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.: 110263 (FluAS25-008 EXT:003 Y2)

Title: Reactogenicity and immunogenicity of GSK Biologicals' influenza vaccine GSK576389A in elderly adults (≥ 66 years) previously vaccinated with the same candidate vaccine. Fluarix™ will be used as reference.
GSK576389A (FluAS25): GlaxoSmithKline (GSK) Biologicals' AS25 adjuvanted influenza vaccine.
Fluarix™ (Flu): GSK Biologicals' licensed influenza vaccine.

Rationale: The aim of this study was to evaluate the safety and immunogenicity of a re-vaccination dose of the FluAS25 vaccine (2007-2008 season) compared to that of the Flu vaccine (2007-2008 season) administered in 2 groups of adults, one aged 19 to 42 years (Flu vaccine only) and one aged 66 years or older.
Subjects participating in this study had received the same vaccine in FluAS25-004 (104887) study.

Phase: II

Study Period: 10 October 2007 to 28 November 2007.

Study Design: Single centre, open, controlled study with 3 parallel groups.

Centres: 1 study centre in Belgium

Indication: Immunisation against influenza disease.

Treatment: The study groups were as follows:

- FluAS25 Group: subjects aged ≥ 66 years who previously received 1 dose of FluAS25 vaccine were administered 1 dose of FluAS25 vaccine in this study.
- Flu_Yng Group: subjects aged 19-42 years who previously received 1 dose of Flu vaccine were administered 1 dose of Flu vaccine in this study.
- Flu_Eld Group: subjects aged ≥ 66 years who previously received 1 dose of Flu vaccine were administered 1 dose of Flu vaccine in this study.

All vaccines were administered by intramuscular injection into the deltoid region of the non-dominant arm.

Objectives:
To evaluate in elderly adults, the safety of repeated vaccination with FluAS25, during the 21 days following the intramuscular administration of the vaccine. Flu vaccine administered to young (19-42 years) and elderly (≥ 66 years) adults 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 (ER) visits, hospitalizations or physician visits and that were 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 and relationship to vaccination of serious adverse events (SAEs) during the entire study period, in each group.

*Duration of unsolicited symptoms and MSCs was not analysed.

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

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

Derived variables:

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

***SPR was defined as the percentage of vaccinees with a serum HI titre ≥1:40 that usually was accepted as indicating protection.

Cell-Mediated Immunity (CMI) response

Observed variables:

- Frequency of immune response marker-positive cluster of differentiation 4 and 8 (CD4/CD8) cells per million in tests producing at least 2 different immune response markers [cluster of differentiation 40 Ligand (CD40L), interleukin 2 (IL-2), tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ)], in each group.
- Frequency of immune response marker-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 immune response marker-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 immune response marker-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 immune response marker-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 (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 outcome variables were available. This cohort included subjects for whom assay results for antibodies against at least one study vaccine antigen component after vaccination (Day 21) were available.

Analysis of Immunogenicity:

The analysis of immunogenicity was performed on the ATP cohort for immunogenicity.

GMTs of HI antibody titres, seropositivity rates and SPRs at Day 0 and 21 and SCRs and SCFs at Day 21 were calculated with their 95% confidence intervals (CI) for each vaccination group and each strain. The frequencies of influenza-specific immune response marker-positive CD4/CD8 T-lymphocytes were summarized for each vaccine group at Days 0 and 21, for each different immune response marker test, for separate and 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 solicited follow-up period was tabulated with exact 95% CI, in each group. The same tabulation was performed for grade 3 symptoms and for symptoms assessed by the investigator as related to vaccination. All solicited local symptoms were assessed as causally related to the study vaccination. The duration of the solicited local and general symptoms during the 7-day solicited follow-up period was tabulated in each group. 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 in each group. The same tabulation was done for grade 3 unsolicited AEs and AEs assessed by the investigator as related to vaccination. The proportion of subjects with at least one report of MSC classified by MedDRA and reported up to 21 days after vaccination was tabulated. The same tabulation was done for grade 3 MSC and MSC with relationship to vaccination. The occurrence of SAEs and that of SAEs assessed by the investigators as causally related to study vaccination during the entire study period was tabulated according to MedDRA preferred terms.

Study Population: A healthy man or woman aged ≥ 66 years or aged 19 to 42 years at the time of the revaccination, who previously received the same vaccine during the FluAS25-004 study (104887). If the subject was female, she had to be of non-childbearing potential or if she was of childbearing potential, she had practiced adequate contraception for 30 days prior to vaccination, had a negative pregnancy test and had agreed to continue such precautions for 2 months after vaccination. Written informed consent was obtained from the subject.

Number of subjects	**FluAS25 Group**	**Flu_Eld Group**	**Flu_Yng Group**
Planned, N	62	45	55

Entered, N (Total Vaccinated Cohort)	55	40	38
Completed, n (%)	55 (100)	40 (100)	38 (100)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Demographics	**FluAS25 Group**	**Flu_Eld Group**	**Flu_Yng Group**
N (Total Vaccinated Cohort)	55	40	38
Females: Males	22:33	17:23	16:22
Mean Age, years (SD)	71.2 (3.07)	71.2 (3.47)	27.4 (6.08)
White - Caucasian / European heritage, n (%)	55 (100)	40 (100)	37 (97.4)

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

Symptom	Intensity	FluAS25 Group					Flu_Eld Group					Flu_Yng Group				
		N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL				LL	UL
Ecchymosis	Any	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
	> 100 mm	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
Pain	Any	55	40	72.7	59.0	83.9	40	12	30.0	16.6	46.5	38	34	89.5	75.2	97.1
	Grade 3	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
Redness	Any	55	13	23.6	13.2	37.0	40	6	15.0	5.7	29.8	38	1	2.6	0.1	13.8
	> 100 mm	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
Swelling	Any	55	6	10.9	4.1	22.2	40	4	10.0	2.8	23.7	38	0	0.0	0.0	9.3
	> 100 mm	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3

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 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 local symptoms during the 7-day post-vaccination period (Total Vaccinated Cohort)

Solicited symptom	Group	N	Mean	Median
Pain	FluAS25	40	2.4	2.0
	Flu_Eld	12	1.8	1.5
	Flu_Yng	34	2.1	2.0
Redness	FluAS25	13	2.4	3.0
	Flu_Eld	6	1.5	1.0
	Flu_Yng	1	1.0	1.0
Swelling	FluAS25	6	3.3	3.0
	Flu_Eld	4	1.5	1.0

N = number of subjects with the symptom reported and for whom complete information on duration was available.

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

Symptom	Intensity/ Relationship	FluAS25 Group					Flu_Eld Group					Flu_Yng Group				
		N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL				LL	UL
Arthralgia	Any	55	6	10.9	4.1	22.2	40	6	15.0	5.7	29.8	38	2	5.3	0.6	17.7
	Grade 3	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
	Related	55	4	7.3	2.0	17.6	40	3	7.5	1.6	20.4	38	2	5.3	0.6	17.7
Fatigue	Any	55	19	34.5	22.2	48.6	40	6	15.0	5.7	29.8	38	9	23.7	11.4	40.2
	Grade 3	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
	Related	55	19	34.5	22.2	48.6	40	3	7.5	1.6	20.4	38	8	21.1	9.6	37.3
Headache	Any	55	13	23.6	13.2	37.0	40	5	12.5	4.2	26.8	38	8	21.1	9.6	37.3
	Grade 3	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
	Related	55	11	20.0	10.4	33.0	40	2	5.0	0.6	16.9	38	7	18.4	7.7	34.3
Myalgia	Any	55	10	18.2	9.1	30.9	40	3	7.5	1.6	20.4	38	10	26.3	13.4	43.1

	Grade 3	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	1	2.6	0.1	13.8
	Related	55	10	18.2	9.1	30.9	40	1	2.5	0.1	13.2	38	10	26.3	13.4	43.1
Nausea	Any	55	4	7.3	2.0	17.6	40	0	0.0	0.0	8.8	38	3	7.9	1.7	21.4
	Grade 3	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
	Related	55	4	7.3	2.0	17.6	40	0	0.0	0.0	8.8	38	1	2.6	0.1	13.8
Shivering	Any	55	10	18.2	9.1	30.9	40	0	0.0	0.0	8.8	38	2	5.3	0.6	17.7
	Grade 3	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	1	2.6	0.1	13.8
	Related	55	9	16.4	7.8	28.8	40	0	0.0	0.0	8.8	38	2	5.3	0.6	17.7
Temperature (Axillary)	≥ 38.0°C	55	4	7.3	2.0	17.6	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
	≥ 39.0°C	55	0	0.0	0.0	6.5	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3
	Related	55	4	7.3	2.0	17.6	40	0	0.0	0.0	8.8	38	0	0.0	0.0	9.3

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 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 general symptoms during the 7-day post-vaccination period using (Total Vaccinated Cohort)

Solicited symptom	Group	N	Mean	Median
Arthralgia	FluAS25	6	2.8	2.5
	Flu_Eld	6	3.0	2.0
	Flu_Yng	2	1.5	1.5
Fatigue	FluAS25	19	2.3	2.0
	Flu_Eld	6	1.3	1.0
	Flu_Yng	9	1.8	2.0
Headache	FluAS25	13	1.5	1.0
	Flu_Eld	5	1.2	1.0
	Flu_Yng	8	2.0	2.0
Myalgia	FluAS25	10	2.3	2.0
	Flu_Eld	3	2.3	2.0
	Flu_Yng	10	2.1	2.0
Nausea	FluAS25	4	1.3	1.0
	Flu_Yng	3	1.3	1.0
Shivering	FluAS25	10	1.2	1.0
	Flu_Yng	2	3.5	3.5
Temperature	FluAS25	4	1.0	1.0

N = number of subjects with the symptom reported and for whom complete information on duration was available.

Primary Efficacy Results: Number (%) of subjects with MSCs during the 21-day (Days 0-20) post-vaccination period (Total Vaccinated cohort)

Medically significant conditions (MSC)	FluAS25 N = 55				Flu_Eld N = 40				Flu_Yng N = 38			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL			LL	UL
Subjects with at least one MSC	5	9.1	3.0	20.0	1	2.5	0.1	13.2	2	5.3	0.6	17.7
Subjects with Grade 3 MSC	0	0.0	0.0	6.5	0	0.0	0.0	8.8	1	2.6	0.1	13.8
Subjects with related MSC	0	0.0	-*	-*	0	0.0	-*	-*	0	0.0	-*	-*
Polycythaemia	1	1.8	0.0	9.7	0	0.0	0.0	8.8	0	0.0	0.0	9.3
Conjunctivitis	1	1.8	0.0	9.7	0	0.0	0.0	8.8	0	0.0	0.0	9.3
Influenza like illness	0	0.0	0.0	6.5	0	0.0	0.0	8.8	1	2.6	0.1	13.8
Bronchitis	1	1.8	0.0	9.7	0	0.0	0.0	8.8	0	0.0	0.0	9.3
Cystitis	0	0.0	0.0	6.5	0	0.0	0.0	8.8	1	2.6	0.1	13.8
Upper respiratory tract infection	1	1.8	0.0	9.7	0	0.0	0.0	8.8	0	0.0	0.0	9.3
Tooth fracture	0	0.0	0.0	6.5	1	2.5	0.1	13.2	0	0.0	0.0	9.3
Pain in extremity	1	1.8	0.0	9.7	0	0.0	0.0	8.8	0	0.0	0.0	9.3

At least one MSC = at least one MSC experienced

Grade 3 = MSC that prevented normal activities
Related = MSC assessed by the investigator to be causally related to the study vaccination
N = number of subjects with the administered dose
n (%) = number(percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
*Not available in the report

Primary Efficacy Results: Please refer to the safety results section of the document for the results on unsolicited AEs and SAEs.

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

Antibody	Group	Timing	N	≥ 1:10				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Solomon Islands	FluAS25	PRE	52	19	36.5	23.6	51.0	8.5	6.7	10.8
		PI(D21)	51	48	94.1	83.8	98.8	91.6	64.1	131.0
	Flu_Eld	PRE	39	12	30.8	17.0	47.6	6.9	5.7	8.5
		PI(D21)	39	28	71.8	55.1	85.0	30.3	18.7	49.2
	Flu_Yng	PRE	38	33	86.8	71.9	95.6	56.0	35.2	89.1
		PI(D21)	38	37	97.4	86.2	99.9	110.0	76.5	158.3
A/Wisconsin	FluAS25	PRE	52	50	96.2	86.8	99.5	141.9	103.1	195.3
		PI(D21)	51	51	100	93.0	100	384.5	301.7	489.8
	Flu_Eld	PRE	39	37	94.9	82.7	99.4	70.6	47.4	105.2
		PI(D21)	39	39	100	91.0	100	147.6	105.9	205.6
	Flu_Yng	PRE	38	37	97.4	86.2	99.9	115.1	77.5	171.1
		PI(D21)	38	38	100	90.7	100	190.1	144.0	251.0
B/Malaysia	FluAS25	PRE	52	52	100	93.2	100	82.6	64.7	105.6
		PI(D21)	51	51	100	93.0	100	163.2	129.6	205.7
	Flu_Eld	PRE	39	38	97.4	86.5	99.9	59.6	42.3	83.8
		PI(D21)	39	38	97.4	86.5	99.9	93.8	68.4	128.8
	Flu_Yng	PRE	38	37	97.4	86.2	99.9	139.4	98.5	197.2
		PI(D21)	38	38	100	90.7	100	210.3	158.6	278.7

GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination Dose 1 at Day 0
PI(D21) = Post-vaccination Dose 1 at Day 21

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

Antibody	Group	N	SCR			
			n	%	95% CI	
					LL	UL
A/Solomon Islands	FluAS25	51	39	76.5	62.5	87.2
	Flu_Eld	39	19	48.7	32.4	65.2
	Flu_Yng	38	6	15.8	6.0	31.3
A/Wisconsin	FluAS25	51	18	35.3	22.4	49.9
	Flu_Eld	39	6	15.4	5.9	30.5
	Flu_Yng	38	4	10.5	2.9	24.8
B/Malaysia	FluAS25	51	10	19.6	9.8	33.1
	Flu_Eld	39	4	10.3	2.9	24.2
	Flu_Yng	38	2	5.3	0.6	17.7

SCR was defined as:
For initially seronegative subjects, antibody titre ≥ 1:40 after vaccination
For initially seropositive subjects, antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre
N = number of subjects with pre- and post-vaccination results available
n (%) = number (percentage) of seroconverted subjects

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

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

Antibody	Group	N	SCF		
			Value	95% CI	
				LL	UL
A/Solomon Islands	FluAS25	51	10.6	7.4	15.2
	Flu_Eld	39	4.4	2.8	6.8
	Flu_Yng	38	2.0	1.5	2.5
A/Wisconsin	FluAS25	51	2.7	2.2	3.3
	Flu_Eld	39	2.1	1.7	2.5
	Flu_Yng	38	1.7	1.4	2.0
B/Malaysia	FluAS25	51	2.0	1.7	2.3
	Flu_Eld	39	1.6	1.3	1.9
	Flu_Yng	38	1.5	1.3	1.8

SCF = Seroconversion factor of the within-subject ratios of the post-vaccination reciprocal HI titre to the Day 0 reciprocal HI titre
N = number of subjects with pre- and post-vaccination results available
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

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

Antibody	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Solomon Islands	FluAS25	PRE	52	6	11.5	4.4	23.4
		PI(D21)	51	42	82.4	69.1	91.6
	Flu_Eld	PRE	39	1	2.6	0.1	13.5
		PI(D21)	39	21	53.8	37.2	69.9
	Flu_Yng	PRE	38	25	65.8	48.6	80.4
		PI(D21)	38	32	84.2	68.7	94.0
A/Wisconsin	FluAS25	PRE	52	49	94.2	84.1	98.8
		PI(D21)	51	50	98.0	89.6	100
	Flu_Eld	PRE	39	31	79.5	63.5	90.7
		PI(D21)	39	35	89.7	75.8	97.1
	Flu_Yng	PRE	38	33	86.8	71.9	95.6
		PI(D21)	38	37	97.4	86.2	99.9
B/Malaysia	FluAS25	PRE	52	47	90.4	79.0	96.8
		PI(D21)	51	51	100	93.0	100
	Flu_Eld	PRE	39	31	79.5	63.5	90.7
		PI(D21)	39	37	94.9	82.7	99.4
	Flu_Yng	PRE	38	35	92.1	78.6	98.3
		PI(D21)	38	37	97.4	86.2	99.9

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

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

Immune marker	Stimulating antigen	Group	Timing	N	Nmiss	GM	SD	Median
CD4- All doubles	A/Solomon Islands	FluAS25	PRE	44	8	289.37	316.11	432
			PI(D21)	44	8	700.62	634.14	744
		Flu_Eld	PRE	36	3	180.39	228.07	253
			PI(D21)	36	3	337.23	500.65	482
		Flu_Yng	PRE	36	2	331.14	494.08	562

			PI(D21)	35	3	258.27	637.94	603
	A/Wisconsin	FluAS25	PRE	44	8	603.80	540.62	717
			PI(D21)	44	8	1020.35	830.08	1068
		Flu_Eld	PRE	36	3	489.94	426.96	543
			PI(D21)	36	3	776.74	654.62	869
		Flu_Yng	PRE	36	2	905.24	750.96	991
			PI(D21)	35	3	868.45	946.28	1140
	B/Malaysia	FluAS25	PRE	44	8	448.88	497.51	718
			PI(D21)	44	8	925.46	607.25	935
		Flu_Eld	PRE	35	4	381.99	341.08	430
			PI(D21)	36	3	681.59	593.45	602
		Flu_Yng	PRE	36	2	566.22	581.71	788
			PI(D21)	35	3	786.37	723.64	955
	Pool FLU	FluAS25	PRE	44	8	1054.11	945.41	1464
			PI(D21)	44	8	2115.03	1368.50	2349
		Flu_Eld	PRE	36	3	983.41	598.15	1067
			PI(D21)	36	3	1509.46	1159.17	1459
		Flu_Yng	PRE	36	2	1693.14	1045.17	1738
			PI(D21)	35	3	1998.24	1287.85	1915
CD4- CD40L	A/Solomon Islands	FluAS25	PRE	44	8	270.70	307.98	401
			PI(D21)	44	8	642.40	596.29	646
		Flu_Eld	PRE	36	3	165.45	211.89	246
			PI(D21)	36	3	302.95	473.99	441
		Flu_Yng	PRE	36	2	309.92	437.51	530
			PI(D21)	35	3	236.63	553.12	517
	A/Wisconsin	FluAS25	PRE	44	8	549.05	509.04	680
			PI(D21)	44	8	930.92	790.99	1025
		Flu_Eld	PRE	36	3	447.08	404.96	493
			PI(D21)	36	3	709.71	622.14	770
		Flu_Yng	PRE	36	2	851.31	663.11	892
			PI(D21)	35	3	726.97	809.91	1059
	B/Malaysia	FluAS25	PRE	44	8	429.49	476.96	629
			PI(D21)	44	8	858.29	562.66	847
		Flu_Eld	PRE	35	4	332.83	337.05	415
			PI(D21)	36	3	648.87	571.71	582
		Flu_Yng	PRE	36	2	595.14	562.39	785
			PI(D21)	35	3	748.64	673.49	938
	Pool FLU	FluAS25	PRE	44	8	987.45	890.57	1291
			PI(D21)	44	8	1941.32	1283.08	2097
		Flu_Eld	PRE	36	3	923.21	555.48	1078
			PI(D21)	36	3	1399.44	1125.57	1268
		Flu_Yng	PRE	36	2	1625.21	968.97	1663
			PI(D21)	35	3	1891.90	1180.76	1853
CD4- IFNγ	A/Solomon Islands	FluAS25	PRE	44	8	225.18	246.92	269
			PI(D21)	44	8	444.36	446.32	454
		Flu_Eld	PRE	36	3	178.68	209.78	179
			PI(D21)	36	3	297.00	380.68	270
		Flu_Yng	PRE	36	2	321.79	394.96	444
			PI(D21)	35	3	276.77	478.52	399
	A/Wisconsin	FluAS25	PRE	44	8	327.24	327.82	407
			PI(D21)	44	8	594.70	547.10	570
		Flu_Eld	PRE	36	3	280.71	243.51	311
			PI(D21)	36	3	425.95	366.97	475
		Flu_Yng	PRE	36	2	431.80	490.54	426

			PI(D21)	35	3	374.53	618.57	490
	B/Malaysia	FluAS25	PRE	44	8	314.05	343.68	388
			PI(D21)	44	8	565.96	386.51	655
		Flu_Eld	PRE	35	4	254.50	268.96	295
			PI(D21)	36	3	395.62	445.62	408
		Flu_Yng	PRE	36	2	471.54	429.46	451
			PI(D21)	35	3	612.24	529.06	619
	Pool FLU	FluAS25	PRE	44	8	702.42	642.37	838
			PI(D21)	44	8	1231.82	926.67	1339
		Flu_Eld	PRE	36	3	575.66	442.31	625
			PI(D21)	36	3	892.48	794.53	936
		Flu_Yng	PRE	36	2	924.86	704.75	1020
			PI(D21)	35	3	1108.49	956.85	1026
CD4- IL2	A/Solomon Islands	FluAS25	PRE	44	8	253.44	281.09	399
			PI(D21)	44	8	616.24	527.94	630
		Flu_Eld	PRE	36	3	146.65	216.35	235
			PI(D21)	36	3	386.68	403.33	443
		Flu_Yng	PRE	36	2	314.65	418.81	521
			PI(D21)	35	3	278.09	479.01	548
	A/Wisconsin	FluAS25	PRE	44	8	500.73	465.55	629
			PI(D21)	44	8	836.51	650.10	914
		Flu_Eld	PRE	36	3	425.33	377.19	498
			PI(D21)	36	3	649.78	561.75	687
		Flu_Yng	PRE	36	2	735.18	560.20	836
			PI(D21)	35	3	507.19	747.26	748
	B/Malaysia	FluAS25	PRE	44	8	423.52	454.12	611
			PI(D21)	44	8	837.64	530.27	852
		Flu_Eld	PRE	35	4	317.95	314.42	384
			PI(D21)	36	3	609.36	501.15	544
		Flu_Yng	PRE	36	2	598.54	495.94	711
			PI(D21)	35	3	797.20	619.24	903
	Pool FLU	FluAS25	PRE	44	8	861.71	826.31	1271
			PI(D21)	44	8	1711.92	1141.42	1902
		Flu_Eld	PRE	36	3	852.92	562.42	897
			PI(D21)	36	3	1253.42	962.58	1244
		Flu_Yng	PRE	36	2	1398.63	889.24	1424
			PI(D21)	35	3	1643.55	1047.94	1556
CD4- TFNα	A/Solomon Islands	FluAS25	PRE	44	8	213.84	261.37	291
			PI(D21)	44	8	438.22	458.26	547
		Flu_Eld	PRE	36	3	157.07	191.42	214
			PI(D21)	36	3	200.94	422.70	275
		Flu_Yng	PRE	36	2	257.79	414.20	372
			PI(D21)	35	3	234.56	509.44	405
	A/Wisconsin	FluAS25	PRE	44	8	505.57	480.19	538
			PI(D21)	44	8	765.11	686.36	764
		Flu_Eld	PRE	36	3	398.34	330.78	418
			PI(D21)	36	3	567.86	528.70	575
		Flu_Yng	PRE	36	2	626.76	667.79	760
			PI(D21)	35	3	787.77	804.78	837
	B/Malaysia	FluAS25	PRE	44	8	257.07	342.41	457
			PI(D21)	44	8	495.31	410.07	576
		Flu_Eld	PRE	35	4	180.31	263.66	248
			PI(D21)	36	3	304.21	460.57	369
		Flu_Yng	PRE	36	2	381.85	435.63	550

			PI(D21)	35	3	494.64	550.12	519
	Pool FLU	FluAS25	PRE	44	8	700.87	778.74	1056
			PI(D21)	44	8	1368.75	1094.14	1529
		Flu_Eld	PRE	36	3	687.37	473.04	638
			PI(D21)	36	3	1016.67	899.04	983
		Flu_Yng	PRE	36	2	1236.53	885.31	1277
			PI(D21)	35	3	1356.89	1093.09	1379

CD4- All doubles: T-cells expressing at least 2 immune response markers
CD4- CD40L: T cells expressing at least CD40L and another immune response marker
CD4- IFNγ: T cells expressing at least IFNγ and another immune response marker
CD4- IL2: T cells expressing at least IL2 and another immune response marker
CD4- TFNα: T cells expressing at least TFNα and another immune response marker
Pool Flu: Pooled influenza strains
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 at Day 0
PI(D21) = Post-vaccination Dose 1 at Day 21

Secondary Outcome Variable(s): Descriptive Statistics on the frequency of immune response marker-positive CD8 T-cells (per million CD8 T-cells) for each strain and for pooled strains at Days 0 and 21 (ATP cohort for immunogenicity)

Immune marker	**Stimulating antigen**	**Group**	**Timing**	**N**	**Nmiss**	**GM**	**SD**	**Median**
CD8- All doubles	A/Solomon Islands	FluAS25	PRE	44	8	2.26	136.77	1.00
			PI(D21)	44	8	1.84	88.15	1.00
		Flu_Eld	PRE	36	3	3.28	101.08	1.00
			PI(D21)	36	3	1.92	55.86	1.00
		Flu_Yng	PRE	36	2	4.14	186.27	1.00
			PI(D21)	35	3	3.60	138.60	1.00
	A/Wisconsin	FluAS25	PRE	43	9	2.75	60.50	1.00
			PI(D21)	44	8	2.04	65.79	1.00
		Flu_Eld	PRE	36	3	5.30	264.71	1.00
			PI(D21)	36	3	2.55	54.17	1.00
		Flu_Yng	PRE	36	2	2.44	39.72	1.00
			PI(D21)	35	3	3.69	62.67	1.00
	B/Malaysia	FluAS25	PRE	44	8	3.28	159.00	1.00
			PI(D21)	44	8	3.03	89.02	1.00
		Flu_Eld	PRE	35	4	4.12	154.66	1.00
			PI(D21)	36	3	2.69	83.37	1.00
		Flu_Yng	PRE	36	2	2.39	72.34	1.00
			PI(D21)	35	3	2.28	44.43	1.00
	Pool FLU	FluAS25	PRE	44	8	8.91	213.18	1.00
			PI(D21)	44	8	9.98	149.19	3.00
		Flu_Eld	PRE	36	3	10.47	89.43	3.50
			PI(D21)	36	3	8.02	158.53	1.00
		Flu_Yng	PRE	36	2	9.43	153.80	1.50
			PI(D21)	35	3	6.50	95.79	1.00
CD8- CD40L	A/Solomon Islands	FluAS25	PRE	44	8	2.17	124.96	1.00
			PI(D21)	44	8	1.43	40.80	1.00
		Flu_Eld	PRE	36	3	1.97	88.18	1.00
			PI(D21)	36	3	1.64	30.98	1.00
		Flu_Yng	PRE	36	2	1.61	22.41	1.00
			PI(D21)	35	3	1.94	47.82	1.00
	A/Wisconsin	FluAS25	PRE	43	9	2.14	32.90	1.00
			PI(D21)	44	8	1.52	45.12	1.00

		Flu_Eld	PRE	36	3	2.67	222.75	1.00
			PI(D21)	36	3	1.68	40.13	1.00
		Flu_Yng	PRE	36	2	1.70	35.64	1.00
			PI(D21)	35	3	2.55	44.60	1.00
	B/Malaysia	FluAS25	PRE	44	8	3.44	150.26	1.00
			PI(D21)	44	8	2.49	90.52	1.00
		Flu_Eld	PRE	35	4	2.27	96.08	1.00
			PI(D21)	36	3	1.62	40.21	1.00
		Flu_Yng	PRE	36	2	2.49	57.45	1.00
			PI(D21)	35	3	2.59	45.37	1.00
	Pool FLU	FluAS25	PRE	44	8	7.70	171.70	1.00
			PI(D21)	44	8	4.92	129.03	1.00
		Flu_Eld	PRE	36	3	6.52	67.52	1.00
			PI(D21)	36	3	4.64	135.66	1.00
		Flu_Yng	PRE	36	2	4.42	49.26	1.00
			PI(D21)	35	3	3.41	60.34	1.00
CD8- IFNγ	A/Solomon Islands	FluAS25	PRE	44	8	2.07	36.81	1.00
			PI(D21)	44	8	1.77	72.15	1.00
		Flu_Eld	PRE	36	3	1.49	49.87	1.00
			PI(D21)	36	3	2.12	38.86	1.00
		Flu_Yng	PRE	36	2	3.15	173.10	1.00
			PI(D21)	35	3	3.53	113.89	1.00
	A/Wisconsin	FluAS25	PRE	43	9	1.71	31.52	1.00
			PI(D21)	44	8	1.80	26.18	1.00
		Flu_Eld	PRE	36	3	2.76	45.51	1.00
			PI(D21)	36	3	2.73	55.42	1.00
		Flu_Yng	PRE	36	2	1.27	16.73	1.00
			PI(D21)	35	3	1.88	33.19	1.00
	B/Malaysia	FluAS25	PRE	44	8	1.93	47.54	1.00
			PI(D21)	44	8	2.15	35.22	1.00
		Flu_Eld	PRE	35	4	2.75	135.21	1.00
			PI(D21)	36	3	2.24	59.72	1.00
		Flu_Yng	PRE	36	2	2.43	53.85	1.00
			PI(D21)	35	3	1.47	19.69	1.00
	Pool FLU	FluAS25	PRE	44	8	2.86	46.18	1.00
			PI(D21)	44	8	2.55	47.59	1.00
		Flu_Eld	PRE	36	3	2.48	50.62	1.00
			PI(D21)	36	3	4.17	75.18	1.00
		Flu_Yng	PRE	36	2	3.88	117.16	1.00
			PI(D21)	35	3	2.57	50.74	1.00
CD8- IL2	A/Solomon Islands	FluAS25	PRE	44	8	2.17	135.56	1.00
			PI(D21)	44	8	1.54	76.05	1.00
		Flu_Eld	PRE	36	3	3.16	92.06	1.00
			PI(D21)	36	3	1.46	28.82	1.00
		Flu_Yng	PRE	36	2	2.49	125.60	1.00
			PI(D21)	35	3	4.26	129.70	1.00
	A/Wisconsin	FluAS25	PRE	43	9	2.55	65.54	1.00
			PI(D21)	44	8	2.30	65.28	1.00
		Flu_Eld	PRE	36	3	4.58	263.11	1.00
			PI(D21)	36	3	1.87	46.74	1.00
		Flu_Yng	PRE	36	2	1.69	30.56	1.00
			PI(D21)	35	3	2.95	74.62	1.00
	B/Malaysia	FluAS25	PRE	44	8	2.35	136.20	1.00
			PI(D21)	44	8	3.12	97.43	1.00

		Flu_Eld	PRE	35	4	3.18	142.54	1.00
			PI(D21)	36	3	2.36	73.10	1.00
		Flu_Yng	PRE	36	2	1.90	32.04	1.00
			PI(D21)	35	3	3.69	50.07	1.00
	Pool FLU	FluAS25	PRE	44	8	7.71	210.95	1.00
			PI(D21)	44	8	9.19	155.66	1.00
		Flu_Eld	PRE	36	3	8.20	96.31	1.00
			PI(D21)	36	3	8.89	149.48	1.00
		Flu_Yng	PRE	36	2	6.61	63.15	1.00
			PI(D21)	35	3	5.36	73.11	1.00
CD8- TFNα	A/Solomon Islands	FluAS25	PRE	44	8	2.42	49.99	1.00
			PI(D21)	44	8	1.97	68.53	1.00
		Flu_Eld	PRE	36	3	1.99	70.11	1.00
			PI(D21)	36	3	2.40	41.63	1.00
		Flu_Yng	PRE	36	2	3.75	175.10	1.00
			PI(D21)	35	3	2.99	132.56	1.00
	A/Wisconsin	FluAS25	PRE	43	9	3.54	76.40	1.00
			PI(D21)	44	8	2.84	42.13	1.00
		Flu_Eld	PRE	36	3	5.58	70.98	1.00
			PI(D21)	36	3	2.76	65.68	1.00
		Flu_Yng	PRE	36	2	2.44	44.31	1.00
			PI(D21)	35	3	2.19	48.45	1.00
	B/Malaysia	FluAS25	PRE	44	8	2.73	80.16	1.00
			PI(D21)	44	8	2.76	52.39	1.00
		Flu_Eld	PRE	35	4	8.42	104.25	1.00
			PI(D21)	36	3	3.42	64.32	1.00
		Flu_Yng	PRE	36	2	2.38	72.34	1.00
			PI(D21)	35	3	1.66	30.79	1.00
	Pool FLU	FluAS25	PRE	44	8	6.74	92.88	1.00
			PI(D21)	44	8	5.86	58.58	1.00
		Flu_Eld	PRE	36	3	8.70	72.98	3.50
			PI(D21)	36	3	5.55	104.44	1.00
		Flu_Yng	PRE	36	2	3.32	142.50	1.00
			PI(D21)	35	3	4.56	70.82	1.00

CD8- All doubles: T-cells expressing at least 2 immune response markers
CD8- CD40L: T cells expressing at least CD40L and another immune response marker
CD8- IFNγ: T cells expressing at least IFNγ and another immune response marker
CD8- IL2: T cells expressing at least IL2 and another immune response marker
CD8- TFNα: T cells expressing at least TFNα and another immune response marker
Pool Flu: Pooled influenza strains
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 at Day 0
PI(D21) = Post-vaccination Dose 1 at Day

Safety Results: Number (%) of subjects with unsolicited AEs within the 21-day post-vaccination period (Total Vaccinated Cohort)

Most frequent adverse events–On-Therapy (occurring within Days 0-20 following vaccination)	**FluAS25 Group N = 55**	**Flu_Eld Group N = 40**	**Flu_Yng Group N = 38**
Subjects with any AE(s), n (%)	18 (32.7)	9 (22.5)	19 (50.0)
Subjects with grade 3* AE(s), n (%)	1 (1.8)	1 (2.5)	1 (2.6)
Subjects with related** AE(s), n (%)	6 (10.9)	2 (5.0)	3 (7.9)
Upper respiratory tract infection	5 (9.1)	3 (7.5)	1 (2.6)
Pharyngolaryngeal pain	-	2 (5.0)	4 (10.5)

Rhinitis	2 (3.6)	1 (2.5)	2 (5.3)
Gastroenteritis	-	1 (2.5)	2 (5.3)
Headache	-	-	3 (7.9)
Influenza like illness	-	-	3 (7.9)
Injection site pruritus	1 (1.8)	2 (5.0)	-
Cough	1 (1.8)	1 (2.5)	-
Vertigo	2 (3.6)	-	-
Back pain	1 (1.8)	-	-
Bronchitis	1 (1.8)	-	-
Conjunctivitis	1 (1.8)	-	-
Cystitis	-	-	1 (2.6)
Diarrhea	-	-	1 (2.6)
Dizziness	-	-	1 (2.6)
Foot deformity	1 (1.8)	-	-
Injection site induration	1 (1.8)	-	-
Injection site reaction	1 (1.8)	-	-
Muscle spasms	1 (1.8)	-	-
Nausea	-	-	1 (2.6)
Pain in extremity	1 (1.8)	-	-
Paraesthesia	-	-	1 (2.6)
Polycythaemia	1 (1.8)	-	-
Productive cough	-	-	1 (2.6)
Tooth fracture	-	1 (2.5)	-
Vomiting	-	-	1 (2.6)

- : AE absent
*Grade 3 = event that prevented normal activities
**Related = event assessed by the investigator to be causally related to the study vaccination

Safety Results: Number (%) of subjects with SAEs 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	**FluAS25 Group N = 55**	**Flu_Eld Group N = 40**	**Flu_Yng Group N = 38**
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**FluAS25 Group N = 55**	**Flu_Eld Group N = 40**	**Flu_Yng Group N = 38**
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

During the 7-day post-vaccination period, across groups, pain was the most frequently reported solicited local symptom (between 30.0% and 89.5% of the subjects), with a mean duration of at least 1.8 days. No grade 3 pain was reported. During the same period, the most frequently reported solicited general symptoms were fatigue for 19 (34.5%) subjects in the FluAS25 Group (mean duration 2.3 days), fatigue and arthralgia for 6 (15.0%) subjects in the Flu_Eld Group (mean duration 1.3 & 3.0 days, respectively) and myalgia for 10 (26.3%) subjects in the Flu_Yng Group (mean duration 2.1 days). The percentages of subjects reporting fatigue assessed by the investigator as related to vaccination were 34.5% and 7.5% in the FluAS25 and the Flu-Eld groups, respectively. In the Flu_Eld Group, 7.5% of the subjects reported arthralgia assessed by the investigator as related to the study vaccination. In the Flu_Yng Group, 26.3% of the subjects reported myalgia assessed by the investigator as related to the study vaccination. Grade 3 myalgia and grade 3 shivering were reported by 1 subject in the Flu_Yng Group.

During the 21-day follow-up period after vaccination, at least one medically significant condition was reported by 5 (9.1%), 1 (2.5%) and 2 (5.3%) subjects in FluAS25, Flu_Eld and Flu_Yng Groups, respectively. One (2.6%) subject in the Flu_Yng Group reported a grade 3 event with a medically-attended visit. No adverse events with a medically-attended visit were assessed by the investigator as related to the vaccination.

Within the 21-day post-vaccination period, at least one unsolicited AE was reported by 18 (32.7%), 9 (22.5%) and 19 (50.0%) subjects in FluAS25, Flu_Eld and Flu_Yng Groups, respectively. Overall, 3 subjects (1 subject in each of the 3 groups) reported grade 3 unsolicited AEs. In the FluAS25 Group, the Flu_Eld Group and the Flu_Yng Group, 6 (10.9%), 2

(5.0%) and 3 (7.9%) subjects reported AEs related to the study vaccination, respectively. No SAEs (fatal or non fatal) were reported during the study period.

Date updated: 08-July-2014