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Study No.: 113459 (FLU D-PAN H1N1-008)
Title: Safety and immunogenicity study of GSK Biologicals' influenza vaccine GSK2340272A in adults aged 18 years and above. GSK2340272A (Flu): GlaxoSmithKline (GSK) Biologicals' Pandemic influenza vaccine comprising A/California/7/2009 (H1N1)v-like strain.
Rationale: The aim of the study was to assess the immunogenicity and safety of Flu 1 vaccine administered following a 1- or 2- dose schedule. Note: This summary presents results up to Day 42 and will be updated when additional data become available.
Phase: III
Study Period: 08 September 2009 to 03 December 2009 (Data lock point Day 42)
Study Design: Open, randomized study with 2 parallel groups. Enrolment was age-stratified, with 2 age strata (18-60 years and >60 years, in 1:1 ratio).
Centres: 1 centre in Belgium.
Indication: Immunization against A/California/7/2009 (H1N1)v-like influenza in male and female subjects aged 18 years and above.
Treatment: Study groups were as follows: <ul style="list-style-type: none"> • 1 dose Group: subjects received a single dose of Flu vaccine at Day 0. • 2 doses Group: subjects received 2 doses of Flu vaccine, one at Day 0 and one at Day 21. Vaccine was given intramuscularly in the deltoid region of the non-dominant arm at Day 0 and of the dominant arm at Day 21 (for the 2 doses Group only).
Objectives: To demonstrate that vaccination with one dose of Flu vaccine results in an Haemagglutination Inhibition (HI) immune response to the vaccine-homologous virus that meets 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 vaccination in adults within the 18 to 60 years and above 60 years age strata.
Primary Outcome/Efficacy Variable: <i>Humoral immune response in terms of HI antibodies</i> In subjects receiving two doses of Flu vaccine: <ul style="list-style-type: none"> • SCR* at 21 days after first dose of Flu vaccine (Day 21) • SPR** at 21 days after first dose of Flu vaccine (Day 21) • GMFR*** (also called seroconversion factor [SCF]) at 21 days after first dose of Flu vaccine (Day 21) *SCR: defined as the proportion of subjects who have either a pre-vaccination reciprocal HI titre < 10 and a post-vaccination reciprocal titre ≥ 40, or a pre-vaccination reciprocal HI titre ≥ 10 and at least a 4-fold increase in post-vaccination reciprocal titre against the vaccine virus. The CHMP criterion was fulfilled if the point estimated for SCR was > 40% in subjects 18 to 60 years of age or > 30% for subjects > 60 years of age. **SPR: The proportion of subjects with H1N1 reciprocal HI titres ≥ 40 against the vaccine-homologous virus. The CHMP criterion was fulfilled if the post-vaccination point estimate for SPR was > 70% in subjects 18 to 60 years of age or > 60% for subjects > 60 years of age. ***GMFR of the within-subject ratios of the post-vaccination reciprocal HI titre to the pre-vaccination reciprocal HI titre for the vaccine virus. The Committee for Medicinal Products for Human Use (CHMP) criterion was fulfilled if the point estimate for GMFR was > 2.5 in subjects 18 to 60 years of age or > 2% for subjects > 60 years of age.
Secondary Outcome/Efficacy Variable(s): <i>Humoral immune response in terms of HI antibodies</i> In subjects receiving 1 or 2 dose(s) of Flu vaccine: <ul style="list-style-type: none"> • Geometric Mean Titres (GMTs) and seropositivity rates at Day 0, 21, 42, 182# and 364# • SCR* at Day 21, 182# and 364# • SPR* at Day 0, 21, 182# and 364# • GMFR* at Day 21, 182# and 364# *Criteria for evaluation were the same as that for the primary outcome variables for each age stratum.

Humoral immune response in terms of neutralizing antibodies §

In a subset of subjects against A/California/7/2009 (H1N1)v-like:

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

**SCR was defined as the percentage of vaccinees that have a four-fold increase between pre- and post-vaccination Titres.

Safety

- Occurrence, intensity and duration of each solicited local symptom during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination
- Occurrence, intensity, duration and relationship to vaccination of each solicited general symptom during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination
- Occurrence, intensity and relationship to vaccination of unsolicited adverse events (AEs) within 21 or 84 days after the first vaccination and 63 days after the second vaccination (Day 0 - Day 20, Day 0 - Day 84# and Day 21- Day 84#), according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence and relationship to vaccination of adverse events of specific interest (AESIs) during the entire study period (up to Day 364#).
- Occurrence and relationship to vaccination of serious adverse events (SAEs) during the entire study period (up to Day 364#).

Safety evaluation in terms of biochemical parameters

- The number and percentage of subjects with normal or abnormal values of biochemical parameters at Day 0, Day 21, Day 42, Day 182# and Day 364#.

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

§ Results were 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 at Day 42.

- 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), who complied with the procedures and intervals defined in the protocol, who did not meet any of the criteria for elimination from an ATP analysis during the study, who did not receive a product leading to exclusion from an ATP analysis, who did not present with a medical condition leading to exclusion from an ATP analysis, for whom 1 dose was administered and assay result was available for antibodies against H1N1 antigen for the blood sample taken 42 days after the first vaccine dose and for whom 2 doses were administered and assay result was available for antibodies against H1N1 antigen for the blood sample taken 21 days after second vaccine dose.

Analysis of immunogenicity:

The analysis was based on the ATP cohort for immunogenicity at Day 42.

The HI immune response to the vaccine-homologous virus was described, by estimating the following parameters (with 95% confidence intervals [CI]): GMT and SPR on Days 0, 21 & 42, SCR and SCF on Days 21 & 42 in both groups and both age strata.

Analysis of safety:

The analysis was based on the Total Vaccinated cohort.

The incidence of solicited local and general symptoms occurring during the 7 days after the first vaccination was tabulated with exact 95% CI for the pooled groups and per age stratum. The incidence of solicited local and general symptoms occurring during the 7 days after each vaccination was tabulated with exact 95% CI for the 2 doses group and per age stratum. The same calculation was performed for symptoms of any intensity, those with intensity of grade 3, as well as for solicited general symptoms with relationship to vaccination.

The percentage of subjects with at least one report of an unsolicited AE classified by MedDRA Preferred Term up to 42 days after first dose and up to 21 days after second dose was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs that were assessed by the investigator as causally related to vaccination.

SAEs and AESIs were collected and summarized up to Day 42 by MedDRA Preferred Term.

The number and proportion of subjects with normal or abnormal values for each haematological and biochemical parameter were tabulated per group at Days 0, 21 & 42.

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

Number of subjects	1 dose Group		2 doses Group	
	18y-60y	>60y	18y-60y	>60y
Randomized, N (Total Vaccinated cohort)	52	50	68	70
Completed at Day 42, n (%)	52 (100)	50 (100)	68 (100)	70 (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	1 dose Group		2 doses Group	
	18y-60y	>60y	18y-60y	>60y
N (Total Vaccinated cohort)	52	50	68	70
Females:Males	26:26	23:27	39:29	29:41
Mean Age, years (SD)	39.0 (13.76)	68.8 (5.76)	40.2 (14.09)	69.4 (6.40)
White - Caucasian / European heritage, n (%)	52 (100)	50 (100)	68 (100)	70 (100)

18-60y = Subject aged between and including 18 years to 60 years

>60y = Subjects aged more than 60 years

Primary Efficacy Results: SCR for HI antibodies against Flu A/CAL/7/2009 in 2 doses Group (ATP cohort for immunogenicity at Day 42)

				SCR			
						95% CI	
Antibodies against	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/2009	18y-60y	PI(21)*	66	63	95.5	87.3	99.1
		PII(D42)	66	65	98.5	91.8	100
	>60y	PI(21)*	67	53	79.1	67.4	88.1
		PII(D42)	67	63	94.0	85.4	98.3

Seroconversion defined as:

For initially seronegative subjects, antibody titre $\geq 1:40$ 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: SPR for HI antibodies against Flu A/CAL/7/2009 in 2 doses Group (ATP cohort for immunogenicity at Day 42)

				SPR			
						95% CI	
Antibodies against	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/2009	18y-60y	PRE	66	6	9.1	3.4	18.7
		PI(21)*	66	65	98.5	91.8	100
		PII(D42)	66	66	100	94.6	100
	>60y	PRE	67	6	9.0	3.4	18.5
		PI(21)*	67	59	88.1	77.8	94.7
		PII(D42)	67	66	98.5	92.0	100

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(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/7/2009 in 2 doses Group (ATP cohort for immunogenicity at Day 42)														
											GMFR			
											95% CI			
Antibodies against	Group	Sub-group	Timing	N	Value	LL	UL							
Flu A/CAL/7/2009 (1/DIL)	2 doses	18y-60y	PI(21)*	66	38.71	29.10	51.51							
			PII(D42)	66	69.70	53.79	90.32							
		>60y	PI(21)*	67	13.86	10.29	18.65							
			PII(D42)	67	33.57	24.87	45.31							
<p>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</p>														
Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/2009 in 2 doses Group (ATP cohort for immunogenicity at Day 42)														
				≥ 1:10				≥ 1:40				GMT		
				95% CI				95% CI				95% CI		
Antibodies against	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Flu A/CAL/7/2009	18y-60y	PRE	66	24	36.4	24.9	49.1	6	9.1	3.4	18.7	8.8	7.0	10.9
		PI(21)	66	66	100	94.6	100	65	98.5	91.8	100	339.1	258.6	444.8
		PII(D42)	66	66	100	94.6	100	66	100	94.6	100	610.6	507.9	734.0
	>60y	PRE	67	28	41.8	29.8	54.5	6	9.0	3.4	18.5	10.3	7.7	13.7
		PI(21)	67	67	100	94.6	100	59	88.1	77.8	94.7	142.7	108.5	187.8
		PII(D42)	67	67	100	94.6	100	66	98.5	92.0	100	345.8	278.0	430.1
<p>Seroprotection = Flu A/CAL/7/2009 antibody titre ≥ 1:40 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(21)= Post-dose 1 Day 21 PII(D42)= Post-dose 2 Day 42</p>														
Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/2009 in 1 dose Group (ATP cohort for immunogenicity at Day 42)														
				≥ 1:10				≥ 1:40				GMT		
				95% CI				95% CI				95% CI		
Antibodies against	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Flu A/CAL/7/2009	18y-60y	PRE	50	20	40.0	26.4	54.8	4	8.0	2.2	19.2	8.6	6.8	10.8
		PI(21)	50	50	100	92.9	100	48	96.0	86.3	99.5	388.6	262.0	576.2
		PII(D42)	50	50	100	92.9	100	47	94.0	83.5	98.7	331.2	220.7	497.1
	>60y	PRE	49	21	42.9	28.8	57.8	5	10.2	3.4	22.2	9.7	7.3	13.0
		PI(21)	49	47	95.9	86.0	99.5	42	85.7	72.8	94.1	129.3	89.9	186.0
		PII(D42)	49	48	98.0	89.1	99.9	43	87.8	75.2	95.4	117.1	82.4	166.4
<p>Seroprotection = Flu A/CAL/7/2009 Ab antibody titre ≥ 1:40 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</p>														

PI(21)= Post-dose 1 Day 21 PI(D42)= Post-dose 1 Day 42							
Secondary Outcome Variable(s): SCR for HI antibodies against Flu A/CAL/7/2009 in 1 dose Group (ATP cohort for immunogenicity at Day 42)							
				SCR			
				95% CI			
Antibodies against	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/2009	18y-60y	PI(21)	50	47	94.0	83.5	98.7
		PI(D42)	50	46	92.0	80.8	97.8
	>60y	PI(21)	49	38	77.6	63.4	88.2
		PI(D42)	49	39	79.6	65.7	89.8
<p>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(21)= Post-dose 1 Day 21 PI(D42)= Post-dose 1 Day 42</p>							
Secondary Outcome Variable(s): SPR for HI antibodies against Flu A/CAL/7/2009 in 1 dose Group (ATP cohort for immunogenicity at Day 42)							
				SPR			
				95% CI			
Antibodies against	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/2009	18y-60y	PRE	50	4	8.0	2.2	19.2
		PI(21)	50	48	96.0	86.3	99.5
		PI(D42)	50	47	94.0	83.5	98.7
	>60y	PRE	49	5	10.2	3.4	22.2
		PI(21)	49	42	85.7	72.8	94.1
		PI(D42)	49	43	87.8	75.2	95.4
<p>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(21)= Post-dose 1 Day 21 PI(D42)= Post-dose 1 Day 42</p>							
Secondary Outcome Variable(s): GMFR for HI antibodies against Flu A/CAL/7/2009 in 1 dose Group (ATP cohort for immunogenicity at Day 42)							
				GMFR			
				95% CI			
Antibodies against	Sub-group	Timing	N	Value	LL	UL	
Flu A/CAL/7/2009 (1/DIL)	18y-60y	PI(21)	50	45.30	30.32	67.68	
		PI(D42)	50	38.62	25.96	57.45	
	>60y	PI(21)	49	13.32	9.04	19.61	
		PI(D42)	49	12.06	8.39	17.33	
<p>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 PI(D42)= Post-dose 1 Day 42</p>							
Secondary Outcome Variable(s): Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-dose 1 vaccination period – Pooled Group (Total Vaccinated cohort)							
				Pooled Group			
				18y-60y		>60y	

Symptom	Intensity				95 % CI					95 % CI	
		N	n	%	LL	UL	N	n	%	LL	UL
Pain	Any	120	105	87.5	80.2	92.8	120	78	65.0	55.8	73.5
	Grade 3	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
Redness	Any	120	1	0.8	0.0	4.6	120	9	7.5	3.5	13.8
	> 100 mm	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
Swelling	Any	120	11	9.2	4.7	15.8	120	12	10.0	5.3	16.8
	> 100 mm	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0

N= number of subjects with at least one 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= pain that prevented normal activity

Secondary Outcome Variable(s): Number of days with any local symptoms during the solicited post-dose 1 vaccination period – **Pooled Group** (Total Vaccinated cohort)

Solicited symptom	Dose	Group	Sub-group	N	Mean	Median
Pain	Dose 1	Pooled	18y-60y	105	3.1	3.0
			>60y	78	2.8	2.5
Redness	Dose 1	Pooled	18y-60y	1	1.0	1.0
			>60y	9	2.0	2.0
Swelling	Dose 1	Pooled	18y-60y	11	2.2	2.0
			>60y	12	2.2	2.0

N = number of subjects with the symptom

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, for subjects who received 2 doses of Flu vaccine (**2 doses Group**) (Total Vaccinated cohort)

		2 doses Group									
		18y-60y					>60y				
				95 % CI				95 % CI			
Symptom	Intensity	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Pain	Any	68	57	83.8	72.9	91.6	70	46	65.7	53.4	76.7
	Grade 3	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
Redness	Any	68	0	0.0	0.0	5.3	70	3	4.3	0.9	12.0
	>100 mm	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
Swelling	Any	68	5	7.4	2.4	16.3	70	4	5.7	1.6	14.0
	>100 mm	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
Dose 2											
Pain	Any	68	51	75.0	63.0	84.7	70	42	60.0	47.6	71.5
	Grade 3	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
Redness	Any	68	1	1.5	0.0	7.9	70	5	7.1	2.4	15.9
	>100 mm	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
Swelling	Any	68	3	4.4	0.9	12.4	70	3	4.3	0.9	12.0
	>100 mm	68	0	0.0	0.0	5.3	70	1	1.4	0.0	7.7
Across doses											
Pain	Any	68	61	89.7	79.9	95.8	70	52	74.3	62.4	84.0
	Grade 3	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
Redness	Any	68	1	1.5	0.0	7.9	70	6	8.6	3.2	17.7
	>100 mm	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
Swelling	Any	68	7	10.3	4.2	20.1	70	6	8.6	3.2	17.7
	>100 mm	68	0	0.0	0.0	5.3	70	1	1.4	0.0	7.7

N= number of subjects with at least one documented dose

n/%= number/percentage of subjects reporting at least once the symptom

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

Any= occurrence of any local symptom regardless of intensity grade

Grade 3 pain= pain that prevented normal activity											
Secondary Outcome Variable(s): Number of days with symptoms during the 7-day post-vaccination period for subjects who received 2 doses of Flu vaccine (2 doses Group) (Total Vaccinated cohort)											
Solicited symptom	Dose	Sub-group	N	Mean	Median						
Pain	Dose 1	18y-60y	57	3.0	3.0						
		>60y	46	2.7	2.0						
	Dose 2	18y-60y	51	3.0	3.0						
		>60y	42	2.5	2.0						
	Overall/dose	18y-60y	108	3.0	3.0						
		>60y	88	2.6	2.0						
Redness	Dose 1	18y-60y	0	0.0	0.0						
		>60y	3	1.7	1.0						
	Dose 2	18y-60y	1	1.0	1.0						
		>60y	5	1.8	2.0						
	Overall/dose	18y-60y	1	1.0	1.0						
		>60y	8	1.8	1.5						
Swelling	Dose 1	18y-60y	5	2.0	2.0						
		>60y	4	2.0	2.0						
	Dose 2	18y-60y	3	2.3	2.0						
		>60y	3	1.0	1.0						
	Overall/dose	18y-60y	8	2.1	2.0						
		>60y	7	1.6	1.0						
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-dose 1 vaccination period – Pooled Group (Total Vaccinated cohort)											
		Pooled Group									
		18y-60y					>60y				
					95 % CI					95 % CI	
Symptom	Intensity/Relationship	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	Any	120	43	35.8	27.3	45.1	120	26	21.7	14.7	30.1
	Grade 3	120	2	1.7	0.2	5.9	120	1	0.8	0.0	4.6
	Related	120	40	33.3	25.0	42.5	120	24	20.0	13.3	28.3
Headache	Any	120	44	36.7	28.1	45.9	120	22	18.3	11.9	26.4
	Grade 3	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
	Related	120	43	35.8	27.3	45.1	120	21	17.5	11.2	25.5
Joint pain at other location	Any	120	19	15.8	9.8	23.6	120	17	14.2	8.5	21.7
	Grade 3	120	0	0.0	0.0	3.0	120	1	0.8	0.0	4.6
	Related	120	17	14.2	8.5	21.7	120	14	11.7	6.5	18.8
Muscle aches	Any	120	29	24.2	16.8	32.8	120	25	20.8	14.0	29.2
	Grade 3	120	2	1.7	0.2	5.9	120	1	0.8	0.0	4.6
	Related	120	25	20.8	14.0	29.2	120	23	19.2	12.6	27.4
Shivering	Any	120	23	19.2	12.6	27.4	120	7	5.8	2.4	11.6
	Grade 3	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
	Related	120	22	18.3	11.9	26.4	120	7	5.8	2.4	11.6
Sweating	Any	120	19	15.8	9.8	23.6	120	6	5.0	1.9	10.6
	Grade 3	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
	Related	120	17	14.2	8.5	21.7	120	6	5.0	1.9	10.6
Temperature/ (Axillary)	>37.5 °C	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
	≥ 39 °C	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
	Related	120	1	0.8	0.0	4.6	120	0	0.0	0.0	3.0
N= number of subjects with at least one 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 and relationship to vaccination
 Grade 3 = event that 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

Secondary Outcome Variable(s): Number of days with any general symptoms during the solicited post-dose 1 vaccination period – **Pooled Group** (Total Vaccinated cohort)

Solicited symptom	Dose	Sub-group	N	Mean	Median
Fatigue	Dose 1	18y-60y	43	2.7	2.0
		>60y	26	2.2	1.5
Headache	Dose 1	18y-60y	44	1.9	1.0
		>60y	22	2.4	2.0
Joint pain at other location	Dose 1	18y-60y	19	2.5	2.0
		>60y	17	2.8	2.0
Muscle aches	Dose 1	18y-60y	29	2.6	2.0
		>60y	25	3.0	3.0
Shivering	Dose 1	18y-60y	23	1.7	1.0
		>60y	7	1.9	1.0
Sweating	Dose 1	18y-60y	19	1.7	2.0
		>60y	6	1.7	1.5
Temperature	Dose 1	18y-60y	1	1.0	1.0
		>60y	0	0.0	0.0

N = number of subjects 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 overall, for subjects who received 2 doses of Flu vaccine (**2 doses Group**) (Total Vaccinated cohort)

		2 doses Group									
		18y-60y					>60y				
				95 % CI				95 % CI			
Symptom	Intensity/Relationship	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Fatigue	Any	68	24	35.3	24.1	47.8	70	15	21.4	12.5	32.9
	Grade 3	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
	Related	68	21	30.9	20.2	43.3	70	14	20.0	11.4	31.3
Headache	Any	68	23	33.8	22.8	46.3	70	12	17.1	9.2	28.0
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	22	32.4	21.5	44.8	70	11	15.7	8.1	26.4
Joint pain at other location	Any	68	12	17.6	9.5	28.8	70	9	12.9	6.1	23.0
	Grade 3	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
	Related	68	10	14.7	7.3	25.4	70	6	8.6	3.2	17.7
Muscle aches	Any	68	19	27.9	17.7	40.1	70	12	17.1	9.2	28.0
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	15	22.1	12.9	33.8	70	10	14.3	7.1	24.7
Shivering	Any	68	14	20.6	11.7	32.1	70	2	2.9	0.3	9.9
	Grade 3	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
	Related	68	13	19.1	10.6	30.5	70	2	2.9	0.3	9.9
Sweating	Any	68	12	17.6	9.5	28.8	70	5	7.1	2.4	15.9
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	11	16.2	8.4	27.1	70	5	7.1	2.4	15.9
Temperature (Axillary)	>37.5°C	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	≥ 39.0°C	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
	Related	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
Dose 2											
Fatigue	Any	68	19	27.9	17.7	40.1	70	15	21.4	12.5	32.9

	Grade 3	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
	Related	68	19	27.9	17.7	40.1	70	15	21.4	12.5	32.9
Headache	Any	68	15	22.1	12.9	33.8	70	12	17.1	9.2	28.0
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	15	22.1	12.9	33.8	70	12	17.1	9.2	28.0
Joint pain at other location	Any	68	11	16.2	8.4	27.1	70	13	18.6	10.3	29.7
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	11	16.2	8.4	27.1	70	13	18.6	10.3	29.7
Muscle aches	Any	68	15	22.1	12.9	33.8	70	13	18.6	10.3	29.7
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	15	22.1	12.9	33.8	70	13	18.6	10.3	29.7
Shivering	Any	68	18	26.5	16.5	38.6	70	5	7.1	2.4	15.9
	Grade 3	68	2	2.9	0.4	10.2	70	1	1.4	0.0	7.7
	Related	68	18	26.5	16.5	38.6	70	5	7.1	2.4	15.9
Sweating	Any	68	11	16.2	8.4	27.1	70	5	7.1	2.4	15.9
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	11	16.2	8.4	27.1	70	5	7.1	2.4	15.9
Temperature (Axillary)	>37.5°C	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
	≥ 39.0°C	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
	Related	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
Across doses											
Fatigue	Any	68	29	42.6	30.7	55.2	70	26	37.1	25.9	49.5
	Grade 3	68	3	4.4	0.9	12.4	70	0	0.0	0.0	5.1
	Related	68	27	39.7	28.0	52.3	70	25	35.7	24.6	48.1
Headache	Any	68	29	42.6	30.7	55.2	70	20	28.6	18.4	40.6
	Grade 3	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
	Related	68	28	41.2	29.4	53.8	70	19	27.1	17.2	39.1
Joint pain at other location	Any	68	16	23.5	14.1	35.4	70	18	25.7	16.0	37.6
	Grade 3	68	1	1.5	0.0	7.9	70	0	0.0	0.0	5.1
	Related	68	15	22.1	12.9	33.8	70	16	22.9	13.7	34.4
Muscle aches	Any	68	26	38.2	26.7	50.8	70	22	31.4	20.9	43.6
	Grade 3	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
	Related	68	23	33.8	22.8	46.3	70	20	28.6	18.4	40.6
Shivering	Any	68	22	32.4	21.5	44.8	70	7	10.0	4.1	19.5
	Grade 3	68	2	2.9	0.4	10.2	70	1	1.4	0.0	7.7
	Related	68	21	30.9	20.2	43.3	70	7	10.0	4.1	19.5
Sweating	Any	68	19	27.9	17.7	40.1	70	9	12.9	6.1	23.0
	Grade 3	68	2	2.9	0.4	10.2	70	0	0.0	0.0	5.1
	Related	68	18	26.5	16.5	38.6	70	9	12.9	6.1	23.0
Temperature (Axillary)	>37.5°C	68	3	4.4	0.9	12.4	70	0	0.0	0.0	5.1
	≥ 39.0°C	68	0	0.0	0.0	5.3	70	0	0.0	0.0	5.1
	Related	68	3	4.4	0.9	12.4	70	0	0.0	0.0	5.1
<p>N= number of subjects with at least one 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 and relationship to vaccination Grade 3 = event that 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</p>											
Secondary Outcome Variable(s): Number of days with symptoms during the 7-day post-vaccination period, for subjects who received 2 doses of Flu vaccine (2 doses Group) (Total Vaccinated cohort)											
Solicited symptom	Dose	Sub-group		N	Mean	Median					
Fatigue	Dose 1	18y-60y		24	2.9	2.0					
		>60y		15	1.4	1.0					

	Dose 2	18y-60y	19	2.7	2.0
		>60y	15	1.4	1.0
	Overall/dose	18y-60y	43	2.8	2.0
Headache	Dose 1	18y-60y	23	1.7	1.0
		>60y	12	2.1	2.0
	Dose 2	18y-60y	15	1.7	1.0
		>60y	12	1.6	1.0
	Overall/dose	18y-60y	38	1.7	1.0
		>60y	24	1.8	1.5
Joint pain at other location	Dose 1	18y-60y	12	2.4	2.0
		>60y	9	2.4	1.0
	Dose 2	18y-60y	11	2.0	2.0
		>60y	13	1.6	1.0
	Overall/dose	18y-60y	23	2.2	2.0
		>60y	22	2.0	1.0
Muscle aches	Dose 1	18y-60y	19	2.7	2.0
		>60y	12	2.8	2.5
	Dose 2	18y-60y	15	2.4	2.0
		>60y	13	2.3	1.0
	Overall/dose	18y-60y	34	2.6	2.0
		>60y	25	2.5	1.0
Sweating	Dose 1	18y-60y	12	1.8	2.0
		>60y	5	1.4	1.0
	Dose 2	18y-60y	11	2.2	2.0
		>60y	5	1.2	1.0
	Overall/dose	18y-60y	23	2.0	2.0
		>60y	10	1.3	1.0
Shivering	Dose 1	18y-60y	14	1.6	1.0
		>60y	2	1.0	1.0
	Dose 2	18y-60y	18	1.6	1.0
		>60y	5	1.0	1.0
	Overall/dose	18y-60y	32	1.6	1.0
		>60y	7	1.0	1.0
Temperature	Dose 1	18y-60y	1	1.0	1.0
		>60y	0	0.0	0.0
	Dose 2	18y-60y	2	2.0	2.0
		>60y	0	0.0	0.0
	Overall/dose	18y-60y	3	1.7	2.0
		>60y	0	0.0	0.0

N = number of doses with the symptom

Secondary Outcome Variable(s): Number (%) of subjects with adverse events of specific interest (AESI) up to Day 42 (Total Vaccinated cohort)

Most frequent adverse events of specific interest	1 dose Group		2 doses Group	
	18y-60y N = 52	>60y N = 50	18y-60y N = 68	>60y N = 70
Subjects with any AESI(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with related AESI(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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

Secondary Outcome Variable(s): Distribution of haematology and biochemistry with respect to normal laboratory ranges up to Day 42 (Total Vaccinated cohort)

1 dose Group	
18y-60y N = 52	>60y N = 50

Laboratory parameter	Timing	N	Unknown		Below		Within		Above		N	Unknown		Below		Within		Above	
			n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%
ALAT	PRE	52	0	0.0	0	0.0	44	84.6	8	15.4	50	0	0.0	0	0.0	48	96.0	2	4.0
	PI(21)	52	0	0.0	0	0.0	45	86.5	7	13.5	50	0	0.0	0	0.0	46	92.0	4	8.0
	PI(D42)	52	0	0.0	0	0.0	46	88.5	6	11.5	50	0	0.0	0	0.0	44	88.0	6	12.0
AP	PRE	52	0	0.0	0	0.0	51	98.1	1	1.9	50	0	0.0	0	0.0	45	90.0	5	10.0
	PI(21)	52	0	0.0	0	0.0	52	100	0	0.0	50	0	0.0	0	0.0	46	92.0	4	8.0
	PI(D42)	52	0	0.0	0	0.0	52	100	0	0.0	50	0	0.0	0	0.0	44	88.0	6	12.0
ASAT	PRE	52	0	0.0	0	0.0	47	90.4	5	9.6	50	0	0.0	0	0.0	48	96.0	2	4.0
	PI(21)	52	0	0.0	0	0.0	49	94.2	3	5.8	50	0	0.0	0	0.0	48	96.0	2	4.0
	PI(D42)	52	0	0.0	0	0.0	45	86.5	7	13.5	50	0	0.0	0	0.0	48	96.0	2	4.0
Bilirubin	PRE	52	0	0.0	0	0.0	49	94.2	3	5.8	50	0	0.0	0	0.0	48	96.0	2	4.0
	PI(21)	52	0	0.0	0	0.0	49	94.2	3	5.8	50	0	0.0	0	0.0	49	98.0	1	2.0
	PI(D42)	52	0	0.0	0	0.0	50	96.2	2	3.8	50	0	0.0	0	0.0	49	98.0	1	2.0
Creatinine	PRE	52	0	0.0	0	0.0	50	96.2	2	3.8	50	0	0.0	0	0.0	42	84.0	8	16.0
	PI(21)	52	0	0.0	0	0.0	49	94.2	3	5.8	50	0	0.0	0	0.0	41	82.0	9	18.0
	PI(D42)	52	0	0.0	0	0.0	51	98.1	1	1.9	50	0	0.0	0	0.0	41	82.0	9	18.0
BUN	PRE	52	0	0.0	0	0.0	51	98.1	1	1.9	50	0	0.0	0	0.0	47	94.0	3	6.0
	PI(21)	52	0	0.0	0	0.0	51	98.1	1	1.9	50	0	0.0	0	0.0	42	84.0	8	16.0
	PI(D42)	52	0	0.0	0	0.0	51	98.1	1	1.9	50	0	0.0	0	0.0	43	86.0	7	14.0

2 doses Group

		18y-60y N = 68										>60y N = 70							
		Unknown		Below		Within		Above		N		Unknown		Below		Within		Above	
Laboratory parameter	Timing	N	n	%	n	%	n	%	n	%	N	n	%	n	%	n	%	n	%
ALAT	PRE	68	0	0.0	0	0.0	56	82.4	12	17.6	70	0	0.0	0	0.0	66	94.3	4	5.7
	PI(21)	68	0	0.0	0	0.0	56	82.4	12	17.6	70	0	0.0	0	0.0	65	92.9	5	7.1
	PII(D42)	68	0	0.0	0	0.0	57	83.8	11	16.2	70	0	0.0	0	0.0	68	97.1	2	2.9
AP	PRE	68	0	0.0	0	0.0	67	98.5	1	1.5	70	0	0.0	0	0.0	70	100	0	0.0
	PI(21)	68	0	0.0	0	0.0	67	98.5	1	1.5	70	0	0.0	0	0.0	69	98.6	1	1.4
	PII(D42)	68	0	0.0	0	0.0	66	97.1	2	2.9	70	0	0.0	0	0.0	68	97.1	2	2.9
ASAT	PRE	68	0	0.0	0	0.0	63	92.6	5	7.4	70	0	0.0	0	0.0	66	94.3	4	5.7
	PI(21)	68	0	0.0	0	0.0	67	98.5	1	1.5	70	0	0.0	0	0.0	67	95.7	3	4.3
	PII(D42)	68	0	0.0	0	0.0	63	92.6	5	7.4	70	0	0.0	0	0.0	66	94.3	4	5.7
Bilirubin	PRE	68	0	0.0	0	0.0	64	94.1	4	5.9	70	0	0.0	0	0.0	68	97.1	2	2.9
	PI(21)	68	0	0.0	0	0.0	64	94.1	4	5.9	70	0	0.0	0	0.0	66	94.3	4	5.7
	PII(D42)	68	0	0.0	0	0.0	64	94.1	4	5.9	70	0	0.0	0	0.0	67	95.7	3	4.3
Creatinine	PRE	68	0	0.0	0	0.0	59	86.8	9	13.2	70	0	0.0	0	0.0	52	74.3	18	25.7
	PI(21)	68	0	0.0	0	0.0	60	88.2	8	11.8	70	0	0.0	0	0.0	51	72.9	19	27.1
	PII(D42)	68	0	0.0	0	0.0	60	88.2	8	11.8	70	0	0.0	0	0.0	54	77.1	16	22.9
BUN	PRE	68	0	0.0	0	0.0	66	97.1	2	2.9	70	0	0.0	0	0.0	58	82.9	12	17.1
	PI(21)	68	0	0.0	0	0.0	66	97.1	2	2.9	70	0	0.0	0	0.0	59	84.3	11	15.7
	PII(D42)	68	0	0.0	0	0.0	64	94.1	4	5.9	70	0	0.0	0	0.0	57	81.4	13	18.6

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 aminotransferase

AP= Alkaline phosphatase

ASAT= Aspartate aminotransferase

BUN= Blood urea nitrogen

PRE= Pre-vaccination Day 0 PI(21)= Post-dose 1 Day 21 PI(D42)= Post-dose 1 Day 42 PII(D42)= Post-dose 2 Day 42				
Safety results: Number (%) of subjects with unsolicited adverse events during the 42-days (Day 0-41) follow-up period after the first vaccination and 21 days (Day 21-42) follow-up period after the second vaccination (Total Vaccinated cohort)				
Most frequent adverse events - On-Therapy (occurring within Day 0-41 following the first vaccination and within Day 21-42 following the second vaccination)	1 dose Group		2 doses Group	
	18y-60y N = 52	>60y N = 50	18y-60y N = 68	>60y N = 70
Subjects with any AE(s), n (%)	29 (55.8)	17 (34.0)	30 (44.1)	31 (44.3)
Subjects with grade 3 AE(s), n (%)	3 (5.8)	2 (4.0)	8 (11.8)	4 (5.7)
Subjects with related AE(s), n (%)	9 (17.3)	7 (14.0)	16 (23.5)	10 (14.3)
Abdominal pain	3 (5.8)	-	-	-
Diarrhoea	2 (3.8)	-	-	2 (2.9)
Nausea	-	-	3 (4.4)	-
Fatigue	-	-	2 (2.9)	-
Influenza like illness	-	-	4 (5.9)	-
Injection site pruritus	-	2 (4.0)	-	-
Malaise	-	-	-	2 (2.9)
Gastroenteritis	-	-	2 (2.9)	-
Laryngitis	2 (3.8)	-	-	-
Nasopharyngitis	9 (17.3)	3 (6.0)	10 (14.7)	4 (5.7)
Rhinitis	-	2 (4.0)	-	-
Upper respiratory tract infection	-	-	2 (2.9)	2 (2.9)
Back pain	-	2 (4.0)	-	2 (2.9)
Tendonitis	-	2 (4.0)	-	-
Headache	4 (7.7)	-	3 (4.4)	3 (4.3)
Renal impairment	-	-	-	2 (2.9)
Cough	-	-	-	2 (2.9)
Oropharyngeal pain	3 (5.8)	-	-	3 (4.3)
Erythema	-	-	-	2 (2.9)
- : Adverse event absent or not meeting the selected rule: If more than 30 subjects per group and > 3 groups, then only the 5 most frequent adverse events in each group are to be listed. Grade 3= event that prevented normal everyday 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 42 (Total Vaccinated cohort)				
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]				
All SAEs	1 dose Group		2 doses Group	
	18y-60y N = 52	>60y N = 50	18y-60y N = 68	>60y N = 70
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	1 (2.0) [0]	0 (0.0) [0]	2 (2.9) [0]
Atrial fibrillation	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.4) [0]
Intervertebral disc disorder	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.4) [0]
Headache	0 (0.0) [0]	1 (2.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	1 dose Group		2 doses Group	
	18y-60y N = 52	>60y N = 50	18y-60y N = 68	>60y N = 70
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: At 21 days after the first vaccine dose, in the 2 doses Group, seroconversion and seroprotection rates were 95.5% and 98.5% in the 18-60y subgroup and 79.1% and 88.1% in the >60y subgroup, respectively. Seroconversion factor value was 38.71 in the 18-60y subgroup and 13.86 in the >60y subgroup.

Up to Day 42, at least one unsolicited AE was reported by 29 (55.8%) subjects of 1 dose Group (18y-60y), 17 (34.0%) subjects of 1 dose Group (>60y), 30 (44.1%) subjects of 2 doses Group (18y-60y) and 31 (44.3%) subjects of 2 doses Group (>60y).

Up to Day 42, SAEs were reported by 1 (2.0%) subject in the 1 dose Group (>60y) and 2 subjects (2.9%) in the 2 doses Group (>60y). None of the SAEs were assessed as causally related to the study vaccination by the investigator. No fatal SAEs were reported up to Day 42.

Publications: None

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