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Study No.: 111756 (FLU Q-PAN-011 PRI)
Title: Immunogenicity and safety of GSK Biologicals' (pre-) pandemic influenza candidate vaccine GSK 1557484A. GSK 1557484A (Flu): GlaxoSmithKline (GSK) Biologicals' adjuvanted (pre-) pandemic influenza split virus (H5N1) vaccine.
Rationale: The aim of the study was to assess the safety and immunogenicity of two doses of Flu vaccine administered to healthy Japanese adults aged between 20 and 64 years.
Phase: II
Study Period: 01 September 2008 to 07 March 2009
Study Design: Open-label, single group study
Centres: 2 centres in Japan
Indication: Immunisation of healthy adults aged between 20 to 64 years against H5N1 influenza
Treatment: All subjects received 2 doses of Flu vaccine, at Days 0 and 21, and were stratified by age: <ul style="list-style-type: none"> • 20-40Y: subjects between 20 and 40 years inclusive • 41-64Y: subjects between 41 and 64 years inclusive Flu vaccine was administered intramuscularly in the deltoid region of the non-dominant arm.
Objectives: To evaluate the humoral immune response induced by 2 doses of Flu vaccine in terms of H5N1 haemagglutination-inhibition (HI) antibody titres.
Primary Outcome/Efficacy Variable: <i>For the humoral immune response in terms of H5N1 HI antibodies:</i> Observed variables at Days 0 and 42: <ul style="list-style-type: none"> • Serum H5N1 HI antibody titres against the H5N1 vaccine strain. Derived variables [with 95% confidence intervals (CIs)]: <ul style="list-style-type: none"> • Geometric mean titres (GMTs) of H5N1 HI antibody titres at Days 0 and 42. • Seroconversion rates (SCRs), defined as the percentage of vaccinees with either a prevaccination titre < 1:10 and a post-vaccination titre ≥ 1:40 or a pre-vaccination titre ≥ 1:10 and at least a fourfold increase in post-vaccination titre, at Day 42. • Seroconversion factors (SCFs), defined as the fold increase in serum H5N1 HI antibody GMTs post-vaccination compared to Day 0, at Day 42. • Seroprotection rates (SPRs), defined as the percentage of vaccinees with a serum H5N1 HI antibody titre ≥1:40, at Day 42.
Secondary Outcome/Efficacy Variable(s): <i>For the safety evaluation:</i> <ul style="list-style-type: none"> • 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 and overall per subject considering both post-immunisation periods. • Percentage, intensity and relationship to vaccination of unsolicited local and general adverse events (AEs) during a 21-day follow-up period for each vaccine administration, as well as overall (Day 0 through Day 84). • Occurrence of serious adverse events (SAEs) during the entire study. • Medically-attended visits throughout the study. <i>For the humoral immune response in terms of H5N1 HI antibodies:</i> Observed variables at Days 0, 21 and 182: <ul style="list-style-type: none"> • Serum H5N1 HI antibody titres against the H5N1 vaccine strain. Derived variables (with 95% CIs): <ul style="list-style-type: none"> • GMTs of H5N1 HI antibody titres at Days 0, 21 and 182. • SCRs, defined as the percentage of vaccinees with either a prevaccination titre < 1:10 and a post-vaccination titre ≥ 1:40 or a pre-vaccination titre ≥ 1:10 and at least a fourfold increase in post-vaccination titre, at Days 21 and 182. • SCFs, defined as the fold increase in serum H5N1 HI antibody GMTs post-vaccination compared to Day 0, at Days 21 and 182. • SPRs, defined as the percentage of vaccinees with a serum H5N1 HI antibody titre ≥1:40, at Days 21 and 182.

For the humoral immune response in terms of neutralising antibodies:

Observed variables at Days 0, 42 and 182:

- Serum anti-H5N1 neutralising antibody titres against the H5N1 vaccine strain.

Derived variables (with 95% CIs):

- GMTs of serum anti-H5N1 neutralising antibodies at Days 0, 42 and 182.
- SCRs, defined as the percentage of vaccinees with a minimum fourfold increase in titre at post-vaccination for neutralising antibody response at Days 42 and 182.

For the safety evaluation in terms of haematological, biochemical and urine parameters:

- The number and percentage of subjects with normal or abnormal haematological and biochemical values at Day 0, Day 7 and Day 42 were calculated.
- The number and percentage of subjects with normal or abnormal urine values at Day 0, Day 7 and Day 42 were calculated.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort, the According-To-Protocol (ATP) cohort for immunogenicity and the ATP cohort for persistence.

- The Total Vaccinated cohort included all vaccinated subjects for whom data were available.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e., who met all eligibility criteria, who complied with the protocol procedures, with no elimination criteria assigned during the study) and for whom data concerning immunogenicity outcome measures were available. These included subjects for whom assay results were available for antibodies against the study vaccine antigen component after vaccination.
- The ATP cohort for persistence included all evaluable subjects (who met all eligibility criteria; who complied with the procedures and intervals defined in the protocol up to and including Day 182; who did not meet the elimination criteria up to Day 182) and for whom data concerning immunogenicity outcome measures were available. These included subjects for whom assay results were available for antibodies against the study vaccine antigen component on Day 182.

Analysis of immunogenicity:

The analysis was done on the ATP cohort for immunogenicity and the ATP cohort for persistence, for each age stratum.

For the humoral immune response in terms of H5N1 HI antibodies (with 95% CIs):

- GMTs of H5N1 HI antibody titres at Day 0, Day 21, Day 42 and Day 182.
- SCRs at Day 21, Day 42 and Day 182.
- SCFs at Day 21, Day 42 and Day 182.
- SPRs at Day 0, Day 21, Day 42 and Day 182.

For the humoral immune response in terms of neutralising antibodies (with 95% CIs):

- GMTs of H5N1 neutralising antibody titres at Day 0, Day 21, Day 42 and Day 182.
- SCRs at Day 21, Day 42 and Day 182.

Analysis of safety:

The analysis was based on the Total Vaccinated cohort.

The percentage of subjects reporting each individual solicited local and general symptoms during the solicited follow-up period was tabulated with exact 95% CI. The same tabulation was 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 unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 21 days after each vaccination and, additionally, up to 84 days following initial vaccination was tabulated with exact 95% CI by age strata. The same tabulation by age strata was performed for grade 3 unsolicited AEs and for unsolicited AEs assessed by the investigator as related to vaccination.

The percentage of subjects with at least one report of an unsolicited AE related to medically-significant conditions prompting emergency room visits or physician visits classified by MedDRA and reported between Day 0 and Day 182 was tabulated, with exact 95% CI.

SAEs, classified by MedDRA, were also tabulated during the entire study period.

The number and proportion of subjects with normal or abnormal values for each hematology and selected biochemistry parameter were tabulated for each study group at Day 0, Day 7 and Day 42.

The number and proportion of subjects with normal or abnormal values for each urine parameter were tabulated at Day 0, Day 7 and Day 42.

Study Population: Healthy Japanese male or female aged 20 to 64 years at the time of first vaccination. Woman had to be of non-childbearing potential or, if of childbearing potential, had used a reliable contraceptive practice and have a negative pregnancy test. Written informed consent was obtained from the subject prior to any study procedure.

Number of subjects	20-40Y	41-64Y
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Planned, N				50				50			
Randomised, N (Total Vaccinated cohort)				50				50			
Completed to Day 42, n (%)				50 (100)				50 (100)			
Completed to Day 182, n (%)				49 (98.0)				50 (100)			
Total Number Subjects Withdrawn, n (%)				1 (2.0)				0 (0.0)			
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 (%)				1 (2.0)				0 (0.0)			
Demographics				20-40Y				41-64Y			
N (Total Vaccinated cohort)				50				50			
Females:Males				25:25				32:18			
Mean Age, years (SD)				31.1 (5.69)				49.6 (6.04)			
Asian - japanese heritage, n (%)				50 (100)				50 (100)			
Primary Efficacy Results: Seropositivity rates and GMTs of H5N1 HI antibody titres against A/Indonesia/05/2005 strain by age category (ATP cohort for immunogenicity)											
				≥ 1:10				GMT			
				95% CI				95% CI			
Antibodies against	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	
A/Indonesia	20-40Y	PRE	50	0	0.0	0.0	7.1	5.0	5.0	5.0	
		PII(D42)	50	45	90.0	78.2	96.7	156.8	105.8	232.3	
	41-64Y	PRE	50	5	10.0	3.3	21.8	5.4	5.0	5.8	
		PII(D42)	50	48	96.0	86.3	99.5	142.1	104.0	194.3	
<p>N = Number of subjects with available results n(%) = number(percentage) of seropositive subjects (HI titre ≥ 1:10) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination at Day 0 PII(D42) = Post-vaccination two at Day 42</p>											
Primary Efficacy Results: SCR for H5N1 HI antibody titers against A/Indonesia/05/2005 strain by age category (ATP cohort for immunogenicity)											
				SCR							
				95% CI							
Antibodies against	Sub-Group	Timing	N	n	%	LL	UL	LL	UL		
A/Indonesia	20-40Y	PII(D42)	50	45	90.0	78.2	96.7	80.8	97.8		
	41-64Y	PII(D42)	50	46	92.0	80.8	97.8				
<p>Seroconversion defined as: For initially seronegative subjects, antibody titre ≥ 1:40 after vaccination For initially seropositive subjects, antibody titre after vaccination ≥ 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 at Day 42</p>											
Primary Efficacy Results: SCF for H5N1 HI antibody titers against A/Indonesia/05/2005 strain (ATP cohort for immunogenicity)											
				SCF							
				95% CI							
Antibodies against	Sub-Group	Timing	N	Value	LL	UL	LL	UL			
A/Indonesia	20-40Y	PII(D42)	50	31.4	21.2	46.5					
	41-64Y	PII(D42)	50	26.2	19.2	35.8					
<p>N = Number of subjects with pre- and post-vaccination results available SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PII(D42) = Post-vaccination two at Day 42</p>											
Primary Efficacy Results: SPRs for H5N1 HI antibody titers against A/Indonesia/05/2005, strain (ATP cohort for immunogenicity)											

				SPR						
				95% CI						
Antibodies against	Sub-Group	Timing	N	n	%	LL	UL			
A/Indonesia	20-40Y	PRE	50	0	0.0	0.0	7.1			
		PII(D42)	50	45	90.0	78.2	96.7			
	41-64Y	PRE	50	0	0.0	0.0	7.1			
		PII(D42)	50	46	92.0	80.8	97.8			
<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 at Day 0 PII(D42) = Post-vaccination two at Day 42</p>										
Secondary Outcome Variable(s): Seropositivity rates and GMTs of H5N1 HI antibody titres against A/Indonesia/05/2005 strain by age strata 20-40 years and 41-64 years (ATP cohort for persistence)										
				\geq 1:10		GMT				
				95% CI		95% CI				
Antibody	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
A/Indonesia	20-40Y	PRE	50	0	0.0	0.0	7.1	5.0	5.0	5.0
		PI(D21)	50	24	48.0	33.7	62.6	15.8	11.0	22.8
		PII(D182)	49	30	61.2	46.2	74.8	25.6	17.3	38.1
	41-64Y	PRE	50	5	10.0	3.3	21.8	5.4	5.0	5.8
		PI(D21)	50	27	54.0	39.3	68.2	15.4	10.7	22.0
		PII(D182)	50	40	80.0	66.3	90.0	37.4	27.5	50.8
<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 PI(D21) = Post-vaccination one at Day 21 PII(D182) = Post-vaccination two at Day 182</p>										
Secondary Outcome Variable(s): SCR for H5N1 HI antibody titers against A/Indonesia/05/2005 strain by age strata 20-40 years and 41-64 years (ATP cohort for persistence)										
				SCR						
				95% CI						
Antibodies against	Group	Timing	N	n	%	LL	UL			
A/Indonesia	20-40Y	PI(D21)	50	19	38.0	24.7	52.8			
		PII(D182)	49	29	59.2	44.2	73.0			
	41-64Y	PI(D21)	50	16	32.0	19.5	46.7			
		PII(D182)	50	38	76.0	61.8	86.9			
<p>Seroconversion defined as: 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 PRE = Pre-vaccination at Day 0 PI(D21) = Post-vaccination one at Day 21 PII(D182) = Post-vaccination two at Day 182</p>										
Secondary Outcome Variable(s): SCF for H5N1 HI antibody titers against A/Indonesia/05/2005 strain by age strata 20-40 years and 41-64 years (ATP cohort for persistence)										
				SCF						
				95% CI						
Antibodies against	Group	Timing	N	Value	LL	UL				
A/Indonesia	20-40Y	PI(D21)	50	3.2	2.2	4.6				
		PII(D182)	49	5.1	3.5	7.6				

	41-64Y	PI(D21)	50	2.8	2.0	4.0					
		PII(D182)	50	6.9	5.1	9.2					
<p>N = Number of subjects with pre- and post-vaccination results available SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination at Day 0 PI(D21) = Post-vaccination one at Day 21 PII(D182) = Post-vaccination two at Day 182</p>											
Secondary Outcome Variable(s): SPRs for H5N1 HI antibody titers against A/Indonesia/05/2005 strain by age strata 20-40 years and 41-64 years (ATP cohort for persistence)											
				SPR							
				95% CI							
Antibodies against	Group	Timing	N	n	%	LL	UL				
A/Indonesia	20-40Y	PRE	50	0	0.0	0.0	7.1				
		PI(D21)	50	19	38.0	24.7	52.8				
		PII(D182)	49	29	59.2	44.2	73.0				
	41-64Y	PRE	50	0	0.0	0.0	7.1				
		PI(D21)	50	16	32.0	19.5	46.7				
		PII(D182)	50	38	76.0	61.8	86.9				
<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 at Day 0 PI(D21) = Post-vaccination one at Day 21 PII(D182) = Post-vaccination two at Day 182</p>											
Secondary Outcome Variable(s): Seropositivity rates and GMTs of neutralising antibody titres against A/Indonesia/05/2005 strain at Days 0, 42, 182 by age strata 20-40 years and 41-64 years (ATP cohort for persistence)											
				\geq 1:28				GMT			
				95% CI				95% CI			
Antibodies against	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	
A/Indonesia	20-40Y	PRE	50	1	2.0	0.1	10.6	14.4	13.6	15.2	
		PII(D42)	50	50	100	92.9	100	579.6	466.5	720.0	
		PII(D182)	49	49	100	92.7	100	240.5	210.3	275.0	
	41-64Y	PRE	49	10	20.4	10.2	34.3	18.3	15.4	21.8	
		PII(D42)	50	50	100	92.9	100	473.8	379.9	591.0	
		PII(D182)	50	50	100	92.9	100	240.1	210.0	274.5	
<p>N = Number of subjects with available results n(%) = number(percentage) of seropositive subjects (neutralising antibody titre \geq1:28) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination at Day 0 PII (D42) = Post-vaccination two at Day 42 PII (D182) = Post-vaccination two at Day 182</p>											
Secondary Outcome Variable(s): SCR for neutralizing antibody titre against A/Indonesia/05/2005 at Day 42 and Day 182 by age strata 20-40 years and 41-64 years (ATP cohort for persistence)											
								SCR			
								95% CI			
Antibodies against	Group	Timing	N	n	%	LL	UL	n	%	LL	UL
A/Indonesia	20-40Y	PII(D42)	50	49	98.0	89.4	99.9				
		PII(D182)	49	48	98.0	89.1	99.9				
	41-64Y	PII(D42)	49	47	95.9	86.0	99.5				
		PII(D182)	49	44	89.8	77.8	96.6				
<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</p>											

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 at Day 42 PII (D182) = Post-vaccination two at Day 182																		
Secondary Outcome Variable(s): Haematological and biochemical levels with respect to normal ranges by age strata 20-40y and 41-64y (Total Vaccinated cohort)																		
		20-40Y N = 50									41-64Y N = 50							
		Unknown			Below		Within		Above		Unknown		Below		Within		Above	
Laboratory parameter	Timing	N	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ALT	PRE	50	0	0.0	0	0.0	47	94.0	3	6.0	0	0.0	0	0.0	46	92.0	4	8.0
	PI(D7)	50	0	0.0	1	2.0	47	94.0	2	4.0	0	0.0	0	0.0	45	90.0	5	10.0
	PII(D42)	50	0	0.0	1	2.0	45	90.0	4	8.0	0	0.0	0	0.0	46	92.0	4	8.0
AST	PRE	50	0	0.0	0	0.0	49	98.0	1	2.0	0	0.0	0	0.0	49	98.0	1	2.0
	PI(D7)	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	49	98.0	1	2.0
	PII(D42)	50	0	0.0	0	0.0	49	98.0	1	2.0	0	0.0	0	0.0	50	100.0	0	0.0
BAS	PRE	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	49	98.0	1	2.0
	PI(D7)	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	50	100.0	0	0.0
	PII(D42)	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	50	100.0	0	0.0
BUN	PRE	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	1	2.0	48	96.0	1	2.0
	PI(D7)	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	50	100.0	0	0.0
	PII(D42)	50	0	0.0	1	2.0	49	98.0	0	0.0	0	0.0	0	0.0	49	98.0	1	2.0
CREA	PRE	50	0	0.0	1	2.0	48	96.0	1	2.0	0	0.0	2	4.0	44	88.0	4	8.0
	PI(D7)	50	0	0.0	1	2.0	46	92.0	3	6.0	0	0.0	3	6.0	44	88.0	3	6.0
	PII(D42)	50	0	0.0	2	4.0	47	94.0	1	2.0	0	0.0	3	6.0	45	90.0	2	4.0
EOS	PRE	50	0	0.0	0	0.0	44	88.0	6	12.0	0	0.0	0	0.0	46	92.0	4	8.0
	PI(D7)	50	0	0.0	0	0.0	45	90.0	5	10.0	0	0.0	0	0.0	46	92.0	4	8.0
	PII(D42)	50	0	0.0	0	0.0	47	94.0	3	6.0	0	0.0	0	0.0	46	92.0	4	8.0
HB	PRE	50	0	0.0	1	2.0	49	98.0	0	0.0	0	0.0	4	8.0	45	90.0	1	2.0
	PI(D7)	50	0	0.0	1	2.0	49	98.0	0	0.0	0	0.0	4	8.0	44	88.0	2	4.0
	PII(D42)	50	0	0.0	2	4.0	48	96.0	0	0.0	0	0.0	5	10.0	44	88.0	1	2.0
HC	PRE	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	1	2.0	45	90.0	4	8.0
	PI(D7)	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	1	2.0	46	92.0	3	6.0
	PII(D42)	50	0	0.0	0	0.0	49	98.0	1	2.0	0	0.0	1	2.0	44	88.0	5	10.0
LYM	PRE	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	2	4.0	48	96.0	0	0.0
	PI(D7)	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	1	2.0	49	98.0	0	0.0
	PII(D42)	50	0	0.0	5	10.0	45	90.0	0	0.0	0	0.0	1	2.0	49	98.0	0	0.0
MON	PRE	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	49	98.0	1	2.0
	PI(D7)	50	0	0.0	0	0.0	48	96.0	2	4.0	0	0.0	0	0.0	49	98.0	1	2.0
	PII(D42)	50	0	0.0	0	0.0	49	98.0	1	2.0	0	0.0	0	0.0	50	100.0	0	0.0
NEU	PRE	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	48	96.0	2	4.0
	PI(D7)	50	0	0.0	1	2.0	48	96.0	1	2.0	0	0.0	1	2.0	48	96.0	1	2.0
	PII(D42)	50	0	0.0	0	0.0	46	92.0	4	8.0	0	0.0	0	0.0	49	98.0	1	2.0
PLA	PRE	50	0	0.0	0	0.0	50	100.0	0	0.0	2	4.0	0	0.0	48	96.0	0	0.0
	PI(D7)	50	0	0.0	0	0.0	50	100.0	0	0.0	1	2.0	0	0.0	48	96.0	1	2.0
	PII(D42)	50	0	0.0	0	0.0	50	100.0	0	0.0	0	0.0	0	0.0	50	100.0	0	0.0
RBC	PRE	50	0	0.0	2	4.0	48	96.0	0	0.0	0	0.0	1	2.0	47	94.0	2	4.0
	PI(D7)	50	0	0.0	2	4.0	48	96.0	0	0.0	0	0.0	1	2.0	46	92.0	3	6.0
	PII(D42)	50	0	0.0	2	4.0	46	92.0	2	4.0	0	0.0	0	0.0	48	96.0	2	4.0
WBC	PRE	50	0	0.0	2	4.0	47	94.0	1	2.0	0	0.0	2	4.0	46	92.0	2	4.0
	PI(D7)	50	0	0.0	1	2.0	49	98.0	0	0.0	0	0.0	1	2.0	48	96.0	1	2.0
	PII(D42)	50	0	0.0	1	2.0	47	94.0	2	4.0	0	0.0	1	2.0	47	94.0	2	4.0

<p>PRE = Pre-vaccination at Day 0 PI (D7)= Post-vaccination one at Day 7 PI(D21) = Post-vaccination one at Day 21 PII(D42) = Post-vaccination two at Day 42 N = number of available results for subjects with administered dose n(%) = number(percentage) of subjects in the specified category ALT= Alanine transaminase; AST= Aspartate transaminase; BAS= Basophils; BUN= Blood urea nitrogen; CREA= Creatinine; EOS= Eosinophils; HB= Hemoglobin; HC= Hematocrit; LYM= Lymphocytes; MON= Monocytes; NEU= Neutrophils; PLA= Platelets; RBC= Red blood cells count; WBC= White blood cells count</p>											
<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 overall by age strata 20-40y and 41-64y (Total Vaccinated cohort)</p>											
		20-40Y					41-64Y				
					95 % CI					95 % CI	
Symptom	Intensity	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	Any	50	49	98.0	89.4	99.9	50	49	98.0	89.4	99.9
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
Redness	Any	50	9	18.0	8.6	31.4	50	8	16.0	7.2	29.1
	> 100 mm	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
Swelling/ Induration	Any	50	14	28.0	16.2	42.5	50	15	30.0	17.9	44.6
	> 100 mm	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
Dose 2											
Pain	Any	50	46	92.0	80.8	97.8	50	47	94.0	83.5	98.7
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
Redness	Any	50	9	18.0	8.6	31.4	50	12	24.0	13.1	38.2
	> 100 mm	50	2	4.0	0.5	13.7	50	2	4.0	0.5	13.7
Swelling/ Induration	Any	50	13	26.0	14.6	40.3	50	17	34.0	21.2	48.8
	> 100 mm	50	3	6.0	1.3	16.5	50	2	4.0	0.5	13.7
Across doses											
Pain	Any	50	49	98.0	89.4	99.9	50	49	98.0	89.4	99.9
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
Redness	Any	50	12	24.0	13.1	38.2	50	16	32.0	19.5	46.7
	> 100 mm	50	2	4.0	0.5	13.7	50	2	4.0	0.5	13.7
Swelling/ Induration	Any	50	17	34.0	21.2	48.8	50	23	46.0	31.8	60.7
	> 100 mm	50	3	6.0	1.3	16.5	50	2	4.0	0.5	13.7
<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 symptoms regardless of their intensity grade Grade 3 pain= Significant pain at rest; prevented normal activities as assessed by inability to attend/do work or school</p>											
<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 overall by age strata 20-40y and 41-64y (Total Vaccinated cohort)</p>											
		20-40Y					41-64Y				
					95 % CI					95 % CI	
Symptom	Intensity/ Relationship	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Fatigue	Any	50	33	66.0	51.2	78.8	50	24	48.0	33.7	62.6
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	Related	50	32	64.0	49.2	77.1	50	24	48.0	33.7	62.6
Headache	Any	50	17	34.0	21.2	48.8	50	13	26.0	14.6	40.3
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	15	30.0	17.9	44.6	50	13	26.0	14.6	40.3
Joint pain	Any	50	9	18.0	8.6	31.4	50	6	12.0	4.5	24.3
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1

	Related	50	8	16.0	7.2	29.1	50	6	12.0	4.5	24.3
Muscle aches	Any	50	31	62.0	47.2	75.3	50	24	48.0	33.7	62.6
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	Related	50	30	60.0	45.2	73.6	50	24	48.0	33.7	62.6
Shivering	Any	50	5	10.0	3.3	21.8	50	1	2.0	0.1	10.6
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	Related	50	4	8.0	2.2	19.2	50	1	2.0	0.1	10.6
Increase Sweating	Any	50	7	14.0	5.8	26.7	50	3	6.0	1.3	16.5
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	6	12.0	4.5	24.3	50	3	6.0	1.3	16.5
Fever	≥ 38.0°C	50	2	4.0	0.5	13.7	50	1	2.0	0.1	10.6
	≥ 39.0°C	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	1	2.0	0.1	10.6	50	1	2.0	0.1	10.6
Dose 2											
Fatigue	Any	50	34	68.0	53.3	80.5	50	29	58.0	43.2	71.8
	Grade 3	50	2	4.0	0.5	13.7	50	0	0.0	0.0	7.1
	Related	50	34	68.0	53.3	80.5	50	29	58.0	43.2	71.8
Headache	Any	50	22	44.0	30.0	58.7	50	15	30.0	17.9	44.6
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	21	42.0	28.2	56.8	50	15	30.0	17.9	44.6
Joint pain	Any	50	13	26.0	14.6	40.3	50	15	30.0	17.9	44.6
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	13	26.0	14.6	40.3	50	14	28.0	16.2	42.5
Muscle aches	Any	50	29	58.0	43.2	71.8	50	23	46.0	31.8	60.7
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	29	58.0	43.2	71.8	50	22	44.0	30.0	58.7
Shivering	Any	50	10	20.0	10.0	33.7	50	6	12.0	4.5	24.3
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	Related	50	9	18.0	8.6	31.4	50	6	12.0	4.5	24.3
Increase Sweating	Any	50	9	18.0	8.6	31.4	50	5	10.0	3.3	21.8
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	9	18.0	8.6	31.4	50	5	10.0	3.3	21.8
Fever	≥ 38.0°C	50	6	12.0	4.5	24.3	50	4	8.0	2.2	19.2
	≥ 39.0°C	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	Related	50	6	12.0	4.5	24.3	50	4	8.0	2.2	19.2
Across doses											
Fatigue	Any	50	39	78.0	64.0	88.5	50	32	64.0	49.2	77.1
	Grade 3	50	3	6.0	1.3	16.5	50	0	0.0	0.0	7.1
	Related	50	39	78.0	64.0	88.5	50	32	64.0	49.2	77.1
Headache	Any	50	30	60.0	45.2	73.6	50	21	42.0	28.2	56.8
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	27	54.0	39.3	68.2	50	21	42.0	28.2	56.8
Joint pain	Any	50	16	32.0	19.5	46.7	50	18	36.0	22.9	50.8
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	Related	50	16	32.0	19.5	46.7	50	17	34.0	21.2	48.8
Muscle aches	Any	50	36	72.0	57.5	83.8	50	34	68.0	53.3	80.5
	Grade 3	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	Related	50	36	72.0	57.5	83.8	50	33	66.0	51.2	78.8
Shivering	Any	50	13	26.0	14.6	40.3	50	7	14.0	5.8	26.7
	Grade 3	50	2	4.0	0.5	13.7	50	0	0.0	0.0	7.1
	Related	50	11	22.0	11.5	36.0	50	7	14.0	5.8	26.7
Increase Sweating	Any	50	13	26.0	14.6	40.3	50	8	16.0	7.2	29.1
	Grade 3	50	0	0.0	0.0	7.1	50	0	0.0	0.0	7.1
	Related	50	12	24.0	13.1	38.2	50	8	16.0	7.2	29.1

Fever	≥ 38.0°C	50	6	12.0	4.5	24.3	50	5	10.0	3.3	21.8	
	≥ 39.0°C	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1	
	Related	50	6	12.0	4.5	24.3	50	5	10.0	3.3	21.8	
<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 general symptoms regardless of their intensity grade or their relationship to vaccination Grade 3= general symptom that prevented normal everyday activities as assessed by inability to attend/do work or school, or required intervention of a physician/healthcare provider Related= general symptom assessed by the investigator as causally related to the study vaccination</p>												
<p>Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of unsolicited symptoms with medically attended visit, within the 182-day (Days 0-181) post-vaccination period by age strata 20-40 years and 41-64 years (Total Vaccinated cohort)</p>												
							20-40Y					
							N = 50					
									41-64Y			
									N = 50			
Subjects with any medically attended visit(s), n (%)							34 (68.0)		26 (52.0)			
Conjunctivitis							2 (4.0)		-			
Abdominal pain							-		1 (2.0)			
Abdominal pain lower							-		1 (2.0)			
Abdominal pain upper							-		1 (2.0)			
Constipation							2 (4.0)		-			
Gastritis							-		1 (2.0)			
Chest pain							-		1 (2.0)			
Hepatic steatosis							-		1 (2.0)			
Seasonal allergy							2 (4.0)		-			
Bronchitis							5 (10.0)		1 (2.0)			
Gastroenteritis							-		2 (4.0)			
Hordeolum							-		1 (2.0)			
Nasopharyngitis							13 (26.0)		8 (16.0)			
Oral herpes							-		1 (2.0)			
Paronychia							-		1 (2.0)			
Rhinitis							2 (4.0)		-			
Upper respiratory tract infection							4 (8.0)		2 (4.0)			
Contusion							-		1 (2.0)			
Tendon rupture							-		1 (2.0)			
Back pain							2 (4.0)		1 (2.0)			
Neck pain							-		1 (2.0)			
Pain in extremity							-		1 (2.0)			
Temporomandibular joint syndrome							-		1 (2.0)			
Tenosynovitis							-		2 (4.0)			
Uterine leiomyoma							-		1 (2.0)			
Dizziness							-		1 (2.0)			
Insomnia							-		1 (2.0)			
Prostatitis							-		1 (2.0)			
Asthma							2 (4.0)		-			
Rhinitis allergic							-		1 (2.0)			
Rhinorrhoea							-		1 (2.0)			
Acne							-		1 (2.0)			
Dry skin							-		1 (2.0)			
Eczema							-		3 (6.0)			
Pruritus							-		1 (2.0)			
Urticaria							2 (4.0)		-			
<p>-: 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.</p>												

Safety results: Number (%) of subjects with unsolicited adverse events within the 21 Day (Days 0-20) post vaccination period (Total Vaccinated cohort)		
Most frequent adverse events - On-Therapy (occurring within Day 0-20 following vaccination)	20-40Y N = 50	41-64Y N = 50
Subjects with any AE(s), n (%)	27 (54.0)	24 (48.0)
Subjects with grade 3 AE(s), n (%)	3 (6.0)	0 (0.0)
Subjects with related AE(s), n (%)	11 (22.0)	17 (34.0)
Injection site pruritus	5 (10.0)	9 (18.0)
Injection site warmth	6 (12.0)	8 (16.0)
Nasopharyngitis	7 (14.0)	1 (2.0)
Headache	2 (4.0)	2 (4.0)
Diarrhoea	3 (6.0)	-
Muscular weakness	1 (2.0)	2 (4.0)
Abdominal pain upper	-	2 (4.0)
Bronchitis	2 (4.0)	-
Constipation	2 (4.0)	-
Decreased appetite	1 (2.0)	1 (2.0)
Gastritis	1 (2.0)	1 (2.0)
Nausea	1 (2.0)	1 (2.0)
Pharyngolaryngeal pain	-	2 (4.0)
Rhinitis	1 (2.0)	1 (2.0)
Abdominal distension	-	1 (2.0)
Abdominal pain	-	1 (2.0)
Anorexia	-	1 (2.0)
Arthropod sting	1 (2.0)	-
Asthma	1 (2.0)	-
Back pain	-	1 (2.0)
Enteritis infectious	-	1 (2.0)
Epistaxis	1 (2.0)	-
Eyelid oedema	-	1 (2.0)
Feeling hot	1 (2.0)	-
Joint sprain	1 (2.0)	-
Mumps	-	1 (2.0)
Musculoskeletal stiffness	-	1 (2.0)
Myalgia	-	1 (2.0)
Paronychia	-	1 (2.0)
Residual urine	-	1 (2.0)
Stomach discomfort	-	1 (2.0)
Thirst	-	1 (2.0)
Toothache	1 (2.0)	-
Upper respiratory tract inflammation	1 (2.0)	-
Urticaria	1 (2.0)	-
- : 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. Grade 3= AE that prevented normal activity Related= AE assessed by the investigator as causally related to the study vaccination		
Safety results: Number (%) of subjects with unsolicited adverse events from Day 0 to Day 83 (Total Vaccinated cohort)		
Most frequent adverse events - On-Therapy (occurring within day 0-83 following vaccination)	20-40Y N = 50	41-64Y N = 50
Subjects with any AE(s), n (%)	33 (66.0)	36 (72.0)
Subjects with grade 3 AE(s), n (%)	3 (6.0)	2 (4.0)
Subjects with related AE(s), n (%)	11 (22.0)	17 (34.0)
Nasopharyngitis	9 (18.0)	8 (16.0)
Injection site pruritus	5 (10.0)	9 (18.0)

Injection site warmth	6 (12.0)	8 (16.0)
Headache	3 (6.0)	6 (12.0)
Bronchitis	5 (10.0)	-
Abdominal pain upper	-	3 (6.0)
Diarrhoea	3 (6.0)	-
Asthma	2 (4.0)	-
Back pain	-	2 (4.0)
Constipation	2 (4.0)	-
Decreased appetite	-	2 (4.0)
Gastroenteritis	-	2 (4.0)
Muscular weakness	-	2 (4.0)
Oropharyngeal pain	-	2 (4.0)
Upper respiratory tract infection	2 (4.0)	-
Urticaria	2 (4.0)	-
- : 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. Grade 3= AE that prevented normal activity Related= AE assessed by the investigator as causally related to the study vaccination		
Safety results: Number (%) of subjects with serious adverse events during the entire study period (Day 0 to Day 181)(Total Vaccinated cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	20-40Y N = 50	41-64Y N = 50
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	20-40Y N = 50	41-64Y N = 50
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

At Day 21 after the last dose of Flu vaccine, GMTs of HI antibodies against the H5N1 vaccine strain (A/Indonesia) were 156.8 in subjects aged 20-40Y and 142.1 in subjects aged 41-64Y. At the same time point, SCRs was 90.0% and 92.0%, SCF was 31.4 and 26.2 and SPR was 90.0% and 92.0% in subjects aged 20-40Y and 41-64Y, respectively.

During the 21-day follow-up period following each dose, at least one unsolicited AE was reported by 27 (54.0%) subjects aged between 20 and 40 years and 24 (48.0%) subjects aged 41 to 64 years. Eleven subjects (22.0%) aged between 20 and 40 years and 17 (34.0%) subjects aged 41 to 64 years reported unsolicited AEs assessed by the investigator as causally related to study vaccination.

Between Day 0 and Day 83, at least one unsolicited AE was reported for 33 (66.0%) subjects aged between 20 and 40 years and for 36 (72.0%) subjects aged between 41 and 64 years. Eleven subjects (22.0%) aged between 20 and 40 years and 17 (34.0%) subjects aged 41 to 64 years reported unsolicited AEs assessed by the investigator as causally related to study vaccination.

No SAE was reported throughout the study period.

Publications:

Nagai H et al. (2010) A phase II, open-label, multicentre study to evaluate the immunogenicity and safety of an adjuvanted pre-pandemic (H5N1) influenza vaccine in healthy Japanese adults. BMC Infectious Diseases. 10:338.

Date updated: 20-May-2011