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.: 112662 (FLU NG-042 PRI)

Title: Immunogenicity & safety study of GSK Biologicals' influenza vaccine GSK2186877A in elderly adults. GSK2186877A (FLU NG): GSK Biologicals' candidate trivalent influenza vaccine (TIV).

Rationale: This study was designed to assess the immunological non-inferiority of an aged lot of FLU NG vaccine compared to a fresh lot.

Phase: III

Study Period: 30 July 2009 to 05 October 2009

Study Design: Double-blind, randomized (1:1) study in 2 parallel groups.

Centers: 6 centers: 4 in Slovakia and 2 in Estonia

Indication: Immunization against influenza in male and female subjects aged ≥ 65 years.

Treatment: The study groups were as follows:

- NGaged Group: subjects received 1 dose of an aged lot of FLU NG vaccine
- NGfresh Group: subjects received 1 dose of a fresh lot of FLU NG vaccine

The vaccines were administered at Day 0 in the deltoid region of the non-dominant arm.

Objectives:

- To assess the immunological non-inferiority (in terms of hemagglutination-inhibition [HI] antibody geometric mean titers [GMTs]) of an aged lot of the FLU NG vaccine 21 days after vaccination in elderly subjects aged ≥ 65 years old compared to a fresh lot of FLU NG vaccine.

Criterion for non-inferiority:

The non-inferiority would be concluded if the upper limit of the two-sided 95% confidence interval (CI) of the GMT ratio (NGfresh over NGaged) was below 1.5 in terms of antibody titers for each of the 3 vaccine strains.

Primary Outcome/Efficacy Variable:

- Humoral immune response in terms of HI antibodies:
  - Serum HI antibody titers, against the 3 vaccine strains, in each group at Days 0 and 21.
  - GMTs of HI antibody titers on Days 0 and 21.

Secondary Outcome/Efficacy Variable(s):

Immunogenicity

- Humoral immune response in terms of HI antibodies:
  - Serum HI antibody titers, against each of the 3 vaccine strains in each group at Days 0 and 21.
  - Seroconversion rates (SCRs)* at Day 21, in each group.
  - Seroconversion factors (SCFs)** at Day 21, in each group.
  - Seroprotection rates (SPRs)*** at Days 0 and 21, in each group.

* SCR 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 defined as the fold increase in serum HI GMTs post-vaccination compared to Day 0.

*** SPR defined as the percentage of vaccinees with a serum HI titer ≥ 1:40 that usually was accepted as indicating protection.

Safety

- Occurrence of solicited general signs and symptoms
  - Intensity, duration and relationship to vaccination during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after vaccination, in each group.
- Occurrence of solicited local signs and symptoms
  - Intensity and duration during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after vaccination, in each group.
- Occurrence of unsolicited adverse events (AEs):
  - Intensity and relationship to vaccination during a 21-day follow-up period (i.e., day of vaccination and 20 subsequent days) after vaccination, in each group.
- Occurrence of serious adverse events (SAEs) and adverse events of specific interest (AESIs) including autoimmune diseases (AIDs)
  - Relationship to vaccination during the entire study period in each group.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort and the ATP cohort for analysis of 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 outcome variable measures were available.

Analysis of immunogenicity
The analysis was based on the ATP cohort for analysis of immunogenicity.
Inferential analysis
For the 3 vaccine strains, adjusted geometric means antibody titers at Day 21 were computed for NGaged and NGfresh groups. The ratios of NGfresh over NGaged were calculated and tabulated with 95% confidence intervals (CIs). Non-inferiority of NGaged compared to NGfresh at Day 21 after vaccination would be demonstrated if the upper limit of the two-sided 95% CI of the GMT ratio was < 1.5 for each of the 3 vaccine strains.
Descriptive analysis
Analysis of the humoral immune response in terms of HI antibodies.
For each vaccine group and each vaccine strain, the following parameters were calculated:

- GMTs on Days 0 and 21, calculated with 95% CI
- Seropositivity rates with exact 95% CI on Days 0 and 21
- SCRs with exact 95% CI on Day 21
- SPRs with exact 95% CI on Days 0 and 21
- SCFs with 95% CI on Days

Analysis of safety
The analysis was based on the Total Vaccinated cohort.
For each vaccine group, the following parameters were tabulated:
- The percentage of subjects reporting each individual solicited local and general symptom during the 7-day solicited follow-up period (Day 0 to Day 6) with exact 95% CI. The same tabulation was performed for Grade 3 symptoms and for general symptoms assessed by the investigators as related to vaccination. The number of days experiencing each solicited local and general symptom during the 7-day solicited follow-up period was tabulated for each group.
- The percentage of subjects with at least one report of an unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms and reported within the 21-day follow-up period after vaccination (Day 0 to Day 20). The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs assessed by the investigators as related to vaccination.
- The percentage of subjects with at least one report of adverse events of specific interest (AESIs) including autoimmune diseases (AIDs) classified by the MedDRA Preferred Terms and reported during the entire study period.
- The percentage of subjects with at least one report of SAE classified by the MedDRA Preferred Terms and reported during the entire study period.

Study Population: Male or female subjects aged 65 years or older at the time of vaccination who the investigator believed that they could and would comply with the requirements of the protocol. Specific attention had been given to the compliance potential of subjects with suspected or known drug or alcohol abuse. Subjects had to be free of an acute aggravation of the health status as established by clinical evaluation before entering into the study. Written informed consent was obtained from the subjects prior to any study procedure.

Number of Subjects:	**NGaged Group**	**NGfresh Group**
Planned, N	362	362
Randomized, N (Total Vaccinated cohort)	362	362
Completed, n (%)	360 (99.4)	358 (98.9)
Total Number Subjects Withdrawn, n (%)	2 (0.6)	4 (1.1)
Withdrawn due to Adverse Events n (%)	0 (0.0)	1 (0.3)
Withdrawn due to Lack of Efficacy n (%)	Not applicable	Not applicable
Withdrawn for other reasons n (%)	2 (0.6)	3 (0.8)
Demographics	**NGaged Group**	**NGfresh Group**
N (Total Vaccinated cohort)	362	362
Females: Males	239:123	243:119
Mean Age, years (SD)	73.3 (6.09)	73.5 (6.36)
White – Caucasian/European heritage, n (%)	362 (100)	361 (99.7)

Primary Efficacy Results: Adjusted GMT ratios of A/Brisbane, A/Uruguay and B/Brisbane at Day 21 (ATP cohort for

immunogenicity)

					Adjusted GMT ratio (NGfresh/NGaged)		
	NGfresh Group		NGaged Group			95% CI	
Strain	**N**	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL***
A/Brisbane	354	109.2	356	108.2	1.01	0.84	1.21
A/Uruguay	355	281.1	356	294.8	0.95	0.79	1.16
B/Brisbane	355	538.0	356	536.0	1.00	0.87	1.16

Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio; LL = lower limit, UL = upper limit
*Non-inferiority criterion: upper limit of the two-sided 95% CI for the ratio of GMT < 1.5

Primary Efficacy Results: Seropositivity rates and GMTs for HI antibodies against A/Brisbane, A/Uruguay and B/Brisbane at Day 0 and Day 21 (ATP cohort for immunogenicity)

				≥ 1:10				GMT		
						95% CI			95% CI	
Strain	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
A/Brisbane	NGaged	PRE	356	224	62.9	57.7	68.0	14.1	12.7	15.8
		PI(D21)	357	353	98.9	97.2	99.7	108.4	95.8	122.6
	NGfresh	PRE	355	220	62.0	56.7	67.0	13.4	12.1	14.9
		PI(D21)	354	349	98.6	96.7	99.5	108.7	95.1	124.1
A/Uruguay	NGaged	PRE	356	231	64.9	59.7	69.8	18.5	16.1	21.3
		PI(D21)	357	353	98.9	97.2	99.7	291.5	251.9	337.4
	NGfresh	PRE	355	236	66.5	61.3	71.4	19.1	16.7	21.8
		PI(D21)	355	353	99.4	98.0	99.9	282.7	244.6	326.8
B/Brisbane	NGaged	PRE	356	326	91.6	88.2	94.2	68.2	59.3	78.4
		PI(D21)	357	357	100	99.0	100	537.9	483.6	598.3
	NGfresh	PRE	355	335	94.4	91.4	96.5	62.3	54.8	70.7
		PI(D21)	355	355	100	99.0	100	534.2	483.5	590.3

GMT = geometric mean antibody titer calculated on all subjects
N = Number of subjects with pre- and post-vaccination results available
n/% = number/percentage of seropositive subjects (HI titer ≥ 1:10)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination Dose 1 (Day 0)
PI(D21) = Post-vaccination Dose 1 (Day 21)

Secondary Outcome Variable(s): Seroconversion rates for HI antibodies against A/Brisbane, A/Uruguay and B/Brisbane at Day 21 (ATP cohort for immunogenicity)

				SCR		
					95% CI	
Strain	**Group**	**N**	**n**	**%**	**LL**	**UL**
A/Brisbane	NGaged	356	228	64.0	58.8	69.0
	NGfresh	354	227	64.1	58.9	69.1
A/Uruguay	NGaged	356	292	82.0	77.6	85.9
	NGfresh	355	292	82.3	77.9	86.1
B/Brisbane	NGaged	356	224	62.9	57.7	68.0
	NGfresh	355	247	69.6	64.5	74.3

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

Secondary Outcome Variable(s): Seroconversion factor for HI antibodies against A/Brisbane, A/Uruguay and B/Brisbane at Day 21 (ATP cohort for immunogenicity)

			SCF		
				95% CI	
Strain	**Group**	**N**	**Value**	**LL**	**UL**
A/Brisbane	NGaged	356	7.7	6.6	8.9
	NGfresh	354	8.1	6.9	9.5
A/Uruguay	NGaged	356	15.8	13.4	18.6
	NGfresh	355	14.8	12.7	17.3
B/Brisbane	NGaged	356	7.9	6.8	9.3
	NGfresh	355	8.6	7.4	9.9

N = Number of subjects with pre- and post-vaccination results available
SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)])
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): Seroprotection rates for HI antibodies against A/Brisbane, A/Uruguay and B/Brisbane at Day 0 and Day 21 (ATP cohort for immunogenicity)

				SPR			
						95% CI	
Strain	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**
A/Brisbane	NGaged	PRE	356	87	24.4	20.1	29.2
		PI(D21)	357	318	89.1	85.4	92.1
	NGfresh	PRE	355	85	23.9	19.6	28.7
		PI(D21)	354	308	87.0	83.1	90.3
A/Uruguay	NGaged	PRE	356	120	33.7	28.8	38.9
		PI(D21)	357	338	94.7	91.8	96.8
	NGfresh	PRE	355	131	36.9	31.9	42.2
		PI(D21)	355	337	94.9	92.1	97.0
B/Brisbane	NGaged	PRE	356	261	73.3	68.4	77.8
		PI(D21)	357	357	100	99.0	100
	NGfresh	PRE	355	260	73.2	68.3	77.8
		PI(D21)	355	355	100	99.0	100

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

Secondary Outcome Variable(s): Number (%) of subjects reporting solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

		NGaged Group					NGfresh Group				
					95 % CI					95 % CI	
Symptom	**Intensity**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Ecchymosis (mm)	Any	360	9	2.5	1.1	4.7	360	11	3.1	1.5	5.4
	>100	360	0	0.0	0.0	1.0	360	0	0.0	0.0	1.0
Pain	Any	360	180	50.0	44.7	55.3	360	190	52.8	47.5	58.0
	Grade 3	360	0	0.0	0.0	1.0	360	2	0.6	0.1	2.0
Redness (mm)	Any	360	99	27.5	23.0	32.4	360	106	29.4	24.8	34.4
	>100	360	0	0.0	0.0	1.0	360	2	0.6	0.1	2.0
Swelling (mm)	Any	360	45	12.5	9.3	16.4	360	69	19.2	15.2	23.6
	>100	360	0	0.0	0.0	1.0	360	2	0.6	0.1	2.0

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 = occurrence of any local symptom regardless of intensity grade
Grade 3 Pain= considerable pain at rest, prevented normal everyday activities

Secondary Outcome Variable(s): Number of days with local symptoms (any grade) during the 7-day (Days 0-6) post-vaccination period (Total vaccinated cohort)

Solicited Symptom	**Group**	**N**	**Mean**	**Median**

Ecchymosis	NGaged	8	3.9	4.0
	NGfresh	11	3.9	4.0
Pain	NGaged	180	2.8	2.0
	NGfresh	190	2.7	3.0
Redness	NGaged	99	3.2	3.0
	NGfresh	106	3.3	3.0
Swelling	NGaged	45	3.0	3.0
	NGfresh	69	3.5	3.0

N = Number of subjects with the symptom

Secondary Outcome Variable(s): Number (%) of subjects reporting solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

		NGaged Group					NGfresh Group				
					95 % CI					95 % CI	
Symptom	**Intensity/Relationship**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Arthralgia	Any	360	49	13.6	10.2	17.6	360	63	17.5	13.7	21.8
	Grade 3	360	2	0.6	0.1	2.0	360	0	0.0	0.0	1.0
	Related	360	28	7.8	5.2	11.0	360	44	12.2	9.0	16.1
Fatigue	Any	360	86	23.9	19.6	28.6	360	98	27.2	22.7	32.1
	Grade 3	360	1	0.3	0.0	1.5	360	1	0.3	0.0	1.5
	Related	360	68	18.9	15.0	23.3	360	80	22.2	18.0	26.9
Gastrointestinal symptoms	Any	360	29	8.1	5.5	11.4	360	29	8.1	5.5	11.4
	Grade 3	360	0	0.0	0.0	1.0	360	1	0.3	0.0	1.5
	Related	360	17	4.7	2.8	7.5	360	15	4.2	2.4	6.8
Headache	Any	360	66	18.3	14.5	22.7	360	82	22.8	18.5	27.5
	Grade 3	360	0	0.0	0.0	1.0	360	0	0.0	0.0	1.0
	Related	360	47	13.1	9.8	17.0	360	62	17.2	13.5	21.5
Muscle aches	Any	360	60	16.7	13.0	20.9	360	62	17.2	13.5	21.5
	Grade 3	360	2	0.6	0.1	2.0	360	1	0.3	0.0	1.5
	Related	360	47	13.1	9.8	17.0	360	49	13.6	10.2	17.6
Shivering	Any	360	28	7.8	5.2	11.0	360	26	7.2	4.8	10.4
	Grade 3	360	2	0.6	0.1	2.0	360	0	0.0	0.0	1.0
	Related	360	20	5.6	3.4	8.4	360	23	6.4	4.1	9.4
Temperature/ (Orally)	≥ 38.0 °C	360	6	1.7	0.6	3.6	360	9	2.5	1.1	4.7
	≥ 39 °C	360	1	0.3	0.0	1.5	360	1	0.3	0.0	1.5
	Related	360	4	1.1	0.3	2.8	360	9	2.5	1.1	4.7

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 = incidence of a particular symptom regardless of grade or relationship to vaccination
Related = general symptom assessed by the investigator as related to study vaccination
Grade 3 = general symptom that prevented normal everyday activities

Secondary Outcome Variable(s): Number of days with general symptoms (any grade) during the 7-day post-vaccination period (Total vaccinated cohort)

Solicited Symptom	**Group**	**N**	**Mean**	**Median**
Arthralgia	NGaged	49	4.0	4.0
	NGfresh	63	3.6	3.0
Fatigue	NGaged	86	3.0	2.5
	NGfresh	98	2.8	2.0
Gastrointestinal symptoms	NGaged	28	2.5	2.0
	NGfresh	29	2.9	2.0
Headache	NGaged	66	2.7	2.0
	NGfresh	82	2.5	2.0
Muscle aches	NGaged	60	2.9	3.0
	NGfresh	62	2.8	2.0

Shivering	NGaged	27	1.9	1.0
	NGfresh	26	2.0	1.5
Temperature	NGaged	4	1.0	1.0
	NGfresh	9	1.1	1.0

N = Number of subjects with the symptom

Secondary Outcome Variable(s): Number (%) of subjects with AEs of specific interest including AID reported during the entire study period (Total vaccinated cohort)

Most frequent adverse events of specific interest	**NGaged Group N = 362**	**NGfresh Group N = 362**
Subjects with any AE(s), n (%)	0 (0.0)	0 (0.0)

Safety results: Number (%) of subjects with unsolicited AEs during a 21-day follow-up period after vaccination, in each group (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within day 0-20 following vaccination)	**NGaged Group N = 362**	**NGfresh Group N = 362**
Subjects with any AE(s), n (%)	13 (3.6)	24 (6.6)
Subjects with grade 3 AE(s), n (%)	1 (0.3)	1 (0.3)
Subjects with related AE(s), n (%)	5 (1.4)	12 (3.3)
Injection site pruritus	2 (0.6)	7 (1.9)
Angina pectoris	1 (0.3)	1 (0.3)
Dizziness	2 (0.6)	-
Injection site induration	1 (0.3)	1 (0.3)
Abdominal pain lower	-	1 (0.3)
Acute myocardial infarction	1 (0.3)	-
Arthralgia	1 (0.3)	-
Asthenia	1 (0.3)	-
Blindness transient	1 (0.3)	-
Blood pressure increased	1 (0.3)	-
Cerumen impaction	-	1 (0.3)
Chills	-	1 (0.3)
Chronic obstructive pulmonary disease	-	1 (0.3)
Dry mouth	-	1 (0.3)
Eye irritation	1 (0.3)	-
Fatigue	1 (0.3)	-
Genitourinary tract infection	-	1 (0.3)
Headache	1 (0.3)	-
Hepatic pain	1 (0.3)	-
Hot flush	1 (0.3)	-
Hypertensive crisis	-	1 (0.3)
Hypoaesthesia	-	1 (0.3)
Injection site joint redness	-	1 (0.3)
Liver tenderness	1 (0.3)	-
Muscle spasms	-	1 (0.3)
Oral herpes	-	1 (0.3)
Otitis externa	-	1 (0.3)
Pharyngitis	1 (0.3)	-
Pruritus	-	1 (0.3)
Pyrexia	-	1 (0.3)
Rhinitis	-	1 (0.3)
Sleep disorder	-	1 (0.3)
Somnolence	1 (0.3)	-
Tachycardia	-	1 (0.3)
Tinnitus	-	1 (0.3)
Urinary tract infection	-	1 (0.3)
Urinary tract infection bacterial	1 (0.3)	-

- : AE absent
Grade 3= event that prevented normal activities
Related= event assessed by the investigator as causally related to the study vaccination

Safety results: Number (%) of subjects with serious adverse events (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	**NGaged Group N = 362**	**NGfresh Group N = 362**
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	1 (0.3) [0]	1 (0.3) [0]
Acute myocardial infarction	1 (0.3) [0]	0 (0.0) [0]
Hypertensive crisis	0 (0.0) [0]	1 (0.3) [0]
Urinary tract infection bacterial	1 (0.3) [0]	0 (0.0) [0]
Fatal SAEs	**NGaged Group N = 362**	**NGfresh Group N = 362**
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:
The GMTs for HI antibodies were 14.1 & 13.4 at Day 0 and 108.4 & 108.7 at Day 21 against the A/Brisbane strain, 18.5 & 19.1 at Day 0 and 291.5 & 282.7 at Day 21 against the A/Uruguay strain, and 68.2 & 62.3 at Day 0 and 537.9 & 534.2 at Day 21 against the B/Brisbane in the NGaged and NGfresh groups, respectively. Unsolicited AEs were reported by 13 (3.6%) and 24 (6.6%) subjects of the NGaged and NGfresh groups, respectively. In each vaccine group, a single Grade 3 unsolicited AE was recorded; 5 (1.4%) subjects in the NGaged Group and 12 (3.3%) subjects in the NGfresh Group reported unsolicited AEs assessed as related to the vaccination by the investigators. SAEs were reported by 1 subject in both NGaged and NGfresh Group; these SAEs were assessed by the investigators as not related to the vaccination. No fatal SAEs were reported throughout the study.

Date updated: 03-November-2014