Synopsis for study Fluarix-071 (116663)

Pharmaceutical entrepreneur:

Fluarix:
GlaxoSmithKline Biologicals s. a.
Rue de l'Institut 89
1330 Rixensart
Belgium

Influsplit SSW:
GlaxoSmithKline GmbH & Co. KG
Prinzregentenplatz 9
81675 Munich
Germany

Sponsor:

GlaxoSmithKline Biologicals s. a.
Rue de l'Institut 89
1330 Rixensart
Belgium

The study summarized below may involve approved and non-approved uses, formulations or treatment regimens. The results reported for any single study may not reflect the overall results obtained during all studies involving the same product. Before prescribing any product mentioned in this Register, healthcare professionals should consult the prescribing information for the product approved in their country.

Name of company: **GlaxoSmithKline Biologicals, Rixensart, Belgium** **Name of finished product:** Fluarix®/Influsplit SSW® 2012/2013 **Name of active substance: [antigen(s)]** [A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Hubei-Wujiagang/158/2009]	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Study No.: 116663 (FLUARIX-071)

Title of the study: A Phase III, open, non-randomized, multi-centre, single dose study to assess immunogenicity and safety of *Fluarix/Influsplit SSW* 2012/2013 injected intramuscularly in adults (18 to 60 years) and in elderly (over 60 years).

Principal investigator(s): This study was conducted by four principal investigators in Germany.

Study Centre(s): Multi-centre study conducted in 4 centres across Germany.

Publication (reference): Not published as of 27-September-2012

After publishing of the original report dated 09 August 2012, an error was noticed in the synopsis table presenting demographic data for the elderly population: mean age presented in this table was the mean age of the total population instead of being the mean age of the elderly population. This table has been corrected. Furthermore, it was noticed that grading of the local solicited symptoms used for the analysis was not the one described in the protocol. It was decided to clarify this in the section: changes in the conduct of the study (other changes) and to keep the analysis as performed since this is the grading GlaxoSmithKline (GSK) uses as standard for its adult influenza studies. Furthermore the grading used allows to assess the solicited local symptoms of redness, swelling, induration and ecchymosis between > 50 mm and > 100 mm. Finally, an error was noticed in text presenting duration of solicited local symptoms. This text has been corrected: the median duration of the solicited local AEs was 2 to 2.5 days and not 1.5 to 2.5 days.

Study period: **Study initiation date:** 10-July-2012 **Study completion date:** 31-July-2012 **Data lock point (Date of database freeze):** 08-August-2012	**Phase:** III

Indication: Immunization of adults against influenza.

Treatment: The study groups were as follows:

- Adult group: subjects aged between 18 and 60 years, received 1 dose of *Fluarix/Influsplit SSW* 2012/2013 at Visit 1 (Day 0).
- Elderly group: subjects aged over 60 years received 1 dose of *Fluarix/Influsplit SSW* 2012/2013 at Visit 1 (Day 0).

Objectives:

Primary:

- To evaluate the humoral response (anti-haemagglutinin [HA] antibodies tested by haemagglutination inhibition [HI]) against each vaccine strain in adults 18-60 years and > 60 years of age, 21 days after vaccination with *Fluarix/Influsplit SSW* 2012/2013.

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Secondary:

- To evaluate the humoral response (anti-HA antibodies tested by HI) against each vaccine strain, 21 days after vaccination, in adults > 60 years of age who had not and who had received an influenza vaccine in the 2011-2012 season.
- To describe the reactogenicity and safety of *Fluarix/Influsplit SSW* 2012/2013 in adults 18-60 years and > 60 years of age, in terms of solicited adverse events (AEs), unsolicited AEs and serious AEs (SAEs).

Study design: Open, non-randomized, multi-centre study with 2 age groups (18 - 60 years and > 60 years). Blood samples were collected prior to vaccination at Day 0 and at Day 21.

Study vaccine, dose, mode of administration, lot no.:

Vaccination schedule /site:

Fluarix/Influsplit SSW 2012/2013 was administered intramuscularly into the deltoid of the non-dominant arm at Day 0.

Vaccine composition /dose /lot number:

HA from three influenza strains: A/Christchurch/16/2010 (H1N1); A/Victoria/361/2011 (H3N2); B/Hubei-Wujiagang/158/2009.

Lot number: DFLUA694AB.

Reference vaccine /Comparator, dose and mode of administration, lot no.:

Not applicable.

Study Population:

Healthy male or female subjects aged 18 years and above at the time of vaccination or subjects with well-controlled chronic diseases as established by medical history and clinical examination before entering the study. Written informed consent was obtained from the subject.

Approximately 30 subjects in the Elderly group and a maximum of 15 subjects in the Adult group who had received a seasonal influenza vaccination the year before (i.e. season 2011-2012) were planned to be included in the study.

Duration of treatment: The duration of the study was approximately 3 weeks for each subject.

Primary Outcome/Efficacy Variable:

Immunogenicity

Observed variable:

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 (CIs):

- At Days 0 and 21:
  - Geometric mean titres (GMTs) of anti-HA antibody titres.
  - Seroprotection rates (SPR), defined as the percentage of vaccinees with a serum HI titre $\geq$ 1:40 that usually is accepted as indicating protection in adults.

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- At Day 21:
  - Seroconversion rates (SCR), defined as the percentage of vaccinees that have 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.
  - Mean geometric increase ([MGI] also known as the seroconversion factor [SCF]), defined as the fold increase in serum HI GMTs post-vaccination compared to pre-vaccination.
  - Seroprotection power (SPP), defined as the percentage of vaccinees that have a pre-vaccination titre < 1:40 and a post-vaccination titre ≥ 1:40.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

Observed variable:

Humoral immune response in terms of anti-HA antibodies against each of the three vaccine influenza strains, by influenza vaccination status in the 2011-2012 season, in subjects aged > 60 years.

Derived variables:

The following parameters were calculated with 95% CIs:

- At Days 0 and 21:
  - GMTs of anti-HA antibody titres and SPRs, by influenza vaccination status in the 2011-2012 season.
- At Day 21:
  - SCRs and MGI, by influenza vaccination status in the 2011-2012 season.

Reactogenicity and safety

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

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Statistical methods:

All data were analyzed as planned in the protocol and in the Statistical Analysis Plan.

Demography:

- Demographic characteristics (age, gender and race) of all subjects were tabulated by age group.
- The mean age (plus range and standard deviation) by gender of the enrolled subjects, as a whole, and per group, was calculated.
- History of any influenza vaccination within the previous 3 seasons was also tabulated.
- The distribution of subjects enrolled among the study sites was tabulated as a whole and per group.

Analysis of immunogenicity:

The analysis of immunogenicity was performed on the According to Protocol (ATP) cohort for analysis of immunogenicity. GMT at Day 0 and 21, SCR and MGI at Day 21, SPR at Day 0 and Day 21, SPP at Day 21, proportion of subjects who were seronegative at Day 0 and seroprotected at Day 21 and proportion of subjects who were seropositive at Day 0 and had a 4-fold increase at Day 21 were calculated with their 95% CI for each of the three influenza vaccine strains.

GMT at Day 0 and 21, SCR and MGI at Day 21 and SPR at Day 0 and 21 were calculated with their 95% CI for each of the three influenza vaccine strains and by previous vaccination status (2011-2012) in subjects aged > 60 years.

Analysis of Safety

The primary analysis was based on the Total vaccinated cohort.

The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the solicited follow-up period after vaccination, was tabulated per age group with exact 95% CI. The same tabulation was performed for grade 3 AEs, related AEs and grade 3 related AEs.

The percentage of subjects reporting each individual solicited local (any, grade 3) and general (any, grade 3, related, grade 3 related) AE during the solicited follow-up period was tabulated with exact 95% CI, in each age group.

The duration (in terms of number of days) of each solicited local and general AE during the 4-day solicited follow-up period was tabulated. The percentage of subjects reporting ongoing solicited (local and general) AEs at the end of the solicited follow-up period was also tabulated with exact 95%CI in each age group.

The percentage of subjects with at least one report of an unsolicited AE (any, grade 3, related, grade 3 related) classified by the Medical Dictionary for Regulatory Activities (MedDRA) during the follow-up period was tabulated with exact 95% CI, in each age group.

The percentage of subjects with at least one report of a SAE classified by MedDRA during the study period was tabulated with exact 95% CI.

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Study population (Total vaccinated cohort) -

Number of subjects	**Adults (18-60 years of age)**	**Elderly (>60 years of age)**
Planned, N	60	60
Randomised, N (Total Vaccinated Cohort)	60	59
Completed, n (%)	60 (100%)	59 (100%)
Demographics	**Adults (18-60 years of age)**	**Elderly (>60 years of age)**
N (Total Vaccinated Cohort)	60	59
Females: Males	30:30	34:25
Mean Age, years (SD)	35.7 (11.98)	70.3 (5.87)
White - Caucasian / European heritage, n (%)	60 (100%)	59 (100%)

Summary:

Immunogenicity:

Immunogenicity analysis was performed on the ATP cohort for immunogenicity (primary analysis).

- In this study, in both the Adults (18-60 years of age) and Elderly (>60 years of age) age groups, the *Fluarix/Influsplit* SSW 2012/2013 vaccine met the immunogenicity acceptance criteria defined in the European Committee for Medicinal Products for Human Use (CHMP) guidelines for annual influenza vaccine licensure since at least one of the three criteria (SPR > 70%, SCR > 40%, and MGI > 2.5 for adults 18-60 years and SPR > 60%, SCR > 30%, and MGI > 2.0 for elderly > 60 years) for each of the antigenic strains contained in the vaccine was met.
- Except for the SCR criteria for the A/Victoria/361/2011 (H3N2) vaccine strain in the Elderly group, all other CHMP criteria in the Elderly and the Adult groups were met.

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Synopsis Table 1 – Summary of Immunogenicity Results (ATP cohort for analysis of immunogenicity)

Group	Timing	N	≥ 1:10				GMT			SPR			
			n	%	95% CI		Value	95% CI		n	%	95% CI	
					LL	UL		LL	UL			LL	UL
A/Christchurch/16/2010 (H1N1)													
ADULTS	PRE	59	39	66.1	52.6	77.9	20.57	13.98	30.27	20	33.9	22.1	47.4
	PI(D21)	59	59	100	93.9	100	366.04	264.22	507.09	55	93.2	83.5	98.1
ELDERLY	PRE	58	48	82.8	70.6	91.4	19.02	14.35	25.22	14	24.1	13.9	37.2
	PI(D21)	58	58	100	93.8	100	110.44	79.50	153.43	47	81.0	68.6	90.1
A/Victoria/361/2011 (H3N2)													
ADULTS	PRE	59	41	69.5	56.1	80.8	16.17	12.07	21.65	15	25.4	15.0	38.4
	PI(D21)	59	59	100	93.9	100	93.19	73.75	117.76	51	86.4	75.0	94.0
ELDERLY	PRE	58	44	75.9	62.8	86.1	23.90	17.07	33.45	23	39.7	27.0	53.4
	PI(D21)	58	56	96.6	88.1	99.6	65.63	48.37	89.05	41	70.7	57.3	81.9
B/Hubei-Wujiagang/158/2009													
ADULTS	PRE	59	56	94.9	85.9	98.9	68.60	50.26	93.63	42	71.2	57.9	82.2
	PI(D21)	59	59	100	93.9	100	431.85	332.61	560.70	59	100	93.9	100
ELDERLY	PRE	58	58	100	93.8	100	70.19	58.98	83.53	51	87.9	76.7	95.0
	PI(D21)	58	58	100	93.8	100	223.56	183.62	272.19	58	100	93.8	100

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Group	Timing	N	SCR				MGI			SPP			
			n	%	95% CI		Value	95% CI		n	%	95% CI	
					LL	UL		LL	UL			LL	UL
A/Christchurch/16/2010 (H1N1)													
ADULTS	PI(D21)	59	45	76.3	63.4	86.4	17.8	11.5	27.6	35	89.7	75.8	97.1
ELDERLY	PI(D21)	58	34	58.6	44.9	71.4	5.8	4.2	8.0	33	75.0	59.7	86.8
A/Victoria/361/2011 (H3N2)													
ADULTS	PI(D21)	59	34	57.6	44.1	70.4	5.8	4.2	7.8	36	81.8	67.3	91.8
ELDERLY	PI(D21)	58	14	24.1	13.9	37.2	2.7	2.2	3.4	18	51.4	34.0	68.6
B/Hubei-Wujiagang/158/2009													
ADULTS	PI(D21)	59	38	64.4	50.9	76.4	6.3	4.6	8.7	17	100	80.5	100
ELDERLY	PI(D21)	58	24	41.4	28.6	55.1	3.2	2.6	3.9	7	100	59.0	100

ADULTS = 18-60 years; ELDERLY = >60 years
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results (for ≥ 1:10, GMT and SPR)
N= Number of subjects with pre- and post-vaccination results available (for SCR and MGI),
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; PI(D21) = 21 days post vaccine
SPR n/% = Number/percentage of seroprotected subjects (HI titre ≥ 1:40)
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/percentage of seroconverted subjects
MGI = Fold increase in serum HI GMTs post-vaccination compared to pre-vaccination
SPP = percentage of vaccinees that have a pre-vaccination titre < 1:40 and a post-vaccination titre ≥ 1:40.

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Safety /reactogenicity:

The safety analysis was performed on the Total vaccinated cohort (primary analysis).

- *Any Symptom*: During the 4-day post-vaccination follow-up period at least one symptom (solicited or unsolicited, local or general) was reported by 66.7% of subjects in the Adults group and by 57.6% of subjects in the Elderly group, at least one local symptom (solicited or unsolicited) was reported by 58.3% of subjects in the Adults group and by 44.1% of subjects in the Elderly group, and at least one general symptom (solicited or unsolicited) was reported by 41.7% of subjects in the Adults group and by 35.6% of subjects in the Elderly group.
- *Solicited local symptoms*: During the 4-day follow-up period, injection site pain was the most frequently reported local AE across both age strata (reported by 55.0% of subjects in the Adults group and by 39.0% of subjects in the Elderly group). One subject (1.7%) in the Adults group reported Grade 3 injection site pain. No other Grade 3 solicited local AEs were reported.
- The median duration of the solicited local AEs was 2 to 2.5 days. All solicited local symptoms resolved during the 4 days post-vaccination period, except eight symptoms (3 in the Adult group and 5 in the Elderly group) that were ongoing beyond the 4 days post-vaccination period.
- *Solicited general symptoms*: During the 4-day follow-up period, headache (25.0%), fatigue (18.3%) and myalgia (18.3%) were the most frequently reported general AEs in the Adults group. Fatigue was the most frequently reported solicited general AEs (23.7%), in the Elderly group, followed by sweating (15.3%) and headache/myalgia (each 11.9%). Grade 3 fatigue was reported by 1 subject in the Adult group and grade 3 headache was reported by 1 subject in the Adult group and by 1 subject in the Elderly group. Grade 3 fatigue and headache, both related to the vaccination were reported by 1 subject in the Adult group.

  The median duration of the solicited general AEs was 1 to 4 days. Eight symptoms (1 in the Adult group and 7 in the Elderly group were ongoing beyond the 4 days post-vaccination period.
- *Unsolicited symptoms*: Overall, 8 (13.3%) subjects from the Adults group and 11 (18.6%) subjects from the Elderly group experienced at least one unsolicited AE within the 21-day post vaccination period. Grade 3 unsolicited AE were reported by 1 (1.7%) subject from the Elderly group. No Grade 3 unsolicited AEs were reported in the Adults group. The most frequently reported unsolicited AE classified by MedDRA Primary System Organ Class and preferred term was 'Injection site pruritus' in both age strata (reported by 5.0% of subjects in the Adults group and by 3.4% of subjects in the Elderly group). In addition to the cases of 'injection site pruritus', that were assessed as causally related to the vaccination, one subject (1.7%) in the Adults group and one subject (1.7%) in the Elderly group reported an unsolicited AE (lymphadenopathy and musculoskeletal stiffness, respectively) with causal relationship to vaccination assessed by the investigator. There were no grade 3 unsolicited AEs that were causally related to the vaccination.

Serious adverse events: None of the subjects reported SAEs during study period.
Pregnancies: There were no cases of pregnancy reported during the entire study period (Day 0-20).
Other safety parameters: There were no other significant AEs reported during the entire study period (Day 0-20).

Conclusion:

- In this study, in both the Adults (18-60 years of age) and Elderly (>60 years of age) age groups, the

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Fluarix/Influsplit SSW 2012/2013 vaccine met the immunogenicity acceptance criteria defined in the European CHMP guidelines for annual influenza vaccine licensure since at least one of the three criteria (SPR > 70%, SCR > 40%, and MGI > 2.5 for adults 18-60 years and SPR > 60%, SCR > 30%, and MGI > 2.0 for elderly > 60 years) for each of the antigenic strains contained in the vaccine was met.

- Except for the SCR criteria for the A/Victoria/361/2011 (H3N2) vaccine strain in the Elderly group, all other CHMP criteria in the Elderly and the Adult groups were met.
- In this study, the study vaccine was generally well tolerated.

Date of report amendment: Final: 27-September-2012

Appendix 1 to Synopsis for study Fluarix-071 (116663)

Overview of Protocol Amendments

No protocol amendments were submitted for this study.

Appendix 2 to Synopsis for study Fluarix-071 (116663)

List of study sites

Worldwide study centres Fluarix-071 (116663)

Country	Principal Investigator Full Name	Clinical Site Institution Name	Clinical Site Street	Clinical Site ZIP Code	Clinical Site City
Germany	Andre Markendorf	Praxis Dr. med. Andre Markendorf	Bautzner Str. 125	01099	Dresden
Germany	Beatrice Gerlach	Praxis Dr. med. Beatrice Gerlach	Hauptstr. 36	01097	Dresden
Germany	Abdo Taraben	Praxis Dr. med. Abdo Taraben	Industriestr. 52	01129	Dresden
Germany	Ascan Schindler	Praxis Dr. med. Ascan Schindler	Commeniusstr. 66	01309	Dresden