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.: 111631 (Fluarix-066 PRI)

Title: A Phase III study for evaluation of immunogenicity and reactogenicity of Fluarix™ / Influsplit SSW® 2008/2009 in people aged 18 years or above
Fluarix™ (Influsplit SSW®) 2008/2009: GlaxoSmithKline (GSK) Biologicals' inactivated influenza split vaccine (Flu)

Rationale: To evaluate immunogenicity and safety of the influenza split vaccine containing the strains recommended for the 2008-2009 season (Northern Hemisphere).

Phase: III

Study Period: 07 July 2008 to 30 July 2008.

Study Design: Open, non-randomized, multi-centric study with 2 parallel age groups.

Centers: Multi-centre (5 centers in Germany)

Indication: Seasonal vaccination against influenza virus in subjects 18 years or older.

Treatment: All subjects (Flu Group) received one dose of Flu vaccine. The study group was sub-divided into 2 age groups:

- Adult Group: subjects aged 18-60 years
- Elderly Group subjects aged >60 years

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

Objectives: To evaluate the humoral response (anti-hemagglutinin antibody tested by hemagglutination inhibition (HI)) against each vaccine strain in adults (18 to 60 years) and elderly (over 60 years), 21 days after vaccination with the influenza vaccine.

Primary Outcome/Efficacy Variable:

Observed variables:

- Evaluation of the humoral immune response in terms of HI antibodies against each of the 3 vaccine influenza strains.

Derived variables:

The following parameters were calculated with 95% confidence intervals:

At Days 0 and 21

- Geometric mean titers (GMTs) of HI antibodies
- Seroprotection rates (SPR)

At Day 21

- Seroconversion rates (SCR)
- Seroconversion factors (SCF)
- Seroprotection power (SPP)

SPR was defined as the percentage of vaccinees with a serum HI titer ≥ 1:40, which is usually accepted as indicating protection.
SCR was defined as the percentage of vaccinees who had either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and at least a 4-fold -increase in post-vaccination titer
SCF was defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.
SPP was defined as the percentage of subjects who had a pre-vaccination titer <1:40 and a post-vaccination titer ≥ 1:40.

Secondary Outcome/Efficacy Variable(s):

- Percentage, intensity, duration 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 local and general signs and symptoms during the 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:

Analyses were performed on the Total Vaccinated Cohort and on 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., who met all eligibility criteria, who complied

with the protocol procedures, with no elimination criteria assigned during the study) of the immunogenicity subset 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 the humoral immune response in terms of HI antibodies against each of the 3 vaccine influenza strains, the following parameters (with 95% confidence intervals) were calculated for each age group: GMTs of HI titers and SPR at Days 0 & 21, SCR, SCF and SPP at Day 21.

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 4-day (Day 0-3) solicited follow-up period was tabulated with exact 95% CI in each age group. 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 an unsolicited adverse events (AEs) classified by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and reported in the 21 days (Day 0-20) following vaccination was tabulated in each age-group. The same tabulation was performed for grade 3 unsolicited AEs and for unsolicited AEs with relationship to vaccination. Occurrence of SAEs during the entire study period was tabulated per age group according to MedDRA preferred term.

Study Population: Male or female aged 18 years or above at the time of enrolment, healthy or with well-controlled chronic diseases as established by medical history and clinical examination before entering into the study. If of childbearing potential, female subjects had practiced adequate contraception for 30 days prior to vaccination, had a negative pregnancy test and were to continue such precautions for 2 months after completion of the vaccination series. Written informed consent was obtained from the subject before study entry.

Number of Subjects:	**Adult Group**	**Elderly Group**
Planned, N	60	60
Randomized, N (Total Vaccinated Cohort)	61	59
Completed, n (%)	61 (100)	59 (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	**Adult Group**	**Elderly Group**
N, (Total Vaccinated Cohort)	61	59
Females: Males	36:25	34:25
Mean Age, years (SD)	39.1 (13.26)	68.8 (5.25)
White – Caucasian, n (%)	61 (100)	59 (100)

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

					≥ 10 1/DIL				**GMT**		
							95% CI			**95% CI**	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
A/ Brisbane	Flu	ADULT	PRE	61	36	59.0	45.7	71.4	13.6	10.1	18.2
			PI(D21)	61	61	100	94.1	100	165.5	119.2	229.7
		ELDERLY	PRE	59	35	59.3	45.7	71.9	11.6	9.1	14.9
			PI(D21)	59	58	98.3	90.9	100	68.2	48.4	96.3
A/Uruguay	Flu	ADULT	PRE	61	19	31.1	19.9	44.3	7.6	6.2	9.3
			PI(D21)	61	57	93.4	84.1	98.2	90.7	60.2	136.5
		ELDERLY	PRE	59	23	39.0	26.5	52.6	9.7	7.3	12.9
			PI(D21)	59	58	98.3	90.9	100	120.6	76.1	191.0
B/ Brisbane	Flu	ADULT	PRE	61	60	98.4	91.2	100	102.1	74.4	140.0
			PI(D21)	61	61	100	94.1	100	785.3	634.0	972.7
		ELDERLY	PRE	59	58	98.3	90.9	100	108.0	76.9	151.8
			PI(D21)	59	59	100	93.9	100	524.0	404.9	678.2

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

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

					SPR			
							95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
A/ Brisbane	Flu	ADULT	PRE	61	15	24.6	14.5	37.3
			PI(D21)	61	55	90.2	79.8	96.3
		ELDERLY	PRE	59	9	15.3	7.2	27.0
			PI(D21)	59	40	67.8	54.4	79.4
A/Uruguay	Flu	ADULT	PRE	61	5	8.2	2.7	18.1
			PI(D21)	61	47	77.0	64.5	86.8
		ELDERLY	PRE	59	8	13.6	6.0	25.0
			PI(D21)	59	43	72.9	59.7	83.6
B/ Brisbane	Flu	ADULT	PRE	61	48	78.7	66.3	88.1
			PI(D21)	61	61	100	94.1	100
		ELDERLY	PRE	59	50	84.7	73.0	92.8
			PI(D21)	59	59	100	93.9	100

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

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

					SCR			
							95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
A/ Brisbane	Flu	ADULT	PI(D21)	61	44	72.1	59.2	82.9
		ELDERLY	PI(D21)	59	30	50.8	37.5	64.1
A/Uruguay	Flu	ADULT	PI(D21)	61	44	72.1	59.2	82.9
		ELDERLY	PI(D21)	59	39	66.1	52.6	77.9
B/ Brisbane	Flu	ADULT	PI(D21)	61	39	63.9	50.6	75.8
		ELDERLY	PI(D21)	59	30	50.8	37.5	64.1

Seroconversion defined as:
For initially seronegative subjects, antibody titer ≥ 40 1/DIL 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
PI(D21) = Post-vaccination (Day 21)

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

					SCF		
						95% CI	
Vaccine strain	**Group**	**Sub-group**	**Timing**	**N**	**Value**	**LL**	**UL**
A/ Brisbane (1/DIL)	Flu	ADULT	PI(D21)	61	12.2	8.1	18.4
		ELDERLY	PI(D21)	59	5.9	4.0	8.5
A/Uruguay (1/DIL)	Flu	ADULT	PI(D21)	61	12.0	8.1	17.8
		ELDERLY	PI(D21)	59	12.4	8.2	18.7
B/ Brisbane (1/DIL)	Flu	ADULT	PI(D21)	61	7.7	5.4	10.9
		ELDERLY	PI(D21)	59	4.9	3.6	6.6

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

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

Vaccine strain	Group	N	n	%	LL	UL
A/ Brisbane	Flu/ADULT	46	40	87.0	73.7	95.1
A/ Brisbane	Flu/ELDERLY	50	32	64.0	49.2	77.1
A/Uruguay	Flu/ADULT	56	42	75.0	61.6	85.6
A/Uruguay	Flu/ELDERLY	51	35	68.6	54.1	80.9
B/ Brisbane	Flu/ADULT	13	13	100	75.3	100
B/ Brisbane	Flu/ELDERLY	9	9	100	66.4	100

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): Number (percentage) of subjects with solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)

Symptom	Type	Adult Group					Elderly Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Ecchymosis	>0 mm	61	3	4.9	1.0	13.7	59	0	0.0	0.0	6.1
	>50 mm	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
Induration	>0 mm	61	19	31.1	19.9	44.3	59	7	11.9	4.9	22.9
	>50 mm	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
Pain	Any	61	36	59.0	45.7	71.4	59	22	37.3	25.0	50.9
	Grade 3	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
Redness	>0 mm	61	24	39.3	27.1	52.7	59	11	18.6	9.7	30.9
	>50 mm	61	6	9.8	3.7	20.2	59	2	3.4	0.4	11.7
Swelling	>0 mm	61	16	26.2	15.8	39.1	59	6	10.2	3.8	20.8
	>50 mm	61	1	1.6	0.0	8.8	59	0	0.0	0.0	6.1

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 = any solicited local symptom irrespective of intensity grade
Grade 3 Pain = pain that prevented normal activity

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

Symptom	Type	Adult Group					Elderly Group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Arthralgia	Any	61	6	9.8	3.7	20.2	59	2	3.4	0.4	11.7
	Grade 3	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
	Related	61	2	3.3	0.4	11.3	59	0	0.0	0.0	6.1
Fatigue	Any	61	10	16.4	8.2	28.1	59	8	13.6	6.0	25.0
	Grade 3	61	0	0.0	0.0	5.9	59	1	1.7	0.0	9.1
	Related	61	5	8.2	2.7	18.1	59	5	8.5	2.8	18.7
Headache	Any	61	8	13.1	5.8	24.2	59	8	13.6	6.0	25.0
	Grade 3	61	0	0.0	0.0	5.9	59	1	1.7	0.0	9.1
	Related	61	2	3.3	0.4	11.3	59	4	6.8	1.9	16.5
Myalgia	Any	61	15	24.6	14.5	37.3	59	7	11.9	4.9	22.9
	Grade 3	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
	Related	61	10	16.4	8.2	28.1	59	4	6.8	1.9	16.5
Shivering	Any	61	4	6.6	1.8	15.9	59	5	8.5	2.8	18.7
	Grade 3	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
	Related	61	1	1.6	0.0	8.8	59	4	6.8	1.9	16.5
Sweating	Any	61	5	8.2	2.7	18.1	59	4	6.8	1.9	16.5
	Grade 3	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
	Related	61	2	3.3	0.4	11.3	59	2	3.4	0.4	11.7
Fever (Axillary)	≥ 37.5 °C	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1
	≥39°C	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1

	Related	61	0	0.0	0.0	5.9	59	0	0.0	0.0	6.1

N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
Any = any solicited general symptom irrespective of intensity grade or relationship to vaccination
Grade 3 Symptom = symptom that prevented normal activity
Related = symptoms considered by the investigator to have a causal relationship to vaccination
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

N = number of documented doses
Ns = total number of reports for a given symptom
n = number of symptoms that were ongoing after the follow-up period
Time to resolution : number of days beyond the end of the follow-up period
q1 = 25% quartile, q3 = 75% quartile

Safety results: Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort)

Most frequent adverse events–On-Therapy (occurring within Day 0-20 following vaccination)	**Adult Group N = 61**	**Elderly Group N = 59**
Subjects with any AE(s), n (%)	7 (11.5)	6 (10.2)
Subjects with Grade 3 AE(s) *, n (%)	1 (1.6)	0 (0.0)
Subjects with related AE(s) **, n (%)	4 (6.6)	2 (3.4)
Injection site pruritus	3 (4.9)	1 (1.7)
Injection site warmth	1 (1.6)	1 (1.7)
Pharyngolaryngeal pain	1 (1.6)	1 (1.7)
Vertigo	2 (3.3)	-
Abdominal pain upper	1 (1.6)	-
Asthenia	-	1 (1.7)
Back pain	-	1 (1.7)
Chest pain	1 (1.6)	-
Hyperhidrosis	-	1 (1.7)
Injection site hematoma	1 (1.6)	-
Rhinitis	-	1 (1.7)

- = Adverse event absent
*Severe 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 (Total Vaccinated Cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs	**Adult Group N = 61**	**Elderly Group N = 59**
Subjects with any SAE(s), n (%) [n related]	1 (1.6) [0]	0 (0.0) [0]
Chest pain	1* (1.6) [0]	0 (0.0) [0]
Fatal SAEs	**Adult Group N = 61**	**Elderly Group N = 59**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]

*Intensity = Grade 2 : SAE which was sufficiently discomforting to interfere with normal everyday activities

Conclusion: At Day 0, GMT values for HI titers were 13.6, 7.6 & 102.1 in the Adult Group and 11.6, 9.7 & 108.0 in the Elderly Group for A/Brisbane, A/Uruguay and B/Brisbane viral strains, respectively. At Day 21 after vaccination, GMT values for HI titers were 165.5, 90.7 & 785.3 in the Adult Group and 68.2, 120.6 & 524.0 in the Elderly Group for A/Brisbane, A/Uruguay and B/Brisbane viral strains, respectively. At Day 0, at least 24.6%, 8.2% and 78.7% subjects in the Adult Group and 15.3%, 13.6% and 84.7% subjects in the Elderly Group had seroprotection rates (HI titers $\geq$ 1:40) for A/Brisbane, A/Uruguay and B/Brisbane viral strains, respectively. At Day 21 after vaccination, at least 90.2%, 77.0% & 100% of subjects in the Adult Group and 67.8%, 72.9% & 100% of subjects in Elderly Group had seroprotection rates (HI titers $\geq$ 1:40) for A/Brisbane, A/Uruguay and B/Brisbane viral strains, respectively.
During the 21-day follow-up period, unsolicited AEs were reported by 7 (11.5%) and 6 (10.2%) subjects in the Adult Group and Elderly Group, respectively; 1 (1.6%) subject reported at least one Grade 3 unsolicited AE in the Adult Group; 4 (6.6%) and 2 (3.4%) subjects reported at least one AE considered by the investigators to be causally related to the study vaccination, in the Adult and Elderly age groups, respectively. One SAE was reported in a subject in the Adult Group, it was not considered by the investigator to be related to study vaccination.

Date updated: 03-November-2014