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<b>Study No.:</b> 113525 (FLU D-PAN H1N1-018)
<b>Title:</b> Immunogenicity, safety and reactogenicity of GSK Biologicals' influenza GSK2340272A and <i>Fluarix</i> <sup>TM</sup> 2009-2010 vaccines when co-administered in elderly subjects aged 61 years and older. GSK2340272A (Flu Pan): GlaxoSmithKline (GSK) Biologicals' Pandemic influenza vaccine comprising A/California/7/2009 (H1N1)v-like strain. <i>Fluarix</i> <sup>TM</sup> (Flu S): GSK Biologicals' licensed seasonal Trivalent Influenza Vaccine (TIV)
<b>Rationale:</b> 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. This summary presents results up to Day 21 based on preliminary data and will be updated when additional data become available. As results are based on preliminary data, the numbers may change when the final data become available.
<b>Phase:</b> II
<b>Study Period:</b> 12 September 2009 to 29 October 2009 (data lock point Day 21)
<b>Study Design:</b> Randomized (1:1) study with 2 parallel groups, open for Flu Pan vaccine and observer-blind for Flu S vaccine.
<b>Centers:</b> 2 centers in Sweden
<b>Indication:</b> 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.
<b>Treatment:</b> Study groups were as follows: <ul style="list-style-type: none"> <li>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).</li> <li>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).</li> </ul> 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.
<b>Objectives:</b> <ul style="list-style-type: none"> <li>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.</li> <li>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.</li> </ul>
<b>Primary Outcome/Efficacy Variable:</b> Humoral immune responses in terms of vaccine HI antibodies: <ul style="list-style-type: none"> <li>SCR* at 21 days after the second dose of the Flu Pan vaccine (Day 42) #</li> <li>SPR** at 21 days after the second dose of the Flu Pan vaccine (Day 42) #</li> <li>GMFR*** at 21 days after the second dose of the Flu Pan vaccine (Day 42) #</li> <li>SCR* at 21 days after vaccination with Flu S vaccine<sup>§</sup></li> <li>SPR** at 21 days after vaccination with Flu S vaccine<sup>§</sup></li> <li>GMFR*** (also called seroconversion factor [SCF]) at 21 days after vaccination with Flu S vaccine</li> </ul> *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. **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. ***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.

# Data not available at the time of writing the summary.

\$Data currently available until Day 21; therefore seasonal influenza vaccine results are disclosed for Flu 1 Group only – at this stage, Flu 2 Group has not received the Flu S dose yet.

The CTRS will be updated when additional results become available.

**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.

# Data not available at the time of writing the summary. The CTRS will be updated when results become available.

**Statistical Methods:**

Analyses were performed on the Total Vaccinated Cohort.

- The Total Vaccinated cohort included all vaccinated subjects.

The analyses were performed on preliminary data.

*Analysis of immunogenicity:*

The analysis was done on the Total Vaccinated Cohort.

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 and SCR & SCF on Day 21. 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.

The percentage of subjects with at least one report of an unsolicited AE classified by MedDRA Preferred Term up to 21 days after first dose and 63 days after second dose of vaccine was tabulated with exact 95% CI for the 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 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.

<b>Number of subjects</b>	<b>Flu 1 Group</b>	<b>Flu 2 Group</b>
Planned, N	84	84
Randomized, N (Total Vaccinated Cohort)	84	84
Completed, 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)				
<b>Demographics</b>		<b>Flu 1 Group</b>	<b>Flu 2 Group</b>				
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)				
<b>Primary Efficacy Results: Seroconversion rate (SCR) for HI antibodies against Flu A/CAL/09, Flu A/Bri/07, Flu A/Uru/07, and FluB/Bri/08 at PI(D21) (Total vaccinated cohort)</b>							
Antibodies against	Group	Timing	N	SCR			
				n	%	95% CI	
						LL	UL
<b>Flu A/CAL/09</b>	Flu 1	PI(D21)	84	74	88.1	79.2	94.1
	Flu 2	PI(D21)	84	78	92.9	85.1	97.3
<b>Flu A/Bri/07*</b>	Flu 1	PI(D21)	84	31	36.9	26.6	48.1
<b>Flu A/Uru/07*</b>	Flu 1	PI(D21)	84	36	42.9	32.1	54.1
<b>FluB/Bri/08*</b>	Flu 1	PI(D21)	84	41	48.8	37.7	60.0
Seroconversion defined as: For initially seronegative subjects, antibody titer $\geq 40$ 1/DIL after vaccination For initially seropositive subjects, antibody titer after vaccination $\geq 4$ 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 *Primary outcome results							
<b>Primary Efficacy Results: Seroprotection rates (SPR) for HI antibodies against Flu A/CAL/09, Flu A/Bri/07, Flu A/Uru/07 and FluB/Bri/08 at Day 0 and at PI(D21) (Total vaccinated cohort)</b>							
Antibodies against	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
<b>Flu A/CAL/09</b>	Flu 1	PRE	84	6	7.1	2.7	14.9
		PI(D21)	84	75	89.3	80.6	95.0
	Flu 2	PRE	84	7	8.3	3.4	16.4
		PI(D21)	84	81	96.4	89.9	99.3
<b>Flu A/Bri/07</b>	Flu 1	PRE	84	23	27.4	18.2	38.2
		PI(D21)*	84	58	69.0	58.0	78.7
	Flu 2	PRE	84	17	20.2	12.3	30.4
		PI(D21)*	84	66	78.6	68.3	86.8
<b>Flu A/Uru/07</b>	Flu 1	PRE	84	30	35.7	25.6	46.9
		PI(D21)*	84	66	78.6	68.3	86.8
	Flu 2	PRE	84	31	36.9	26.6	48.1
		PI(D21)*	84	66	78.6	68.3	86.8
<b>FluB/Bri/08</b>	Flu 1	PRE	84	57	67.9	56.8	77.6
		PI(D21)*	84	84	100	95.7	100
	Flu 2	PRE	84	78	92.9	85.1	97.3
		PI(D21)*	84	84	100	95.7	100
N = Number of subjects with available results n/% = Number/percentage of seroprotected subjects (HI titer $\geq 40$ 1/DIL) 95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit PRE =Pre-vaccination at Day 0 PI(D21) =Post-vaccination at Day 21 *Primary outcome results							
<b>Primary Efficacy Results: Seroconversion factor (SCF) for HI antibody titer at PI (D21) (Total vaccinated cohort)</b>							
Antibodies against	Group	Timing	N	SCF			
				Value	95% CI		
					LL	UL	
<b>Flu A/CAL/09</b>	Flu 1	PI(D21)	84	18.8	14.8	23.9	
	Flu 2	PI(D21)	84	19.8	15.7	25.0	
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 PI(D21) =Post-vaccination at Day 21											
<b>Primary Efficacy Results:</b> Seroconversion factor (SCF) for HI antibody titer at PI(D21) (Total vaccinated cohort)											
Antibodies against	Group	Timing	N	SCF							
				Value	95% CI						
					LL	UL					
Flu A/Bri/07	Flu 1	PI(D21)	84	3.5	2.8	4.2					
Flu A/Uru/07	Flu 1	PI(D21)	84	4.1	3.2	5.3					
FluB/Bri/08	Flu 1	PI(D21)	84	4.7	3.7	6.1					
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											
<b>Secondary Outcome Variable(s):</b> Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/09, Flu A/Bri/07, Flu A/Uru/07 and FluB/Bri/08 (Total vaccinated cohort)											
Antibodies against	Group	Timing	N	≥ 10 1/DIL				GMT			
				n	%	95% CI		value	95% CI		
						LL	UL		LL	UL	
Flu A/CAL/09	Flu 1	PRE	84	20	23.8	15.2	34.3	7.4	6.1	9.0	
		PI(D21)	84	83	98.8	93.5	100	139.1	108.2	178.6	
	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	
Flu A/Bri/07	Flu 1	PRE	84	60	71.4	60.5	80.8	15.4	12.6	18.9	
		PI(D21)	84	83	98.8	93.5	100	53.4	43.1	66.1	
	Flu 2	PRE	84	68	81.0	70.9	88.7	16.0	13.3	19.2	
		PI(D21)	84	84	100	95.7	100	168.2	137.5	205.7	
Flu A/Uru/07	Flu 1	PRE	84	59	70.2	59.3	79.7	18.0	14.1	23.0	
		PI(D21)	84	80	95.2	88.3	98.7	74.6	57.6	96.5	
	Flu 2	PRE	84	57	67.9	56.8	77.6	19.7	15.0	25.8	
		PI(D21)	84	84	100	95.7	100	235.8	200.6	277.3	
FluB/Bri/08	Flu 1	PRE	84	77	91.7	83.6	96.6	49.7	38.8	63.8	
		PI(D21)	84	84	100	95.7	100	235.8	200.6	277.3	
	Flu 2	PRE	84	84	100	95.7	100	115.5	96.3	138.5	
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 PRE =Pre-vaccination at Day 0 PI(D21) =Post-vaccination at Day 21											
<b>Secondary Outcome Variable(s):</b> Incidence of solicited local symptoms by maximum grading reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)											
Symptom	Intensity	Flu 1 Group					Flu 2 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Pain	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
Redness	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
Swelling	Any	84	15	17.9	10.4	27.7	84	20	23.8	15.2	34.3
	>100 mm	84	0	0.0	0.0	4.3	84	1	1.2	0.0	6.5
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 or school N= number of subjects with the documented dose n/%= number/percentage of subjects reporting at least once the symptom when the intensity is maximum 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit											
<b>Secondary Outcome Variable(s):</b> Incidence of solicited general symptoms by maximum grading reported during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)											

Symptom	Intensi ty/relat ionshi p	Flu 1 Group					Flu 2 Group				
		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL
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/(A xillary) (°C)	Any	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

Any = occurrence of any local symptom regardless of intensity grade and relationship to vaccination

Grade 3 = 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

N= number of subjects with the documented dose

n/%= number/percentage of subjects reporting at least once the symptom when the intensity is maximum

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

**Secondary Outcome Variable(s):** Percentage of subjects reporting the occurrence of AESI reported during the 21-day (Days 0-20) post-vaccination period (Total vaccinated cohort)

<b>Most frequent adverse events – On-Therapy (occurring within Day 0-20 following vaccination)</b>	<b>Flu 1 Group N = 84</b>	<b>Flu 2 Group N = 84</b>
Subjects with any AESI(s), n (%)	0 (0.0)	0 (0.0)

**Safety Results:** Number (%) of subjects with adverse events (Total vaccinated cohort)

<b>Most frequent adverse events - On-Therapy (occurring within day 0-20 following vaccination)</b>	<b>Flu 1 Group N = 84</b>	<b>Flu 2 Group N = 84</b>
Subjects with any AE(s), n (%)	13 (15.5)	14 (16.7)
-----*	-	4 (4.8)
Back pain	3 (3.6)	-
Contusion	1 (1.2)	2 (2.4)
Oropharyngeal pain	1 (1.2)	2 (2.4)
Headache	2 (2.4)	-
Myalgia	1 (1.2)	1 (1.2)
Nasopharyngitis	-	2 (2.4)
Abdominal pain upper	-	1 (1.2)
Arthralgia	-	1 (1.2)
Arthropod bite	1 (1.2)	-
Chills	-	1 (1.2)
Cough	1 (1.2)	-
Diarrhoea	-	1 (1.2)

Dizziness	1 (1.2)	-
Dry eye	-	1 (1.2)
Epistaxis	-	1 (1.2)
Fatigue	-	1 (1.2)
Gastroenteritis	1 (1.2)	-
Haematuria	1 (1.2)	-
Haemorrhoids	1 (1.2)	-
Hypertension	1 (1.2)	-
Insomnia	-	1 (1.2)
Musculoskeletal pain	1 (1.2)	-
Nausea	-	1 (1.2)
Onychomycosis	-	1 (1.2)
Pain in extremity	1 (1.2)	-
Pruritus	-	1 (1.2)
Pyrexia	1 (1.2)	-
Tinnitus	-	1 (1.2)
Torticollis	-	1 (1.2)

- : Adverse event absent

\* AE not yet classified by MedDRA Preferred Term

**Safety results:** Number (%) of subjects with serious adverse events (Total vaccinated cohort)

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

<b>All SAEs</b>	<b>Flu 1 Group N = 84</b>	<b>Flu 2 Group N = 84</b>
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	1 (1.2) [0]	0 (0.0) [0]
Hypertension	1 (1.2) [0]	0 (0.0) [0]
<b>Fatal SAEs</b>	<b>Flu 1 Group N = 84</b>	<b>Flu 2 Group N = 84</b>
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]

**Conclusion:** At Day 21 after vaccination with Flu S vaccine, 69.0%, 78.6% and 100% of subjects had antibody titers  $\geq$  1:40 against the Flu A/Bri/07, Flu A/Uru/07 and Flu B/Bri/08 strains, respectively.

At 21 days after vaccination, 13 (15.5%) subjects in Flu 1 Group and 14 (16.7%) subjects in Flu 2 Group reported at least one unsolicited adverse event. SAEs were reported by 1 (1.2%) subject in Flu 1 Group; it was not assessed by the investigator as related to study vaccination. No fatal SAEs were reported up to Day 21.

**Publications:** None.

Date updated: 10-Nov-2009