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Study No.: 113525 (FLU D-PAN H1N1-018)
<p>Title: Immunogenicity, safety and reactogenicity of GSK Biologicals' influenza GSK2340272A and <i>Fluarix</i>TM 2009-2010 vaccines when co-administered in elderly subjects aged 61 years and older.</p> <p>GSK2340272A (Flu Pan): GlaxoSmithKline (GSK) Biologicals' Pandemic influenza vaccine comprising A/California/7/2009 (H1N1)v-like strain.</p> <p><i>Fluarix</i>TM (Flu S): GSK Biologicals' licensed seasonal Trivalent Influenza Vaccine (TIV)</p>
<p>Rationale: The aim of this study was to assess the immunogenicity and safety of a 2-dose schedule with GSK Biologicals' Flu Pandemic vaccine when co-administered with Flu Seasonal vaccine either at the time of first or second vaccination in elderly subjects aged 61 years and older.</p>
Phase: II
Study Period: 12 September 2009 to 23 September 2010
Study Design: Randomized (1:1) study with 2 parallel groups, open for Flu Pan vaccine and observer-blind for Flu S vaccine.
Centers: 2 centers in Sweden
Indication: Immunization against A/California/7/2009 (H1N1)v-like influenza and seasonal influenza (2009-2010) in male and female subjects aged 61 years and older.
<p>Treatment: Study groups were as follows:</p> <ul style="list-style-type: none"> Flu 1 Group: subjects received 2 doses Flu Pan vaccine co-administered with 1 dose of Flu S vaccine at the time of first vaccination (Day 0) and with a placebo vaccine at the time of second vaccination (Day 21). Flu 2 Group: subjects received 2 doses Flu Pan vaccine co-administered with a placebo vaccine at the time of first vaccination (Day 0) and with 1 dose of Flu S vaccine at the time of second vaccination (Day 21). <p>Flu Pan vaccine was administered intramuscularly in the deltoid region of the non-dominant arm. Flu S vaccine and Placebo vaccine were administered intramuscularly in the deltoid region of the dominant arm.</p>
<p>Objectives:</p> <ul style="list-style-type: none"> To assess whether vaccination with two doses of Flu Pan vaccine resulted in an hemagglutination inhibition (HI) immune response to the vaccine-homologous virus that met or exceeded the European Medicines Agency (EMA) (Committee for Medicinal Products for Human Use [CHMP]) guidance targets for pandemic influenza vaccines (seroconversion rate [SCR], seroprotection rate [SPR], and geometric mean fold rise [GMFR]) at 21 days after the second dose of Flu Pan vaccine when co-administered with Flu S vaccine either at the time of first or second vaccination in elderly subjects aged 61 years and older. To assess whether vaccination with one dose of Flu S vaccine resulted in an HI immune response that met or exceeded for each vaccine strain of the seasonal vaccine at least one of the EMA (CHMP) guidance targets for seasonal influenza vaccines (SCR and/or SPR and/or GMFR) at 21 days after vaccination when co-administered with either the first or second dose of the Flu Pan vaccine in elderly subjects aged 61 years and older.
<p>Primary Outcome/Efficacy Variable:</p> <p>Humoral immune responses in terms of vaccine HI antibodies:</p> <ul style="list-style-type: none"> SCR* at 21 days after the second dose of the Flu Pan vaccine (Day 42) SPR** at 21 days after the second dose of the Flu Pan vaccine (Day 42) GMFR*** at 21 days after the second dose of the Flu Pan vaccine (Day 42) SCR* at 21 days after vaccination with Flu S vaccine SPR** at 21 days after vaccination with Flu S vaccine GMFR*** (also called seroconversion factor [SCF]) at 21 days after vaccination with Flu S vaccine <p>*SCR is defined as the proportion of subjects who had either a pre-vaccination reciprocal HI titer < 10 and a post-vaccination reciprocal titer ≥ 40, or a pre-vaccination reciprocal HI titer ≥ 10 and at least a 4-fold increase in post vaccination reciprocal titer against the vaccine virus. The CHMP criterion was fulfilled if the point estimate for SCR was > 30% in subjects > 60 years of age.</p> <p>**SPR is defined as the proportion of subjects with reciprocal HI titers ≥ 40 against the vaccine homologous virus. The CHMP criterion was fulfilled if the post-vaccination point estimate for SPR was > 60% in subjects > 60 years of age.</p> <p>***GMFR, also called seroconversion factor (SCF), is defined as the geometric mean of the within subject ratios of the post-vaccination reciprocal HI titer to the pre-vaccination reciprocal HI titer for the vaccine virus. The criterion was fulfilled if the point estimate for GMFR was > 2.0 in subjects > 60 years of age.</p>

Secondary Outcome/Efficacy Variable(s):

Humoral immune response in terms of vaccine HI antibodies:

- Geometric mean titers (GMTs) and seropositivity rates at Day 0, Day 21, Day 42, Day 182, and Day 364.
- SCR* at Days 21, 182 and 364.
- SPR* at Days 0, 21, 182 and 364.
- GMFR* at Day 21, 182 and 364.

Safety:

- Occurrence, duration and intensity of each solicited local symptom (any and grade 3) within 7 days (Day 0 – Day 6) after each vaccination.
- Occurrence, duration, intensity and relation to vaccination of each solicited general symptom (any, grade 3 and related) 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 84), according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence and relationship to vaccination of AEs of specific interest (AESIs) and serious adverse events (SAEs) during the entire study period (up to Day 364)

*Criteria for evaluation were the same as for the primary outcome variables.

Statistical Methods:

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.
- 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) for whom blood samples were taken and assay results were available for antibodies against at least one study vaccine antigen component after vaccination.
- The ATP cohort for persistence 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 entire study) for whom data concerning immunogenicity outcome measures were available. This cohort included subjects for whom assay results were available for antibodies against the study vaccine antigen component at Days 182 and 364.

Analysis of immunogenicity:

The analysis was done on the ATP cohort for immunogenicity and the ATP cohort for persistence.

For each treatment group, the point estimate for SCR, SPR, GMFR and the associated 95% CI was computed at Day 21 after the second dose of the Flu Pan vaccine

The HI immune response to Flu Pan vaccine was described by estimating the following parameters (with 95% confidence intervals [CI]): Geometric Mean Titers (GMT) & SPR on Days 0, 21, 42, 182 & 364 and SCR & SCF on Days 21, 42, 182 & 364. The same parameters were calculated at the same time points for each of the Flu S vaccine strains.

Analysis of safety:

The analysis was based on the Total Vaccinated Cohort.

The incidence of solicited local and general symptoms occurring within 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 events with relationship to vaccination. All solicited local AEs were deemed causally related. Duration of local and general symptoms was also calculated within the same period.

The percentage of subjects with at least one report of an unsolicited AE classified by MedDRA Preferred Term up to 84 days after first dose and up to 63 days after second dose was tabulated with exact 95% CI for the treatment groups. 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 through the entire follow-up period.

Study Population: Healthy male or female 61 years of age or older at the time of first vaccination. A written informed consent was obtained from the subjects prior to study entry.

Number of subjects	Flu 1 Group	Flu 2 Group
Planned, N	84	84
Randomized, N (Total Vaccinated Cohort)	84	84
Completed to Day 21, n (%)	84 (100)	84 (100)

Completed to Day 42, n (%)			84 (100)		84 (100)		
Completed to Day 364, n (%)			84 (100)		84 (100)		
Total Number Subjects Withdrawn, n (%)			0 (0.0)		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 (%)			0 (0.0)		0 (0.0)		
Demographics			Flu 1 Group		Flu 2 Group		
N (Total Vaccinated Cohort)			84		84		
Females:Males			42:42		47:37		
Mean Age, years (SD)			68.9 (4.63)		69.1 (4.70)		
White - Caucasian / European heritage, n (%)			84 (100)		84 (100)		
Primary Efficacy Results: SCR for HI antibodies against Flu A/CAL/09, FluB/Bri/08, Flu A/Uru/07 and Flu A/Bri/07 at Day 21 and Day 42 (ATP cohort for immunogenicity)							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
Flu A/CAL/09	Flu 1	PI(D21)	83	73	88.0	79.0	94.1
		PII(D42)*	83	79	95.2	88.1	98.7
	Flu 2	PI(D21)	84	78	92.9	85.1	97.3
		PII(D42)*	84	82	97.6	91.7	99.7
FluB/Bri/08	Flu 1	PI(D21)*	83	40	48.2	37.1	59.4
	Flu 2	PII(D42)*	84	22	26.2	17.2	36.9
Flu A/Uru/07	Flu 1	PI(D21)*	83	36	43.4	32.5	54.7
	Flu 2	PII(D42)*	84	23	27.4	18.2	38.2
Flu A/Bri/07	Flu 1	PI(D21)*	83	31	37.3	27.0	48.7
	Flu 2	PII(D42)*	84	23	27.4	18.2	38.2
Seroconversion defined as: For initially seronegative subjects, antibody titer $\geq 1:40$ 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 PI(D21)= Post-dose 1 Day 21 PII(D42)= Post-dose 2 Day 42 * Primary Results							
Primary Efficacy Results: SPR for HI antibodies against Flu A/CAL/09, Flu A/Bri/07, Flu A/Uru/07 and FluB/Bri/08 at Day 0, Day 21 and Day 42 (ATP cohort for immunogenicity)							
Antibodies against	Group	Timing	N	SPR			
				n	%	95%CI	
						LL	UL
Flu A/CAL/09	Flu 1	PRE	83	6	7.2	2.7	15.1
		PI(D21)	83	74	89.2	80.4	94.9
		PII(D42)*	83	82	98.8	93.5	100
	Flu 2	PRE	84	7	8.3	3.4	16.4
		PI(D21)	84	81	96.4	89.9	99.3
		PII(D42)*	84	84	100	95.7	100
Flu A/Bri/07	Flu 1	PRE	83	22	26.5	17.4	37.3
		PI(D21)*	83	57	68.7	57.6	78.4
	Flu 2	PRE	84	17	20.2	12.3	30.4
		PII(D42)*	84	52	61.9	50.7	72.3
Flu A/Uru/07	Flu 1	PRE	83	29	34.9	24.8	46.2
		PI(D21)*	83	65	78.3	67.9	86.6
	Flu 2	PRE	84	31	36.9	26.6	48.1
		PII(D42)*	84	54	64.3	53.1	74.4
FluB/Bri/08	Flu 1	PRE	83	56	67.5	56.3	77.4

		PI(D21)*	83	83	100	95.7	100			
	Flu 2	PRE	84	78	92.9	85.1	97.3			
		PII(D42)*	84	84	100	95.7	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 Day 0 PI(D21)= Post-dose 1 Day 21 PII(D42)= Post-dose 2 Day 42 * Primary Results										
Primary Efficacy Results: GMFR for HI antibody titer against Flu A/CAL/09, Flu A/Bri/07, Flu A/Uru/07 and FluB/Bri/08 at each post-vaccination time point (ATP cohort for immunogenicity)										
Antibodies against	Group	Timing	N	GMFR						
				Value	95% CI					
					LL	UL				
Flu A/CAL/09	Flu 1	PI(D21)	83	18.7	14.6	23.8				
		PII(D42)*	83	33.1	26.0	42.1				
	Flu 2	PI(D21)	84	19.8	15.7	25.0				
		PII(D42)*	84	32.2	25.6	40.4				
FluB/Bri/08	Flu 1	PI(D21)*	83	4.7	3.6	6.1				
	Flu 2	PII(D42)*	84	2.1	1.8	2.5				
Flu A/Uru/07	Flu 1	PI(D21)*	83	4.2	3.3	5.4				
	Flu 2	PII(D42)*	84	3.0	2.4	3.9				
Flu A/Bri/07	Flu 1	PI(D21)*	83	3.5	2.9	4.3				
	Flu 2	PII(D42)*	84	2.7	2.2	3.3				
N = Number of subjects with pre- and post-vaccination results available 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PI(D21)= Post-dose 1 Day 21 PII(D42)= Post dose 2 Day 42 * Primary Results										
Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09, Flu A/Bri/07, Flu A/Uru/07 and FluB/Bri/08 (ATP cohort for immunogenicity)										
antibodies against	Group	Timing	N	≥ 1:10				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
Flu A/CAL/09	Flu 1	PRE	83	20	24.1	15.4	34.7	7.4	6.1	9.0
		PI(D21)	83	82	98.8	93.5	100	138.8	107.7	178.9
		PII(D42)	83	83	100	95.7	100	246.1	201.3	300.8
	Flu 2	PRE	84	32	38.1	27.7	49.3	8.5	7.1	10.2
		PI(D21)	84	84	100	95.7	100	168.2	137.5	205.7
		PII(D42)	84	84	100	95.7	100	273.6	231.4	323.4
Flu A/Bri/07	Flu 1	PRE	83	59	71.1	60.1	80.5	15.2	12.4	18.7
		PI(D21)	83	82	98.8	93.5	100	53.6	43.1	66.5
	Flu 2	PRE	84	68	81.0	70.9	88.7	16.0	13.3	19.2
		PII(D42)	84	82	97.6	91.7	99.7	42.5	34.5	52.4
Flu A/Uru/07	Flu 1	PRE	83	58	69.9	58.8	79.5	17.9	14.0	22.8
		PI(D21)	83	79	95.2	88.1	98.7	74.8	57.6	97.1
	Flu 2	PRE	84	57	67.9	56.8	77.6	19.7	15.0	25.8
		PII(D42)	84	80	95.2	88.3	98.7	59.7	44.5	80.0
FluB/Bri/08	Flu 1	PRE	83	76	91.6	83.4	96.5	49.9	38.8	64.1
		PI(D21)	83	83	100	95.7	100	235.0	199.5	276.8
	Flu 2	PRE	84	84	100	95.7	100	115.5	96.3	138.5
		PII(D42)	84	84	100	95.7	100	246.7	208.5	292.0
GMT = geometric mean antibody titer calculated on all subjects N = number of subjects with pre-vaccination results available										

PII(D42)= Post-dose 2 Day 42

For initially seronegative subjects, antibody titer ≥ 1.40 after vaccination

For initially seronegative subjects, antibody titer $\geq 1:40$ after vaccination

PII(D364) = Post-vaccination at Day 364

Secondary Outcome Variable(s): SPR for HI antibodies against Flu A/CAL/7/09, FLU A/Bri/59/07, Flu A/Uru/716/07 and FluB/Bri/60/08 at Day 182 and Day 364 (ATP cohort for persistence)

FluA/B Infection at Day 102 and Day 604 (Viral Load for persistence)				SPR			
						95% CI	
Strain	Group	Timing	N	n	%	LL	UL
Flu A/CAL/7/09	Flu 1	PII(D182)	84	67	79.8	69.6	87.7
		PII(D364)	84	32	38.1	27.7	49.3
	Flu 2	PII(D182)	84	75	89.3	80.6	95.0
		PII(D364)	84	40	47.6	36.6	58.8
FLU A/Bri/59/07	Flu 1	PII(D182)	84	48	57.1	45.9	67.9
		PII(D364)	84	36	42.9	32.1	54.1
	Flu 2	PII(D182)	84	44	52.4	41.2	63.4
		PII(D364)	84	34	40.5	29.9	51.7
Flu A/Uru/716/07	Flu 1	PII(D182)	84	44	52.4	41.2	63.4
		PII(D364)	84	36	42.9	32.1	54.1
	Flu 2	PII(D182)	84	43	51.2	40.0	62.3
		PII(D364)	84	40	47.6	36.6	58.8
FluB/Bri/60/08	Flu 1	PII(D182)	84	84	100	95.7	100
		PII(D364)	84	78	92.9	85.1	97.3
	Flu 2	PII(D182)	84	84	100	95.7	100
		PII(D364)	84	77	91.7	83.6	96.6

PII(D364) = Post-vaccination at Day 364

Secondary Outcome Variable(s): GMFR for HI antibodies against Flu A/CAL/7/09, FLU A/Bri/59/07, Flu A/Uru/716/07 and FluB/Bri/60/08 at Day 182 and Day 364 (ATP cohort for persistence)

				GMFR		
					95% CI	
Strain	Group	Timing	N	Value	LL	UL
Flu A/CAL/7/09	Flu 1	PII(D182)	84	9.6	7.8	11.9
		PII(D364)	84	3.9	3.2	4.8
	Flu 2	PII(D182)	84	9.9	8.1	12.0
		PII(D364)	84	4.0	3.3	4.9
FLU A/Bri/59/07	Flu 1	PII(D182)	84	2.5	2.1	2.9
		PII(D364)	84	1.9	1.7	2.2
	Flu 2	PII(D182)	84	2.3	2.0	2.7
		PII(D364)	84	1.8	1.6	2.1
Flu A/Uru/716/07	Flu 1	PII(D182)	84	2.0	1.6	2.4
		PII(D364)	84	1.6	1.4	1.9
	Flu 2	PII(D182)	84	1.8	1.5	2.1
		PII(D364)	84	1.4	1.2	1.7
FluB/Bri/60/08	Flu 1	PII(D182)	84	4.4	3.6	5.5
		PII(D364)	84	2.1	1.7	2.6
	Flu 2	PII(D182)	84	1.9	1.7	2.2
		PII(D364)	84	1.0	0.9	1.1

GMFR = Geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titer to the Day 0 reciprocal HI

titer												
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit												
PII(D182) = Post-vaccination at Day 182												
PII(D364) = Post-vaccination at Day 364												
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 by vaccine (Total vaccinated cohort)												
Symptom	Product	Intensity	Flu 1 Group					Flu 2 Group				
			N	n	%	95 % CI		N	n	%	95 % CI	
						LL	UL				LL	UL
Dose 1												
Pain	Flu Pan	Any	84	58	69.0	58.0	78.7	84	66	78.6	68.3	86.8
		Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Flu S	Any	84	18	21.4	13.2	31.7	-	-	-	-	-
		Grade 3	84	0	0.0	0.0	4.3	-	-	-	-	-
	Placebo	Any	-	-	-	-	-	84	8	9.5	4.2	17.9
		Grade 3	-	-	-	-	-	84	0	0.0	0.0	4.3
Redness	Flu Pan	Any	84	6	7.1	2.7	14.9	84	11	13.1	6.7	22.2
		>100 mm	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Flu S	Any	84	0	0.0	0.0	4.3	-	-	-	-	-
		>100 mm	84	0	0.0	0.0	4.3	-	-	-	-	-
	Placebo	Any	-	-	-	-	-	84	0	0.0	0.0	4.3
		>100 mm	-	-	-	-	-	84	0	0.0	0.0	4.3
Swelling	Flu Pan	Any	84	13	15.5	8.5	25.0	84	18	21.4	13.2	31.7
		>100 mm	84	0	0.0	0.0	4.3	84	1	1.2	0.0	6.5
	Flu S	Any	84	3	3.6	0.7	10.1	-	-	-	-	-
		>100 mm	84	0	0.0	0.0	4.3	-	-	-	-	-
	Placebo	Any	-	-	-	-	-	84	2	2.4	0.3	8.3
		>100 mm	-	-	-	-	-	84	0	0.0	0.0	4.3
Dose 2												
Pain	Flu Pan	Any	84	49	58.3	47.1	69.0	84	56	66.7	55.5	76.6
		Grade 3	84	0	0.0	0.0	4.3	84	1	1.2	0.0	6.5
	Flu S	Any	-	-	-	-	-	84	26	31.0	21.3	42.0
		Grade 3	-	-	-	-	-	84	0	0.0	0.0	4.3
	Placebo	Any	84	0	0.0	0.0	4.3	-	-	-	-	-
		Grade 3	84	0	0.0	0.0	4.3	-	-	-	-	-
Redness	Flu Pan	Any	84	12	14.3	7.6	23.6	84	15	17.9	10.4	27.7
		>100 mm	84	3	3.6	0.7	10.1	84	2	2.4	0.3	8.3
	Flu S	Any	-	-	-	-	-	84	1	1.2	0.0	6.5
		>100 mm	-	-	-	-	-	84	0	0.0	0.0	4.3
	Placebo	Any	84	0	0.0	0.0	4.3	-	-	-	-	-
		>100 mm	84	0	0.0	0.0	4.3	-	-	-	-	-
Swelling	Flu Pan	Any	84	16	19.0	11.3	29.1	84	15	17.9	10.4	27.7
		>100 mm	84	1	1.2	0.0	6.5	84	0	0.0	0.0	4.3
	Flu S	Any	-	-	-	-	-	84	4	4.8	1.3	11.7
		>100 mm	-	-	-	-	-	84	0	0.0	0.0	4.3
	Placebo	Any	84	0	0.0	0.0	4.3	-	-	-	-	-
		>100 mm	84	0	0.0	0.0	4.3	-	-	-	-	-
Across doses												
Pain	Flu Pan	Any	84	64	76.2	65.7	84.8	84	74	88.1	79.2	94.1
		Grade 3	84	0	0.0	0.0	4.3	84	1	1.2	0.0	6.5
	Flu S	Any	84	18	21.4	13.2	31.7	84	26	31.0	21.3	42.0
		Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Placebo	Any	84	0	0.0	0.0	4.3	84	8	9.5	4.2	17.9
		Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3

Redness	Flu Pan	Any	84	15	17.9	10.4	27.7	84	19	22.6	14.2	33.0
		>100 mm	84	3	3.6	0.7	10.1	84	2	2.4	0.3	8.3
	Flu S	Any	84	0	0.0	0.0	4.3	84	1	1.2	0.0	6.5
		>100 mm	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Placebo	Any	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
		>100 mm	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
Swelling	Flu Pan	Any	84	22	26.2	17.2	36.9	84	27	32.1	22.4	43.2
		>100 mm	84	1	1.2	0.0	6.5	84	1	1.2	0.0	6.5
	Flu S	Any	84	3	3.6	0.7	10.1	84	4	4.8	1.3	11.7
		>100 mm	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Placebo	Any	84	0	0.0	0.0	4.3	84	2	2.4	0.3	8.3
		>100 mm	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3

Any = occurrence of any local symptom regardless of intensity grade

Grade 3 pain = Significant pain at rest; prevented normal activities as assessed by inability to attend/do work

N= number of subjects with the 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 local symptoms during the solicited post-vaccination period (Total Vaccinated cohort)

Solicited symptom	Dose	Group	N		Mean		Median	
Pain	Dose 1	Flu 1 Group	58		2.6		3.0	
		Flu 2 Group	66		2.8		3.0	
	Dose 2	Flu 1 Group	49		2.1		2.0	
		Flu 2 Group	57		2.6		2.0	
Redness	Dose 1	Flu 1 Group	6		1.8		2.0	
		Flu 2 Group	11		2.8		2.0	
	Dose 2	Flu 1 Group	12		2.3		2.0	
		Flu 2 Group	15		2.7		2.0	
Swelling	Dose 1	Flu 1 Group	15		2.1		1.0	
		Flu 2 Group	20		2.6		2.0	
	Dose 2	Flu 1 Group	16		1.8		2.0	
		Flu 2 Group	15		3.1		3.0	

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)

Symptom	Intensity/ relationship	Flu 1 Group					Flu 2 Group				
		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL
Dose 1											
Fatigue	Any	84	14	16.7	9.4	26.4	84	19	22.6	14.2	33.0
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	14	16.7	9.4	26.4	84	13	15.5	8.5	25.0
Headache	Any	84	12	14.3	7.6	23.6	84	15	17.9	10.4	27.7
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	6	7.1	2.7	14.9	84	11	13.1	6.7	22.2
Joint pain at other location	Any	84	7	8.3	3.4	16.4	84	9	10.7	5.0	19.4
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	7	8.3	3.4	16.4	84	7	8.3	3.4	16.4
Muscle aches	Any	84	13	15.5	8.5	25.0	84	16	19.0	11.3	29.1
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	13	15.5	8.5	25.0	84	14	16.7	9.4	26.4
Shivering	Any	84	7	8.3	3.4	16.4	84	10	11.9	5.9	20.8
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3

	Related	84	6	7.1	2.7	14.9	84	8	9.5	4.2	17.9
Sweating	Any	84	1	1.2	0.0	6.5	84	4	4.8	1.3	11.7
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	1	1.2	0.0	6.5	84	2	2.4	0.3	8.3
Temperature/(Axillary) (°C)	≥ 38.0	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	≥ 39.0 - ≤40.0	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
Dose 2											
Fatigue	Any	84	16	19.0	11.3	29.1	84	20	23.8	15.2	34.3
	Grade 3	84	3	3.6	0.7	10.1	84	1	1.2	0.0	6.5
	Related	84	14	16.7	9.4	26.4	84	20	23.8	15.2	34.3
Headache	Any	84	18	21.4	13.2	31.7	84	18	21.4	13.2	31.7
	Grade 3	84	1	1.2	0.0	6.5	84	0	0.0	0.0	4.3
	Related	84	14	16.7	9.4	26.4	84	18	21.4	13.2	31.7
Joint pain at other location	Any	84	10	11.9	5.9	20.8	84	11	13.1	6.7	22.2
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	9	10.7	5.0	19.4	84	11	13.1	6.7	22.2
Muscle aches	Any	84	11	13.1	6.7	22.2	84	18	21.4	13.2	31.7
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	11	13.1	6.7	22.2	84	18	21.4	13.2	31.7
Shivering	Any	84	7	8.3	3.4	16.4	84	10	11.9	5.9	20.8
	Grade 3	84	2	2.4	0.3	8.3	84	0	0.0	0.0	4.3
	Related	84	6	7.1	2.7	14.9	84	10	11.9	5.9	20.8
Sweating	Any	84	1	1.2	0.0	6.5	84	5	6.0	2.0	13.3
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	1	1.2	0.0	6.5	84	5	6.0	2.0	13.3
Temperature/(Axillary) (°C)	≥ 38.0	84	3	3.6	0.7	10.1	84	0	0.0	0.0	4.3
	≥ 39.0 - ≤40.0	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	2	2.4	0.3	8.3	84	0	0.0	0.0	4.3
Across doses											
Fatigue	Any	84	25	29.8	20.3	40.7	84	27	32.1	22.4	43.2
	Grade 3	84	3	3.6	0.7	10.1	84	1	1.2	0.0	6.5
	Related	84	23	27.4	18.2	38.2	84	24	28.6	19.2	39.5
Headache	Any	84	23	27.4	18.2	38.2	84	23	27.4	18.2	38.2
	Grade 3	84	1	1.2	0.0	6.5	84	0	0.0	0.0	4.3
	Related	84	14	16.7	9.4	26.4	84	20	23.8	15.2	34.3
Joint pain at other location	Any	84	13	15.5	8.5	25.0	84	17	20.2	12.3	30.4
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	12	14.3	7.6	23.6	84	16	19.0	11.3	29.1
Muscle aches	Any	84	18	21.4	13.2	31.7	84	26	31.0	21.3	42.0
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	18	21.4	13.2	31.7	84	25	29.8	20.3	40.7
Shivering	Any	84	12	14.3	7.6	23.6	84	16	19.0	11.3	29.1
	Grade 3	84	2	2.4	0.3	8.3	84	0	0.0	0.0	4.3
	Related	84	10	11.9	5.9	20.8	84	14	16.7	9.4	26.4
Sweating	Any	84	2	2.4	0.3	8.3	84	8	9.5	4.2	17.9
	Grade 3	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	2	2.4	0.3	8.3	84	6	7.1	2.7	14.9
Temperature/(Axillary) (°C)	≥ 38.0	84	3	3.6	0.7	10.1	84	0	0.0	0.0	4.3
	≥ 39.0 - ≤40.0	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3
	Related	84	2	2.4	0.3	8.3	84	0	0.0	0.0	4.3
Any = occurrence of any general symptom regardless of intensity grade and relationship to vaccination Grade 3 = prevented normal everyday activities as assessed by inability to attend/do work or required intervention of a physician/healthcare provider											

Related = general symptom assessed by the investigator as causally related to the study vaccination N= number of subjects with the 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 general symptoms during the solicited post-vaccination period (Total Vaccinated cohort)					
Solicited symptom	Dose	Group	N	Mean	Median
Fatigue	Dose 1	Flu 1 Group	14	1.7	1.0
		Flu 2 Group	19	2.2	2.0
	Dose 2	Flu 1 Group	16	1.5	1.0
		Flu 2 Group	20	2.0	1.0
Headache	Dose 1	Flu 1 Group	12	1.1	1.0
		Flu 2 Group	15	1.6	1.0
	Dose 2	Flu 1 Group	18	1.2	1.0
		Flu 2 Group	18	1.8	1.0
Joint pain at other location	Dose 1	Flu 1 Group	7	2.4	2.0
		Flu 2 Group	9	2.0	1.0
	Dose 2	Flu 1 Group	10	1.3	1.0
		Flu 2 Group	11	2.2	1.0
Muscle aches	Dose 1	Flu 1 Group	13	1.7	1.0
		Flu 2 Group	16	1.7	1.5
	Dose 2	Flu 1 Group	11	1.3	1.0
		Flu 2 Group	18	1.7	1.0
Sweating	Dose 1	Flu 1 Group	1	1.0	1.0
		Flu 2 Group	4	2.5	2.0
	Dose 2	Flu 1 Group	1	1.0	1.0
		Flu 2 Group	5	1.2	1.0
Shivering	Dose 1	Flu 1 Group	7	1.1	1.0
		Flu 2 Group	10	1.6	1.0
	Dose 2	Flu 1 Group	7	1.4	1.0
		Flu 2 Group	10	1.4	1.0
Temperature	Dose 2	Flu 1 Group	3	1.0	1.0
N = number of doses with the symptom					
Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of AESI reported up to Day 364 (Total Vaccinated Cohort)					
Most frequent AESIs			Flu 1 Group N = 84	Flu 2 Group N = 84	
Subjects with any AESI(s), n (%)			0 (0.0)	0 (0.0)	
Safety Results: Number (%) of subjects with adverse events up to 84 days after the first vaccination (Total Vaccinated Cohort)					
Most frequent adverse events - On-Therapy (occurring within day 0-83 following vaccination)			Flu 1 Group N = 84	Flu 2 Group N = 84	
Subjects with any AE(s), n (%)			41 (48.8)	41 (48.8)	
Subjects with Grade 3 AE(s), n (%)			6 (7.1)	5 (6.0)	
Subjects with related AE(s), n (%)			7 (8.3)	11 (13.1)	
Nasopharyngitis			15 (17.9)	14 (16.7)	
Oropharyngeal pain			2 (2.4)	6 (7.1)	
Arthralgia			5 (6.0)	2 (2.4)	
Back pain			3 (3.6)	4 (4.8)	
Headache			4 (4.8)	3 (3.6)	
Nausea			2 (2.4)	5 (6.0)	
Pyrexia			4 (4.8)	3 (3.6)	
Cough			2 (2.4)	4 (4.8)	

Dizziness	5 (6.0)	-
Myalgia	2 (2.4)	3 (3.6)
Urinary tract infection	4 (4.8)	-
Diarrhoea	-	3 (3.6)
Abdominal pain upper	-	2 (2.4)
Contusion	-	2 (2.4)
Fatigue	2 (2.4)	-
Feeling cold	-	2 (2.4)
Hypertension	2 (2.4)	-
Injection site pruritus	-	2 (2.4)
Nasal congestion	2 (2.4)	-
Pain in extremity	2 (2.4)	-
-: Adverse event absent or not meeting the selected AEs counting rule: > 30 subjects/treatment group and ≤ 3 groups, the most frequent 10 events in each treatment group are to be listed. 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 = 84	Flu 2 Group N = 84
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	2 (2.4) [0]	3 (3.6) [0]
Cardiac failure	0 (0.0) [0]	1 (1.2) [0]
Hypertension	1 (1.2) [0]	0 (0.0) [0]
Lymphoma	1 (1.2) [0]	0 (0.0) [0]
Prostate cancer	0 (0.0) [0]	1 (1.2) [0]
Retinal detachment	0 (0.0) [0]	1 (1.2) [0]
Fatal SAEs	Flu 1 Group N = 84	Flu 2 Group N = 84
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 first dose of vaccination:

88.0% of subjects in Flu 1 group and 92.9% of subjects in Flu 2 group showed seroconversion against Flu A/CAL/09 strain & 48.2%, 43.4 % and 37.3% of subjects in Flu 1 group showed seroconversion against Flu B/Bri/08, Flu A/Uru/07 and Flu A/Bri/07 strains, respectively. Seroprotection against Flu A/CAL/09 strain was reached for 89.2% of subjects in Flu 1 group and 96.4% of subjects in Flu 2 while 68.7%, 78.3% and 100% of subjects in Flu 1 group reached seroprotective titers against Flu A/Bri/07, Flu A/Uru/07 and Flu B/Bri/08 strains, respectively. The GMFR value was of 18.7 in Flu 1 group and of 19.8 in Flu 2 group against Flu A/CAL/09 strain & of 4.7, of 4.2 and of 3.5 in Flu 1 group against Flu B/Bri/08, Flu A/Uru/07 and Flu A/Bri/07 strains, respectively.

At Day 42 after the second dose of vaccination:

95.2% of subjects in Flu 1 group and 97.6% of subjects in Flu 2 group showed seroconversion against Flu A/CAL/09 strain & 26.2%, 27.4 % and 27.4% of subjects in Flu 2 group showed seroconversion against Flu B/Bri/08, Flu A/Uru/07 and Flu A/Bri/07 strains, respectively. Seroprotection against Flu A/CAL/09 strain was reached for 98.8% of subjects in Flu 1 group and 100% of subjects in Flu 2 while 61.9%, 64.3% and 100% of subjects in Flu 2 group reached seroprotective titers against Flu A/Bri/07, Flu A/Uru/07 and Flu B/Bri/08 strains, respectively. The GMFR value was 33.1 in Flu 1 group and 32.2 in Flu 2 group against Flu A/CAL/09 strain & 2.1, 3.0 and 2.7 in Flu 1 group against Flu B/Bri/08, Flu A/Uru/07 and Flu A/Bri/07 strains, respectively.

During the 84-day follow-up period after the first vaccination, 41 (48.8%) subjects in each group reported at least one unsolicited AE. 2 (2.4%) subjects in the Flu 1 Group and 3 (3.6%) subjects in the Flu 2 Group reported SAEs during the study. These SAEs were assessed by the investigator as unrelated to the study vaccination. No fatal SAEs were reported during the study.