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Study No.: 113638 (FLU D-PAN H1N1-023)
Title: Safety and immunogenicity study of GSK Biologicals' pandemic influenza candidate vaccine (GSK2340272A) in children aged 3 to 17 years GSK2340272A (Flu): GlaxoSmithKline (GSK) Biologicals' A/California/7/2009 (H1N1)v-like vaccine adjuvanted with AS03
Rationale: The aim of this study was to assess the safety and immunogenicity of a prime-boost schedule of Flu vaccine in children aged between 3 to 17 years. This summary presents results up to Day 42 and will be updated when additional data become available.
Phase: III
Study Period: 29 September 2009 to 04-January-2010 (data lock point Day 42)
Study Design: Non-randomised, open-label study with 2 parallel groups.
Centres: 8 centres in Germany
Indication: Immunization against A/California/7/2009 (H1N1)v-like influenza of healthy children aged 3 to 17 years
Treatment: Study groups were as follows: <ul style="list-style-type: none"> • Flu BS1 Group: subjects received 2 doses of Flu vaccine (at Day 0 and Day 21) and will receive a third dose at Month 6. In this group, blood sampling followed the schedule 1: <ul style="list-style-type: none"> – On Day 0 (before the first vaccination); – On Day 21 (before the second vaccination); – On Day 42 (21 days after the second vaccination); – At Month 6 (six months after the first vaccination); • Flu BS2 Group: subjects received 2 doses of Flu vaccine (at Day 0 and Day 21) and will receive a third dose at Month 6. In this group, blood sampling followed the schedule 2: <ul style="list-style-type: none"> – On Day 42 (21 days after the second vaccination); – At Month 6 (six months after the first vaccination); – At Month 6+7 Days (seven days after the booster vaccination); – At Month 12 (one year after the first vaccination). <p>Subjects of both groups were also stratified by age (3-5 years, 6-9 years, and 10-17 years) and for some analysis the 2 groups were pooled (Flu pooled Group). Flu vaccine was administered intramuscularly, in the deltoid region of the arm.</p>
Objectives: <ul style="list-style-type: none"> • To evaluate the humoral immune response after 2 primary administrations of the Flu vaccine that meet or exceeds the European Medicines Agency (EMA) (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 vaccine in children aged 3 to 17 years. <i>Criterion for success:</i> The CHMP criteria are fulfilled if the point estimate for SCR is > 40%, the point estimate for SPR is > 70%, and the point estimate for GMFR is > 2.5 in children aged 3 to 17 years. • To evaluate the superiority in terms of vaccine virus homologous hemagglutination inhibition (HI) antibody response of a single dose of the Flu vaccine administered as a 6-month booster after 2-dose primary vaccination compared to the response after the first dose of primary vaccination. <i>Criterion for success:</i> If the lower limit of the two-sided 95% confidence interval (CI) for the geometric mean titre (GMT) ratio (at 7 days after a 6-month booster after 2-dose primary vaccination/21 days after the first dose) is > 2.0.
Primary Outcome/Efficacy Variable: <i>For the humoral immune response in terms of Flu vaccine HI antibodies against A/California/7/2009 (H1N1)v-like virus, the following parameters were calculated with 95% confidence intervals (CIs):</i> <i>Observed variable:</i> H1N1 HI antibodies on Day 0, Day 21, Day 42, and at Month 6+7 Days#. <i>Derived variable:</i> <ul style="list-style-type: none"> • GMTs of H1N1 HI antibodies. • SCR* on Day 42. • SPR** on Day 42.

- GMFR*** on Day 42.

*SCR is defined as the percentage of vaccinees that have either a pre-vaccination titre < 1:10 and a post-vaccination titre \geq 1:40 or a pre-vaccination titre \geq 1:10 and at least a 4-fold increase in post-vaccination titre. The CHMP criterion was fulfilled if the point estimate for SCR was > 40% in children aged 3 to 17 years.

**SPR is defined as the percentage of vaccinees with a serum HI titre \geq 1:40, that usually is accepted as indicating protection. The CHMP criterion was fulfilled if the post-vaccination time point estimate for SPR the point estimate for SPR was > 70% in children aged 3 to 17 years.

***GMFR, also called seroconversion factor (SCF), is defined the fold increase in serum HI GMTs post-vaccination compared to pre-vaccination. The CHMP criterion was fulfilled if the point estimate for GMFR was > 2.5 in children aged 3 to 17 years.

At the time of writing this summary, data were available up to Day 42 only. This summary will be updated when additional results become available.

Secondary Outcome/Efficacy Variable(s):

For the humoral immune response in terms of Flu vaccine HI antibodies against A/California/7/2009 (H1N1)v-like virus, 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[#].

Derived variable:

- GMTs and seropositivity rates
- SCR*
- SPR*
- SCF*
- Booster SCR** §
- Booster SCF*** §

*Criteria for evaluation are the same as for the primary outcome results.

**Booster SCR is defined as the percentage of vaccinees that are seronegative at pre-booster (Month 6) and have antibody titre \geq 1:40 at Month post-booster time points or are seropositive at pre-booster and have antibody titre at post-booster time points \geq 4-fold the pre-boost antibody titre.

*** Booster SCF is 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.

For the humoral immune response in terms of neutralising antibodies against A/California/7/2009 (H1N1)v-like virus (in a subset of one third of the subjects randomly selected), the following parameters were calculated with 95% CIs:§

Observed variable:

Serum neutralizing antibody titres on Day 0, Day 21, Day 42, Month 6, Month 6+7 Days and Month 12..

Derived variable:

- GMTs of serum neutralizing antibody titres
- SCRs
- Booster SCR

Safety evaluation:

- Percentage, intensity of solicited local signs and symptoms during a 7-day follow-up period (i.e. day of vaccination and six subsequent days after each vaccination on Day 0, Day 21, and at Month 6[#]).
- Percentage, intensity and relationship to vaccination of solicited general signs and symptoms during a 7-day follow-up period (i.e. day of vaccination and six subsequent days after each vaccination on Day 0, Day 21, and at Month 6[#]).
- Percentage, intensity and relationship to vaccination of unsolicited adverse events (AEs) during a 21-day follow-up period after the first vaccination, during a 63-day follow-up period after the second vaccination[#], and during a 30-day follow-up period after the booster vaccination[#].
- Occurrence of medically-attended event (MAEs), AEs of specific interest (AESIs), 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 only. This summary will be updated when additional results become available.

§ Not available at the time of writing this summary.

Statistical Methods:

Analyses were performed on the Total Vaccinated cohort and the according-to-protocol (ATP) cohort for immunogenicity.

- 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 two doses were taken and assay results were available for antibodies against H1N1 antigen for the blood sample taken 21 days after the second vaccine dose on Day 21.

Analysis of immunogenicity:

The analysis was done on the ATP cohort for immunogenicity.

The HI immune response to the vaccine-homologous virus was described for all groups, overall and per age stratum on Day 0, Day 21 (in Flu BS1 Group) and Day 42 (in both groups) by estimating the following parameters (with 95% CIs): GMT, SPR, SCR and SCF.

Analysis of safety:

The analysis was based on the Total Vaccinated cohort.

The incidence of solicited local and general symptoms occurring during 7 days after each vaccination was tabulated with exact 95% CI for Flu pooled groups and for all age strata. 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 symptoms were assessed as causally related to the vaccination.

The percentage of subjects with at least one report of an unsolicited AE classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms up to Day 42 after the first primary vaccination was tabulated for Flu pooled Group and for all age strata. 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. The proportion of subjects with MAEs, AESIs and SAEs reported up to Day 42 after the first primary vaccination was tabulated for Flu pooled Group and for all age strata and classified by MedDRA preferred terms. Distribution of haematology and biochemistry were also tabulated with respect to normal laboratory ranges for Flu pooled Group and for all age strata.

Study Population: Healthy children, male or female, aged between 3 and 17 years at the time of first vaccination. A written informed consent was obtained from the subjects' parent(s) or legally acceptable representative(s) prior to study entry. An assent was also obtained from the subjects when applicable.

	FLU BS1 Group		
Number of subjects	3-5 Years	6-9 Years	10-17 Years
Planned, N	29	29	58
Randomised, N (Total Vaccinated cohort)	31	31	60
Completed at Day 42, n (%)	31 (100)	30 (96.8)	59 (98.3)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	1 (3.2)	1 (1.7)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	1 (1.7)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	0 (0.0)	1 (3.2)	0 (0.0)
Demographics	3-5 Years	6-9 Years	10-17 Years
N (Total Vaccinated cohort)	31	31	60
Females:Males	13:18	18:13	25:35
Mean Age, years (SD)	4.1 (0.91)	7.3 (1.09)	12.8 (2.12)
White - Caucasian / European heritage, n (%)	29 (93.5)	30 (96.8)	58 (96.7)
	FLU BS2 Group		
Number of subjects	3-5 Years	6-9 Years	10-17 Years
Planned, N	29	29	58
Randomised, N (Total Vaccinated cohort)	30	34	58
Completed at Day 42, n (%)	28 (93.3)	33 (97.1)	58 (100)
Total Number Subjects Withdrawn, n (%)	2 (6.7)	1 (2.9)	0 (0.0)
Withdrawn due to Adverse Events, n (%)	1 (3.3)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	1 (3.3)	1 (2.9)	0 (0.0)
Demographics	3-5 Years	6-9 Years	10-17 Years
N (Total Vaccinated cohort)	30	34	58
Females:Males	15:15	16:18	29:29
Mean Age, years (SD)	4.0 (0.74)	7.3 (1.17)	13.1 (2.30)
White - Caucasian / European heritage, n (%)	29 (96.7)	34 (100)	55 (94.8)

Primary Efficacy Results: Seropositivity rates, Seroprotection rates and GMTs for HI antibodies against Flu A/CAL/7/09 by pre-vaccination status (ATP cohort for immunogenicity)																
				≥ 1:10					≥ 1:40				GMT			
				N		%	95% CI		n		%	95% CI		value	95% CI	
Antibody against	Group	Sub-group	Timing	N	N	%	LL	UL	n	%	LL	UL	value	LL	UL	
Flu A/CAL/7/09	FLU BS1	3-5 Years	PRE	28	2	7.1	0.9	23.5	1	3.6	0.1	18.3	5.7	4.5	7.2	
			PI(21)	28	28	100	87.7	100	28	100	87.7	100	192.6	145.6	254.8	
			PII(D42)	28	28	100	87.7	100	28	100	87.7	100	1361.7	1107.0	1674.9	
		6-9 Years	PRE	30	1	3.3	0.1	17.2	0	0.0	0.0	0.0	11.6	5.2	4.8	5.8
			PI(21)	30	30	100	88.4	100	30	100	88.4	100	190.3	147.0	246.3	
			PII(D42)	30	30	100	88.4	100	30	100	88.4	100	970.1	765.8	1228.8	
		10-17 Years	PRE	54	17	31.5	19.5	45.6	6	11.1	4.2	22.6	9.9	7.0	14.1	
			PI(21)	54	54	100	93.4	100	53	98.1	90.1	100	479.3	361.8	634.9	
			PII(D42)	54	54	100	93.4	100	54	100	93.4	100	1069.4	892.6	1281.3	
	Overall	PRE	112	20	17.9	11.3	26.2	7	6.3	2.5	12.5	7.3	6.1	8.8		
		PI(21)	112	112	100	96.8	100	111	99.1	95.1	100	297.9	247.8	358.3		
		PII(D42)*	112	112	100	96.8	100	112	100	96.8	100	1106.7	983.2	1245.8		
	FLU BS2	3-5 Years	PII(D42)	25	25	100	86.3	100	25	100	86.3	100	1161.7	905.2	1490.9	
		6-9 Years	PII(D42)	30	30	100	88.4	100	30	100	88.4	100	915.7	759.1	1104.6	
10-17 Years		PII(D42)	57	57	100	93.7	100	57	100	93.7	100	979.6	845.3	1135.2		
Overall*		PII(D42)*	112	112	100	96.8	100	112	100	96.8	100	999.4	900.7	1108.8		
Seroprotection = Flu A/CAL/7/09 antibody titre ≥ 1:40 GMT = geometric mean antibody titre calculated on all subjects N = number of subjects with pre-vaccination results available 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(21)= Post dose 1 (Day 21) PII(D42)= Post dose 2 (Day 42) * Primary outcome variable																
Primary Efficacy Results: SCR for HI antibodies against Flu A/CAL/7/09 at Day 21 and Day 42 (ATP cohort for immunogenicity)																
												SCR				
												95% CI				
Antibody against	Group	Sub-group	Timing	N	n	%	LL	UL								
Flu A/CAL/7/09	FLU BS1	3-5 Years	PI(21)	28	28	100	87.7	100								
			PII(D42)	28	28	100	87.7	100								
		6-9 Years	PI(21)	30	30	100	88.4	100								
			PII(D42)	30	30	100	88.4	100								
		10-17 Years	PI(21)	54	52	96.3	87.3	99.5								
			PII(D42)	54	53	98.1	90.1	100								
		Overall	PI(21)	112	110	98.2	93.7	99.8								
			PII(D42)*	112	111	99.1	95.1	100								
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(21)= Post dose 1 (Day 21) PII(D42)= Post dose 2 (Day 42) * Primary outcome variable																
Primary Efficacy Results: GMFR for HI antibodies against Flu A/CAL/7/09 at day 21 and day 42 (ATP cohort for immunogenicity)																
												GMFR				

Antibody against	Group	Sub-group	Timing	N	Value	95% CI	
						LL	UL
Flu A/CAL/7/09	FLU BS1	3-5 Years	PI(21)	28	33.62	26.25	43.05
			PII(D42)	28	237.68	175.28	322.29
		6-9 Years	PI(21)	30	36.33	27.96	47.22
			PII(D42)	30	185.25	142.09	241.52
		10-17 Years	PI(21)	54	48.29	35.64	65.42
			PII(D42)	54	107.74	76.64	151.45
		Overall	PI(21)	112	40.87	34.41	48.55
			PII(D42)*	112	151.82	124.27	185.48

N = Number of subjects with pre- and post-vaccination results available

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

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

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

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

* Primary outcome variable

Secondary Outcome Variable(s): Number/percentage of subjects reporting solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort)

		FLU Pooled Group														
		3-5 Years					6-9 Years					10-17 Years				
		95 % CI					95 % CI					95 % CI				
Symptom	Intensity	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Pain	Any	60	36	60.0	46.5	72.4	65	41	63.1	50.2	74.7	118	87	73.7	64.8	81.4
	Grade 3	60	2	3.3	0.4	11.5	65	4	6.2	1.7	15.0	118	9	7.6	3.5	14.0
Redness	Any	60	16	26.7	16.1	39.7	65	15	23.1	13.5	35.2	118	27	22.9	15.7	31.5
	> 50 mm	60	0	0.0	0.0	6.0	65	1	1.5	0.0	8.3	118	0	0.0	0.0	3.1
Swelling	Any	60	13	21.7	12.1	34.2	65	15	23.1	13.5	35.2	118	36	30.5	22.4	39.7
	> 50 mm	60	0	0.0	0.0	6.0	65	2	3.1	0.4	10.7	118	5	4.2	1.4	9.6
Dose 2																
Pain	Any	56	31	55.4	41.5	68.7	63	41	65.1	52.0	76.7	117	80	68.4	59.1	76.7
	Grade 3	56	3	5.4	1.1	14.9	63	7	11.1	4.6	21.6	117	4	3.4	0.9	8.5
Redness	Any	56	23	41.1	28.1	55.0	63	21	33.3	22.0	46.3	117	37	31.6	23.3	40.9
	> 50 mm	56	4	7.1	2.0	17.3	63	1	1.6	0.0	8.5	117	4	3.4	0.9	8.5
Swelling	Any	56	16	28.6	17.3	42.2	63	16	25.4	15.3	37.9	117	30	25.6	18.0	34.5
	> 50 mm	56	2	3.6	0.4	12.3	63	1	1.6	0.0	8.5	117	7	6.0	2.4	11.9
Across Doses																
Pain	Any	60	40	66.7	53.3	78.3	65	49	75.4	63.1	85.2	118	96	81.4	73.1	87.9
	Grade 3	60	4	6.7	1.8	16.2	65	9	13.8	6.5	24.7	118	11	9.3	4.7	16.1
Redness	Any	60	28	46.7	33.7	60.0	65	28	43.1	30.8	56.0	118	46	39.0	30.1	48.4
	> 50 mm	60	4	6.7	1.8	16.2	65	2	3.1	0.4	10.7	118	4	3.4	0.9	8.5
Swelling	Any	60	22	36.7	24.6	50.1	65	22	33.8	22.6	46.6	118	46	39.0	30.1	48.4
	> 50 mm	60	2	3.3	0.4	11.5	65	3	4.6	1.0	12.9	118	10	8.5	4.1	15.0

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

Any= occurrence of any local symptom regardless of intensity grade

Grade 3 pain (Child < 6 years)= cried when limb was moved/spontaneously painful

Grade 3 pain (Child ≥ 6 years) = Pain that prevented normal activity

Secondary Outcome Variable(s): Number/percentage of subjects reporting solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort)

		FLU Pooled Group														
		3-5 Years					6-9 Years					10-17 Years				
		95 % CI					95 % CI					95 % CI				

Symptom	Intensity/ Relationship	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Arthralgia	Any	60	-	-	-	-	65	10	15.4	7.6	26.5	118	12	10.2	5.4	17.1
	Grade 3	60	-	-	-	-	65	0	0.0	0.0	5.5	118	2	1.7	0.2	6.0
	Related	60	-	-	-	-	65	10	15.4	7.6	26.5	118	11	9.3	4.7	16.1
Diarrhoea	Any	60	6	10.0	3.8	20.5	65	-	-	-	-	118	-	-	-	-
	Grade 3	60	1	1.7	0.0	8.9	65	-	-	-	-	118	-	-	-	-
	Related	60	3	5.0	1.0	13.9	65	-	-	-	-	118	-	-	-	-
Drowsiness	Any	60	15	25.0	14.7	37.9	65	-	-	-	-	118	-	-	-	-
	Grade 3	60	1	1.7	0.0	8.9	65	-	-	-	-	118	-	-	-	-
	Related	60	14	23.3	13.4	36.0	65	-	-	-	-	118	-	-	-	-
Fatigue	Any	60	-	-	-	-	65	19	29.2	18.6	41.8	118	38	32.2	23.9	41.4
	Grade 3	60	-	-	-	-	65	1	1.5	0.0	8.3	118	3	2.5	0.5	7.3
	Related	60	-	-	-	-	65	18	27.7	17.3	40.2	118	33	28.0	20.1	37.0
Gastro-intestinal symptoms	Any	60	-	-	-	-	65	12	18.5	9.9	30.0	118	17	14.4	8.6	22.1
	Grade 3	60	-	-	-	-	65	1	1.5	0.0	8.3	118	4	3.4	0.9	8.5
	Related	60	-	-	-	-	65	9	13.8	6.5	24.7	118	13	11.0	6.0	18.1
Headache	Any	60	-	-	-	-	65	14	21.5	12.3	33.5	118	50	42.4	33.3	51.8
	Grade 3	60	-	-	-	-	65	2	3.1	0.4	10.7	118	8	6.8	3.0	12.9
	Related	60	-	-	-	-	65	14	21.5	12.3	33.5	118	42	35.6	27.0	44.9
Irritability	Any	60	12	20.0	10.8	32.3	65	-	-	-	-	118	-	-	-	-
	Grade 3	60	1	1.7	0.0	8.9	65	-	-	-	-	118	-	-	-	-
	Related	60	12	20.0	10.8	32.3	65	-	-	-	-	118	-	-	-	-
Loss of appetite	Any	60	13	21.7	12.1	34.2	65	-	-	-	-	118	-	-	-	-
	Grade 3	60	0	0.0	0.0	6.0	65	-	-	-	-	118	-	-	-	-
	Related	60	12	20.0	10.8	32.3	65	-	-	-	-	118	-	-	-	-
Myalgia	Any	60	-	-	-	-	65	11	16.9	8.8	28.3	118	27	22.9	15.7	31.5
	Grade 3	60	-	-	-	-	65	0	0.0	0.0	5.5	118	2	1.7	0.2	6.0
	Related	60	-	-	-	-	65	11	16.9	8.8	28.3	118	26	22.0	14.9	30.6
Shivering	Any	60	9	15.0	7.1	26.6	65	8	12.3	5.5	22.8	118	26	22.0	14.9	30.6
	Grade 3	60	0	0.0	0.0	6.0	65	0	0.0	0.0	5.5	118	1	0.8	0.0	4.6
	Related	60	8	13.3	5.9	24.6	65	7	10.8	4.4	20.9	118	24	20.3	13.5	28.7
Sweating	Any	60	7	11.7	4.8	22.6	65	5	7.7	2.5	17.0	118	10	8.5	4.1	15.0
	Grade 3	60	0	0.0	0.0	6.0	65	0	0.0	0.0	5.5	118	1	0.8	0.0	4.6
	Related	60	6	10.0	3.8	20.5	65	4	6.2	1.7	15.0	118	9	7.6	3.5	14.0
Temperature (Axillary)	≥37.5°C	60	19	31.7	20.3	45.0	65	10	15.4	7.6	26.5	118	12	10.2	5.4	17.1
	>39°C	60	1	1.7	0.0	8.9	65	1	1.5	0.0	8.3	118	2	1.7	0.2	6.0
	Related	60	16	26.7	16.1	39.7	65	8	12.3	5.5	22.8	118	8	6.8	3.0	12.9
Dose 2																
Arthralgia	Any	56	-	-	-	-	63	9	14.3	6.7	25.4	117	19	16.2	10.1	24.2
	Grade 3	56	-	-	-	-	63	1	1.6	0.0	8.5	117	1	0.9	0.0	4.7
	Related	56	-	-	-	-	63	9	14.3	6.7	25.4	117	18	15.4	9.4	23.2
Diarrhoea	Any	56	5	8.9	3.0	19.6	63	-	-	-	-	117	-	-	-	-
	Grade 3	56	1	1.8	0.0	9.6	63	-	-	-	-	117	-	-	-	-
	Related	56	3	5.4	1.1	14.9	63	-	-	-	-	117	-	-	-	-
Drowsiness	Any	56	11	19.6	10.2	32.4	63	-	-	-	-	117	-	-	-	-
	Grade 3	56	2	3.6	0.4	12.3	63	-	-	-	-	117	-	-	-	-
	Related	56	10	17.9	8.9	30.4	63	-	-	-	-	117	-	-	-	-
Fatigue	Any	56	-	-	-	-	63	14	22.2	12.7	34.5	117	35	29.9	21.8	39.1
	Grade 3	56	-	-	-	-	63	3	4.8	1.0	13.3	117	3	2.6	0.5	7.3
	Related	56	-	-	-	-	63	13	20.6	11.5	32.7	117	32	27.4	19.5	36.4
Gastro-intestinal symptoms	Any	56	-	-	-	-	63	6	9.5	3.6	19.6	117	17	14.5	8.7	22.2
	Grade 3	56	-	-	-	-	63	1	1.6	0.0	8.5	117	1	0.9	0.0	4.7
	Related	56	-	-	-	-	63	5	7.9	2.6	17.6	117	14	12.0	6.7	19.3

Headache	Any	56	-	-	-	-	63	13	20.6	11.5	32.7	117	43	36.8	28.0	46.2	
	Grade 3	56	-	-	-	-	63	3	4.8	1.0	13.3	117	4	3.4	0.9	8.5	
	Related	56	-	-	-	-	63	13	20.6	11.5	32.7	117	41	35.0	26.5	44.4	
Irritability	Any	56	15	26.8	15.8	40.3	63	-	-	-	-	117	-	-	-	-	
	Grade 3	56	0	0.0	0.0	6.4	63	-	-	-	-	117	-	-	-	-	
	Related	56	15	26.8	15.8	40.3	63	-	-	-	-	117	-	-	-	-	
Loss of appetite	Any	56	11	19.6	10.2	32.4	63	-	-	-	-	117	-	-	-	-	
	Grade 3	56	1	1.8	0.0	9.6	63	-	-	-	-	117	-	-	-	-	
	Related	56	10	17.9	8.9	30.4	63	-	-	-	-	117	-	-	-	-	
Myalgia	Any	56	-	-	-	-	63	11	17.5	9.1	29.1	117	28	23.9	16.5	32.7	
	Grade 3	56	-	-	-	-	63	1	1.6	0.0	8.5	117	1	0.9	0.0	4.7	
	Related	56	-	-	-	-	63	11	17.5	9.1	29.1	117	27	23.1	15.8	31.8	
Shivering	Any	56	5	8.9	3.0	19.6	63	4	6.3	1.8	15.5	117	20	17.1	10.8	25.2	
	Grade 3	56	0	0.0	0.0	6.4	63	0	0.0	0.0	5.7	117	2	1.7	0.2	6.0	
	Related	56	4	7.1	2.0	17.3	63	4	6.3	1.8	15.5	117	19	16.2	10.1	24.2	
Sweating	Any	56	3	5.4	1.1	14.9	63	5	7.9	2.6	17.6	117	10	8.5	4.2	15.2	
	Grade 3	56	0	0.0	0.0	6.4	63	0	0.0	0.0	5.7	117	0	0.0	0.0	3.1	
	Related	56	3	5.4	1.1	14.9	63	5	7.9	2.6	17.6	117	8	6.8	3.0	13.0	
Temperature (Axillary)	≥37.5°C	56	20	35.7	23.4	49.6	63	8	12.7	5.6	23.5	117	22	18.8	12.2	27.1	
	>39°C	56	3	5.4	1.1	14.9	63	2	3.2	0.4	11.0	117	2	1.7	0.2	6.0	
	Related	56	18	32.1	20.3	46.0	63	8	12.7	5.6	23.5	117	17	14.5	8.7	22.2	
Across Doses																	
Arthralgia	Any	60	-	-	-	-	65	14	21.5	12.3	33.5	118	25	21.2	14.2	29.7	
	Grade 3	60	-	-	-	-	65	1	1.5	0.0	8.3	118	3	2.5	0.5	7.3	
	Related	60	-	-	-	-	65	14	21.5	12.3	33.5	118	23	19.5	12.8	27.8	
Diarrhoea	Any	60	9	15.0	7.1	26.6	65	-	-	-	-	118	-	-	-	-	
	Grade 3	60	2	3.3	0.4	11.5	65	-	-	-	-	118	-	-	-	-	
	Related	60	5	8.3	2.8	18.4	65	-	-	-	-	118	-	-	-	-	
Drowsiness	Any	60	20	33.3	21.7	46.7	65	-	-	-	-	118	-	-	-	-	
	Grade 3	60	3	5.0	1.0	13.9	65	-	-	-	-	118	-	-	-	-	
	Related	60	18	30.0	18.8	43.2	65	-	-	-	-	118	-	-	-	-	
Fatigue	Any	60	-	-	-	-	65	24	36.9	25.3	49.8	118	53	44.9	35.7	54.3	
	Grade 3	60	-	-	-	-	65	4	6.2	1.7	15.0	118	6	5.1	1.9	10.7	
	Related	60	-	-	-	-	65	23	35.4	23.9	48.2	118	50	42.4	33.3	51.8	
Gastro-intestinal symptoms	Any	60	-	-	-	-	65	13	20.0	11.1	31.8	118	30	25.4	17.9	34.3	
	Grade 3	60	-	-	-	-	65	1	1.5	0.0	8.3	118	5	4.2	1.4	9.6	
	Related	60	-	-	-	-	65	10	15.4	7.6	26.5	118	23	19.5	12.8	27.8	
Headache	Any	60	-	-	-	-	65	19	29.2	18.6	41.8	118	61	51.7	42.3	61.0	
	Grade 3	60	-	-	-	-	65	4	6.2	1.7	15.0	118	10	8.5	4.1	15.0	
	Related	60	-	-	-	-	65	19	29.2	18.6	41.8	118	56	47.5	38.2	56.9	
Irritability	Any	60	18	30.0	18.8	43.2	65	-	-	-	-	118	-	-	-	-	
	Grade 3	60	1	1.7	0.0	8.9	65	-	-	-	-	118	-	-	-	-	
	Related	60	18	30.0	18.8	43.2	65	-	-	-	-	118	-	-	-	-	
Loss of appetite	Any	60	18	30.0	18.8	43.2	65	-	-	-	-	118	-	-	-	-	
	Grade 3	60	1	1.7	0.0	8.9	65	-	-	-	-	118	-	-	-	-	
	Related	60	17	28.3	17.5	41.4	65	-	-	-	-	118	-	-	-	-	
Myalgia	Any	60	-	-	-	-	65	13	20.0	11.1	31.8	118	45	38.1	29.4	47.5	
	Grade 3	60	-	-	-	-	65	1	1.5	0.0	8.3	118	3	2.5	0.5	7.3	
	Related	60	-	-	-	-	65	13	20.0	11.1	31.8	118	43	36.4	27.8	45.8	
Shivering	Any	60	10	16.7	8.3	28.5	65	10	15.4	7.6	26.5	118	35	29.7	21.6	38.8	
	Grade 3	60	0	0.0	0.0	6.0	65	0	0.0	0.0	5.5	118	3	2.5	0.5	7.3	
	Related	60	9	15.0	7.1	26.6	65	9	13.8	6.5	24.7	118	33	28.0	20.1	37.0	
Sweating	Any	60	9	15.0	7.1	26.6	65	10	15.4	7.6	26.5	118	18	15.3	9.3	23.0	
	Grade 3	60	0	0.0	0.0	6.0	65	0	0.0	0.0	5.5	118	1	0.8	0.0	4.6	
	Related	60	8	13.3	5.9	24.6	65	9	13.8	6.5	24.7	118	15	12.7	7.3	20.1	

Temperature (Axillary)	≥37.5° C	60	27	45.0	32.1	58.4	65	13	20.0	11.1	31.8	118	30	25.4	17.9	34.3
	>39° C	60	4	6.7	1.8	16.2	65	3	4.6	1.0	12.9	118	4	3.4	0.9	8.5
	Related	60	23	38.3	26.1	51.8	65	11	16.9	8.8	28.3	118	23	19.5	12.8	27.8

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

Any= occurrence of any general symptom regardless of intensity grade or relationship to vaccination

Related= general symptom assessed by the investigator as causally related to the study vaccination

For subjects < 6 years:

Grade 3 Diarrhoea, Drowsiness, Irritability, Shivering and Sweating = general symptom that prevented normal activity

Grade 3 Loss of appetite = Not eating at all

For subjects ≥ 6 years:

Grade 3= general symptom that prevented normal activity

Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of unsolicited adverse events with medically attended visit, within the 42-day (Days 0-41) post-vaccination period (Total Vaccinated cohort)

Most frequent Adverse Events with medically attended visit	Flu pooled Group		
	3-5 Years N = 61	6-9 Years N = 65	10-17 Years N = 118
Subjects with any MAE(s), n (%)	24 (39.3)	11 (16.9)	23 (19.5)
Lymphadenopathy	-	-	1 (0.8)
Vertigo	-	-	1 (0.8)
Conjunctivitis	3 (4.9)	-	1 (0.8)
Abdominal pain	-	-	1 (0.8)
Constipation	1 (1.6)	-	-
Enteritis	-	1 (1.5)	-
Gingivitis	1 (1.6)	-	-
Nausea	-	1 (1.5)	1 (0.8)
Vomiting	1 (1.6)	-	1 (0.8)
Influenza like illness	1 (1.6)	-	1 (0.8)
Pyrexia	3 (4.9)	1 (1.5)	1 (0.8)
Acute tonsillitis	1 (1.6)	-	-
Bronchitis	5 (8.2)	-	1 (0.8)
Croup infectious	-	1 (1.5)	-
Fungal infection	-	1 (1.5)	-
Gastroenteritis	1 (1.6)	-	-
Herpangina	-	1 (1.5)	-
Laryngitis	-	1 (1.5)	-
Lice infestation	1 (1.6)	1 (1.5)	1 (0.8)
Nasopharyngitis	5 (8.2)	-	5 (4.2)
Oral herpes	1 (1.6)	-	-
Otitis externa	-	-	1 (0.8)
Otitis media	1 (1.6)	-	-
Pharyngitis	-	-	1 (0.8)
Pharyngitis streptococcal	1 (1.6)	-	-
Pharyngotonsillitis	1 (1.6)	-	-
Tinea pedis	-	-	1 (0.8)
Upper respiratory tract infection	3 (4.9)	-	4 (3.4)
Urinary tract infection	1 (1.6)	-	-
Viral infection	1 (1.6)	2 (3.1)	1 (0.8)
Vulvitis	1 (1.6)	-	-
Facial bones fracture	-	-	1 (0.8)
Forearm fracture	-	1 (1.5)	-
Laceration	1 (1.6)	-	-
Back pain	-	-	1 (0.8)
Pain in extremity	-	1 (1.5)	-

Torticollis		1 (1.6)	-	-						
Headache		-	-	1 (0.8)						
Attention deficit/hyperactivity disorder		-	-	1 (0.8)						
Bronchospasm		-	1 (1.5)	-						
Cough		1 (1.6)	2 (3.1)	-						
Epistaxis		1 (1.6)	-	-						
Acne		-	-	1 (0.8)						
Eczema		1 (1.6)	-	-						
Urticaria		1 (1.6)	-	-						
Dental operation		1 (1.6)	-	-						
- : Adverse event absent										
Secondary Outcome Variable(s): Percentage of subjects reporting the occurrence of Adverse Events of Specific Interest (AESIs) reported within the 42-day (Days 0-41) post-vaccination period (Total Vaccinated cohort)										
Most frequent Adverse Events of Specific Interest		Flu pooled Group								
		3-5 Years N = 61	6-9 Years N = 65	10-17 Years N = 118						
Subjects with any AESI(s), n (%)		0 (0.0)	0 (0.0)	0 (0.0)						
Secondary Outcome Variable(s): Distribution of haematology and biochemistry with respect to normal laboratory ranges (Total Vaccinated cohort)										
Flu pooled Group										
3-5 Years N = 57										
			Unknown	Below	Within	Above				
Laboratory parameter	Timing	N	n	%	n	%	n	%	n	%
ALAT	PRE	30	1	3.3	0	0.0	29	96.7	0	0.0
	PI(21)	31	1	3.2	0	0.0	30	96.8	0	0.0
	PII(D42)	57	0	0.0	0	0.0	57	100	0	0.0
ASAT	PRE	30	1	3.3	0	0.0	26	86.7	3	10.0
	PI(21)	31	1	3.2	0	0.0	30	96.8	0	0.0
	PII(D42)	57	0	0.0	0	0.0	56	98.2	1	1.8
Bilirubin*	PRE	30	1	3.3	0	0.0	29	96.7	0	0.0
		30	1	3.3	0	0.0	29	96.7	0	0.0
	PI(21)	31	1	3.2	0	0.0	30	96.8	0	0.0
		31	1	3.2	0	0.0	30	96.8	0	0.0
	PII(D42)	57	0	0.0	0	0.0	57	100	0	0.0
		57	0	0.0	0	0.0	57	100	0	0.0
Creatinine	PRE	30	1	3.3	2	6.7	27	90.0	0	0.0
	PI(21)	31	1	3.2	3	9.7	27	87.1	0	0.0
	PII(D42)	57	0	0.0	2	3.5	52	91.2	3	5.3
BUN	PRE	30	1	3.3	0	0.0	28	93.3	1	3.3
	PI(21)	31	1	3.2	1	3.2	29	93.5	0	0.0
	PII(D42)	57	0	0.0	2	3.5	52	91.2	3	5.3
6-9 Years N = 64										
			Unknown	Below	Within	Above				
Laboratory parameter	Timing	N	n	%	n	%	n	%	n	%
ALAT	PRE	31	1	3.2	0	0.0	30	96.8	0	0.0
	PI(21)	30	0	0.0	0	0.0	30	100	0	0.0
	PII(D42)	63	0	0.0	0	0.0	62	98.4	1	1.6
ASAT	PRE	31	1	3.2	0	0.0	29	93.5	1	3.2
	PI(21)	30	0	0.0	0	0.0	29	96.7	1	3.3
	PII(D42)	63	1	1.6	0	0.0	60	95.2	2	3.2
Bilirubin*	PRE	31	1	3.2	0	0.0	28	90.3	2	6.5

		31	1	3.2	0	0.0	30	96.8	0	0.0
	PI(21)	30	0	0.0	0	0.0	28	93.3	2	6.7
		30	0	0.0	0	0.0	30	100	0	0.0
	PII(D42)	63	0	0.0	0	0.0	63	100	0	0.0
		63	0	0.0	0	0.0	63	100	0	0.0
Creatinine	PRE	31	1	3.2	0	0.0	29	93.5	1	3.2
	PI(21)	30	0	0.0	0	0.0	28	93.3	2	6.7
	PII(D42)	63	0	0.0	2	3.2	60	95.2	1	1.6
BUN	PRE	31	1	3.2	0	0.0	30	96.8	0	0.0
	PI(21)	30	0	0.0	2	6.7	27	90.0	1	3.3
	PII(D42)	63	0	0.0	2	3.2	60	95.2	1	1.6
10-17 Years N = 117										
			Unknown		Below		Within		Above	
Laboratory parameter	Timing	N	n	%	n	%	n	%	n	%
ALAT	PRE	60	1	1.7	0	0.0	58	96.7	1	1.7
	PI(21)	59	1	1.7	0	0.0	58	98.3	0	0.0
	PII(D42)	115	2	1.7	0	0.0	111	96.5	2	1.7
ASAT	PRE	60	1	1.7	0	0.0	58	96.7	1	1.7
	PI(21)	59	1	1.7	0	0.0	58	98.3	0	0.0
	PII(D42)	115	2	1.7	0	0.0	110	95.7	3	2.6
Bilirubin*	PRE	60	1	1.7	0	0.0	57	95.0	2	3.3
		60	1	1.7	0	0.0	58	96.7	1	1.7
	PI(21)	59	1	1.7	0	0.0	55	93.2	3	5.1
		59	1	1.7	0	0.0	58	98.3	0	0.0
	PII(D42)	115	2	1.7	0	0.0	110	95.7	3	2.6
		115	2	1.7	0	0.0	113	98.3	0	0.0
Creatinine	PRE	60	1	1.7	1	1.7	52	86.7	6	10.0
	PI(21)	59	1	1.7	4	6.8	48	81.4	6	10.2
	PII(D42)	115	2	1.7	5	4.3	103	89.6	5	4.3
BUN	PRE	60	1	1.7	2	3.3	57	95.0	0	0.0
	PI(21)	59	1	1.7	3	5.1	55	93.2	0	0.0
	PII(D42)	115	2	1.7	1	0.9	111	96.5	1	0.9
<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 visit 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 aminotransferase ASAT= Aspartate aminotransferase BUN= Blood urea nitrogen PRE= Pre-vaccination (Day 0) PI(21)= Post dose 1 (Day 21) PII(D42)= Post dose 2 (Day 42) *Bilirubin: at each time point, the first row is "Bilirubin Total" measurement and the second is "Bilirubin Direct" measurement.</p>										
Safety results: Number (%) of subjects with unsolicited adverse events within the 42-day (Days 0-41) post-vaccination period (Total Vaccinated cohort)										
Most frequent adverse events - On-Therapy (occurring within Day 0-41 following vaccination)							Flu pooled Group			
							3-5 Years N = 61	6-9 Years N = 65	10-17 Years N = 118	
Subjects with any AE(s), n (%)							34 (55.7)	16 (24.6)	34 (28.8)	
Subjects with grade 3 AE(s), n (%)							2 (3.3)	1 (1.5)	2 (1.7)	
Subjects with related AE(s), n (%)							9 (14.8)	2 (3.1)	4 (3.4)	

Upper respiratory tract infection	5 (8.2)	1 (1.5)	7 (5.9)
Nasopharyngitis	5 (8.2)	1 (1.5)	6 (5.1)
Cough	6 (9.8)	2 (3.1)	-
Pyrexia	4 (6.6)	2 (3.1)	1 (0.8)
Rhinitis	3 (4.9)	1 (1.5)	3 (2.5)
Bronchitis	5 (8.2)	-	1 (0.8)
Headache	5 (8.2)	-	1 (0.8)
Conjunctivitis	3 (4.9)	-	1 (0.8)
Viral infection	1 (1.6)	2 (3.1)	1 (0.8)
Lice infestation	1 (1.6)	1 (1.5)	1 (0.8)
Abdominal pain	1 (1.6)	-	1 (0.8)
Arthralgia	2 (3.3)	-	-
Influenza like illness	1 (1.6)	-	1 (0.8)
Injection site haematoma	-	1 (1.5)	1 (0.8)
Injection site pruritus	-	1 (1.5)	1 (0.8)
Nausea	-	1 (1.5)	1 (0.8)
Pharyngitis	-	-	2 (1.7)
Vomiting	1 (1.6)	-	1 (0.8)
Abnormal dreams	1 (1.6)	-	-
Acne	-	-	1 (0.8)
Acute tonsillitis	1 (1.6)	-	-
Attention deficit/hyperactivity disorder	-	-	1 (0.8)
Back pain	-	-	1 (0.8)
Bronchospasm	-	1 (1.5)	-
Constipation	1 (1.6)	-	-
Croup infectious	-	1 (1.5)	-
Decreased appetite	-	-	1 (0.8)
Dental operation	1 (1.6)	-	-
Dysphonia	-	1 (1.5)	-
Eczema	1 (1.6)	-	-
Enteritis	-	1 (1.5)	-
Epistaxis	1 (1.6)	-	-
Facial bones fracture	-	-	1 (0.8)
Forearm fracture	-	1 (1.5)	-
Fungal infection	-	1 (1.5)	-
Gastroenteritis	1 (1.6)	-	-
Gingivitis	1 (1.6)	-	-
Growing pains	1 (1.6)	-	-
Herpangina	-	1 (1.5)	-
Injection site induration	1 (1.6)	-	-
Laceration	1 (1.6)	-	-
Laryngitis	-	1 (1.5)	-
Lymphadenopathy	-	-	1 (0.8)
Menarche	-	-	1 (0.8)
Myalgia	1 (1.6)	-	-
Oral herpes	1 (1.6)	-	-
Otitis externa	-	-	1 (0.8)
Otitis media	1 (1.6)	-	-
Pain in extremity	-	1 (1.5)	-
Pharyngitis streptococcal	1 (1.6)	-	-
Pharyngotonsillitis	1 (1.6)	-	-
Pruritus	-	1 (1.5)	-
Rash pruritic	-	1 (1.5)	-
Rhinorrhoea	-	-	1 (0.8)
Tinea pedis	-	-	1 (0.8)

Torticollis	1 (1.6)	-	-
Urinary tract infection	1 (1.6)	-	-
Urticaria	1 (1.6)	-	-
Vertigo	-	-	1 (0.8)
Vulvitis	1 (1.6)	-	-
- : Adverse event absent Grade 3= event that prevented normal activity Related= event assessed by the investigator as causally related to the study vaccination			
Safety results: Number (%) of subjects with serious adverse events within the 42-day (Days 0-41) post-vaccination period (Total Vaccinated cohort)			
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]			
All SAEs	Flu Pooled Group		
	3-5 Years N = 61	6-9 Years N = 65	10-17 Years N = 118
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	1 (1.6) [0]	1 (1.5) [0]	1 (0.8) [0]
Facial bones fracture	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Forearm fracture	0 (0.0) [0]	1 (1.5) [0]	0 (0.0) [0]
Urinary tract infection	1 (1.6) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	3-5 Years N = 61	6-9 Years N = 65	10-17 Years N = 118
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

At Day 42, 21 days after the second dose, the GMT value for HI antibodies against A/California/7/2009 (H1N1)v-like virus was 1106.7 in Flu BS1 Group and 999.4 in Flu BS2 Group, the GMFR value was 151.82 in Flu BS1 Group, 99.1% of subjects in Flu BS1 Group seroconverted and all subjects had HI titres of 1:40 or greater. During the 21 days follow-up period after each dose, 84 (34.4%) subjects reported at least one unsolicited AE (34 subjects aged 3-5 years, 16 subjects aged 6-9 years and 34 subjects aged 10-17 years). During the same period, 3 SAEs were reported (1 in each age strata). These SAEs were assessed by the investigators as not causally related to the study vaccination. No fatal SAEs were reported.

Publications: None

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