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.: 111738 (FLU NG-037 Ext:005 Y2)

Title: Safety and immunogenicity of the influenza vaccine GSK2186877A in the elderly**.**
GSK2186877 - also referred to as FluAS25 (Flu NG): GlaxoSmithKline (GSK) Biologicals' AS adjuvanted influenza vaccine.

Rationale: The aim of this study was to assess the safety and immunogenicity of GSK Biologicals' Flu NG vaccine in elderly subjects (≥ 66 years of age) after repeated vaccinations. The subjects previously enrolled in study FluAS25-005 (104888) received a dose of the 2006-2007 season formulations of the vaccine and a year later received a dose of the 2007-2008 season formulations in study FluAS25-010 (109821). In this study, they received a third vaccine dose of the 2008-2009 season formulations. *Fluarix*™, administered in young adults and elderly subjects previously vaccinated with *Fluarix*™ in studies 104888 and 109821, was used as control.
For results on the previous vaccinations, please refer to CTRS on study 104888 and study 109821.
Fluarix™ (Flu): GSK Biologicals' licensed influenza vaccine.

Phase: III

Study Period: 14 October 2008 to 15 January 2010

Study Design: Multi-country, multi-centre, observer-blind for the elderly subjects (≥ 66 years of age), open for the young adults (19-43 years of age), controlled study with 3 parallel groups.

Centres: 29 centres (1 in Belgium, 12 in Germany, 7 in Norway and 9 in the United States)

Indication: Immunisation against influenza disease in the elderly (≥ 66 years of age) and adults (19-43 years of age).

Treatment: Study groups were as follows:

- Flu-NG Group: subjects aged ≥ 66 years (previously vaccinated with FluAS25 vaccine in studies 104888 & 109821) received 1 dose of the Flu NG vaccine.
- Flu-Eld Group: subjects aged ≥ 66 years (previously vaccinated with Flu vaccine in studies 104888 & 109821) received 1 dose of Flu vaccine.
- Flu-Yng Group: subjects aged 19-43 years (previously vaccinated with Flu vaccine in studies 104888 & 109821) received 1 dose of Flu vaccine.

Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm.

Objectives: To evaluate the safety of the Flu NG vaccine in elderly subjects (previously vaccinated with FluAS25 in study 109821), during the 21 days following vaccination. Flu vaccine administered in young adults and elderly subjects (previously vaccinated with Flu vaccine in study 109821) was used as a reference.

Primary Outcome/Efficacy Variable:

- Occurrence, intensity and duration of solicited local symptoms within 7 days (Day 0 to Day 6) following vaccination, in each group.
- Occurrence, intensity, duration and relationship to vaccination of solicited general symptoms within 7 days (Day 0 to Day 6) following vaccination, in each group.
- Occurrence, intensity and relationship to vaccination of unsolicited adverse events ([AEs]; including AEs with medically attended visit ([MAEs]) within 21 days (Day 0 to Day 20) following vaccination, in each group.
  MAEs refer to non-serious and serious events for which the subject receive medical attention defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason.
- Occurrence, intensity and relationship to vaccination of AEs of specific interest (AESI) including autoimmune diseases (AIDs) within 21 days (Day 0 to Day 20) following vaccination, in each group.
  Adverse events of specific interest for safety monitoring are a subset of AEs that include both clearly autoimmune diseases and also other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology.
- Occurrence and relationship to vaccination of serious adverse events (SAEs) within 21 days (Day 0 to Day 20) following vaccination, in each group

Secondary Outcome/Efficacy Variable(s):

Safety

- Occurrence, intensity and relationship to vaccination of AEs with medically attended visit following the administration of the study vaccines up to Visit 3 (Day 21 to Day 179), in each group.
- Occurrence, intensity and relationship to vaccination of AEs of specific interest including autoimmune diseases following administration of the study vaccines throughout the entire follow-up phase (Day 21 to Day 364), in each group.

- Occurrence and relationship to vaccination of SAEs following administration of the study vaccines throughout the entire follow-up phase (Day 21 to Day 364), in each group.

Immunogenicity

Before vaccination and 21 days following the administration of the single vaccine dose of Flu NG or Flu vaccines:

- Haemagglutination-inhibition (HI) antibody titres against each of the 3 vaccine influenza strains.
- Seroprotection rate (SPR) defined as: HI antibody titres ≥ 1:40
- Seropositivity rate defined as: HI antibody titres ≥ 1:10

21 days following the administration of the single vaccine dose of Flu NG or Flu vaccines:

- Seroconversion rate (SCR) defined as the percentage of vaccinees having either pre-vaccination HI antibody titres < 1:10 and HI antibody titres ≥ 1:40 post-vaccination or pre-vaccination HI antibody titres ≥ 1:10 and at least a 4-fold increase in HI antibody titres post-vaccination.
- Seroconversion factor (SCF) defined as the fold increase in serum HI antibody titres post-vaccination compared to pre-vaccination HI antibody titres.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort and the According-To-Protocol (ATP) Immunogenicity cohort.

- The Total Vaccinated cohort included all vaccinated subjects.
- The ATP Immunogenicity cohort 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 measures 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 based on the ATP Immunogenicity cohort.

For each treatment group and for the 3 vaccine influenza strains , the following parameters were calculated:

- Geometric Mean Titres (GMTs) of HI for each vaccine strain at Day 0 and Day 21 with 95% confidence interval (CI).
- SCF for each vaccine strain with 95% CI at Day 21.
- SCR for each vaccine strain with exact 95% CI at Day 21.
- SPR for each vaccine strain with exact 95% CI at Day 0 and Day 21.

Analysis of safety

The analysis was based on the Total Vaccinated cohort.

The percentage of subjects reporting each solicited local and general symptom during the 7-day (Days 0-6) follow-up period was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 symptoms and for general symptoms assessed by the investigators as related to study vaccination. The duration of each solicited local and general symptom during the 7-day (Days 0-6) solicited follow-up period was also tabulated.

The proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms and reported within 21 days post-vaccination (Days 0 – 20) was tabulated. The same tabulation was performed for Grade 3 AEs and for AEs assessed by the investigator as related to study vaccination.

The proportion of subjects with at least one report of MAE or AESI classified by the MedDRA preferred term and reported within 21 days post vaccination (Day 0 – 20) and from Day 21 to Day 179 was tabulated, The same tabulation was performed for Grade 3 MAEs & AESIs and for MAEs & AESIs assessed by the investigators as related to study vaccination. The proportion of subjects with at least one report of a SAE classified by MedDRA preferred term and reported within 21 days post vaccination (Day 0 – 20) and from Day 21 to Day 364 was tabulated.

Study Population: Male or female subjects previously enrolled in study 109821 in the ≥ 65 years or 18-41 years of age group and having received the study vaccine, free of an acute aggravation of the health status. Written informed consent was obtained from the subject prior to study start. Women were to be of non-childbearing potential or if of childbearing potential had to practice adequate contraception for 30 days prior to vaccination, to have a negative pregnancy test and to continue such precautions for 2 months after vaccination.

Number of subjects	**Flu NG Group**	**Flu Eld Group**	**Flu Yng Group**
Planned, N	475	488	289
Randomised, N (Total Vaccinated cohort)	375	393	203
Completed, n (%) at Day 21	374 (99.7)	390 (99.2)	203 (100)
Completed, n (%) at Day 364	353 (94.1)	375 (95.4)	187 (92.1)
Total Number Subjects Withdrawn, n (%)	22 (5.9)	18 (4.6)	16 (7.9)
Withdrawn due to Adverse Events, n (%)	7 (1.9)	4 (1.0)	0 (0.0)

Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	15 (4.0)	14 (3.6)	16 (7.9)
Demographics	**Flu NG Group**	**Flu Eld Group**	**Flu Yng Group**
N (Total Vaccinated cohort)	375	393	203
Females: Males	190:185	203:190	118:85
Mean Age, years (SD)	74.4 (5.23)	74.7 (5.74)	32.4 (6.78)
White - Caucasian / European heritage, n (%)	372 (99.2)	390 (99.2)	198 (97.5)

Primary Efficacy Results: Number (%) of subjects reporting solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

		Flu NG Group					Flu Eld Group					Flu Yng Group				
		N	n	%	95 % CI		N	n	%	95 % CI		N	n	%	95 % CI	
Symptom	**Intensity**				LL	UL				LL	UL				LL	UL
Ecchymosis	>20 mm	375	2	0.5	0.1	1.9	392	3	0.8	0.2	2.2	203	1	0.5	0.0	2.7
	>100 mm	375	0	0.0	0.0	1.0	392	0	0.0	0.0	0.9	203	0	0.0	0.0	1.8
Pain	Any	375	159	42.4	37.3	47.6	392	49	12.5	9.4	16.2	203	122	60.1	53.0	66.9
	Grade 3	375	0	0.0	0.0	1.0	392	0	0.0	0.0	0.9	203	0	0.0	0.0	1.8
Redness	>20 mm	375	57	15.2	11.7	19.2	392	10	2.6	1.2	4.6	203	9	4.4	2.0	8.2
	>100 mm	375	3	0.8	0.2	2.3	392	0	0.0	0.0	0.9	203	0	0.0	0.0	1.8
Swelling	>20 mm	375	23	6.1	3.9	9.1	392	6	1.5	0.6	3.3	203	7	3.4	1.4	7.0
	>100 mm	375	0	0.0	0.0	1.0	392	0	0.0	0.0	0.9	203	0	0.0	0.0	1.8

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, that prevented normal everyday activities.

Primary Efficacy Results: Number of days with local symptoms (any grade) during the 7-day (Day 0-6) post-vaccination period (Total Vaccinated cohort)

Solicited symptom	**Group**	**N**	**Mean**	**Median**
Ecchymosis	Flu NG	2	6.5	6.5
	Flu Eld	3	4.3	5.0
	Flu Yng	1	2.0	2.0
Pain	Flu NG	159	2.2	2.0
	Flu Eld	49	2.1	2.0
	Flu Yng	122	2.1	2.0
Redness	Flu NG	57	2.7	3.0
	Flu Eld	9	3.1	2.0
	Flu Yng	9	2.3	1.0
Swelling	Flu NG	23	2.4	2.0
	Flu Eld	6	2.5	1.5
	Flu Yng	7	1.6	1.0

N = Number of subjects with the symptom and without the missing confirmed grade.

Primary Efficacy Results: Number (%) of subjects reporting solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)

Symptom	**Intensity/ Relationship**	**Flu NG Group**					**Flu Eld Group**					**Flu Yng Group**				
		N	**n**	**%**	**95 % CI**		**N**	**n**	**%**	**95 % CI**		**N**	**n**	**%**	**95 % CI**	
					LL	**UL**				**LL**	**UL**				**LL**	**UL**
Arthralgia	Any	375	44	11.7	8.7	15.4	392	20	5.1	3.1	7.8	203	11	5.4	2.7	9.5
	Grade 3	375	0	0.0	0.0	1.0	392	0	0.0	0.0	0.9	203	1	0.5	0.0	2.7
	Related	375	25	6.7	4.4	9.7	392	8	2.0	0.9	4.0	203	9	4.4	2.0	8.2
Fatigue	Any	375	72	19.2	15.3	23.6	392	37	9.4	6.7	12.8	203	39	19.2	14.0	25.3
	Grade 3	375	1	0.3	0.0	1.5	392	2	0.5	0.1	1.8	203	2	1.0	0.1	3.5
	Related	375	40	10.7	7.7	14.2	392	17	4.3	2.5	6.9	203	28	13.8	9.4	19.3
Gastrointestinal symptoms	Any	375	26	6.9	4.6	10.0	392	18	4.6	2.7	7.2	203	9	4.4	2.0	8.2
	Grade 3	375	1	0.3	0.0	1.5	392	1	0.3	0.0	1.4	203	0	0.0	0.0	1.8

	Related	375	11	2.9	1.5	5.2	392	10	2.6	1.2	4.6	203	7	3.4	1.4	7.0
Headache	Any	375	54	14.4	11.0	18.4	392	38	9.7	7.0	13.1	203	31	15.3	10.6	21.0
	Grade 3	375	2	0.5	0.1	1.9	392	2	0.5	0.1	1.8	203	0	0.0	0.0	1.8
	Related	375	33	8.8	6.1	12.1	392	18	4.6	2.7	7.2	203	21	10.3	6.5	15.4
Myalgia	Any	375	68	18.1	14.4	22.4	392	33	8.4	5.9	11.6	203	36	17.7	12.7	23.7
	Grade 3	375	0	0.0	0.0	1.0	392	1	0.3	0.0	1.4	203	1	0.5	0.0	2.7
	Related	375	44	11.7	8.7	15.4	392	16	4.1	2.4	6.5	203	26	12.8	8.5	18.2
Shivering	Any	375	32	8.5	5.9	11.8	392	16	4.1	2.4	6.5	203	10	4.9	2.4	8.9
	Grade 3	375	1	0.3	0.0	1.5	392	2	0.5	0.1	1.8	203	0	0.0	0.0	1.8
	Related	375	21	5.6	3.5	8.4	392	8	2.0	0.9	4.0	203	10	4.9	2.4	8.9
Temperature (Orally)	≥38.0°C	375	3	0.8	0.2	2.3	392	1	0.3	0.0	1.4	203	2	1.0	0.1	3.5
	≥39.0°C	375	0	0.0	0.0	1.0	392	0	0.0	0.0	0.9	203	0	0.0	0.0	1.8
	Related	375	3	0.8	0.2	2.3	392	0	0.0	0.0	0.9	203	2	1.0	0.1	3.5

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 solicited general symptom regardless of intensity grade or relationship to the study vaccination.
Grade 3 symptom = symptoms that prevented normal activity.
Related = general symptoms assessed by the investigator as causally related to the study vaccination.

Primary Efficacy Results: Number of days with general symptoms (any grade) during the 7-day (Day 0-6) post-vaccination period (Total Vaccinated cohort)

Solicited symptom	**Group**	**N**	**Mean**	**Median**
Arthralgia	Flu NG	44	2.3	2.0
	Flu Eld	20	4.0	3.0
	Flu Yng	11	2.4	2.0
Fatigue	Flu NG	72	2.2	2.0
	Flu Eld	37	2.2	2.0
	Flu Yng	39	2.7	2.0
Gastrointestinal	Flu NG	26	2.1	2.0
	Flu Eld	18	2.2	2.0
	Flu Yng	9	3.3	2.0
Headache	Flu NG	54	1.9	1.0
	Flu Eld	38	2.5	2.0
	Flu Yng	31	1.9	1.0
Myalgia	Flu NG	68	2.2	2.0
	Flu Eld	33	3.2	3.0
	Flu Yng	36	1.9	2.0
Shivering	Flu NG	32	1.8	1.0
	Flu Eld	16	1.9	1.5
	Flu Yng	10	2.0	2.0
Fever	Flu NG	3	1.0	1.0
	Flu Eld	1	1.0	1.0
	Flu Yng	1	3.0	3.0

N = Number of subjects with the symptom and without the missing confirmed grade.

Primary Efficacy Results: Number (%) of subjects with unsolicited AEs that resulted in a medically attended visit (MAEs) during the active phase (Day 0 to Day 20) of the study (Total Vaccinated cohort)

All MAEs (occurring within Days 0-20 following vaccination)	**FLU NG Group N = 375**	**Flu Eld Group N = 393**	**Flu Yng Group N = 203**
Subjects with any MAE(s), n (%)	17 (4.5)	22 (5.6)	9 (4.4)
Subjects with grade 3 MAE(s), n (%)	3 (0.8)	6 (1.5)	1 (0.5)
Subjects with related MAE(s), n (%)	0 (0.0)	0 (0.0)	1 (0.5)
Upper respiratory tract infection	1 (0.3)	2 (0.5)	-
Bronchitis	-	2 (0.5)	-
Pyrexia	1 (0.3)	-	1 (0.5)
Urinary tract infection	1 (0.3)	-	1 (0.5)

Adenoiditis	-	-	1 (0.5)
Back pain	-	1 (0.3)	-
Bursitis	-	1 (0.3)	-
Cerebral infarction	-	1 (0.3)	-
Cervicobrachial syndrome	1 (0.3)	-	-
Chronic obstructive pulmonary disease	1 (0.3)	-	-
Colon cancer	-	1 (0.3)	-
Contusion	-	-	1 (0.5)
Cystitis	-	1 (0.3)	-
Diarrhoea	-	1 (0.3)	-
Diverticulitis	1 (0.3)	-	-
Drug hypersensitivity	-	1 (0.3)	-
Dyspnoea	1 (0.3)	-	-
Erythema	1 (0.3)	-	-
Eustachian tube obstruction	1 (0.3)	-	-
Excoriation	-	1 (0.3)	-
Eye pain	1 (0.3)	-	-
Fatigue	1 (0.3)	-	-
Gastritis	1 (0.3)	-	-
Gastrooesophageal reflux disease	1 (0.3)	-	-
Gingivitis	-	1 (0.3)	-
Glaucoma	-	1 (0.3)	-
Hyperkeratosis	1 (0.3)	-	-
Interstitial lung disease	1 (0.3)	-	-
Joint sprain	-	1 (0.3)	-
Middle ear effusion	-	1 (0.3)	-
Muscle spasms	-	-	1 (0.5)
Musculoskeletal chest pain	-	1 (0.3)	-
Myalgia	-	-	1 (0.5)
Nasopharyngitis	-	1 (0.3)	-
Oropharyngeal pain	-	-	1 (0.5)
Osteoporosis	-	1 (0.3)	-
Pain in extremity	1 (0.3)	-	-
Peripheral arterial occlusive disease	-	1 (0.3)	-
Phlebitis	-	1 (0.3)	-
Presyncope	-	1 (0.3)	-
Rash	-	-	1 (0.5)
Sciatica	-	1 (0.3)	-
Sinusitis	-	-	1 (0.5)
Small intestinal obstruction	1 (0.3)	-	-
Tendon rupture	1 (0.3)	-	-
Tinnitus	-	-	1 (0.5)
Tooth extraction	-	1 (0.3)	-
Tooth infection	1 (0.3)	-	-
Toothache	-	-	1 (0.5)
Trigger finger	-	1 (0.3)	-
Urosepsis	-	1 (0.3)	-
Vertigo	1 (0.3)	-	-
Wound infection	-	1 (0.3)	-

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

Primary Efficacy Results: Number (%) of subjects with AESI including autoimmune diseases from Day 0 to Day 20 (Total Vaccinated cohort)

All AESIs (occurring within Days 0-20 following vaccination)	**Flu NG Group N=375**	**Flu Eld Group N=393**	**Flu Yng Group N = 203**

Subjects with any AESI, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Primary Efficacy Results: Occurrence of unsolicited AEs and of SAEs during the active phase, please refer to the safety section of the document.

Secondary Outcome Variable(s): Number (%) of subjects with unsolicited AEs that resulted in medically attended visit (MAEs) between Day 21 and Day 179 (Total Vaccinated cohort)

Most frequent MAEs (occurring within Days 21-179 following vaccination)	**Flu NG Group N=375**	**Flu Eld Group N=393**	**Flu Yng Group N = 203**
Subjects with any MAE(s), n (%)	89 (23.7)	111 (28.2)	55 (27.1)
Subjects with grade 3 MAE(s), n (%)	22 (5.9)	26 (6.6)	14 (6.9)
Subjects with related MAE(s), n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	5 (1.3)	12 (3.1)	7 (3.4)
Upper respiratory tract infection	5 (1.3)	10 (2.5)	6 (3.0)
Nasopharyngitis	4 (1.1)	-	3 (1.5)
Cough	4 (1.1)	-	-
Atrial fibrillation	3 (0.8)	-	-
Arthralgia	3 (0.8)	-	-
Urinary tract infection	2 (0.5)	3 (0.8)	2 (1.0)
Oedema peripheral	2 (0.5)	-	-
Chronic obstructive pulmonary disease	2 (0.5)	-	-
Influenza like illness	2 (0.5)	-	4 (2.0)
Bursitis	2 (0.5)	-	-
Dizziness	2 (0.5)	-	2 (1.0)
Headache	2 (0.5)	-	-
Hip fracture	2 (0.5)	-	-
Humerus fracture	2 (0.5)	-	-
Squamous cell carcinoma	2 (0.5)	-	-
Insomnia	2 (0.5)	-	-
Hypertensive crisis	2 (0.5)	-	-
Pneumonia	-	6 (1.5)	-
Sinusitis	-	5 (1.3)	7 (3.4)
Vertigo	-	3 (0.8)	-
Diarrhoea	-	3 (0.8)	-
Back pain	-	3 (0.8)	-
Arthritis	-	3 (0.8)	-
Neck pain	-	3 (0.8)	-
Gastroenteritis	-	-	6 (3.0)
Pharyngitis	-	-	3 (1.5)
Rhinitis	-	-	3 (1.5)
Cystitis	-	-	2 (1.0)
Oropharyngeal pain	-	-	2 (1.0)
Ear infection	-	-	2 (1.0)
Otitis media	-	-	2 (1.0)
Migraine	-	-	2 (1.0)

Grade 3 = event that prevented normal activity
Related = event assessed by the investigator as causally related to the study vaccination
Counting rule applied: As there were more than 30 subjects per treatment group and ≤ 3 groups, only the 10 most frequent events in each treatment group are to be listed.
-: Implies that the MAE was not reported in the particular group or that the MAE was reported in the particular group but did not fall within the pre-defined counting rule of 10 most frequent events for that group.

Secondary Outcome Variable(s): Number (%) of subjects with AESI, including autoimmune diseases throughout the entire follow-up phase between Day 21 and Day 364 (Total Vaccinated cohort)

All AESIs (occurring within Days 21-364 following vaccination)	**Flu NG Group N=375**	**Flu Eld Group N=393**	**Flu Yng Group N = 203**
Subjects with any AESI, n (%)	2 (0.5)	0 (0.0)	0 (0.0)
Subjects with grade 3 AESI, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Subjects with related AESI, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Scleroderma	1 (0.3)	-	-
Neuropathy peripheral	1 (0.3)	-	-

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

Secondary Outcome Variable(s): Seropositivity rates and GMTs for HI antibody titres at Day 0 and Day 21 (ATP Immunogenicity cohort)

Vaccine strain	Group	Timing	N	≥ 1:10				GMT		
				n	%	95% CI		value	95% CI	
						LL	UL		LL	UL
A/Brisbane	Flu NG	PRE	366	336	91.8	88.5	94.4	28.5	25.7	31.5
		PI(D21)	367	364	99.2	97.6	99.8	70.8	64.7	77.4
	Flu Eld	PRE	374	315	84.2	80.1	87.8	22.9	20.7	25.3
		PI(D21)	375	366	97.6	95.5	98.9	51.9	47.0	57.2
	Flu Yng	PRE	194	186	95.9	92.0	98.2	52.8	44.6	62.5
		PI(D21)	194	193	99.5	97.2	100	112.5	98.4	128.5
A/Uruguay	Flu NG	PRE	366	344	94.0	91.0	96.2	48.9	43.5	54.8
		PI(D21)	368	368	100	99.0	100	331.3	296.7	370.0
	Flu Eld	PRE	374	320	85.6	81.6	89.0	29.2	25.7	33.1
		PI(D21)	375	368	98.1	96.2	99.2	149.2	131.1	169.9
	Flu Yng	PRE	194	167	86.1	80.4	90.6	29.2	25.1	34.0
		PI(D21)	194	191	98.5	95.5	99.7	161.7	137.8	189.8
B/Brisbane	Flu NG	PRE	366	366	100	99.0	100	169.1	153.2	186.7
		PI(D21)	368	368	100	99.0	100	576.5	526.5	631.1
	Flu Eld	PRE	374	374	100	99.0	100	157.4	143.2	173.1
		PI(D21)	375	375	100	99.0	100	463.5	422.0	509.1
	Flu Yng	PRE	194	192	99.0	96.3	99.9	196.4	167.3	230.5
		PI(D21)	194	194	100	98.1	100	765.2	682.3	858.1

GMT = Geometric Mean antibody Titre
N = number of subjects with available results
n(%) = number (percentage) of seropositive subjects (HI titre ≥ 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): SPR for HI antibody titres at Day 0 and Day 21 (ATP Immunogenicity cohort)

Vaccine strain	Group	Timing	N	SPR			
				n	%	95% CI	
						LL	UL
A/Brisbane	Flu NG	PRE	366	171	46.7	41.5	52.0
		PI(D21)	367	314	85.6	81.5	89.0
	Flu Eld	PRE	374	142	38.0	33.0	43.1
		PI(D21)	375	276	73.6	68.8	78.0
	Flu Yng	PRE	194	137	70.6	63.7	76.9
		PI(D21)	194	179	92.3	87.6	95.6
A/Uruguay	Flu NG	PRE	366	247	67.5	62.4	72.3
		PI(D21)	368	361	98.1	96.1	99.2
	Flu Eld	PRE	374	178	47.6	42.4	52.8
		PI(D21)	375	341	90.9	87.6	93.6
	Flu Yng	PRE	194	102	52.6	45.3	59.8
		PI(D21)	194	181	93.3	88.8	96.4
B/Brisbane	Flu NG	PRE	366	359	98.1	96.1	99.2
		PI(D21)	368	368	100	99.0	100
	Flu Eld	PRE	374	363	97.1	94.8	98.5
		PI(D21)	375	375	100	99.0	100

	Flu Yng	PRE	194	186	95.9	92.0	98.2
		PI(D21)	194	194	100	98.1	100

N = Number of subjects with available results
n (%) = Number (percentage) of seroprotected subjects (HI titre ≥ 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): SCR for HI antibody titres at Day 21 (ATP Immunogenicity cohort)

Vaccine strain	**Group**	**N**	**SCR**			
			n	**%**	**95% CI**	
					LL	**UL**
A/Brisbane	Flu NG	366	107	29.2	24.6	34.2
	Flu Eld	374	94	25.1	20.8	29.9
	Flu Yng	194	54	27.8	21.7	34.7
A/Uruguay	Flu NG	366	285	77.9	73.3	82.0
	Flu Eld	374	228	61.0	55.8	65.9
	Flu Yng	194	124	63.9	56.7	70.7
B/Brisbane	Flu NG	366	168	45.9	40.7	51.2
	Flu Eld	374	140	37.4	32.5	42.6
	Flu Yng	194	104	53.6	46.3	60.8

Seroconversion 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 of subjects with available results
N (%) = Number (percentage) of seroconverted subjects
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Secondary Outcome Variable(s): SCF for HI antibody titres at Day 21 (ATP Immunogenicity cohort)

Vaccine strain	**Group**	**N**	**SCF**		
			Value	**95% CI**	
				LL	**UL**
A/Brisbane	Flu NG	366	2.5	2.3	2.7
	Flu Eld	374	2.3	2.1	2.5
	Flu Yng	194	2.1	1.9	2.4
A/Uruguay	Flu NG	366	6.8	6.1	7.5
	Flu Eld	374	5.1	4.6	5.7
	Flu Yng	194	5.5	4.7	6.5
B/Brisbane	Flu NG	366	3.4	3.1	3.7
	Flu Eld	374	2.9	2.7	3.2
	Flu Yng	194	3.9	3.3	4.5

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

Safety results: Number (%) of subjects with unsolicited adverse events within the 21-day (Day 0 to Day 20) post-vaccination period (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Days 0-20 following vaccination)	**Flu NG Group N = 375**	**Flu Eld Group N = 393**	**Flu Yng Group N = 203**
Subjects with any AE(s), n (%)	45 (12.0)	47 (12.0)	38 (18.7)
Subjects with grade 3 AE(s), n (%)	3 (0.8)	8 (2.0)	1 (0.5)
Subjects with related AE(s), n (%)	8 (2.1)	5 (1.3)	3 (1.5)
Upper respiratory tract infection	5 (1.3)	5 (1.3)	4 (2.0)
Cough	4 (1.1)	1 (0.3)	2 (1.0)
Nasopharyngitis	3 (0.8)	3 (0.8)	3 (1.5)
Influenza like illness	2 (0.5)	1 (0.3)	2 (1.0)
Injection site pruritus	2 (0.5)	1 (0.3)	-
Vertigo	2 (0.5)	1 (0.3)	-

Pyrexia	2 (0.5)	-	-
Dyspnoea	2 (0.5)	1 (0.3)	-
Oropharyngeal pain	2 (0.5)	1 (0.3)	6 (3.0)
Ear pain	1 (0.3)	-	-
Eustachian tube obstruction	1 (0.3)	-	-
Eye pain	1 (0.3)	-	-
Abdominal pain upper	1 (0.3)	-	-
Diarrhoea	1 (0.3)	1 (0.3)	-
Gastritis	1 (0.3)	-	-
Gastrooesophageal reflux disease	1 (0.3)	1 (0.3)	-
Nausea	1 (0.3)	-	-
Small intestinal obstruction	1 (0.3)	-	-
Tongue ulceration	1 (0.3)	-	-
Facial pain	1 (0.3)	-	-
Fatigue	1 (0.3)	2 (0.5)	-
Injection site induration	1 (0.3)	-	-
Diverticulitis	1 (0.3)	-	-
Tooth infection	1 (0.3)	-	-
Urinary tract infection	1 (0.3)	1 (0.3)	-
Contusion	1 (0.3)	-	-
Joint sprain	1 (0.3)	1 (0.3)	-
Tendon rupture	1 (0.3)	-	-
Arthralgia	1 (0.3)	1 (0.3)	-
Neck pain	1 (0.3)	-	-
Pain in extremity	1 (0.3)	1 (0.3)	-
Cervicobrachial syndrome	1 (0.3)	-	-
Dizziness	1 (0.3)	-	-
Headache	1 (0.3)	-	4 (2.0)
Anxiety	1 (0.3)	-	-
Dysuria	1 (0.3)	-	-
Chronic obstructive pulmonary disease	1 (0.3)	-	-
Interstitial lung disease	1 (0.3)	-	-
Postnasal drip	1 (0.3)	-	-
Erythema	1 (0.3)	-	-
Hyperkeratosis	1 (0.3)	-	-
Pruritus	1 (0.3)	-	-
Haematoma	1 (0.3)	-	-
Bronchitis	-	2 (0.5)	-
Back pain	-	2 (0.5)	-
Musculoskeletal chest pain	-	2 (0.5)	-
Middle ear effusion	-	1 (0.3)	-
Glaucoma	-	1 (0.3)	-
Abdominal pain	-	1 (0.3)	-
Gingivitis	-	1 (0.3)	-
Toothache	-	1 (0.3)	-
Drug hypersensitivity	-	1 (0.3)	-
Multiple allergies	-	1 (0.3)	-
Cystitis	-	1 (0.3)	-
Urosepsis	-	1 (0.3)	-
Wound infection	-	1 (0.3)	-
Excoriation	-	1 (0.3)	-
Bursitis	-	1 (0.3)	-
Osteoarthritis	-	1 (0.3)	-
Osteoporosis	-	1 (0.3)	-

Trigger finger	-	1 (0.3)	-
Colon cancer	-	1 (0.3)	-
Cerebral infarction	-	1 (0.3)	-
Hypoaesthesia	-	1 (0.3)	-
Presyncope	-	1 (0.3)	-
Sciatica	-	1 (0.3)	-
Epistaxis	-	1 (0.3)	-
Nasal congestion	-	1 (0.3)	-
Respiratory disorder	-	1 (0.3)	-
Rhinorrhoea	-	1 (0.3)	-
Tooth extraction	-	1 (0.3)	-
Peripheral arterial occlusive disease	-	1 (0.3)	-
Phlebitis	-	1 (0.3)	-
Pain	-	-	2 (1.0)
Sinusitis	-	-	2 (1.0)
Myalgia	-	-	2 (1.0)
Urticaria	-	-	2 (1.0)

Grade 3 =event that prevented normal everyday activity
Related = event assessed by the investigator as causally related to the study vaccination
Counting rule applied: As there were more than 30 subjects per treatment group and ≤ 3 groups, only the 10 most frequent events in each treatment group are to be listed.
-: Implies that the AE was not reported in the particular group or that the AE was reported in the particular group but did not fall within the pre-defined counting rule of 10 most frequent events for that group.

Safety results: Number (%) of subjects with SAEs from Day 0 to Day 20 (Total Vaccinated cohort)

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

All SAEs	**Flu NG Group N = 375**	**Flu Eld Group N = 393**	**Flu Yng Group N = 203**
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	3 (0.8) [0]	4 (1.0) [0]	0 (0.0) [0]
Tendon rupture	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Interstitial lung disease	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Small intestinal obstruction	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Peripheral arterial occlusive disease	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Colon cancer	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Cerebral infarction	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Urosepsis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Fatal SAEs	**Flu NG Group N = 375**	**Flu Eld Group N = 393**	**Flu Yng Group N = 203**
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Interstitial lung disease*	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]

* The SAE started between Day 0 and Day 20 but had a fatal outcome after Day 21.

Safety results: Number (%) of subjects with SAEs from Day 21 to Day 364 (Total Vaccinated cohort)*

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

All SAEs	**Flu NG Group N = 375**	**Flu Eld Group N = 393**	**Flu Yng Group N = 203**
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	40 (10.7) [0]	43 (10.9) [0]	4 (2.0) [0]
Hip fracture	3 (0.8) [0]	1 (0.3) [0]	0 (0.0) [0]
Diarrhoea	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Prostate cancer	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Pyelonephritis	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Urosepsis	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Coronary artery occlusion	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Pneumonia bacterial	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Scleroderma	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Pulmonary embolism	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]

Pneumonia aspiration	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Pneumonia staphylococcal	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Gastrointestinal haemorrhage	1 (0.3) [0]	2 (0.5) [0]	0 (0.0) [0]
Atrial fibrillation	2 (0.5) [0]	1 (0.3) [0]	0 (0.0) [0]
Myocardial infarction	1 (0.3) [0]	3 (0.8) [0]	0 (0.0) [0]
Rectal cancer	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Humerus fracture	2 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]
Cholecystitis	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Cerebral haemorrhage	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Chronic obstructive pulmonary disease	2 (0.5) [0]	2 (0.5) [0]	0 (0.0) [0]
Road traffic accident	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Ventricular fibrillation	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Diverticulitis	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Chest pain	1 (0.3) [0]	2 (0.5) [0]	0 (0.0) [0]
Multiple myeloma	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Pneumonia	3 (0.8) [0]	3 (0.8) [0]	0 (0.0) [0]
Fatigue	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Angina pectoris	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Restrictive pulmonary disease	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Small intestinal obstruction	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Squamous cell carcinoma	2 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]
Breast cancer	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Nephrolithiasis	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Arrhythmia	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Renal failure acute	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Adverse drug reaction	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Vertigo	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Neuropathy peripheral	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Anaemia	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Osteoarthritis	1 (0.3) [0]	1 (0.3) [0]	0 (0.0) [0]
Carotid artery stenosis	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Cerebrovascular accident	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Volvulus	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Viral infection	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Death	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Bronchitis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Cystocele	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Osteonecrosis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Gastroenteritis viral	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Haemorrhagic stroke	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Left ventricular failure	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Pulmonary arterial hypertension	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Enterocolitis infectious	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Lymphatic fistula	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Wound infection	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Factor XIII deficiency	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Cerebral infarction	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Acetabulum fracture	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Pelvic fracture	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Herpes zoster	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Colon cancer	0 (0.0) [0]	2 (0.5) [0]	0 (0.0) [0]
Pancreatitis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Arterial occlusive disease	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Radius fracture	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]

Stress cardiomyopathy	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Aesthesioneuroblastoma	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Cholelithiasis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Aortic aneurysm	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Benign prostatic hyperplasia	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Atrial flutter	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Sepsis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Peptic ulcer	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Chest discomfort	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Femoral arterial stenosis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Haemoptysis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Gastroenteritis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Gastric ulcer	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Renal cell carcinoma	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Coronary artery disease	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Wrist fracture	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Appendicitis	0 (0.0) [0]	1 (0.3) [0]	2 (1.0) [0]
Cardiac failure congestive	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Excoriation	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Pleural effusion	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Dizziness	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Gun shot wound	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Fatal SAEs	**Flu NG Group N = 375**	**Flu Eld Group N = 393**	**Flu Yng Group N = 203**
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	5 (1.3) [0]	2 (0.5) [0]	0 (0.0) [0]
Death	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Pneumonia aspiration	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Cerebral haemorrhage	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Road traffic accident	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Ventricular fibrillation	1 (0.3) [0]	0 (0.0) [0]	0 (0.0) [0]
Prostate cancer	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Atrial flutter	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Sepsis	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]

* The analysis was performed on the Total Vaccinated cohort. Subjects without any information during the Day 21 - Day 364 safety follow-up period, due to withdrawal between Day 0 and Day 21, were counted as subjects without any event during this period.
Note: One SAE (Pneumonia) occurred after Day 364 in a subject of the Flu Eld Group; it was assessed by the investigator as not related to the study vaccination.

Conclusion:
During the 7-day (Days 0-6) post-vaccination period, in all groups, pain was the most frequent solicited local symptom. This symptom was reported by 159 (42.4%) subjects in the Flu NG Group, 49 (12.5%) subjects in the Flu Eld Group and 122 (60.1%) subjects in the Flu Yng Group. In the Flu NG and the Flu Yng groups, fatigue was the most frequent solicited general symptom (it was reported by 72 (19.2%) and 39 (19.2%) subjects, respectively). In the Flu Eld Group, headache was the most frequent symptom and was reported by 38 (9.7%) subjects.
During the active phase, 45 (12.0%) subjects of the Flu NG Group, 47 (12.0%) subjects of the Flu Eld Group and 38 (18.7%) subjects of the Flu Yng Group reported unsolicited adverse events; in 17 (4.5%), 22 (5.6%) and 9 (4.4%) subjects from the Flu NG Group, the Flu Eld Group and the Flu Yng Group, the AEs resulted in a medically attended visit; no subjects reported AESI.
Up to Day 20, SAEs were reported in 3 (0.8%) subjects in the Flu NG Group and 4 (1.0%) subjects in the Flu Eld Group. One SAE was fatal for one subject in the Flu NG Group.
From Day 21 up to Day 364, SAEs were reported in 40 (10.7%) subjects in the Flu NG Group, 43 (10.9%) subjects in the Flu Eld Group and 4 (2.0%) subjects in the Flu Yng Group; fatal SAEs were reported for 5 subjects in the Flu NG Group and for 2 subjects in the Flu Eld Group.
All the SAEs reported during the whole study period were assessed by the investigators as not causally related to the study

vaccination.

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