion is met according to the European Committee for Medicinal Products for Human Use (CHMP) criteria if the geometric mean increase GMR (day 43/day 1) in HI antibody titer is >2.5.

As no CHMP criteria are established for the pediatric population, criteria given for subjects 18-60 years of age were applied.

Dataset used: FAS

End point type	Secondary
End point timeframe:	
End point timeframe: Day 1, Day 22, Day 43, and Day 387	

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	297		
Units: GM titer/ GM Ratio				
geometric mean (confidence interval 97.5%)				
Day 1	5.15 (4.91 to 5.39)	5.23 (5 to 5.48)		
Day 22	34 (24 to 48)	64 (46 to 90)		
Day 43	431 (312 to 595)	1356 (985 to 1866)		
Day 387	29 (21 to 40)	62 (45 to 86)		
Day 22/Day 1	6.63 (4.71 to 9.34)	13 (9 to 18)		
Day 43/Day 1	84 (61 to 116)	262 (190 to 361)		
Day 387/Day 1	5.62 (4.05 to 7.81)	12 (8.76 to 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: The Percentages Of Subjects Achieving Seroconversion Against A/H5N1 Strain

End point title	Secondary Immunogenicity: The Percentages Of Subjects Achieving Seroconversion Against A/H5N1 Strain
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End point description:

Immunogenicity was assessed in terms of percentages of subjects achieving seroconversion in HI titers, 3 weeks after first vaccination, 3 weeks after second vaccination and 12 months after second vaccination of either low dose or high dose aH5N1c vaccine according to the CHMP criterion. Seroconversion is defined as the percentages of subjects with a prevaccination HI titer <10, a postvaccination titer ≥40; or in subjects with prevaccination HI titer ≥10, and a minimum four-fold rise in postvaccination HI antibody titer.

The criterion is met according to the European (CHMP) guideline if the percentage of subjects achieving seroconversion (at day 43) is >40%.

Dataset used: FAS

End point type	Secondary
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End point timeframe:

End point timeframe: Day 22, Day 43, and Day 387

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	281		
Units: percentage				
number (confidence interval 97.5%)				
Day 22	38 (31 to 44)	52 (45 to 58)		
Day 43	86 (81 to 90)	96 (93 to 98)		
Day 387	31 (25 to 38)	47 (40 to 54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: Percentages Of Subjects With HI Titers ≥1:40 Against A/H5N1 Strain

End point title	Secondary Immunogenicity: Percentages Of Subjects With HI Titers ≥1:40 Against A/H5N1 Strain
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End point description:

Immunogenicity was assessed in terms of percentage of subjects achieving HI titers ≥1:40, 3 weeks

after first vaccination, 3 weeks after second vaccination and 12 months after second vaccination of either low dose or high dose of aH5N1c according to the CHMP criterion.
European Licensure (CHMP) criterion is met if the percentage of subjects achieving (at day 43) HI titers ≥ 40 is $>70\%$.
Dataset used: FAS

End point type	Secondary
End point timeframe:	
End point timeframe: Day 1, Day 22, Day 43, and Day 387	

End point values	aH5N1c low dose	aH5N1c high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	294		
Units: percentage				
number (confidence interval 97.5%)				
Day 1	0 (0 to 2)	1 (0 to 3)		
Day 22	38 (32 to 45)	51 (44 to 58)		
Day 43	86 (81 to 90)	96 (92 to 98)		
Day 387	31 (25 to 38)	47 (40 to 54)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: Day 1 to end of study (Day 1 to Day 387)

Nonserious Unsolicited AEs: Day 1 to Day 43

Adverse event reporting additional description:

Nonserious Unsolicited AEs and SAEs were reported

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	High dose aH5N1c
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Reporting group description:

Randomised subjects who received high dose aH5N1c and had any assessment of unsolicited AEs

Reporting group title	Low dose aH5N1c
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Reporting group description:

Randomised subjects who received low dose aH5N1c and had any assessment of unsolicited AEs

Serious adverse events	High dose aH5N1c	Low dose aH5N1c	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 329 (2.43%)	11 / 329 (3.34%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tibia fracture			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	1 / 329 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
food poisoning			
subjects affected / exposed	1 / 329 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoeic attack			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			

subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	1 / 329 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 329 (0.30%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 329 (0.61%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 329 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenza			
subjects affected / exposed	0 / 329 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 329 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 329 (0.30%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	High dose aH5N1c	Low dose aH5N1c	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 329 (79.94%)	257 / 329 (78.12%)	
Nervous system disorders			
Headache			
subjects affected / exposed	40 / 329 (12.16%)	48 / 329 (14.59%)	
occurrences (all)	40	48	
Somnolence			
subjects affected / exposed	42 / 329 (12.77%)	41 / 329 (12.46%)	
occurrences (all)	42	41	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	44 / 329 (13.37%)	50 / 329 (15.20%)	
occurrences (all)	44	50	
Injection site erythema			
subjects affected / exposed	60 / 329 (18.24%)	54 / 329 (16.41%)	
occurrences (all)	60	54	
Injection site haemorrhage			
subjects affected / exposed	23 / 329 (6.99%)	19 / 329 (5.78%)	
occurrences (all)	23	19	
Injection site induration			
subjects affected / exposed	45 / 329 (13.68%)	39 / 329 (11.85%)	
occurrences (all)	45	39	
Injection site pain			
subjects affected / exposed	209 / 329 (63.53%)	213 / 329 (64.74%)	
occurrences (all)	209	213	
Malaise			
subjects affected / exposed	40 / 329 (12.16%)	38 / 329 (11.55%)	
occurrences (all)	40	38	
Pyrexia			

subjects affected / exposed occurrences (all)	48 / 329 (14.59%) 48	32 / 329 (9.73%) 32	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	25 / 329 (7.60%) 25	29 / 329 (8.81%) 29	
Psychiatric disorders Eating disorder subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all)	29 / 329 (8.81%) 29 49 / 329 (14.89%) 49	20 / 329 (6.08%) 20 47 / 329 (14.29%) 47	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	23 / 329 (6.99%) 23 50 / 329 (15.20%) 50	20 / 329 (6.08%) 20 45 / 329 (13.68%) 45	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	18 / 329 (5.47%) 18 55 / 329 (16.72%) 55	16 / 329 (4.86%) 16 58 / 329 (17.63%) 58	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	22 / 329 (6.69%) 22	21 / 329 (6.38%) 21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2011	<p>Version 1.0 to Version 2.0</p> <p>The main reasons for the protocol amendment were the following:</p> <ol style="list-style-type: none">1. Increased the duration of the follow-up period from 6 months to 12 months after third (booster) vaccination, for total trial participation for each subject of approximately 24 months, instead of 18 months.2. Inclusion of a separate section for clarification on criteria that would necessitate a delay to enrollment.
29 March 2012	<p>Version 2.0 to Version 3.0</p> <p>The main reasons for the protocol amendment were the following:</p> <ol style="list-style-type: none">1. Planned day 387 analysis was not to be performed. Analyses were planned for day 43 data and at trial completion only.2. Planned analyses (include reference to safety profile): clarification that the vaccine formulation to be tested in phase 3 was to be the lowest antigen/adjuvant formulation able to achieve all CBER criteria 3 weeks after 2 doses as measured by strain specific HI assays and with an acceptable safety profile.3. Exclusion criterion 21 added: Individuals diagnosed with any disorders in growth such as failure to thrive or short stature were not eligible for the trial.4. Appendix A: List of AESI based on list provided by CBER on 9 December 2011.5. Subgroup analysis, comparing the antibody response in subjects who had received a seasonal influenza vaccine in the past year compared to those who had not had been added, as per CBER request.
09 November 2012	<p>Between protocol versions 3 and 5, following were collective major changes:</p> <ol style="list-style-type: none">1. Exploratory objective 'A' amended to extend to all heterologous influenza strains, not only H5N1.2. New exploratory objective was added "For each aH5N1c vaccine (low dose or high dose), to evaluate the antibody responses against heterologous and homologous influenza strain(s) as measured by MN assay.3. Subjects with a recent history of Guillain-Barré disease (instead of those with current Guillain-Barré disease) were excluded. Exclusion criterion 6 adapted accordingly.4. Revision of age subgroup ages from: 6 to 35 months, 3 to 8 years and 9 to 17 years TO: 6 to <36 months, 3 to <9 years and 9 to <18 years.5. Criteria for delay of vaccination and for repeat vaccination added.6. Change of solicited AEs that were to be collected (deletion of injection site swelling, persistent crying, vomiting diarrhea, and chills and addition of ecchymosis, loss of appetite and malaise) and the ages across which they were to be collected
17 April 2013	<p>Version 5.0 to Version 6.0</p> <p>The main reasons for the protocol amendment were the following:</p> <ol style="list-style-type: none">1. The majority of the changes reflected the removal of the booster dose at day 366 and subsequent safety follow-up.2. Clarifications to exclusion criteria (including the specification of any diagnosis on the AESI list in Appendix A of clinical study protocol as a chronic disease under Exclusion #3).

31 October 2013	Version 6.0 to Version 7.0 The main reasons for the protocol amendment were the following: 1. Further documentation of the acceptable time interval to obtain the ICF prior to the first vaccine administration.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: