The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 113809 (FLU D-PAN H1N1-024)

Title: Immunological non-inferiority between two process-manufactured influenza vaccines in adults aged 18 to 60 years.

Rationale: The aim of this study was to assess the immunogenicity of a Flu H1N1 vaccine containing the A/California/7/2009 (H1N1) v-like strain manufactured with a new procedure compared to the initial process-manufactured vaccine.
H1N1 vaccine: GlaxoSmithKline (GSK) Biologicals' Pandemic influenza vaccine comprising A/California/7/2009 (H1N1)v-like strain.

Phase: III

Study Period: 14 October 2009 to:

- 09 November 2009 (Day 21)
- 30 November 2009 (Day 42)
- 28 April 2010 (Day 182)
- 09 November 2010 (Day 364)

Study Design: Double-blind, randomized (1:1:1:1) study with 4 parallel groups.

Centres: 5 centres in Germany

Indication: Immunization against A/California/7/2009 (H1N1)v-like influenza in subjects aged between 18 and 60 years.

Treatment: The study groups were as follows:

- D-INI-1D Group: subjects received 1 dose (at Day 0) of the initial process-manufactured H1N1 vaccine.
- D-INI-2D Group: subjects received 2 doses (at Days 0 and 21) of the initial process-manufactured H1N1 vaccine.
- D-NEW-1D Group: subjects received 1 dose (at Day 0) of the new process-manufactured H1N1 vaccine.
- D-NEW-2D Group: subjects received 2 doses (at Days 0 and 21) of the new process-manufactured H1N1 vaccine.

Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm (first dose) and of the dominant arm (second dose) for the groups receiving 2 doses.

Objectives:

- To evaluate the immunological non-inferiority (in terms of vaccine-homologous virus H1N1 Haemagglutinin Inhibition [HI] antibody geometric mean titres [GMTs]) of the new process-manufactured A/California/7/2009 (H1N1)v-like antigen compared to the initial process-manufactured A/California/7/2009 (H1N1)v-like antigen, 21 days after first vaccination in healthy subjects aged 18 to 60 years.
  Criterion for non-inferiority:
  Non-inferiority is reached if the upper limit of the two-sided 95% Confidence Interval (CI) for the ratio of GMT between the initial process-manufactured vaccine and (over) new process-manufactured vaccine is less than or equal to 2 in terms of Haemagglutination Inhibition (HI) antibody titre against A/California/7/2009 (H1N1)v-like antigen.

Primary Outcome/Efficacy Variable:

Humoral immune response in terms of HI antibodies in all subjects against A/California/7/2009 (H1N1)v-like antigen

- GMTs 21 days after first dose of vaccine (Day 21)

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

- Humoral immune response in terms of HI antibodies
  - In all subjects against A/California/7/2009 (H1N1)v-like antigen:
    - GMTs and seropositivity rates at Days 0, 21, 42, 182, 364
    - Seroconversion rate (SCR*) at Days 21, 42,182, 364
    - Seroprotection rate (SPR**) at Days 0, 21, 42,182, 364
    - Geometric Mean Fold Rise (GMFR***) at Days 21, 42, 182, 364

*SCR is defined as the percentage of vaccinees that have either a pre-vaccination titre < 1:10 and a post-vaccination titre ≥ 1:40 or a pre-vaccination titre ≥ 1:10 and at least a four-fold increase in post-vaccination titre.
**SPR is defined as the percentage of vaccinees with a serum HI titre ≥ 1:40, that usually is accepted as indicating protection.
***GMFR (also known as Seroconversion Factor [SCF]) is defined as the fold increase in serum HI GMTs post-vaccination compared to pre-vaccination.

- Humoral immune response in terms of neutralising antibodies§
  - In a subset of subjects against A/California/7/2009 (H1N1)v-like antigen:

- GMTs at Days 0, 21, 42, 182, 364
- SCR* at Days 21, 42,182, 364

§ Per protocol amendment 1 it was decided not to analyse the humoral immune response in terms of neutralising antibodies.
*SCR is defined as the percentage of vaccinees that have a four-fold increase between pre- and post-vaccination titres.

Safety

- Solicited local and general symptoms
  - Occurrence, duration and intensity of each solicited local adverse event (AE) during the 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination.
  - Occurrence, intensity, duration and relation to vaccination of each solicited general AE during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after each vaccination.
- Unsolicited adverse events
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs within 21 days after the first vaccination (Day 0 – Day 20) and up to 63 days after the second vaccination for the 2 groups with 2 vaccination doses (Day 21 – Day 83*), according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Potential Immune-Mediated-Diseases (pIMDs).
  - Occurrence and relationship to vaccination of pIMDs during the entire study period (up to Day 364). pIMDs are a subset of AEs that include both clearly autoimmune diseases and also other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology.
- Serious adverse events (SAEs).
  - Occurrence and relationship to vaccination of SAEs during the entire study (up to Day 364).

*Unsolicited AEs are presented for the period between Day 0 and Day 83.

Statistical Methods:

Analyses were performed on the Total Vaccinated cohort, the According-To-Protocol (ATP) cohort for immunogenicity, the ATP cohort for persistence at Month 6 and the ATP cohort for persistence at Month 12

- The Total Vaccinated cohort included all subjects with at least one vaccine administration documented.
- 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 one or two doses were taken and assay results were available for antibodies against H1N1 antigen for the blood sample taken twenty one days after each vaccine dose.
- The ATP cohort for antibody persistence at Month 6 included all evaluable subjects (i.e. who met all eligibility criteria, complied with the procedures defined in the protocol, did not meet any of the elimination criteria during the entire study) for whom one or two doses were taken and for whom data concerning immunogenicity outcome measures were available. This cohort included subjects for whom assay results were available for antibodies against the study vaccine antigen component at Month 6.
- The ATP cohort for antibody persistence at Month 12 included all evaluable subjects (i.e. who met all eligibility criteria, complied with the procedures defined in the protocol, did not meet any of the elimination criteria during the entire study) for whom one or two doses were taken and for whom data concerning immunogenicity outcome measures were available. This cohort included subjects for whom assay results were available for antibodies against the study vaccine antigen component at Month 12.

Analysis of immunogenicity:

The analysis was based on the ATP cohort for immunogenicity, the ATP cohort for persistence at Month 6 and the ATP cohort for persistence at Month 12.

Inferential analysis:

The 95% CIs of the GMT ratio (initial process-manufactured H1N1 vaccine over new process-manufactured H1N1 vaccine) for HI antibodies against A/California/7/2009 (H1N1)v-like strain, 21 days after first vaccination was computed. The objective of non-inferiority of new process-manufactured H1N1 vaccine compared to initial process-manufactured H1N1 vaccine was reached if the upper limits of two-sided 95% CIs for the GMT ratio (initial process-manufactured H1N1 vaccine over new process-manufactured H1N1 vaccine) were less than and equal to 2 in terms of HI antibodies against A/California/7/2009 (H1N1)v-like antigen.

Descriptive analysis:

For the humoral response in terms of H1N1 HI antibodies, GMTs, seropositivity rates and SPR were calculated with their 95 % CIs at Day 0, Day 21, Day 42, Day 182 and Day 364 and SCR and SCF were calculated with their 95 % CIs at Day 21, Day 42, Day 182 and Day 364 for all the groups.

Analysis of safety

The analysis was based on the Total Vaccinated cohort.

The incidence of solicited local and general symptoms occurring during the solicited follow-up period following each vaccination was tabulated during the 7-day solicited follow-up period (Day 0 to Day 6) with exact 95% CI for each treatment group and for all subjects aged 18 to 60 years. The same tabulations were performed for Grade 3 symptoms and for solicited general symptoms assessed by the investigators as related to vaccination. The duration of each solicited local and general symptom during the 7-day (Day 0-6) solicited follow-up period was tabulated.

The percentage of subjects with at least one report of an unsolicited AE classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms was reported for each treatment group within 21 days after first dose and up to 63 days after second dose for the 2 groups with two vaccination doses. The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs that were assessed by the investigators as possibly related to vaccination. SAEs and pIMDs were summarized up to Day 364 according to MedDRA preferred terms. The same tabulation was performed for SAEs and pIMDs that were assessed by the investigators as possibly related to vaccination.

Study Population: Male or female subjects aged 18 to 60 years at the time of first vaccination were enrolled in the study if results from a baseline medical assessment by history and physical were satisfactory and that subject had a stable health status. If the subject was female and of childbearing potential, she had to be abstinent or to have used contraceptive precautions for 30 days prior to vaccination; she had to have a negative pregnancy test at study entry and had to agree to continue contraceptive precautions for 2 months after completion of the vaccination series. Written informed consent was obtained from the subject prior to study entry.

Number of subjects	**D-NEW-1D Group**	**D-NEW-2D Group**	**D-INI-1D Group**	**D-INI-2D Group**
Planned, N	75	75	75	75
Randomised, N (Total Vaccinated cohort)	76	73	76	75
Completed at Day 42, n (%)	76 (100)	73 (100)	76 (100)	75 (100)
Completed at Day 364, n (%)	74 (97.4)	73 (100)	74 (97.4)	70 (93.3)
Total Number Subjects Withdrawn, n (%)	2 (2.6)	0 (0.0)	2 (2.6)	5 (6.7)
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 (%)	2 (2.6)	0 (0.0)	2 (2.6)	5 (6.7)
Demographics	**D-NEW-1D Group**	**D-NEW-2D Group**	**D-INI-1D Group**	**D-INI-2D Group**
N (Total Vaccinated cohort)	76	73	76	75
Females:Males	42:34	39:34	43:33	38:37
Mean Age, years (SD)	39.4 (13.02)	40.9 (12.20)	40.5 (12.45)	38.6 (12.10)
White - Caucasian / European heritage, n (%)	76 (100)	73 (100)	76 (100)	74 (98.7)

Primary Efficacy Results: Adjusted GMT ratios between D-INI and D-NEW for HI antibodies against Flu A/CAL/7/09 (H1N1) at Day 21 (ATP cohort for immunogenicity)

						Adjusted GMT ratio			
								95% CI	
Group description	**N**	**Adjusted GMT**	**Group description**	**N**	**Adjusted GMT**	**Ratio order**	**Value**	**LL**	**UL***
D-INI-1D	70	421.6	D-NEW-1D	74	397.5	D-INI-1D /D-NEW-1D	1.06	0.77	1.46
D-INI-2D	74	453.9	D-NEW-2D	72	386.8	D-INI-2D /D-NEW-2D	1.17	0.86	1.61
D-INI	144	437.9	D-NEW	146	392.2	D-INI /D-NEW	1.12	0.89	1.40

Adjusted GMT = geometric mean antibody titre adjusted for baseline titre

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

95% CI = 95% confidence interval for the adjusted GMT ratio; LL = lower limit, UL = upper limit

*Criterion for non-inferiority: upper limit of the two-sided 95% Confidence Interval (CI) for the ratio of GMT ≤ 2

Primary Efficacy Results: Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09 (ATP cohort for immunogenicity)

				≥ 1:10				**GMT***		
						95% CI			**95% CI**	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PRE	74	28	37.8	26.8	49.9	8.6	7.0	10.6
		PI(D21)*	74	74	100	95.1	100	323.0	253.4	411.8

		PII(D42)	74	74	100	95.1	100	226.4	176.8	289.8
	D-NEW-2D	PRE	64	23	35.9	24.3	48.9	8.0	6.7	9.6
		PI(D21)*	64	64	100	94.4	100	334.2	267.9	416.9
		PII(D42)	64	64	100	94.4	100	470.0	387.9	569.6
	D-INI-1D	PRE	71	30	42.3	30.6	54.6	8.9	7.2	11.0
		PI(D21)*	69	69	100	94.8	100	341.5	261.7	445.6
		PII(D42)	71	71	100	94.9	100	268.4	206.2	349.3
	D-INI-2D	PRE	63	22	34.9	23.3	48.0	8.4	6.8	10.3
		PI(D21)*	63	63	100	94.3	100	398.9	294.8	539.7
		PII(D42)	62	62	100	94.2	100	676.8	564.7	811.3

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-vaccination Day 21
PII(D42) = Post-vaccination Day 42
* Primary outcome variable

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09 (ATP cohort for persistence at Month 6)

				≥ 1:10				**GMT**		
						95% CI			**95% CI**	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PRE	72	27	37.5	26.4	49.7	8.5	6.9	10.4
		PII(D182)	72	71	98.6	92.5	100	102.7	79.4	132.9
	D-NEW-2D	PRE	68	23	33.8	22.8	46.3	7.8	6.6	9.2
		PII(D182)	68	68	100	94.7	100	147.5	120.9	180.0
	D-INI-1D	PRE	69	29	42.0	30.2	54.5	9.0	7.3	11.1
		PII(D182)	69	68	98.6	92.2	100	128.3	94.9	173.3
	D-INI-2D	PRE	65	24	36.9	25.3	49.8	8.8	7.1	11.0
		PII(D182)	65	65	100	94.5	100	226.3	183.5	279.1

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
PII(D182) = Post-vaccination Day 182

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09 (ATP cohort for persistence at Month 12)

				≥ 1:10				**GMT**		
						95% CI			**95% CI**	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PRE	65	23	35.4	23.9	48.2	8.4	6.7	10.5
		PII(D364)	65	64	98.5	91.7	100	63.9	48.8	83.7
	D-NEW-2D	PRE	63	22	34.9	23.3	48.0	7.9	6.6	9.5
		PII(D364)	63	63	100	94.3	100	75.7	59.8	96.0
	D-INI-1D	PRE	62	25	40.3	28.1	53.6	9.1	7.2	11.5
		PII(D364)	62	60	96.8	88.8	99.6	81.3	58.6	112.7
	D-INI-2D	PRE	58	23	39.7	27.0	53.4	9.2	7.2	11.7
		PII(D364)	58	58	100	93.8	100	123.7	95.2	160.8

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

PII(D364) = Post-vaccination Day 364

Secondary Outcome Variable(s): 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**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PI(D21)	74	71	95.9	88.6	99.2
		PII(D42)	74	68	91.9	83.2	97.0
	D-NEW-2D	PI(D21)	64	62	96.9	89.2	99.6
		PII(D42)	64	62	96.9	89.2	99.6
	D-INI-1D	PI(D21)	69	65	94.2	85.8	98.4
		PII(D42)	71	65	91.5	82.5	96.8
	D-INI-2D	PI(D21)	63	61	96.8	89.0	99.6
		PII(D42)	62	62	100	94.2	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(D21) = Post-vaccination Day 21
PII(D42) = Post-vaccination Day 42

Secondary Outcome Variable(s): SCR for HI antibodies against Flu A/CAL/7/09 at Day 182 (ATP cohort for persistence at Month 6)

			SCR			
					95% CI	
Antibody against	**Group**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	72	60	83.3	72.7	91.1
	D-NEW-2D	68	63	92.6	83.7	97.6
	D-INI-1D	69	55	79.7	68.3	88.4
	D-INI-2D	65	64	98.5	91.7	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

Secondary Outcome Variable(s): SCR for HI antibodies against Flu A/CAL/7/09 at Day 364 (ATP cohort for persistence at Month 12)

			SCR			
					95% CI	
Antibody against	**Group**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	65	43	66.2	53.4	77.4
	D-NEW-2D	63	49	77.8	65.5	87.3
	D-INI-1D	62	41	66.1	53.0	77.7
	D-INI-2D	58	50	86.2	74.6	93.9

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

Secondary Outcome Variable(s): SPR for HI antibodies against Flu A/CAL/7/09 at Day 0, Day 21 and Day 42 (ATP cohort for immunogenicity)

	SPR

						95% CI	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PRE	74	6	8.1	3.0	16.8
		PI(D21)	74	73	98.6	92.7	100
		PII(D42)	74	71	95.9	88.6	99.2
	D-NEW-2D	PRE	64	4	6.3	1.7	15.2
		PI(D21)	64	64	100	94.4	100
		PII(D42)	64	64	100	94.4	100
	D-INI-1D	PRE	71	6	8.5	3.2	17.5
		PI(D21)	69	67	97.1	89.9	99.6
		PII(D42)	71	68	95.8	88.1	99.1
	D-INI-2D	PRE	63	2	3.2	0.4	11.0
		PI(D21)	63	62	98.4	91.5	100
		PII(D42)	62	62	100	94.2	100

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-vaccination Day 21
PII(D42) = Post-vaccination Day 42

Secondary Outcome Variable(s): SPR for HI antibodies against Flu A/CAL/7/09 at Day 0 and Day 182 (ATP cohort for persistence Month 6)

				SPR			
						95% CI	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PRE	72	5	6.9	2.3	15.5
		PII(D182)	72	63	87.5	77.6	94.1
	D-NEW-2D	PRE	68	4	5.9	1.6	14.4
		PII(D182)	68	66	97.1	89.8	99.6
	D-INI-1D	PRE	69	6	8.7	3.3	18.0
		PII(D182)	69	60	87.0	76.7	93.9
	D-INI-2D	PRE	65	3	4.6	1.0	12.9
		PII(D182)	65	65	100	94.5	100

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
PII(D182) = Post-vaccination Day 182

Secondary Outcome Variable(s): SPR for HI antibodies against Flu A/CAL/7/09 at Day 0 and Day 364 (ATP cohort for persistence Month 12)

				SPR			
						95% CI	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PRE	65	5	7.7	2.5	17.0
		PII(D364)	65	47	72.3	59.8	82.7
	D-NEW-2D	PRE	63	4	6.3	1.8	15.5
		PII(D364)	63	54	85.7	74.6	93.3
	D-INI-1D	PRE	62	6	9.7	3.6	19.9
		PII(D364)	62	48	77.4	65.0	87.1
	D-INI-2D	PRE	58	3	5.2	1.1	14.4
		PII(D364)	58	53	91.4	81.0	97.1

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

PII(D364) = Post-vaccination Day 364

Secondary Outcome Variable(s): SCF for HI antibodies against Flu A/CAL/7/09 at Day 21 and Day 42 (ATP cohort for immunogenicity)

				SCF		
					95% CI	
Antibody against	**Group**	**Timing**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	PI(D21)	74	37.4	28.8	48.6
		PII(D42)	74	26.2	20.2	33.9
	D-NEW-2D	PI(D21)	64	41.8	31.5	55.3
		PII(D42)	64	58.7	44.6	77.3
	D-INI-1D	PI(D21)	69	38.0	28.3	51.0
		PII(D42)	71	30.1	22.6	40.0
	D-INI-2D	PI(D21)	63	47.7	35.7	63.7
		PII(D42)	62	82.5	66.4	102.5

N = Number of subjects with pre- and post-vaccination results available
SCF = Fold increase in serum HI GMTs post-vaccination
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PI(D21)= Post-vaccination Day 21
PII(D42) = Post-vaccination Day 42

Secondary Outcome Variable(s): SCF for HI antibodies against Flu A/CAL/7/09 at Day 182 (ATP cohort for persistence Month 6)

			SCF		
				95% CI	
Antibody against	**Group**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	72	12.1	9.6	15.3
	D-NEW-2D	68	18.9	15.3	23.5
	D-INI-1D	69	14.3	10.6	19.2
	D-INI-2D	65	25.6	20.9	31.5

N = Number of subjects with pre- and post-vaccination results available
SCF = Fold increase in serum HI GMTs post-vaccination
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): SCF for HI antibodies against Flu A/CAL/7/09 at Day 364 (ATP cohort for persistence Month 12)

			SCF		
				95% CI	
Antibody against	**Group**	**N**	**Value**	**LL**	**UL**
Flu A/CAL/7/09	D-NEW-1D	65	7.6	6.0	9.8
	D-NEW-2D	63	9.5	7.6	11.9
	D-INI-1D	62	8.9	6.4	12.5
	D-INI-2D	58	13.5	10.7	17.0

N = Number of subjects with pre- and post-vaccination results available
SCF = Fold increase in serum HI GMTs post-vaccination
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

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 (Total Vaccinated cohort)

		D-NEW-1D Group					D-NEW-2D Group					D-INI-1D Group					D-INI-2D Group				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	**Intensity**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1																					
Pain	Any	76	71	93.4	85.3	97.8	73	62	84.9	74.6	92.2	74	69	93.2	84.9	97.8	75	66	88.0	78.4	94.4
	Grade 3	76	2	2.6	0.3	9.2	73	2	2.7	0.3	9.5	74	1	1.4	0.0	7.3	75	2	2.7	0.3	9.3
Redness	Any	76	1	1.3	0.0	7.1	73	1	1.4	0.0	7.4	74	4	5.4	1.5	13.3	75	1	1.3	0.0	7.2
	>100 mm	76	1	1.3	0.0	7.1	73	0	0.0	0.0	4.9	74	0	0.0	0.0	4.9	75	0	0.0	0.0	4.8
Swelling	Any	76	4	5.3	1.5	12.9	73	4	5.5	1.5	13.4	74	3	4.1	0.8	11.4	75	7	9.3	3.8	18.3
	>100 mm	76	0	0.0	0.0	4.7	73	0	0.0	0.0	4.9	74	0	0.0	0.0	4.9	75	0	0.0	0.0	4.8

Dose 2																					
Pain	Any	-	-	-	-	-	70	61	87.1	77.0	93.9	-	-	-	-	-	71	59	83.1	72.3	91.0
	Grade 3	-	-	-	-	-	70	0	0.0	0.0	5.1	-	-	-	-	-	71	3	4.2	0.9	11.9
Redness	Any	-	-	-	-	-	70	3	4.3	0.9	12.0	-	-	-	-	-	71	3	4.2	0.9	11.9
	>100 mm	-	-	-	-	-	70	0	0.0	0.0	5.1	-	-	-	-	-	71	0	0.0	0.0	5.1
Swelling	Any	-	-	-	-	-	70	5	7.1	2.4	15.9	-	-	-	-	-	71	7	9.9	4.1	19.3
	>100 mm	-	-	-	-	-	70	0	0.0	0.0	5.1	-	-	-	-	-	71	0	0.0	0.0	5.1
Across doses																					
Pain	Any	76	71	93.4	85.3	97.8	73	67	91.8	83.0	96.9	74	69	93.2	84.9	97.8	75	68	90.7	81.7	96.2
	Grade 3	76	2	2.6	0.3	9.2	73	2	2.7	0.3	9.5	74	1	1.4	0.0	7.3	75	5	6.7	2.2	14.9
Redness	Any	76	1	1.3	0.0	7.1	73	3	4.1	0.9	11.5	74	4	5.4	1.5	13.3	75	4	5.3	1.5	13.1
	>100 mm	76	1	1.3	0.0	7.1	73	0	0.0	0.0	4.9	74	0	0.0	0.0	4.9	75	0	0.0	0.0	4.8
Swelling	Any	76	4	5.3	1.5	12.9	73	7	9.6	3.9	18.8	74	3	4.1	0.8	11.4	75	11	14.7	7.6	24.7
	>100 mm	76	0	0.0	0.0	4.7	73	0	0.0	0.0	4.9	74	0	0.0	0.0	4.9	75	0	0.0	0.0	4.8

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

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

Symptom	**Dose**	**Group**	**N**	**Mean**	**Median**
Pain	Dose 1	D-NEW-1D	71	3.0	3.0
		D-NEW-2D	62	3.0	3.0
		D-INI-1D	69	3.3	3.0
		D-INI-2D	66	3.1	3.0
	Dose 2	D-NEW-2D	61	2.9	3.0
		D-INI-2D	59	3.0	3.0
Redness	Dose 1	D-NEW-1D	1	5.0	5.0
		D-NEW-2D	1	2.0	2.0
		D-INI-1D	4	2.0	1.5
		D-INI-2D	1	2.0	2.0
	Dose 2	D-NEW-2D	3	2.7	2.0
		D-INI-2D	3	3.7	4.0
Swelling	Dose 1	D-NEW-1D	4	4.0	4.0
		D-NEW-2D	4	2.8	3.0
		D-INI-1D	3	2.3	1.0
		D-INI-2D	7	3.3	3.0
	Dose 2	D-NEW-2D	5	2.8	3.0
		D-INI-2D	7	2.6	2.0

N = number of doses with the symptom

Secondary Outcome Variable(s): Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and across doses (Total Vaccinated cohort)

		D-NEW-1D Group					**D-NEW-2D Group**					**D-INI-1D Group**					**D-INI-2D Group**				
					95 % CI					**95 % CI**					**95 % CI**					**95 % CI**	
Symptom	**Intensity/ Relationship**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1																					
Fatigue	Any	76	19	25.0	15.8	36.3	73	30	41.1	29.7	53.2	74	19	25.7	16.2	37.2	75	31	41.3	30.1	53.3
	Grade 3	76	1	1.3	0.0	7.1	73	2	2.7	0.3	9.5	74	0	0.0	0.0	4.9	75	2	2.7	0.3	9.3
	Related	76	17	22.4	13.6	33.4	73	22	30.1	19.9	42.0	74	17	23.0	14.0	34.2	75	29	38.7	27.6	50.6
Headache	Any	76	25	32.9	22.5	44.6	73	22	30.1	19.9	42.0	74	21	28.4	18.5	40.1	75	31	41.3	30.1	53.3
	Grade 3	76	0	0.0	0.0	4.7	73	2	2.7	0.3	9.5	74	0	0.0	0.0	4.9	75	3	4.0	0.8	11.2
	Related	76	18	23.7	14.7	34.8	73	17	23.3	14.2	34.6	74	15	20.3	11.8	31.2	75	27	36.0	25.2	47.9

Joint pain at other location	Any	76	13	17.1	9.4	27.5	73	14	19.2	10.9	30.1	74	9	12.2	5.7	21.8	75	15	20.0	11.6	30.8
	Grade 3	76	1	1.3	0.0	7.1	73	1	1.4	0.0	7.4	74	0	0.0	0.0	4.9	75	1	1.3	0.0	7.2
	Related	76	13	17.1	9.4	27.5	73	12	16.4	8.8	27.0	74	6	8.1	3.0	16.8	75	14	18.7	10.6	29.3
Muscle aches	Any	76	26	34.2	23.7	46.0	73	22	30.1	19.9	42.0	74	25	33.8	23.2	45.7	75	28	37.3	26.4	49.3
	Grade 3	76	1	1.3	0.0	7.1	73	1	1.4	0.0	7.4	74	1	1.4	0.0	7.3	75	0	0.0	0.0	4.8
	Related	76	24	31.6	21.4	43.3	73	20	27.4	17.6	39.1	74	17	23.0	14.0	34.2	75	28	37.3	26.4	49.3
Shivering	Any	76	9	11.8	5.6	21.3	73	19	26.0	16.5	37.6	74	12	16.2	8.7	26.6	75	29	38.7	27.6	50.6
	Grade 3	76	0	0.0	0.0	4.7	73	0	0.0	0.0	4.9	74	1	1.4	0.0	7.3	75	2	2.7	0.3	9.3
	Related	76	8	10.5	4.7	19.7	73	16	21.9	13.1	33.1	74	10	13.5	6.7	23.5	75	27	36.0	25.2	47.9
Sweating	Any	76	7	9.2	3.8	18.1	73	9	12.3	5.8	22.1	74	6	8.1	3.0	16.8	75	12	16.0	8.6	26.3
	Grade 3	76	0	0.0	0.0	4.7	73	0	0.0	0.0	4.9	74	0	0.0	0.0	4.9	75	2	2.7	0.3	9.3
	Related	76	5	6.6	2.2	14.7	73	4	5.5	1.5	13.4	74	5	6.8	2.2	15.1	75	10	13.3	6.6	23.2
Temperature (Axillary)	≥ 37.5°C	76	2	2.6	0.3	9.2	73	1	1.4	0.0	7.4	74	2	2.7	0.3	9.4	75	2	2.7	0.3	9.3
	≥ 39.0-≤40°C	76	0	0.0	0.0	4.7	73	0	0.0	0.0	4.9	74	0	0.0	0.0	4.9	75	0	0.0	0.0	4.8
	Related	76	2	2.6	0.3	9.2	73	1	1.4	0.0	7.4	74	2	2.7	0.3	9.4	75	2	2.7	0.3	9.3
Dose 2																					
Fatigue	Any	-	-	-	-	-	70	29	41.4	29.8	53.8	-	-	-	-	-	71	33	46.5	34.5	58.7
	Grade 3	-	-	-	-	-	70	2	2.9	0.3	9.9	-	-	-	-	-	71	2	2.8	0.3	9.8
	Related	-	-	-	-	-	70	27	38.6	27.2	51.0	-	-	-	-	-	71	26	36.6	25.5	48.9
Headache	Any	-	-	-	-	-	70	24	34.3	23.3	46.6	-	-	-	-	-	71	32	45.1	33.2	57.3
	Grade 3	-	-	-	-	-	70	2	2.9	0.3	9.9	-	-	-	-	-	71	3	4.2	0.9	11.9
	Related	-	-	-	-	-	70	17	24.3	14.8	36.0	-	-	-	-	-	71	26	36.6	25.5	48.9
Joint pain at other location	Any	-	-	-	-	-	70	15	21.4	12.5	32.9	-	-	-	-	-	71	22	31.0	20.5	43.1
	Grade 3	-	-	-	-	-	70	1	1.4	0.0	7.7	-	-	-	-	-	71	3	4.2	0.9	11.9
	Related	-	-	-	-	-	70	15	21.4	12.5	32.9	-	-	-	-	-	71	19	26.8	16.9	38.6
Muscle aches	Any	-	-	-	-	-	70	21	30.0	19.6	42.1	-	-	-	-	-	71	26	36.6	25.5	48.9
	Grade 3	-	-	-	-	-	70	1	1.4	0.0	7.7	-	-	-	-	-	71	3	4.2	0.9	11.9
	Related	-	-	-	-	-	70	21	30.0	19.6	42.1	-	-	-	-	-	71	26	36.6	25.5	48.9
Shivering	Any	-	-	-	-	-	70	21	30.0	19.6	42.1	-	-	-	-	-	71	21	29.6	19.3	41.6
	Grade 3	-	-	-	-	-	70	2	2.9	0.3	9.9	-	-	-	-	-	71	4	5.6	1.6	13.8
	Related	-	-	-	-	-	70	21	30.0	19.6	42.1	-	-	-	-	-	71	18	25.4	15.8	37.1
Sweating	Any	-	-	-	-	-	70	10	14.3	7.1	24.7	-	-	-	-	-	71	10	14.1	7.0	24.4
	Grade 3	-	-	-	-	-	70	1	1.4	0.0	7.7	-	-	-	-	-	71	1	1.4	0.0	7.6
	Related	-	-	-	-	-	70	9	12.9	6.1	23.0	-	-	-	-	-	71	9	12.7	6.0	22.7
Temperature (Axillary)	≥ 37.5°C	-	-	-	-	-	70	4	5.7	1.6	14.0	-	-	-	-	-	71	5	7.0	2.3	15.7
	≥ 39.0-≤40°C	-	-	-	-	-	70	1	1.4	0.0	7.7	-	-	-	-	-	71	0	0.0	0.0	5.1
	Related	-	-	-	-	-	70	4	5.7	1.6	14.0	-	-	-	-	-	71	5	7.0	2.3	15.7
Across doses																					
Fatigue	Any	76	19	25.0	15.8	36.3	73	43	58.9	46.8	70.3	74	19	25.7	16.2	37.2	75	43	57.3	45.4	68.7
	Grade 3	76	1	1.3	0.0	7.1	73	4	5.5	1.5	13.4	74	0	0.0	0.0	4.9	75	4	5.3	1.5	13.1
	Related	76	17	22.4	13.6	33.4	73	36	49.3	37.4	61.3	74	17	23.0	14.0	34.2	75	38	50.7	38.9	62.4
Headache	Any	76	25	32.9	22.5	44.6	73	36	49.3	37.4	61.3	74	21	28.4	18.5	40.1	75	43	57.3	45.4	68.7
	Grade 3	76	0	0.0	0.0	4.7	73	4	5.5	1.5	13.4	74	0	0.0	0.0	4.9	75	5	6.7	2.2	14.9
	Related	76	18	23.7	14.7	34.8	73	26	35.6	24.7	47.7	74	15	20.3	11.8	31.2	75	36	48.0	36.3	59.8
Joint pain at other location	Any	76	13	17.1	9.4	27.5	73	23	31.5	21.1	43.4	74	9	12.2	5.7	21.8	75	27	36.0	25.2	47.9
	Grade 3	76	1	1.3	0.0	7.1	73	2	2.7	0.3	9.5	74	0	0.0	0.0	4.9	75	4	5.3	1.5	13.1
	Related	76	13	17.1	9.4	27.5	73	22	30.1	19.9	42.0	74	6	8.1	3.0	16.8	75	23	30.7	20.5	42.4
Muscle aches	Any	76	26	34.2	23.7	46.0	73	35	47.9	36.1	60.0	74	25	33.8	23.2	45.7	75	37	49.3	37.6	61.1
	Grade 3	76	1	1.3	0.0	7.1	73	2	2.7	0.3	9.5	74	1	1.4	0.0	7.3	75	3	4.0	0.8	11.2
	Related	76	24	31.6	21.4	43.3	73	33	45.2	33.5	57.3	74	17	23.0	14.0	34.2	75	37	49.3	37.6	61.1
Shivering	Any	76	9	11.8	5.6	21.3	73	33	45.2	33.5	57.3	74	12	16.2	8.7	26.6	75	40	53.3	41.4	64.9
	Grade 3	76	0	0.0	0.0	4.7	73	2	2.7	0.3	9.5	74	1	1.4	0.0	7.3	75	6	8.0	3.0	16.6
	Related	76	8	10.5	4.7	19.7	73	30	41.1	29.7	53.2	74	10	13.5	6.7	23.5	75	35	46.7	35.1	58.6
Sweating	Any	76	7	9.2	3.8	18.1	73	17	23.3	14.2	34.6	74	6	8.1	3.0	16.8	75	20	26.7	17.1	38.1

	Grade 3	76	0	0.0	0.0	4.7	73	1	1.4	0.0	7.4	74	0	0.0	0.0	4.9	75	3	4.0	0.8	11.2
	Related	76	5	6.6	2.2	14.7	73	13	17.8	9.8	28.5	74	5	6.8	2.2	15.1	75	17	22.7	13.8	33.8
Temperatu	≥ 37.5°C	76	2	2.6	0.3	9.2	73	5	6.8	2.3	15.3	74	2	2.7	0.3	9.4	75	6	8.0	3.0	16.6
re (Axillary)	≥ 39.0-≤40°C	76	0	0.0	0.0	4.7	73	1	1.4	0.0	7.4	74	0	0.0	0.0	4.9	75	0	0.0	0.0	4.8
	Related	76	2	2.6	0.3	9.2	73	5	6.8	2.3	15.3	74	2	2.7	0.3	9.4	75	6	8.0	3.0	16.6

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 general symptom regardless of intensity grade or relationship to vaccination
Grade 3 symptoms = 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-vaccination period (Total Vaccinated cohort)

Solicited symptom	Dose	Group	N	Mean	Median
Fatigue	Dose 1	D-NEW-1D	19	2.5	2.0
		D-NEW-2D	30	2.2	2.0
		D-INI-1D	19	2.1	2.0
		D-INI-2D	31	2.3	2.0
	Dose 2	D-NEW-2D	29	2.0	2.0
		D-INI-2D	33	2.2	2.0
Headache	Dose 1	D-NEW-1D	25	2.0	2.0
		D-NEW-2D	22	2.2	1.0
		D-INI-1D	21	2.0	1.0
		D-INI-2D	31	2.1	2.0
	Dose 2	D-NEW-2D	24	1.9	1.0
		D-INI-2D	32	2.4	2.0
Joint pain at other location	Dose 1	D-NEW-1D	13	2.1	2.0
		D-NEW-2D	14	2.7	2.0
		D-INI-1D	9	2.3	2.0
		D-INI-2D	15	2.0	2.0
	Dose 2	D-NEW-2D	15	2.1	2.0
		D-INI-2D	22	2.0	1.0
Muscle aches	Dose 1	D-NEW-1D	26	2.3	2.0
		D-NEW-2D	22	2.6	2.0
		D-INI-1D	25	2.4	2.0
		D-INI-2D	28	2.4	2.0
	Dose 2	D-NEW-2D	21	2.4	2.0
		D-INI-2D	26	2.7	3.0
Sweating	Dose 1	D-NEW-1D	7	1.1	1.0
		D-NEW-2D	9	1.6	1.0
		D-INI-1D	6	3.7	4.0
		D-INI-2D	12	2.0	2.0
	Dose 2	D-NEW-2D	10	1.4	1.0
		D-INI-2D	10	2.1	1.0
Shivering	Dose 1	D-NEW-1D	9	1.8	1.0
		D-NEW-2D	19	2.1	1.0
		D-INI-1D	12	2.2	1.5
		D-INI-2D	29	1.8	1.0
	Dose 2	D-NEW-2D	21	1.5	1.0
		D-INI-2D	21	1.6	1.0
Temperature	Dose 1	D-NEW-1D	2	1.0	1.0
		D-NEW-2D	1	1.0	1.0
		D-INI-1D	2	1.0	1.0

		D-INI-2D	2	1.0	1.0
	Dose 2	D-NEW-2D	4	1.8	1.5
		D-INI-2D	5	1.0	1.0

N = number of doses with the symptom

Secondary Outcome Variable(s): Number (%) of subjects with AE of Specific Interest (AESI) / potential Immune-Mediated Diseases (pIMDs) up to Day 42 (Total Vaccinated cohort)

AESIs/pIMDs	**D-NEW-1D Group N = 76**	**D-NEW-2D Group N = 73**	**D-INI-1D Group N = 76**	**D-INI-2D Group N = 75**
Subjects with any AE(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with related AE(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Related AE: event assessed by the investigator as possibly related to the study vaccination.

Secondary Outcome Variable(s): Number (%) of subjects with AE of Specific Interest (AESI) / potential Immune-Mediated Diseases (pIMDs) up to Day 364 (Total Vaccinated cohort)

AESIs/pIMDs	**D-NEW-1D Group N = 76**	**D-NEW-2D Group N = 73**	**D-INI-1D Group N = 76**	**D-INI-2D Group N = 75**
Subjects with any AE(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with related AE(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Related AE: event assessed by the investigator as possibly related to the study vaccination.

Safety results: Number (%) of subjects with unsolicited adverse events classified within the 21-day (Days 0-20) post-vaccination period (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Days 0-20 following vaccination)	**D-NEW-1D Group N = 76**	**D-NEW-2D Group N = 73**	**D-INI-1D Group N = 76**	**D-INI-2D Group N = 75**
Subjects with any AE(s), n (%)	17 (22.4)	20 (27.4)	28 (36.8)	18 (24.0)
Subjects with grade 3 AE(s), n (%)	2 (2.6)	2 (2.7)	2 (2.6)	1 (1.3)
Subjects with related AE(s), n (%)	5 (6.6)	13 (17.8)	5 (6.6)	4 (5.3)
Cardiac disorder	-	-	1 (1.3)	-
Vertigo	-	1 (1.4)	1 (1.3)	1 (1.3)
Conjunctivitis	1 (1.3)	-	1 (1.3)	1 (1.3)
Abdominal pain	-	1 (1.4)	-	-
Abdominal pain upper	-	-	-	1 (1.3)
Diarrhoea	1 (1.3)	-	1 (1.3)	1 (1.3)
Dyspepsia	-	1 (1.4)	-	-
Gastritis	-	-	2 (2.6)	-
Nausea	-	1 (1.4)	-	-
Toothache	-	-	-	1 (1.3)
Injection site induration	-	1 (1.4)	-	-
Injection site pain	-	1 (1.4)	-	-
Injection site pruritus	1 (1.3)	-	-	-
Bronchitis	-	-	1 (1.3)	-
Gastroenteritis	-	-	1 (1.3)	-
Gastrointestinal infection	-	1 (1.4)	-	-
Herpes simplex	-	-	1 (1.3)	1 (1.3)
Nasopharyngitis	11 (14.5)	4 (5.5)	7 (9.2)	5 (6.7)
Rhinitis	1 (1.3)	1 (1.4)	1 (1.3)	3 (4.0)
Salpingitis	-	-	1 (1.3)	-
Tonsillitis	1 (1.3)	-	-	1 (1.3)
Upper respiratory tract infection	-	-	-	1 (1.3)
Contusion	-	1 (1.4)	1 (1.3)	-
Decreased appetite	-	1 (1.4)	-	-
Iron deficiency	1 (1.3)	-	-	-
Arthralgia	-	-	-	2 (2.7)

Back pain	-	1 (1.4)	-	-
Intervertebral disc protrusion	-	-	1 (1.3)	-
Musculoskeletal chest pain	-	-	1 (1.3)	-
Myalgia	-	-	-	1 (1.3)
Headache	-	3 (4.1)	3 (3.9)	4 (5.3)
Migraine	-	1 (1.4)	-	-
Paraesthesia	1 (1.3)	1 (1.4)	1 (1.3)	1 (1.3)
Burnout syndrome	-	1 (1.4)	-	-
Calculus urethral	-	-	1 (1.3)	-
Breast discomfort	-	-	-	1 (1.3)
Metrorrhagia	1 (1.3)	-	-	-
Bronchial hyperreactivity	-	1 (1.4)	-	-
Cough	1 (1.3)	1 (1.4)	2 (2.6)	-
Dyspnoea	-	1 (1.4)	-	-
Epistaxis	1 (1.3)	1 (1.4)	-	-
Oropharyngeal pain	3 (3.9)	-	-	1 (1.3)
Pruritus	-	-	1 (1.3)	-
Cataract operation	-	-	1 (1.3)	-
Hot flush	-	-	1 (1.3)	-
Hypertension	1 (1.3)	-	-	-
Peripheral coldness	-	1 (1.4)	-	-
Peripheral vascular disorder	-	-	-	1 (1.3)
2 AEs reported in the D-INI-1D Group were not classified by MedDRA Preferred Term. -: Adverse event absent Grade 3 AE: an AE which prevented normal, everyday activities. Related AE: assessed by the investigator as possibly related to the study vaccination				
Safety results: Number (%) of subjects with unsolicited adverse events up to Day 42 (Total Vaccinated cohort) - interim analysis posted at Day 42				
Most frequent adverse events - On-Therapy (occurring within Day 0-41 following vaccination)	**D-NEW-1D Group N = 76**	**D-NEW-2D Group N = 73**	**D-INI-1D Group N = 76**	**D-INI-2D Group N = 75**
Subjects with any AE(s), n (%)	27 (35.5)	27 (37.0)	37 (48.7)	30 (40.0)
Subjects with grade 3 AE(s), n (%)	4 (5.3)	6 (8.2)	3 (3.9)	3 (4.0)
Subjects with related AE(s), n (%)	5 (6.6)	15 (20.5)	5 (6.6)	7 (9.3)
Nasopharyngitis	19 (25.0)	7 (9.6)	8 (10.5)	10 (13.3)
Headache	-	4 (5.5)	4 (5.3)	6 (8.0)
Rhinitis	-	3 (4.1)	3 (3.9)	3 (4.0)
Oropharyngeal pain	4 (5.3)	-	-	2 (2.7)
Vertigo	-	3 (4.1)	-	3 (4.0)
Cough	2 (2.6)	-	2 (2.6)	-
Nausea	-	4 (5.5)	-	-
Back pain	-	3 (4.1)	-	-
Arthralgia	-	-	-	2 (2.7)
Conjunctivitis	2 (2.6)	-	-	-
Gastritis	-	-	2 (2.6)	-
Gastroenteritis	-	-	2 (2.6)	-
Iron deficiency	2 (2.6)	-	-	-
Upper respiratory tract infection	-	-	-	2 (2.7)
Grade 3 AE = event which prevented normal, everyday activities. Related AE = event assessed by the investigator as possibly related to the study vaccination - : Adverse event absent or not meeting the selected rule: More than 30 subjects per treatment group and > 3 groups: only the 5 most frequent events in each treatment group are to be listed. *Note: This interim analysis is superseded by the final analysis*				
Safety results: Number (%) of subjects with unsolicited adverse events within 84 days after dose 1 and 63 days after dose 2 for the 2 groups with 2 vaccination doses (Total Vaccinated cohort)				

Most frequent adverse events - On-Therapy (occurring within Day 0-83 following vaccination and up to 63 days after second vaccination)	**D-NEW-2D Group N = 73**	**D-INI-2D Group N = 75**
Subjects with any AE(s), n (%)	30 (41.1)	35 (46.7)
Subjects with grade 3 AE(s), n (%)	7 (9.6)	6 (8.0)
Subjects with related AE(s), n (%)	15 (20.5)	7 (9.3)
Nasopharyngitis	7 (9.6)	11 (14.7)
Headache	7 (9.6)	9 (12.0)
Nausea	4 (5.5)	-
Upper respiratory tract infection	3 (4.1)	6 (8.0)
Vertigo	3 (4.1)	3 (4.0)
Rhinitis	3 (4.1)	3 (4.0)
Arthralgia	2 (2.7)	2 (2.7)
Back pain	3 (4.1)	-
Oropharyngeal pain	-	2 (2.7)
Fatigue	2 (2.7)	1 (1.3)
Lymphadenitis	-	1 (1.3)
Decreased appetite	2 (2.7)	-
Conjunctivitis	-	1 (1.3)
Abdominal pain upper		1 (1.3)
Osteoarthritis	2 (2.7)	-
Diarrhoea	-	1 (1.3)
Dyspepsia	-	1 (1.3)
Peripheral coldness	2 (2.7)	-
Toothache	-	1 (1.3)
Influenza like illness	-	1 (1.3)
Injection site lymphadenopathy	-	1 (1.3)
Injection site pruritus		1 (1.3)
Injection site warmth	-	1 (1.3)
Pyrexia	-	1 (1.3)
Gastroenteritis	-	1 (1.3)
Gastroenteritis viral	-	1 (1.3)
Herpes simplex	-	1 (1.3)
Sinusitis	-	1 (1.3)
Tonsillitis	-	1 (1.3)
Ankle fracture	-	1 (1.3)
Face injury	-	1 (1.3)
Myalgia	-	1 (1.3)
Pain in extremity	-	1 (1.3)
Paraesthesia	-	1 (1.3)
Depression	-	1 (1.3)
Insomnia	-	1 (1.3)
Breast discomfort	-	1 (1.3)
Breast pain	-	1 (1.3)
Cough	-	1 (1.3)
Hypertension	-	1 (1.3)
Peripheral vascular disorder	-	1 (1.3)

- : Adverse event absent or not meeting the selected rule: More than 30 subjects per treatment group and ≤ 3 groups: only the 10 most frequent events in each treatment group are to be listed.
Grade 3 AE = event which prevented normal, everyday activities.
Related AE = event assessed by the investigator as possibly 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	**D-NEW-1D**	**D-NEW-2D**	**D-INI-1D**	**D-INI-2D**

	Group N = 76	Group N = 73	Group N = 76	Group N = 75
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]	2 (2.6) [0]	2 (2.7) [1]
Calculus urethral	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Gastritis	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Pain in extremity	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [1]
Peripheral vascular disorder	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]
Salpingitis	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Fatal SAEs	**D-NEW-1D Group N = 76**	**D-NEW-2D Group N = 73**	**D-INI-1D Group N = 76**	**D-INI-2D Group N = 75**
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]
Safety results: Number (%) of subjects with serious adverse events up to Day 364 (Total Vaccinated cohort)				
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]				
All SAEs	**D-NEW-1D Group N = 76**	**D-NEW-2D Group N = 73**	**D-INI-1D Group N = 76**	**D-INI-2D Group N = 75**
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	7 (9.2) [0]	2 (2.7) [0]	3 (3.9) [0]	5 (6.7) [1]
Asthma	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Bartholin's abscess	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Bronchial hyperreactivity	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Calculus urethral	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Cerebral haemorrhage	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cerebral thrombosis	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cholecystitis chronic	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]
Coronary artery disease	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Epilepsy	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Foot deformity	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]
Gastritis	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Limb injury	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Malignant peritoneal neoplasm	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]
Osteitis deformans	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]
Osteoarthritis	0 (0.0) [0]	1 (1.4) [0]	0 (0.0) [0]	0 (0.0) [0]
Pain in extremity	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [1]
Peripheral vascular disorder	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]
Prostatic adenoma	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Radius fracture	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Rotator cuff syndrome	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Salpingitis	0 (0.0) [0]	0 (0.0) [0]	1 (1.3) [0]	0 (0.0) [0]
Status epilepticus	1 (1.3) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Tachycardia paroxysmal	0 (0.0) [0]	1 (1.4) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**D-NEW-1D Group N = 76**	**D-NEW-2D Group N = 73**	**D-INI-1D Group N = 76**	**D-INI-2D Group N = 75**
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 Day 21 GMT value for HI antibodies against Flu A/CAL/7/09 was at least 323.0 across groups.
Up to Day 21, at least one unsolicited AE was reported by 17 subjects (22.4%) in the D-NEW-1D Group, 20 subjects (27.4%) in the D-NEW-2D Group, 28 subjects (36.8%) in the D-INI-1D Group and 18 subjects (24.0%) in the D-INI 2D Group, respectively.
Up to Day 83, 30 (41.1%) subjects in D-NEW-2D Group and 35 (46.7%) subjects in D-INI-2D Group reported at least one

unsolicited AE.
From Day 0 to Day 364, SAEs were reported for 7 (9.2%), 2 (2.7%), 3 (3.9%) and 5 (6.7%) subjects in the D-NEW 1D, D-NEW-2D, D-INI-1D and D-INI-2D groups, respectively; 1 SAE in the D-INI-2D Group was assessed by the investigator as causally related to the study vaccination. No fatal SAE was reported from Day 0 to Day 364.

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