



## Clinical trial results:

### **Phase III, Stratified, Randomized, Controlled, Observer-Blind, Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of Two Doses of aH5N1 when Administered to Adult and Elderly Subjects With and Without Underlying Medical Conditions. Summary**

EudraCT number	2011-003603-37
Trial protocol	DE
Global end of trial date	02 April 2015

#### **Results information**

Result version number	v1 (current)
This version publication date	10 October 2018
First version publication date	10 October 2018

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	V87_25
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02091908
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	Seqirus
Sponsor organisation address	The Point, 29 Market Street, Maidenhead, United Kingdom,
Public contact	Clinical Trial Disclosure Manager, Seqirus, seqirus.clinicaltrials@seqirus.com
Scientific contact	Clinical Trial Disclosure Manager, Seqirus, seqirus.clinicaltrials@seqirus.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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 April 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Primary Immunogenicity Objective:

To evaluate homologous antibody responses to aH5N1 vaccine 3 weeks after second vaccination (day 43) according to CHMP immunogenicity criteria<sup>1</sup> in adult (18 through 60 years of age) and elderly ( $\geq 61$  years of age) subjects who are healthy or with underlying medical condition, as measured by hemagglutination inhibition (HI) assay.

Primary Safety Objective:

To evaluate in pooled age groups 18 years of age and older solicited and unsolicited adverse events in adults and elderly subjects who are healthy or with underlying medical condition who have received aTIV or aH5N1 vaccine.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US CFR Title 21), the Sponsor's codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations 1997, ICH 1997, Declaration of Helsinki).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 April 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 540
Worldwide total number of subjects	540
EEA total number of subjects	540

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	348
From 65 to 84 years	191
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled from 6 study sites in Germany

### Pre-assignment

Screening details:

All enrolled subjects were included in the trial.

### Period 1

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

Blinding implementation details:

This is an observer-blind study. All vaccines were administered only by unblinded personnel who were qualified to perform that function under applicable local laws and regulations for the specific study site.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	aH5N1, $\geq 18$ to $\leq 60$ years/with medical conditions

Arm description:

Subjects  $\geq 18$  to  $\leq 60$  years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

FAS for secondary (SRH) objective: All subjects in the All Enrolled Set who are randomized, received at least one study vaccination and provide immunogenicity data (SRH assay, homologous strain) at baseline (Day 1), 3 weeks after first vaccination (Day 22) and 3 weeks after (planned) second vaccination (Day 43) – FAS Secondary SRH.

Arm type	Experimental
Investigational medicinal product name	Monovalent MF59-adjuvanted A/H5N1 influenza vaccine (aH5N1)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 IM injections administered 3 weeks apart to the deltoid muscle.

<b>Arm title</b>	aTIV, $\geq 18$ to $\leq 60$ years/with medical conditions
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Arm description:

Subjects  $\geq 18$  to  $\leq 60$  years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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Arm type	Experimental
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Investigational medicinal product name	Trivalent inactivated MF59-adjuvanted subunit influenza vaccine (aTIV)
Investigational medicinal product code	
Other name	Fluad
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 IM injections administered 3 weeks apart in the deltoid muscle.

<b>Arm title</b>	aH5N1, ≥ 18 to ≤ 60 years/healthy
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Arm description:

Healthy subjects ≥ 18 to ≤ 60 years of age who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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

Dosage and administration details:

2 IM injections administered 3 weeks apart to the deltoid muscle.

<b>Arm title</b>	aTIV, ≥ 18 to ≤ 60 years/healthy
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Arm description:

Healthy subjects ≥ 18 to ≤ 60 years of age who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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

Dosage and administration details:

2 IM injections administered 3 weeks apart in the deltoid muscle.

<b>Arm title</b>	aH5N1, ≥61 years/with medical conditions
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Arm description:

Subjects ≥ 61 years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1)

and 3 weeks after (planned) second vaccination (Day 43).

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Arm type	Experimental
Investigational medicinal product name	Monovalent MF59-adjuvanted A/H5N1 influenza vaccine (aH5N1)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: 2 IM injections administered 3 weeks apart to the deltoid muscle.	
<b>Arm title</b>	aTIV, ≥61 years/with medical conditions

Arm description:

Subjects ≥ 61 years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43.

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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Arm type	Experimental
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Investigational medicinal product code	
Other name	Fluad
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use
Dosage and administration details: 2 IM injections administered 3 weeks apart in the deltoid muscle.	
<b>Arm title</b>	aH5N1, ≥61 years/healthy

Arm description:

Healthy subjects ≥ 61 years of age who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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Dosage and administration details:

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<b>Arm title</b>	aTIV, ≥61 years/healthy
Arm description:	
Healthy subjects ≥ 61 years of age who provided immunogenicity data at Day 1 and Day 43.	
FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).	
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Other name	Fluad
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 IM injections administered 3 weeks apart in the deltoid muscle.

<b>Number of subjects in period 1</b>	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy
Started	146	34	59
Completed	138	34	57
Not completed	8	0	2
Adverse event, serious fatal	2	-	-
Consent withdrawn by subject	3	-	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	3	-	2

<b>Number of subjects in period 1</b>	aTIV, ≥ 18 to ≤ 60 years/healthy	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions
Started	31	149	31
Completed	31	142	31
Not completed	0	7	0
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	-	3	-
Adverse event, non-fatal	-	1	-
Lost to follow-up	-	1	-

<b>Number of subjects in period 1</b>	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Started	58	32
Completed	58	32
Not completed	0	0
Adverse event, serious fatal	-	-

Consent withdrawn by subject	-	-
Adverse event, non-fatal	-	-
Lost to follow-up	-	-

## Baseline characteristics

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### Reporting groups

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Reporting group title	aH5N1, $\geq 18$ to $\leq 60$ years/with medical conditions
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Reporting group description:

Subjects  $\geq 18$  to  $\leq 60$  years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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Reporting group title	aTIV, $\geq 18$ to $\leq 60$ years/with medical conditions
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Reporting group description:

Subjects  $\geq 18$  to  $\leq 60$  years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

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Reporting group title	aH5N1, $\geq 18$ to $\leq 60$ years/healthy
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Reporting group description:

Healthy subjects  $\geq 18$  to  $\leq 60$  years of age who who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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Reporting group title	aH5N1, $\geq 61$ years/with medical conditions
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Reporting group description:

Subjects  $\geq 61$  years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

FAS for secondary (SRH) objective: All subjects in the All Enrolled Set who are randomized, received at least one study vaccination and provide immunogenicity data (SRH assay, homologous strain) at baseline (Day 1), 3 weeks after first vaccination (Day 22) and 3 weeks after (planned) second vaccination (Day 43) – FAS Secondary SRH.

Reporting group title	aTIV, ≥61 years/with medical conditions
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Reporting group description:

Subjects ≥ 61 years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43.

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

FAS for secondary (SRH) objective: All subjects in the All Enrolled Set who are randomized, received at least one study vaccination and provide immunogenicity data (SRH assay, homologous strain) at baseline (Day 1), 3 weeks after first vaccination (Day 22) and 3 weeks after (planned) second vaccination (Day 43) – FAS Secondary SRH.

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Reporting group title	aTIV, ≥61 years/healthy
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Healthy subjects ≥ 61 years of age who provided immunogenicity data at Day 1 and Day 43.

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Reporting group values	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy
Number of subjects	146	34	59
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	146	34	59
From 65-84 years	0	0	0
85 years and over	0	0	0

Age continuous Units: years arithmetic mean standard deviation	49.8 ± 9.37	46.9 ± 11.59	37.6 ± 11.81
Gender categorical Units: Subjects			
Female	51	11	34
Male	95	23	25
Race Units: Subjects			
Black	0	0	1
White	146	34	58
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	143	33	59
Not reported	1	0	0
Unknown	1	0	0
Weight Units: kilogram(s) arithmetic mean standard deviation	88.5 ± 22.20	88.4 ± 22.55	74.7 ± 14.63
BMI Units: kilogram(s)/square meter arithmetic mean standard deviation	29.2 ± 6.82	28.5 ± 6.02	25.1 ± 3.94

<b>Reporting group values</b>	aTIV, ≥ 18 to ≤ 60 years/healthy	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions
Number of subjects	31	149	31
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	50	7
From 65-84 years	0	99	24
85 years and over	0	0	0
Age continuous Units: years arithmetic mean standard deviation	41.1 ± 11.59	68.1 ± 5.53	69.9 ± 6.08
Gender categorical Units: Subjects			
Female	19	33	7
Male	12	116	24

Race			
Units: Subjects			
Black	0	0	0
White	31	149	31
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	31	148	30
Not reported	0	0	0
Unknown	0	0	1
Weight			
Units: kilogram(s)			
arithmetic mean	77.7	87.1	85.1
standard deviation	± 14.35	± 17.41	± 7.55
BMI			
Units: kilogram(s)/square meter			
arithmetic mean	26.4	29.3	28.7
standard deviation	± 4.32	± 5.59	± 2.97

<b>Reporting group values</b>	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy	Total
Number of subjects	58	32	540
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)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	14	7	348
From 65-84 years	44	24	191
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	68.9	69.3	-
standard deviation	± 5.28	± 5.63	-
Gender categorical			
Units: Subjects			
Female	35	20	210
Male	23	12	330
Race			
Units: Subjects			
Black	0	0	1
White	58	32	539
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	0	4
Not Hispanic or Latino	57	32	533
Not reported	0	0	1
Unknown	0	0	2

Weight			
Units: kilogram(s)			
arithmetic mean	77.4	76.1	
standard deviation	± 13.66	± 16.13	-
BMI			
Units: kilogram(s)/square meter			
arithmetic mean	27.4	26.8	
standard deviation	± 3.58	± 4.43	-

## End points

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### End points reporting groups

Reporting group title	aH5N1, $\geq 18$ to $\leq 60$ years/with medical conditions
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Reporting group description:

Subjects  $\geq 18$  to  $\leq 60$  years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

FAS for secondary (SRH) objective: All subjects in the All Enrolled Set who are randomized, received at least one study vaccination and provide immunogenicity data (SRH assay, homologous strain) at baseline (Day 1), 3 weeks after first vaccination (Day 22) and 3 weeks after (planned) second vaccination (Day 43) – FAS Secondary SRH.

Reporting group title	aTIV, $\geq 18$ to $\leq 60$ years/with medical conditions
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Reporting group description:

Subjects  $\geq 18$  to  $\leq 60$  years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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Reporting group title	aH5N1, $\geq 18$ to $\leq 60$ years/healthy
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Reporting group description:

Healthy subjects  $\geq 18$  to  $\leq 60$  years of age who who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

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Reporting group title	aTIV, ≥61 years/with medical conditions
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Reporting group description:

Subjects ≥ 61 years of age with underlying medical conditions who provided immunogenicity data at Day 1 and Day 43.

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Reporting group description:

Healthy subjects ≥ 61 years of age who provided immunogenicity data at Day 1 and Day 43

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

FAS for secondary (SRH) objective: All subjects in the All Enrolled Set who are randomized, received at least one study vaccination and provide immunogenicity data (SRH assay, homologous strain) at baseline (Day 1), 3 weeks after first vaccination (Day 22) and 3 weeks after (planned) second vaccination (Day 43) – FAS Secondary SRH.

Reporting group title	aTIV, ≥61 years/healthy
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Reporting group description:

Healthy subjects ≥ 61 years of age who provided immunogenicity data at Day 1 and Day 43.

FAS for primary objective: All subjects in the All Enrolled Set who were randomized, receive at least one study vaccination and provide immunogenicity data (HI assay, homologous strain) at baseline (Day 1) and 3 weeks after (planned) second vaccination (Day 43).

FAS for secondary (SRH) objective: All subjects in the All Enrolled Set who are randomized, received at least one study vaccination and provide immunogenicity data (SRH assay, homologous strain) at baseline (Day 1), 3 weeks after first vaccination (Day 22) and 3 weeks after (planned) second vaccination (Day 43) – FAS Secondary SRH.

Subject analysis set title	aH5N1, ≥18 years of age
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects in the exposed set who were in the solicited safety set and/or in the unsolicited safety set who received aH5N1.

Subject analysis set title	aTIV, ≥18 years of age
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects in the exposed set who were in the solicited safety set and/or in the unsolicited safety set who received aTIV.

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**Primary: Immunogenicity Endpoint: Geometric Mean Ratios (Day 43/Day 1), as determined by HI assay**

End point title	Immunogenicity Endpoint: Geometric Mean Ratios (Day 43/Day 1), as determined by HI assay <sup>[1]</sup>
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End point description:

Geometric Mean ratios (GMRs) on Day 43 versus Day 1 (baseline) in adult (18 through 60 years of age) and elderly (≥61 years of age) 3 weeks after the second vaccination (Day 43) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by Hemagglutination Inhibition (HI) assay.

Full Analysis Set (FAS) for primary objective: All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (HI assay) at baseline (Day 1) and 3 weeks after the (planned) second vaccination (Day 43).

End point type	Primary
End point timeframe:	
Day 43: Day 1	

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: Analyses for this endpoint were performed with descriptive statistics

End point values	aH5N1, $\geq 18$ to $\leq 60$ years/with medical conditions	aTIV, $\geq 18$ to $\leq 60$ years/with medical conditions	aH5N1, $\geq 18$ to $\leq 60$ years/healthy	aTIV, $\geq 18$ to $\leq 60$ years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[2]</sup>	33	40 <sup>[3]</sup>	21
Units: titer ratios				
geometric mean (confidence interval 95%)	2.42 (2.04 to 2.88)	1.13 (0.80 to 1.60)	3.44 (2.47 to 4.78)	1.09 (0.69 to 1.70)

Notes:

[2] - N for Day 43 = 133

[3] - N for Day 43 = 39

End point values	aH5N1, $\geq 61$ years/with medical conditions	aTIV, $\geq 61$ years/with medical conditions	aH5N1, $\geq 61$ years/healthy	aTIV, $\geq 61$ years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[4]</sup>	29 <sup>[5]</sup>	42 <sup>[6]</sup>	27
Units: titer ratios				
geometric mean (confidence interval 95%)	2.64 (2.19 to 3.18)	1.19 (0.78 to 1.82)	2.44 (1.83 to 3.26)	1.30 (0.91 to 1.86)

Notes:

[4] - N for Day 43 = 137

[5] - N for Day 43 = 27

[6] - N for Day 43 = 41

## Statistical analyses

No statistical analyses for this end point

### Primary: Immunogenicity Endpoint: Percentage of subjects achieving seroconversion on Day 43 as determined by HI assay

End point title	Immunogenicity Endpoint: Percentage of subjects achieving seroconversion on Day 43 as determined by HI assay <sup>[7]</sup>
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End point description:

Percentage of subjects achieving seroconversion (defined as HI  $\geq 1:40$  for subjects who were seronegative at baseline [Day 1 HI titer  $< 1:10$ ] or a minimum 4-fold increase in HI titer for subjects who were seropositive at baseline [Day 1 HI titer  $\geq 1:10$ ]) on Day 43 in adult (18 through 60 years of age) and elderly ( $\geq 61$  years of age) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by Hemagglutination Inhibition (HI) assay.

Full Analysis Set (FAS) for primary objective: All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (HI assay) at baseline (Day 1) and 3 weeks after the (planned) second vaccination (Day 43).

End point type	Primary
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End point timeframe:

Day 43

Notes:

[7] - 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: Analyses for this endpoint were performed with descriptive statistics

<b>End point values</b>	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy	aTIV, ≥ 18 to ≤ 60 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136	33	40	21
Units: percentage of subjects				
number (confidence interval 95%)	26.47 (19.3 to 34.7)	3.03 (0.08 to 15.8)	37.50 (22.7 to 54.2)	0 (0 to 0)

<b>End point values</b>	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140	29	42	27
Units: percentage of subjects				
number (confidence interval 95%)	27.86 (20.6 to 36.1)	3.45 (0.09 to 17.8)	21.43 (10.3 to 36.8)	3.70 (0.09 to 19)

## Statistical analyses

No statistical analyses for this end point

### **Primary: Immunogenicity Endpoint: Percentage of subjects with HI titer ≥1:40 (Day 43)**

End point title	Immunogenicity Endpoint: Percentage of subjects with HI titer ≥1:40 (Day 43) <sup>[8]</sup>
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End point description:

Percentage of subjects with HI titer ≥1:40 on Day 43 in adult (18 through 60 years of age) and elderly (≥61 years of age) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by Hemagglutination Inhibition (HI) assay.

Full Analysis Set (FAS) for primary objective: All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (HI assay) at baseline (Day 1) and 3 weeks after the (planned) second vaccination (Day 43).

End point type	Primary
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End point timeframe:

Day 43

Notes:

[8] - 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: Analyses for this endpoint were performed with descriptive statistics

<b>End point values</b>	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy	aTIV, ≥ 18 to ≤ 60 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[9]</sup>	33	40 <sup>[10]</sup>	21
Units: percentage of subjects				
number (confidence interval 95%)	30 (22.4 to 38.6)	6 (0.7 to 20.2)	38 (23.4 to 55.4)	0 (0 to 0)

Notes:

[9] - N for Day 43 = 133

[10] - N for Day 43 = 39

<b>End point values</b>	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[11]</sup>	29 <sup>[12]</sup>	42 <sup>[13]</sup>	27
Units: percentage of subjects				
number (confidence interval 95%)	33 (25.1 to 41.4)	7 (0.9 to 24.3)	24 (12.4 to 40.3)	4 (0.09 to 19)

Notes:

[11] - N for Day 43 = 137

[12] - N for Day 43 = 27

[13] - N for Day 43 = 41

## Statistical analyses

No statistical analyses for this end point

## Primary: Safety Endpoint: Percentage of subjects with solicited local, solicited systemic, and other AEs

End point title	Safety Endpoint: Percentage of subjects with solicited local, solicited systemic, and other AEs <sup>[14]</sup>
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End point description:

Percentage of subjects with solicited AEs that occur within 7 days following each vaccination

Solicited Safety Set: All subjects in the Exposed Set with any solicited AE data and/or indicators of solicited AEs (ie, use of analgesics/antipyretics).

End point type	Primary
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End point timeframe:

Day 1 through Day 7

Notes:

[14] - 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: Analyses for this endpoint were performed with descriptive statistics

<b>End point values</b>	aH5N1, ≥18 years of age	aTIV, ≥18 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	411	128		
Units: percentage of subjects				
number (not applicable)				
Solicited AEs, Any	75.2	85.2		

Solicited Local AEs	63.5	76.6		
Solicited Systemic AEs	52.8	58.6		
Other	7.3	6.3		

## Statistical analyses

No statistical analyses for this end point

### Primary: Safety Endpoint: Percentage of subjects with unsolicited AEs reported

End point title	Safety Endpoint: Percentage of subjects with unsolicited AEs reported <sup>[15]</sup>
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End point description:

Percentage of subjects with any unsolicited AEs reported within 21 days after each vaccination within each vaccine group.

Unsolicited Safety Set: All subjects in the Exposed Set with unsolicited AE data.

End point type	Primary
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End point timeframe:

Day 1 through Day 21

Notes:

[15] - 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: Analyses for this endpoint were performed with descriptive statistics

End point values	aH5N1, ≥18 years of age	aTIV, ≥18 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	408	128		
Units: percentage of subjects				
number (not applicable)				
Unsolicited AEs, Any	40.2	30.5		
Unsolicited AEs, Mild	13.7	13.3		
Unsolicited AEs, Moderate	17.2	10.9		
Unsolicited AEs, Severe	9.3	6.3		
Unsolicited AEs, Related	8.6	12.5		

## Statistical analyses

No statistical analyses for this end point

### Primary: Safety Endpoint: Percentage of subjects with SAEs, NOCDs, medically attended AEs, AESIs, AEs leading to withdrawal from the study

End point title	Safety Endpoint: Percentage of subjects with SAEs, NOCDs, medically attended AEs, AESIs, AEs leading to withdrawal from the study <sup>[16]</sup>
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End point description:

Percentage of subjects reporting SAEs, NOCDs, medically attended AEs, AESIs, AEs leading to withdrawal from the study as collected from Day 1 through Day 202.

Unsolicited Safety Set: All subjects in the Exposed Set with unsolicited AE data.

End point type	Primary
End point timeframe:	
Day 1 through Day 202	

Notes:

[16] - 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: Analyses for this endpoint were performed with descriptive statistics

End point values	aH5N1, ≥18 years of age	aTIV, ≥18 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	411 <sup>[17]</sup>	128		
Units: percentage of subjects				
number (not applicable)				
Serious Adverse Events (SAE)	11	2.3		
Related SAEs	0	0		
Medically attended AEs	32.8	25.0		
AESIs	0	0		
NOCDs	1.7	2.3		
AEs leading to withdrawal	1.7	2.3		
AEs leading to death	1.0	0		

Notes:

[17] - Ns for SAEs, related SAEs, AEs leading to withdrawal = 408

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Geometric Mean Ratios: Day 22/Day 1 and Day 43/Day 1 as determined by SRH

End point title	Immunogenicity Endpoint: Geometric Mean Ratios: Day 22/Day 1 and Day 43/Day 1 as determined by SRH
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End point description:

Geometric Mean ratios (GMRs) on Day 22/Day 1 and Day 43/Day 1 as determined by single radial hemolysis (SRH) in adult (18 through 60 years of age) and elderly (≥61 years of age) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions.

FAS for Secondary Objective. SRH - All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (SRH assay) at baseline (Day 1), 3 weeks after the first vaccination (Day 22) and 3 weeks after the (planned) second vaccination (Day 43).

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

End point values	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy	aTIV, ≥ 18 to ≤ 60 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[18]</sup>	33 <sup>[19]</sup>	40 <sup>[20]</sup>	21
Units: titer ratios				
geometric mean (confidence interval 95%)				
Day 22/Day 1 - SRH	2.39 (2.09 to 2.73)	2.04 (1.55 to 2.67)	3.31 (2.55 to 4.30)	2.55 (1.79 to 3.63)
Day 43/ Day 1 - SRH	3.47 (3.05 to 3.94)	1.75 (1.36 to 2.27)	6.84 (5.47 to 8.56)	2.23 (1.64 to 3.03)

Notes:

[18] - N for Day 22 = 130

N for Day 43 = 133

[19] - N for Day 22 = 32

[20] - N for Day 22 = 38

N for Day 43 = 39

End point values	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[21]</sup>	29 <sup>[22]</sup>	42 <sup>[23]</sup>	27
Units: titer ratios				
geometric mean (confidence interval 95%)				
Day 22/Day 1 - SRH	1.52 (1.37 to 1.69)	1.45 (1.15 to 1.84)	1.88 (1.48 to 2.38)	1.59 (1.19 to 2.13)
Day 43/ Day 1 - SRH	2.34 (2.08 to 2.64)	1.58 (1.20 to 2.07)	3.13 (2.44 to 4.01)	1.69 (1.24 to 2.29)

Notes:

[21] - N for Day 22 = 136

N for Day 43 = 137

[22] - N for Day 43 = 27

[23] - N for Day 22 = 41

N for Day 43 = 41

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Percentage of subject achieving seroconversion on Day 22 and Day 43 as determined by SRH assay

End point title	Immunogenicity Endpoint: Percentage of subject achieving seroconversion on Day 22 and Day 43 as determined by SRH assay
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End point description:

Percentage of subjects achieving seroconversion on Day 22 and Day 43 in adult (18 through 60 years of age) and elderly (≥61 years of age) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by single radial hemolysis (SRH) assay.

FAS for Secondary Objective. SRH - All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (SRH assay) at baseline (Day 1), 3 weeks after the first vaccination (Day 22) and 3 weeks after the (planned) second vaccination (Day 43).

End point type	Secondary
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End point timeframe:

Day 22 and Day 43

<b>End point values</b>	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy	aTIV, ≥ 18 to ≤ 60 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[24]</sup>	33 <sup>[25]</sup>	40 <sup>[26]</sup>	21
Units: percentage of subjects				
number (confidence interval 95%)				
Day 22 - SRH	59.23 (50.3 to 67.8)	46.88 (29.1 to 65.3)	84.21 (68.7 to 94)	61.90 (38.4 to 81.9)
Day 43 - SRH	75.19 (67 to 82.3)	42.42 (25.5 to 60.8)	97.44 (86.5 to 99.94)	52.38 (29.8 to 74.3)

Notes:

[24] - N for Day 22 = 130

N for Day 43 = 133

[25] - N for Day 22 = 32

[26] - N for Day 22 = 38

N for Day 43 = 39

<b>End point values</b>	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[27]</sup>	29 <sup>[28]</sup>	42 <sup>[29]</sup>	27
Units: percentage of subjects				
number (confidence interval 95%)				
Day 22 - SRH	36.76 (28.7 to 45.5)	20.69 (8 to 39.7)	48.78 (32.9 to 64.9)	37.04 (19.4 to 57.6)
Day 43 - SRH	64.23 (55.6 to 72.2)	18.52 (6.3 to 38.1)	68.29 (51.9 to 81.9)	44.44 (25.5 to 64.7)

Notes:

[27] - N for Day 22 = 136

N for Day 43 = 137

[28] - N for Day 43 = 27

[29] - N for Day 22 = 41

N for Day 43 = 41

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Percentage of subjects with SRH area ≥25mm<sup>2</sup> on Day 1, Day 22 and Day 43

End point title	Immunogenicity Endpoint: Percentage of subjects with SRH area ≥25mm <sup>2</sup> on Day 1, Day 22 and Day 43
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End point description:

Percentage of subjects with with SRH area ≥25mm<sup>2</sup> on Day 1, Day 22 and Day 43 in adult (18 through 60 years of age) and elderly (≥61 years of age) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by single radial hemolysis (SRH) assay.

FAS for Secondary Objective. SRH - All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (SRH assay) at baseline (Day 1), 3 weeks after the first vaccination (Day 22) and 3 weeks after the (planned) second vaccination (Day 43).

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

End point values	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy	aTIV, ≥ 18 to ≤ 60 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[30]</sup>	33 <sup>[31]</sup>	40 <sup>[32]</sup>	21
Units: percentage of subjects				
number (confidence interval 95%)				
Day 1 - SRH	16.91 (11 to 24.3)	6.06 (0.7 to 20.2)	2.50 (0.06 to 13.2)	14.29 (3 to 36.3)
Day 22 - SRH	49.23 (40.4 to 58.1)	46.88 (29.1 to 65.3)	47.37 (31 to 64.2)	52.38 (29.8 to 74.3)
Day 43 - SRH	65.41 (56.7 to 73.4)	39.39 (22.9 to 57.9)	84.62 (69.5 to 94.1)	52.38 (29.8 to 74.3)

Notes:

[30] - N for Day 22 = 130

N for Day 43 = 133

[31] - N for Day 22 = 32

[32] - N for Day 22 = 38

N for Day 43 = 39

End point values	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[33]</sup>	29 <sup>[34]</sup>	42 <sup>[35]</sup>	27
Units: percentage of subjects				
number (confidence interval 95%)				
Day 1 - SRH	22.14 (15.6 to 29.9)	31.03 (15.3 to 50.8)	11.90 (4 to 25.6)	11.11 (2.4 to 29.2)
Day 22 - SRH	41.18 (32.8 to 49.6)	48.28 (29.4 to 67.5)	34.15 (20.1 to 50.6)	25.93 (11.1 to 46.3)
Day 43 - SRH	59.12 (50.4 to 67.4)	51.85 (31.9 to 71.3)	53.66 (37.4 to 69.3)	29.63 (13.8 to 50.2)

Notes:

[33] - N for Day 22 = 136

N for Day 43 = 137

[34] - N for Day 43 = 27

[35] - N for Day 22 and Day 43 = 41

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Geometric Mean Ratios (Day 22/Day 1) as determined by HI assay

End point title	Immunogenicity Endpoint: Geometric Mean Ratios (Day 22/Day 1) as determined by HI assay
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End point description:

Geometric Mean ratios (GMRs) on Day 22 versus Day 1 (baseline) in adult (18 through 60 years of age) and elderly ( $\geq 61$  years of age) 3 weeks after the first vaccination (Day 22) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by Hemagglutination Inhibition (HI) assay.

FAS for Secondary Objective, HI: All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (HI assay) at baseline (Day 1) and 3 weeks after the first vaccination (Day 22).

End point type	Secondary
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End point timeframe:

Day 22:Day 1

End point values	aH5N1, $\geq 18$ to $\leq 60$ years/with medical conditions	aTIV, $\geq 18$ to $\leq 60$ years/with medical conditions	aH5N1, $\geq 18$ to $\leq 60$ years/healthy	aTIV, $\geq 18$ to $\leq 60$ years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[36]</sup>	33 <sup>[37]</sup>	40 <sup>[38]</sup>	21
Units: titer ratios				
geometric mean (confidence interval 95%)	1.57 (1.34 to 1.83)	1.07 (0.78 to 1.46)	1.95 (1.44 to 2.63)	1.18 (0.79 to 1.77)

Notes:

[36] - N for Day 22 = 130

[37] - N for Day 22 = 32

[38] - N for Day 22 = 38

End point values	aH5N1, $\geq 61$ years/with medical conditions	aTIV, $\geq 61$ years/with medical conditions	aH5N1, $\geq 61$ years/healthy	aTIV, $\geq 61$ years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[39]</sup>	29	42 <sup>[40]</sup>	27
Units: titer ratios				
geometric mean (confidence interval 95%)	1.59 (1.37 to 1.85)	1.24 (0.89 to 1.72)	1.66 (1.28 to 2.16)	1.12 (0.81 to 1.55)

Notes:

[39] - N for Day 22 = 136

[40] - N for Day 22 = 41

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Percentage of subjects achieving seroconversion (Day 22) as determined by HI assay

End point title	Immunogenicity Endpoint: Percentage of subjects achieving seroconversion (Day 22) as determined by HI assay
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End point description:

Percentage of subjects achieving seroconversion (defined as HI  $\geq 1:40$  for subjects who were seronegative at baseline [Day 1 HI titer  $< 1:10$ ] or a minimum 4-fold increase in HI titer for subjects who were seropositive at baseline [Day 1 HI titer  $\geq 1:10$ ]) on Day 22 in adult (18 through 60 years of

age) and elderly ( $\geq 61$  years of age) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by Hemagglutination Inhibition (HI) assay.

FAS for Secondary Objective, HI: All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (HI assay) at baseline (Day 1) and 3 weeks after the first vaccination (Day 22).

End point type	Secondary
End point timeframe:	Day 22

End point values	aH5N1, $\geq 18$ to $\leq 60$ years/with medical conditions	aTIV, $\geq 18$ to $\leq 60$ years/with medical conditions	aH5N1, $\geq 18$ to $\leq 60$ years/healthy	aTIV, $\geq 18$ to $\leq 60$ years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[41]</sup>	33 <sup>[42]</sup>	40 <sup>[43]</sup>	21
Units: percentage of subjects				
number (confidence interval 95%)	13.85 (8.4 to 21)	3.13 (0.08 to 16.2)	21.05 (9.6 to 37.3)	4.76 (0.12 to 23.8)

Notes:

[41] - N for Day 22 = 130

[42] - N for Day 22 = 32

[43] - N for Day 22 = 38

End point values	aH5N1, $\geq 61$ years/with medical conditions	aTIV, $\geq 61$ years/with medical conditions	aH5N1, $\geq 61$ years/healthy	aTIV, $\geq 61$ years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[44]</sup>	29	42 <sup>[45]</sup>	27
Units: percentage of subjects				
number (confidence interval 95%)	13.24 (8.0 to 20.1)	3.45 (0.09 to 17.8)	9.76 (2.7 to 23.1)	3.70 (0.09 to 19.0)

Notes:

[44] - N for Day 22 = 136

[45] - N for Day 22 = 41

## Statistical analyses

No statistical analyses for this end point

### Secondary: Immunogenicity Endpoint: Percentage of subjects with HI titer $\geq 1:40$ on Day 1 and Day 22 as determined by HI assay

End point title	Immunogenicity Endpoint: Percentage of subjects with HI titer $\geq 1:40$ on Day 1 and Day 22 as determined by HI assay
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End point description:

Percentage of subjects with HI titer  $\geq 1:40$  on Day 22 in adult (18 through 60 years of age) and elderly ( $\geq 61$  years of age) according to CHMP immunogenicity criteria in subjects who are healthy or with underlying medical conditions as determined by Hemagglutination Inhibition (HI) assay.

FAS for Secondary Objective, HI: All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data (HI assay) at baseline (Day 1) and 3 weeks after the first vaccination (Day 22).

End point type	Secondary
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End point timeframe:

Day 1 and Day 22

<b>End point values</b>	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy	aTIV, ≥ 18 to ≤ 60 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[46]</sup>	33 <sup>[47]</sup>	40 <sup>[48]</sup>	21
Units: percentage of subjects				
number (confidence interval 95%)				
Day 1 - HI	2 (0.46 to 6.3)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Day 22 - HI	15 (9.7 to 22.8)	3 (0.08 to 16.2)	21 (9.6 to 37.3)	5 (0.12 to 23.8)

Notes:

[46] - N for Day 22 = 130

[47] - N for Day 22 = 32

[48] - N for Day 22 = 38

<b>End point values</b>	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[49]</sup>	29	42 <sup>[50]</sup>	27
Units: percentage of subjects				
number (confidence interval 95%)				
Day 1 - HI	2 (0.44 to 6.1)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Day 22 - HI	15 (9.8 to 22.6)	7 (0.8 to 22.8)	12 (4.1 to 26.2)	4 (0.09 to 19)

Notes:

[49] - N for Day 22 = 136

[50] - N for Day 22 = 41

## Statistical analyses

No statistical analyses for this end point

## Secondary: Immunogenicity Endpoint: Geometric Mean Titers (HI) and Geometric Mean Area (SRH) at Day 1, Day 22 and Day 43 as determined by HI and SRH

End point title	Immunogenicity Endpoint: Geometric Mean Titers (HI) and Geometric Mean Area (SRH) at Day 1, Day 22 and Day 43 as determined by HI and SRH
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End point description:

Geometric mean titers (HI) and Geometric Mean Area (SRH) at the following time points: Day 1, Day 22 (3 weeks after the first vaccination), Day 43 (3 weeks after the second vaccination) in adult (18 through 60 years of age) and elderly (≥61 years of age) subjects.

FAS for Secondary Objective. SRH and HI- All subjects in the All Enrolled Set who were randomized, received at least one study vaccination and provided immunogenicity data at baseline (Day 1, SRH and HI assay), 3 weeks after the first vaccination (Day 22, SRH and HI assay) and 3 weeks after the (planned) second vaccination (Day 43, SRH assay).

End point type	Secondary
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End point timeframe:

Day 1, Day 22 and Day 43

<b>End point values</b>	aH5N1, ≥ 18 to ≤ 60 years/with medical conditions	aTIV, ≥ 18 to ≤ 60 years/with medical conditions	aH5N1, ≥ 18 to ≤ 60 years/healthy	aTIV, ≥ 18 to ≤ 60 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	136 <sup>[51]</sup>	33 <sup>[52]</sup>	40 <sup>[53]</sup>	21
Units: titer ratios				
geometric mean (confidence interval 95%)				
Day 1 - HI	5.47 (5.12 to 5.84)	5.27 (4.61 to 6.02)	5.00 (5.00 to 5.00)	5.00 (5.00 to 5.00)
Day 1 - SRH	9.42 (8.29 to 10.70)	7.55 (5.83 to 9.79)	7.01 (5.74 to 8.56)	9.26 (7.03 to 12.19)
Day 22 - HI	8.43 (7.22 to 9.85)	5.75 (4.20 to 7.87)	9.73 (7.19 to 13.16)	5.90 (3.93 to 8.86)
Day 22 - SRH	21.93 (19.18 to 25.06)	18.69 (14.26 to 24.50)	25.25 (19.45 to 32.77)	19.40 (13.62 to 27.63)
Day 43 - HI	13.17 (11.08 to 15.65)	6.13 (4.33 to 8.67)	17.20 (12.36 to 23.92)	5.43 (3.46 to 8.51)
Day 43 - SRH	31.53 (27.75 to 35.83)	15.94 (12.32 to 20.62)	51.76 (41.37 to 64.75)	16.87 (12.39 to 22.95)

Notes:

[51] - N for Day 22 = 130

N for Day 43 = 133

[52] - N for Day 22 = 32

[53] - N for Day 22 = 38

N for Day 43 = 39

<b>End point values</b>	aH5N1, ≥61 years/with medical conditions	aTIV, ≥61 years/with medical conditions	aH5N1, ≥61 years/healthy	aTIV, ≥61 years/healthy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140 <sup>[54]</sup>	29 <sup>[55]</sup>	42 <sup>[56]</sup>	27
Units: titer ratios				
geometric mean (confidence interval 95%)				
Day 1 - HI	5.80 (5.36 to 6.28)	6.20 (5.21 to 7.38)	5.21 (4.86 to 5.58)	5.13 (4.71 to 5.59)
Day 1 - SRH	11.92 (10.40 to 13.67)	15.70 (11.63 to 21.20)	9.10 (7.38 to 11.22)	8.88 (6.84 to 11.52)
Day 22 - HI	9.31 (8.01 to 10.83)	7.23 (5.21 to 10.03)	8.61 (6.63 to 11.19)	5.81 (4.21 to 8.03)
Day 22 - SRH	18.99 (17.04 to 21.15)	18.14 (14.34 to 22.95)	16.86 (13.31 to 21.36)	14.29 (10.68 to 19.13)
Day 43 - HI	15.42 (12.78 to 18.61)	6.96 (4.56 to 10.64)	12.66 (9.47 to 16.91)	6.73 (4.71 to 9.62)
Day 43 - SRH	29.62 (26.29 to 33.36)	19.98 (15.25 to 26.17)	27.97 (22.81 to 35.87)	15.08 (11.09 to 20.48)

Notes:

[54] - N for Day 22 = 136

N for Day 43 = 137

[55] - N for Day 43 = 27

[56] - N for Day 22 and Day 43 = 41

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 through Day 202

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	aH5N1
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Reporting group description: -

Reporting group title	aTIV
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Reporting group description: -

<b>Serious adverse events</b>	aH5N1	aTIV	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 411 (10.95%)	3 / 128 (2.34%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Respiratory failure			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 411 (0.73%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Acute psychosis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Meniscus injury			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury cervical			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular bypass dysfunction			
subjects affected / exposed	2 / 411 (0.49%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 411 (0.73%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	2 / 411 (0.49%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Strabismus			
subjects affected / exposed	0 / 411 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis microscopic			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
Chronic kidney disease			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 411 (0.73%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ketoacidosis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 128 (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 %

<b>Non-serious adverse events</b>	aH5N1	aTIV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	306 / 411 (74.45%)	109 / 128 (85.16%)	
Nervous system disorders			
Headache			
subjects affected / exposed	78 / 411 (18.98%)	30 / 128 (23.44%)	
occurrences (all)	214	72	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	131 / 411 (31.87%)	39 / 128 (30.47%)	
occurrences (all)	398	94	
Injection site erythema			
subjects affected / exposed	101 / 411 (24.57%)	37 / 128 (28.91%)	
occurrences (all)	233	102	
Injection site haemorrhage			
subjects affected / exposed	23 / 411 (5.60%)	14 / 128 (10.94%)	
occurrences (all)	93	38	
Injection site induration			
subjects affected / exposed	74 / 411 (18.00%)	41 / 128 (32.03%)	
occurrences (all)	227	114	
Injection site pain			
subjects affected / exposed	222 / 411 (54.01%)	82 / 128 (64.06%)	
occurrences (all)	650	257	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	49 / 411 (11.92%)	13 / 128 (10.16%)	
occurrences (all)	128	22	
Nausea			

subjects affected / exposed occurrences (all)	26 / 411 (6.33%) 43	4 / 128 (3.13%) 5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	43 / 411 (10.46%)	19 / 128 (14.84%)	
occurrences (all)	154	46	
Myalgia			
subjects affected / exposed	124 / 411 (30.17%)	41 / 128 (32.03%)	
occurrences (all)	343	112	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	35 / 411 (8.52%)	9 / 128 (7.03%)	
occurrences (all)	99	23	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported