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Study No.: 113462 (FLU D-PAN H1N1-009)
Title: Safety and immunogenicity study of GSK Biologicals' pandemic influenza candidate vaccine (GSK2340272A) in children aged 6 to 35 months. GSK2340272A (Flu 1): GlaxoSmithKline (GSK) Biologicals' Pandemic influenza vaccine comprising 1.9 µg haemagglutinin (HA) from the A/California/7/2009 (H1N1)v-like strain combined with AS03 _B adjuvant. GSK2340272A (Flu 2): GSK Biologicals' Pandemic influenza vaccine comprising 3.75 µg HA from the A/California/7/2009 (H1N1)v-like strain combined with AS03 _A adjuvant.
Rationale: The aim of the study was to assess the safety and immunogenicity of a prime-boost schedule of Flu 1 or Flu 2 vaccines in children aged between 6 and 35 months. Note: This summary presents results up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group 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.
Phase: II
Study Period: 10 September 2009 to 24 Nov 2009 (Data Lock Point Day 42)
Study Design: Randomised, open-label study with two parallel groups. The enrolment was divided in 3 steps: <ul style="list-style-type: none"> - Step 1: Open enrolment of subjects into Flu 1 Group. - Step 2: Open-label, randomised enrolment of subjects in a 1:1 randomisation ratio between Flu 1 Group (completion of enrolment) and Flu 2 Group - Step 3: Open enrolment of subjects into Flu 2 Group
Centres: 5 centres in Spain
Indication: Immunization against A/California/7/2009 (H1N1)v-like influenza of healthy children aged 6 to 35 months.
Treatment: Study groups were as follows: <ul style="list-style-type: none"> • Flu 1 Group: subjects received two doses of Flu 1 vaccine according to a 0, 21-day schedule and will receive one dose as a booster at Month 6. • Flu 2 Group: subjects received two doses of Flu 2 vaccine according to a 0, 21-day schedule and will receive one dose as a booster at Month 6. <p>The vaccine was administered intramuscularly in the deltoid region of the arm or in the anterolateral part of the thigh if the subject was < 12 months at the entry of the study.</p>
Objectives: <ul style="list-style-type: none"> • To evaluate the superiority in terms of vaccine homologous haemagglutination inhibition (HI) antibody response of a single dose of Flu 1 vaccine administered as a 6-month homologous booster for subjects who received 2 doses of Flu 1 vaccine primary vaccination compared to the response after the first dose. <p><i>Criterion for success:</i> <i>Lower limit of the two-sided 95% confidence interval (CI) for the geometric mean titre (GMT) ratio (at seven days after a 6-month booster after 2- dose primary vaccination/21 days after the first dose) > 2.0.</i></p> <ul style="list-style-type: none"> • To evaluate the superiority in terms of vaccine homologous HI antibody response of a single dose of Flu 2 vaccine administered as a 6-month homologous booster for subjects who received 2 doses of Flu 2 vaccine primary vaccination compared to the response after the first dose. <p><i>Criterion for success:</i> <i>Lower limit of the two-sided 95% CI for the GMT ratio (at seven days after a 6-month booster after 2-dose primary vaccination/21 days after the first dose) > 2.0.</i></p>
Primary Outcome/Efficacy Variable: <i>Immunogenicity</i> <ul style="list-style-type: none"> • For the humoral immune response in terms of HI antibodies, the following parameters were calculated with 95% CIs: Observed variable: <ul style="list-style-type: none"> - H1N1 HI antibodies on Day 0, on Day 21, on Day 42, and at Month 6+7 Days#. Derived variable: <ul style="list-style-type: none"> - GMTs of H1N1 HI antibodies - SCR* on Day 42 - SPR** on Day 42

- Geometric Mean Fold Rise (GMFR)^{***} on Day 42

*SCR was defined as the percentage of vaccinees that have either a pre-vaccination titre < 1:10 and a postvaccination titre ≥ 1:40, or a pre-vaccination titre ≥ 1:10 and at least a 4-fold increase in post-vaccination titre. The Committee for Medicinal Products for Human Use (CHMP) criterion was fulfilled if the point estimate for SCR was > 40% in subjects 18 to 60 years of age. The same CHMP criterion was used for this paediatric study.

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

***GMFR or Seroconversion factor (SCF) was defined as the fold increase in serum HI GMTs post-vaccination compared to pre-vaccination. The criterion was fulfilled if the point estimate for GMFR was > 2.5 in subjects 18 to 60 years of age. The same CHMP criterion was used for this paediatric study.

At the time of writing this summary, data were only available up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group. This summary will be updated when additional results become available.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

- For the humoral immune response in terms of HI antibodies, the following parameters were calculated with 95% CIs:

Observed variable:

- H1N1 HI antibodies on Day 0, Day 21, Day 42, at Month 6[#], Month 6+7 Days[#], Month 12[#], and Month 18[#].

Derived variables:

- GMTs and seropositivity rates;
- SCRs;
- SPRs
- Seroconversion factors (SCFs)
- Booster Seroconversion rate (Booster SCR)^{*} #
- Booster Seroconversion factor (Booster SCF)^{**} #

* Booster SCR: For seronegative subjects at pre-booster (Month 6), antibody titre ≥ 1:40 at postbooster time point(s). For seropositive subjects at pre-booster (Month 6), antibody titre at post-booster time point(s) ≥ 4-fold the pre-boost antibody titre.

** Booster SCF was defined as the fold increase in serum H1N1 HI antibody GMTs post-booster compared to pre-booster (Month 6).

The same analyses as above were performed in each age stratum (6 to 11 months, 12 to 23 months, and 24 to 35 months).

- For the humoral immune response in terms of neutralising antibodies (in a subset of subjects randomly selected), the following parameters[§] were calculated with 95% CIs:

Observed variable:

- Serum neutralising antibody titres on Day 0, Day 21, Day 42, at Month 6, Month 6+7 Days, Month 12, and Month 18.

Derived variables:

- GMTs of serum neutralising antibody titres;
- SCRs;
- Booster SCR.

Safety:

- 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 six subsequent days after each vaccination up to and inclusive the Month 6[#] administration.
- Percentage, intensity and relationship to vaccination of unsolicited adverse events (AEs) during the 21-day follow-up period after the first vaccination, during the 62-day follow-up period after the second vaccination[#], and during the 30-day follow-up period after the booster vaccination[#].
- Occurrence of medically-attended events (MAEs), adverse events of specific interest (AESIs)/potential immune-mediated disease (pIMDs), serious adverse events (SAEs) and relationship to vaccination[§] during the entire study period[#].
- The number and percentage of subjects with normal or abnormal values of biochemical parameters on Day 0, Day 21, Day 42, at Month 6, and Month 6+7 Days.*

At the time of writing this summary, data were available up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group

only. This summary will be updated when additional results become available.

§ Not available at the time of writing this summary.

* Available only for Flu 2 Group, at Day 21.

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 analysis of immunogenicity was done as a descriptive analysis of the humoral immune response in children 6 to 35 months of age and also within age sub-strata: 6 to 11 months, 12 to 23 months, and 24 to 35 months.

For the humoral immune response in terms of H1N1 HI antibodies (with 95% CIs):

- Seropositivity rates and GMTs of H1N1 HI antibody titres at Day 0, Day 21 for both groups, and Day 42 for Flu 1 Group.
- SCR at Day 21 for both groups, and Day 42 for Flu 1 Group.
- SCF at Day 21 for both groups, and Day 42 for Flu 1 Group.
- SPR at Day 0 and Day 21 for both groups, and Day 42 for Flu 1 Group.

Analysis of safety:

The analysis was done on the Total Vaccinated cohort.

The percentage of subjects reporting each individual solicited local and general symptom during the solicited follow-up period, i.e., day of vaccination and six subsequent days after each primary vaccination dose 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) preferred terms during the 21-day follow-up period after each primary vaccination was tabulated with exact 95% CI. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs assessed by the investigator as related to vaccination.

The proportion of subjects with MAEs, and with AESIs/pIMDs reported after each primary vaccination was tabulated up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group.

SAEs reported up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group and classified by the MedDRA preferred terms were tabulated.

Study Population: Healthy children, male or female, aged between 6 and 35 months at the time of first study vaccination. A written informed consent was obtained from the parent(s) or legally acceptable representative(s) of the subject prior to study entry.

Number of Subjects: (Study Step 1)	Flu 1 Group			
	Total	6-11M	12-23M	24-35M
Planned, N	51	17	17	17
Randomised, N (Total Vaccinated cohort)	51	17	17	17
Completed at Day 21, n (%)	51 (100)	17 (100)	17 (100)	17 (100)
Completed at Day 42, n (%)	51 (100)	17 (100)	17 (100)	17 (100)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Adverse Events n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not applicable	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Demographics	Flu 1 Group			
	Total	6-11M	12-23M	24-35M
N (Total Vaccinated cohort)	51	17	17	17
Females: Males	20:31	8:9	6:11	6:11
Mean Age, months (SD)	18.9 (9.35)	8.8 (1.39)	17.6 (2.91)	30.3 (3.74)
White - Caucasian / European heritage, n (%)	48 (94.1)	15 (88.2)	17 (100)	16 (94.1)
Number of subjects	Flu 2 Group			
	Total	6-11M	12-23M	24-35M
Planned, N	102	34	34	34
Randomised, N (Total Vaccinated Cohort)	51	16	19	16
Completed at Day 21, n (%)	51 (100)	16 (100)	19 (100)	16 (100)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Withdrawn due to Adverse Events, n (%)				0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				
Withdrawn due to Lack of Efficacy, n (%)				Not applicable	Not applicable	Not applicable	Not applicable				
Withdrawn for other reasons, n (%)				0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				
Demographics				Total	6-11M	12-23M	24-35M				
N (Total Vaccinated Cohort)				51	16	19	16				
Females:Males				25:26	7:9	10:9	8:8				
Mean Age, months (SD)				19.5 (8.95)	9.4 (1.31)	18.5 (2.78)	30.8 (3.17)				
White - caucasian / european heritage, n (%)				44 (86.3)	16 (100)	15 (78.9)	13 (81.3)				
Primary Efficacy Results: Seropositivity rates and GMTs for A/California/7/2009 antibodies (Total Vaccinated cohort)											
				≥ 1:10		GMT					
				95% CI		95% CI					
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	
A/California /7/2009	Flu 1	PRE	51	3	5.9	1.2	16.2	5.97	4.74	7.51	
		PI(D21)	50	50	100	92.9	100	340.64	278.73	416.31	
		PII(D42)	50	50	100	92.9	100	1939.99	1687.75	2229.94	
	Flu 2	PRE	51	6	11.8	4.4	23.9	6.7	5.2	8.6	
		PI(D21)	50	50	100	92.9	100	317.8	263.3	383.6	
<p>GMT = geometric mean antibody titre calculated on all subjects N = number of subjects with available results n (%) = number (percentage) of subjects with titre within the specified range 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = Pre-vaccination (Day 0) PI (D21) = Post-dose 1 (Day 21) PII(D42)= Post-dose 2 (Day 42)</p>											
Primary Efficacy Results: SCRs for HI antibodies against A/California/7/2009(H1N1) (Total Vaccinated cohort)											
						SCR					
								95% CI			
Strain	Group	Timing	N	n	%	LL	UL	LL	UL	UL	
Flu A/CAL/7/09.HA1 Ab	Flu 1	PI(D21)	50	49	98.0	89.4	99.9				
		PII(D42)*	50	50	100	92.9	100				
	Flu 2	PI(D21)	50	49	98.0	89.4	99.9				
<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 PI (D21) = Post-dose 1 (Day 21) PII(D42)= Post-dose 2 (Day 42) * Primary outcome variable</p>											
Primary Efficacy Results: SPRs for HI antibodies against A/California/7/2009(H1N1) (Total Vaccinated cohort)											
						SPR					
								95% CI			
Strain	Group	Timing	N	n	%	LL	UL	LL	UL	UL	
A/California/7/2009(H1N1)	Flu 1	PRE	51	2	3.9	0.5	13.5				
		PI(D21)	50	50	100	92.9	100				
		PII(D42)*	50	50	100	92.9	100				
	Flu 2	PRE	51	4	7.8	2.2	18.9				
		PI(D21)	50	50	100	92.9	100				
<p>N = Number of subjects with available results n (%) = Number (percentage) of seroprotected subjects (HI titre ≥ 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)</p>											

* Primary outcome variable											
Primary Efficacy Results: SCFs for HI antibody titre at each post-vaccination time point (Total Vaccinated cohort)											
				SCF							
				95% CI							
Vaccine strain	Group	Timing	N	Value	LL	UL					
Flu A/CAL/7/09.HA1 Ab (1/DIL)	Flu 1	PI(D21)	50	56.89	44.68	72.45					
		PII(D42)*	50	324.01	244.63	429.15					
	Flu 2	PI(D21)	50	47.2	36.6	60.9					
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 PI (D21) = Post-dose 1 (Day 21) PII(D42)= Post-dose 2 (Day 42) * Primary outcome variable											
Secondary Outcome Variable(s): Seropositivity rates and GMTs for A/California/7/2009 antibodies, by age stratum (Total Vaccinated cohort)											
				≥ 1:10		GMT					
				95% CI		95% CI					
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
A/California/7/2009	Flu 1	6-11M	PRE	17	3	17.6	3.8	43.4	8.50	4.19	17.24
			PI(D21)	17	17	100	80.5	100	376.88	238.23	596.23
			PII(D42)	17	17	100	80.5	100	1885.40	1478.61	2404.09
		12-23M	PRE	17	0	0.0	0.0	19.5	5.00	5.00	5.00
			PI(D21)	17	17	100	80.5	100	384.46	278.61	530.51
			PII(D42)	16	16	100	79.4	100	1890.21	1410.18	2533.65
	24-35M	PRE	17	0	0.0	0.0	19.5	5.00	5.00	5.00	
		PI(D21)	16	16	100	79.4	100	269.04	203.70	355.34	
		PII(D42)	17	17	100	80.5	100	2045.61	1603.50	2609.62	
	Flu 2	6-11M	PRE	16	1	6.3	0.2	30.2	5.9	4.1	8.6
			PI(D21)	16	16	100	79.4	100	293.3	216.1	398.1
		12-23M	PRE	19	1	5.3	0.1	26.0	5.3	4.7	5.9
PI(D21)			18	18	100	81.5	100	326.3	222.1	479.5	
24-35M		PRE	16	4	25.0	7.3	52.4	10.0	4.8	20.7	
		PI(D21)	16	16	100	79.4	100	334.2	237.1	471.0	
6-11M = Children aged between and including 6 months to 11 months 12-23M = Children aged between and including 12 months to 23 months 24-35M = Children aged between and including 24 months to 35 months GMT = geometric mean antibody titre calculated on all subjects N = number of subjects with available results n (%) = number (percentage) of subjects with titre within the specified range 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE= pre-vaccination (Day 0) PI (D21) = Post-dose 1 (Day 21) PII(D42)= Post-dose 2 (Day 42)											
Secondary Outcome Variable(s): SCRs for HI antibody titre by age stratum (Total Vaccinated cohort)											
				SCR							
				95% CI							
Vaccine strain	Group	Sub-group	Timing	N	n	%	LL	UL			
A/California/7/2009	Flu 1	6-11M	PI(D21)	17	16	94.1	71.3	99.9			
			PII(D42)	17	17	100	80.5	100			
		12-23M	PI(D21)	17	17	100	80.5	100			
			PII(D42)	16	16	100	79.4	100			
		24-35M	PI(D21)	16	16	100	79.4	100			
			PII(D42)	17	17	100	80.5	100			

	Flu 2	6-11M	PI(D21)	16	16	100	79.4	100
		12-23M	PI(D21)	18	18	100	81.5	100
		24-35M	PI(D21)	16	15	93.8	69.8	99.8

6-11M = Children aged between and including 6 months to 11 months
12-23M = Children aged between and including 12 months to 23 months
24-35M = Children aged between and including 24 months to 35 months

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

PI (D21) = Post-dose 1 (Day 21)

PII(D42)= Post-dose 2 (Day 42)

Secondary Outcome Variable(s): SPRs for HI antibodies against A/California/7/2009 at each time point, by age stratum (Total Vaccinated cohort)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
A/California/7/2009	Flu 1	6-11M	PRE	17	2	11.8	1.5	36.4
			PI(D21)	17	17	100	80.5	100
			PII(D42)	17	17	100	80.5	100
		12-23M	PRE	17	0	0.0	0.0	19.5
			PI(D21)	17	17	100	80.5	100
			PII(D42)	16	16	100	79.4	100
		24-35M	PRE	17	0	0.0	0.0	19.5
			PI(D21)	16	16	100	79.4	100
			PII(D42)	17	17	100	80.5	100
	Flu 2	6-11M	PRE	16	1	6.3	0.2	30.2
			PI(D21)	16	16	100	79.4	100
		12-23M	PRE	19	0	0.0	0.0	17.6
			PI(D21)	18	18	100	81.5	100
		24-35M	PRE	16	3	18.8	4.0	45.6
			PI(D21)	16	16	100	79.4	100

6-11M = Children aged between and including 6 months to 11 months
12-23M = Children aged between and including 12 months to 23 months
24-35M = Children aged between and including 24 months to 35 months

N = Number of subjects with available results

n (%) = Number (percentage) of seroprotected subjects (HI titre \geq 1:40)

95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

PRE = Pre-vaccination (Day 0)

PI (D21) = Post-dose 1 (Day 21)

PII(D42)= Post-dose 2 (Day 42)

Secondary Outcome Variable(s): SCFs for HI antibody titre, by age stratum (Total Vaccinated cohort)

					SCF		
					95% CI		
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
A/California/7/2009 (1/DIL)	Flu 1	6-11M	PI(D21)	17	44.4	24.1	81.5
			PII(D42)	17	221.9	102.6	480.8
		12-23M	PI(D21)	17	76.9	55.7	106.1
			PII(D42)	16	378.0	282.0	506.7
		24-35M	PI(D21)	16	53.8	40.7	71.1
			PII(D42)	17	409.1	320.7	521.9
	Flu 2	6-11M	PI(D21)	16	49.3	37.5	64.9
		12-23M	PI(D21)	18	61.6	39.2	96.9

		24-35M	PI(D21)	16	33.4	18.6	60.2
6-11M = Children aged between and including 6 months to 11 months 12-23M = Children aged between and including 12 months to 23 months 24-35M = Children aged between and including 24 months to 35 months 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-dose 1 (Day 21) PII(D42)= Post-dose 2 (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 overall (Total Vaccinated cohort)							
				Flu 1 Group			
				95 % CI			
Symptom	Intensity	N	n	%	LL	UL	
Dose 1							
Pain	Any	51	16	31.4	19.1	45.9	
	Grade 3	51	0	0.0	0.0	7.0	
Redness	Any	51	10	19.6	9.8	33.1	
	> 50 mm	51	0	0.0	0.0	7.0	
Swelling	Any	51	8	15.7	7.0	28.6	
	> 50 mm	51	0	0.0	0.0	7.0	
Dose 2							
Pain	Any	51	21	41.2	27.6	55.8	
	Grade 3	51	2	3.9	0.5	13.5	
Redness	Any	51	15	29.4	17.5	43.8	
	> 50 mm	51	1	2.0	0.0	10.4	
Swelling	Any	51	12	23.5	12.8	37.5	
	> 50 mm	51	0	0.0	0.0	7.0	
Across doses							
Pain	Any	51	25	49.0	34.8	63.4	
	Grade 3	51	2	3.9	0.5	13.5	
Redness	Any	51	19	37.3	24.1	51.9	
	> 50 mm	51	1	2.0	0.0	10.4	
Swelling	Any	51	18	35.3	22.4	49.9	
	> 50 mm	51	0	0.0	0.0	7.0	
				Flu 2 Group			
				95 % CI			
Symptom	Intensity	N	n	%	LL	UL	
Dose 1							
Pain	Any	51	30	58.8	44.2	72.4	
	Grade 3	51	0	0.0	0.0	7.0	
Redness	Any	51	16	31.4	19.1	45.9	
	> 50 mm	51	2	3.9	0.5	13.5	
Swelling	Any	51	10	19.6	9.8	33.1	
	> 50 mm	51	1	2.0	0.0	10.4	
N= number of subjects with the administered dose n (%)= number (percentage) of subjects reporting at least once the symptom 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit Any= occurrence of any local symptom regardless of intensity grade Grade 3 pain= cried when limb was moved/spontaneously painful							
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 (Total Vaccinated cohort)							
				Flu 1 Group			
				95 % CI			
Symptom	Intensity/ Relationship	N	n	%	LL	UL	

Dose 1						
Drowsiness	Any	51	8	15.7	7.0	28.6
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	4	7.8	2.2	18.9
Irritability	Any	51	14	27.5	15.9	41.7
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	11	21.6	11.3	35.3
Loss of appetite	Any	51	9	17.6	8.4	30.9
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	5	9.8	3.3	21.4
Temperature/(Axillary) (°C)	≥ 37.5	51	8	15.7	7.0	28.6
	> 39	51	0	0.0	0.0	7.0
	Related	51	7	13.7	5.7	26.3
Dose 2						
Drowsiness	Any	51	19	37.3	24.1	51.9
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	18	35.3	22.4	49.9
Irritability	Any	51	20	39.2	25.8	53.9
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	19	37.3	24.1	51.9
Loss of appetite	Any	51	21	41.2	27.6	55.8
	Grade 3	51	2	3.9	0.5	13.5
	Related	51	20	39.2	25.8	53.9
Temperature/(Axillary) (°C)	≥ 37.5	51	35	68.6	54.1	80.9
	> 39	51	2	3.9	0.5	13.5
	Related	51	30	58.8	44.2	72.4
Across doses						
Drowsiness	Any	51	21	41.2	27.6	55.8
	Grade 3	51	0	0.0	0.0	7.0
	Related	51	19	37.3	24.1	51.9
Irritability	Any	51	28	54.9	40.3	68.9
	Grade 3	51	2	3.9	0.5	13.5
	Related	51	25	49.0	34.8	63.4
Loss of appetite	Any	51	25	49.0	34.8	63.4
	Grade 3	51	2	3.9	0.5	13.5
	Related	51	23	45.1	31.1	59.7
Temperature/(Axillary) (°C)	≥ 37.5	51	37	72.5	58.3	84.1
	> 39	51	2	3.9	0.5	13.5
	Related	51	31	60.8	46.1	74.2
Flu 2 Group						
				95 % CI		
Symptom	Intensity/ Relationship	N	n	%	LL	UL
Dose 1						
Drowsiness	Any	51	14	27.5	15.9	41.7
	Grade 3	51	2	3.9	0.5	13.5
	Related	51	11	21.6	11.3	35.3
Irritability	Any	51	16	31.4	19.1	45.9
	Grade 3	51	5	9.8	3.3	21.4
	Related	51	12	23.5	12.8	37.5
Loss of appetite	Any	51	17	33.3	20.8	47.9
	Grade 3	51	1	2.0	0.0	10.4
	Related	51	11	21.6	11.3	35.3
Temperature/(Axillary) (°C)	≥ 37.5	51	13	25.5	14.3	39.6
	> 39	51	1	2.0	0.0	10.4

	Related	51	10	19.6	9.8	33.1
<p>N= number of subjects with the administered dose n (%)= number (percentage) of subjects reporting at least once the symptom 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit Any= occurrence of any general symptom regardless of intensity grade Grade 3= general symptom that prevented normal activity Grade 3 Loss of appetite: not eating at all Related= general symptom assessed by the investigator as causally related to the study vaccination</p>						
Secondary Outcome Variable(s): Percentage of subjects reporting medically-attended events (MAEs), up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group (Total Vaccinated cohort)						
Most frequent MAEs occurring within the 42-day (Days 0-41) post-vaccination period			Flu 1 Group N=51			
Subjects with any MAEs, n (%)			32 (62.7)			
Conjunctivitis			1 (2.0)			
Diarrhoea			1 (2.0)			
Pyrexia			2 (3.9)			
Bronchitis			2 (3.9)			
Gastroenteritis			3 (5.9)			
Laryngitis			5 (9.8)			
Otitis media			1 (2.0)			
Otitis media acute			2 (3.9)			
Pharyngitis			1 (2.0)			
Respiratory tract infection			3 (5.9)			
Upper respiratory tract infection			17 (33.3)			
Injury			1 (2.0)			
Bronchial hyperreactivity			1 (2.0)			
Rash			1 (2.0)			
Skin lesion			1 (2.0)			
Most frequent MAEs occurring within the 21-day (Days 0-20) post-vaccination period			Flu 2 Group N = 51			
Subjects with any MAEs, n (%)			15 (29.4)			
Ear pain			1 (2.0)			
Conjunctival hyperaemia			1 (2.0)			
Ear infection			1 (2.0)			
Herpangina			1 (2.0)			
Pharyngitis			1 (2.0)			
Respiratory tract infection			1 (2.0)			
Tonsillitis			1 (2.0)			
Upper respiratory tract infection			7 (13.7)			
Asthma			1 (2.0)			
Dermatitis allergic			1 (2.0)			
Prurigo			1 (2.0)			
Urticaria			1 (2.0)			
Secondary Outcome Variable(s): Occurrence of AE of Specific Interest (AESI) / potential Immune-Mediated Diseases (pIMDs) up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group (Total Vaccinated cohort)						
Most frequent AESI / pIMDs occurring within the 42-day (Days 0-41) post-vaccination period			Flu 1 Group N=51			
Subjects with any AESI(s)/pIMD(s)			0 (0.0)			
Secondary Outcome Variable(s): Occurrence of AE of Specific Interest (AESI) / potential Immune-Mediated Diseases (pIMDs) up to Day 21 (Total Vaccinated cohort)						
Most frequent AESI / pIMDs occurring within the 21-day (Days 0-20) post-vaccination period			Flu 2 Group N=51			
Subjects with any AESI(s)/pIMD(s)			0 (0.0)			
Secondary Outcome Variable(s): Distribution of haematology and biochemistry with respect to normal laboratory ranges (Total Vaccinated cohort)						

		Flu 2 Group N = 51								
			Unknown		Below		Within		Above	
Laboratory parameter	Timing	N	n	%	n	%	n	%	n	%
ALAT	PRE	44	2	4.5	0	0.0	42	95.5	0	0.0
	PI(D21)	50	1	2.0	0	0.0	48	96.0	1	2.0
ASAT	PRE	44	2	4.5	0	0.0	42	95.5	0	0.0
	PI(D21)	50	2	4.0	0	0.0	47	94.0	1	2.0
Bilirubin	PRE	44	2	4.5	0	0.0	42	95.5	0	0.0
	PI(D21)	50	1	2.0	0	0.0	49	98.0	0	0.0
Creatinine	PRE	44	2	4.5	13	29.5	29	65.9	0	0.0
	PI(D21)	50	2	4.0	18	36.0	29	58.0	1	2.0
BUN	PRE	44	2	4.5	0	0.0	33	75.0	9	20.5
	PI(D21)	50	1	2.0	0	0.0	35	70.0	14	28.0
<p>N = number of subjects with laboratory results for the specified time point and laboratory parameter n/% = number/percentage of subjects in a given category Unknown = value unknown for the specified time point and laboratory parameter Below = value below the laboratory reference range defined for the specified time point and laboratory parameter Within = value within the laboratory reference range defined for the specified time point and laboratory parameter Above = value above the laboratory reference range defined for the specified time point and laboratory parameter ALAT = Alanine Amino Transferase ASAT = Aspartate Amino Transferase BUN = Blood Urea Nitrogen PRE = Pre-vaccination (Day 0) PI (D21) = Post-dose 1 (Day 21)</p>										
Safety results: Number (%) of subjects with unsolicited adverse events up to Day 42 for Flu 1 Group and up to Day 21 for Flu 2 Group (Total Vaccinated cohort)										
Most frequent adverse events - On-Therapy (occurring within Day 0-41 following vaccination)							Flu 1 Group N = 51			
Subjects with any AE(s), n (%)							41 (80.4)			
Subjects with grade 3 AE(s), n (%)							8 (15.7)			
Subjects with related AE(s), n (%)							4 (7.8)			
Upper respiratory tract infection							24 (47.1)			
Diarrhoea							5 (9.8)			
Laryngitis							5 (9.8)			
Otitis media acute							4 (7.8)			
Gastroenteritis							3 (5.9)			
Nasal congestion							3 (5.9)			
Pyrexia							3 (5.9)			
Rash							3 (5.9)			
Respiratory tract infection							3 (5.9)			
-----*							2 (3.9)			
Bronchitis							2 (3.9)			
Cough							2 (3.9)			
Most frequent adverse events - On-Therapy (occurring within day 0-20 following vaccination)							Flu 2 Group N = 51			
Subjects with any AE(s), n (%)							26 (51.0)			
Subjects with grade 3 AE(s), n (%)							1 (2.0)			
Subjects with related AE(s), n (%)							3 (5.9)			
Upper respiratory tract infection							8 (15.7)			
Diarrhoea							3 (5.9)			
Pyrexia							3 (5.9)			
Vomiting							3 (5.9)			
Urticaria							2 (3.9)			

Abnormal faeces	1 (2.0)
Arthropod bite	1 (2.0)
Asthma	1 (2.0)
Bronchitis	1 (2.0)
Cold sweat	1 (2.0)
Conjunctival hyperaemia	1 (2.0)
Cough	1 (2.0)
Dermatitis allergic	1 (2.0)
Ear infection	1 (2.0)
Ear pain	1 (2.0)
Epistaxis	1 (2.0)
Gastrointestinal disorder	1 (2.0)
Herpangina	1 (2.0)
Injection site reaction	1 (2.0)
Nasal congestion	1 (2.0)
Pharyngitis	1 (2.0)
Prurigo	1 (2.0)
Respiratory tract infection	1 (2.0)
Rhinitis	1 (2.0)
Tonsillitis	1 (2.0)
Grade 3= event that prevented normal activities Related= event assessed by the investigator as causally related to the study vaccination Detail of unsolicited AE counting rule: > 30 subjects per treatment group and ≤ 3 groups, display the most frequent 10 events in each group * AE not yet classified by MedDRA Preferred Term	
Safety results: Number (%) of subjects with serious adverse events reported up to Day 42 for Flu 1 Group (Total Vaccinated cohort)	
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]	
All SAEs	Flu 1 Group N= 51
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]
Fatal SAEs	Flu 1 Group N= 51
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]
Safety results: Number (%) of subjects with serious adverse events reported up to Day 21 for Flu 2 Group (Total Vaccinated cohort)	
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]	
All SAEs	Flu 2 Group N = 51
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]
Fatal SAEs	Flu 2 Group N = 51
Subjects with fatal sae(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]

Conclusion: At Day 21, the GMT values for antibodies against A/California/7/2009 were 340.64 in Flu 1 Group and 317.8 in Flu 2 Group. At Day 42, the GMT value was 1939.99 in Flu 1 Group. At Day 42, all subjects of Flu 1 Group have shown seroconversion and reached HI antibody titres usually accepted as indicating seroprotection The SCF at Day 42 was of 324.01.
Up to Day 42, at least one unsolicited AE was reported for 41 (80.4%) subjects in Flu 1 Group. Up to Day 21, at least one unsolicited AE was reported for 26 (51.0%) subjects in Flu 2 Group. No SAE was reported during this part of the study.

Publications: None

Date updated: 15-January-2010