The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 113456 (FLU D-PAN H1N1-007)

Title: Safety and immunogenicity study of GSK Biologicals' influenza vaccine GSK2340272A in adults aged 18 to 60 years**.** GSK2340272A (Flu 1): GlaxoSmithKline (GSK) Biologicals' Pandemic influenza vaccine comprising A/California/7/2009 (H1N1)v-like strain.

Rationale: The aim of the study was to assess the immunogenicity and safety of Flu 1 vaccine compared to GSK2340269A. GSK2340269A (Flu 2): alternative formulation of GSK Biologicals' Pandemic influenza vaccine comprising A/California/7/2009 (H1N1)v-like strain.

Phase: III

Study Period: 08 September 2009 to 28-September 2010

Study Design: Randomized (1:1) observer-blind study with 2 parallel groups.

Centers: 1 center in Belgium.

Indication: Immunization against A/California/7/2009 (H1N1)v-like influenza in male and female subjects aged 18 to 60 years.

Treatment: Study groups were as follows:

- Flu 1 Group: subjects received two doses of Flu 1 vaccine (one at Day 0 and one at Day 21).
- Flu 2 Group: subjects received two doses of Flu 2 vaccine (one at Day 0 and one at Day 21).

Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm at Day 0 and of the dominant arm at Day 21.

Objectives:

To demonstrate that vaccination with two doses of the Flu 1 vaccine resulted in an hemagglutination inhibition (HI) immune response to the vaccine-homologous virus that meets or exceeds the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) guidance targets for pandemic vaccine seroconversion rate (SCR), seroprotection rate (SPR), and geometric mean fold rise (GMFR) at 21 days after the second dose of Flu 1 vaccine in adults 18 to 60 years of age.

Primary Outcome/Efficacy Variable:

Humoral immune response in terms of HI antibodies

In subjects receiving two doses of Flu 1 vaccine:

- SCR* at 21 days after second dose of Flu 1 vaccine (Day 42)
- SPR** at 21 days after second dose of Flu 1 vaccine (Day 42)
- GMFR*** at 21 days after second dose of Flu 1 vaccine (Day 42)

*SCR is defined as the percentage of vaccinees that have either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a four-fold increase in post-vaccination titer. The CHMP criterion is fulfilled if the point estimate for SCR is > 40% in subjects 18 to 60 years of age.

**SPR is defined as the percentage of vaccinees with a serum HI titer ≥ 1:40, that usually is accepted as indicating protection. The CHMP criterion is fulfilled if the post-vaccination time point estimated for SPR is > 70% in subjects 18 to 60 years of age.

***GMFR, also called seroconversion factor (SCF), is defined as the fold increase in serum HI geometric mean titers (GMTs) post-vaccination compared to pre-vaccination. The criterion is fulfilled if the point estimate for GMFR is > 2.5 in subjects 18 to 60 years of age.

Secondary Outcome/Efficacy Variable(s):

Humoral immune response in terms of HI antibodies

In subjects receiving two doses of Flu 1 vaccine:

- GMTs and seropositivity rates at Day 0, 21, 42, 182, and 364
- SCR* at Day 21, 182 and 364
- SPR* at Day 0, 21, 182 and 364
- SCF* at Day 21, 182 and 364

In subjects receiving two doses of Flu 2 vaccine:

- GMTs and seropositivity rates at Day 0, 21, 42, 182, and 364
- SCR* at Day 21, 42, 182 and 364
- SPR* at Day 0, 21, 42, 182 and 364
- SCF* at Day 21, 42, 182 and 364

*Criteria for evaluation were the same as that for the primary outcome variables.
Serum neutralizing antibody titers
In subjects from both groups:

- GMTs at Day 0, 21, 42, 182§, and 364§
- SCR* at Day 21, 42,182§, and 364§

§Analyses was not performed.
*SCR is defined as the percentage of vaccinees that have a four-fold increase between pre- and post-vaccination titers.

Safety

- Occurrence, duration and intensity of each solicited local symptoms within 7 days (Day 0 – Day 6) after each vaccination.
- Occurrence, duration, intensity and relation to vaccination of each solicited general symptoms within 7 days (Day 0 – Day 6) after each vaccination.
- Occurrence, intensity and relationship to vaccination of unsolicited adverse events (AEs) within 21 days after the first vaccination and 63 days after the second vaccination (Day 0 – Day 20 and Day 21 – Day 83), according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence and relationship to vaccination of adverse events of specific interest (AESIs) and serious adverse events (SAEs) during the entire study period (up to Day 364).

Statistical Methods:
Analyses were performed on the Total Vaccinated cohort, the According-To-Protocol (ATP) cohort for immunogenicity, the ATP cohort for persistence at Month 6 and the ATP cohort for persistence at Month 12.

- The Total Vaccinated cohort included all vaccinated subjects.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e. those who met all eligibility criteria, complied with the procedures defined in the protocol, with no elimination criteria during the study) who received 2 vaccine doses and for whom assay results were available for antibodies against H1N1 antigen for the blood sample taken up to 21 days after the second vaccine dose.
- The ATP cohort for persistence at Month 6 included all evaluable subjects who met all eligibility criteria, who complied with the procedures defined in the protocol during the entire study period and with the intervals defined in the protocol for visit at Month 6, who did not meet the elimination criteria during the entire study and for whom data concerning immunogenicity outcome measures were available. This included subjects for whom assay results were available for antibodies against the study vaccine antigen component at Month 6.
- The ATP cohort for persistence at Month 12 included all evaluable subjects who met all eligibility criteria, who complied with the procedures defined in the protocol during the entire study period and with the intervals defined in the protocol for visit at Month 12, who did not meet the elimination criteria during the entire study and for whom data concerning immunogenicity outcome measures were available. This included subjects for whom assay results were available for antibodies against the study vaccine antigen component at Month 12.

Analysis of immunogenicity:
The analysis was based on the ATP cohort for immunogenicity, the ATP cohort for persistence at Month 6 and the ATP cohort for persistence at Month 12.
Inferential analysis
The primary objective was evaluated by examining the immunogenicity response in Flu 1 Group.
Point estimate for SCR, SPR, SCF and the associated 95% confidence intervals (CI) were computed 21 days after the second dose (at Day 42). If the point estimate for SCR ≥ 40% and SPR ≥ 70%, the CHMP criteria for SCR and SPR were met, and if the SCF was greater than 2.5, the study primary objective was met.
Descriptive analysis
For the humoral immune response in terms of H1N1 HI antibodies, for each treatment group, the following parameters (with 95% CI) were calculated:

- GMTs of H1N1 antibody titers at Day 0, 21, 42, 182 and 364.
- SCRs at Day 21, 42, 182 and 364.
- SCFs at Day 21, 42, 182 and 364.
- SPRs at Day 0, 21, 42, 182 and 364.

For the humoral immune response in terms of neutralizing antibodies, for each treatment group, the following parameters (with 95% CI) were calculated:

- GMTs of H1N1 antibody titers at Day 0, 21 and 42.

- SCRs at Day 21 and 42.

Analysis of safety:

The analysis was based on the Total Vaccinated cohort.

The incidence of solicited local and general symptoms occurring during the 7 days after each vaccination was tabulated with exact 95% CI for each treatment group. The same calculations were performed for symptoms of any intensity, those with intensity of grade 3, as well as for solicited general symptoms assessed by the investigator as related to vaccination. All solicited local AEs were assessed as causally related to the vaccination. Duration of local and general symptoms was also calculated.

The percentage of subjects with at least one report of an unsolicited AE classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred term up to 21 days after the first vaccination (Days 0-20) and 63 days after the second vaccination (Days 21-83) was tabulated for each treatment group. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs that were assessed by the investigator as possibly related to vaccination.

SAEs and AESIs were collected and summarized by MedDRA preferred terms during the entire study period.

Study Population: Healthy male or female adults 18 to 60 years of age at the time of first vaccination. Women were to be of non-childbearing potential or if of childbearing potential, had to practice adequate contraception for 30 days prior to vaccination, to have a negative pregnancy test, and to continue such precautions during the entire treatment period and for 2 months after completion of the vaccination series. A written informed consent was obtained from the subjects prior to study entry.

Number of Subjects:	**Flu 1 Group**	**Flu 2 Group**
Planned, N	64	64
Randomized, N (Total Vaccinated cohort)	64	66
Completed at Day 21, n (%)	63 (98.4)	66 (100)
Completed at Day 42, n (%)	63 (98.4)	66 (100)
Completed at Day 182, n (%)	63 (98.4)	66 (100)
Completed at Day 364, n (%)	63 (98.4)	66 (100)
Total Number Subjects Withdrawn, n (%)	1 (1.6)	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 (1.6)	0 (0.0)
Demographics	**Flu 1 Group**	**Flu 2 Group**
N (Total Vaccinated cohort)	64	66
Females: Males	41: 23	39: 27
Mean Age, years (SD)	39.1 (13.53)	38.2 (14.10)
White - Caucasian / European heritage, n (%)	64 (100)	65 (98.5)

Primary Efficacy Results: SCR for HI antibodies against Flu A/CAL/09 at Day 21 and Day 42 (ATP cohort for immunogenicity)

				SCR			
						95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/09	Flu 1	PI(D21)	60	59	98.3	91.1	100
		PII(D42)*	59	58	98.3	90.9	100
	Flu 2	PI(D21)	66	56	84.8	73.9	92.5
		PII(D42)	66	61	92.4	83.2	97.5

Seroconversion defined as:

For initially seronegative subjects (antibody titer < 1:10 prior to vaccination), antibody titer ≥ 1:40 after vaccination

For initially seropositive subjects (antibody titer ≥ 1:10 prior to vaccination), antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer

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

PI(D21) = Post-vaccination at Day 21

PII(D42) = Post-vaccination at Day 42

* Primary outcome variable: If the point estimate for SCR > 40%, the CHMP criterion for SCR was met.

Primary Efficacy Results: SPR for HI antibodies against Flu A/CAL/09 at Day 0, Day 21 and Day 42 (ATP cohort for immunogenicity)

				SPR			
						95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/09	Flu 1	PRE	60	7	11.7	4.8	22.6
		PI(D21)	60	60	100	94.0	100
		PII(D42)*	59	59	100	93.9	100
	Flu 2	PRE	66	12	18.2	9.8	29.6
		PI(D21)	66	62	93.9	85.2	98.3
		PII(D42)	66	66	100	94.6	100

N = Number of subjects with available results
n (%) = Number (percentage) of seroprotected subjects (HI titer ≥ 1: 40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE =Pre-vaccination at Day 0
PI(D21) = Post-vaccination at Day 21
PII(D42) = Post-vaccination at Day 42
* Primary outcome variable: If the point estimate for SPR > 70%, the CHMP criterion for SPR was met

Primary Efficacy Results: SCF for HI antibody titer against Flu A/CAL/09 at each post-vaccination time point (ATP cohort for immunogenicity)

				SCF		
					95% CI	
Antibodies against	**Group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/09.	Flu 1	PI(D21)	60	38.1	28.6	50.7
		PII(D42)*	59	72.9	55.4	95.9
	Flu 2	PI(D21)	66	28.7	20.0	41.2
		PII(D42)	66	31.5	23.1	43.2

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
PI(D21) = Post-vaccination at Day 21
PII(D42) = Post-vaccination at Day 42
* Primary outcome variable: If SCF was greater than 2.5, the study primary objective was met.

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09 at Day 0, Day 21 and Day 42 (ATP cohort for immunogenicity)

				≥ 1:10				GMT		
						95% CI			95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Flu A/CAL/09	Flu 1	PRE	60	23	38.3	26.1	51.8	8.8	7.0	11.1
		PI(D21)	60	60	100	94.0	100	335.2	250.1	449.2
		PII(D42)	59	59	100	93.9	100	636.3	520.9	777.3
	Flu 2	PRE	66	28	42.4	30.3	55.2	10.8	8.1	14.4
		PI(D21)	66	65	98.5	91.8	100	310.2	218.8	439.7
		PII(D42)	66	66	100	94.6	100	341.0	259.9	447.3

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(D21) = Post-vaccination at Day 21
PII(D42) = Post-vaccination at Day 42
PRE =Pre-vaccination at Day 0

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09 at Day 182 (ATP cohort for persistence at Month 6)

				≥ 1:10				GMT		
						95% CI			95% CI	
Antibodies	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**

against										
Flu A/CAL/7/09	Flu 1	PII(D182)	59	59	100	93.9	100	204.8	161.5	259.8
	Flu 2	PII(D182)	61	61	100	94.1	100	146.1	108.5	196.7

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n (%) = number (percentage) of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(D182) = Post-vaccination at Day 182

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09 at Day 364 (ATP cohort for persistence at Month 12)

				≥ 1:10				GMT		
						95% CI			95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Flu A/CAL/7/09	Flu 1	PII(D364)	59	59	100	93.9	100	85.8	64.4	114.3
	Flu 2	PII(D364)	65	62	95.4	87.1	99.0	87.6	64.7	118.8

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(D364)= Post-vaccination at Day 364

Secondary Outcome Variable(s): SCR for HI antibodies against Flu A/CAL/09 at Day 182 (ATP cohort for persistence at Month 6)

				SCR			
						95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	Flu 1	PII(D182)	59	57	96.6	88.3	99.6
	Flu 2	PII(D182)	61	47	77.0	64.5	86.8

Seroconversion defined as:
For initially seronegative subjects (antibody titer < 1:10 prior to vaccination), antibody titer ≥ 1:40 after vaccination
For initially seropositive subjects (antibody titer ≥ 1:10 prior to vaccination), antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
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(D182) = Post-vaccination at Day 182

Secondary Outcome Variable(s): SCR for HI antibodies against Flu A/CAL/7/09 at Day 364 (ATP cohort for persistence at Month 12)

			SCR			
					95% CI	
Antibodies against	**Group**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	Flu 1	59	41	69.5	56.1	80.8
	Flu 2	65	46	70.8	58.2	81.4

Seroconversion defined as:
For initially seronegative subjects, antibody titer ≥ 1:40 after vaccination
For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
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

Secondary Outcome Variable(s): SPR for HI antibodies against Flu A/CAL/09 at Day 182 (ATP cohort for persistence at Month 6)

				SPR			
						95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	Flu 1	PII(D182)	59	59	100	93.9	100
	Flu 2	PII(D182)	61	52	85.2	73.8	93.0

N = Number of subjects with available results
n(%) = number(percentage) of seroprotected subjects (HI titer ≥ 1:40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PII(D182) = Post-vaccination at Day 182

Secondary Outcome Variable(s): SPR for HI antibodies against Flu A/CAL/7/09 at Day 364 (ATP cohort for persistence at Month 12)

			SPR			
					95% CI	
Antibodies against	**Group**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	Flu 1	59	46	78.0	65.3	87.7
	Flu 2	65	55	84.6	73.5	92.4

N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer ≥ 1:40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): SCF for HI antibodies against Flu A/CAL/09 at Day 182 (ATP cohort for persistence at Month 6)

				SCF		
					95% CI	
Antibodies against	**Group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09	Flu 1	PII(D182)	59	22.5	18.0	28.2
	Flu 2	PII(D182)	61	13.9	10.2	18.9

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(D182) = Post-vaccination at Day 182

Secondary Outcome Variable(s): SCF for HI antibodies against Flu A/CAL/7/09 at Day 364 (ATP cohort for persistence at Month 12)

			SCF		
				95% CI	
Antibodies against	**Group**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09	Flu 1	59	9.7	7.4	12.5
	Flu 2	65	8.3	6.2	11.0

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

Secondary Outcome Variable(s): Seropositivity rates and GMTs of neutralizing antibodies against Flu A/Neth/602/09 (ATP cohort for immunogenicity)

				≥ 1:8				GMT		
						95% CI			95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Flu A/Neth/602/09	Flu 1	PRE	28	8	28.6	13.2	48.7	6.1	4.6	8.0
		PI(D21)	28	27	96.4	81.7	99.9	152.3	78.4	295.9
		PII(D42)	28	28	100	87.7	100	243.8	163.4	363.7
	Flu 2	PRE	30	17	56.7	37.4	74.5	9.6	6.7	13.6
		PI(D21)	30	29	96.7	82.8	99.9	89.9	51.6	156.6
		PII(D42)	30	30	100	88.4	100	144.9	88.7	236.6

GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(D21)= Post-vaccination at Day 21
PII(D42)= Post-vaccination at Day 42
PRE =Pre-vaccination at Day 0

Secondary Outcome Variable(s): SCR for neutralizing antibodies against Flu A/Neth/602/09 at Day 21 and Day 42 (ATP cohort for immunogenicity)

				SCR			
						95% CI	
Antibodies against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/Neth/602/09	Flu 1	PI(D21)	28	21	75.0	55.1	89.3
		PII(D42)	28	27	96.4	81.7	99.9
	Flu 2	PI(D21)	30	22	73.3	54.1	87.7
		PII(D42)	30	23	76.7	57.7	90.1

Seroconversion defined as:
For initially seronegative subjects, antibody titer ≥ 1:32 after vaccination
For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
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
PI(D21)= Post-vaccination at Day 21
PII(D42)= Post-vaccination at Day 42

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)

		Flu 1 Group					Flu 2 Group				
					95% CI					95% CI	
Symptom	**Intensity**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Pain	Any	63	57	90.5	80.4	96.4	65	23	35.4	23.9	48.2
	Grade 3	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
Redness	Any	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
	>100 mm	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
Swelling	Any	63	5	7.9	2.6	17.6	65	0	0.0	0.0	5.5
	>100 mm	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
Dose 2											
Pain	Any	62	56	90.3	80.1	96.4	66	20	30.3	19.6	42.9
	Grade 3	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
Redness	Any	62	3	4.8	1.0	13.5	66	0	0.0	0.0	5.4
	>100 mm	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
Swelling	Any	62	9	14.5	6.9	25.8	66	0	0.0	0.0	5.4
	>100 mm	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
Across Doses											
Pain	Any	63	61	96.8	89.0	99.6	66	32	48.5	36.0	61.1
	Grade 3	63	3	4.8	1.0	13.3	66	0	0.0	0.0	5.4
Redness	Any	63	4	6.3	1.8	15.5	66	0	0.0	0.0	5.4
	>100 mm	63	0	0.0	0.0	5.7	66	0	0.0	0.0	5.4
Swelling	Any	63	11	17.5	9.1	29.1	66	0	0.0	0.0	5.4
	>100 mm	63	0	0.0	0.0	5.7	66	0	0.0	0.0	5.4

Any= occurrence of any local symptom regardless of intensity grade
Grade 3 pain= pain that prevented normal activity
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

Secondary Outcome Variable(s): Number of days with solicited local symptoms during the solicited post-vaccination period (Total Vaccinated cohort)

Solicited symptom	**Dose**	**Group**	**N**	**Mean**	**Median**
Pain	Dose 1	Flu 1	57	3.1	3.0
		Flu 2	23	1.8	1.0
	Dose 2	Flu 1	56	3.1	3.0
		Flu 2	20	2.2	2.0
	Overall/dose	Flu 1	113	3.1	3.0
		Flu 2	43	2.0	2.0

Redness	Dose 1	Flu 1	1	3.0	3.0
	Dose 2	Flu 1	3	2.3	2.0
	Overall/dose	Flu 1	4	2.5	2.5
Swelling	Dose 1	Flu 1	5	2.2	2.0
	Dose 2	Flu 1	9	2.0	2.0
	Overall/dose	Flu 1	14	2.1	2.0

N = number of doses with the symptom

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)

		Flu 1 Group					**Flu 2 Group**				
					95% CI					**95% CI**	
Symptom	**Intensity/ Relationship**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1											
Fatigue	Any	63	22	34.9	23.3	48.0	65	18	27.7	17.3	40.2
	Grade 3	63	0	0.0	0.0	5.7	65	1	1.5	0.0	8.3
	Related	63	21	33.3	22.0	46.3	65	16	24.6	14.8	36.9
Headache	Any	63	17	27.0	16.6	39.7	65	11	16.9	8.8	28.3
	Grade 3	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
	Related	63	15	23.8	14.0	36.2	65	8	12.3	5.5	22.8
Joint pain at other location	Any	63	7	11.1	4.6	21.6	65	4	6.2	1.7	15.0
	Grade 3	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
	Related	63	7	11.1	4.6	21.6	65	3	4.6	1.0	12.9
Muscle aches	Any	63	20	31.7	20.6	44.7	65	6	9.2	3.5	19.0
	Grade 3	63	1	1.6	0.0	8.5	65	0	0.0	0.0	5.5
	Related	63	20	31.7	20.6	44.7	65	4	6.2	1.7	15.0
Shivering	Any	63	6	9.5	3.6	19.6	65	4	6.2	1.7	15.0
	Grade 3	63	0	0.0	0.0	5.7	65	1	1.5	0.0	8.3
	Related	63	6	9.5	3.6	19.6	65	2	3.1	0.4	10.7
Sweating	Any	63	6	9.5	3.6	19.6	65	7	10.8	4.4	20.9
	Grade 3	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
	Related	63	6	9.5	3.6	19.6	65	5	7.7	2.5	17.0
Temperature/(Axillary)	≥ 37.5°C	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
	≥ 39.0°C	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
	Related	63	0	0.0	0.0	5.7	65	0	0.0	0.0	5.5
Dose 2											
Fatigue	Any	62	28	45.2	32.5	58.3	66	13	19.7	10.9	31.3
	Grade 3	62	2	3.2	0.4	11.2	66	2	3.0	0.4	10.5
	Related	62	27	43.5	31.0	56.7	66	13	19.7	10.9	31.3
Headache	Any	62	22	35.5	23.7	48.7	66	9	13.6	6.4	24.3
	Grade 3	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	Related	62	20	32.3	20.9	45.3	66	8	12.1	5.4	22.5
Joint pain at other location	Any	62	13	21.0	11.7	33.2	66	4	6.1	1.7	14.8
	Grade 3	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	Related	62	13	21.0	11.7	33.2	66	4	6.1	1.7	14.8
Muscle aches	Any	62	23	37.1	25.2	50.3	66	7	10.6	4.4	20.6
	Grade 3	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	Related	62	23	37.1	25.2	50.3	66	6	9.1	3.4	18.7
Shivering	Any	62	11	17.7	9.2	29.5	66	3	4.5	0.9	12.7
	Grade 3	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	Related	62	11	17.7	9.2	29.5	66	2	3.0	0.4	10.5
Sweating	Any	62	12	19.4	10.4	31.4	66	7	10.6	4.4	20.6
	Grade 3	62	1	1.6	0.0	8.7	66	0	0.0	0.0	5.4
	Related	62	12	19.4	10.4	31.4	66	6	9.1	3.4	18.7

Temperature/(Axillary)	≥ 37.5°C	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
	≥ 39.0°C	62	0	0.0	0.0	5.8	66	0	0.0	0.0	5.4
	Related	62	2	3.2	0.4	11.2	66	0	0.0	0.0	5.4
Across Doses											
Fatigue	Any	63	34	54.0	40.9	66.6	66	22	33.3	22.2	46.0
	Grade 3	63	2	3.2	0.4	11.0	66	3	4.5	0.9	12.7
	Related	63	33	52.4	39.4	65.1	66	22	33.3	22.2	46.0
Headache	Any	63	29	46.0	33.4	59.1	66	14	21.2	12.1	33.0
	Grade 3	63	3	4.8	1.0	13.3	66	0	0.0	0.0	5.4
	Related	63	27	42.9	30.5	56.0	66	12	18.2	9.8	29.6
Joint pain at other location	Any	63	14	22.2	12.7	34.5	66	6	9.1	3.4	18.7
	Grade 3	63	0	0.0	0.0	5.7	66	0	0.0	0.0	5.4
	Related	63	14	22.2	12.7	34.5	66	6	9.1	3.4	18.7
Muscle aches	Any	63	27	42.9	30.5	56.0	66	12	18.2	9.8	29.6
	Grade 3	63	3	4.8	1.0	13.3	66	0	0.0	0.0	5.4
	Related	63	27	42.9	30.5	56.0	66	10	15.2	7.5	26.1
Shivering	Any	63	14	22.2	12.7	34.5	66	6	9.1	3.4	18.7
	Grade 3	63	0	0.0	0.0	5.7	66	1	1.5	0.0	8.2
	Related	63	14	22.2	12.7	34.5	66	4	6.1	1.7	14.8
Sweating	Any	63	14	22.2	12.7	34.5	66	11	16.7	8.6	27.9
	Grade 3	63	1	1.6	0.0	8.5	66	0	0.0	0.0	5.4
	Related	63	14	22.2	12.7	34.5	66	9	13.6	6.4	24.3
Temperature/(Axillary)	≥ 37.5°C	63	2	3.2	0.4	11.0	66	0	0.0	0.0	5.4
	≥ 39.0°C	63	0	0.0	0.0	5.7	66	0	0.0	0.0	5.4
	Related	63	2	3.2	0.4	11.0	66	0	0.0	0.0	5.4

Any = occurrence of any general symptom regardless of intensity grade and relationship to vaccination
Grade 3 = event that prevented normal activities
Related = general symptom assessed by the investigator as causally related to the study vaccination
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

Secondary Outcome Variable(s): Number of days with solicited general symptoms during the solicited post-vaccination period (Total Vaccinated cohort)

Solicited symptom	Dose	Group	N	Mean	Median
Fatigue	Dose 1	Flu 1	22	2.3	2.0
		Flu 2	18	2.2	2.0
	Dose 2	Flu 1	28	2.0	1.5
		Flu 2	13	3.2	3.0
	Overall/dose	Flu 1	50	2.1	2.0
		Flu 2	31	2.6	2.0
Headache	Dose 1	Flu 1	17	2.3	2.0
		Flu 2	11	1.7	1.0
	Dose 2	Flu 1	22	2.2	2.0
		Flu 2	9	2.2	2.0
	Overall/dose	Flu 1	39	2.3	2.0
		Flu 2	20	2.0	2.0
Joint pain at other location	Dose 1	Flu 1	7	2.7	3.0
		H1N1	4	2.3	2.0
	Dose 2	Flu 1	13	1.9	1.0
		Flu 2	4	2.3	2.0
	Overall/dose	Flu 1	20	2.2	1.5
		Flu 2	8	2.3	2.0
Muscle aches	Dose 1	Flu 1	20	2.2	2.0
		Flu 2	6	1.5	1.0

	Dose 2	Flu 1	23	2.3	2.0
		Flu 2	7	1.7	1.0
	Overall/dose	Flu 1	43	2.2	2.0
		Flu 2	13	1.6	1.0
Sweating	Dose 1	Flu 1	6	2.3	2.0
		Flu 2	7	2.1	1.0
	Dose 2	Flu 1	12	1.7	1.5
		Flu 2	7	2.3	2.0
	Overall/dose	Flu 1	18	1.9	2.0
		Flu 2	14	2.2	1.0
Shivering	Dose 1	Flu 1	6	1.7	1.0
		Flu 2	4	1.5	1.0
	Dose 2	Flu 1	11	1.7	2.0
		Flu 2	3	2.0	2.0
	Overall/dose	Flu 1	17	1.7	1.0
		Flu 2	7	1.7	1.0
Temperature	Dose 2	Flu 1	2	2.0	2.0
	Overall/dose	Flu 1	2	2.0	2.0

N = number of doses with the symptom

Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of AESIs up to Day 364 post-vaccination period (Total Vaccinated cohort)

Most frequent AESIs - On-Therapy (occurring within Day 0-364 following vaccination)	**Flu 1 Group N = 64**	**Flu 2 Group N = 66**
Subjects with any AESI(s), n (%)	1 (1.6)	1 (1.5)
Subjects with related AESI(s), n (%)	0 (0.0)	0 (0.0)
Pharyngeal oedema	1 (1.6)	-
Uveitis	-	1 (1.5)

- : AESI absent

Safety results: Percentage of subjects reporting the occurrence of unsolicited AEs within the 84-day (Days 0-83) post-vaccination period (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Day 0-83 following vaccination)	**Flu 1 Group N = 64**	**Flu Analye2 Group N = 66**
Subjects with any AE(s), n (%)	39 (60.9)	38 (57.6)
Subjects with grade 3 AE(s), n (%)	7 (10.9)	9 (13.6)
Subjects with related AE(s), n (%)	12 (18.8)	7 (10.6)
Upper respiratory tract infection	6 (9.4)	11 (16.7)
Headache	7 (10.9)	7 (10.6)
Rhinitis	10 (15.6)	3 (4.5)
Influenza like illness	4 (6.3)	6 (9.1)
Gastroenteritis	3 (4.7)	3 (4.5)
Nausea	4 (6.3)	2 (3.0)
Oropharyngeal pain	4 (6.3)	2 (3.0)
Diarrhoea	2 (3.1)	3 (4.5)
Sinusitis	2 (3.1)	3 (4.5)
Cough	2 (3.1)	2 (3.0)
Lymphadenopathy	3 (4.7)	-
Abdominal pain	-	2 (3.0)
Abdominal pain upper	-	2 (3.0)
Arthropod bite	2 (3.1)	-
Fatigue	-	2 (3.0)
Feeling hot	2 (3.1)	-
Injection site lymphadenopathy	2 (3.1)	-
Malaise	2 (3.1)	-
Pharyngitis	2 (3.1)	-

Toothache	-	2 (3.0)
Urinary tract infection	-	2 (3.0)
Vulvovaginal candidiasis	2 (3.1)	-
- : Adverse event absent or not meeting the selected AEs counting rule: > 30 subjects/treatment group and ≤ 3 groups, display the most frequent 10 events in each treatment group Grade 3= event that prevented normal activities Related= event assessed by the investigator as causally related to the study vaccination		
Safety results: Number (%) of subjects with serious adverse events up to Day 364 (Total Vaccinated cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	**Flu 1 Group N = 64**	**Flu 2 Group N = 66**
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	2 (3.1) [0]	1 (1.5) [0]
Ectopic pregnancy	1 (1.6) [0]	0 (0.0) [0]
Migraine	0 (0.0) [0]	1 (1.5) [0]
Spinal osteoarthritis	1 (1.6) [0]	0 (0.0) [0]
Fatal SAEs	**Flu 1 Group N = 64**	**Flu 2 Group N = 66**
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

At Day 42, 21 days after the second dose of Flu 1 vaccine administered to healthy adults aged 18 to 60 years, all CHMP and Center for Biologics Evaluation & Research regulatory acceptance criteria for vaccine homologous virus HI antibody response were met. Administration of two doses of Flu 2 vaccine also induced an immune response meeting the regulatory criteria.

Up to Day 83, 39 (60.9%) subjects in the Flu 1 Group and 38 (57.6%) subjects in the Flu 2 Group reported at least one unsolicited adverse event.

Up to Day 364, two SAEs were reported by two subjects in the Flu 1 Group and one SAE was reported by one subject in the Flu 2 Group. They were assessed by the investigator as not related to study vaccination. No fatal SAEs were reported during the study.

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