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.: 110794 (FLU-LD-012 PRI)

Title: Immunogenicity, safety and reactogenicity of GSK Biologicals' low dose influenza vaccine with various doses of the AS03 adjuvant in subjects aged 18-64 years.

Rationale: The aim of the study was to evaluate the immunogenicity and safety of the low dose influenza vaccine with various doses of adjuvant compared to *Fluarix*™ administered intramuscularly in adults aged 18-64 years.
Fluarix™ (Flu): GlaxoSmithKline (GSK) Biologicals' licensed influenza vaccine
FluLD: GSK Biologicals' low dose influenza vaccine

Phase: II

Study Period: 05 October 2007 to 08 May 2008

Study Design: Multi-center, single blind, randomized (1:1:1:1:1), controlled study with 5 parallel groups.

Centers: Fifteen centers in Europe (France, Germany and Spain)

Indication: Immunization of healthy male and female subjects aged 18-64 years old against influenza

Treatment: The 5 study groups were as follows:

- FluLD1/1 group: subjects received 1 low dose of influenza vaccine adjuvanted with full dose of adjuvant,
- FluLD1/2 group: subjects received 1 low dose of influenza vaccine adjuvanted with 1/2 dose of adjuvant,
- FluLD1/4 group: subjects received 1 low dose of influenza vaccine adjuvanted with 1/4 dose of adjuvant,
- FluLD1/8 group: subjects received 1 low dose of influenza vaccine adjuvanted with 1/8 dose of adjuvant,
- Flu group: subjects received 1 dose of Flu vaccine.

The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm.

Objectives: To demonstrate the immunological non-inferiority (geometric mean titer [GMT]) of the low dose influenza vaccine with various adjuvant dosages (1/1, 1/2, 1/4, 1/8 dose of adjuvant) versus Flu vaccine, 21 days following vaccination in all subjects.

Primary Outcome/Efficacy Variable:

- At Days 0 and 21: serum hemagglutination-inhibition (HI) antibody titer, against each of the 3 vaccine strains in all subjects.

Secondary Outcome/Efficacy Variable(s):

Safety

- Occurrence, intensity and relationship to vaccination of solicited local and general signs and symptoms during a 7-day follow-up period (i.e. day of vaccination and 6 subsequent days) after vaccination in all subjects.
- Occurrence, intensity and relationship to vaccination of unsolicited adverse events (AEs) during a 21-day follow-up period (i.e. day of vaccination and 20 subsequent days) after vaccination in all subjects.
- Occurrence and relationship to vaccination of serious adverse events (SAEs) during the entire study period in all subjects.
- Occurrence, intensity, duration*, and relationship to vaccination of medically-significant conditions prompting hospitalization, emergency room visits or physician visits that were not routine visits for physical examination or vaccination, during the entire study period (up to Day 180) in all subjects.

*Duration was mentioned by error in the protocol and was not analyzed.

Humoral immune response

Observed variables:

- At Days 0, 21 and 180: serum HI antibody titers, against each of the 3 vaccine strains, in all subjects
- At Days 0, 21 and 180: neutralizing antibody titers, tested separately against each of the 3 influenza virus strains§ represented in the vaccine in in a subset of subjects.

Derived variables:

- GMTs of HI antibody titers at Days 0, 21 and 180
- Seroconversion rates (SCRs)* for HI titers at Days 21 and 180†
- Seroconversion factors (SCFs)** for HI titers at Days 21 and 180†
- Seroprotection rates (SPRs)*** for HI titers at Days 0, 21 and 180†
- GMTs of neutralizing antibody titers† at Days 0 and 21

* SCR was defined as the percentage of vaccinees who had either a prevaccination serum HI antibody titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a four-fold increase in post-vaccination titer.
** SCF was defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.

*** SPR was defined as the percentage of vaccinees with a serum HI titer ≥ 1:40 that is usually accepted as indicating protection.
†SCR, SCF, SPR at Day 180 were not foreseen in the protocol. The decision to analyze those data was made at the time of analysis.
§A/Brisbane (H3N2) and B/Florida (B) were used to test the cross-reactivity against drifted strains. No drifted H1N1 strain was available at the time of testing. For this reason, neutralising antibodies against H1N1 strain were not evaluated.

Cell-mediated immune response (in a subset of subjects)

Observed variables at Days 0, 21 and 180 :

- Frequency of cytokine-positive cluster of differentiation (CD4/CD8) cells per 10^6 in tests producing at least two different signal molecules (interleukin-2 [IL-2], interferon-gamma [IFN-γ], tumor necrosis factor [TNF-α] and CD40 ligand [CD40L]).
- Frequency of cytokine-positive CD4/CD8 cells per 10^6 in tests producing at least CD40L and another signal molecule (IL-2, IFN-γ, TNF-α).
- Frequency of cytokine-positive CD4/CD8 cells per 10^6 in tests producing at least IL-2 and another signal molecule (CD40L, IFN-γ, TNF-α).
- Frequency of cytokine-positive CD4/CD8 cells per 10^6 in tests producing at least TNF-α and another signal molecule (IL-2, IFN-γ, CD40L).
- Frequency of cytokine-positive CD4/CD8 cells per 10^6 in tests producing at least IFN-γ and another signal molecule (CD40L, IL-2, TNF-α).

Derived variables:

For each test, geometric mean of specific influenza CD4/CD8 T lymphocytes at Day 0, 21 and 180

Statistical Methods:

The 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 and intervals defined in the protocol, with no elimination criteria during the study) for whom immunogenicity data were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

Immunogenicity analysis:

The analysis was based on the ATP cohort for immunogenicity.

Inferential analysis

The 90% confidence interval (CI) lower limits of the Geometric Mean Titer (GMT) ratio (Flu Low Dose vaccine over Flu vaccine) were computed to assess the immunogenicity of influenza adjuvanted vaccines compared to Flu vaccine. All the adjuvanted doses among 1/1, 1/2, 1/4, and 1/8 having the 3 lower limits of the GMT ratio higher than 0.63 for each strain: A/Solomon Islands (H1N1), A/Wisconsin (H3N2) and B/Malaysia (B), would be considered as a candidate dose for the final vaccine formulation.

Descriptive analysis

For each vaccine group and each vaccine strain, the GMTs with 95% CI & SPR with exact 95% CI were calculated at Days 0, 21 and 180; the SCR with exact 95% CI & SCF with 95% CI were tabulated at Days 21 and 180.
At Days 0, 21 and 180, neutralizing antibody titers were tabulated with their 95% CIs in a subset of subjects.
Descriptive statistics (Geometric Mean, Mean, Standard Deviation and Median) of the frequency of immune response marker-positive CD4 T-cells and CD8 T-cells for all vaccine strains at Days 0, 21 and 180 were tabulated in a subset of subjects.

Safety analysis:

The analysis was based on the Total Vaccinated cohort.
The percentage of subjects reporting each individual solicited local and general symptom during the 7-day (Days 0 -6) solicited follow-up period was tabulated with exact 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The percentage of subjects with at least one report of unsolicited AEs classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and reported up to 21 days (Days 0-20) after vaccination was tabulated. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with relationship to vaccination. Occurrence of SAEs during the entire study period was tabulated according to MedDRA preferred terms. The occurrence of adverse events associated to medically significant conditions (MSC) between Day 0 and Day 180 was tabulated according to MedDRA preferred terms. The same tabulation was performed for MSCs with relationship to vaccination and for grade 3 & related MSCs.

Study Population: Male or female aged 18 - 64 years at the time of enrolment. Healthy subjects as established by medical history and clinical examination before entering into the study. Written informed consent was obtained from the subject before study entry. If the subject was female and of childbearing potential, she had to be abstinent or use adequate contraceptive precautions for 30 days before vaccination and to have a negative pregnancy test, and was to agree to continue such precautions for 2 months after vaccination.

Number of Subjects:	**FluLD1/1 Group**	**FluLD1/2 Group**	**FluLD1/4 Group**	**FluLD1/8 Group**	**Flu Group**
Planned, N	200	200	200	200	200
Randomized, N (Total Vaccinated cohort)	200	198	204	202	202
Completed, n (%)	197 (98.5)	197 (99.5)	204 (100)	202 (100)	202 (100)
Total Number Subjects Withdrawn, n (%)	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Adverse Events n (%)	2 (1.0)	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	Not applicable
Withdrawn for other reasons n (%)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Demographics	**FluLD1/1 Group**	**FluLD1/2 Group**	**FluLD1/4 Group**	**FluLD1/8 Group**	**Flu Group**
N (Total Vaccinated cohort)	200	198	204	202	202
Females: Males	115:85	116:82	115:89	140:62	123:79
Mean Age, years (SD)	40.5 (14.14)	40.3 (13.79)	39.7 (14.37)	39.7 (14.31)	40.1 (14.11)
Caucasian / European heritage, n (%)	190 (95.0)	184 (92.9)	194 (95.1)	193 (95.5)	191 (94.6)

Primary Efficacy Results: Non-inferiority of adjuvanted low dose vaccines with respect to Flu vaccine in terms of GMT ratios at Day 21 for the 3 viral strains (ATP cohort for immunogenicity)

AS03 Dose Proportion	**Antibody**	**Flu Low Dose Group**				**Flu Vaccine Group**				**LD/Flu**		
				95% CI				**95% CI**			**90%CI**	
		N	**GMT**	**LL**	**UL**	**N**	**GMT**	**LL**	**UL**	**Ratio**	**LL**	**UL**
1/1	**A/Solomon Islands**	187	202.3	168.3	243.2	185	191.0	158.7	229.9	1.06	0.85	1.32
	A/Wisconsin	187	378.6	320.0	447.8	185	335.3	286.5	392.3	1.13	0.93	1.37
	B/Malaysia	187	236.0	206.1	270.4	185	217.8	184.5	257.2	1.08	0.91	1.30
1/2	**A/Solomon Islands**	189	160.5	135.7	189.9	185	191.0	158.7	229.9	0.84	0.68	1.04
	A/Wisconsin	189	336.0	288.2	391.8	185	335.3	286.5	392.3	1.00	0.83	1.20
	B/Malaysia	189	226.2	204.8	249.7	185	217.8	184.5	257.2	1.04	0.88	1.22
1/4	**A/Solomon Islands**	190	155.5	139.2	173.7	185	191.0	158.7	229.9	0.81	0.68	0.98
	A/Wisconsin	190	302.0	272.9	334.1	185	335.3	286.5	392.3	0.90	0.77	1.05
	B/Malaysia	190	205.7	181.9	232.6	185	217.8	184.5	257.2	0.94	0.79	1.12
1/8	**A/Solomon Islands**	192	156.3	132.8	183.8	185	191.0	158.7	229.9	0.82	0.67	1.01
	A/Wisconsin	192	282.9	244.0	328.1	185	335.3	286.5	392.3	0.84	0.70	1.01
	B/Malaysia	192	169.4	145.1	197.7	185	217.8	184.5	257.2	0.78	0.64	0.94

GMT = Geometric Mean antibody titer
N = Number of subjects with available results
95% CI = 95% confidence interval; 90% CI = 90% confidence interval; LL = Lower Limit, UL = Upper Limit
Non-inferiority Criterion: LL of GMT ratio (Flu Low Dose over Flu vaccine)> 0.67 for the 3 strains

Primary Efficacy Results: Seropositivity rates and GMTs for HI antibody titer at Days 0, 21 and 180 (ATP cohort for immunogenicity)

Antibody	**Group**	**Timing**	**N**	**≥ 1:10**				**GMT**		
						95% CI		**Value**	**95% CI**	
				n	**%**	**LL**	**UL**		**LL**	**UL**
A/Solomon Islands	FluLD1/1	PRE*	187	94	50.3	42.9	57.6	13.0	10.9	15.5
		PI(DAY21)*	187	187	100	98.0	100	203.2	171.7	240.3
		PI(DAY180)	189	183	96.8	93.2	98.8	81.3	68.3	96.8
	FluLD1/2	PRE*	189	83	43.9	36.7	51.3	12.3	10.2	14.8
		PI(DAY21)*	189	185	97.9	94.7	99.4	155.8	128.2	189.4
		PI(DAY180)	190	178	93.7	89.2	96.7	71.1	58.8	86.1
	FluLD1/4	PRE*	190	84	44.2	37.0	51.6	12.9	10.6	15.8

		PI(DAY21)*	190	186	97.9	94.7	99.4	164.9	137.6	197.8
		PI(DAY180)	192	181	94.3	90.0	97.1	76.3	63.2	92.0
	FluLD1/8	PRE*	192	100	52.1	44.8	59.3	14.9	12.3	18.2
		PI(DAY21)*	192	187	97.4	94.0	99.1	151.1	124.7	183.1
		PI(DAY180)	192	179	93.2	88.7	96.3	80.7	66.7	97.5
	Flu	PRE*	185	106	57.3	49.8	64.5	15.1	12.5	18.2
		PI(DAY21)*	185	183	98.9	96.1	99.9	191.0	158.5	230.2
		PI(DAY180)	187	186	99.5	97.1	100	97.6	82.5	115.5
A/Wisconsin	FluLD1/1	PRE*	187	142	75.9	69.2	81.9	29.4	23.8	36.4
		PI(DAY21)*	187	187	100	98.0	100	380.1	321.3	449.8
		PI(DAY180)	189	187	98.9	96.2	99.9	174.3	145.6	208.8
	FluLD1/2	PRE*	189	141	74.6	67.8	80.6	30.0	24.3	37.2
		PI(DAY21)*	189	188	99.5	97.1	100	326.4	275.6	386.7
		PI(DAY180)	190	188	98.9	96.2	99.9	149.5	125.3	178.3
	FluLD1/4	PRE*	190	141	74.2	67.4	80.3	29.9	24.5	36.5
		PI(DAY21)*	190	188	98.9	96.2	99.9	319.9	270.0	379.1
		PI(DAY180)	192	188	97.9	94.8	99.4	164.0	138.0	195.0
	FluLD1/8	PRE*	192	149	77.6	71.0	83.3	27.2	22.6	32.8
		PI(DAY21)*	192	191	99.5	97.1	100	273.9	232.0	323.3
		PI(DAY180)	192	190	99.0	96.3	99.9	133.0	112.5	157.3
	Flu	PRE*	185	155	83.8	77.7	88.8	37.4	30.2	46.4
		PI(DAY21)*	185	185	100	98.0	100	335.3	286.2	392.7
		PI(DAY180)	187	186	99.5	97.1	100	176.2	151.7	204.6
B/Malaysia	FluLD1/1	PRE*	187	142	75.9	69.2	81.9	25.8	21.3	31.3
		PI(DAY21)*	187	187	100	98.0	100	225.8	195.3	261.1
		PI(DAY180)	189	186	98.4	95.4	99.7	106.6	91.7	124.0
	FluLD1/2	PRE*	189	145	76.7	70.0	82.5	27.3	22.6	32.9
		PI(DAY21)*	189	188	99.5	97.1	100	246.1	210.9	287.2
		PI(DAY180)	190	189	99.5	97.1	100	119.6	103.7	138.0
	FluLD1/4	PRE*	190	138	72.6	65.7	78.8	22.6	18.8	27.1
		PI(DAY21)*	190	188	98.9	96.2	99.9	195.5	165.1	231.4
		PI(DAY180)	192	188	97.9	94.8	99.4	97.2	83.2	113.5
	FluLD1/8	PRE*	192	142	74.0	67.1	80.0	23.2	19.5	27.8
		PI(DAY21)*	192	188	97.9	94.8	99.4	171.2	144.2	203.2
		PI(DAY180)	192	187	97.4	94.0	99.1	95.7	82.1	111.7
	Flu	PRE*	185	139	75.1	68.3	81.2	27.0	22.2	32.7
		PI(DAY21)*	185	183	98.9	96.1	99.9	217.8	184.3	257.4
		PI(DAY180)	187	185	98.9	96.2	99.9	108.8	93.1	127.0

N = Number of subjects with available results
n/% = number/percentage of seropositive subjects (HI titer ≥ 1:10)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
* Primary outcome variables
PRE = Pre-vaccination at Day 0
PI(DAY21) = Post-vaccination at Day 21
PI(DAY180) = Post-vaccination at Day 180

Secondary Outcome Variable: SCR for HI antibody titer at each time point (ATP cohort for immunogenicity)

Vaccine strain	**Group**	**Timing**	**N**	**SCR**			
						95% CI	
				n	**%**	**LL**	**UL**
A/Solomon Islands	FluLD1/1	PI(DAY21)	187	154	82.4	76.1	87.5
		PI(DAY180)	189	117	61.9	54.6	68.9
	FluLD1/2	PI(DAY21)	189	141	74.6	67.8	80.6
		PI(DAY180)	190	108	56.8	49.5	64.0
	FluLD1/4	PI(DAY21)	190	133	70.0	62.9	76.4

		PI(DAY180)	192	102	53.1	45.8	60.3
	FluLD1/8	PI(DAY21)	192	119	62.0	54.7	68.9
		PI(DAY180)	192	102	53.1	45.8	60.3
	Flu	PI(DAY21)	185	131	70.8	63.7	77.2
		PI(DAY180)	187	110	58.8	51.4	66.0
A/Wisconsin	FluLD1/1	PI(DAY21)	187	150	80.2	73.8	85.7
		PI(DAY180)	189	112	59.3	51.9	66.3
	FluLD1/2	PI(DAY21)	189	147	77.8	71.2	83.5
		PI(DAY180)	190	97	51.1	43.7	58.4
	FluLD1/4	PI(DAY21)	190	142	74.7	67.9	80.7
		PI(DAY180)	192	112	58.3	51.0	65.4
	FluLD1/8	PI(DAY21)	192	142	74.0	67.1	80.0
		PI(DAY180)	192	106	55.2	47.9	62.4
	Flu	PI(DAY21)	185	118	63.8	56.4	70.7
		PI(DAY180)	187	100	53.5	46.1	60.8
B/Malaysia	FluLD1/1	PI(DAY21)	187	136	72.7	65.7	79.0
		PI(DAY180)	189	99	52.4	45.0	59.7
	FluLD1/2	PI(DAY21)	189	127	67.2	60.0	73.8
		PI(DAY180)	190	99	52.1	44.8	59.4
	FluLD1/4	PI(DAY21)	190	128	67.4	60.2	74.0
		PI(DAY180)	192	98	51.0	43.7	58.3
	FluLD1/8	PI(DAY21)	192	127	66.1	59.0	72.8
		PI(DAY180)	192	102	53.1	45.8	60.3
	Flu	PI(DAY21)	185	125	67.6	60.3	74.3
		PI(DAY180)	187	88	47.1	39.7	54.5

Seroconversion defined as:
For initially seronegative subjects, antibody titer ≥ 1:40 after vaccination
For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of seroconverted subjects
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PI(DAY21)= Post-vaccination at Day 21
PI(DAY180) = Post-vaccination at Day 180
Remark: Day 0 and Day 21 samples were tested in pairs. Day 180 samples were tested independently of Day 0 and Day 21 samples. It explains the difference in N's on Days 0-21 and Day 180.

Secondary Outcome Variable: SCF for HI antibody titer at Days 21 and 180 (ATP cohort for immunogenicity)

Vaccine strain	**Group**	**Timing**	**N**	**SCF**		
				Value	**95% CI**	
					LL	**UL**
A/Solomon Islands	FluLD1/1	PI(DAY21)	187	15.6	12.7	19.2
		PI(DAY180)	189	6.4	5.3	7.7
	FluLD1/2	PI(DAY21)	189	12.7	10.2	15.8
		PI(DAY180)	190	5.9	4.8	7.2
	FluLD1/4	PI(DAY21)	190	12.8	10.1	16.1
		PI(DAY180)	192	5.9	4.8	7.2
	FluLD1/8	PI(DAY21)	192	10.1	8.0	12.8
		PI(DAY180)	192	5.4	4.4	6.7
	Flu	PI(DAY21)	185	12.7	9.9	16.2
		PI(DAY180)	187	6.5	5.2	8.0
A/Wisconsin	FluLD1/1	PI(DAY21)	187	12.9	10.5	16.0
		PI(DAY180)	189	6.0	5.0	7.2
	FluLD1/2	PI(DAY21)	189	10.9	8.9	13.3
		PI(DAY180)	190	5.0	4.2	6.1
	FluLD1/4	PI(DAY21)	190	10.7	8.6	13.2

		PI(DAY180)	192	5.4	4.5	6.6
	FluLD1/8	PI(DAY21)	192	10.1	8.2	12.3
		PI(DAY180)	192	4.9	4.1	5.9
	Flu	PI(DAY21)	185	9.0	7.2	11.2
		PI(DAY180)	187	4.7	3.9	5.8
B/Malaysia	FluLD1/1	PI(DAY21)	187	8.7	7.2	10.6
		PI(DAY180)	189	4.2	3.5	4.9
	FluLD1/2	PI(DAY21)	189	9.0	7.3	11.2
		PI(DAY180)	190	4.4	3.6	5.3
	FluLD1/4	PI(DAY21)	190	8.7	7.0	10.8
		PI(DAY180)	192	4.4	3.6	5.3
	FluLD1/8	PI(DAY21)	192	7.4	6.1	8.9
		PI(DAY180)	192	4.1	3.5	4.8
	Flu	PI(DAY21)	185	8.1	6.6	9.9
		PI(DAY180)	187	4.0	3.3	4.8

N = Number of subjects with pre- and post-vaccination results available
SCF defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PI(DAY21)= Post-vaccination at Day 21
PI(DAY180) = Post-vaccination at Day 180
Remark: Day 0 and Day 21 samples were tested in pairs. Day 180 samples were tested independently of Day 0 and Day 21 samples. It explains the difference in N's on Days 0-21 and Day 180.

Secondary Outcome Variable: SPR for HI antibody titer at Days 0, 21 and 180 (ATP cohort for immunogenicity)

Vaccine strain	**Group**	**Timing**	**N**	**SPR**			
						95% CI	
				n	**%**	**LL**	**UL**
A/Solomon Islands	FluLD1/1	PRE	187	45	24.1	18.1	30.8
		PI(DAY21)	187	177	94.7	90.4	97.4
		PI(DAY180)	189	157	83.1	76.9	88.1
	FluLD1/2	PRE	189	46	24.3	18.4	31.1
		PI(DAY21)	189	170	89.9	84.7	93.8
		PI(DAY180)	190	144	75.8	69.1	81.7
	FluLD1/4	PRE	190	43	22.6	16.9	29.2
		PI(DAY21)	190	169	88.9	83.6	93.0
		PI(DAY180)	192	144	75.0	68.3	81.0
	FluLD1/8	PRE	192	52	27.1	20.9	34.0
		PI(DAY21)	192	166	86.5	80.8	91.0
		PI(DAY180)	192	151	78.6	72.2	84.2
	Flu	PRE	185	50	27.0	20.8	34.0
		PI(DAY21)	185	172	93.0	88.3	96.2
		PI(DAY180)	187	159	85.0	79.1	89.8
A/Wisconsin	FluLD1/1	PRE	187	90	48.1	40.8	55.5
		PI(DAY21)	187	183	97.9	94.6	99.4
		PI(DAY180)	189	175	92.6	87.9	95.9
	FluLD1/2	PRE	189	90	47.6	40.3	55.0
		PI(DAY21)	189	186	98.4	95.4	99.7
		PI(DAY180)	190	173	91.1	86.1	94.7
	FluLD1/4	PRE	190	96	50.5	43.2	57.8
		PI(DAY21)	190	185	97.4	94.0	99.1
		PI(DAY180)	192	175	91.1	86.2	94.8
	FluLD1/8	PRE	192	91	47.4	40.2	54.7
		PI(DAY21)	192	184	95.8	92.0	98.2
		PI(DAY180)	192	173	90.1	85.0	93.9
	Flu	PRE	185	95	51.4	43.9	58.8

		PI(DAY21)	185	183	98.9	96.1	99.9
		PI(DAY180)	187	183	97.9	94.6	99.4
B/Malaysia	FluLD1/1	PRE	187	80	42.8	35.6	50.2
		PI(DAY21)	187	183	97.9	94.6	99.4
		PI(DAY180)	189	174	92.1	87.2	95.5
	FluLD1/2	PRE	189	88	46.6	39.3	53.9
		PI(DAY21)	189	186	98.4	95.4	99.7
		PI(DAY180)	190	177	93.2	88.6	96.3
	FluLD1/4	PRE	190	81	42.6	35.5	50.0
		PI(DAY21)	190	180	94.7	90.5	97.4
		PI(DAY180)	192	167	87.0	81.4	91.4
	FluLD1/8	PRE	192	86	44.8	37.6	52.1
		PI(DAY21)	192	180	93.8	89.3	96.7
		PI(DAY180)	192	171	89.1	83.8	93.1
	Flu	PRE	185	88	47.6	40.2	55.0
		PI(DAY21)	185	178	96.2	92.4	98.5
		PI(DAY180)	187	169	90.4	85.2	94.2

N = Number of subjects with available results
n (%) = Number (percentage) of seroprotected subjects (HI titer ≥1:40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE= Pre-vaccination at Day 0
PI(DAY21) = Post-vaccination at Day 21
PI(DAY180)= Post-vaccination at Day 180

Secondary Outcome Variable: Seropositivity rates and GMTs for A/Wisconsin, B/Malaysia, B/Florida and A/Brisbane neutralizing antibodies in a subset of subjects (ATP cohort for immunogenicity)

Antibody	**Group**	**Timing**	**N**	**≥ 1:28**				**GMT**		
						95% CI		**Value**	**95% CI**	
				n	**%**	**LL**	**UL**		**LL**	**UL**
A/Wisconsin	FluLD1/1	PRE	43	40	93.0	80.9	98.5	134.3	94.6	190.8
		PI(DAY21)	47	47	100	92.5	100	1193.7	876.6	1625.5
	FluLD1/2	PRE	47	45	95.7	85.5	99.5	136.3	101.4	183.1
		PI(DAY21)	48	48	100	92.6	100	859.6	637.8	1158.5
	FluLD1/4	PRE	44	42	95.5	84.5	99.4	160.8	111.0	232.9
		PI(DAY21)	44	44	100	92.0	100	1027.9	760.3	1389.8
	FluLD1/8	PRE	43	41	95.3	84.2	99.4	148.0	107.0	204.5
		PI(DAY21)	47	47	100	92.5	100	842.3	641.9	1105.2
	Flu	PRE	42	40	95.2	83.8	99.4	212.5	138.2	326.6
		PI(DAY21)	42	42	100	91.6	100	864.0	654.2	1140.9
B/Malaysia	FluLD1/1	PRE	46	27	58.7	43.2	73.0	34.1	25.7	45.1
		PI(DAY21)	44	42	95.5	84.5	99.4	162.5	117.6	224.5
	FluLD1/2	PRE	48	26	54.2	39.2	68.6	36.5	25.9	51.3
		PI(DAY21)	48	48	100	92.6	100	161.5	128.6	202.9
	FluLD1/4	PRE	44	22	50.0	34.6	65.4	33.3	24.4	45.4
		PI(DAY21)	43	42	97.7	87.7	99.9	141.0	103.8	191.3
	FluLD1/8	PRE	44	20	45.5	30.4	61.2	27.7	21.1	36.2
		PI(DAY21)	42	41	97.6	87.4	99.9	130.5	98.7	172.7
	Flu	PRE	42	29	69.0	52.9	82.4	49.7	35.2	70.0
		PI(DAY21)	42	38	90.5	77.4	97.3	166.0	111.2	247.7
A/Brisbane	FluLD1/1	PRE	47	47	100	92.5	100	494.2	389.0	627.7
		PI(DAY21)	47	47	100	92.5	100	1151.5	901.8	1470.4
	FluLD1/2	PRE	48	48	100	92.6	100	365.9	298.3	449.0
		PI(DAY21)	48	48	100	92.6	100	847.5	668.0	1075.3
	FluLD1/4	PRE	44	44	100	92.0	100	392.5	319.1	482.8
		PI(DAY21)	44	44	100	92.0	100	884.2	673.2	1161.2

	FluLD1/8	PRE	47	47	100	92.5	100	445.7	369.2	538.0
		PI(DAY21)	47	47	100	92.5	100	1038.2	799.3	1348.6
	Flu	PRE	41	41	100	91.4	100	466.8	355.2	613.5
		PI(DAY21)	42	42	100	91.6	100	867.1	658.9	1141.1
B/Florida	FluLD1/1	PRE	45	31	68.9	53.4	81.8	48.9	35.2	67.9
		PI(DAY21)	43	39	90.7	77.9	97.4	94.3	68.8	129.3
	FluLD1/2	PRE	48	35	72.9	58.2	84.7	56.9	38.6	83.9
		PI(DAY21)	48	46	95.8	85.7	99.5	113.6	79.7	162.0
	FluLD1/4	PRE	44	29	65.9	50.1	79.5	51.0	35.2	73.9
		PI(DAY21)	43	36	83.7	69.3	93.2	92.1	60.6	139.9
	FluLD1/8	PRE	47	31	66.0	50.7	79.1	46.8	32.7	66.9
		PI(DAY21)	43	37	86.0	72.1	94.7	82.7	57.9	118.2
	Flu	PRE	42	32	76.2	60.5	87.9	76.7	51.1	115.3
		PI(DAY21)	42	40	95.2	83.8	99.4	131.1	93.3	184.2

N = Number of subjects with available results
n (%) = number (percentage) of seropositive subjects (HI titer ≥ 1:28)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Day 0
PI(DAY21) = Post-vaccination at Day 21

Secondary Outcome Variable: Descriptive statistics of the frequency of immune response marker-positive CD4 T-cells (per million CD4 T-cells) for all vaccine strains at Days 0, 21 and 180 in a subset of subjects (ATP cohort for immunogenicity)

Test description	Group	Timing	N	GM	Mean	SD	Median
ALL DOUBLES	FluLD1/1	PRE	45	1762.08	2106.16	1274.90	1886.00
		PI(DAY21)	45	3196.51	3857.76	2195.47	3467.00
		PI(DAY180)	46	2282.46	2628.96	1353.46	2410.00
	FluLD1/2	PRE	47	1854.17	2043.17	894.18	1960.00
		PI(DAY21)	45	2977.77	3366.93	1693.40	3176.00
		PI(DAY180)	42	1894.56	2249.88	1325.73	2100.00
	FluLD1/4	PRE	43	1724.38	2252.44	1726.88	1774.00
		PI(DAY21)	40	2647.19	3103.30	1549.21	3025.00
		PI(DAY180)	42	1590.08	1963.38	1245.21	1721.50
	FluLD1/8	PRE	47	1763.36	2103.66	1370.89	1852.00
		PI(DAY21)	45	2477.76	2827.84	1561.60	2374.00
		PI(DAY180)	43	1789.96	2153.12	1473.45	1748.00
	Flu	PRE	39	1714.27	1976.23	1051.16	1996.00
		PI(DAY21)	39	2089.37	2489.15	1468.71	2027.00
		PI(DAY180)	41	1642.33	1952.02	1240.63	1733.00
CD40L	FluLD1/1	PRE	45	1564.04	1914.96	1241.38	1640.00
		PI(DAY21)	45	2704.93	3337.89	1982.59	2879.00
		PI(DAY180)	46	1691.25	2108.04	1190.42	2100.00
	FluLD1/2	PRE	47	1689.20	1863.96	830.55	1759.00
		PI(DAY21)	45	2584.59	2947.20	1487.13	2800.00
		PI(DAY180)	42	1415.79	1758.95	1093.80	1444.50
	FluLD1/4	PRE	43	1527.30	2045.86	1638.11	1560.00
		PI(DAY21)	40	2164.87	2624.30	1316.60	2552.00
		PI(DAY180)	42	1154.44	1581.31	1184.99	1269.50
	FluLD1/8	PRE	47	1632.67	1954.13	1290.77	1560.00
		PI(DAY21)	45	2131.69	2472.98	1378.17	2121.00
		PI(DAY180)	43	1362.43	1731.00	1331.05	1387.00
	Flu	PRE	39	1570.31	1827.67	1033.38	1867.00
		PI(DAY21)	39	1806.92	2223.74	1398.63	1826.00
		PI(DAY180)	41	1309.80	1560.76	1009.77	1311.00
IFN-γ	FluLD1/1	PRE	45	1104.38	1379.33	987.07	1141.00

		PI(DAY21)	45	1980.75	2525.91	1615.78	2173.00
		PI(DAY180)	46	1496.54	1792.74	1075.76	1531.00
	FluLD1/2	PRE	47	1198.61	1377.13	741.31	1267.00
		PI(DAY21)	45	1833.54	2233.24	1371.05	2072.00
		PI(DAY180)	42	1243.25	1546.55	1055.94	1399.50
	FluLD1/4	PRE	43	1053.36	1510.84	1349.58	1033.00
		PI(DAY21)	40	1615.14	2056.40	1205.90	2016.00
		PI(DAY180)	42	1040.20	1335.62	970.49	1040.00
	FluLD1/8	PRE	47	1068.77	1342.57	1040.63	952.00
		PI(DAY21)	45	1491.02	1824.69	1265.29	1533.00
		PI(DAY180)	43	1117.38	1440.09	1199.84	973.00
	Flu	PRE	39	886.22	1260.97	809.24	1187.00
		PI(DAY21)	39	1160.87	1565.79	1064.31	1320.00
		PI(DAY180)	41	1057.79	1299.95	894.25	1120.00
IL2	FluLD1/1	PRE	45	1422.77	1684.24	983.48	1545.00
		PI(DAY21)	45	2485.32	3020.09	1741.78	2727.00
		PI(DAY180)	46	1827.55	2121.67	1088.48	1880.00
	FluLD1/2	PRE	47	1496.80	1657.28	744.17	1597.00
		PI(DAY21)	45	2274.35	2634.64	1415.24	2455.00
		PI(DAY180)	42	1497.50	1816.26	1116.55	1646.00
	FluLD1/4	PRE	43	1226.24	1796.33	1354.89	1454.00
		PI(DAY21)	40	1938.16	2343.15	1199.20	2191.00
		PI(DAY180)	42	1267.60	1571.19	987.96	1393.50
	FluLD1/8	PRE	47	1438.17	1732.91	1140.54	1521.00
		PI(DAY21)	45	1977.61	2256.02	1251.58	1812.00
		PI(DAY180)	43	1485.78	1797.79	1228.49	1442.00
	Flu	PRE	39	1361.12	1572.69	812.49	1494.00
		PI(DAY21)	39	1602.41	1933.10	1153.35	1564.00
		PI(DAY180)	41	1308.51	1581.73	1028.49	1350.00
TNF-α	FluLD1/1	PRE	45	1298.82	1606.64	1087.17	1454.00
		PI(DAY21)	45	2277.67	2767.02	1598.41	2548.00
		PI(DAY180)	46	1688.48	1980.39	1078.92	1767.00
	FluLD1/2	PRE	47	1360.59	1522.70	747.67	1453.00
		PI(DAY21)	45	2092.66	2337.38	1068.82	2314.00
		PI(DAY180)	42	1417.08	1654.90	944.90	1455.50
	FluLD1/4	PRE	43	1330.63	1712.42	1355.23	1335.00
		PI(DAY21)	40	1812.17	2109.45	1075.51	1952.00
		PI(DAY180)	42	1176.48	1454.40	898.01	1323.00
	FluLD1/8	PRE	47	1274.82	1548.00	1094.03	1307.00
		PI(DAY21)	45	1718.16	1990.60	1157.58	1625.00
		PI(DAY180)	43	1338.01	1627.67	1155.63	1307.00
	Flu	PRE	39	1222.90	1421.82	781.48	1253.00
		PI(DAY21)	39	1382.63	1639.31	975.93	1480.00
		PI(DAY180)	41	1147.22	1392.05	933.32	1267.00

All doubles: T-cells producing at least 2 cytokines
N = number of subjects with available results
GM= geometric mean
SD= standard deviation
PRE= Pre-vaccination at Day 0
PI(DAY21) = Post-vaccination at Day 21
PI(DAY180)= Post-vaccination at Day 180

Secondary Outcome Variable: Descriptive statistics of the frequency of immune response marker-positive CD8 T-cells (per million CD8 T-cells) for all vaccine strains at Days 0, 21 and 180 (ATP cohort for immunogenicity)

Test description	Group	Timing	N	GM	Mean	SD	Median

ALL DOUBLES	FluLD1/1	PRE	44	5.61	50.02	113.85	1.00
		PI(DAY21)	44	5.14	47.18	106.55	1.00
		PI(DAY180)	44	5.99	44.32	99.11	1.00
	FluLD1/2	PRE	46	9.91	109.63	405.09	11.00
		PI(DAY21)	43	5.93	50.09	101.55	1.00
		PI(DAY180)	40	8.10	126.13	323.68	1.00
	FluLD1/4	PRE	43	3.03	17.33	33.12	1.00
		PI(DAY21)	40	6.23	38.53	67.21	1.00
		PI(DAY180)	42	3.10	36.31	95.06	1.00
	FluLD1/8	PRE	45	5.27	64.47	181.32	1.00
		PI(DAY21)	42	11.04	109.86	282.04	31.00
		PI(DAY180)	41	8.05	97.27	258.53	1.00
	Flu	PRE	39	6.39	48.38	82.57	1.00
		PI(DAY21)	38	5.21	55.11	126.17	1.00
		PI(DAY180)	41	3.64	30.98	62.35	1.00
CD40L	FluLD1/1	PRE	44	1.20	3.64	12.37	1.00
		PI(DAY21)	44	1.67	8.82	28.38	1.00
		PI(DAY180)	44	1.62	9.45	35.59	1.00
	FluLD1/2	PRE	46	1.56	5.91	15.92	1.00
		PI(DAY21)	43	2.02	10.09	21.58	1.00
		PI(DAY180)	40	1.58	15.88	61.59	1.00
	FluLD1/4	PRE	43	1.18	2.63	8.06	1.00
		PI(DAY21)	40	1.59	6.45	16.03	1.00
		PI(DAY180)	42	1.19	2.86	8.48	1.00
	FluLD1/8	PRE	45	1.92	16.27	56.56	1.00
		PI(DAY21)	42	2.64	50.83	193.00	1.00
		PI(DAY180)	41	1.09	1.68	4.37	1.00
	Flu	PRE	39	1.59	7.05	20.43	1.00
		PI(DAY21)	38	2.46	37.55	117.41	1.00
		PI(DAY180)	41	1.17	2.27	5.83	1.00
IFN-γ	FluLD1/1	PRE	44	3.52	29.50	53.27	1.00
		PI(DAY21)	44	2.97	24.86	61.18	1.00
		PI(DAY180)	44	7.19	38.18	50.84	1.00
	FluLD1/2	PRE	46	7.79	96.91	375.61	1.00
		PI(DAY21)	43	4.94	48.07	106.65	1.00
		PI(DAY180)	40	7.35	110.75	303.91	1.00
	FluLD1/4	PRE	43	2.36	14.42	32.92	1.00
		PI(DAY21)	40	3.43	25.65	49.98	1.00
		PI(DAY180)	42	2.52	20.62	47.56	1.00
	FluLD1/8	PRE	45	4.33	44.80	137.59	1.00
		PI(DAY21)	42	5.50	64.98	178.63	1.00
		PI(DAY180)	41	4.84	79.85	239.36	1.00
	Flu	PRE	39	2.38	17.31	38.50	1.00
		PI(DAY21)	38	2.31	32.11	104.54	1.00
		PI(DAY180)	41	3.17	19.80	37.25	1.00
IL2	FluLD1/1	PRE	44	3.77	35.59	91.49	1.00
		PI(DAY21)	44	4.87	36.98	85.05	1.00
		PI(DAY180)	44	2.93	27.36	87.59	1.00
	FluLD1/2	PRE	46	4.95	75.41	309.22	1.00
		PI(DAY21)	43	3.29	21.51	42.47	1.00
		PI(DAY180)	40	6.09	74.03	183.59	1.00
	FluLD1/4	PRE	43	2.09	8.81	16.65	1.00
		PI(DAY21)	40	5.00	31.28	59.89	1.00
		PI(DAY180)	42	2.06	24.50	82.62	1.00

	FluLD1/8	PRE	45	3.96	46.22	130.46	1.00
		PI(DAY21)	42	7.00	87.86	244.84	1.00
		PI(DAY180)	41	5.43	57.15	136.73	1.00
	Flu	PRE	39	5.29	43.59	81.53	1.00
		PI(DAY21)	38	4.84	50.84	116.74	1.00
		PI(DAY180)	41	3.72	28.73	55.08	1.00
TNF-α	FluLD1/1	PRE	44	4.50	42.98	109.79	1.00
		PI(DAY21)	44	3.01	37.93	109.46	1.00
		PI(DAY180)	44	4.62	34.70	86.94	1.00
	FluLD1/2	PRE	46	8.03	102.72	391.96	5.00
		PI(DAY21)	43	4.65	44.16	99.17	1.00
		PI(DAY180)	40	5.87	111.10	299.67	1.00
	FluLD1/4	PRE	43	3.41	15.42	28.60	1.00
		PI(DAY21)	40	4.93	31.55	59.52	1.00
		PI(DAY180)	42	3.30	33.60	80.50	1.00
	FluLD1/8	PRE	45	3.85	54.73	156.41	1.00
		PI(DAY21)	42	7.98	90.48	239.47	1.00
		PI(DAY180)	41	7.17	79.54	208.13	1.00
	Flu	PRE	39	5.99	46.18	91.78	1.00
		PI(DAY21)	38	3.65	37.82	110.79	1.00
		PI(DAY180)	41	3.03	25.63	56.06	1.00

All doubles: T-cells producing at least 2 cytokines
N = number of subjects with available results
GM= geometric mean
SD= standard deviation
PRE = Pre-vaccination at Day 0
PI(DAY21) = Post-vaccination at Day 21
PI(DAY180) = Post-vaccination at Day 180

Secondary Outcome Variable: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

		FluLD1/1 Group					**FluLD1/2 Group**				
					95% CI					**95% CI**	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Ecchymosis	Any	200	11	5.5	2.8	9.6	198	9	4.5	2.1	8.5
	> 50 mm	200	1	0.5	0.0	2.8	198	0	0.0	0.0	1.8
Pain	Any	200	182	91.0	86.1	94.6	198	175	88.4	83.1	92.5
	Grade 3	200	5	2.5	0.8	5.7	198	5	2.5	0.8	5.8
Redness	Any	200	75	37.5	30.8	44.6	198	66	33.3	26.8	40.4
	> 50 mm	200	17	8.5	5.0	13.3	198	4	2.0	0.6	5.1
Swelling	Any	200	69	34.5	27.9	41.5	198	54	27.3	21.2	34.0
	> 50 mm	200	11	5.5	2.8	9.6	198	4	2.0	0.6	5.1
		FluLD1/4 Group					**FluLD1/8 Group**				
Ecchymosis	Any	204	8	3.9	1.7	7.6	202	14	6.9	3.8	11.4
	> 50 mm	204	0	0.0	0.0	1.8	202	1	0.5	0.0	2.7
Pain	Any	204	167	81.9	75.9	86.9	202	151	74.8	68.2	80.6
	Grade 3	204	3	1.5	0.3	4.2	202	1	0.5	0.0	2.7
Redness	Any	204	53	26.0	20.1	32.6	202	64	31.7	25.3	38.6
	> 50 mm	204	3	1.5	0.3	4.2	202	2	1.0	0.1	3.5
Swelling	Any	204	49	24.0	18.3	30.5	202	48	23.8	18.1	30.2
	> 50 mm	204	5	2.5	0.8	5.6	202	3	1.5	0.3	4.3

		Flu Group				
					95% CI	
		N	**n**	**%**	**LL**	**UL**
Ecchymosis	Any	202	7	3.5	1.4	7.0

	> 50 mm	202	1	0.5	0.0	2.7
Pain	Any	202	121	59.9	52.8	66.7
	Grade 3	202	1	0.5	0.0	2.7
Redness	Any	202	49	24.3	18.5	30.8
	> 50 mm	202	2	1.0	0.1	3.5
Swelling	Any	202	27	13.4	9.0	18.8
	> 50 mm	202	2	1.0	0.1	3.5

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 all solicited local symptom regardless of their intensity grade
Grade 3 pain: considerable pain at rest that prevented normal everyday activity

Secondary Outcome Variable: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

		FluLD1/1 Group					**FluLD1/2 Group**				
					95% CI					95% CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Arthralgia	Any	200	64	32.0	25.6	38.9	198	51	25.8	19.8	32.4
	Grade 3	200	4	2.0	0.5	5.0	198	4	2.0	0.6	5.1
	Related	200	52	26.0	20.1	32.7	198	49	24.7	18.9	31.4
Fatigue	Any	200	103	51.5	44.3	58.6	198	90	45.5	38.4	52.7
	Grade 3	200	5	2.5	0.8	5.7	198	4	2.0	0.6	5.1
	Related	200	81	40.5	33.6	47.7	198	83	41.9	35.0	49.1
Fever (Orally)	>38°C	200	27	13.5	9.1	19.0	198	16	8.1	4.7	12.8
	≥ 39°C	200	2	1.0	0.1	3.6	198	0	0.0	0.0	1.8
	Related	200	23	11.5	7.4	16.8	198	13	6.6	3.5	11.0
Headache	Any	200	90	45.0	38.0	52.2	198	77	38.9	32.1	46.1
	Grade 3	200	7	3.5	1.4	7.1	198	2	1.0	0.1	3.6
	Related	200	72	36.0	29.4	43.1	198	61	30.8	24.5	37.7
Myalgia	Any	200	102	51.0	43.9	58.1	198	85	42.9	35.9	50.1
	Grade 3	200	6	3.0	1.1	6.4	198	6	3.0	1.1	6.5
	Related	200	81	40.5	33.6	47.7	198	77	38.9	32.1	46.1
Nausea	Any	200	25	12.5	8.3	17.9	198	28	14.1	9.6	19.8
	Grade 3	200	1	0.5	0.0	2.8	198	2	1.0	0.1	3.6
	Related	200	19	9.5	5.8	14.4	198	22	11.1	7.1	16.3
Shivering	Any	200	74	37.0	30.3	44.1	198	53	26.8	20.7	33.5
	Grade 3	200	4	2.0	0.5	5.0	198	5	2.5	0.8	5.8
	Related	200	64	32.0	25.6	38.9	198	50	25.3	19.4	31.9
		FluLD1/4 Group					**FluLD1/8 Group**				
		95% CI						**95% CI**			
		N		**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Arthralgia	Any	204		38	18.6	13.5	24.7	202	39	19.3	14.1	25.4
	Grade 3	204		2	1.0	0.1	3.5	202	0	0.0	0.0	1.8
	Related	204		32	15.7	11.0	21.4	202	31	15.3	10.7	21.1
Fatigue	Any	204		86	42.2	35.3	49.3	202	78	38.6	31.9	45.7
	Grade 3	204		2	1.0	0.1	3.5	202	2	1.0	0.1	3.5
	Related	204		72	35.3	28.7	42.3	202	62	30.7	24.4	37.6
Fever (Orally)	>38°C	204		8	3.9	1.7	7.6	202	6	3.0	1.1	6.4
	≥ 39°C	204		0	0.0	0.0	1.8	202	0	0.0	0.0	1.8
	Related	204		8	3.9	1.7	7.6	202	6	3.0	1.1	6.4
Headache	Any	204		68	33.3	26.9	40.3	202	66	32.7	26.3	39.6
	Grade 3	204		4	2.0	0.5	4.9	202	3	1.5	0.3	4.3
	Related	204		49	24.0	18.3	30.5	202	49	24.3	18.5	30.8
Myalgia	Any	204		74	36.3	29.7	43.3	202	70	34.7	28.1	41.7

	Grade 3	204	4	2.0	0.5	4.9	202	0	0.0	0.0	1.8
	Related	204	59	28.9	22.8	35.7	202	57	28.2	22.1	35.0
Nausea	Any	204	12	5.9	3.1	10.0	202	13	6.4	3.5	10.8
	Grade 3	204	3	1.5	0.3	4.2	202	0	0.0	0.0	1.8
	Related	204	10	4.9	2.4	8.8	202	11	5.4	2.7	9.5
Shivering	Any	204	40	19.6	14.4	25.7	202	34	16.8	11.9	22.7
	Grade 3	204	1	0.5	0.0	2.7	202	1	0.5	0.0	2.7
	Related	204	31	15.2	10.6	20.9	202	29	14.4	9.8	20.0

		Flu Group				
		N	**n**	**%**	**95% CI**	
					LL	**UL**
Arthralgia	Any	202	25	12.4	8.2	17.7
	Grade 3	202	1	0.5	0.0	2.7
	Related	202	20	9.9	6.2	14.9
Fatigue	Any	202	47	23.3	17.6	29.7
	Grade 3	202	2	1.0	0.1	3.5
	Related	202	34	16.8	11.9	22.7
Fever (Orally)	>38°C	202	3	1.5	0.3	4.3
	≥ 39°C	202	0	0.0	0.0	1.8
	Related	202	3	1.5	0.3	4.3
Headache	Any	202	51	25.2	19.4	31.8
	Grade 3	202	1	0.5	0.0	2.7
	Related	202	36	17.8	12.8	23.8
Myalgia	Any	202	49	24.3	18.5	30.8
	Grade 3	202	2	1.0	0.1	3.5
	Related	202	40	19.8	14.5	26.0
Nausea	Any	202	11	5.4	2.7	9.5
	Grade 3	202	0	0.0	0.0	1.8
	Related	202	6	3.0	1.1	6.4
Shivering	Any	202	12	5.9	3.1	10.1
	Grade 3	202	2	1.0	0.1	3.5
	Related	202	8	4.0	1.7	7.7

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 all solicited local symptom regardless their intensity grade or relationship to vaccination
Related: general symptom considered by the investigator to be causally related to the study vaccination
Grade 3 : symptom that prevented normal everyday activity

Secondary Outcome Variable: Number (%) of subjects with adverse events associated to medically significant conditions (MSC) between Day 0 and Day 180 (Total Vaccinated cohort)

MSCs	**FluLD1/1 Group N = 200**	**FluLD1/2 Group N = 198**	**FluLD1/4 Group N = 204**	**FluLD1/8 Group N = 202**	**Flu Group N = 202**
Subjects with any MSC, n (%)	70 (35.0)	56 (28.3)	53 (26.0)	64 (31.7)	45 (22.3)
Subjects with grade 3 and related MSC, n (%)	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	1 (0.5)
Subjects with related MSC, n (%)	5 (2.5)	2 (1.0)	0 (0.0)	0 (0.0)	1 (0.5)
Influenza like illness	8 (4.0)	5 (2.5)	5 (2.5)	7 (3.5)	5 (2.5)
Bronchitis	4 (2.0)	2 (1.0)	-	4 (2.0)	3 (1.5)
Sinusitis	4 (2.0)	-	-	-	5 (2.5)
Arthralgia	-	-	-	6 (3.0)	4 (2.0)
Cough	5 (2.5)	-	-	5 (2.5)	-
Back pain	4 (2.0)	3 (1.5)	3 (1.5)	-	-
Gastroenteritis	4 (2.0)	3 (1.5)	-	-	-
Diarrhoea	-	-	3 (1.5)	3 (1.5)	-

Nasopharyngitis	-	3 (1.5)	-	3 (1.5)	-
Upper respiratory tract infection	-	-	5 (2.5)	-	-
Toothache	-	-	4 (2.0)	-	-
Headache	-	-	-	3 (1.5)	-
Rhinitis	-	-	3 (1.5)	-	-
Urinary tract infection	-	-	-	-	3 (1.5)
Cystitis	-	2 (1.0)	-	-	-
Hypertension	-	2 (1.0)	-	-	-
Osteoarthritis	-	2 (1.0)	-	-	-

Counting rule applied: As there were more than 30 subjects per treatment group and > 3 groups, only the 5 most frequent events in each treatment group are to be listed.
-: Implies that adverse event was absent or was reported in the particular group but did not fall within the pre-defined counting rule of 5 most frequent events for that group
Grade 3 = event which prevented normal activities
Related = event assessed by the investigator as causally related to the study vaccination

Safety results: Number (%) of subjects with unsolicited adverse events during the 21-day follow-up period after vaccination (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Days 0-20 following vaccination)	**FluLD1/1 Group N = 200**	**FluLD1/2 Group N = 198**	**FluLD1/4 Group N = 204**	**FluLD1/8 Group N = 202**	**Flu Group N = 202**
Subjects with any AE(s), n (%)	85 (42.5)	91 (46.0)	70 (34.3)	82 (40.6)	80 (39.6)
Subjects with grade 3 AE(s), n (%)	4 (2.0)	10 (5.0)	3 (1.5)	10 (5.0)	5 (2.5)
Subjects with related AE(s), n (%)	37 (18.5)	41 (20.7)	25 (12.3)	19 (9.4)	14 (6.9)
Headache	14 (7.0)	12 (6.1)	16 (7.8)	19 (9.4)	14 (6.9)
Rhinitis	-	8 (4.0)	6 (2.9)	9 (4.5)	13 (6.4)
Nasopharyngitis	7 (3.5)	6 (3.0)	5 (2.5)	5 (2.5)	5 (2.5)
Influenza like illness	8 (4.0)	6 (3.0)	7 (3.4)	6 (3.0)	-
Pharyngolaryngeal pain	-	-	5 (2.5)	8 (4.0)	8 (4.0)
Cough	9 (4.5)	-	5 (2.5)	5 (2.5)	-
Injection site pruritus	7 (3.5)	7 (3.5)	-	-	-
Dysmenorrhoea	-	-	5 (2.5)	-	7 (3.5)
Malaise	7 (3.5)	-	5 (2.5)	-	-
Migraine	-	-	-	5 (2.5)	5 (2.5)
Back pain	-	-	-	5 (2.5)	-

Counting rule applied: As there were more than 30 subjects per treatment group and > 3 groups, only the 5 most frequent events in each treatment group are to be listed.
-: Implies that adverse event was absent or was reported in the particular group but did not fall within the pre-defined counting rule of 5 most frequent events for that group
Grade 3 = event which prevented normal activities
Related = event assessed by the investigator as causally related to the study vaccination

Safety results: Number (%) of subjects with serious adverse events occurring between Day 0 and Day 180 (Total Vaccinated cohort)

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

All SAEs	**FluLD1/1 Group N = 200**	**FluLD1/2 Group N = 198**	**FluLD1/4 Group N = 204**	**FluLD1/8 Group N = 202**	**Flu Group N = 202**
Subjects with any SAE(s), n (%) [n related]	7 (3.5) [2]	3 (1.5) [0]	3 (1.5) [0]	4 (2.0) [0]	2 (1.0) [0]
Angina unstable	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Breast cancer	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cerebrovascular accident	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cervical spinal stenosis	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Contusion	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]
Dermatitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]
Ectopic pregnancy	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Gastritis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]

Haemorrhoids	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]
Hand fracture	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hypersensitivity	1 (0.5) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hypertension	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hypotension	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Mania	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]
Migraine	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]
Optic neuritis	1 (0.5) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Palpitations	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Pancreatitis acute	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Renal cell carcinoma	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Subcutaneous abscess	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]
Fatal SAEs	**FluLD1/1 Group N = 200**	**FluLD1/2 Group N = 198**	**FluLD1/4 Group N = 204**	**FluLD1/8 Group N = 202**	**Flu Group N = 202**
Subjects with fatal SAEs, n (%) [n related]	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pancreatitis acute	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:
On Day 0 across all vaccine strains, the HI GMTs were at least 13.0, 12.3, 12.9, 14.9, and 15.1 in the FluLD1/1, the FluLD1/2, the FluLD1/4, the FluLD1/8, and the Flu group, respectively; on Day 21, the HI GMTs were at least 203.2, 155.8, 164.9, 151.1, and 191.0 in the FluLD1/1, the FluLD1/2, the FluLD1/4, the FluLD1/8, and the Flu group, respectively.
During the 21-day follow-up period after vaccination, at least one unsolicited AE was reported for 85 (42.5%), 91 (46.0%), 70 (34.3%), 82 (40.6%), and 80 (39.6%) subjects in the FluLD1/1, the FluLD1/2, the FluLD1/4, the FluLD1/8, and the Flu group, respectively.
Between Day 0 and Day 180, SAEs were reported for 7 (3.5%), 3 (1.5%), 3 (1.5%), 4 (2.0%), and 2 (1.0%) subjects in the FluLD1/1, the FluLD1/2, the FluLD1/4, the FluLD1/8, and the Flu group, respectively. Two SAEs (hypersensitivity and optic neuritis) in the FluLD1/1 were considered by the investigator as related to the vaccination. A fatal SAE (pancreatitis acute) was reported in the FluLD1/1 Group; it was considered by the investigators not to be related to the study vaccination.

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