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.: 110221 (Fluarix-064 PRI)

Title: A Phase III, open, non-randomized, multi-centric, single dose study to assess immunogenicity and safety of Fluarix™ (Influsplit SSW®) 2007/2008 injected intramuscularly in young adults (18 to 60 years) and in elderly (over 60 years).
Fluarix™ (Influsplit SSW®) 2007/2008: GSK Biologicals' inactivated influenza split vaccine

Rationale: To evaluate immunogenicity and safety of the influenza split vaccine containing the strains recommended for the 2007-2008 season (Northern Hemisphere).

Phase: III

Study Period: 19 June 2007 to 11 July 2007

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

Centers: Multicentre (3 centers in Germany)

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

Treatment: All subjects received one dose of the influenza vaccine. The study group was sub-divided into 2 age groups:

- Subjects aged 18-60 years
- 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) against each vaccine strain in adults aged 18 years or above 21 days after vaccination with the study vaccine.

Primary Outcome/Efficacy Variable:
Evaluation of the humoral immune response in terms of anti-hemagglutinin (anti-HA) antibodies against each of the three vaccine influenza strains. The following parameters were calculated with 95% confidence intervals:

- Geometric mean titers (GMTs) of anti-HA antibody titers at Days 0 and 21.
- Seroconversion Rates (SCR) at Day 21.
- Seroconversion Factors (SCF) at Day 21.
- Seroprotection Rates (SPR) at Days 0 and 21.
- Seroprotection power (SPP) at Day 21.

Seroconversion Rate (SCR) was 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 fourfold increase in post-vaccination titer.
Seroconversion Factor (SCF) was defined as the fold increase in serum Hemagglutination Inhibition (HI) GMTs post-vaccination compared to Day 0.
Seroprotection Rate (SPR) was defined as the percentage of vaccinees with a serum HI titer ≥1:40 that usually is accepted as indicating protection.
Seroprotection Power (SPP) was defined as the percentage of subjects who have a prevaccination 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 21-day 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 subjects with study vaccine administered. Thus, the Total Vaccinated cohort for analysis of safety included all subjects with vaccine administration documented.
- 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 for whom immunogenicity data were available. This included all 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 anti-HA antibodies against each of the 3 vaccine influenza strains, the following parameters were calculated with 95% confidence intervals (CIs) for each age group: Geometric mean titers (GMTs) of anti-HA antibody titers at Days 0 and 21, Seroconversion Rates at Day 21, Seroconversion Factors at Day 21, Seroprotection rates at Days 0 and 21 and Seroprotection power at Day 21.
Analysis of Safety
The analysis was performed on the Total Vaccinated Cohort.
The percentage of subjects with at least one solicited local or general symptom during the 4-Day (Day 0-3) follow-up period was tabulated per age-group with exact 95% CI after vaccination. The same tabulation was done for grade 3 symptoms and for solicited general symptoms related to vaccination.
The percentage of subjects with at least one report of an unsolicited adverse event (AE) classified by the Medical Dictionary for Regulatory Activities (MedDRA) during the 21-Day (Day 0-20) follow-up period was tabulated in each age-group. The same tabulation was done for grade 3 AEs and AEs related to vaccination. SAEs were also tabulated per age group according to MedDRA preferred terms.

Study Population: Male or female subjects 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 had agreed to continue such precautions for the duration of the study. Written informed consent was obtained from the subject before study entry.

Number of Subjects:	**18-60 years Group**	**>60 years Group**
Planned, N	60	60
Randomized, N (Total Vaccinated Cohort)	63	53
Completed, n (%)	63 (100)	52 (98.1)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	1 (1.9)
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)	1 (1.9)
Demographics	**18-60 years Group**	**>60 years Group**
N, (Total Vaccinated Cohort)	63	53
Females: Males	38:25	29:24
Mean Age, years (SD)	36.6 (12.75)	68.6 (6.76)
White – Caucasian, n (%)	63 (100)	53 (100)

Primary Efficacy Results:
GMTs for HI antibodies (ATP Cohort for immunogenicity)

Antibody	**Age Group**	**Timing**	**N**	**GMT**		
				value	**95% CI**	
					LL	**UL**
A/Solomon islands	**18-60 years**	PRE	63	16.1	10.9	23.8
		PI(D21)	63	152.3	103.8	223.5
	>60 years	PRE	51	8.7	6.7	11.3
		PI(D21)	51	71.3	47.4	107.2
A/Wisconsin	**18-60 years**	PRE	63	18.3	13.1	25.5
		PI(D21)	63	143.4	112.4	182.8
	>60 years	PRE	51	11.7	8.5	16.0
		PI(D21)	51	152.6	95.5	243.8
B/Malaysia	**18-60 years**	PRE	63	21.1	15.6	28.6
		PI(D21)	63	236.3	177.2	315.1
	>60 years	PRE	51	30.2	21.4	42.6
		PI(D21)	51	248.9	173.3	357.5

N = Number of subjects with available results
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination
PI(D21) = 21 days after vaccination

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

Vaccine strain	Group	N	SCF		
			value	95%CI	
				LL	UL
A/Solomon islands	**18-60 years**	63	9.4	6.0	14.9
	>60 years	51	8.2	5.4	12.3
A/Wisconsin	**18-60 years**	63	7.8	5.4	11.3
	>60 years	51	13.1	8.0	21.3
B/Malaysia	**18-60 years**	63	11.2	7.9	15.8
	>60 years	51	8.2	5.1	13.3

N = Number of subjects with available results
SCF = Seroconversion Factor or geometric mean ratio
95% CI = 95% confidence interval
LL = Lower Limit, UL = Upper Limit

Primary Efficacy Results:
Seroprotection rates (SPR) for HI antibody titer at Days 0 and 21 (ATP Cohort for immunogenicity)

Vaccine strain	Group	Timing	N	SPR			
				n	%	95%CI	
						LL	UL
A/Solomon islands	**18-60 years**	PRE	63	17	27.0	16.6	39.7
		PI(D21)	63	57	90.5	80.4	96.4
	>60 years	PRE	51	6	11.8	4.4	23.9
		PI(D21)	51	36	70.6	56.2	82.5
A/Wisconsin	**18-60 years**	PRE	63	21	33.3	22.0	46.3
		PI(D21)	63	61	96.8	89.0	99.6
	>60 years	PRE	51	13	25.5	14.3	39.6
		PI(D21)	51	40	78.4	64.7	88.7
B/Malaysia	**18-60 years**	PRE	63	21	33.3	22.0	46.3
		PI(D21)	63	58	92.1	82.4	97.4
	>60 years	PRE	51	24	47.1	32.9	61.5
		PI(D21)	51	49	96.1	86.5	99.5

PRE = Pre-vaccination; PI(D21)= 21 days after vaccination
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

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

Vaccine Strain	Group	N	SCR			
			n	%	95%CI	
					LL	UL
A/Solomon islands	**18-60 years**	63	40	63.5	50.4	75.3
	>60 years	51	30	58.8	44.2	72.4
A/Wisconsin	**18-60 years**	63	42	66.7	53.7	78.0
	>60 years	51	35	68.6	54.1	80.9
B/Malaysia	**18-60 years**	63	46	73.0	60.3	83.4
	>60 years	51	31	60.8	46.1	74.2

N = number of subjects with available results
n (%) = number (percentage) who seroconverted at day 21
95% CI = 95% confidence interval
LL = Lower Limit, UL = Upper Limit

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

Vaccine Strain	Group	N	SPP			
			n	%	95%CI	
					LL	UL

A/Solomon islands	**18-60 years**	46	40	87.0	73.7	95.1
	>60 years	45	30	66.7	51.0	80.0
A/Wisconsin	**18-60 years**	42	40	95.2	83.8	99.4
	>60 years	38	27	71.1	54.1	84.6
B/Malaysia	**18-60 years**	42	37	88.1	74.4	96.0
	>60 years	27	25	92.6	75.7	99.1

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 (Day 0-3) post-vaccination period (Total vaccinated Cohort)

Symptom	**Intensity**	**18-60 years Group**					**>60 years Group**				
		N	**n**	**%**	**95 % CI**		**N**	**n**	**%**	**95 % CI**	
					LL	**UL**				**LL**	**UL**
Ecchymosis	Any	63	1	1.6	0.0	8.5	52	0	0.0	0.0	6.8
	> 50 mm	63	0	0.0	0.0	5.7	52	0	0.0	0.0	6.8
Induration	Any	63	4	6.3	1.8	15.5	52	4	7.7	2.1	18.5
	> 50 mm	63	0	0.0	0.0	5.7	52	0	0.0	0.0	6.8
Pain	Any	63	42	66.7	53.7	78.0	52	13	25.0	14.0	38.9
	Grade 3	63	1	1.6	0.0	8.5	52	1	1.9	0.0	10.3
Redness	Any	63	9	14.3	6.7	25.4	52	7	13.5	5.6	25.8
	> 50 mm	63	1	1.6	0.0	8.5	52	0	0.0	0.0	6.8
Swelling	Any	63	7	11.1	4.6	21.6	52	4	7.7	2.1	18.5
	> 50 mm	63	0	0.0	0.0	5.7	52	0	0.0	0.0	6.8

N= number of subjects with the documented dose
n (%) = number (percentage) of subjects reporting the symptom at least once
Any = any solicited local symptom irrespective of intensity grade
Grade 3 pain = symptom that prevented normal activity
95%CI= Exact 95% confidence interval
LL = lower limit, UL = upper limit

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

Symptom	**Intensity/ relationship**	**18-60 years Group**					**>60 years Group**				
		N	**n**	**%**	**95 % CI**		**N**	**n**	**%**	**95 % CI**	
					LL	**UL**				**LL**	**UL**
Arthralgia	Any	63	5	7.9	2.6	17.6	51	5	9.8	3.3	21.4
	Grade 3	63	0	0.0	0.0	5.7	51	0	0.0	0.0	7.0
	Related	63	5	7.9	2.6	17.6	51	4	7.8	2.2	18.9
Fatigue	Any	63	14	22.2	12.7	34.5	51	6	11.8	4.4	23.9
	Grade 3	63	0	0.0	0.0	5.7	51	0	0.0	0.0	7.0
	Related	63	9	14.3	6.7	25.4	51	5	9.8	3.3	21.4
Fever (axillary)	≥ 37.5 °C	63	1	1.6	0.0	8.5	51	0	0.0	0.0	7.0
	> 39 °C	63	0	0.0	0.0	5.7	51	0	0.0	0.0	7.0
	Related	63	1	1.6	0.0	8.5	51	0	0.0	0.0	7.0
Headache	Any	63	8	12.7	5.6	23.5	51	4	7.8	2.2	18.9
	Grade 3	63	0	0.0	0.0	5.7	51	0	0.0	0.0	7.0
	Related	63	5	7.9	2.6	17.6	51	3	5.9	1.2	16.2
Myalgia	Any	63	17	27.0	16.6	39.7	51	4	7.8	2.2	18.9
	Grade 3	63	0	0.0	0.0	5.7	51	0	0.0	0.0	7.0
	Related	63	15	23.8	14.0	36.2	51	3	5.9	1.2	16.2
Shivering	All	63	1	1.6	0.0	8.5	51	1	2.0	0.0	10.4
	Grade 3	63	0	0.0	0.0	5.7	51	0	0.0	0.0	7.0

	Related	63	1	1.6	0.0	8.5	51	1	2.0	0.0	10.4
Sweating increase	Any	63	5	7.9	2.6	17.6	51	4	7.8	2.2	18.9
	Grade 3	63	0	0.0	0.0	5.7	51	0	0.0	0.0	7.0
	Related	63	3	4.8	1.0	13.3	51	3	5.9	1.2	16.2

N= number of subjects with the documented dose
n (%) = number (percentage) of subjects reporting the symptom at least once
Any = any solicited general symptom irrespective of intensity grade or relationship to vaccination
Grade 3 = 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

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)	**18-60 years Group N = 62**	**>60 years Group N = 55.**
Subjects with any AE(s), n (%)	11 (17.5)	4 (7.5)
Subjects with related AE(s) *, n (%)	2 (3.2)	2 (3.8)
Subjects with severe AE(s) **, n (%)	0 (0.0)	0 (0.0)
Pharyngolaryngeal pain	3 (4.8)	1 (1.9)
Headache	2 (3.2)	1 (1.9)
Rhinitis	2 (3.2)	0 (0.0)
Upper respiratory tract infection	1 (1.6)	1 (1.9)
Arthralgia	0 (0.0)	1 (1.9)
Cough	1 (1.6)	0 (0.0)
Diarrhea	1 (1.6)	0 (0.0)
Fatigue	1 (1.6)	0 (0.0)
Gastroenteritis	1 (1.6)	0 (0.0)
Hemorrhoids	0 (0.0)	1 (1.9)
Influenza	1 (1.6)	0 (0.0)
Lymph node pain	1 (1.6)	0 (0.0)
Myosclerosis	1 (1.6)	0 (0.0)
Pain in extremity	1 (1.6)	0 (0.0)
Tooth disorder	1 (1.6)	0 (0.0)

*Related AE: AE considered by the investigator to be causally related to the study vaccination
**Severe AE: AE that prevented normal activity

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	**18-60 years Group N=62**	**>60 years Group N=55**
Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	**18-60 years Group N=62**	**>60 years Group N=55**
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: On Day 21, the GMTs for HI antibodies were 152.3 & 71.3 for A/Solomon strain, 143.4 & 152.6 for A/Wisconsin strain and 236.3 & 248.9 for B/Malaysia strain in the 18-60 years Group and in the >60 years Group, respectively; at least 70.6%, 78.4% and 92.1% of subjects had HI antibody titres $\geq$ 1:40 against A/Solomon, A/Wisconsin and B/Malaysia, respectively. In the 18-60 years group, pain was the most frequently reported solicited local symptom; fatigue and myalgia were the most frequently reported solicited general symptoms. In the >60 years group pain and fatigue were the most frequently reported solicited local and general symptoms, respectively. Unsolicited adverse events were reported by 11 (17.5%) and 4 (7.5%) subjects in the 18-60 years and in the >60 years group, respectively. No SAEs were reported during the study period.

Date Updated: 08-September-2014