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Study No.: 111954 (H5N1-041)
Title: Non-inferiority study of GSK Biologicals' pandemic influenza vaccine 1562902A. 1562902A (H5N1): GlaxoSmithKline (GSK) Biologicals' adjuvanted pandemic influenza candidate vaccine (derived from A/Indonesia/5/2005 strain)
Rationale: The aim of the study was to show the immunological non-inferiority of the new-processed (NP) H5N1 vaccine as compared to the comparative-processed (CP) H5N1 vaccine.
Phase: III
Study Period: 15 November 2008 to 08 July 2009 (data lock point D51) 09 May 2009 to 07 Jun 2009 (data lock point D180)
Study Design: Observer-blind, randomised (1:1) study with 2 parallel groups.
Centres: 1 centre in Taiwan
Indication: Immunisation against H5N1 influenza infection in subjects aged 18 to 60 years.
Treatment: Study groups were as follows: <ul style="list-style-type: none"> • NP Group: subjects received two doses of NP H5N1 vaccine (at Days 0 and 21) • CP Group: subjects receiving two doses of CP H5N1 vaccine (at Days 0 and 21) Vaccines were given intramuscularly, in the deltoid region of the non-dominant arm.
Objectives: To demonstrate the immunological non-inferiority (in terms of H5N1 haemagglutination-inhibition [HI] antibody geometric mean titre [GMT]) of the NP H5N1 vaccine as compared to the CP H5N1 vaccine 21 days after second vaccination in healthy subjects aged 18 to 60 years.
Primary Outcome/Efficacy Variable: <i>Observed variable:</i> <ul style="list-style-type: none"> • H5N1 HI antibodies against the H5N1 influenza vaccine strain (vaccine homologous virus) at Day 42. <i>Derived variables:</i> The following parameter was calculated with 95 % confidence intervals (CIs) in each study vaccine: <ul style="list-style-type: none"> • GMTs of H5N1 HI antibodies at Day 42.
Secondary Outcome/Efficacy Variable(s): <i>For the humoral immune response in terms of H5N1 HI antibodies, the following parameters were calculated with 95 % CIs in each study vaccine:</i> <i>Observed variable:</i> <ul style="list-style-type: none"> • H5N1 HI antibodies against vaccine-homologous virus and one or more drift virus at Day 0, Day 42 and Day 180. <i>Derived variables:</i> <ul style="list-style-type: none"> • GMTs and seropositivity of H5N1 HI antibodies at Day 0 and Day 180. • Seropositivity of H5N1 HI antibodies at Day 42. • Seroconversion rates (SCR) at Day 42 and Day 180. • Seroconversion factors (SCF) at Day 42 and Day 180. • Seroprotection rates (SPR) at Day 0, Day 42 and Day 180. <i>For the humoral immune response evaluation in terms of neutralising antibodies, the following parameters were calculated with 95 % CIs, in a subset of subjects:</i> <i>Observed variable:</i> <ul style="list-style-type: none"> • Serum neutralising antibody titres against one or more drift variant H5N1 virus at Day 0, Day 42 and Day 180. <i>Derived variables:</i> <ul style="list-style-type: none"> • GMTs and seropositivity rates of serum neutralising antibodies at Day 0, Day 42, and Day 180. • SCR at Day 42 and Day 180.
Safety: <ul style="list-style-type: none"> • The percentage, intensity and relationship to vaccination of solicited local and general signs and symptoms during a 7-day follow-up period, i.e. day of vaccination and 6 subsequent days after each vaccination.

- The percentage, intensity and relationship to vaccination of unsolicited local and general signs and symptoms from Day 0 up to 30 days after the second vaccination%.
- The occurrence of all unsolicited adverse events (AEs) during a 21-day follow-up period for each vaccine administration%, as well as overall (Day 0 through Day 51) §.
- The occurrence of adverse events of specific interest (AESIs) from Day 0 through Day 180.
- The occurrence of serious adverse events (SAEs) from Day 0 through Day 180.

% Analysis was neither performed separately during the 21 days follow-up period after each vaccination nor for the period from Day 0 up to 30 days after the second vaccination.

§ Data were also analyzed from Day 0 to Day 180

Statistical Methods:

Analyses were performed on the Total Vaccinated Cohort and the According-To-Protocol (ATP) cohort for immunogenicity.

- The Total Vaccinated Cohort included all vaccinated subjects for whom safety data were available.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study, with no major deviation that could have an impact on the immune response) for whom data concerning immunogenicity outcome variables were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination. Subjects who received the wrong vaccine were analysed according to the randomisation.

Analysis of immunogenicity:

The analysis of immunogenicity was based on the ATP cohort for immunogenicity.

Inferential analysis:

For the non-inferiority of the NP H5N1 vaccine over CP H5N1 vaccine analysis, the 95% CI of the GMT ratio (CP H5N1 vaccine over NP H5N1 vaccine) against the A/Indonesia/05/2005 strain, 42 days post-vaccination was computed using the analysis of covariance (ANCOVA) model. The ANCOVA model included the vaccine group as the fixed effect and log-pre-vaccination results as the regressor.

The criterion was the following: upper limit of two-sided 95%CI of the GMT ratio (CP H5N1 vaccine over NP H5N1 vaccine) below 2.0 in terms of HI antibody titre against A/Indonesia/5/05 strain.

Descriptive analysis:

For the humoral immune response in terms of H5N1 HI antibodies against vaccine-homologous virus and one or more drift variant virus, the following parameters (with 95% CIs) were calculated for each vaccine group:

- GMTs and seropositivity rates on Days 0, 42 and 180;
- SCRs* on Days 42 and 180;
- SCFs** on Days 42 and 180;
- SPRs*** on Days 0, 42 and 180.

*SCRs are defined as the percentage of vaccinees with either a pre-vaccination titre < 1:10 and a post-vaccination titre \geq 40 or a pre-vaccination titre \geq 10 and at least a 4-fold increase in post-vaccination titre.

**SCFs are defined as the fold increase in H5N1 antibody GMTs post-vaccination compared to Day 0.

***SPRs are defined as the percentage of vaccinees with a vaccination titre \geq 40.

For the humoral immune response in terms of neutralising antibodies, the following parameters (95 % CIs) were calculated for each vaccine group:

- GMTs and seropositivity rates of serum neutralising antibodies at Day 0, Day 42, and Day 180.
- SCRs[∞] at Day 42 and Day 180.

[∞]SCRs are defined as the percentage of vaccinees with at least a 4-fold or greater increase in neutralising antibody titre post-vaccination.

Analysis of safety:

The analysis of safety was based on the Total Vaccinated Cohort.

The percentage of subjects reporting each individual solicited local and general symptom during the 7-day follow-up period following vaccination was tabulated with exact 95% CI. The same tabulations were performed for grade 3 symptoms and for general symptoms assessed by the investigator as related to vaccination.

The proportion of subjects with at least one report of an unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and reported up to 21 days after the first vaccination and 30 days after the second vaccination was tabulated. The same tabulations were performed for grade 3 unsolicited AEs and for unsolicited AEs assessed by investigators as causally related to vaccination. The percentage of subjects with unsolicited adverse events was also computed within the 180-Day period (Day 0 – Day 179).

The proportion of subjects with AESIs was tabulated within the 180-Day period. The occurrence of SAEs was tabulated within the 180-Day period according to MedDRA preferred terms.

Study Population: Healthy adults aged 18 to 60 years at the time of the first vaccination. Female subjects were to be of non-childbearing potential, or, if of childbearing potential, practised adequate contraception for 30 days prior to vaccination, had a negative pregnancy test and were to continue such precautions for 2 months after completion of the vaccination series. Written informed consent was obtained from the subject prior to study entry.										
Number of Subjects:					NP Group		CP Group			
Planned, N					160		160			
Randomised, N (Total Vaccinated cohort)					160		160			
Completed to Day 51, n (%)					160 (100)		159 (99.4)			
Completed to visit 4, Day 180, n (%)					160 (100)		159 (99.4)			
Total Number Subjects Withdrawn, n (%)					0 (0.0)		1 (0.6)			
Withdrawn due to Adverse Events n (%)					0 (0.0)		0 (0.0)			
Withdrawn due to Lack of Efficacy n (%)					Not Applicable		Not applicable			
Withdrawn for other reasons n (%)					0 (0.0)		1 (0.6)			
Demographics					NP Group		CP Group			
N (Total Vaccinated cohort)					160		160			
Females: Males					80:80		83:77			
Mean Age, years (SD)					31.3 (7.95)		32.6 (9.10)			
Asian - East-Asian heritage, n (%)					160 (100)		160 (100)			
Primary Efficacy Results: GMT ratio between NP H5N1 vaccine and CP H5N1 on Day 42 against vaccine strain A/Indonesia/05/2005 (ATP cohort for immunogenicity)										
						Adjusted GMT ratio				
						95% CI				
Group description	N	Adjusted GMT	Group description	N	Adjusted GMT	Ratio order	Value	LL	UL*	
CP	155	620.2	NP	156	741.2	CP /NP	0.84	0.71	0.99	
NP	156	741.2	CP	155	620.2	NP /CP	1.20	1.01	1.42	
N = Number of subjects with both pre- and post-vaccination results available 95% CI = 95% confidence interval for the adjusted GMT ratio (ANCOVA model: adjustment for baseline titre - pooled variance); LL = lower limit, UL = upper limit *Criterion for non-inferiority = upper limit of two-sided 95%CI of the GMT ratio below 2.0										
Primary Efficacy Results: Seropositivity rates and GMTs of H5N1 HI antibodies against A/Indonesia/05/2005 and A/Vietnam/1194/2004 strains on Days 0, 42 and 180 (ATP cohort for immunogenicity)										
				≥ 1:10				GMT*		
				95% CI				95% CI		
Antibodies against	Group	Timing	N	n	%	LL	UL	value	LL	UL
A/Indonesia	NP	PRE	156	0	0.0	0.0	2.3	5.0	5.0	5.0
		PII(D42)*	156	156	100	97.7	100	739.5	667.8	818.8
		PII(D180)	156	145	92.9	87.7	96.4	51.9	45.1	59.7
	CP	PRE	156	3	1.9	0.4	5.5	5.1	5.0	5.2
		PII(D42)*	155	154	99.4	96.5	100	621.7	542.9	712.0
		PII(D180)	155	128	82.6	75.7	88.2	33.0	28.0	39.0
A/Vietnam	NP	PRE	156	2	1.3	0.2	4.6	5.1	4.9	5.3
		PII(D42)	156	149	95.5	91.0	98.2	79.7	69.4	91.5
		PII(D180)	156	82	52.6	44.4	60.6	12.6	10.8	14.8
	CP	PRE	156	3	1.9	0.4	5.5	5.2	5.0	5.5
		PII(D42)	155	140	90.3	84.5	94.5	56.1	47.6	66.0
		PII(D180)	155	50	32.3	25.0	40.2	8.4	7.3	9.5
GMT = geometric mean antibody titre calculated on all subjects N = number of subjects with available results n (%) = number (percentage) of subjects with titre within the specified range 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination Day 0										

PII(D42) = Post-vaccination two Day 42 PII(D180) = Post-vaccination two Day 180 * Primary outcome variable							
Secondary Outcome Variable(s): SCR for H5N1 HI antibodies against A/Indonesia/05/2005 and A/Vietnam/1194/2004 strains on Days 42 and 180 (ATP cohort for immunogenicity)							
				SCR			
				95% CI			
Antibodies against	Group	Timing	N	n	%	LL	UL
A/Indonesia	NP	PII(D42)	156	156	100	97.7	100
		PII(D180)	156	129	82.7	75.8	88.3
	CP	PII(D42)	155	153	98.7	95.4	99.8
		PII(D180)	155	104	67.1	59.1	74.4
A/Vietnam	NP	PII(D42)	156	143	91.7	86.2	95.5
		PII(D180)	156	34	21.8	15.6	29.1
	CP	PII(D42)	155	126	81.3	74.2	87.1
		PII(D180)	155	13	8.4	4.5	13.9
Seroconversion defined as: <ul style="list-style-type: none"> - For initially seronegative subjects, antibody titre \geq 1:40 after vaccination - For initially seropositive subjects, antibody titre after vaccination \geq 4-fold the pre-vaccination antibody titre N = Number of subjects with pre- and post-vaccination results available n (%) = Number (percentage) of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(D42) = Post-vaccination two Day 42 PII(D180) = Post-vaccination two Day 180							
Secondary Outcome Variable(s): SCF for H5N1 HI antibodies against A/Indonesia/05/2005 and A/Vietnam/1194/2004 strains on Days 42 and 180 (ATP cohort for immunogenicity)							
				SCF			
				95% CI			
Antibodies against	Group	Timing	N	Value	LL	UL	
A/Indonesia	NP	PII(D42)	156	147.9	133.6	163.8	
		PII(D180)	156	10.4	9.0	11.9	
	CP	PII(D42)	155	121.9	106.3	139.7	
		PII(D180)	155	6.5	5.5	7.6	
A/Vietnam	NP	PII(D42)	156	15.6	13.5	17.9	
		PII(D180)	156	2.5	2.1	2.9	
	CP	PII(D42)	155	10.8	9.1	12.7	
		PII(D180)	155	1.6	1.4	1.8	
N = Number of subjects with pre- and post-vaccination results available SCF = Seroconversion Factor or geometric mean ratio ($\text{mean}[\log_{10}(\text{POST}/\text{PRE})]$) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(D42) = Post-vaccination two Day 42 PII(D180) = Post-vaccination two Day 180							
Secondary Outcome Variable(s): SPR for H5N1 HI antibodies against A/Indonesia/05/2005 and A/Vietnam/1194/2004 strains on Days 0, 42 and 180 (ATP cohort for immunogenicity)							
				SPR			
				95% CI			
Antibodies against	Group	Timing	N	n	%	LL	UL
A/Indonesia	NP	PRE	156	0	0.0	0.0	2.3
		PII(D42)	156	156	100	97.7	100
		PII(D180)	156	129	82.7	75.8	88.3
	CP	PRE	156	0	0.0	0.0	2.3
		PII(D42)	155	153	98.7	95.4	99.8
		PII(D180)	155	104	67.1	59.1	74.4
A/Vietnam	NP	PRE	156	1	0.6	0.0	3.5
		PII(D42)	156	144	92.3	86.9	96.0

		PII(D180)	156	34	21.8	15.6	29.1				
	CP	PRE	156	3	1.9	0.4	5.5				
		PII(D42)	155	127	81.9	75.0	87.6				
		PII(D180)	155	16	10.3	6.0	16.2				
<p>N = Number of subjects with available results n (%) = Number (percentage) of seroprotected subjects (HI titre \geq 1:40) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination Day 0 PII(D42) = Post-vaccination two Day 42 PII(D180) = Post-vaccination two Day 180</p>											
Secondary Outcome Variable(s): Seropositivity rates and GMTs of neutralising antibody titres on Days 0, 42 and 180 for H5N1 vaccine strain (ATP cohort for immunogenicity)											
			\geq 1: 28				GMT				
							95% CI		95% CI		
Antibodies against	Group	Timing	N	n	%	LL	UL	value	LL	UL	
A/Vietnam	NP	PRE	58	56	96.6	88.1	99.6	189.1	149.8	238.7	
		PII(D42)	58	57	98.3	90.8	100	376.7	308.2	460.4	
		PII(D180)	58	57	98.3	90.8	100	184.5	151.6	224.6	
	CP	PRE	60	59	98.3	91.1	100	166.3	135.4	204.2	
		PII(D42)	59	59	100	93.9	100	359.2	320.9	402.0	
		PII(D180)	59	59	100	93.9	100	197.3	159.6	244.0	
<p>GMT = geometric mean antibody titre N = Number of subjects with available results n/% = number/percentage of seropositive subjects (HI titre \geq 1:10) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination at Day 0 PII(D42)= Post-vaccination two Day 42 PII(D180)= Post-vaccination two Day 180</p>											
Secondary Outcome Variable(s): SCR for HI neutralising antibodies against A/Vietnam/1194/2004 on Days 42 and 180 (ATP cohort for immunogenicity)											
							SCR				
									95% CI		
Antibodies against	Group	Timing	N	n	%	LL	UL				
A/Vietnam	NP	PII(D42)	58	15	25.9	15.3	39.0				
		PII(D180)	58	7	12.1	5.0	23.3				
	CP	PII(D42)	59	13	22.0	12.3	34.7				
		PII(D180)	59	9	15.3	7.2	27.0				
<p>Seroconversion defined as: For initially seronegative subjects, antibody titre \geq 1: 56 after vaccination For initially seropositive subjects, antibody titre after vaccination \geq 4 fold the pre-vaccination antibody titre N = Number of subjects with pre- and post-vaccination results available n/% = Number/percentage of seroconverted subjects 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(D42)= Post-vaccination two Day 42 PII(D180)= Post-vaccination two Day 180</p>											
Secondary Outcome Variable(s): Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and across doses (Total Vaccinated Cohort)											
			NP Group				CP Group				
							95 % CI		95 % CI		
Symptom	Intensity	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	Any	160	141	88.1	82.1	92.7	159	137	86.2	79.8	91.1
	Grade 3	160	9	5.6	2.6	10.4	159	4	2.5	0.7	6.3
Redness	Any	160	3	1.9	0.4	5.4	159	2	1.3	0.2	4.5
	> 100 mm	160	0	0.0	0.0	2.3	159	0	0.0	0.0	2.3
Swelling	Any	160	13	8.1	4.4	13.5	159	14	8.8	4.9	14.3

	> 100 mm	160	0	0.0	0.0	2.3	159	0	0.0	0.0	2.3
Dose 2											
Pain	Any	159	137	86.2	79.8	91.1	157	133	84.7	78.1	90.0
	Grade 3	159	9	5.7	2.6	10.5	157	4	2.5	0.7	6.4
Redness	Any	159	4	2.5	0.7	6.3	157	3	1.9	0.4	5.5
	> 100 mm	159	0	0.0	0.0	2.3	157	0	0.0	0.0	2.3
Swelling	Any	159	17	10.7	6.4	16.6	157	12	7.6	4.0	13.0
	> 100 mm	159	0	0.0	0.0	2.3	157	2	1.3	0.2	4.5
Across Doses											
Pain	Any	160	152	95.0	90.4	97.8	159	146	91.8	86.4	95.6
	Grade 3	160	12	7.5	3.9	12.7	159	8	5.0	2.2	9.7
Redness	Any	160	4	2.5	0.7	6.3	159	5	3.1	1.0	7.2
	> 100 mm	160	0	0.0	0.0	2.3	159	0	0.0	0.0	2.3
Swelling	Any	160	21	13.1	8.3	19.4	159	19	11.9	7.4	18.0
	> 100 mm	160	0	0.0	0.0	2.3	159	2	1.3	0.2	4.5
<p>N= number of subjects with at least one documented dose n (%)= number (percentage) of subjects reporting at least once the symptom 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit Any= occurrence of any local symptom regardless of intensity grade Grade 3 pain= pain that prevented normal activity</p>											
Secondary Outcome Variable(s): Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and across doses (Total Vaccinated Cohort)											
		NP Group					CP Group				
					95 % CI					95 % CI	
Symptom	Intensity/ Relationship	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Arthralgia	Any	160	10	6.3	3.0	11.2	159	14	8.8	4.9	14.3
	Grade 3	160	0	0.0	0.0	2.3	159	0	0.0	0.0	2.3
	Related	160	10	6.3	3.0	11.2	159	13	8.2	4.4	13.6
Fatigue	Any	160	62	38.8	31.2	46.8	159	68	42.8	35.0	50.8
	Grade 3	160	2	1.3	0.2	4.4	159	2	1.3	0.2	4.5
	Related	160	60	37.5	30.0	45.5	159	65	40.9	33.2	48.9
Headache	Any	160	31	19.4	13.6	26.4	159	43	27.0	20.3	34.7
	Grade 3	160	1	0.6	0.0	3.4	159	2	1.3	0.2	4.5
	Related	160	27	16.9	11.4	23.6	159	40	25.2	18.6	32.6
Myalgia	Any	160	90	56.3	48.2	64.1	159	78	49.1	41.1	57.1
	Grade 3	160	2	1.3	0.2	4.4	159	2	1.3	0.2	4.5
	Related	160	88	55.0	46.9	62.9	159	75	47.2	39.2	55.2
Shivering	Any	160	2	1.3	0.2	4.4	159	4	2.5	0.7	6.3
	Grade 3	160	0	0.0	0.0	2.3	159	0	0.0	0.0	2.3
	Related	160	2	1.3	0.2	4.4	159	4	2.5	0.7	6.3
Sweating	Any	160	9	5.6	2.6	10.4	159	10	6.3	3.1	11.3
	Grade 3	160	0	0.0	0.0	2.3	159	0	0.0	0.0	2.3
	Related	160	9	5.6	2.6	10.4	159	8	5.0	2.2	9.7
Temperature (/Axillary)	≥ 38°C	160	0	0.0	0.0	2.3	159	4	2.5	0.7	6.3
	≥ 39°C	160	0	0.0	0.0	2.3	159	1	0.6	0.0	3.5
	Related	160	0	0.0	0.0	2.3	159	4	2.5	0.7	6.3
Dose 2											
Arthralgia	Any	159	27	17.0	11.5	23.7	157	27	17.2	11.6	24.0
	Grade 3	159	2	1.3	0.2	4.5	157	2	1.3	0.2	4.5
	Related	159	26	16.4	11.0	23.0	157	27	17.2	11.6	24.0
Fatigue	Any	159	87	54.7	46.6	62.6	157	82	52.2	44.1	60.3
	Grade 3	159	8	5.0	2.2	9.7	157	4	2.5	0.7	6.4

	Related	159	87	54.7	46.6	62.6	157	82	52.2	44.1	60.3
Headache	Any	159	51	32.1	24.9	39.9	157	49	31.2	24.1	39.1
	Grade 3	159	4	2.5	0.7	6.3	157	2	1.3	0.2	4.5
	Related	159	51	32.1	24.9	39.9	157	49	31.2	24.1	39.1
Myalgia	Any	159	67	42.1	34.4	50.2	157	62	39.5	31.8	47.6
	Grade 3	159	7	4.4	1.8	8.9	157	3	1.9	0.4	5.5
	Related	159	66	41.5	33.8	49.6	157	62	39.5	31.8	47.6
Shivering	Any	159	16	10.1	5.9	15.8	157	11	7.0	3.5	12.2
	Grade 3	159	2	1.3	0.2	4.5	157	0	0.0	0.0	2.3
	Related	159	16	10.1	5.9	15.8	157	11	7.0	3.5	12.2
Sweating	Any	159	11	6.9	3.5	12.0	157	11	7.0	3.5	12.2
	Grade 3	159	0	0.0	0.0	2.3	157	0	0.0	0.0	2.3
	Related	159	11	6.9	3.5	12.0	157	10	6.4	3.1	11.4
Temperature /(Axillary)	≥ 38°C	159	10	6.3	3.1	11.3	157	12	7.6	4.0	13.0
	≥ 39°C	159	1	0.6	0.0	3.5	157	1	0.6	0.0	3.5
	Related	159	10	6.3	3.1	11.3	157	12	7.6	4.0	13.0

Across Doses

Arthralgia	Any	160	32	20.0	14.1	27.0	159	33	20.8	14.7	27.9
	Grade 3	160	2	1.3	0.2	4.4	159	2	1.3	0.2	4.5
	Related	160	31	19.4	13.6	26.4	159	32	20.1	14.2	27.2
Fatigue	Any	160	104	65.0	57.1	72.4	159	99	62.3	54.2	69.8
	Grade 3	160	9	5.6	2.6	10.4	159	6	3.8	1.4	8.0
	Related	160	102	63.8	55.8	71.2	159	98	61.6	53.6	69.2
Headache	Any	160	59	36.9	29.4	44.9	159	68	42.8	35.0	50.8
	Grade 3	160	4	2.5	0.7	6.3	159	4	2.5	0.7	6.3
	Related	160	59	36.9	29.4	44.9	159	67	42.1	34.4	50.2
Myalgia	Any	160	110	68.8	61.0	75.8	159	101	63.5	55.5	71.0
	Grade 3	160	8	5.0	2.2	9.6	159	5	3.1	1.0	7.2
	Related	160	109	68.1	60.3	75.3	159	101	63.5	55.5	71.0
Shivering	Any	160	16	10.0	5.8	15.7	159	14	8.8	4.9	14.3
	Grade 3	160	2	1.3	0.2	4.4	159	0	0.0	0.0	2.3
	Related	160	16	10.0	5.8	15.7	159	14	8.8	4.9	14.3
Sweating	Any	160	16	10.0	5.8	15.7	159	18	11.3	6.8	17.3
	Grade 3	160	0	0.0	0.0	2.3	159	0	0.0	0.0	2.3
	Related	160	16	10.0	5.8	15.7	159	15	9.4	5.4	15.1
Temperature /(Axillary)	≥ 38°C	160	10	6.3	3.0	11.2	159	16	10.1	5.9	15.8
	≥ 39°C	160	1	0.6	0.0	3.4	159	2	1.3	0.2	4.5
	Related	160	10	6.3	3.0	11.2	159	16	10.1	5.9	15.8

N= number of subjects with at least one documented dose

n (%)= number (percentage) of subjects reporting at least once the symptom

95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Any= occurrence of any general symptom regardless of intensity grade or relationship

Grade 3 = symptoms that prevented normal activity

Related = solicited symptom assessed by the investigator as causally related to the study vaccination

Secondary Outcome Variable(s): Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) follow-up period after each dose and overall (Total Vaccinated Cohort – modified grading)

	Group	Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	NP	160	150	93.8	88.8	97.0	160	111	69.4	61.6	76.4	160	142	88.8	82.8	93.2
	CP	159	144	90.6	84.9	94.6	159	106	66.7	58.8	73.9	159	137	86.2	79.8	91.1
Dose 2	NP	159	144	90.6	84.9	94.6	159	105	66.0	58.1	73.4	159	137	86.2	79.8	91.1
	CP	157	140	89.2	83.2	93.6	157	104	66.2	58.3	73.6	157	133	84.7	78.1	90.0
Across	NP	160	155	96.9	92.9	99.0	160	131	81.9	75.0	87.5	160	152	95.0	90.4	97.8

doses																
	CP	159	150	94.3	89.5	97.4	159	128	80.5	73.5	86.4	159	146	91.8	86.4	95.6
<p>N = number of subjects with at least one documented dose n/%= number/percentage of subjects presenting at least one type of symptom 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit Grading for quantifiable symptoms: Fever: $\geq 38.0^{\circ}\text{C}$, Redness, Swelling or Induration</p>																
Secondary Outcome Variable(s): Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) follow-up period after each dose and overall (Total Vaccinated Cohort – modified grading)																
	Group	Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	NP	160	11	6.9	3.5	12.0	160	5	3.1	1.0	7.1	160	9	5.6	2.6	10.4
	CP	159	10	6.3	3.1	11.3	159	8	5.0	2.2	9.7	159	4	2.5	0.7	6.3
Dose 2	NP	159	16	10.1	5.9	15.8	159	12	7.5	4.0	12.8	159	9	5.7	2.6	10.5
	CP	157	12	7.6	4.0	13.0	157	10	6.4	3.1	11.4	157	5	3.2	1.0	7.3
Across doses	NP	160	20	12.5	7.8	18.6	160	14	8.8	4.9	14.2	160	12	7.5	3.9	12.7
	CP	159	21	13.2	8.4	19.5	159	17	10.7	6.4	16.6	159	9	5.7	2.6	10.5
<p>N = number of subjects with at least one documented dose n/%= number/percentage of subjects presenting at least one type of symptom 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit Grading for quantifiable symptoms: Fever: $\geq 38.0^{\circ}\text{C}$, Redness, Swelling or Induration</p>																
Secondary Outcome Variable(s): Incidence and nature of related symptoms (solicited and unsolicited) with causal relationship to vaccination reported during the 7-day (Days 0-6) follow-up period after each dose and overall (Total Vaccinated Cohort – modified grading)																
	Group	Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	NP	160	150	93.8	88.8	97.0	160	109	68.1	60.3	75.3	160	142	88.8	82.8	93.2
	CP	159	143	89.9	84.2	94.1	159	102	64.2	56.2	71.6	159	137	86.2	79.8	91.1
Dose 2	NP	159	144	90.6	84.9	94.6	159	103	64.8	56.8	72.2	159	137	86.2	79.8	91.1
	CP	157	140	89.2	83.2	93.6	157	104	66.2	58.3	73.6	157	133	84.7	78.1	90.0
Across doses	NP	160	155	96.9	92.9	99.0	160	130	81.3	74.3	87.0	160	152	95.0	90.4	97.8
	CP	159	150	94.3	89.5	97.4	159	126	79.2	72.1	85.3	159	146	91.8	86.4	95.6
<p>N = number of subjects with at least one documented dose n/%= number/percentage of subjects presenting at least one type of symptom 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit Grading for quantifiable symptoms: Fever: $\geq 38.0^{\circ}\text{C}$, Redness, Swelling or Induration</p>																
Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of adverse events of specific interest (AESI) up to 51 days after the first vaccination (Total Vaccinated Cohort)																
Adverse events of Specific Interest (occurring up to Day 51)										NP Group N = 160			CP Group N = 160			
Subjects with any AESI(s), n (%)										1 (0.6)			0 (0.0)			
Psoriasis										1 (0.6)			0 (0.0)			
Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of adverse events of specific interest (AESI) within the 180-day (Days 0-179) post-vaccination period (Total Vaccinated Cohort)																
Adverse events of Specific Interest (occurring up to Day 179)										NP Group N = 160			CP Group N = 160			
Subjects with any AESI(s), n (%)										1 (0.6)			0 (0.0)			
Psoriasis										1 (0.6)			0 (0.0)			
Safety results: Number (%) of subjects with unsolicited adverse events during the 21-day follow-up period after the first vaccination and 30-day follow-up period after the second vaccination (Total Vaccinated Cohort)																
Adverse events–On-Therapy (occurring during the 21-day follow-up period after the first vaccination and 30-day follow-up period after										NP Group N = 160			CP Group N = 160			

the second vaccination)		
Subjects with any AE(s), n (%)	49 (30.6)	53 (33.1)
Subjects with grade 3 adverse events, n (%)	4 (2.5)	8 (5.0)
Subjects with related adverse events, n (%)	15 (9.4)	12 (7.5)
Lymphadenopathy	-	2 (1.3)
Conjunctivitis	-	2 (1.3)
Abdominal pain upper	3 (1.9)	-
Diarrhoea	2 (1.3)	3 (1.9)
Injection site pruritus	-	2 (1.3)
Herpes simplex	2 (1.3)	-
Nasopharyngitis	16 (10.0)	19 (11.9)
Rhinitis	2 (1.3)	2 (1.3)
Upper respiratory tract infection	4 (2.5)	-
Excoriation	2 (1.3)	-
Dizziness	3 (1.9)	-
Hypoaesthesia	2 (1.3)	-
Cough	2 (1.3)	2 (1.3)
Nasal congestion	5 (3.1)	3 (1.9)
Pharyngolaryngeal pain	7 (4.4)	6 (3.8)
Rhinitis allergic	-	2 (1.3)
Rhinorrhoea	2 (1.3)	3 (1.9)
Rash	2 (1.3)	-
Grade 3 = event that prevented normal activities Related = event assessed by the investigator as causally related to the study vaccination -: adverse event absent or not meeting the selected rule: If more than 30 subjects per group and ≤ 3 groups, then only the 10 most frequent adverse events in each group are to be listed.		
Safety results: Number (%) of subjects with unsolicited adverse events within 180-Day period (Day 0-Day 179) (Total Vaccinated Cohort)		
Most frequent adverse events - On-Therapy (occurring within Day 0-179 following vaccination)	NP Group N = 160	CP Group N = 160
Subjects with any AE(s), n (%)	54 (33.8)	62 (38.8)
Subjects with grade 3 adverse events, n (%)	5 (3.1)	8 (5.0)
Subjects with related adverse events, n (%)	15 (9.4)	12 (7.5)
Nasopharyngitis	20 (12.5)	27 (16.9)
Pharyngolaryngeal pain	9 (5.6)	7 (4.4)
Nasal congestion	6 (3.8)	4 (2.5)
Diarrhoea	2 (1.3)	3 (1.9)
Rhinorrhoea	2 (1.3)	3 (1.9)
Cough	2 (1.3)	2 (1.3)
Rhinitis	2 (1.3)	2 (1.3)
Upper respiratory tract infection	4 (2.5)	-
Abdominal pain upper	3 (1.9)	-
Dizziness	3 (1.9)	-
Acne	-	2 (1.3)
Back pain	-	2 (1.3)
Conjunctivitis	-	2 (1.3)
Excoriation	2 (1.3)	-
Gastroenteritis	-	2 (1.3)
Herpes simplex	2 (1.3)	-
Hypoaesthesia	2 (1.3)	-
Injection site pruritus	-	2 (1.3)
Lymphadenopathy	-	2 (1.3)
Rash	2 (1.3)	-
Rhinitis allergic	-	2 (1.3)
Grade 3 = event that prevented normal activities		

Related = event assessed by the investigator as causally related to the study vaccination
 -: adverse event absent or not meeting the selected rule: If more than 30 subjects per group and ≤ 3 groups, then only the 10 most frequent adverse events in each group are to be listed.

Safety results: Number (%) of subjects with SAEs up to Day 51 (Total Vaccinated cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs	NP Group N = 160	CP Group N = 160
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	3 (1.9) [0]	0 (0.0) [0]
Injury	1 (0.6)	0 (0.0)
Endometrial cancer stage II	1 (0.6)	0 (0.0)
Calculus urinary	1 (0.6)	0 (0.0)
Fatal SAEs	NP Group N = 160	CP Group N = 160
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Safety results: Number (%) of subjects with SAEs within 180-Day period (Day 0 – Day 179) (Total Vaccinated Cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs	NP Group N = 160	CP Group N = 160
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	4 (2.5) [0]	2 (1.3) [0]
Calculus urinary	1 (0.6) [0]	0 (0.0) [0]
Endometrial cancer stage II	1 (0.6) [0]	0 (0.0) [0]
Erythema	1 (0.6) [0]	0 (0.0) [0]
Gastritis	0 (0.0) [0]	1 (0.6) [0]
Gastroenteritis	0 (0.0) [0]	1 (0.6) [0]
Injury	1 (0.6) [0]	0 (0.0) [0]
Fatal SAEs	NP Group N = 160	CP Group N = 160
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

At Day 42, GMT values for H5N1 HI antibody against A/Indonesia strain were of 739.5 in NP Group and 621.7 in CP Group.

During the 21-day follow-up period after the first vaccination and the 30-day follow-up period after the second vaccination, 49 (30.6%) subjects in NP Group and 53 (33.1%) subjects in CP Group reported at least one unsolicited AE.

From Day 0 to Day 180, 54 (33.8%) subjects in NP Group & 62 (38.8%) subjects in CP Group reported at least one unsolicited AE.

Up to Day 51, SAEs were reported for 3 subjects in NP Group. From Day 0 to Day 180, SAEs were reported for 4 subjects in NP Group and 2 subjects in CP Group. None of these SAEs were assessed by the investigators as related to the study vaccination. No fatal SAEs were reported until Day 180.

Publications: None

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