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.: 114292 (Fluarix-068)

Title: A Phase III study for evaluation of immunogenicity and reactogenicity of *Fluarix*™ / *Influsplit SSW*® 2010/2011 in people aged 18 years or above
Fluarix™/*Influsplit SSW*® 2010/2011 (Flu): GlaxoSmithKline (GSK) Biologicals' trivalent inactivated split virion influenza vaccine for influenza season 2010/2011

Rationale: The aim of this study was to assess the immunogenicity and safety of Flu vaccine containing the influenza strains recommended for the 2010-2011 season.

Phase: III

Study Period: 17 June 2010 to 10 July 2010

Study Design: Open, non-randomized, uncontrolled, multicentre study with two parallel age groups

Centers: 6 centers in Germany.

Indication: Immunization against influenza of healthy adults.

Treatment: The study groups were as follows:

- Flu Adult Group: Subjects aged 18 to 60 years received one dose of Flu vaccine at Day 0.
- Flu Elderly Group: Subjects aged over 60 years received one dose of Flu vaccine at Day 0.

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

Objectives:
To evaluate the humoral response (anti-hemagglutinin [anti-HA] antibody tested by hemagglutination inhibition [HI]) against each vaccine strain in adults aged 18 years or above, 21 days after vaccination with Flu vaccine.

Primary Outcome/Efficacy Variable:
Immunogenicity
Observed variables:

- Evaluation of the humoral immune response in terms of anti-HA antibodies against each of the three vaccine influenza strains

Derived variables:
The following parameters were calculated with 95% confidence intervals (CI):
At Days 0 and 21

- Geometric mean titers (GMTs) of anti-HA antibody titers.
- Seroprotection rates (SPR-defined as percentage of vaccines with serum HI titer ≥ 1:40 usually accepted as indicating protection).

At Day 21

- Seroconversion rates (SCR-defined as the percentage of vaccinees with either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least 4-fold increase in post-vaccination titer).
- Seroconversion factors (SCF-defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0).
- Seroprotection power (SPP-defined as the percentage of subjects who have a pre-vaccination titer < 1:40 and a post-vaccination titer ≥ 1:40).

Secondary Outcome/Efficacy Variable(s):
Safety

- Percentage, intensity and relationship to vaccination of solicited local and general signs and symptoms during a 4-day follow-up period (i.e. day of vaccination and 3 subsequent days) after vaccination
- Percentage, intensity and relationship to vaccination of unsolicited signs and symptoms during 21-days following the vaccination (i.e. day of vaccination and 20 subsequent days)
- Percentage, intensity and relationship to vaccination of serious adverse events (SAEs) during the entire study period

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 protocol procedures and with no elimination criteria assigned during the study) for whom immunogenicity data

were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination.

Analysis of Immunogenicity:
The analysis was performed on the ATP cohort for immunogenicity.
For each treatment group, the following parameters were calculated using 95% CI:

- Seropositivity and GMTs of HI antibody titers at Days 0 and 21.
- SCR at Day 21
- SCF at Day 21
- SPR at Days 0 and 21
- SPP at Day 21

Analysis of Safety
The analysis of safety was performed on the Total Vaccinated Cohort.
The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 0-Day 3) follow-up period after vaccination was tabulated with exact 95% CI. The same tabulation was performed for grade 3 symptoms and general symptoms assessed by the investigator as related to the vaccination. The percentage of subjects with at least one report of unsolicited adverse events (AEs) classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and reported up to 21days (Day 0-Day 20) after vaccination was tabulated. The same tabulation was performed for grade 3 AEs and for AEs assessed by the investigators as having a causal relationship to vaccination. SAEs recorded during the entire study period were also tabulated.

Study Population: Healthy subjects (male or female) or with well-controlled chronic diseases as established by medical history and clinical examination before entering the study, aged 18 years or above at the time of the vaccination, were enrolled in the study. If the subject was female and of childbearing potential, she had to be abstinent or to have used contraceptive precautions for 30 days prior to vaccination; she had to have a negative pregnancy test at study entry and had to agree to continue contraceptive precautions for 2 months after completion of the vaccination series. Subjects with administration of an influenza vaccine within 6 months preceding the study start were not included in the study. Written informed consent was obtained from the subject prior to study entry.

Number of subjects	**Flu Adult Group**	**Flu Elderly Group**
Planned, N	60	60
Randomized, N (Total Vaccinated Cohort)	60	54
Completed, n (%)	58 (96.7)	54 (100)
Total Number Subjects Withdrawn, n (%)	2 (3.3)	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 (%)	2 (3.3)	0 (0.0)
Demographics	**Flu Adult Group**	**Flu Elderly Group**
N (Total Vaccinated Cohort)	60	54
Females: Males	32:28	26:28
Mean Age, years (SD)	37.1 (13.10)	68.6 (5.08)
White - Caucasian / European heritage, n (%)	60 (100)	54 (100)

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

				≥ 1:10				**GMT**		
						95% CI			**95% CI**	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
A/California (H1N1)	Flu Adult	PRE	55	20	36.4	23.8	50.4	10.2	7.7	13.6
		PI(D21)	55	55	100	93.5	100	314.1	237.5	415.4
	Flu Elderly	PRE	53	17	32.1	19.9	46.3	8.7	6.6	11.4
		PI(D21)	53	49	92.5	81.8	97.9	89.4	60.1	133.0
A/Victoria (H3N2)	Flu Adult	PRE	55	38	69.1	55.2	80.9	15.2	11.6	20.0
		PI(D21)	55	55	100	93.5	100	89.6	70.8	113.3
	Flu Elderly	PRE	53	29	54.7	40.4	68.4	10.5	8.3	13.3
		PI(D21)	53	52	98.1	89.9	100	75.4	56.8	100.2

B/Brisbane	Flu Adult	PRE	55	50	90.9	80.0	97.0	36.3	26.4	50.1
		PI(D21)	55	55	100	93.5	100	271.6	213.3	345.9
	Flu Elderly	PRE	53	49	92.5	81.8	97.9	42.1	30.6	57.9
		PI(D21)	53	53	100	93.3	100	132.3	99.0	176.9

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

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

				SPR			
						95% CI	
Antibody against	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
A/California (H1N1)	Flu Adult	PRE	55	9	16.4	7.8	28.8
		PI(D21)	55	54	98.2	90.3	100
	Flu Elderly	PRE	53	4	7.5	2.1	18.2
		PI(D21)	53	41	77.4	63.8	87.7
A/Victoria (H3N2)	Flu Adult	PRE	55	14	25.5	14.7	39.0
		PI(D21)	55	48	87.3	75.5	94.7
	Flu Elderly	PRE	53	7	13.2	5.5	25.3
		PI(D21)	53	45	84.9	72.4	93.3
B/Brisbane	Flu Adult	PRE	55	29	52.7	38.8	66.3
		PI(D21)	55	55	100	93.5	100
	Flu Elderly	PRE	53	29	54.7	40.4	68.4
		PI(D21)	53	47	88.7	77.0	95.7

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
PI(D21) = Post-vaccination (Day 21)
PRE = Pre-vaccination (Day 0)

Primary Efficacy Results: SCR for HI antibody titer at Day 21 (ATP cohort for immunogenicity)

			SCR			
					95% CI	
Antibody against	**Group**	**N**	**n**	**%**	**LL**	**UL**
A/California (H1N1)	Flu Adult	55	50	90.9	80.0	97.0
	Flu Elderly	53	35	66.0	51.7	78.5
A/Victoria (H3N2)	Flu Adult	55	35	63.6	49.6	76.2
	Flu Elderly	53	36	67.9	53.7	80.1
B/Brisbane	Flu Adult	55	33	60.0	45.9	73.0
	Flu Elderly	53	18	34.0	21.5	48.3

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

Primary Efficacy Results: SCF for HI antibody titer at Day 21 (ATP cohort for immunogenicity)

			SCF		
				95% CI	
Antibody against	**Group**	**N**	**Value**	**LL**	**UL**
A/California (H1N1)	Flu Adult	55	30.8	21.8	43.5
	Flu Elderly	53	10.3	7.0	15.2
A/Victoria (H3N2)	Flu Adult	55	5.9	4.5	7.8
	Flu Elderly	53	7.2	5.1	10.1

B/Brisbane	Flu Adult	55	7.5	5.1	11.0
	Flu Elderly	53	3.1	2.2	4.4

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

Primary Efficacy Results: SPP for HI antibody titer at Day 21 (ATP cohort for immunogenicity)

			SPP			
					95% CI	
Antibody against	**Group**	**N**	**n**	**%**	**LL**	**UL**
A/California (H1N1)	Flu Adult	46	45	97.8	88.5	99.9
	Flu Elderly	49	37	75.5	61.1	86.7
A/Victoria (H3N2)	Flu Adult	41	34	82.9	67.9	92.8
	Flu Elderly	46	38	82.6	68.6	92.2
B/Brisbane	Flu Adult	26	26	100	86.8	100
	Flu Elderly	24	18	75.0	53.3	90.2

N = number of subjects unprotected at pre-vaccination and with available results
n/% = number/percentage of subjects unprotected at PRE and protected at day 21
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

Symptom	**Intensity**	**Flu Adult Group**					**Flu Elderly Group**				
					95% CI					**95% CI**	
		N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Ecchymosis	Any	59	3	5.1	1.1	14.1	54	0	0.0	0.0	6.6
	> 50 mm	59	1	1.7	0.0	9.1	54	0	0.0	0.0	6.6
Induration	Any	59	9	15.3	7.2	27.0	54	9	16.7	7.9	29.3
	> 50 mm	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
Pain	Any	59	40	67.8	54.4	79.4	54	17	31.5	19.5	45.6
	Grade 3	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
Redness	Any	59	10	16.9	8.4	29.0	54	15	27.8	16.5	41.6
	> 50 mm	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
Swelling	Any	59	8	13.6	6.0	25.0	54	7	13.0	5.4	24.9
	> 50 mm	59	0	0.0	0.0	6.1	54	1	1.9	0.0	9.9

N= number of subjects with at least one 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 = incidence of a local symptom regardless of intensity
Grade 3 pain = pain that prevented normal activity

Secondary Outcome Variable(s): Incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

Symptom	**Intensity/ Relationship**	**Flu Adult Group**					**Flu Elderly Group**				
					95% CI					**95% CI**	
		N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Arthralgia	Any	59	6	10.2	3.8	20.8	54	4	7.4	2.1	17.9
	Grade 3	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
	Related	59	4	6.8	1.9	16.5	54	3	5.6	1.2	15.4
Fatigue	Any	59	13	22.0	12.3	34.7	54	8	14.8	6.6	27.1
	Grade 3	59	1	1.7	0.0	9.1	54	0	0.0	0.0	6.6
	Related	59	7	11.9	4.9	22.9	54	5	9.3	3.1	20.3
Headache	Any	59	11	18.6	9.7	30.9	54	9	16.7	7.9	29.3
	Grade 3	59	0	0.0	0.0	6.1	54	2	3.7	0.5	12.7
	Related	59	3	5.1	1.1	14.1	54	7	13.0	5.4	24.9
Myalgia	Any	59	11	18.6	9.7	30.9	54	9	16.7	7.9	29.3
	Grade 3	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
	Related	59	9	15.3	7.2	27.0	54	5	9.3	3.1	20.3

Shivering	Any	59	5	8.5	2.8	18.7	54	3	5.6	1.2	15.4
	Grade 3	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
	Related	59	4	6.8	1.9	16.5	54	2	3.7	0.5	12.7
Sweating	Any	59	3	5.1	1.1	14.1	54	3	5.6	1.2	15.4
	Grade 3	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
	Related	59	0	0.0	0.0	6.1	54	3	5.6	1.2	15.4
Fever (Axillary)	≥37.5°C	59	1	1.7	0.0	9.1	54	0	0.0	0.0	6.6
	> 39.0°C	59	0	0.0	0.0	6.1	54	0	0.0	0.0	6.6
	Related	59	1	1.7	0.0	9.1	54	0	0.0	0.0	6.6

N= number of subjects with at least one 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 = incidence of a general symptom regardless of grade or relationship to vaccination
Grade 3 arthralgia, fatigue, headache, myalgia, shivering and sweating = symptom that prevented normal activity
Related = symptom assessed by the investigator as causally related to the vaccination

Safety results: Number (%) of subjects with unsolicited AEs during 21-days following the vaccination (Total Vaccinated Cohort)

Most frequent adverse events - On-Therapy (occurring within Day 0-Day 20 following vaccination)	**Flu Adult Group N = 60**	**Flu Elderly Group N = 54**
Subjects with any AE(s), n (%)	12 (20.0)	6 (11.1)
Subjects with grade 3 AE(s), n (%)	2 (3.3)	0 (0.0)
Subjects with related AE(s), n (%)	2 (3.3)	1 (1.9)
Cough	3 (5.0)	1 (1.9)
Headache	2 (3.3)	-
Nasopharyngitis	1 (1.7)	1 (1.9)
Conjunctival irritation	1 (1.7)	-
Emotional disorder	1 (1.7)	-
Fatigue	-	1 (1.9)
Gastroenteritis	1 (1.7)	-
Gingivitis	-	1 (1.9)
Influenza like illness	-	1 (1.9)
Joint sprain	1 (1.7)	-
Myalgia	-	1 (1.9)
Oedema peripheral	-	1 (1.9)
Pain in extremity	1 (1.7)	-
Pyrexia	1 (1.7)	-
Rhinorrhoea	1 (1.7)	-
Skin hyperpigmentation	-	1 (1.9)
Vertigo	1 (1.7)	-

- : Adverse event absent
Grade 3 = an AE which prevented normal activities
Related = an AE assessed by the investigator as causally related to 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	**Flu Adult Group N = 60**	**Flu Elderly Group N = 54**
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**Flu Adult Group N = 60**	**Flu Elderly Group N = 54**
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:
Before vaccination GMTs for the three influenza strains, A/California (H1N1), A/Victoria (H3N2) and B/Brisbane, ranged from 10.2 to 36.3 in the Flu Adult Group and from 8.7 to 42.1 in the Flu Elderly Group. At Day 21 after vaccination the GMTs ranged from 89.6 to 314.1 in the Flu Adult Group and from 75.4 to 132.3 in the Flu Elderly Group.

In the Flu Adult Group, the SPR was at least 16.4% before vaccination and at least 87.3% at Day 21 after vaccination; the SCR, SCF and SPP were at least 60.0%, 5.9 and 82.9%, respectively, at Day 21 after vaccination.
In the Flu Elderly Group, the SPR was at least 7.5% before vaccination and at least 77.4% at Day 21 after vaccination; the SCR, SCF and SPP were at least 34.0%, 3.1 and 75.0%, respectively, at Day 21 after vaccination.
During 21-days following the vaccination, 12 (20%) subjects in the Flu Adult Group and 6 (11.1%) subjects in the Flu Elderly Group reported at least one unsolicited AE, 2 (3.3%) subjects in the Flu Adult Group and none in the Flu Elderly Group reported grade 3 unsolicited AEs, 2 (3.3%) subjects in the Flu Adult Group and 1 (1.9%) subject in the Flu Elderly Group reported unsolicited AEs assessed by the investigator as related to study vaccination. No SAEs (fatal or non-fatal) were reported during the study period.

Date updated: 03-September-2014