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

Study No.:110223 (FluAS25-018 Ext Y3)

Title: Reactogenicity and immunogenicity of GSK Biologicals' influenza vaccine GSK576389A in elderly adults (≥67 years) previously vaccinated with the same candidate vaccine. *Fluarix*™ will be used as reference.
FluAS25 (Flu-1): GlaxoSmithKline (GSK) Biologicals' AS25 adjuvanted influenza vaccine.
Fluarix™ (Flu-2): GSK Biologicals' licensed influenza vaccine.

Rationale: The aim of the study was to evaluate the safety and immunogenicity of Flu-1 vaccine after repeated vaccine administrations. Adults aged 67 years and over who were previously vaccinated in the 103304, 104540 and 107973 studies, received again a dose of the same vaccine (2007-2008 season).

Phase: II

Study Period: 23 October 2007 to 12 December 2007.

Study Design: Single centre, open, controlled study with 2 parallel groups.

Centers: 1 center in Belgium.

Indication: Immunization against influenza

Treatment: The study groups were as follows:

- Flu Group: subjects received 1 dose of Flu-1 vaccine
- Reference Group: subjects received 1 dose of Flu-2 vaccine

Vaccines were administered by intramuscular injection into the deltoid region of the non-dominant arm. All subjects had received 3 previous administrations of the same vaccine, 36, 24 and 12 months prior to this one.

Objectives:
To evaluate the safety of repeated vaccination with Flu-1 vaccine, during the 21 days following the intramuscular administration of the vaccine. Flu-2 vaccine was used as reference.

Primary Outcome/Efficacy Variable:

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

*Duration of unsolicited AEs and MSCs was not analyzed during the 21-day follow-up period.
**It was decided to analyze the medically significant conditions as all adverse events that resulted in a medically-attended visit instead, because this was considered to be an objective approach.

Secondary Outcome/Efficacy Variable(s):
Humoral immune response
Observed variable:

- At Days 0 and 21: Serum haemagglutination-inhibition (HI) antibody titer, against each of the 3 vaccine strains, in each group.

Derived variables:

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

*SCR is defined as the percentage of vaccinees who have either a prevaccination 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.
**SCF is defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.
***SPR is defined as the percentage of vaccinees with a serum HI titer ≥1:40 that usually is accepted as indicating protection.

Cell-Mediated Immunity (CMI) response

Observed variables:
At Days 0 and 21:

- Frequency of cytokine-positive CD4/CD8 cells per million in tests producing at least 2 different cytokines [Cluster of Differentiation 40L (CD40L), Interleukin-2 (IL-2), Tumor Necrosis Factor alpha (TNF-α), Interferon gamma (IFN-γ)], in each group.
- Frequency of cytokine-positive CD4/CD8 cells per million in tests producing at least CD40L and another signal molecule (IL-2, IFN-γ, TNF-α), in each group.
- Frequency of cytokine-positive CD4/CD8 cells per million in tests producing at least IL-2 and another signal molecule (CD40L, IFN-γ, TNF-α), in each group.
- Frequency of cytokine-positive CD4/CD8 cells per million in tests producing at least IFN-γ and another signal molecule (IL-2, CD40L, TNF-α), in each group.
- Frequency of cytokine-positive CD4/CD8 cells per million in tests producing at least TNF-α and another signal molecule (IL-2, CD40L, IFN-γ), in each group.

Derived variables:

- For each test, geometric mean (GM) of specific influenza CD4/CD8 T lymphocytes at Days 0 and 21, in each group.

Statistical Methods:
The analyses were performed on the Total Vaccinated cohort and on the According-To-Protocol (ATP) cohort for immunogenicity

- The Total Vaccinated cohort included all subjects with study vaccine administered.
- The ATP cohort for immunogenicity included all evaluable subjects who met all eligible criteria, who complied with the procedures and intervals defined in the protocol, with no elimination criteria during the study, for whom data concerning immunogenicity measures were available. These included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

Analysis of Immunogenicity:
The analysis was performed on the ATP cohort for immunogenicity.
Geometric Mean Titer (GMT) of HI antibody titers & seropositivity rates with their 95% confidence intervals (CI) and SPRs with exact 95% CI were calculated at Day 0 and 21; SCRs with exact 95% CI and SCFs with 95% CI at Day 21 were calculated for each vaccine group and for each strain. Antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation. The frequency of influenza-specific cytokine-positive CD4/CD8 T-lymphocytes was summarized with descriptive statistics at Days 0 and 21, for each different cytokine test and for separate and for pooled vaccine strains.

Analysis of Safety
The analysis was performed on the Total Vaccinated cohort.
The percentage of subjects reporting each individual solicited local and general symptom during the 7-day 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 duration of each solicited local and general symptom during the 7-day solicited follow-up period was tabulated.
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 up to 21 days after vaccination was tabulated. The same tabulation was performed for grade 3 AEs and AEs with relationship to vaccination. The proportion of subjects with at least one report of unsolicited adverse event classified by MedDRA preferred terms, which resulted in a medically-attended visit (MAEs) and was reported up to 21 days after vaccination, was tabulated with exact 95% CI. The same tabulation was performed for grade 3 MAEs and MAEs with relationship to vaccination. SAEs classified by MedDRA preferred terms were also tabulated during the entire study period.

Study Population: A healthy man or woman aged ≥ 67 years at the time of revaccination, who had previously received the same vaccine during the 107973 study. Written informed consent was obtained from the subject before study enrolment.

Number of Subjects:	**Flu Group**	**Reference Group**
Planned, N	36	38
Randomized, N (Total Vaccinated cohort)	33	35
Completed, n (%)	32 (97.0)	35 (100)
Total Number Subjects Withdrawn, n (%)	1 (3.0)	0 (0.0)
Withdrawn due to Adverse Events n (%)	1 (3.0)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not applicable	Not applicable

Withdrawn for other reasons n (%)	0 (0.0)	0 (0.0)
Demographics	**Flu Group**	**Reference Group**
N (Total Vaccinated cohort)	33	35
Females:Males	20:13	20:15
Mean Age, years (SD)	73.1 (4.53)	73.2 (5.34)
White - Caucasian / European heritage, n (%)	33 (100)	35 (100)

Primary Efficacy Results: Number (percentage) of subjects reporting solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

Symptom	Intensity	Flu Group					Reference Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Ecchymosis	Any	33	0	0.0	0.0	10.6	35	1	2.9	0.1	14.9
	>100 mm	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
Pain	Any	33	17	51.5	33.5	69.2	35	7	20.0	8.4	36.9
	Grade 3	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
Redness	Any	33	10	30.3	15.6	48.7	35	4	11.4	3.2	26.7
	>100 mm	33	1	3.0	0.1	15.8	35	0	0.0	0.0	10.0
Swelling	Any	33	2	6.1	0.7	20.2	35	2	5.7	0.7	19.2
	>100 mm	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0

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

Primary Efficacy Results: Number of days with any* grade of local symptoms during the 7-day post-vaccination period using (Total Vaccinated cohort)

Symptom	Group	N	Mean	Median
Ecchymosis	Reference	1	5.0	5.0
Pain	Flu	17	2.2	2.0
	Reference	7	2.0	2.0
Redness	Flu	10	3.0	2.5
	Reference	4	1.8	2.0
Swelling	Flu	2	1.5	1.5
	Reference	2	2.5	2.5

N = number of subjects with the symptom reported.
*Any: occurrence of any local symptom regardless of their intensity grade

Primary Efficacy Results: Number (percentage) of subjects reporting solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

Symptom	Intensity/ Relationship	Flu Group					Reference Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Arthralgia	Any	33	8	24.2	11.1	42.3	35	5	14.3	4.8	30.3
	Grade 3	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
	Related	33	7	21.2	9.0	38.9	35	1	2.9	0.1	14.9
Fatigue	Any	33	8	24.2	11.1	42.3	35	3	8.6	1.8	23.1
	Grade 3	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
	Related	33	8	24.2	11.1	42.3	35	2	5.7	0.7	19.2
Headache	Any	33	8	24.2	11.1	42.3	35	3	8.6	1.8	23.1
	Grade 3	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
	Related	33	6	18.2	7.0	35.5	35	2	5.7	0.7	19.2
Myalgia	Any	33	8	24.2	11.1	42.3	35	1	2.9	0.1	14.9
	Grade 3	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
	Related	33	8	24.2	11.1	42.3	35	0	0.0	0.0	10.0
Nausea	Any	33	3	9.1	1.9	24.3	35	1	2.9	0.1	14.9

	Grade 3	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
	Related	33	2	6.1	0.7	20.2	35	0	0.0	0.0	10.0
Shivering	Any	33	6	18.2	7.0	35.5	35	3	8.6	1.8	23.1
	Grade 3	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
	Related	33	5	15.2	5.1	31.9	35	2	5.7	0.7	19.2
Fever (Orally)	≥38.0°C	33	1	3.0	0.1	15.8	35	0	0.0	0.0	10.0
	>39.0°C	33	0	0.0	0.0	10.6	35	0	0.0	0.0	10.0
	Related	33	1	3.0	0.1	15.8	35	0	0.0	0.0	10.0

N = number of subjects with the documented dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Any = occurrence of any general symptom regardless of their intensity grade or relationship to vaccination.
Grade 3 Symptoms = symptoms that prevented normal activity
Related = general symptom assessed by the investigator as causally related to the study vaccination

Primary Efficacy Results: Number of days with any* grade of general symptoms during the 7-day post-vaccination period (Total Vaccinated cohort)

Symptom	Group	N	Mean	Median
Arthralgia	Flu	8	2.0	2.0
	Reference	5	4.0	3.0
Fatigue	Flu	8	2.6	2.5
	Reference	3	1.3	1.0
Headache	Flu	8	1.6	1.5
	Reference	3	1.3	1.0
Myalgia	Flu	8	2.8	2.0
	Reference	1	1.0	1.0
Nausea	Flu	3	3.3	4.0
	Reference	1	2.0	2.0
Shivering	Flu	6	1.2	1.0
	Reference	3	1.3	1.0

N = number of subjects with the symptom reported
*Any: occurrence of any general symptom regardless of their intensity grade or relationship to vaccination

Primary Efficacy Results: Percentage of subjects reporting the occurrence of AEs resulting in a medically-attended visit (MAEs), within the 21-day (Days 0-20) post-vaccination period (Total Vaccinated cohort)

MAEs	Flu Group N = 33				Reference Group N = 35			
			95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL
At least one MAE	2	6.1	0.7	20.2	4	11.4	3.2	26.7
Subjects with Grade 3 MAEs, n (%)	1	3.0	0.1	15.8	0	0.0	0.0	10.0
Subjects with related MAEs, n (%)	0	0.0	-	-	0	0.0	-	-
Hypersensitivity	0	0.0	0.0	10.6	1	2.9	0.1	14.9
Upper respiratory tract infection	1	3.0	0.1	15.8	1	2.9	0.1	14.9
Gout	0	0.0	0.0	10.6	1	2.9	0.1	14.9
Cough	0	0.0	0.0	10.6	1	2.9	0.1	14.9
Epistaxis	1	3.0	0.1	15.8	0	0.0	0.0	10.0

N = number of subjects with the administered dose
n (%) = number (percentage) of subjects reporting at least once the MAE
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
At least one MAE = at least one MAE experienced (regardless of the MedDRA Preferred Term)
Grade 3 MAE: MAE that prevented normal activity
Related MAE: MAE assessed by the investigator as causally related to the study vaccination

Primary Efficacy Results: Occurrence, intensity and relationship to vaccination of unsolicited AEs during a 21-day follow-up period (i.e. day of vaccination and 20 subsequent days) after vaccination, in each group and occurrence and relationship to vaccination of serious adverse events during the entire study period, in each group.
Please refer to the safety results section at the end of the document.

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibody titer at Days 0 and 21 (ATP cohort for immunogenicity)

Vaccine strain	Group	Timing	≥ 1:10					GMT		
			N	n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL
A/Solomon Islands	Flu	PRE	32	18	56.3	37.7	73.6	12.7	8.8	18.2
		PI(D21)	32	29	90.6	75.0	98.0	63.0	41.5	95.7
	Reference	PRE	35	15	42.9	26.3	60.6	9.0	6.4	12.5
		PI(D21)	35	32	91.4	76.9	98.2	42.4	28.3	63.5
A/Wisconsin	Flu	PRE	32	30	93.8	79.2	99.2	100.3	67.2	149.7
		PI(D21)	32	32	100	89.1	100	252.2	195.8	324.7
	Reference	PRE	35	35	100	90.0	100	83.1	63.1	109.5
		PI(D21)	35	35	100	90.0	100	158.4	114.1	219.7
B/Malaysia	Flu	PRE	32	31	96.9	83.8	99.9	55.8	37.4	83.3
		PI(D21)	32	32	100	89.1	100	126.1	90.2	176.3
	Reference	PRE	35	34	97.1	85.1	99.9	61.2	44.2	84.6
		PI(D21)	35	35	100	90.0	100	99.4	74.2	133.3

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)

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

Vaccine strain	Group	Timing	SPR				
			N	n	%	95% CI	
						LL	UL
A/Solomon Islands	Flu	PRE	32	9	28.1	13.7	46.7
		PI(D21)	32	27	84.4	67.2	94.7
	Reference	PRE	35	3	8.6	1.8	23.1
		PI(D21)	35	22	62.9	44.9	78.5
A/Wisconsin	Flu	PRE	32	29	90.6	75.0	98.0
		PI(D21)	32	32	100	89.1	100
	Reference	PRE	35	31	88.6	73.3	96.8
		PI(D21)	35	35	100	90.0	100
B/Malaysia	Flu	PRE	32	20	62.5	43.7	78.9
		PI(D21)	32	31	96.9	83.8	99.9
	Reference	PRE	35	29	82.9	66.4	93.4
		PI(D21)	35	34	97.1	85.1	99.9

N = number of subjects with available results
n (%) = number (percentage) of seroprotected subjects (HI titer ≥ 1:40)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination dose 1 (Day 0)
PI(D21) = post-vaccination dose 1 (Day 21)

Secondary Outcome Variable(s): SCR for HI antibody titer at Day 21 (ATP cohort for immunogenicity)

Vaccine strain	Group	SCR				
		N	n	%	95% CI	
					LL	UL
A/Solomon Islands	Flu	32	20	62.5	43.7	78.9
	Reference	35	17	48.6	31.4	66.0
A/Wisconsin	Flu	32	9	28.1	13.7	46.7
	Reference	35	7	20.0	8.4	36.9
B/Malaysia	Flu	32	8	25.0	11.5	43.4
	Reference	35	3	8.6	1.8	23.1

Seroconversion defined as:

- For initially seronegative subjects, antibody titer ≥ 1:40 after vaccination
- For initially seropositive subjects, antibody after vaccination ≥ 4 fold the pre-vaccination antibody

N = Number of subjects with pre- and post-vaccination results available
n (%) = Number (percentage) of seroconverted subjects
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): SCF for HI antibody titer at Day 21 (ATP cohort for immunogenicity)

Vaccine strain	Group	SCF			
		N	Value	95% CI	
				LL	UL
A/Solomon Islands	Flu	32	5.0	3.3	7.5
	Reference	35	4.7	3.2	7.0
A/Wisconsin	Flu	32	2.5	2.0	3.1
	Reference	35	1.9	1.6	2.3
B/Malaysia	Flu	32	2.3	1.8	2.9
	Reference	35	1.6	1.4	1.9

N = Number of subjects with pre- and post-vaccination results available
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
SCF defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.

Secondary Outcome Variable(s): Descriptive statistics of the frequency of cytokine-positive CD4 T-cells (per million CD4 T-cells) for each strain and pooled strains at Days 0 and 21 (ATP cohort for immunogenicity)

Test description	Vaccine strain	Group	Timing	N	Nmiss	GM	SD	Median
CD4-All doubles	A/Solomon Islands	Flu	PRE	30	2	611.15	487.68	630.50
			PI(D21)	25	7	761.22	783.59	1157.00
		Reference	PRE	32	3	353.41	289.83	414.50
			PI(D21)	31	4	285.45	288.42	396.00
	A/Wisconsin	Flu	PRE	30	2	877.26	529.44	925.50
			PI(D21)	25	7	830.38	652.85	826.00
		Reference	PRE	32	3	476.38	438.45	454.50
			PI(D21)	31	4	357.12	376.31	517.00
	B/Malaysia	Flu	PRE	30	2	643.26	382.49	686.50
			PI(D21)	25	7	657.31	542.67	910.00
		Reference	PRE	32	3	391.89	285.28	384.00
			PI(D21)	31	4	200.13	370.22	511.00
	Pooled strains	Flu	PRE	30	2	1401.41	671.68	1346.00
			PI(D21)	25	7	1227.87	1013.31	1625.00
		Reference	PRE	32	3	767.10	490.04	882.50
			PI(D21)	31	4	545.68	480.37	829.00
CD4-CD40L	A/Solomon Islands	Flu	PRE	30	2	606.58	484.99	620.50
			PI(D21)	25	7	758.40	773.73	1145.00
		Reference	PRE	32	3	341.61	291.23	390.50
			PI(D21)	31	4	279.59	284.97	385.00
	A/Wisconsin	Flu	PRE	30	2	871.43	512.44	928.50
			PI(D21)	25	7	829.38	648.50	872.00
		Reference	PRE	32	3	472.33	427.69	444.00
			PI(D21)	31	4	353.78	377.73	503.00
	B/Malaysia	Flu	PRE	30	2	640.49	370.62	688.50
			PI(D21)	25	7	648.93	535.97	874.00
		Reference	PRE	32	3	387.23	280.03	384.00
			PI(D21)	31	4	188.93	361.66	504.00
	Pooled strains	Flu	PRE	30	2	1388.14	661.04	1325.00
			PI(D21)	25	7	1209.75	996.45	1655.00
		Reference	PRE	32	3	757.53	489.79	873.00
			PI(D21)	31	4	539.55	476.23	843.00

CD4-IFNγ	A/Solomon Islands	Flu	PRE	30	2	393.40	328.18	407.00
			PI(D21)	25	7	411.23	509.98	579.00
		Reference	PRE	32	3	180.69	182.12	224.00
			PI(D21)	31	4	150.29	185.78	185.00
	A/Wisconsin	Flu	PRE	30	2	477.81	299.82	489.50
			PI(D21)	25	7	357.56	423.90	479.00
		Reference	PRE	32	3	232.70	278.10	228.00
			PI(D21)	31	4	212.25	191.16	193.00
	B/Malaysia	Flu	PRE	30	2	405.44	279.02	412.00
			PI(D21)	25	7	442.51	384.08	474.00
		Reference	PRE	32	3	175.13	210.56	224.00
			PI(D21)	31	4	174.94	229.30	213.00
	Pooled strains	Flu	PRE	30	2	824.34	491.16	822.50
			PI(D21)	25	7	840.65	671.16	1054.00
		Reference	PRE	32	3	436.69	307.38	472.00
			PI(D21)	31	4	343.86	315.56	400.00
CD4-IL2	A/Solomon Islands	Flu	PRE	30	2	550.06	433.42	578.00
			PI(D21)	25	7	635.35	631.73	845.00
		Reference	PRE	32	3	321.49	258.81	404.50
			PI(D21)	31	4	241.86	225.01	369.00
	A/Wisconsin	Flu	PRE	30	2	738.42	509.02	724.00
			PI(D21)	25	7	682.25	547.67	722.00
		Reference	PRE	32	3	407.21	381.85	426.00
			PI(D21)	31	4	259.27	313.49	438.00
	B/Malaysia	Flu	PRE	30	2	562.01	340.18	621.00
			PI(D21)	25	7	577.43	470.86	812.00
		Reference	PRE	32	3	377.10	257.06	376.50
			PI(D21)	31	4	194.20	319.95	422.00
	Pooled strains	Flu	PRE	30	2	1192.89	595.71	1170.50
			PI(D21)	25	7	977.48	819.44	1319.00
		Reference	PRE	32	3	720.90	421.55	789.00
			PI(D21)	31	4	463.25	390.68	771.00
CD4- TNFα	A/Solomon Islands	Flu	PRE	30	2	270.39	328.20	390.00
			PI(D21)	25	7	371.92	409.87	539.00
		Reference	PRE	32	3	194.00	169.53	222.00
			PI(D21)	31	4	129.21	163.10	203.00
	A/Wisconsin	Flu	PRE	30	2	584.58	352.86	643.50
			PI(D21)	25	7	432.47	428.19	587.00
		Reference	PRE	32	3	334.97	281.45	319.00
			PI(D21)	31	4	271.33	204.03	317.00
	B/Malaysia	Flu	PRE	30	2	278.06	239.29	349.00
			PI(D21)	25	7	299.35	322.28	416.00
		Reference	PRE	32	3	140.68	165.67	210.00
			PI(D21)	31	4	102.33	205.58	188.00
	Pooled strains	Flu	PRE	30	2	794.15	504.33	778.00
			PI(D21)	25	7	674.35	584.50	932.00
		Reference	PRE	32	3	496.30	298.79	541.00
			PI(D21)	31	4	251.59	290.29	516.00

CD4- All doubles: T-cells producing at least 2 cytokines
CD4- CD40L = T-cells producing at least CD40L and another cytokine
CD4- IL2 = T-cells producing at least IL2 and another cytokine
CD4- INFγ = T-cells producing at least INFγ and another cytokine
CD4- TNFα = T-cells producing at least TNFα and another cytokine
N = number of subjects with available results

Nmiss = 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 of the frequency of cytokine-positive CD8 T-cells (per million CD8 T-cells) for each strain and pooled strains at Days 0 and 21 (ATP cohort for immunogenicity)

Test description	Vaccine strain	Group	Timing	N	Nmiss	GM	SD	Median
CD8-All doubles	A/Solomon Islands	Flu	PRE	30	2	2.50	54.81	1.00
			PI(D21)	25	7	6.18	80.49	1.00
		Reference	PRE	32	3	3.01	124.67	1.00
			PI(D21)	31	4	3.81	52.84	1.00
	A/Wisconsin	Flu	PRE	29	3	5.48	87.38	1.00
			PI(D21)	25	7	3.11	95.32	1.00
		Reference	PRE	32	3	1.55	40.24	1.00
			PI(D21)	31	4	2.49	55.29	1.00
	B/Malaysia	Flu	PRE	29	3	6.20	90.23	1.00
			PI(D21)	25	7	3.26	186.70	1.00
		Reference	PRE	32	3	2.51	63.21	1.00
			PI(D21)	31	4	4.59	70.75	1.00
	Pooled strains	Flu	PRE	29	3	8.67	123.74	1.00
			PI(D21)	24	8	10.96	135.32	31.50
		Reference	PRE	32	3	4.43	75.73	1.00
			PI(D21)	31	4	4.16	98.01	1.00
CD8-CD40L	A/Solomon Islands	Flu	PRE	30	2	2.05	27.92	1.00
			PI(D21)	25	7	5.00	52.91	1.00
		Reference	PRE	32	3	2.38	57.63	1.00
			PI(D21)	31	4	3.17	44.66	1.00
	A/Wisconsin	Flu	PRE	29	3	4.28	60.42	1.00
			PI(D21)	25	7	2.14	51.75	1.00
		Reference	PRE	32	3	1.55	40.24	1.00
			PI(D21)	31	4	1.83	41.14	1.00
	B/Malaysia	Flu	PRE	29	3	6.59	77.30	1.00
			PI(D21)	25	7	3.08	75.58	1.00
		Reference	PRE	32	3	2.03	45.49	1.00
			PI(D21)	31	4	3.67	64.11	1.00
	Pooled strains	Flu	PRE	29	3	6.61	69.93	1.00
			PI(D21)	24	8	6.37	88.95	1.00
		Reference	PRE	32	3	3.65	58.75	1.00
			PI(D21)	31	4	2.91	87.43	1.00
CD8-IFNγ	A/Solomon Islands	Flu	PRE	30	2	1.77	25.17	1.00
			PI(D21)	25	7	1.40	18.00	1.00
		Reference	PRE	32	3	1.60	123.31	1.00
			PI(D21)	31	4	1.73	23.95	1.00
	A/Wisconsin	Flu	PRE	29	3	1.96	58.89	1.00
			PI(D21)	25	7	1.41	19.53	1.00
		Reference	PRE	32	3	1.52	26.15	1.00
			PI(D21)	31	4	1.78	33.55	1.00
	B/Malaysia	Flu	PRE	29	3	3.18	60.84	1.00
			PI(D21)	25	7	1.92	127.13	1.00
		Reference	PRE	32	3	2.34	63.80	1.00
			PI(D21)	31	4	1.52	22.73	1.00
	Pooled strains	Flu	PRE	29	3	2.39	93.19	1.00

			PI(D21)	24	8	3.24	61.69	1.00
		Reference	PRE	32	3	1.53	30.78	1.00
			PI(D21)	31	4	1.84	39.83	1.00
CD8-IL2	A/Solomon Islands	Flu	PRE	30	2	2.49	54.69	1.00
			PI(D21)	25	7	4.39	76.84	1.00
		Reference	PRE	32	3	2.46	66.32	1.00
			PI(D21)	31	4	3.38	48.89	1.00
	A/Wisconsin	Flu	PRE	29	3	5.27	69.84	1.00
			PI(D21)	25	7	2.63	95.37	1.00
		Reference	PRE	32	3	1.76	41.38	1.00
			PI(D21)	31	4	1.82	38.90	1.00
	B/Malaysia	Flu	PRE	29	3	4.86	77.20	1.00
			PI(D21)	25	7	2.60	75.43	1.00
		Reference	PRE	32	3	1.78	44.85	1.00
			PI(D21)	31	4	3.72	63.72	1.00
	Pooled strains	Flu	PRE	29	3	7.44	95.70	1.00
			PI(D21)	24	8	6.63	107.41	1.00
		Reference	PRE	32	3	6.54	69.82	1.00
			PI(D21)	31	4	3.39	91.57	1.00
CD8-TNFα	A/Solomon Islands	Flu	PRE	30	2	1.58	23.46	1.00
			PI(D21)	25	7	2.47	55.20	1.00
		Reference	PRE	32	3	2.77	101.63	1.00
			PI(D21)	31	4	2.67	36.03	1.00
	A/Wisconsin	Flu	PRE	29	3	2.36	69.91	1.00
			PI(D21)	25	7	2.08	53.64	1.00
		Reference	PRE	32	3	1.31	18.78	1.00
			PI(D21)	31	4	2.03	32.51	1.00
	B/Malaysia	Flu	PRE	29	3	3.09	61.50	1.00
			PI(D21)	25	7	1.92	127.13	1.00
		Reference	PRE	32	3	3.29	77.18	1.00
			PI(D21)	31	4	1.83	34.42	1.00
	Pooled strains	Flu	PRE	29	3	2.37	82.35	1.00
			PI(D21)	24	8	4.12	88.07	1.00
		Reference	PRE	32	3	1.59	50.66	1.00
			PI(D21)	31	4	2.38	37.12	1.00

CD8- All doubles: T-cells producing at least 2 cytokines
CD8- CD40L = T-cells producing at least CD40L and another cytokine
CD8- IL2 = T-cells producing at least IL2 and another cytokine
CD8- INFγ = T-cells producing at least INFγ and another cytokine
CD8- TNFα = T-cells producing at least TNFα and another cytokine
N = number of subjects with available results
Nmiss = 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)

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

Most frequent adverse events–On-Therapy (occurring within Days 0-20 following vaccination)	**Flu Group N = 33**	**Reference Group N = 35**
Subjects with any AE(s), n (%)	5 (15.2)	7 (20.0)
Subjects with grade 3 AE(s), n (%)	1 (3.0)	0 (0.0)
Subjects with related AE(s), n (%)	1 (3.0)	2 (5.7)
Upper respiratory tract infection	2 (6.1)	1 (2.9)
Cough	-	2 (5.7)

Gastroenteritis	-	2 (5.7)
Injection site pruritus	-	2 (5.7)
Injection site warmth	1 (3.0)	1 (2.9)
Cystitis	-	1 (2.9)
Epistaxis	1 (3.0)	-
Gout	-	1 (2.9)
Hypersensitivity	-	1 (2.9)
Influenza like illness	1 (3.0)	-
- : Adverse event absent Grade 3 = event that prevented normal activities Related = event assessed by the investigator as causally related to the study vaccination		
Safety results: Number (%) of subjects with serious adverse events during the entire study period (Total Vaccinated cohort)		
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	**Flu Group N = 33**	**Reference Group N = 35**
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**Flu Group N = 33**	**Reference Group N = 35**
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: Across groups, during the 7-day post-vaccination period, pain at the site of injection was the most frequently reported solicited local symptom (mean duration: 2.2 days in Flu Group & 2.0 days in Reference Group); arthralgia (mean duration: 2.0 days) fatigue (mean duration: 2.6 days) headache (mean duration: 1.6) and myalgia (mean duration: 2.8 days) were the most frequently reported solicited general symptoms in the Flu Group while arthralgia (mean duration: 4.0 days) was the most frequently reported solicited general symptoms in the Reference Group. One subject reported a Grade 3 redness (>100 mm) in the Flu Group; no other Grade 3 solicited local or general symptoms were reported.
During the 21-day follow-up period after vaccination, 2 (6.1%) and 4 (11.4%) subjects in Flu and Reference groups, respectively, reported at least one AE with medically-attended visit. One subject reported a Grade 3 AE with medically-attended visit (upper respiratory tract infection) in the Flu Group. No AEs with a medically-attended visit were assessed by the investigator as related to the vaccination.
During the same follow-up period, 5 (15.2%) and 7 (20.0%) subjects in the Flu and Reference groups, respectively, reported at least one unsolicited AE. One subject reported a Grade 3 unsolicited AE (upper respiratory tract infection) in the Flu Group. Three subjects (1 (3.0%) and 2 (5.7%) subjects in the Flu and Reference groups, respectively) reported unsolicited AEs that were assessed by the investigator as related to the study vaccination. No SAEs (fatal or non fatal) were reported during the study.

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