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.:110674 (FLU-LD-010 EXT: 004 Y1)

Title Safety and immunogenicity of a second vaccination with GSK Biologicals' low dose influenza vaccine with reduced dose of AS03 adjuvant administered in subjects 18-60 years previously vaccinated in FLU-LD-004 study.

Rationale: To evaluate the safety and immunogenicity of the low dose influenza vaccine with full or half dose of AS03 adjuvant compared to *Fluarix*™ in re-vaccinated adults aged 18-60 years old.
Fluarix™: GlaxoSmithKline Biologicals' licensed influenza vaccine (Flu vaccine)

Phase: II

Study Period: 15 October 2007 to 12 December 2007

Study Design: Controlled study with 2 parallel groups.

Centres: One centre in Belgium.

Indication: Immunization against influenza.

Treatment: The 2 study groups were as follows:

- FluLD-A Group: subjects having received one dose of the low dose adjuvanted (AS03) influenza vaccine during the study FLU-LD-004 (108656), received one dose of influenza vaccine adjuvanted with 1/2 dose of AS03,
- Flu Group: subjects having received one dose of Flu vaccine during the study 108656 received one dose of Flu vaccine

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

Objectives: To assess during the entire study period (30 days) the safety of re-vaccination with the low dose influenza vaccine adjuvanted with half dose of AS03. Flu vaccine was used as reference.

Primary Outcome/Efficacy Variable:

- Occurrence, intensity and relationship to re-vaccination of solicited local and general signs and symptoms during a 7-day follow-up period (i.e. day of re-vaccination and 6 subsequent days) after re-vaccination in each group.
- Occurrence, intensity and relationship to re-vaccination of unsolicited adverse events (AEs) during a 30-day follow-up period (i.e. day of re-vaccination and 29 subsequent days) after re-vaccination in each group.
- Occurrence and relationship to re-vaccination of serious adverse events (SAEs) during the entire study period in each group.

Secondary Outcome/Efficacy Variable(s):

Observed variables:

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

Derived variables

- For each vaccine strain, geometric mean titre (GMT) of serum HI antibody at Days 0 and 21.
- For each vaccine strain, seroconversion rate (SCR) at Day 21 defined as the proportion of subjects with a pre-vaccination serum HI titre <1:10 and a post-vaccination serum HI titre $\geq$ 1:40, or a pre-vaccination serum HI titre $\geq$ 1:10 and a fold increase (post/pre) $\geq$ 4.
- For each vaccine strain, seroprotection rate (SPR) at Days 0 and 21 defined as the proportion of vaccinees with a serum HI antibody titre $\geq$ 1:40.
- For each vaccine strain, seroconversion factor (SCF) at Day 21 defined as the fold increase in serum HI antibody GMT on Day 21 compared to Day 0.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort and the According-To-Protocol (ATP) Cohort for immunogenicity.

- The Total Vaccinated Cohort included all vaccinated subjects.
- The ATP Cohort for immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom 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.

Analysis of Immunogenicity:

The analysis was performed on the ATP Cohort for immunogenicity.
GMTs of HI antibody titres at Days 0 and 21 with 95% CI, SCR with exact 95% CI at Day 21, SPR with exact 95% CI at Days 0 and 21, SCF with 95% CI at Day 21 and and seropositivity rates with exact 95% CI at Days 0 and 21 were calculated for each vaccine group and vaccine strain: A/Solomon Islands (H1N1), A/Wisconsin (H3N2) and B/Malaysia (B). Antibody titres below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.
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-Days (Days 0-6) solicited follow-up period was tabulated with exact 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The percentage of subjects with at least one report of unsolicited AEs classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and reported during a 30-day follow-up period (Days 0-29) after vaccination was tabulated. The same tabulation was performed for grade 3 unsolicited AEs and unsolicited AEs with relationship to vaccination. The occurrence of SAEs during the entire study period was tabulated per vaccine group according to the MedDRA preferred terms**.**

Study Population: Male or female aged 18 - 60 years at the time of enrolment, healthy as established by medical history and clinical examination before entering into the study, who had participated in study Flu-LD-004 (108656).. If the subject was female and of childbearing potential, she had to be abstinent or use adequate contraceptive precautions for 30 days prior to vaccination and to have a negative pregnancy test, and had to agree to continue such precautions for 2 months after vaccination. Written informed consent was obtained from the subject prior to study entry

Number of Subjects:	**FluLD-A Group**	**Flu Group**
Planned, N	200	100
Randomized, N (Total Vaccinated cohort)	160	83
Completed, n (%)	160 (100)	83 (100)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	0 (0.0)
Withdrawn due to Adverse Events n (%)	0 (0.0)	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	**FluLD-A Group**	**Flu Group**
N (Total Vaccinated cohort)	160	83
Females: Males	98:62	44:39
Mean Age, years (SD)	39.4 (13.66)	40.9 (13.66)
Race*, n (%)	Not available	Not available

* Information on race was not captured during this re-vaccination study. In study 108656, 98.0% of the subjects were Caucasians.

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

Symptom	**Intensity**	**FluLD-A Group**					**Flu Group**				
					95 % CI					**95 % CI**	
		N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Ecchymosis	Any	160	8	5.0	2.2	9.6	83	5	6.0	2.0	13.5
	> 50mm	160	1	0.6	0.0	3.4	83	2	2.4	0.3	8.4
Pain	Any	160	143	89.4	83.5	93.7	83	57	68.7	57.6	78.4
	Grade 3	160	9	5.6	2.6	10.4	83	2	2.4	0.3	8.4
Redness (mm)	Any	160	24	15.0	9.9	21.5	83	10	12.0	5.9	21.0
	> 50mm	160	2	1.3	0.2	4.4	83	1	1.2	0.0	6.5
Swelling (mm)	Any	160	29	18.1	12.5	25.0	83	13	15.7	8.6	25.3
	> 50mm	160	4	2.5	0.7	6.3	83	2	2.4	0.3	8.4

N= number of subjects with the documented dose
n (%)= number (percentage) of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = Incidence of a particular symptom regardless of intensity
Grade 3 Pain = pain which prevented normal activity

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

Symptom	Intensity/ relationship	FluLD-A Group					Flu Group				
					95 % CI					95 % CI	
		N	n	%	LL	UL	N	n	%	LL	UL
Arthralgia	Any	160	28	17.5	12.0	24.3	83	5	6.0	2.0	13.5
	Grade 3	160	3	1.9	0.4	5.4	83	0	0.0	0.0	4.3
	Related	160	26	16.3	10.9	22.9	83	5	6.0	2.0	13.5
Fatigue	Any	160	72	45.0	37.1	53.1	83	12	14.5	7.7	23.9
	Grade 3	160	7	4.4	1.8	8.8	83	2	2.4	0.3	8.4
	Related	160	71	44.4	36.5	52.4	83	10	12.0	5.9	21.0
Fever (Orally)	≥37.5°C	160	27	16.9	11.4	23.6	83	2	2.4	0.3	8.4
	>39.0°C	160	0	0.0	0.0	2.3	83	0	0.0	0.0	4.3
	Related	160	27	16.9	11.4	23.6	83	2	2.4	0.3	8.4
Headache	Any	160	65	40.6	32.9	48.7	83	18	21.7	13.4	32.1
	Grade 3	160	6	3.8	1.4	8.0	83	1	1.2	0.0	6.5
	Related	160	61	38.1	30.6	46.1	83	16	19.3	11.4	29.4
Myalgia	Any	160	56	35.0	27.6	42.9	83	8	9.6	4.3	18.1
	Grade 3	160	4	2.5	0.7	6.3	83	0	0.0	0.0	4.3
	Related	160	52	32.5	25.3	40.3	83	8	9.6	4.3	18.1
Nausea	Any	160	23	14.4	9.3	20.8	83	4	4.8	1.3	11.9
	Grade 3	160	0	0.0	0.0	2.3	83	0	0.0	0.0	4.3
	Related	160	21	13.1	8.3	19.4	83	3	3.6	0.8	10.2
Shivering	Any	160	39	24.4	17.9	31.8	83	3	3.6	0.8	10.2
	Grade 3	160	4	2.5	0.7	6.3	83	0	0.0	0.0	4.3
	Related	160	39	24.4	17.9	31.8	83	2	2.4	0.3	8.4

N= number of subjects with the documented dose
n (%)= number (percentage) of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = Incidence of a particular symptom regardless of intensity and relationship
Grade 3 symptom = Symptoms which prevented normal activity
Related symptom = symptom considered by the investigator to have a causal relationship to vaccination

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibodies 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	FluLD-A	PRE	158	130	82.3	75.4	87.9	41.0	32.2	52.3
		PI(D21)	159	159	100	97.7	100	162.4	140.0	188.4
	Flu	PRE	82	67	81.7	71.6	89.4	43.0	29.7	62.1
		PI(D21)	82	79	96.3	89.7	99.2	127.2	97.2	166.5
A/Wisconsin	FluLD-A	PRE	158	154	97.5	93.6	99.3	83.2	71.3	97.1
		PI(D21)	159	159	100	97.7	100	191.7	171.7	214.0
	Flu	PRE	82	79	96.3	89.7	99.2	78.9	61.2	101.8
		PI(D21)	82	82	100	95.6	100	147.0	121.6	177.6
B/Malaysia	FluLD-A	PRE	158	158	100	97.7	100	107.3	89.3	128.8
		PI(D21)	159	159	100	97.7	100	334.2	296.0	377.4
	Flu	PRE	82	76	92.7	84.8	97.3	75.7	57.6	99.4
		PI(D21)	82	82	100	95.6	100	199.3	164.5	241.5

N = Number of subjects with available results
n (%)= number (percentage) of seropositive subjects (HI titre ≥ 1:10)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination at Day 0
PI (D21) = Post-vaccination at Day 21

Secondary Outcome Variable(s): SCF for HI antibody titre at post-vaccination time point (ATP Cohort for immunogenicity)

				SCF		
					95% CI	
Vaccine strain	**Group**	**Timing**	**N**	**Value**	**LL**	**UL**
A/Solomon	FluLD-A	PI(D21)	158	3.9	3.3	4.8
	Flu	PI(D21)	82	3.0	2.3	3.8
A/Wisconsin	FluLD-A	PI(D21)	158	2.3	2.1	2.6
	Flu	PI(D21)	82	1.9	1.6	2.2
B/Malaysia	FluLD-A	PI(D21)	158	3.1	2.7	3.6
	Flu	PI(D21)	82	2.6	2.2	3.2

SCF at Day 21 defined as the fold increase in serum HI antibody GMT on Day 21 compared to Day 0.
N = Number of subjects with pre- and post-vaccination results available
PI (D21) = Post-vaccination at Day 21
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

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

				SCR			
						95% CI	
Vaccine strain	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
A/Solomon	FluLD-A	PI(D21)	158	73	46.2	38.2	54.3
	Flu	PI(D21)	82	30	36.6	26.2	48.0
A/Wisconsin	FluLD-A	PI(D21)	158	40	25.3	18.7	32.8
	Flu	PI(D21)	82	13	15.9	8.7	25.6
B/Malaysia	FluLD-A	PI(D21)	158	61	38.6	31.0	46.7
	Flu	PI(D21)	82	23	28.0	18.7	39.1

SCR defined as:
For initially seronegative subjects, antibody titre ≥ 1:40 after vaccination
For initially seropositive subjects, antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre
N = Number of subjects with pre- and post-vaccination results available
n (%) = number (percentage) of seroconverted subjects
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

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

				SPR			
						95% CI	
Vaccine strain	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
A/Solomon	FluLD-A	PRE	158	87	55.1	47.0	63.0
		PI(D21)	159	155	97.5	93.7	99.3
	Flu	PRE	82	45	54.9	43.5	65.9
		PI(D21)	82	75	91.5	83.2	96.5
A/Wisconsin	FluLD-A	PRE	158	139	88.0	81.9	92.6
		PI(D21)	159	159	100	97.7	100
	Flu	PRE	82	69	84.1	74.4	91.3
		PI(D21)	82	80	97.6	91.5	99.7
B/Malaysia	FluLD-A	PRE	158	133	84.2	77.5	89.5
		PI(D21)	159	159	100	97.7	100
	Flu	PRE	82	67	81.7	71.6	89.4
		PI(D21)	82	82	100	95.6	100

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

Safety results: Number (%) of subjects with unsolicited adverse events during a 30-day follow-up period (Days 0-29) after vaccination (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Days 0-29 following vaccination)	**FluLD-A Group N = 160**	**Flu Group N = 83**
Subjects with any AE(s), n (%)	69 (43.1)	31 (37.3)
Subjects with grade 3 AE(s), n (%)	16 (10.0)	10 (12.0)

Subjects with related AE(s), n (%)	35 (21.9)	8 (9.6)
Nasopharyngitis	15 (9.4)	12 (14.5)
Headache	8 (5.0)	3 (3.6)
Diarrhoea	9 (5.6)	1 (1.2)
Gastroenteritis	4 (2.5)	2 (2.4)
Pharyngolaryngeal pain	5 (3.1)	1 (1.2)
Upper respiratory tract infection	3 (1.9)	3 (3.6)
Abdominal pain upper	4 (2.5)	1 (1.2)
Feeling hot	4 (2.5)	1 (1.2)
Lymphadenopathy	5 (3.1)	-
Musculoskeletal stiffness	4 (2.5)	-
Pharyngitis	3 (1.9)	-
Influenza like illness	-	3 (3.6)
Abdominal pain	-	1 (1.2)
Arthritis	-	1 (1.2)
Cerebrovascular accident	-	1 (1.2)
Circadian rhythm sleep disorder	-	1 (1.2)
Cough	-	1 (1.2)
Fatigue	-	1 (1.2)
Injection site reaction	-	1 (1.2)
Musculoskeletal pain	-	1 (1.2)
Palpitations	-	1 (1.2)
Procedural pain	-	1 (1.2)
Sinusitis	-	1 (1.2)

Counting rule applied: As there were more than 30 subjects per treatment group and ≤ 3 groups, only the 10 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 10 most frequent events for that group
Grade 3 AE: AE that prevented normal activity
Related AE: AE considered by the investigator to be causally related to the study vaccination

Safety results: Number (%) of subjects with serious adverse events during the entire study period (Total Vaccinated cohort)

All SAEs	**FluLD-A Group N = 160**	**Flu Group N = 83**
Subjects with any SAE(s), n (%) [n assessed by the investigators as related]	0 (0.0) [0]	1 (1.2) [0]
Cerebrovascular accident	0 (0.0) [0]	1 (1.2) [0]
Fatal SAEs	**FluLD-A Group N = 160**	**Flu Group N = 83**
Subjects with fatal SAE(s), n (%) [n assessed by the investigators as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: Across groups, pain was the most frequently reported solicited local symptom; headache and fatigue were the most frequently reported solicited general symptoms in the Flu and the FluLD-A groups, respectively. Unsolicited adverse events were reported by 69 (43.1%) and 31 (37.3%) subjects in the FluLD-A and in Flu groups, respectively. One non-fatal SAE was reported in the Flu Group during the study period and was considered by the investigator as not related to the vaccination.

Date updated: 08-September-2014