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Study No.: 104888 (FluAS25-005), 107509 (FluAS25-015 EXT 005 D180)
Title: A phase II/III, observer-blind, multicountry, multicentre, randomized study to demonstrate the superiority in terms of immunogenicity of AS25 adjuvanted influenza vaccine administered in adults aged 50 years and older compared to Fluarix™. FluAS25 (Flu-1): GlaxoSmithKline (GSK) Biologicals' adjuvanted influenza vaccine. Fluarix™ (Flu-2): GSK Biologicals' licensed influenza vaccine.
Rationale: The aim of the FluAS25-005 study was to assess the immunogenicity and safety of the Flu-1 vaccine compared to the Flu-2 vaccine in subjects aged ≥ 50 years. The FLU-AS25-015 study is the extension of the FLU-AS25-005 study until Day 180 for the evaluation of persistence and safety of the vaccine.
Phase: II/III
Study Period: FluAS25-005 (104888): 22 September 2006 to 11 January 2007 FluAS25-015 EXT 005 D180 (107509): 15 November 2006 to 14 June 2007
Study Design: Multi-country, multi-centre controlled study in which eligible subjects were stratified into 3 age strata (50-64 years, 65-74 years and ≥ 75 years). Subjects were randomized (1:1) within each age stratum to one of the 2 study groups. An additional group of subjects aged between 18 and 40 years were all to be vaccinated with Flu-2 vaccine. This study was observer-blind for subjects aged ≥ 50 years and open for subjects aged between 18 and 40 years.
Centers: 30 study centers: 10 in the United States, 1 in Belgium, 12 in Germany and 7 in Norway.
Indication: Immunization against influenza
Treatment: The study groups within each age stratum (18-40 years*, 50-64 years, 65-74 years and ≥ 75 years) were as follows: <ul style="list-style-type: none"> • Flu-1 Group: subjects received 1 dose of Flu-1 vaccine. • Flu-2 Group: subjects received 1 dose of Flu-2 vaccine. The vaccines were administered intramuscularly into the deltoid region of the non-dominant arm. *As per protocol, none of the subjects aged 18 to 40 years should have been allocated to the Flu-1 Group.
Objectives: <ul style="list-style-type: none"> • To demonstrate that the immune response (in terms of haemagglutination-inhibition (HI) antibody geometric mean titer (GMT) and seroconversion rate) induced by the Flu-1 vaccine in elderly adults (≥ 65 years) is superior to that induced by the Flu-2 vaccine, 21 days following vaccination for each vaccine strain. • To demonstrate that the immune response induced by the Flu-1 vaccine in subjects aged between 50 and 64 years is superior to the one induced by the Flu-2 vaccine, 21 days following vaccination for each vaccine strain.
Primary Outcome/Efficacy Variable: At Days 0 and 21, serum HI antibody titer, against each of the 3 vaccine strains, in the following age groups: 50-64 years and ≥ 65 years: <ul style="list-style-type: none"> • GMTs of HI antibody titers at Days 0 and 21. • Seroconversion rates at Day 21 defined as the percentage of vaccinees that have either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4-fold increase in post-vaccination titer.
Secondary Outcome/Efficacy Variable(s): Safety In the following age groups: 50-64 years, ≥ 65 years and 18-40 years: <ul style="list-style-type: none"> • Occurrence, intensity, duration and relationship to vaccination of solicited local and general signs and symptoms during a 7-day (Days 0-6) follow-up period after vaccination. • Occurrence, intensity, duration* and relationship to vaccination of unsolicited adverse events (AEs) during a 21-day (Days 0-20) follow-up period after vaccination. • Occurrence and relationship to vaccination of serious and non serious adverse events (SAEs) during the entire study period (up to Day 180). * The duration of the unsolicited symptoms during the 21-day post-vaccination follow-up period was not analyzed.
<i>Humoral immune response</i>

At Days 0, 21 and 180: serum HI antibody titer, against each of the 3 vaccine strains, in the following age groups: 18-40 years, 50-64 years, and ≥ 65 years (further stratified in 2 age groups: 65-74 years and ≥ 75 years):

- GMTs of HI antibody titers at Days 0, 21 and 180.
- Seroconversion rates* (SCR) at Day 21 and 180.
- Seroconversion factors** (SCF) at Day 21 and 180.
- Seroprotection rates*** (SPR) at Days 0, 21 and 180.

* Seroconversion rate is defined as the percentage of vaccinees who have either a pre-vaccination titer $< 1:10$ and a post-vaccination titer $\geq 1:40$ or a pre-vaccination titer $\geq 1:10$ and at least a 4-fold increase in post-vaccination titer.

** Seroconversion factor is defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.

*** Seroprotection rate is defined as the percentage of vaccinees with a serum HI titer $\geq 1:40$ that usually is accepted as indicating protection.

CMI response

In a subset of subjects and in the following age groups: 18-40 years, 50-64 years and ≥ 65 years (further stratified in 2 age groups: 65-74 years and ≥ 75 years):

- Frequency of cytokine CD4/CD8 cells per 10^6 in tests producing at least 2 different cytokines (*cluster of differentiation-40 ligand [CD40L], interleukin-2 [IL-2], tumor necrosis factor alpha [TNF- α], interferon- γ [IFN- γ]*).
- 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).
- Frequency of cytokine-positive cells evaluated at Day 0, 21 and 180.
- For each test, geometric mean (GM) of specific influenza CD4/CD8 T lymphocytes at Day 0, 21, 180.

Statistical Methods:

Analyses were performed on the Total Vaccinated Cohort, the According-To-Protocol (ATP) cohort for immunogenicity, the Total Cohort for persistence and the ATP cohort for persistence.

- 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 data concerning immunogenicity measures were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination (Day 21).
- The Total Cohort for persistence included all vaccinated subjects in the vaccination phase (104888 – FLU-AS25-005 study) who were contacted at Day 180.
- The ATP cohort for persistence included all evaluable subjects who had received the vaccine during the vaccination phase, who had not met any elimination criteria during the whole study period and who had available assay results for at least one tested antigen at the Day 180 time point.

Analysis of immunogenicity:

The analysis was based on the ATP cohort for immunogenicity.

The superiority of Flu-1 over Flu-2 was demonstrated if the lower limit of the 95% confidence interval (CI) for the GMT ratio (Flu-1 Group over Flu-2 Group) was > 1.0 and if the lower limit of the 95% CI for the difference in seroconversion rate (Flu-1 Group minus Flu-2 Group) was $> 5\%$ for each vaccine strain.

For each treatment group, GMTs of HI antibody titers, SPR at Days 0 and 21, and SCF & SCR at Day 21 were calculated separately for each age category (subjects aged 18-40 years, 50-64 years and ≥ 65 years (further stratified in 2 age groups: 65-74 years and ≥ 75 years)) with 95% CIs for each vaccine strain.

The frequency of influenza-specific cytokine-positive CD4/CD8 T-lymphocytes was summarized with descriptive statistics for each vaccine group at Days 0 and 21 in a subset of subjects, for each different cytokine test and for separate vaccine strains, separately for the age sub-groups (subjects aged between 18 and 40 years, between 50 and 64 years and for those aged 65 years and above (further stratified in 2 age groups: 65-74 years and ≥ 75 years)).

Analysis of persistence

The analysis was performed on the ATP cohort for persistence.

For each treatment group, GMTs of HI antibody titers, SPR, SCF and SCR at Day 180 were calculated separately for each age category (subjects aged 18-40 years, 50-64 years and ≥ 65 years (further stratified in 2 age groups: 65-74 years and ≥ 75 years)) with 95% CIs for each vaccine strain.

The frequency of influenza-specific cytokine-positive CD4/CD8 T-lymphocytes was summarized for each vaccine group in a subset of subjects at Day 180, for each different cytokine test and for each vaccine strain, separately for the age sub-groups (subjects aged between 18 and 40 years, between 50 and 64 years and for those aged 65 years and above (further stratified in 2 age groups: 65-74 years and ≥ 75 years)).

Analysis of safety:

The analysis was performed on the Total Vaccinated Cohort and on the Total Cohort for persistence.

The percentage of subjects with at least one local or general solicited symptom during the 7-day (Days 0-6) follow-up period was tabulated with exact 95% CI. The same tabulation was performed for grade 3 symptoms and for symptoms assessed by the investigators as related to vaccination. The proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and reported during the 21-day (Days 0-20) follow-up period was tabulated. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs assessed by the investigators as related to vaccination. The percentage of subjects with unsolicited adverse events between Day 21 and Day 180 was also tabulated as well as the SAEs (from Day 0 to Day 21 and from Day 21 up to Day 180) according to MedDRA preferred terms.

Study Population: Healthy adults aged between 18-40 years or 50 years and above, free of an acute aggravation of the health status as established by clinical examination before entering into the study were enrolled. If the subject was female, she had to be of non-childbearing potential, or, if of childbearing potential, she was abstinent or had used adequate contraceptive precautions for 30 days prior to vaccination, had a negative pregnancy test and had agreed to continue such precautions for 2 months after vaccination. Subjects who received a previous vaccination against influenza (2006-2007 influenza vaccine) were excluded from the study. Written informed consent was obtained from each subject prior to the performance of any study-specific procedures.

Number of subjects - FluAS25-005 study	18-40y		50-64y		65y+	
	Flu-1 Group	Flu-2 Group	Flu-1 Group	Flu-2 Group	Flu-1 Group	Flu-2 Group
Planned, N	0	500	750	750	750	750
Randomized, N (Total Vaccinated Cohort)	1	489	758	757	737	740
Completed, n (%)	1 (100)	488 (99.8)	756 (99.7)	756 (99.9)	734 (99.6)	736 (99.5)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	1 (0.2)	2 (0.3)	1 (0.1)	3 (0.4)	4 (0.5)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable					
Withdrawn for other reasons, n (%)	0 (0.0)	1 (0.2)	2 (0.3)	1 (0.1)	2 (0.3)	3 (0.4)
Number of subjects - FluAS25-005 study	65-74y		75y+			
	Flu-1 Group	Flu-2 Group	Flu-1 Group	Flu-2 Group		
Planned, N	450	450	300	300		
Randomized, N (Total Vaccinated Cohort)	442	450	295	290		
Completed*, n (%)	441 (99.8)	448 (99.6)	293 (99.3)	288 (99.3)		
Total Number Subjects Withdrawn, n (%)	1 (0.2)	2 (0.4)	2 (0.7)	2 (0.7)		
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)		
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable	Not applicable		
Withdrawn for other reasons, n (%)	1 (0.2)	2 (0.4)	1 (0.3)	1 (0.3)		
Number of subjects - FluAS25-015 study	18-40y		50-64y		65y+	
	Flu-1 Group	Flu-2 Group	Flu-1 Group	Flu-2 Group	Flu-1 Group	Flu-2 Group
Planned, N	0	500	750	750	750	750
Entered, N (Total Cohort for persistence) – phone contact at Day 90	1	485	755	755	726	731
Completed at Day 180, n (%)	1 (100)	474 (97.7)	749 (99.2)	749 (99.2)	716 (98.6)	715 (97.8)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	11 (2.3)	6 (0.8)	6 (0.8)	10 (1.4)	16 (2.2)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.6)	3 (0.4)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Withdrawn for other reasons, n (%)	0 (0.0)	11 (2.3)	6 (0.8)	6 (0.8)	6 (0.8)	13 (1.8)		
Number of subjects - FluAS25-015 study	65-74y			75y+				
	Flu-1 Group		Flu-2 Group		Flu-1 Group	Flu-2 Group		
Planned, N	450		450		300	300		
Randomized, N (Total Cohort for persistence)	440		448		286	283		
Completed at Day 180, n (%)	435 (98.9)		444 (99.1)		281 (98.3)	271 (95.8)		
Total Number Subjects Withdrawn, n (%)	5 (1.1)		4 (0.9)		5 (1.7)	12 (4.2)		
Withdrawn due to Adverse Events, n (%)	2 (0.5)		0		2 (0.7)	3 (1.1)		
Withdrawn due to Lack of Efficacy, n (%)	Not applicable		Not applicable		Not applicable	Not applicable		
Withdrawn for other reasons, n (%)	3 (0.7)		4 (0.9)		3 (1.0)	9 (3.2)		
Demographics*	18-40y		50-64y		65y+			
	Flu-1 Group	Flu-2 Group	Flu-1 Group	Flu-2 Group	Flu-1 Group	Flu-2 Group		
N (Total Vaccinated Cohort)	1	489	758	757	737	740		
Females:Males	0:1	288:201	428:330	448:309	405:332	394:346		
Mean Age, years (SD)	26.0 (NA)	29.5 (6.51)	57.5 (4.38)	57.8 (4.26)	73.2 (5.86)	73.1 (6.07)		
White/Caucasian, n (%)	1 (100)	469 (95.9)	740 (97.6)	743 (98.2)	731 (99.2)	730 (98.6)		
Demographics*	65-74y		75y+					
	Flu-1 Group		Flu-2 Group		Flu-1 Group	Flu-2 Group		
N (Total Vaccinated Cohort)	442		450		295	290		
Females:Males	242:200		244:206		163:132	150:140		
Mean Age, years (SD)	69.2 (2.88)		69.1 (2.85)		79.2 (3.75)	79.5 (3.87)		
White/Caucasian, n (%)	438 (99.1)		444 (98.7)		293 (99.3)	286 (98.6)		
* Data at the time of vaccination in study FluAS25-005								
Primary Efficacy Results:								
Ratio of GMTs for HI antibody titers at Day 21 for subjects aged 65 years and above (ATP cohort for immunogenicity)								
Vaccine strain	65y+/Flu-1 Group		65y+/Flu-2 Group		GMT ratio (65y+/Flu-1 Group/ 65y+/Flu-2 Group)			
	N	GMT	N	GMT	Value	95% CI		
						LL*	UL	
A/New Caledonia	715	121.6	710	120.5	1.01	0.91 1.12		
A/Wisconsin	715	365.3	710	188.8	1.93	1.70 2.20		
B/Malaysia	715	305.0	710	200.6	1.52	1.37 1.68		
N = number of subjects with post-vaccination results available								
95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance); LL = Lower Limit, UL = Upper Limit								
*Superiority criterion: LL of the 95% CI for the GMT ratio (Flu-1 Group over Flu-2 Group) > 1.0								
Primary Efficacy Results:								
Difference between groups in seroconversion rates for HI antibody titers at Day 21 for subjects aged 65 years and above (ATP cohort for immunogenicity)								
Vaccine strain	65y+/Flu-1 Group			65y+/Flu-2 Group			Difference in seroconversion rates (65y+/Flu-1 Group minus 65y+/Flu-2 Group)	
	N	n	%	N	n	%	%	95% CI
								LL*
A/New Caledonia	715	223	31.2	710	199	28.0	3.16	-1.58 7.89
A/Wisconsin	715	540	75.5	710	400	56.3	19.19	14.33 23.96
B/Malaysia	715	429	60.0	710	313	44.1	15.92	10.76 20.99
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 = standardized asymptotic 95% confidence interval; LL = Lower Limit, UL = Upper Limit
 *Superiority criterion: LL of the 95% CI for the difference in Seroconversion rate (Flu-1 group minus Flu-2 group) > 5%

Primary Efficacy Results:
 Ratio of GMTs for HI antibody titers at Day 21 for subjects aged between 50 and 64 years (ATP cohort for immunogenicity)

Vaccine strain	50-64y/Flu-1 Group		50-64y/Flu-2 Group		GMT ratio (50-64y/Flu-1 Group / 50-64y/Flu-2 Group)		
	N	GMT	N	GMT	Value	95% CI	
						LL*	UL
A/New Caledonia	736	192.9	736	187.3	1.03	0.91	1.16
A/Wisconsin	736	339.9	736	203.3	1.67	1.47	1.90
B/Malaysia	736	267.6	736	199.8	1.34	1.21	1.48

N = number of subjects with post-vaccination results available
 95% CI = 95% confidence interval for the GMT ratio (ANOVA model - pooled variance); LL = Lower Limit, UL = Upper Limit
 *Superiority criterion: LL of the 95% CI for the GMT ratio (Flu-1 Group over Flu-2 Group) > 1.0

Primary Efficacy Results:
 Difference between groups in seroconversion rates for HI antibody titers at Day 21 for subjects aged between 50 and 64 years (ATP cohort for immunogenicity)

Vaccine strain	50-64y/Flu-1 Group			50-64y/Flu-2 Group			Difference in seroconversion rates (50-64y/Flu-1 minus 50-64y/Flu-2)		
	N	n	%	N	n	%	%	95% CI	
								LL*	UL
A/New Caledonia	736	378	51.4	735	366	49.8	1.56	-3.54	6.66
A/Wisconsin	736	621	84.4	735	483	65.7	18.66	14.33	22.97
B/Malaysia	736	575	78.1	736	496	67.4	10.73	6.20	15.24

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 = standardized asymptotic 95% confidence interval; LL = Lower Limit, UL = Upper Limit
 *Superiority criterion: LL of the 95% CI for the difference in Seroconversion rate (Flu-1 Group minus Flu-2 Group) > 5%

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

Vaccine strain	Sub-group	Group	Timing	N	≥ 1:10				GMT*		
					n	%	95% CI		Value	95% CI	
							LL	UL		LL	UL
A/New Caledonia	50-64y	Flu-1	PRE	736	679	92.3	90.1	94.1	37.0	34.0	40.2
			PI(D21)	736	736	100	99.5	100	192.9	177.6	209.5
		Flu-2	PRE	735	668	90.9	88.6	92.9	35.7	32.8	38.9
			PI(D21)	736	733	99.6	98.8	99.9	187.3	171.2	204.8
	65-74y	Flu-1	PRE	432	414	95.8	93.5	97.5	42.1	38.4	46.2
			PI(D21)	431	429	99.5	98.3	99.9	123.1	112.7	134.4
		Flu-2	PRE	435	412	94.7	92.2	96.6	40.9	37.2	45.0
			PI(D21)	435	433	99.5	98.3	99.9	124.8	112.5	138.4
	75y+	Flu-1	PRE	284	277	97.5	95.0	99.0	47.9	42.9	53.4
			PI(D21)	284	283	99.6	98.1	100	119.3	107.5	132.5
		Flu-2	PRE	275	269	97.8	95.3	99.2	49.7	44.5	55.4
			PI(D21)	275	274	99.6	98.0	100	114.0	101.2	128.5
	65y+*	Flu-1	PRE	716	691	96.5	94.9	97.7	44.3	41.3	47.5
			PI(D21)	715	712	99.6	98.8	99.9	121.6	113.7	130.1

		Flu-2	PRE	710	681	95.9	94.2	97.2	44.1	41.0	47.4		
			PI(D21)	710	707	99.6	98.8	99.9	120.5	111.4	130.3		
		18-40y	Flu-2	PRE	473	418	88.4	85.1	91.1	45.5	39.5	52.4	
				PI(D21)	473	472	99.8	98.8	100	671.7	597.2	755.4	
A/Wisconsin	50-64y	Flu-1	PRE	736	485	65.9	62.3	69.3	21.0	19.0	23.2		
			PI(D21)	736	733	99.6	98.8	99.9	339.9	311.5	370.8		
		Flu-2	PRE	735	502	68.3	64.8	71.7	22.0	19.8	24.3		
			PI(D21)	736	732	99.5	98.6	99.9	203.3	185.5	222.8		
	65-74y	Flu-1	PRE	432	346	80.1	76.0	83.8	35.4	30.9	40.6		
			PI(D21)	431	427	99.1	97.6	99.7	357.8	320.3	399.7		
		Flu-2	PRE	435	331	76.1	71.8	80.0	31.2	27.2	35.8		
			PI(D21)	435	431	99.1	97.7	99.7	194.2	171.1	220.3		
	75y+	Flu-1	PRE	284	237	83.5	78.6	87.6	37.2	31.4	44.2		
			PI(D21)	284	282	99.3	97.5	99.9	376.8	329.2	431.4		
		Flu-2	PRE	275	231	84.0	79.1	88.1	35.5	30.2	41.8		
			PI(D21)	275	271	98.5	96.3	99.6	180.6	154.2	211.5		
	65y+*	Flu-1	PRE	716	583	81.4	78.4	84.2	36.1	32.5	40.2		
			PI(D21)	715	709	99.2	98.2	99.7	365.3	335.3	397.9		
		Flu-2	PRE	710	562	79.2	76.0	82.1	32.8	29.5	36.5		
			PI(D21)	710	702	98.9	97.8	99.5	188.8	171.1	208.3		
	18-40y	Flu-2	PRE	473	318	67.2	62.8	71.4	21.7	19.1	24.7		
			PI(D21)	473	471	99.6	98.5	99.9	232.8	210.6	257.3		
		B/Malaysia	50-64y	Flu-1	PRE	736	625	84.9	82.1	87.4	26.9	24.8	29.1
					PI(D21)	736	735	99.9	99.2	100	267.6	249.8	286.7
Flu-2	PRE			736	623	84.6	81.8	87.2	26.1	24.2	28.3		
	PI(D21)			736	735	99.9	99.2	100	199.8	185.3	215.5		
65-74y	Flu-1		PRE	432	403	93.3	90.5	95.5	47.0	42.4	52.0		
			PI(D21)	431	430	99.8	98.7	100	284.6	259.9	311.5		
	Flu-2		PRE	435	405	93.1	90.3	95.3	46.5	41.8	51.7		
			PI(D21)	435	435	100	99.2	100	190.7	173.6	209.4		
75y+	Flu-1		PRE	284	276	97.2	94.5	98.8	71.0	63.1	80.0		
			PI(D21)	284	283	99.6	98.1	100	338.9	303.4	378.5		
	Flu-2		PRE	275	269	97.8	95.3	99.2	63.7	56.2	72.2		
			PI(D21)	275	275	100	98.7	100	217.4	193.2	244.5		
65y+	Flu-1		PRE	716	679	94.8	92.9	96.3	55.3	51.1	59.9		
			PI(D21)	715	713	99.7	99.0	100	305.0	284.3	327.2		
	Flu-2		PRE	710	674	94.9	93.0	96.4	52.5	48.4	57.0		
			PI(D21)	710	710	100	99.5	100	200.6	186.4	215.8		
18-40y	Flu-2	PRE	473	383	81.0	77.1	84.4	27.3	24.5	30.5			
		PI(D21)	473	473	100	99.2	100	355.0	323.3	389.8			
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 PRE = pre-vaccination Dose 1 (Day 0) PI(D21) = post-vaccination Dose 1 (Day 21)													
Primary Efficacy Results: Seroconversion rate (SCR) for HI antibody titer at Day 21 (ATP cohort for immunogenicity)													
Vaccine strain	Subgroup	Group	N	SCR									
				n	%	95% CI							
						LL	UL						
A/New Caledonia	50-64y*	Flu-1	736	378	51.4	47.7	55.0						
		Flu-2	735	366	49.8	46.1	53.5						
	65-74y	Flu-1	431	144	33.4	29.0	38.1						
		Flu-2	435	132	30.3	26.1	34.9						

A/Wisconsin	75y+	Flu-1	284	79	27.8	22.7	33.4
		Flu-2	275	67	24.4	19.4	29.9
	65y+*	Flu-1	715	223	31.2	27.8	34.7
		Flu-2	710	199	28.0	24.8	31.5
	18-40y	Flu-2	473	323	68.3	63.9	72.5
	50-64y*	Flu-1	736	621	84.4	81.5	86.9
		Flu-2	735	483	65.7	62.2	69.1
	65-74y	Flu-1	431	321	74.5	70.1	78.5
		Flu-2	435	248	57.0	52.2	61.7
	75y+	Flu-1	284	219	77.1	71.8	81.9
		Flu-2	275	152	55.3	49.2	61.2
	65y+*	Flu-1	715	540	75.5	72.2	78.6
		Flu-2	710	400	56.3	52.6	60.0
B/Malaysia	50-64y*	Flu-1	736	575	78.1	75.0	81.1
		Flu-2	736	496	67.4	63.9	70.8
	65-74y	Flu-1	431	273	63.3	58.6	67.9
		Flu-2	435	198	45.5	40.8	50.3
	75y+	Flu-1	284	156	54.9	48.9	60.8
		Flu-2	275	115	41.8	35.9	47.9
	65y+*	Flu-1	715	429	60.0	56.3	63.6
		Flu-2	710	313	44.1	40.4	47.8
	18-40y	Flu-2	473	375	79.3	75.3	82.8

Seroconversion defined as:

- For initially seronegative subjects, antibody titer $\geq 1:40$ 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 subjects who seroconverted

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

* Primary Efficacy Results

Secondary Outcome Variable (s):

Seropositivity rates and GMTs for HI antibody titer at Day 180 (ATP cohort for persistence)

Vaccine strain	Sub-group	Group	Timing	N	$\geq 1:10$				GMT		
					n	%	95% CI		Value	95% CI	
							LL	UL		LL	UL
A/New Caledonia	50-64y	Flu-1	PI(D180)	682	677	99.3	98.3	99.8	83.5	76.5	91.2
		Flu-2	PI(D180)	690	683	99.0	97.9	99.6	89.1	81.6	97.2
	65-74y	Flu-1	PI(D180)	414	408	98.6	96.9	99.5	61.1	55.7	67.0
		Flu-2	PI(D180)	413	407	98.5	96.9	99.5	65.6	59.6	72.3
	75y+	Flu-1	PI(D180)	261	259	99.2	97.3	99.9	62.0	55.7	68.9
		Flu-2	PI(D180)	244	240	98.4	95.9	99.6	60.4	53.7	68.0
	65y+	Flu-1	PI(D180)	675	667	98.8	97.7	99.5	61.5	57.3	65.9
		Flu-2	PI(D180)	657	647	98.5	97.2	99.3	63.6	59.1	68.6
	18-40y	Flu-2	PI(D180)	431	428	99.3	98.0	99.9	299.6	262.3	342.1
A/Wisconsin	50-64y	Flu-1	PI(D180)	682	668	97.9	96.6	98.9	109.7	99.8	120.6
		Flu-2	PI(D180)	690	661	95.8	94.0	97.2	78.8	71.4	87.0
	65-74y	Flu-1	PI(D180)	414	400	96.6	94.4	98.1	126.3	111.2	143.4
		Flu-2	PI(D180)	413	393	95.2	92.6	97.0	81.4	71.1	93.3
	75y+	Flu-1	PI(D180)	261	253	96.9	94.1	98.7	111.8	95.3	131.2
		Flu-2	PI(D180)	244	229	93.9	90.1	96.5	70.6	59.2	84.3
	65y+	Flu-1	PI(D180)	675	653	96.7	95.1	97.9	120.5	109.1	133.1
		Flu-2	PI(D180)	657	622	94.7	92.7	96.3	77.3	69.4	86.0
	18-40y	Flu-2	PI(D180)	431	425	98.6	97.0	99.5	104.9	93.8	117.4
B/Malaysia	50-64y	Flu-1	PI(D180)	682	673	98.7	97.5	99.4	100.9	93.5	108.9

		Flu-2	PI(D180)	690	682	98.8	97.7	99.5	90.1	83.4	97.4
	65-74y	Flu-1	PI(D180)	414	414	100	99.1	100	136.0	123.4	149.9
		Flu-2	PI(D180)	413	411	99.5	98.3	99.9	109.1	99.3	120.0
	75y+	Flu-1	PI(D180)	261	260	99.6	97.9	100	164.3	145.7	185.3
		Flu-2	PI(D180)	244	243	99.6	97.7	100	128.4	112.1	147.1
	65y+	Flu-1	PI(D180)	675	674	99.9	99.2	100	146.3	135.6	157.8
		Flu-2	PI(D180)	657	654	99.5	98.7	99.9	115.9	107.2	125.3
	18-40y	Flu-2	PI(D180)	431	426	98.8	97.3	99.6	158.1	142.6	175.3

N = number of subjects with available results

n (%) = number (percentage) of seropositive subjects (HI titer $\geq 1:10$)

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

PI(D180) = post-vaccination Dose 1 (Day 180)

Secondary Outcome Variable (s):

Seroconversion rate (SCR) for HI antibody titer at Day 180 (ATP cohort for persistence)

Vaccine strain	Subgroup	Group	N	SCR			
				n	%	95% CI	
						LL	UL
A/New Caledonia	50-64y	Flu-1	679	170	25.0	21.8	28.5
		Flu-2	684	195	28.5	25.2	32.1
	65-74y	Flu-1	413	40	9.7	7.0	13.0
		Flu-2	413	68	16.5	13.0	20.4
	75y+	Flu-1	261	20	7.7	4.7	11.6
		Flu-2	244	14	5.7	3.2	9.4
	65y+	Flu-1	674	60	8.9	6.9	11.3
		Flu-2	657	82	12.5	10.1	15.3
	18-40y	Flu-2	431	256	59.4	54.6	64.1
		Flu-2	431	256	59.4	54.6	64.1
A/Wisconsin	50-64y	Flu-1	679	368	54.2	50.4	58.0
		Flu-2	684	269	39.3	35.6	43.1
	65-74y	Flu-1	413	179	43.3	38.5	48.3
		Flu-2	413	118	28.6	24.3	33.2
	75y+	Flu-1	261	106	40.6	34.6	46.8
		Flu-2	244	55	22.5	17.5	28.3
	65y+	Flu-1	674	285	42.3	38.5	46.1
		Flu-2	657	173	26.3	23.0	29.9
	18-40y	Flu-2	431	223	51.7	46.9	56.5
		Flu-2	431	223	51.7	46.9	56.5
B/Malaysia	50-64y	Flu-1	679	301	44.3	40.6	48.2
		Flu-2	685	266	38.8	35.2	42.6
	65-74y	Flu-1	413	140	33.9	29.3	38.7
		Flu-2	413	108	26.2	22.0	30.7
	75y+	Flu-1	261	70	26.8	21.5	32.6
		Flu-2	244	42	17.2	12.7	22.5
	65y+	Flu-1	674	210	31.2	27.7	34.8
		Flu-2	657	150	22.8	19.7	26.2
	18-40y	Flu-2	431	264	61.3	56.5	65.9
		Flu-2	431	264	61.3	56.5	65.9

Seroconversion defined as:

- For initially seronegative subjects, antibody titer $\geq 1:40$ 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 subjects who seroconverted

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

Secondary Outcome Variable (s):

Seroconversion factor (SCF) for HI antibody titer at Day 21 (ATP cohort for immunogenicity)

Vaccine strain	Subgroup	Group	N	SCF	
				Value	95% CI

					LL	UL
A/New Caledonia	50-64y	Flu-1	736	5.2	4.7	5.8
		Flu-2	735	5.2	4.7	5.8
	65-74y	Flu-1	431	2.9	2.7	3.2
		Flu-2	435	3.1	2.7	3.4
	75y+	Flu-1	284	2.5	2.3	2.8
		Flu-2	275	2.3	2.1	2.5
	65y+	Flu-1	715	2.7	2.6	2.9
		Flu-2	710	2.7	2.5	3.0
	18-40y	Flu-2	473	14.8	12.4	17.5
A/Wisconsin	50-64y	Flu-1	736	16.2	14.6	17.9
		Flu-2	735	9.3	8.3	10.3
	65-74y	Flu-1	431	10.1	8.8	11.5
		Flu-2	435	6.2	5.4	7.1
	75y+	Flu-1	284	10.1	8.6	11.9
		Flu-2	275	5.1	4.4	5.9
	65y+	Flu-1	715	10.1	9.1	11.2
		Flu-2	710	5.8	5.2	6.4
	18-40y	Flu-2	473	10.7	9.4	12.2
B/Malaysia	50-64y	Flu-1	736	10.0	9.1	10.9
		Flu-2	736	7.6	7.0	8.4
	65-74y	Flu-1	431	6.0	5.4	6.8
		Flu-2	435	4.1	3.7	4.6
	75y+	Flu-1	284	4.8	4.2	5.4
		Flu-2	275	3.4	3.0	3.9
	65y+	Flu-1	715	5.5	5.1	6.0
		Flu-2	710	3.8	3.5	4.2
	18-40y	Flu-2	473	13.0	11.5	14.7

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

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

SCF = Seroconversion Factor or fold increase in serum HI GMTs post-vaccination compared to Day 0.

Secondary Outcome Variable (s):

Seroconversion factor (SCF) for HI antibody titer at Day 180 (ATP cohort for persistence)

Vaccine strain	Subgroup	Group	N	SCF		
				Value	95% CI	
					LL	UL
A/New Caledonia	50-64y	Flu-1	679	2.2	2.1	2.5
		Flu-2	684	2.5	2.3	2.7
	65-74y	Flu-1	413	1.4	1.3	1.6
		Flu-2	413	1.6	1.5	1.8
	75y+	Flu-1	261	1.3	1.2	1.4
		Flu-2	244	1.2	1.1	1.3
	65y+	Flu-1	674	1.4	1.3	1.5
		Flu-2	657	1.5	1.4	1.6
	18-40y	Flu-2	431	6.6	5.7	7.7
A/Wisconsin	50-64y	Flu-1	679	5.2	4.7	5.7
		Flu-2	684	3.4	3.1	3.8
	65-74y	Flu-1	413	3.5	3.1	4.0
		Flu-2	413	2.6	2.3	3.0
	75y+	Flu-1	261	3.1	2.7	3.6
		Flu-2	244	1.9	1.7	2.2
	65y+	Flu-1	674	3.3	3.1	3.7
		Flu-2	657	2.4	2.1	2.6
	18-40y	Flu-2	431	4.8	4.2	5.5

B/Malaysia	50-64y	Flu-1	679	3.7	3.4	4.0
		Flu-2	685	3.4	3.1	3.7
	65-74y	Flu-1	413	2.9	2.6	3.1
		Flu-2	413	2.3	2.1	2.6
	75y+	Flu-1	261	2.3	2.1	2.6
		Flu-2	244	1.9	1.7	2.1
	65y+	Flu-1	674	2.6	2.5	2.8
		Flu-2	657	2.2	2.0	2.3
	18-40y	Flu-2	431	5.8	5.2	6.4

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

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

SCF = Seroconversion Factor or fold increase in serum HI GMTs post-vaccination compared to Day 0.

Secondary Outcome Variable (s):

Seroprotection rates (SPR) for HI antibody titer at each time point (ATP cohort for immunogenicity)

Vaccine strain	Subgroup	Group	Timing	N	SPR			
					n	%	95% CI	
							LL	UL
A/New Caledonia	50-64y	Flu-1	PRE	736	359	48.8	45.1	52.5
			PI(D21)	736	712	96.7	95.2	97.9
		Flu-2	PRE	735	363	49.4	45.7	53.1
			PI(D21)	736	701	95.2	93.4	96.7
	65-74y	Flu-1	PRE	432	270	62.5	57.7	67.1
			PI(D21)	431	407	94.4	91.8	96.4
		Flu-2	PRE	435	263	60.5	55.7	65.1
			PI(D21)	435	396	91.0	87.9	93.5
	75y+	Flu-1	PRE	284	186	65.5	59.6	71.0
			PI(D21)	284	262	92.3	88.5	95.1
		Flu-2	PRE	275	195	70.9	65.2	76.2
			PI(D21)	275	254	92.4	88.6	95.2
	65y+	Flu-1	PRE	716	456	63.7	60.0	67.2
			PI(D21)	715	669	93.6	91.5	95.3
		Flu-2	PRE	710	458	64.5	60.9	68.0
			PI(D21)	710	650	91.5	89.3	93.5
	18-40y	Flu-2	PRE	473	248	52.4	47.8	57.0
			PI(D21)	473	466	98.5	97.0	99.4
A/Wisconsin	50-64y	Flu-1	PRE	736	272	37.0	33.5	40.6
			PI(D21)	736	711	96.6	95.0	97.8
		Flu-2	PRE	735	282	38.4	34.8	42.0
			PI(D21)	736	679	92.3	90.1	94.1
	65-74y	Flu-1	PRE	432	231	53.5	48.6	58.3
			PI(D21)	431	414	96.1	93.8	97.7
		Flu-2	PRE	435	205	47.1	42.4	51.9
			PI(D21)	435	394	90.6	87.4	93.2
	75y+	Flu-1	PRE	284	147	51.8	45.8	57.7
			PI(D21)	284	276	97.2	94.5	98.8
		Flu-2	PRE	275	147	53.5	47.4	59.5
			PI(D21)	275	251	91.3	87.3	94.3
	65y+	Flu-1	PRE	716	378	52.8	49.1	56.5
			PI(D21)	715	690	96.5	94.9	97.7
		Flu-2	PRE	710	352	49.6	45.8	53.3
			PI(D21)	710	645	90.8	88.5	92.9
	18-40y	Flu-2	PRE	473	174	36.8	32.4	41.3
			PI(D21)	473	451	95.3	93.0	97.1
B/Malaysia	50-64y	Flu-1	PRE	736	325	44.2	40.5	47.8

		Flu-2	PI(D21)	736	726	98.6	97.5	99.3
			PRE	736	306	41.6	38.0	45.2
			PI(D21)	736	712	96.7	95.2	97.9
	65-74y	Flu-1	PRE	432	281	65.0	60.3	69.5
			PI(D21)	431	424	98.4	96.7	99.3
		Flu-2	PRE	435	280	64.4	59.7	68.9
			PI(D21)	435	420	96.6	94.4	98.1
	75y+	Flu-1	PRE	284	221	77.8	72.5	82.5
			PI(D21)	284	281	98.9	96.9	99.8
		Flu-2	PRE	275	201	73.1	67.4	78.2
			PI(D21)	275	272	98.9	96.8	99.8
	65y+	Flu-1	PRE	716	502	70.1	66.6	73.4
			PI(D21)	715	705	98.6	97.4	99.3
		Flu-2	PRE	710	481	67.7	64.2	71.2
			PI(D21)	710	692	97.5	96.0	98.5
	18-40y	Flu-2	PRE	473	203	42.9	38.4	47.5
			PI(D21)	473	462	97.7	95.9	98.8

N = number of subjects with available results

n (%) = number (percentage) of seroprotected subjects (HI titer \geq 1:40)

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

PRE = pre-vaccination Dose 1 (Day 0)

PI(D21) = post-vaccination Dose 1 (Day 21)

Secondary Outcome Variable (s):

Seroprotection rates (SPR) for HI antibody titer at Day 180 (ATP cohort for persistence)

Vaccine strain	Subgroup	Group	Timing	N	SPR			
					n	%	95% CI	
							LL	UL
A/New Caledonia	50-64y	Flu-1	PI(D180)	682	534	78.3	75.0	81.3
		Flu-2	PI(D180)	690	561	81.3	78.2	84.1
	65-74y	Flu-1	PI(D180)	414	314	75.8	71.4	79.9
		Flu-2	PI(D180)	413	325	78.7	74.4	82.5
	75y+	Flu-1	PI(D180)	261	204	78.2	72.7	83.0
		Flu-2	PI(D180)	244	185	75.8	69.9	81.1
	65y+	Flu-1	PI(D180)	675	518	76.7	73.4	79.9
		Flu-2	PI(D180)	657	510	77.6	74.2	80.8
	18-40y	Flu-2	PI(D180)	431	412	95.6	93.2	97.3
A/Wisconsin	50-64y	Flu-1	PI(D180)	682	565	82.8	79.8	85.6
		Flu-2	PI(D180)	690	524	75.9	72.6	79.1
	65-74y	Flu-1	PI(D180)	414	353	85.3	81.5	88.5
		Flu-2	PI(D180)	413	306	74.1	69.6	78.3
	75y+	Flu-1	PI(D180)	261	219	83.9	78.9	88.1
		Flu-2	PI(D180)	244	167	68.4	62.2	74.2
	65y+	Flu-1	PI(D180)	675	572	84.7	81.8	87.4
		Flu-2	PI(D180)	657	473	72.0	68.4	75.4
	18-40y	Flu-2	PI(D180)	431	363	84.2	80.4	87.5
B/Malaysia	50-64y	Flu-1	PI(D180)	682	607	89.0	86.4	91.3
		Flu-2	PI(D180)	690	583	84.5	81.6	87.1
	65-74y	Flu-1	PI(D180)	414	381	92.0	89.0	94.4
		Flu-2	PI(D180)	413	377	91.3	88.1	93.8
	75y+	Flu-1	PI(D180)	261	253	96.9	94.1	98.7
		Flu-2	PI(D180)	244	224	91.8	87.6	94.9
	65y+	Flu-1	PI(D180)	675	634	93.9	91.8	95.6
		Flu-2	PI(D180)	657	601	91.5	89.1	93.5
	18-40y	Flu-2	PI(D180)	431	402	93.3	90.5	95.4

N = number of subjects with available results

n (%) = number (percentage) of seroprotected subjects (HI titer \geq 1:40)

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

PI(D180) = post-vaccination Dose 1 (Day 180)

Secondary Outcome Variable (s):

Descriptive Statistics on the frequency of cytokine-positive CD4 T-cells (per million CD4 T-cells) for each strain at Day 0 and Day 21 (ATP cohort for immunogenicity in CMI subset)

Test description	Vaccine strain	Sub-group	Group	Timing	N	Nmiss	GM	SD	Median
CD4-All Doubles	A/New Caledonia	50-64y	Flu-1	PRE	26	91	277.43	338.10	431.00
				PI(D21)	25	92	916.00	607.50	1031.00
			Flu-2	PRE	28	92	269.03	272.62	376.00
				PI(D21)	28	92	496.56	419.10	486.50
		65-74y	Flu-1	PRE	55	18	275.63	321.70	349.00
				PI(D21)	55	18	834.40	554.24	860.00
			Flu-2	PRE	51	19	291.36	424.98	441.00
				PI(D21)	53	17	532.93	606.59	668.00
		75y+	Flu-1	PRE	33	8	197.79	288.69	302.00
				PI(D21)	32	9	644.66	599.08	758.00
			Flu-2	PRE	30	9	272.50	333.45	400.00
				PI(D21)	31	8	546.32	331.36	616.00
		65y+	Flu-1	PRE	88	26	243.38	310.83	337.50
				PI(D21)	87	27	758.86	568.91	847.00
			Flu-2	PRE	81	28	284.23	393.47	410.00
				PI(D21)	84	25	537.83	525.01	626.50
		18-40y	Flu-2	PRE	22	56	491.16	420.41	622.00
				PI(D21)	21	57	830.86	584.78	956.00
	A/ Wisconsin	50-64y	Flu-1	PRE	26	91	627.03	438.21	649.50
				PI(D21)	25	92	1539.31	1175.42	1479.00
			Flu-2	PRE	28	92	686.13	446.24	770.50
				PI(D21)	28	92	1169.96	1367.98	1080.00
		65-74y	Flu-1	PRE	55	18	626.13	541.67	779.00
				PI(D21)	55	18	1601.10	1124.57	1606.00
			Flu-2	PRE	51	19	752.47	614.49	727.00
				PI(D21)	53	17	917.43	1108.65	1086.00
		75y+	Flu-1	PRE	33	8	329.93	486.51	530.00
				PI(D21)	32	9	1353.29	1166.44	1535.00
			Flu-2	PRE	30	9	548.54	535.01	614.50
				PI(D21)	31	8	634.03	688.11	823.00
		65y+	Flu-1	PRE	88	26	492.41	529.03	659.50
				PI(D21)	87	27	1505.07	1135.09	1596.00
			Flu-2	PRE	81	28	669.34	586.84	719.00
				PI(D21)	84	25	800.49	989.90	1024.50
		18-40y	Flu-2	PRE	22	56	497.98	469.98	759.50
				PI(D21)	22	56	1062.75	639.33	1381.50
	B/ Malaysia	50-64y	Flu-1	PRE	26	91	497.70	457.39	489.00
				PI(D21)	25	92	1746.63	1214.33	1633.00
			Flu-2	PRE	28	92	403.91	679.11	569.00
				PI(D21)	28	92	1128.74	1289.17	1417.00
		65-74y	Flu-1	PRE	55	18	318.00	433.82	499.00
				PI(D21)	55	18	1471.55	895.04	1484.00
			Flu-2	PRE	51	19	411.86	433.82	528.00
				PI(D21)	53	17	701.69	822.69	949.00
		75y+	Flu-1	PRE	33	8	237.87	353.98	408.00

			Flu-2	PI(D21)	32	9	1379.19	951.72	1654.00
				PRE	30	9	379.75	416.56	493.00
				PI(D21)	31	8	951.09	469.05	1026.00
		65y+	Flu-1	PRE	88	26	285.19	405.59	467.50
				PI(D21)	87	27	1436.88	910.93	1497.00
			Flu-2	PRE	81	28	399.66	425.34	500.00
				PI(D21)	84	25	785.03	709.63	961.50
		18-40y	Flu-2	PRE	22	56	541.54	490.89	651.50
				PI(D21)	22	56	1070.69	1011.26	1282.50
CD4-CD40L	A/New Caledonia	50-64y	Flu-1	PRE	26	91	236.64	331.00	450.00
				PI(D21)	25	92	910.53	584.34	963.00
			Flu-2	PRE	28	92	253.95	254.75	379.50
				PI(D21)	28	92	485.01	382.54	492.00
		65-74y	Flu-1	PRE	55	18	285.20	313.37	351.00
				PI(D21)	55	18	802.49	545.19	859.00
			Flu-2	PRE	51	19	282.27	389.06	441.00
				PI(D21)	53	17	498.85	557.00	668.00
		75y+	Flu-1	PRE	33	8	199.12	275.20	336.00
				PI(D21)	32	9	618.14	585.54	703.50
			Flu-2	PRE	30	9	253.33	327.14	374.50
				PI(D21)	31	8	520.66	322.68	585.00
		65y+	Flu-1	PRE	88	26	249.25	300.84	346.50
				PI(D21)	87	27	729.03	558.46	801.00
			Flu-2	PRE	81	28	271.19	367.36	391.00
				PI(D21)	84	25	506.79	486.04	613.50
		18-40y	Flu-2	PRE	22	56	464.20	398.15	588.50
				PI(D21)	21	57	774.10	564.94	944.00
	A/Wisconsin	50-64y	Flu-1	PRE	26	91	611.33	438.87	616.00
				PI(D21)	25	92	1447.47	1106.39	1446.00
			Flu-2	PRE	28	92	656.56	414.70	767.50
				PI(D21)	28	92	1101.47	1332.19	1033.00
		65-74y	Flu-1	PRE	55	18	604.22	535.57	739.00
				PI(D21)	55	18	1528.84	1075.64	1594.00
			Flu-2	PRE	51	19	732.16	575.43	745.00
				PI(D21)	53	17	873.56	1066.77	1007.00
		75y+	Flu-1	PRE	33	8	349.99	470.91	499.00
				PI(D21)	32	9	1293.12	1144.55	1463.00
			Flu-2	PRE	30	9	525.68	498.91	580.50
				PI(D21)	31	8	599.07	671.66	772.00
		65y+	Flu-1	PRE	88	26	492.34	519.53	658.00
				PI(D21)	87	27	1437.52	1096.30	1534.00
			Flu-2	PRE	81	28	647.61	549.74	707.00
				PI(D21)	84	25	760.04	954.52	984.00
		18-40y	Flu-2	PRE	22	56	464.78	411.81	713.50
				PI(D21)	22	56	980.66	597.71	1237.00
	B/Malaysia	50-64y	Flu-1	PRE	26	91	507.68	434.33	523.50
				PI(D21)	25	92	1686.03	1122.47	1555.00
			Flu-2	PRE	28	92	457.01	534.87	557.50
				PI(D21)	28	92	981.29	1041.72	1381.50
		65-74y	Flu-1	PRE	55	18	302.59	423.48	499.00
				PI(D21)	55	18	1430.14	867.55	1471.00
			Flu-2	PRE	51	19	417.10	410.39	520.00
				PI(D21)	53	17	684.75	783.76	901.00
		75y+	Flu-1	PRE	33	8	244.37	356.70	438.00

			Flu-2	PI(D21)	32	9	1348.32	937.31	1445.50			
				PRE	30	9	372.02	411.38	479.00			
				PI(D21)	31	8	919.63	462.12	964.00			
		65y+	Flu-1	PRE	88	26	279.29	399.14	480.50			
				PI(D21)	87	27	1399.48	888.52	1459.00			
			Flu-2	PRE	81	28	399.80	408.63	492.00			
		18-40y	Flu-2	PI(D21)	84	25	763.48	679.76	921.00			
				PRE	22	56	514.11	463.35	643.00			
				PI(D21)	22	56	1045.57	977.61	1229.50			
		CD4-IFN γ	A/New Caledonia	50-64y	Flu-1	PRE	26	91	216.94	229.42	342.00	
PI(D21)	25					92	552.77	418.03	665.00			
Flu-2	PRE				28	92	182.18	225.99	202.50			
	PI(D21)				28	92	305.81	298.06	269.00			
65-74y	Flu-1			PRE	55	18	188.08	212.82	256.00			
				PI(D21)	55	18	487.06	346.78	535.00			
	Flu-2			PRE	51	19	250.15	263.59	287.00			
				PI(D21)	53	17	317.41	388.41	405.00			
75y+	Flu-1			PRE	33	8	121.93	195.80	169.00			
				PI(D21)	32	9	430.62	434.77	431.50			
	Flu-2			PRE	30	9	166.57	252.00	212.00			
				PI(D21)	31	8	311.84	264.21	361.00			
65y+	Flu-1			PRE	88	26	159.87	209.99	205.00			
				PI(D21)	87	27	465.49	379.80	472.00			
	Flu-2			PRE	81	28	215.18	259.30	269.00			
				PI(D21)	84	25	315.34	349.58	403.50			
18-40y	Flu-2			PRE	22	56	375.96	338.98	393.50			
				PI(D21)	21	57	549.49	425.29	628.00			
	A/Wisconsin			50-64y	Flu-1	PRE	26	91	307.44	245.54	341.50	
						PI(D21)	25	92	813.10	799.87	789.00	
Flu-2					PRE	28	92	303.64	295.73	332.50		
					PI(D21)	28	92	546.01	767.81	538.00		
65-74y				Flu-1	PRE	55	18	350.70	326.28	403.00		
					PI(D21)	55	18	896.27	794.83	968.00		
				Flu-2	PRE	51	19	396.17	448.60	458.00		
					PI(D21)	53	17	553.10	781.57	531.00		
75y+				Flu-1	PRE	33	8	184.09	269.01	240.00		
					PI(D21)	32	9	735.92	910.36	758.00		
				Flu-2	PRE	30	9	229.20	360.62	393.50		
					PI(D21)	31	8	385.37	450.69	467.00		
65y+				Flu-1	PRE	88	26	275.40	313.72	349.00		
					PI(D21)	87	27	833.59	834.34	895.00		
				Flu-2	PRE	81	28	323.49	419.66	458.00		
					PI(D21)	84	25	484.05	689.37	488.50		
18-40y				Flu-2	PRE	22	56	303.07	308.86	282.50		
					PI(D21)	22	56	594.15	339.92	705.50		
				B/Malaysia	50-64y	Flu-1	PRE	26	91	232.80	318.15	337.50
							PI(D21)	25	92	1088.40	927.45	1109.00
Flu-2						PRE	28	92	340.07	603.08	425.00	
						PI(D21)	28	92	697.23	1129.04	773.50	
65-74y					Flu-1	PRE	55	18	209.65	311.26	303.00	
						PI(D21)	55	18	911.41	625.12	927.00	
					Flu-2	PRE	51	19	241.89	346.42	319.00	
						PI(D21)	53	17	493.42	577.21	543.00	
75y+					Flu-1	PRE	33	8	178.02	263.15	282.00	

			Flu-2	PI(D21)	32	9	794.07	764.12	993.50	
				PRE	30	9	290.47	262.64	282.00	
				PI(D21)	31	8	597.88	333.36	669.00	
		65y+	Flu-1	PRE	88	26	197.18	293.21	302.00	
				PI(D21)	87	27	866.36	675.20	945.00	
				Flu-2	PRE	81	28	258.85	316.88	296.00
			PI(D21)		84	25	529.65	498.90	581.50	
			18-40y		Flu-2	PRE	22	56	435.07	373.68
				PI(D21)		22	56	736.36	626.99	807.50
		CD4-IL2		A/New Caledonia		50-64y	Flu-1	PRE	26	91
PI(D21)	25		92		664.99			536.47	860.00	
Flu-2	PRE		28		92		222.69	261.27	308.50	
	PI(D21)		28		92		379.44	378.65	414.00	
65-74y	Flu-1		PRE		55	18	225.52	296.48	285.00	
			PI(D21)		55	18	667.77	446.35	734.00	
			Flu-2		PRE	51	19	220.59	363.90	356.00
	PI(D21)				53	17	445.51	496.91	520.00	
	75y+				Flu-1	PRE	33	8	156.40	249.86
			PI(D21)			32	9	495.27	470.56	599.00
Flu-2		PRE	30	9	225.56	301.39	292.00			
		PI(D21)	31	8	363.93	297.57	490.00			
65y+	Flu-1	PRE	88	26	196.60	280.69	267.00			
		PI(D21)	87	27	598.26	454.03	703.00			
		Flu-2	PRE	81	28	222.42	341.52	318.00		
			PI(D21)	84	25	413.46	437.32	496.00		
	18-40y	Flu-2	PRE	22	56	395.18	354.80	534.00		
			PI(D21)	21	57	669.75	499.96	819.00		
		A/Wisconsin	50-64y	Flu-1	PRE	26	91	489.44	418.98	589.00
					PI(D21)	25	92	1281.88	1058.75	1249.00
Flu-2	PRE			28	92	576.44	433.65	680.00		
	PI(D21)			28	92	994.26	1282.84	939.00		
65-74y	Flu-1		PRE	55	18	544.45	465.29	645.00		
			PI(D21)	55	18	1339.66	976.42	1390.00		
			Flu-2	PRE	51	19	599.11	557.10	719.00	
	PI(D21)			53	17	788.20	992.89	923.00		
	75y+			Flu-1	PRE	33	8	340.57	422.37	431.00
			PI(D21)		32	9	1067.15	986.30	1324.00	
Flu-2		PRE	30	9	410.47	502.30	543.00			
		PI(D21)	31	8	546.31	611.77	704.00			
65y+	Flu-1	PRE	88	26	456.61	453.24	575.50			
		PI(D21)	87	27	1232.16	975.60	1337.00			
		Flu-2	PRE	81	28	520.81	536.48	648.00		
			PI(D21)	84	25	688.47	884.58	841.00		
	18-40y	Flu-2	PRE	22	56	397.02	387.49	564.00		
			PI(D21)	22	56	871.52	564.68	1097.00		
		B/Malaysia	50-64y	Flu-1	PRE	26	91	463.19	427.40	477.50
					PI(D21)	25	92	1519.87	1122.51	1520.00
Flu-2	PRE			28	92	442.09	638.03	505.00		
	PI(D21)			28	92	1033.71	1089.27	1254.50		
65-74y	Flu-1			PRE	55	18	316.30	376.69	421.00	
				PI(D21)	55	18	1332.88	846.23	1346.00	
				Flu-2	PRE	51	19	344.81	401.82	514.00
	PI(D21)				53	17	745.29	796.21	784.00	
	75y+		Flu-1		PRE	33	8	254.31	331.15	411.00
				PI(D21)	32	9	1067.15	986.30	1324.00	

			Flu-2	PI(D21)	32	9	1233.37	876.25	1573.00		
				PRE	30	9	380.05	385.64	410.50		
				PI(D21)	31	8	865.41	436.89	913.00		
		65y+	Flu-1	PRE	88	26	291.46	360.17	414.00		
				PI(D21)	87	27	1295.38	852.42	1367.00		
			Flu-2	PRE	81	28	357.46	393.66	469.00		
		18-40y	Flu-2	PI(D21)	84	25	787.54	682.77	866.00		
				PRE	22	56	471.27	429.06	543.00		
				PI(D21)	22	56	802.87	866.53	1229.00		
		CD4-TNF α	A/New Caledonia	50-64y	Flu-1	PRE	26	91	259.28	255.46	321.50
PI(D21)	25					92	575.24	474.48	783.00		
Flu-2	PRE				28	92	226.60	241.35	353.00		
	PI(D21)			28	92	326.48	320.41	385.00			
65-74y	Flu-1			PRE	55	18	214.42	239.90	286.00		
				PI(D21)	55	18	548.43	459.08	605.00		
	Flu-2			PRE	51	19	193.75	332.75	300.00		
75y+	Flu-1			PI(D21)	53	17	294.50	474.71	450.00		
				PRE	33	8	169.11	228.22	233.00		
	Flu-2			PI(D21)	32	9	415.58	449.71	439.00		
PRE				30	9	164.40	261.40	283.50			
65y+	Flu-1			PI(D21)	31	8	337.44	255.06	440.00		
				PRE	88	26	196.16	236.08	263.00		
	Flu-2			PI(D21)	87	27	495.23	454.55	567.00		
PRE				81	28	182.31	308.78	300.00			
18-40y	Flu-2			PI(D21)	84	25	309.67	408.70	443.50		
				PRE	22	56	350.87	367.54	401.50		
	PI(D21)			21	57	476.36	470.17	647.00			
A/Wisconsin	A/Wisconsin			50-64y	Flu-1	PRE	26	91	472.26	347.78	554.00
						PI(D21)	25	92	1104.68	860.72	1070.00
					Flu-2	PRE	28	92	565.78	373.05	584.00
				PI(D21)		28	92	834.51	1073.20	759.00	
				65-74y	Flu-1	PRE	55	18	439.83	476.46	582.00
						PI(D21)	55	18	1194.14	933.92	1308.00
					Flu-2	PRE	51	19	571.12	519.94	587.00
				75y+	Flu-1	PI(D21)	53	17	664.36	936.52	739.00
						PRE	33	8	296.29	396.62	375.00
					Flu-2	PI(D21)	32	9	988.68	950.25	1084.50
				PRE		30	9	420.59	426.59	482.00	
				65y+	Flu-1	PI(D21)	31	8	542.79	479.25	635.00
		PRE	88			26	379.26	452.43	524.00		
		Flu-2	PI(D21)		87	27	1114.02	936.50	1155.00		
			PRE	81	28	509.94	488.36	567.00			
		18-40y	Flu-2	PI(D21)	84	25	616.61	811.34	669.00		
				PRE	22	56	402.27	412.12	585.50		
			PI(D21)	22	56	731.18	502.02	1000.50			
		B/Malaysia	B/Malaysia	50-64y	Flu-1	PRE	26	91	275.19	320.01	296.00
						PI(D21)	25	92	1045.04	904.21	1058.00
					Flu-2	PRE	28	92	234.13	595.89	399.00
				PI(D21)		28	92	680.13	1030.97	792.00	
				65-74y	Flu-1	PRE	55	18	156.96	301.03	319.00
						PI(D21)	55	18	811.92	672.52	855.00
					Flu-2	PRE	51	19	201.23	292.35	306.00
				75y+	Flu-2	PI(D21)	53	17	371.84	472.30	461.00
						PRE	33	8	109.93	235.83	248.00

			Flu-2	PI(D21)	32	9	786.37	662.88	1060.50
				PRE	30	9	204.25	346.58	286.00
				PI(D21)	31	8	518.03	370.78	517.00
		65y+	Flu-1	PRE	88	26	137.34	277.83	259.50
				PI(D21)	87	27	802.43	665.59	881.00
			Flu-2	PRE	81	28	202.34	311.40	303.00
				PI(D21)	84	25	420.24	435.96	487.00
		18-40y	Flu-2	PRE	22	56	347.35	371.62	423.00
				PI(D21)	22	56	524.85	678.32	718.50

All doubles: T-cells producing at least 2 cytokines
CD40L: T-cells producing at least CD40L and another cytokine (IL-2, IFN- γ and TNF- α)
IFN- γ : T-cells producing at least IFN- γ and another cytokine (IL-2, CD40L and TNF- α)
IL-2: T-cells producing at least IL-2 and another cytokine (TNF- α , CD40L and IFN- γ)
TNF- α : T-cells producing at least TNF- α and another cytokine (IL-2, CD40L and IFN- γ)
N = number of subjects with available results
N miss: number of subjects with missing results
GM= Geometric Mean
SD = Standard Deviation
PRE = pre-vaccination Dose 1 (Day 0)
PI(D21) = post-vaccination Dose 1 (Day 21)

Secondary Outcome Variable (s):

Descriptive Statistics on the frequency of cytokine-positive CD4 T-cells (per million CD4 T-cells) for each strain at Day 180 (ATP cohort for persistence in CMI subset)

Test description	Vaccine strain	Sub-group	Group	N	Nmiss	GM	SD	Median
D4-All Doubles	A/New Caledonia	50-64y	Flu-1	1	110	428.00	-	428.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	444.36	525.01	611.00
			Flu-2	50	14	296.53	371.70	479.00
		75y+	Flu-1	24	14	442.72	348.49	616.00
			Flu-2	21	12	353.72	430.37	394.00
		65y+	Flu-1	77	31	443.85	475.85	611.00
			Flu-2	71	26	312.41	387.48	440.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	534.00	-	534.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	908.82	947.06	960.00
			Flu-2	50	14	588.84	582.64	871.00
		75y+	Flu-1	24	14	658.46	519.26	1096.50
			Flu-2	21	12	592.06	851.91	499.00
		65y+	Flu-1	77	31	821.97	839.47	968.00
			Flu-2	71	26	589.79	667.07	773.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	313.00	-	313.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	604.88	596.66	870.00
			Flu-2	50	14	456.85	526.49	485.50
		75y+	Flu-1	24	14	690.30	588.35	820.50
			Flu-2	21	12	366.40	444.57	517.00
		65y+	Flu-1	77	31	630.31	590.32	866.00
			Flu-2	71	26	427.99	501.43	499.00
		18-40y	Flu-2	0	73	-	-	-
	A/New Caledonia	50-64y	Flu-1	1	110	468.00	-	468.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	445.20	517.95	625.00

			Flu-2	50	14	282.43	368.76	469.50
		75y+	Flu-1	24	14	419.00	342.19	616.00
			Flu-2	21	12	298.07	414.62	315.00
		65y+	Flu-1	77	31	436.86	469.39	625.00
			Flu-2	71	26	286.97	380.84	434.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	554.00	-	554.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	911.07	869.49	951.00
			Flu-2	50	14	572.78	575.96	830.00
		75y+	Flu-1	24	14	645.45	510.57	1069.00
			Flu-2	21	12	594.06	814.37	499.00
		65y+	Flu-1	77	31	818.27	777.99	977.00
			Flu-2	71	26	578.99	649.38	759.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	275.00	-	275.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	608.03	586.78	914.00
			Flu-2	50	14	449.91	521.98	484.50
		75y+	Flu-1	24	14	686.11	580.48	804.00
			Flu-2	21	12	370.28	429.60	515.00
		65y+	Flu-1	77	31	631.36	581.20	848.00
			Flu-2	71	26	424.72	494.29	499.00
		18-40y	Flu-2	0	73	-	-	-
CD4-IFN γ	A/New Caledonia	50-64y	Flu-1	1	110	207.00	-	207.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	313.22	374.41	334.00
			Flu-2	50	14	209.34	252.67	312.00
		75y+	Flu-1	24	14	277.18	229.17	347.50
			Flu-2	21	12	229.13	354.09	206.00
		65y+	Flu-1	77	31	301.51	335.38	334.00
			Flu-2	71	26	215.01	283.75	265.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	365.00	-	365.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	497.46	792.74	564.00
			Flu-2	50	14	359.57	411.35	411.00
		75y+	Flu-1	24	14	367.00	345.76	601.50
			Flu-2	21	12	277.12	514.38	303.00
		65y+	Flu-1	77	31	452.47	688.36	596.00
			Flu-2	71	26	332.91	440.87	401.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	656.00	-	656.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	419.65	444.61	510.00
			Flu-2	50	14	254.25	415.37	298.00
		75y+	Flu-1	24	14	410.01	489.92	540.00
			Flu-2	21	12	323.24	315.73	336.00
		65y+	Flu-1	77	31	416.62	456.07	535.00
			Flu-2	71	26	272.96	386.77	333.00
		18-40y	Flu-2	0	73	-	-	-
CD4-IL2	A/New Caledonia	50-64y	Flu-1	1	110	174.00	-	174.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	400.74	485.81	490.00

	A/Wisconsin	75y+	Flu-2	50	14	277.60	350.02	384.00	
			Flu-1	24	14	379.96	315.15	594.50	
			Flu-2	21	12	261.14	337.13	257.00	
		65y+	Flu-1	77	31	394.14	438.03	499.00	
			Flu-2	71	26	272.62	345.77	364.00	
			18-40y	Flu-2	0	73	-	-	-
		50-64y	Flu-1	1	110	349.00	-	349.00	
			Flu-2	0	116	-	-	-	
			65-74y	Flu-1	53	17	770.64	718.52	707.00
				Flu-2	50	14	515.42	560.99	738.00
			75y+	Flu-1	24	14	596.59	487.69	974.00
				Flu-2	21	12	514.66	689.77	557.00
			65y+	Flu-1	77	31	711.54	653.77	845.00
				Flu-2	71	26	515.20	596.97	723.00
			18-40y	Flu-2	0	73	-	-	-
		B/Malaysia	50-64y	Flu-1	1	110	146.00	-	146.00
				Flu-2	0	116	-	-	-
			65-74y	Flu-1	53	17	591.59	551.74	792.00
	Flu-2			50	14	436.76	506.20	500.00	
	75y+		Flu-1	24	14	659.02	554.31	729.50	
			Flu-2	21	12	432.16	417.59	476.00	
	65y+		Flu-1	77	31	611.83	548.91	761.00	
			Flu-2	71	26	435.39	479.62	483.00	
	18-40y		Flu-2	0	73	-	-	-	
CD4-TNF α	A/New Caledonia		50-64y	Flu-1	1	110	260.00	-	260.00
				Flu-2	0	116	-	-	-
			65-74y	Flu-1	53	17	253.09	392.01	396.00
		Flu-2		50	14	196.67	285.61	319.50	
		75y+	Flu-1	24	14	317.30	308.17	425.50	
			Flu-2	21	12	196.29	358.79	194.00	
		65y+	Flu-1	77	31	271.57	365.90	417.00	
			Flu-2	71	26	196.56	306.83	294.00	
		18-40y	Flu-2	0	73	-	-	-	
		A/Wisconsin	50-64y	Flu-1	1	110	330.00	-	330.00
	Flu-2			0	116	-	-	-	
	65-74y		Flu-1	53	17	585.36	763.70	630.00	
			Flu-2	50	14	476.12	455.35	599.50	
	75y+		Flu-1	24	14	491.20	415.18	764.50	
			Flu-2	21	12	292.06	637.93	304.00	
	65y+		Flu-1	77	31	554.22	675.09	666.00	
			Flu-2	71	26	412.04	512.52	509.00	
	18-40y		Flu-2	0	73	-	-	-	
	B/Malaysia		50-64y	Flu-1	1	110	84.00	-	84.00
		Flu-2		0	116	-	-	-	
		65-74y	Flu-1	53	17	333.28	421.68	449.00	
			Flu-2	50	14	187.99	353.42	263.00	
		75y+	Flu-1	24	14	320.64	452.86	379.50	
			Flu-2	21	12	174.70	308.81	270.00	
65y+		Flu-1	77	31	329.29	428.75	404.00		
		Flu-2	71	26	183.96	338.71	270.00		
18-40y		Flu-2	0	73	-	-	-		
All doubles: T-cells producing at least 2 cytokines CD40L: T-cells producing at least CD40L and another cytokine (IL-2, IFN- γ and TNF- α) IFN- γ : T-cells producing at least IFN- γ and another cytokine (IL-2, CD40L and TNF- α)									

IL-2: T-cells producing at least IL-2 and another cytokine (TNF- α , CD40L and IFN- γ)
 TNF- α : T-cells producing at least TNF- α and another cytokine (IL-2, CD40L and IFN- γ)
 N = number of subjects with available results
 N miss: number of subjects with missing results
 GM= Geometric Mean
 SD = Standard Deviation

Secondary Outcome Variable (s):

Descriptive Statistics on the frequency of cytokine-positive CD8 T-cells (per million CD8 T-cells) for each strain at Day 0 and Day 21 (ATP cohort for immunogenicity in CMI subset)

Test description	Vaccine strain	Sub-group	Group	Timing	N	Nmiss	GM	SD	Median
CD8-All Doubles	A/New Caledonia	50-64y	Flu-1	PRE	26	91	4.12	56.39	1.00
				PI(D21)	25	92	5.43	96.61	1.00
			Flu-2	PRE	28	92	5.97	126.87	1.00
				PI(D21)	28	92	5.49	110.33	1.00
		65-74y	Flu-1	PRE	55	18	5.24	140.67	1.00
				PI(D21)	55	18	7.86	138.01	1.00
			Flu-2	PRE	51	19	6.60	139.02	1.00
				PI(D21)	51	19	6.84	117.65	1.00
		75y+	Flu-1	PRE	32	9	7.49	109.96	1.00
				PI(D21)	32	9	5.92	143.69	1.00
			Flu-2	PRE	30	9	5.82	84.13	1.00
				PI(D21)	31	8	13.57	180.56	62.00
		65y+	Flu-1	PRE	87	27	5.98	129.56	1.00
				PI(D21)	87	27	7.08	139.30	1.00
			Flu-2	PRE	81	28	6.30	121.15	1.00
				PI(D21)	82	27	8.86	145.17	1.00
		18-40y	Flu-2	PRE	22	56	6.89	378.70	1.00
				PI(D21)	21	57	6.68	245.46	1.00
	A/ Wisconsin	50-64y	Flu-1	PRE	26	91	2.50	34.59	1.00
				PI(D21)	25	92	4.12	51.42	1.00
			Flu-2	PRE	28	92	1.92	26.37	1.00
				PI(D21)	28	92	4.30	56.15	1.00
		65-74y	Flu-1	PRE	55	18	3.10	42.76	1.00
				PI(D21)	55	18	3.71	48.66	1.00
			Flu-2	PRE	51	19	3.50	80.09	1.00
				PI(D21)	51	19	5.31	92.08	1.00
		75y+	Flu-1	PRE	32	9	8.26	134.73	1.00
				PI(D21)	32	9	3.74	146.52	1.00
			Flu-2	PRE	30	9	4.56	76.59	1.00
				PI(D21)	31	8	4.40	59.63	1.00
		65y+	Flu-1	PRE	87	27	4.45	90.99	1.00
				PI(D21)	87	27	3.72	96.95	1.00
			Flu-2	PRE	81	28	3.86	78.68	1.00
				PI(D21)	82	27	4.94	81.00	1.00
		18-40y	Flu-2	PRE	22	56	4.82	50.01	1.00
				PI(D21)	22	56	1.21	14.07	1.00
	B/ Malaysia	50-64y	Flu-1	PRE	26	91	3.99	48.74	1.00
				PI(D21)	25	92	3.32	35.98	1.00
			Flu-2	PRE	28	92	3.11	40.76	1.00
				PI(D21)	28	92	3.80	64.03	1.00
		65-74y	Flu-1	PRE	55	18	3.07	78.80	1.00
				PI(D21)	55	18	5.79	92.20	1.00
			Flu-2	PRE	51	19	4.49	84.64	1.00

		75y+	Flu-1	PI(D21)	51	19	4.23	70.65	1.00
				PRE	32	9	5.70	62.32	1.00
			Flu-2	PI(D21)	32	9	4.13	70.90	1.00
				PRE	30	9	9.01	81.79	1.00
		65y+	Flu-1	PI(D21)	31	8	4.41	91.81	1.00
				PRE	87	27	3.85	73.06	1.00
			Flu-2	PI(D21)	87	27	5.11	84.87	1.00
				PRE	81	28	5.81	83.45	1.00
		18-40y	Flu-2	PI(D21)	82	27	4.30	78.80	1.00
				PRE	22	56	1.00	0.00	1.00
			Flu-2	PI(D21)	22	56	1.54	44.98	1.00
				PRE	26	91	2.71	35.29	1.00
CD8-CD40L	A/New Caledonia	50-64y	Flu-1	PI(D21)	25	92	2.01	33.39	1.00
				PRE	28	92	1.16	12.28	1.00
			Flu-2	PI(D21)	28	92	1.19	25.51	1.00
				PRE	55	18	1.37	22.78	1.00
		65-74y	Flu-1	PI(D21)	55	18	2.02	25.18	1.00
				PRE	51	19	1.67	27.78	1.00
			Flu-2	PI(D21)	51	19	1.80	25.35	1.00
				PRE	32	9	1.56	36.69	1.00
		75y+	Flu-1	PI(D21)	32	9	1.65	89.74	1.00
				PRE	30	9	1.33	17.27	1.00
			Flu-2	PI(D21)	31	8	2.39	45.46	1.00
				PRE	87	27	1.44	28.58	1.00
		65y+	Flu-1	PI(D21)	87	27	1.88	57.84	1.00
				PRE	81	28	1.54	24.42	1.00
			Flu-2	PI(D21)	82	27	2.00	34.40	1.00
				PRE	22	56	1.77	23.00	1.00
		18-40y	Flu-2	PI(D21)	21	57	1.00	0.00	1.00
				PRE	26	91	1.95	32.29	1.00
	A/Wisconsin	50-64y	Flu-1	PI(D21)	25	92	1.96	24.51	1.00
				PRE	28	92	1.59	24.45	1.00
			Flu-2	PI(D21)	28	92	2.28	43.78	1.00
				PRE	55	18	1.71	22.01	1.00
		65-74y	Flu-1	PI(D21)	55	18	1.65	21.63	1.00
				PRE	51	19	1.53	26.10	1.00
			Flu-2	PI(D21)	51	19	2.06	89.23	1.00
				PRE	32	9	3.20	67.79	1.00
		75y+	Flu-1	PI(D21)	32	9	2.25	79.38	1.00
				PRE	30	9	2.73	34.47	1.00
			Flu-2	PI(D21)	31	8	2.29	32.70	1.00
				PRE	87	27	2.15	45.61	1.00
		65y+	Flu-1	PI(D21)	87	27	1.85	51.91	1.00
				PRE	81	28	1.90	29.65	1.00
			Flu-2	PI(D21)	82	27	2.14	73.00	1.00
				PRE	22	56	1.47	19.57	1.00
		18-40y	Flu-2	PI(D21)	22	56	1.00	0.00	1.00
				PRE	26	91	1.62	21.18	1.00
	B/Malaysia	50-64y	Flu-1	PI(D21)	25	92	1.18	12.60	1.00
				PRE	28	92	1.35	17.18	1.00
			Flu-2	PI(D21)	28	92	1.16	12.28	1.00
				PRE	55	18	2.66	48.91	1.00
		65-74y	Flu-1	PI(D21)	55	18	1.78	42.06	1.00
				PRE	51	19	2.14	30.36	1.00
			Flu-2	PRE					
				PRE					
				PRE					
				PRE					
				PRE					
				PRE					

		75y+	Flu-1	PI(D21)	51	19	1.67	26.87	1.00
				PRE	32	9	1.74	30.91	1.00
			Flu-2	PI(D21)	32	9	3.14	69.63	1.00
				PRE	30	9	3.91	59.83	1.00
		65y+	Flu-1	PI(D21)	31	8	1.42	16.25	1.00
				PRE	87	27	2.28	43.26	1.00
			Flu-2	PI(D21)	87	27	2.19	54.05	1.00
				PRE	81	28	2.67	44.19	1.00
		18-40y	Flu-2	PI(D21)	82	27	1.57	23.42	1.00
				PRE	22	56	1.00	0.00	1.00
			Flu-2	PI(D21)	22	56	1.21	13.86	1.00
				PRE	26	91	2.43	45.00	1.00
CD8-IFN γ	A/New Caledonia	50-64y	Flu-1	PI(D21)	25	92	2.26	84.29	1.00
				PRE	28	92	5.88	114.73	1.00
			Flu-2	PI(D21)	28	92	4.59	109.75	1.00
				PRE	55	18	4.24	127.83	1.00
		65-74y	Flu-1	PI(D21)	55	18	7.61	144.60	1.00
				PRE	51	19	4.68	136.23	1.00
			Flu-2	PI(D21)	51	19	6.79	107.32	1.00
				PRE	32	9	8.30	103.44	1.00
		75y+	Flu-1	PI(D21)	32	9	3.58	84.89	1.00
				PRE	30	9	5.69	82.45	1.00
			Flu-2	PI(D21)	31	8	8.91	187.90	1.00
				PRE	87	27	5.43	118.89	1.00
		65y+	Flu-1	PI(D21)	87	27	5.76	126.77	1.00
				PRE	81	28	5.03	118.68	1.00
			Flu-2	PI(D21)	82	27	7.53	143.19	1.00
				PRE	22	56	4.67	350.09	1.00
		18-40y	Flu-2	PI(D21)	21	57	8.08	220.59	1.00
				PRE	26	91	1.23	12.74	1.00
	A/Wisconsin	50-64y	Flu-1	PI(D21)	25	92	2.07	39.74	1.00
				PRE	28	92	1.16	12.47	1.00
			Flu-2	PI(D21)	28	92	2.22	37.94	1.00
				PRE	55	18	1.89	31.83	1.00
		65-74y	Flu-1	PI(D21)	55	18	2.69	36.97	1.00
				PRE	51	19	2.10	81.41	1.00
			Flu-2	PI(D21)	51	19	2.65	49.64	1.00
				PRE	32	9	2.89	109.72	1.00
		75y+	Flu-1	PI(D21)	32	9	2.49	131.07	1.00
				PRE	30	9	1.82	42.12	1.00
			Flu-2	PI(D21)	31	8	1.75	25.52	1.00
				PRE	87	27	2.21	71.69	1.00
		65y+	Flu-1	PI(D21)	87	27	2.62	84.56	1.00
				PRE	81	28	1.99	69.37	1.00
			Flu-2	PI(D21)	82	27	2.26	42.41	1.00
				PRE	22	56	3.13	29.49	1.00
		18-40y	Flu-2	PI(D21)	22	56	1.00	0.00	1.00
				PRE	26	91	2.22	52.35	1.00
	B/Malaysia	50-64y	Flu-1	PI(D21)	25	92	2.00	31.92	1.00
				PRE	28	92	2.16	32.23	1.00
			Flu-2	PI(D21)	28	92	3.67	52.97	1.00
				PRE	55	18	2.17	65.39	1.00
		65-74y	Flu-1	PI(D21)	55	18	3.91	91.64	1.00
				PRE	51	19	2.89	76.10	1.00
			Flu-2	PI(D21)	51	19	2.89	76.10	1.00
				PRE	51	19	2.89	76.10	1.00
		18-40y	Flu-2	PI(D21)	51	19	2.89	76.10	1.00
				PRE	51	19	2.89	76.10	1.00

		75y+	Flu-1	PI(D21)	51	19	2.87	64.55	1.00
				PRE	32	9	2.69	52.95	1.00
			Flu-2	PI(D21)	32	9	2.03	42.40	1.00
				PRE	30	9	3.63	34.30	1.00
		65y+	Flu-1	PI(D21)	31	8	3.05	90.64	1.00
				PRE	87	27	2.35	60.81	1.00
			Flu-2	PI(D21)	87	27	3.08	77.91	1.00
				PRE	81	28	3.15	63.90	1.00
		18-40y	Flu-2	PI(D21)	82	27	2.94	75.04	1.00
				PRE	22	56	1.00	0.00	1.00
			Flu-2	PI(D21)	22	56	1.78	23.32	1.00
				PRE	26	91	2.51	49.51	1.00
CD8-IL2	A/New Caledonia	50-64y	Flu-1	PI(D21)	25	92	4.17	68.92	1.00
				PRE	28	92	3.15	60.82	1.00
			Flu-2	PI(D21)	28	92	3.80	93.67	1.00
				PRE	55	18	3.89	108.12	1.00
		65-74y	Flu-1	PI(D21)	55	18	4.58	71.10	1.00
				PRE	51	19	4.47	91.61	1.00
			Flu-2	PI(D21)	51	19	3.98	80.86	1.00
				PRE	32	9	3.55	94.18	1.00
		75y+	Flu-1	PI(D21)	32	9	4.84	118.09	1.00
				PRE	30	9	2.77	35.54	1.00
			Flu-2	PI(D21)	31	8	7.82	65.60	1.00
				PRE	87	27	3.76	102.68	1.00
		65y+	Flu-1	PI(D21)	87	27	4.67	90.77	1.00
				PRE	81	28	3.74	76.32	1.00
			Flu-2	PI(D21)	82	27	5.13	75.20	1.00
				PRE	22	56	3.20	274.05	1.00
		18-40y	Flu-2	PI(D21)	21	57	4.38	166.39	1.00
				PRE	26	91	2.06	33.51	1.00
	A/Wisconsin	50-64y	Flu-1	PI(D21)	25	92	3.93	37.25	1.00
				PRE	28	92	1.40	17.03	1.00
			Flu-2	PI(D21)	28	92	4.20	53.35	1.00
				PRE	55	18	2.33	49.59	1.00
		65-74y	Flu-1	PI(D21)	55	18	2.31	45.62	1.00
				PRE	51	19	3.33	50.15	1.00
			Flu-2	PI(D21)	51	19	3.46	89.94	1.00
				PRE	32	9	6.69	81.43	1.00
		75y+	Flu-1	PI(D21)	32	9	2.82	76.08	1.00
				PRE	30	9	4.34	66.10	1.00
			Flu-2	PI(D21)	31	8	3.70	52.26	1.00
				PRE	87	27	3.43	64.37	1.00
		65y+	Flu-1	PI(D21)	87	27	2.49	58.54	1.00
				PRE	81	28	3.67	56.75	1.00
			Flu-2	PI(D21)	82	27	3.55	77.52	1.00
				PRE	22	56	2.26	48.04	1.00
		18-40y	Flu-2	PI(D21)	22	56	1.21	13.86	1.00
				PRE	26	91	3.37	45.35	1.00
	B/Malaysia	50-64y	Flu-1	PI(D21)	25	92	3.32	35.98	1.00
				PRE	28	92	2.51	34.93	1.00
			Flu-2	PI(D21)	28	92	2.96	36.76	1.00
				PRE	55	18	3.05	74.91	1.00
		65-74y	Flu-1	PI(D21)	55	18	2.89	50.96	1.00
				PRE	51	19	4.06	75.16	1.00
			Flu-2	PRE					
				PRE					
				PRE					
				PRE					
				PRE					
				PRE					

		75y+	Flu-1	PI(D21)	51	19	3.00	52.27	1.00
				PRE	32	9	3.59	51.28	1.00
			Flu-2	PI(D21)	32	9	3.16	61.89	1.00
				PRE	30	9	6.48	78.08	1.00
		65y+	Flu-1	PI(D21)	31	8	3.69	69.90	1.00
				PRE	87	27	3.24	66.89	1.00
			Flu-2	PI(D21)	87	27	2.99	54.91	1.00
				PRE	81	28	4.83	76.03	1.00
		18-40y	Flu-2	PI(D21)	82	27	3.25	59.20	1.00
				PRE	22	56	1.00	0.00	1.00
			Flu-2	PI(D21)	22	56	1.83	33.85	1.00
				PRE	26	91	2.89	52.22	1.00
CD8-TNF α	A/New Caledonia	50-64y	Flu-1	PI(D21)	25	92	3.26	86.56	1.00
				PRE	28	92	4.96	118.78	1.00
			Flu-2	PI(D21)	28	92	4.56	70.35	1.00
				PRE	55	18	4.75	122.17	1.00
		65-74y	Flu-1	PI(D21)	55	18	6.05	127.72	1.00
				PRE	51	19	5.27	132.32	1.00
			Flu-2	PI(D21)	51	19	5.10	109.72	1.00
				PRE	32	9	8.05	73.61	1.00
		75y+	Flu-1	PI(D21)	32	9	6.59	134.36	1.00
				PRE	30	9	5.68	82.97	1.00
			Flu-2	PI(D21)	31	8	7.95	155.54	1.00
				PRE	87	27	5.76	106.42	1.00
		65y+	Flu-1	PI(D21)	87	27	6.24	129.44	1.00
				PRE	81	28	5.42	115.93	1.00
			Flu-2	PI(D21)	82	27	6.03	129.06	1.00
				PRE	22	56	6.70	348.04	1.00
		18-40y	Flu-2	PI(D21)	21	57	6.67	210.21	1.00
				PRE	26	91	2.08	25.00	1.00
	A/Wisconsin	50-64y	Flu-1	PI(D21)	25	92	3.39	47.00	1.00
				PRE	28	92	1.84	26.39	1.00
			Flu-2	PI(D21)	28	92	2.85	28.62	1.00
				PRE	55	18	2.66	41.65	1.00
		65-74y	Flu-1	PI(D21)	55	18	3.14	46.91	1.00
				PRE	51	19	2.66	67.71	1.00
			Flu-2	PI(D21)	51	19	2.79	37.18	1.00
				PRE	32	9	5.98	115.36	1.00
		75y+	Flu-1	PI(D21)	32	9	3.92	137.21	1.00
				PRE	30	9	4.35	73.37	1.00
			Flu-2	PI(D21)	31	8	3.76	57.17	1.00
				PRE	87	27	3.58	78.78	1.00
		65y+	Flu-1	PI(D21)	87	27	3.40	91.42	1.00
				PRE	81	28	3.19	70.00	1.00
			Flu-2	PI(D21)	82	27	3.12	45.80	1.00
				PRE	22	56	3.29	49.28	1.00
		18-40y	Flu-2	PI(D21)	22	56	1.21	14.07	1.00
				PRE	26	91	2.37	37.96	1.00
	B/Malaysia	50-64y	Flu-1	PI(D21)	25	92	2.74	28.56	1.00
				PRE	28	92	1.71	37.08	1.00
			Flu-2	PI(D21)	28	92	2.71	60.23	1.00
				PRE	55	18	2.33	68.31	1.00
		65-74y	Flu-1	PI(D21)	55	18	3.56	86.49	1.00
				PRE	51	19	3.32	56.48	1.00
			Flu-2	PRE					
				PRE					
			Flu-2	PRE					
				PRE					

				PI(D21)	51	19	3.46	54.09	1.00
		75y+	Flu-1	PRE	32	9	4.07	49.61	1.00
				PI(D21)	32	9	2.62	38.57	1.00
			Flu-2	PRE	30	9	5.76	46.77	1.00
				PI(D21)	31	8	3.97	69.17	1.00
		65y+	Flu-1	PRE	87	27	2.86	61.86	1.00
				PI(D21)	87	27	3.18	72.89	1.00
			Flu-2	PRE	81	28	4.07	52.88	1.00
				PI(D21)	82	27	3.65	59.85	1.00
		18-40y	Flu-2	PRE	22	56	1.00	0.00	1.00
				PI(D21)	22	56	1.25	28.78	1.00

All doubles: T-cells producing at least 2 cytokines
CD40L: T-cells producing at least CD40L and another cytokine (IL-2, IFN- γ and TNF- α)
IFN- γ : T-cells producing at least IFN- γ and another cytokine (IL-2, CD40L and TNF- α)
IL-2: T-cells producing at least IL-2 and another cytokine (TNF- α , CD40L and IFN- γ)
TNF- α : T-cells producing at least TNF- α and another cytokine (IL-2, CD40L and IFN- γ)
N = number of subjects with available results
N miss: number of subjects with missing results
GM= Geometric Mean
SD = Standard Deviation
PRE = pre-vaccination Dose 1 (Day 0)
PI(D21) = post-vaccination Dose 1 (Day 21)

Secondary Outcome Variable (s):

Descriptive Statistics on the frequency of cytokine-positive CD8 T-cells (per million CD8 T-cells) for each strain at Day 180 (ATP cohort for persistence in CMI subset)

Test description	Vaccine strain	Sub-group	Group	N	Nmiss	GM	SD	Median
CD8-All Doubles	A/New Caledonia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	8.54	146.25	1.00
			Flu-2	49	15	4.56	111.30	1.00
		75y+	Flu-1	24	14	5.29	51.89	1.00
			Flu-2	20	13	11.98	461.58	32.50
		65y+	Flu-1	77	31	7.35	126.25	1.00
			Flu-2	69	28	6.03	266.35	1.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	1.55	39.64	1.00
			Flu-2	49	15	4.22	48.31	1.00
		75y+	Flu-1	24	14	7.92	143.63	1.00
			Flu-2	20	13	3.21	58.26	1.00
		65y+	Flu-1	76	32	2.60	91.41	1.00
			Flu-2	69	28	3.90	50.95	1.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	5.27	76.70	1.00
			Flu-2	48	16	5.18	108.60	1.00
		75y+	Flu-1	23	15	1.93	74.51	1.00
			Flu-2	19	14	4.31	100.05	1.00
		65y+	Flu-1	75	33	3.87	75.92	1.00
			Flu-2	67	30	4.92	105.51	1.00
		18-40y	Flu-2	0	73	-	-	-
		50-64y	Flu-1	1	110	1.00	-	1.00

	Caledonia		Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	1.39	22.62	1.00
			Flu-2	49	15	1.67	21.60	1.00
		75y+	Flu-1	24	14	2.07	30.30	1.00
			Flu-2	20	13	2.95	37.48	1.00
		65y+	Flu-1	77	31	1.57	25.27	1.00
			Flu-2	69	28	1.97	27.38	1.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	1.91	40.28	1.00
			Flu-2	49	15	2.09	38.62	1.00
		75y+	Flu-1	24	14	3.10	50.68	1.00
			Flu-2	20	13	2.01	48.63	1.00
		65y+	Flu-1	76	32	2.23	43.83	1.00
			Flu-2	69	28	2.07	41.40	1.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	1.64	25.66	1.00
			Flu-2	48	16	1.22	29.81	1.00
		75y+	Flu-1	23	15	1.85	68.31	1.00
			Flu-2	19	14	1.00	0.00	1.00
		65y+	Flu-1	75	33	1.70	43.21	1.00
			Flu-2	67	30	1.15	25.27	1.00
		18-40y	Flu-2	0	73	-	-	-
CD8-IFNγ	A/New Caledonia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	5.38	147.92	1.00
			Flu-2	49	15	3.19	117.70	1.00
		75y+	Flu-1	24	14	2.57	48.61	1.00
			Flu-2	20	13	7.79	447.39	1.00
		65y+	Flu-1	77	31	4.27	127.04	1.00
			Flu-2	69	28	4.13	260.94	1.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	1.08	9.01	1.00
			Flu-2	49	15	2.10	38.14	1.00
		75y+	Flu-1	24	14	2.78	115.32	1.00
			Flu-2	20	13	1.97	39.80	1.00
		65y+	Flu-1	76	32	1.46	66.73	1.00
			Flu-2	69	28	2.06	38.34	1.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	3.13	64.40	1.00
			Flu-2	48	16	3.60	110.59	1.00
		75y+	Flu-1	23	15	1.45	21.49	1.00
			Flu-2	19	14	4.64	87.58	1.00
		65y+	Flu-1	75	33	2.48	55.64	1.00
			Flu-2	67	30	3.87	103.95	1.00
		18-40y	Flu-2	0	73	-	-	-
CD8-IL2	A/New	50-64y	Flu-1	1	110	1.00	-	1.00

CD8-TNFα	Caledonia		Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	5.40	89.80	1.00
			Flu-2	49	15	3.95	58.87	1.00
		75y+	Flu-1	24	14	4.97	37.11	1.00
			Flu-2	20	13	4.69	231.66	1.00
		65y+	Flu-1	77	31	5.26	77.66	1.00
			Flu-2	69	28	4.15	134.47	1.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	1.76	41.18	1.00
			Flu-2	49	15	3.65	41.56	1.00
		75y+	Flu-1	24	14	6.16	80.10	1.00
			Flu-2	20	13	2.58	55.21	1.00
		65y+	Flu-1	76	32	2.61	58.99	1.00
			Flu-2	69	28	3.30	45.51	1.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	3.60	53.95	1.00
			Flu-2	48	16	2.99	82.90	1.00
		75y+	Flu-1	23	15	2.77	72.88	1.00
			Flu-2	19	14	2.56	26.97	1.00
		65y+	Flu-1	75	33	3.33	59.89	1.00
			Flu-2	67	30	2.86	72.02	1.00
		18-40y	Flu-2	0	73	-	-	-
	A/New Caledonia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	53	17	6.68	129.31	1.00
			Flu-2	49	15	3.42	100.84	1.00
		75y+	Flu-1	24	14	3.61	48.34	1.00
			Flu-2	20	13	9.26	430.92	1.00
		65y+	Flu-1	77	31	5.51	111.88	1.00
			Flu-2	69	28	4.56	247.57	1.00
		18-40y	Flu-2	0	73	-	-	-
	A/Wisconsin	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	1.51	23.42	1.00
			Flu-2	49	15	2.40	42.09	1.00
		75y+	Flu-1	24	14	4.98	139.32	1.00
			Flu-2	20	13	2.07	55.73	1.00
		65y+	Flu-1	76	32	2.20	83.02	1.00
			Flu-2	69	28	2.30	46.05	1.00
		18-40y	Flu-2	0	73	-	-	-
	B/Malaysia	50-64y	Flu-1	1	110	1.00	-	1.00
			Flu-2	0	116	-	-	-
		65-74y	Flu-1	52	18	4.42	61.89	1.00
			Flu-2	48	16	4.68	89.08	1.00
		75y+	Flu-1	23	15	2.27	56.76	1.00
			Flu-2	19	14	4.16	97.92	1.00
		65y+	Flu-1	75	33	3.61	60.18	1.00
			Flu-2	67	30	4.53	90.92	1.00
		18-40y	Flu-2	0	73	-	-	-

All doubles: T-cells producing at least 2 cytokines

CD40L: T-cells producing at least CD40L and another cytokine (IL-2, IFN- γ and TNF- α)
 IFN- γ : T-cells producing at least IFN- γ and another cytokine (IL-2, CD40L and TNF- α)
 IL-2: T-cells producing at least IL-2 and another cytokine (TNF- α , CD40L and IFN- γ)
 TNF- α : T-cells producing at least TNF- α and another cytokine (IL-2, CD40L and IFN- γ)
 N = number of subjects with available results
 N miss: number of subjects with missing results
 GM= Geometric Mean
 SD = Standard Deviation

Secondary Outcome Variable (s):

Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort)

Symptom	Intensity	18-40y									
		Flu-1 Group					Flu-2 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Ecchymosis	Any	1	0	0.0	0.0	97.5	487	25	5.1	3.3	7.5
	> 50 mm	1	0	0.0	0.0	97.5	487	0	0.0	0.0	0.8
Pain	Any	1	1	100	2.5	100	487	309	63.4	59.0	67.7
	Grade 3	1	0	0.0	0.0	97.5	487	2	0.4	0.0	1.5
Redness	Any	1	1	100	2.5	100	487	97	19.9	16.5	23.7
	> 50 mm	1	0	0.0	0.0	97.5	487	4	0.8	0.2	2.1
Swelling	Any	1	1	100	2.5	100	487	64	13.1	10.3	16.5
	> 50 mm	1	1	100	2.5	100	487	4	0.8	0.2	2.1
		50-64y									
		Flu-1 Group					Flu-2 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Ecchymosis	Any	755	36	4.8	3.4	6.5	755	34	4.5	3.1	6.2
	> 50 mm	755	4	0.5	0.1	1.4	755	1	0.1	0.0	0.7
Pain	Any	755	625	82.8	79.9	85.4	755	257	34.0	30.7	37.5
	Grade 3	755	46	6.1	4.5	8.0	755	3	0.4	0.1	1.2
Redness	Any	755	241	31.9	28.6	35.4	755	126	16.7	14.1	19.5
	> 50 mm	755	85	11.3	9.1	13.7	755	11	1.5	0.7	2.6
Swelling	Any	755	246	32.6	29.2	36.1	755	83	11.0	8.9	13.4
	> 50 mm	755	70	9.3	7.3	11.6	755	7	0.9	0.4	1.9
		65y+									
		Flu-1 Group					Flu-2 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Ecchymosis	Any	734	26	3.5	2.3	5.1	736	18	2.4	1.5	3.8
	> 50 mm	734	1	0.1	0.0	0.8	736	0	0.0	0.0	0.5
Pain	Any	734	457	62.3	58.6	65.8	736	140	19.0	16.2	22.0
	Grade 3	734	19	2.6	1.6	4.0	736	4	0.5	0.1	1.4
Redness	Any	734	233	31.7	28.4	35.2	736	81	11.0	8.8	13.5
	> 50 mm	734	82	11.2	9.0	13.7	736	3	0.4	0.1	1.2
Swelling	Any	734	166	22.6	19.6	25.8	736	53	7.2	5.4	9.3
	> 50 mm	734	38	5.2	3.7	7.0	736	1	0.1	0.0	0.8

N = number of subjects with the documented dose
 n (%) = number (percentage) of subjects reporting at least once the symptom
 95%CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
 Any = occurrence of any solicited local symptom regardless of their intensity grade.
 Grade 3 pain = pain that prevented normal activity

Secondary Outcome Variable (s):

Number of days with local symptoms during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

Symptom	Sub-group	Group	N	Mean duration	Median duration
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Ecchymosis	50-64y	Flu-1	36	3.6	3.0
		Flu-2	34	3.7	4.0
	65y+	Flu-1	26	3.6	3.0
		Flu-2	18	4.3	4.0
	18-40y	Flu-2	25	3.5	3.0
Pain	50-64y	Flu-1	625	2.9	3.0
		Flu-2	257	2.1	2.0
	65y+	Flu-1	457	2.6	3.0
		Flu-2	140	2.1	2.0
	18-40y	Flu-1	1	4.0	4.0
Redness		Flu-2	309	2.3	2.0
	50-64y	Flu-1	241	3.3	3.0
		Flu-2	126	2.6	2.0
	65y+	Flu-1	233	3.1	3.0
		Flu-2	81	2.9	2.0
Swelling	18-40y	Flu-1	1	3.0	3.0
		Flu-2	97	2.3	2.0
	50-64y	Flu-1	246	3.1	3.0
		Flu-2	83	2.4	2.0
	65y+	Flu-1	166	2.9	3.0
		Flu-2	53	2.3	2.0
	18-40y	Flu-1	1	4.0	4.0
		Flu-2	64	2.3	2.0

N = number of subjects with the documented dose

Secondary Outcome Variable (s):

Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort)

Symptom	Intensity/ relationship	18-40y									
		Flu-1 Group					Flu-2 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Arthralgia	Any	1	0	0.0	0.0	97.5	487	42	8.6	6.3	11.5
	Grade 3	1	0	0.0	0.0	97.5	487	1	0.2	0.0	1.1
	Related	1	0	0.0	0.0	97.5	487	31	6.4	4.4	8.9
Fatigue	Any	1	0	0.0	0.0	97.5	487	156	32.0	27.9	36.4
	Grade 3	1	0	0.0	0.0	97.5	487	5	1.0	0.3	2.4
	Related	1	0	0.0	0.0	97.5	487	108	22.2	18.6	26.1
Fever (orally temperature)	≥ 37.5°C	1	0	0.0	0.0	97.5	487	12	2.5	1.3	4.3
	> 39.0°C	1	0	0.0	0.0	97.5	487	0	0.0	0.0	0.8
	Related	1	0	0.0	0.0	97.5	487	8	1.6	0.7	3.2
Headache	Any	1	0	0.0	0.0	97.5	487	131	26.9	23.0	31.1
	Grade 3	1	0	0.0	0.0	97.5	487	7	1.4	0.6	2.9
	Related	1	0	0.0	0.0	97.5	487	90	18.5	15.1	22.2
Myalgia	Any	1	0	0.0	0.0	97.5	487	157	32.2	28.1	36.6
	Grade 3	1	0	0.0	0.0	97.5	487	1	0.2	0.0	1.1
	Related	1	0	0.0	0.0	97.5	487	114	23.4	19.7	27.4
		50-64y									
		Flu-1 Group					Flu-2 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Arthralgia	Any	755	292	38.7	35.2	42.3	754	71	9.4	7.4	11.7
	Grade 3	755	49	6.5	4.8	8.5	754	2	0.3	0.0	1.0
	Related	755	224	29.7	26.4	33.1	754	40	5.3	3.8	7.2
Fatigue	Any	755	367	48.6	45.0	52.2	754	137	18.2	15.5	21.1

	Grade 3	755	50	6.6	5.0	8.6	754	3	0.4	0.1	1.2
	Related	755	287	38.0	34.5	41.6	754	89	11.8	9.6	14.3
Fever (orally temperature)	≥ 37.5°C	755	138	18.3	15.6	21.2	754	17	2.3	1.3	3.6
	> 39.0°C	755	3	0.4	0.1	1.2	754	0	0.0	0.0	0.5
	Related	755	116	15.4	12.9	18.1	754	14	1.9	1.0	3.1
Headache	Any	755	338	44.8	41.2	48.4	754	143	19.0	16.2	21.9
	Grade 3	755	31	4.1	2.8	5.8	754	6	0.8	0.3	1.7
	Related	755	250	33.1	29.8	36.6	754	92	12.2	10.0	14.8
Myalgia	Any	755	446	59.1	55.5	62.6	754	155	20.6	17.7	23.6
	Grade 3	755	61	8.1	6.2	10.3	754	1	0.1	0.0	0.7
	Related	755	365	48.3	44.7	52.0	754	103	13.7	11.3	16.3

		65y+									
		Flu-1 Group					Flu-2 Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Arthralgia	Any	734	170	23.2	20.2	26.4	736	80	10.9	8.7	13.3
	Grade 3	734	12	1.6	0.8	2.8	736	6	0.8	0.3	1.8
	Related	734	121	16.5	13.9	19.4	736	44	6.0	4.4	7.9
Fatigue	Any	734	256	34.9	31.4	38.4	736	116	15.8	13.2	18.6
	Grade 3	734	20	2.7	1.7	4.2	736	5	0.7	0.2	1.6
	Related	734	190	25.9	22.8	29.2	736	75	10.2	8.1	12.6
Fever (orally temperature)	≥ 37.5°C	734	76	10.4	8.2	12.8	736	10	1.4	0.7	2.5
	> 39.0°C	734	0	0.0	0.0	0.5	736	0	0.0	0.0	0.5
	Related	734	57	7.8	5.9	9.9	736	6	0.8	0.3	1.8
Headache	Any	734	188	25.6	22.5	28.9	736	96	13.0	10.7	15.7
	Grade 3	734	10	1.4	0.7	2.5	736	1	0.1	0.0	0.8
	Related	734	140	19.1	16.3	22.1	736	55	7.5	5.7	9.6
Myalgia	Any	734	302	41.1	37.6	44.8	736	121	16.4	13.8	19.3
	Grade 3	734	17	2.3	1.4	3.7	736	6	0.8	0.3	1.8
	Related	734	218	29.7	26.4	33.2	736	73	9.9	7.9	12.3

N = number of subjects with the documented dose

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

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

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

Grade 3 symptom = symptom that prevented normal activity

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

Secondary Outcome Variable (s):

Number of days with general symptoms during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

Solicited symptom	Sub-group	Group	N	Mean duration	Median duration
Arthralgia	50-64y	Flu-1	292	2.1	2.0
		Flu-2	71	2.5	2.0
	65y+	Flu-1	170	2.4	2.0
		Flu-2	80	3.3	3.0
	18-40y	Flu-2	42	2.1	2.0
Fatigue	50-64y	Flu-1	367	2.3	2.0
		Flu-2	137	2.2	1.0
	65y+	Flu-1	256	2.3	2.0
		Flu-2	116	2.7	2.0
	18-40y	Flu-2	156	2.3	2.0
Fever	50-64y	Flu-1	138	1.6	1.0
		Flu-2	17	1.4	1.0
	65y+	Flu-1	76	1.4	1.0
		Flu-2	10	2.2	2.0

	18-40y	Flu-2	12	1.5	1.0
Headache	50-64y	Flu-1	338	1.9	2.0
		Flu-2	143	2.0	1.0
	65y+	Flu-1	188	1.9	1.0
		Flu-2	96	2.0	1.0
	18-40y	Flu-2	131	1.9	2.0
Myalgia	50-64y	Flu-1	446	2.3	2.0
		Flu-2	155	2.1	2.0
	65y+	Flu-1	302	2.3	2.0
		Flu-2	276	2.4	2.0
	18-40y	Flu-2	157	2.1	2.0

N = number of subjects with the documented dose

Safety Results: Number (%) of subjects with unsolicited adverse events up to Day 20 (Total Vaccinated Cohort)

Most frequent adverse events - On-Therapy (occurring within Days 0-20 following vaccination)	18-40y		50-64y		65y+	
	Flu-1 Group N = 1	Flu-2 Group N = 489	Flu-1 Group N = 758	Flu-2 Group N = 757	Flu-1 Group N = 737	Flu-2 Group N = 740
Subjects with any AE(s), n (%)	1 (100)	137 (28.0)	294 (38.8)	187 (24.7)	205 (27.8)	132 (17.8)
Subjects with Grade 3 AE(s), n (%)	1 (100)	11 (2.2)	50 (6.6)	19 (2.5)	25 (3.4)	12 (1.6)
Subjects with related AE(s), n (%)	0 (0.0)	55 (11.2)	196 (25.9)	57 (7.5)	125 (17.0)	37 (5.0)
Hot flush	1 (100)	-	-	-	-	-
Chills	-	24 (4.9)	115 (15.2)	21 (2.8)	66 (9.0)	12 (1.6)
Nasopharyngitis	-	23 (4.7)	29 (3.8)	21 (2.8)	21 (2.8)	22 (3.0)
Pharyngolaryngeal pain	-	15 (3.1)	12 (1.6)	10 (1.3)	20 (2.7)	9 (1.2)
Nausea	-	-	27 (3.6)	-	17 (2.3)	5 (0.7)
Cough	-	13 (2.7)	12 (1.6)	13 (1.7)	12 (1.6)	7 (0.9)
Injection site pruritus	-	-	18 (2.4)	-	-	-
Headache	-	11 (2.2)	-	9 (1.2)	-	5 (0.7)
Dizziness	-	-	12 (1.6)	-	-	-
Rhinitis	-	-	-	9 (1.2)	-	-
Diarrhea	-	-	-	-	-	5 (0.7)
Nasal congestion	-	-	-	-	-	5 (0.7)
Pain in extremity	-	-	-	-	-	5 (0.7)
Rhinorrhea	-	-	-	-	-	5 (0.7)

Grade 3 = event that prevented normal everyday activity

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

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 not reported in the particular group or that the adverse event was reported in the particular group but did not fall within the pre-defined counting rule of 5 most frequent events for that group.

Safety Results: Number (%) of subjects with unsolicited adverse events between Day 21 and Day 179 (Total Cohort for persistence)

Most frequent adverse events - (occurring within Days 21-179 after vaccination)	18-40y		50-64y		65y+	
	Flu-1 Group N = 1	Flu-2 Group N = 485	Flu-1 Group N = 755	Flu-2 Group N = 755	Flu-1 Group N = 726	Flu-2 Group N = 731
Subjects with any AE(s), n (%)	0 (0.0)	269 (55.5)	380 (50.3)	374 (49.5)	351 (48.3)	337 (46.1)
Nasopharyngitis	-	71 (14.6)	94 (12.5)	101 (13.4)	92 (12.7)	90 (12.3)
Headache	-	53 (10.9)	36 (4.8)	42 (5.6)	33 (4.5)	-
Upper respiratory tract infection	-	23 (4.7)	32 (4.2)	35 (4.6)	20 (2.8)	23 (3.1)
Influenza like illness	-	23 (4.7)	-	27 (3.6)	21 (2.9)	25 (3.4)
Cough	-	-	28 (3.7)	-	43 (5.9)	-
Bronchitis	-	-	31 (4.1)	-	-	31 (4.2)
Back pain	-	-	-	29 (3.8)	-	25 (3.4)

Sinusitis	-	31 (6.4)	-	-	-	-
Pharyngolaryngeal pain	-	28 (5.8)	-	-	-	-
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 not reported in the particular group or that the adverse event was reported in the particular group but did not fall within the pre-defined counting rule of 5 most frequent events for that group.						
Safety Results: Number (%) of subjects with Serious Adverse Events up to Day 21 (SAEs) (Total Vaccinated Cohort)						
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]						
All SAEs	18-40y		50-64y		65y+	
	Flu-1 Group N = 1	Flu-2 Group N = 489	Flu-1 Group N = 758	Flu-2 Group N = 757	Flu-1 Group N = 737	Flu-2 Group N = 740
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	1 (0.2) [0]	7 (0.9) [0]	5 (0.7) [0]	7 (0.9) [0]	7 (0.9) [0]
Appendicitis	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Cellulitis	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Chest pain	0 (0.0) [0]	1 (0.2) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Abdominal pain	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Acute coronary syndrome	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Anemia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Angina pectoris	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Bronchopneumonia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Chronic obstructive pulmonary disease	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Coronary artery disease	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Embolism venous	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Gastroenteritis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Gastrointestinal hemorrhage	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Head injury	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Hypoxia	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Local swelling	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Neoplasm malignant	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pelvic fracture	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pleural effusion	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pleurisy	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Pneumonia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Rectal hemorrhage	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Spinal compression fracture	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Syncope	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Tibia fracture	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Ulna fracture	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Fatal SAEs	18-40y		50-64y		65y+	
	Flu-1 Group N = 1	Flu-2 Group N = 489	Flu-1 Group N = 758	Flu-2 Group N = 757	Flu-1 Group N = 737	Flu-2 Group N = 740
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]	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 reported between Day 21 and Day 179 after vaccination (Total Cohort for persistence)						
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]						
All SAEs	18-40y		50-64y		65y+	

	Flu-1 Group N = 1	Flu-2 Group N = 485	Flu-1 Group N = 755	Flu-2 Group N = 755	Flu-1 Group N = 726	Flu-2 Group N = 731
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	2 (0.4) [0]	18 (2.4) [0]	18 (2.4) [0]	30 (4.1) [0]	25 (3.4) [0]
Chronic obstructive pulmonary disease	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	2 (0.3) [0]	2 (0.3) [0]
Pneumonia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (0.3) [0]	2 (0.3) [0]
Chest pain	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]	0 (0.0) [0]	3 (0.4) [0]	0 (0.0) [0]
Cardiac failure	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (0.3) [0]	1 (0.1) [0]
Bronchopneumonia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	1 (0.1) [0]
Coronary artery disease	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (0.3) [0]
Inguinal hernia	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Intervertebral disc protrusion	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Lung neoplasm malignant	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (0.3) [0]
Myocardial infarction	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Osteomyelitis	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Pancreatic carcinoma	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (0.3) [0]	0 (0.0) [0]
Tibia fracture	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	1 (0.1) [0]	0 (0.0) [0]
Abdominal hernia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Abdominal hernia obstructive	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Abdominal pain	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Abscess intestinal	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Anaemia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Anxiety	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Appendicitis	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Arrhythmia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Arthralgia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Arthritis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Arthropod bite	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Atrial fibrillation	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Atypical mycobacterial infection	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Back pain	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Brain contusion	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Brain neoplasm malignant	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Breast cancer female	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Bronchial carcinoma	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Bronchitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Carpal tunnel syndrome	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Catheter site infection	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cellulitis	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Cerebral infarction	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Cholecystitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cholecystitis acute	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Cholelithiasis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Colon adenoma	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Depression	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Diastolic dysfunction	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Diverticular perforation	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Diverticulitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Dyspnoea	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Encephalitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Failure of implant	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Femoral neck fracture	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Gastroenteritis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]

Gastrointestinal haemorrhage	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Headache	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Hepatic neoplasm malignant	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Humerus fracture	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Hypertension	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hypoaesthesia facial	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Hypokalaemia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Iron deficiency anaemia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Ischiorectal hernia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Joint dislocation	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Joint injury	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Malignant melanoma	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Metastases to lymph nodes	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Metastatic neoplasm	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Myocarditis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Nephrolithiasis	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Non-cardiac chest pain	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Ovarian epithelial cancer	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Pain	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Pancreatitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Peripheral vascular disorder	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Peroneal nerve palsy	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Pleuritic pain	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Postoperative ileus	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Procedural complication	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Prostate cancer	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Pulmonary embolism	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Pyelonephritis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Renal failure	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Renal failure acute	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Scrotal haematoma	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Skin ulcer	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Tachyarrhythmia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Transient ischaemic attack	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Trigeminal neuralgia	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Urethral stenosis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Vertigo	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Wound infection	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Migraine	0 (0.0) [0]	1 (0.2) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	Flu-1 Group N = 1	Flu-2 Group N = 485	Flu-1 Group N = 755	Flu-2 Group N = 755	Flu-1 Group N = 726	Flu-2 Group N = 731
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	3 (0.4) [0]	2 (0.3) [0]
Cardiac failure	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Chronic obstructive pulmonary disease	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Metastatic neoplasm	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]
Pancreatic carcinoma	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]
Procedural complication	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.1) [0]	0 (0.0) [0]

Note: In addition to 5 fatal SAEs reported in the clinical database, 3 subjects aged ≥ 65 years in the Flu-1 Group died between visit at Day 21 and phone contact at Day 90; they were not reported in the clinical database since they had not been enrolled in the FluAS25-015 study because they had died and were not recorded as withdrawn. These fatal SAEs were assessed by the investigators as not related to the study vaccination.

Two non-fatal SAEs were reported after Day 180: Cerebellar infarction for 1 subject in the Flu-1 Group (50-64y) and Pneumonia aspiration for 1 subject in the Flu-2 Group (65y+); they were assessed by the investigators as not related to the study vaccination.

Conclusion: At Day 21 after vaccination, at least 28.0%, 56.3% and 44.1% of the subjects in the 50-64y and 65y+ age strata were seroconverted with minimum HI antibody titers of 120.5, 188.8 and 199.8 against the A/New Caledonia, A/Wisconsin and B/Malaysia vaccine strains, respectively. Across groups, pain and myalgia were the most frequently reported solicited local and general symptoms, respectively.

Up to Day 21, unsolicited AEs were reported in the Flu-1 Group by 1 (100%), 294 (38.8%) and 205 (27.8%) subjects in the 18-40y, 50-64y and 65y+ age strata, respectively. In the Flu-2 Group, unsolicited AEs were reported by 137 (28.0%), 187 (24.7%) and 132 (17.8 %) subjects in the 18-40y, 50-64y and 65y+ age strata, respectively.

Between Day 21 and Day 180, unsolicited AEs were reported by 380 (50.3%) and 351 (48.3%) subjects in the 50-64y and 65y+ age strata, respectively, of the Flu-1 Group, and by 269 (55.5%), 374 (49.5%) and 337 (46.1%) subjects in the 18-40y, 50-64y and 65y+ age strata, respectively, of the Flu-2 Group.

Up to Day 21, SAEs were reported by 14 subjects in the Flu-1 Group (7 (0.9%) in the 50-64y age stratum and 7 (0.9%) in the 65y+ age stratum) and by 13 subjects in the Flu-2 Group (1 (0.2%), 5 (0.7%) and 7(0.9%) in the 18-40y, 50-64y and 65y+ age strata, respectively). All the reported SAEs were assessed by the investigators as not related to the study vaccination. No fatal SAEs were reported up to Day 21.

Between Day 21 and Day 180, SAEs were reported by 48 subjects in the Flu-1 Group (18 (2.4%) in the 50-64y age stratum and 30 (4.1%) in the 65y+ age stratum) and by 45 subjects in the Flu-2 Group (2 (0.4%) in the 18-40y age stratum, 18 (2.4%) in the 50-64y age stratum and 25 (3.4%) in the 65y+ age stratum). During this period, 5 fatal SAEs were reported for 5 subjects in the 65y+ age stratum: 3 (0.4%) subjects from the Flu-1 Group and for 2 (0.3%) subjects from the Flu-2 Group. In addition, 3 fatal SAEs, not recorded in the clinical database, were reported in the Flu-1 Group (in the 65y+ age stratum) between visit at Day 21 and phone contact at Day 90 and 2 non-fatal SAEs were reported from Day 180, one each in the Flu-1 Group (in the 50-64y age stratum) and the Flu-2 Group (in the 65y+ age stratum). All the reported SAEs, fatal or non-fatal, were assessed by the investigators as not related to the study vaccination.

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