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.: 108708 (Flu-LD-007)

Title: A phase IIb, controlled, randomized, multicenter, observer blinded study to evaluate the immunogenicity, safety and reactogenicity of a second vaccination with the low dose influenza vaccine adjuvanted with AS03 compared to a second dose of Fluarix™ (GlaxoSmithKline Biologicals) administered intramuscularly in elderly ≥ 60 years previously vaccinated in FLU-LD-002 clinical trial.
Fluarix™ (Flu): GlaxoSmithKline (GSK) Biologicals' inactivated influenza split vaccine.
FluLD: GSK Biologicals low dose influenza vaccine adjuvanted with AS03.

Rationale: The purpose of the study was to evaluate the immunogenicity and safety of a second vaccination with the low dose influenza vaccine adjuvanted with AS03 compared to Flu vaccine.

Phase: IIb

Study Period: 20 October 2006 until 05 February 2007.

Study Design: Multicenter, observer blind, controlled study with 2 parallel groups. Subjects had been randomized in the previous study, FLU-LD-002 (9:2), and were allocated to the same vaccine group in the present trial.

Centers: 4 centers in Norway.

Indication: Re-vaccination against influenza in male and female subjects aged 60 years and older.

Treatment: The study groups were as follows:

- FluLD Group: subjects received influenza vaccine adjuvanted with AS03; subjects had previously received one dose of FluLD influenza vaccine during study FLU-LD-002 (107192).
- Flu Group: subjects received one dose of Flu vaccine; subjects had previously received one dose of Flu vaccine during study FLU-LD-002 (107192).

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

Objectives:

To assess in elderly subjects ≥ 60 years old, the safety of re-vaccination with the low dose adjuvanted (AS03) influenza vaccine, during the entire study period (30 days). Flu vaccine was used as reference.

Primary Outcome/Efficacy Variable:

- Occurrence, intensity and relationship to re-vaccination of solicited local and general signs and symptoms during a 7-day follow-up period (i.e. day of re-vaccination and 6 subsequent days) after re-vaccination in each group.
- Occurrence, intensity and relationship to re-vaccination of unsolicited adverse events (AEs) during a 30-day follow-up period (i.e. day of re-vaccination and 29 subsequent days) after re-vaccination in each group.
- Occurrence and relationship to re-vaccination of serious adverse events (SAEs) during the entire study period in each group.

Secondary Outcome/Efficacy Variable(s):

At Days 0 and 21: serum hemagglutination-inhibition (HI) antibody titer, against each of the three vaccine influenza virus strains, in each group.

Statistical Methods:

The 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. 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 of immunogenicity was performed on the ATP cohort for immunogenicity.
For each group and each of the 3 vaccine strains A/New Caledonia (H1N1), A/Wisconsin (H3N2) and B/Malaysia (B), the following parameters were tabulated: geometric mean titers (GMT) with 95% confidence interval (CI) at Days 0 and 21, seropositivity rate[1] with exact 95% CI at Days 0 and 21, seroconversion rate[2] with exact 95% CI at Day 21, seroprotection rate[3] with exact 95% CI at Days 0 and 21 and seroconversion factor[4] with 95% CI at Day 21.

[1]The seropositivity rate was defined as the proportion of subjects with anti-HI titer ≥ 1:10
[2]The seroconversion rate was defined as the proportion of subjects with a pre-vaccination serum HI titer <1:10 and a post-vaccination serum HI titer ≥ 1:40, or a pre-vaccination serum HI titer ≥ 1:10 and a fold increase (post/pre) ≥ 4.
[3]The seroprotection rate was defined as the proportion of subjects with a serum HI titer ≥ 1:40.
[4]The seroconversion factor was defined as the fold increase in serum HI GMT on Day 21 compared to Day 0.

Analysis of safety
The analysis of safety was performed on the Total Vaccinated cohort.
For each group, the percentage of subjects reporting each individual solicited local and general symptom during the 7-day (Days 0-6) solicited follow-up period was tabulated with exact 95% CI. The same tabulations were done for Grade 3 solicited local and general symptoms and for related general solicited symptoms. The percentage of subjects with at least one report of an unsolicited AE up to 30 days (Days 0-29) after vaccination was tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The same tabulations were performed for Grade 3 AEs and for AEs with a relationship to vaccination. The occurrence of SAEs during the entire study period was tabulated according to MedDRA.

Study Population: Healthy male or female subject aged 60 years or older at the time of re-vaccination, who previously received either the FluLD influenza vaccine or Flu vaccine during the FLU-LD-002 clinical trial. Subjects were free of an acute aggravation of the health status as established by clinical examination before entering into the study. Written informed consent was obtained from the subject.

Number of subjects	**Flu Group**	**FluLD Group**
Planned, N	110	495
Entered, N (Total Vaccinated cohort)	133	545
Completed, n (%)	129 (97.0)	531 (97.4)
Total Number Subjects Withdrawn, n (%)	4 (3.0)	14 (2.6)
Withdrawn due to Adverse Events, n (%)	1 (0.8)	1 (0.2)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	3 (2.3)	13 (2.4)
Demographics	**Flu Group**	**FluLD Group**
N (Total Vaccinated cohort)	133	545
Females: Males	82:51	284:261
Mean Age, years (SD)	68.1 (5.78)	68.4 (5.95)
White - caucasian / european heritage, n (%)	133 (100)	545 (100)

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

Symptom	**Intensity**	**Flu Group**					**FluLD Group**				
					95 % CI					**95 % CI**	
		N	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Ecchymosis	Any	131	2	1.5	0.2	5.4	542	14	2.6	1.4	4.3
	> 50 mm	131	0	0.0	0.0	2.8	542	1	0.2	0.0	1.0
Pain	Any	131	27	20.6	14.0	28.6	542	282	52.0	47.7	56.3
	Grade 3	131	0	0.0	0.0	2.8	542	0	0.0	0.0	0.7
Redness	Any	131	28	21.4	14.7	29.4	542	245	45.2	41.0	49.5
	> 50 mm	131	4	3.1	0.8	7.6	542	102	18.8	15.6	22.4
Swelling	Any	131	16	12.2	7.1	19.1	542	186	34.3	30.3	38.5
	> 50 mm	131	2	1.5	0.2	5.4	542	56	10.3	7.9	13.2

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

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

Symptom	**Intensity/ Relationship**	**Flu Group**		**FluLD Group**	
			95 % CI		**95 % CI**

		N	n	%	LL	UL	N	n	%	LL	UL
Arthralgia	Any	131	10	7.6	3.7	13.6	542	96	17.7	14.6	21.2
	Grade 3	131	0	0.0	0.0	2.8	542	3	0.6	0.1	1.6
	Related	131	7	5.3	2.2	10.7	542	78	14.4	11.5	17.6
Fatigue	Any	131	16	12.2	7.1	19.1	542	152	28.0	24.3	32.0
	Grade 3	131	0	0.0	0.0	2.8	542	5	0.9	0.3	2.1
	Related	131	13	9.9	5.4	16.4	542	130	24.0	20.4	27.8
Fever (Axillary)	≥ 37.5°C	131	1	0.8	0.0	4.2	542	35	6.5	4.5	8.9
	> 39.0°C	131	0	0.0	0.0	2.8	542	1	0.2	0.0	1.0
	Related	131	0	0.0	0.0	2.8	542	29	5.4	3.6	7.6
Headache	Any	131	15	11.5	6.6	18.2	542	140	25.8	22.2	29.7
	Grade 3	131	0	0.0	0.0	2.8	542	1	0.2	0.0	1.0
	Related	131	10	7.6	3.7	13.6	542	116	21.4	18.0	25.1
Muscle aches	Any	131	12	9.2	4.8	15.5	542	179	33.0	29.1	37.2
	Grade 3	131	0	0.0	0.0	2.8	542	8	1.5	0.6	2.9
	Related	131	6	4.6	1.7	9.7	542	154	28.4	24.7	32.4
Shivering	Any	131	11	8.4	4.3	14.5	542	120	22.1	18.7	25.9
	Grade 3	131	0	0.0	0.0	2.8	542	12	2.2	1.1	3.8
	Related	131	6	4.6	1.7	9.7	542	102	18.8	15.6	22.4

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 general symptom irrespective of intensity grade or relationship to vaccination
Grade 3 symptom = symptom that prevented normal activity
Related = symptom considered by the investigator to have a causal relationship to vaccination

Secondary Outcome Variable (s):
Seropositivity rates and geometric means titers (GMTs) of HI antibody titers at different time points (ATP cohort for immunogenicity).

Antibody	**Group**	**Timing**	**N**	**≥ 1:10**				**GMT**		
						95% CI			**95% CI**	
				n	**%**	**LL**	**UL**	**value**	**LL**	**UL**
A/New Caledonia	**Flu**	PRE	125	122	97.6	93.1	99.5	65.9	54.4	79.9
		PI(D21)	125	125	100	97.1	100	111.6	94.3	132.2
	FluLD	PRE	513	504	98.2	96.7	99.2	61.8	56.6	67.3
		PI(D21)	513	509	99.2	98.0	99.8	114.4	105.8	123.8
A/Wisconsin	**Flu**	PRE	125	118	94.4	88.8	97.7	59.4	46.2	76.4
		PI(D21)	125	125	100	97.1	100	187.4	151.2	232.1
	FluLD	PRE	513	489	95.3	93.1	97.0	82.0	72.6	92.5
		PI(D21)	513	513	100	99.3	100	370.0	339.2	403.6
B/Malaysia	**Flu**	PRE	125	123	98.4	94.3	99.8	100.2	83.1	120.7
		PI(D21)	125	124	99.2	95.6	100	158.7	132.6	189.9
	FluLD	PRE	513	505	98.4	97.0	99.3	112.1	101.7	123.6
		PI(D21)	513	511	99.6	98.6	100	232.4	215.1	251.0

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

Secondary Outcome Variable (s):
Seroconversion rate (SCR) for HI antibody titer at Day 21 (ATP cohort for immunogenicity).

Antibody	**Group**	**Timing**	**N**	**SCR**			
						95% CI	
				n	**%**	**LL**	**UL**
A/New Caledonia	**Flu**	PI(D21)	125	21	16.8	10.7	24.5
	FluLD	PI(D21)	513	78	15.2	12.2	18.6
A/Wisconsin	**Flu**	PI(D21)	125	52	41.6	32.9	50.8

	FluLD	PI(D21)	513	271	52.8	48.4	57.2
B/Malaysia	**Flu**	PI(D21)	125	10	8.0	3.9	14.2
	FluLD	PI(D21)	513	99	19.3	16.0	23.0

Seroconversion rate defined as the proportion of subjects with a pre-vaccination serum HI titer <1:10 and a post-vaccination serum HI titer ≥ 1:40, or a pre-vaccination serum HI titer ≥ 1:10 and a fold increase (post/pre) ≥ 4.
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 at Day 21

Secondary Outcome Variable (s):
Seroprotection rates (SPR) for HI antibody titer at each time point (ATP cohort for immunogenicity).

Antibody	**Group**	**Timing**	**N**	**≥ 1:40**			
						95% CI	
				n	**%**	**LL**	**UL**
A/New Caledonia	**Flu**	PRE	125	100	80.0	71.9	86.6
		PI(D21)	125	119	95.2	89.8	98.2
	FluLD	PRE	513	381	74.3	70.3	78.0
		PI(D21)	513	483	94.2	91.8	96.0
A/Wisconsin	**Flu**	PRE	125	81	64.8	55.8	73.1
		PI(D21)	125	117	93.6	87.8	97.2
	FluLD	PRE	513	397	77.4	73.5	80.9
		PI(D21)	513	507	98.8	97.5	99.6
B/Malaysia	**Flu**	PRE	125	111	88.8	81.9	93.7
		PI(D21)	125	118	94.4	88.8	97.7
	FluLD	PRE	513	442	86.2	82.9	89.0
		PI(D21)	513	507	98.8	97.5	99.6

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
PRE = Pre-vaccination at Day 0
PI(D21) = Post-vaccination at Day 21

Secondary Outcome Variable (s):
Seroconversion factor (SCF) for HI antibody titer at Day 21 (ATP cohort for immunogenicity).

Antibody	**Group**	**Timing**	**N**	**SCF**		
					95% CI	
				Value	**LL**	**UL**
A/New Caledonia	**Flu**	PI(D21)	125	1.7	1.5	1.9
	FluLD	PI(D21)	513	1.9	1.8	2.0
A/Wisconsin	**Flu**	PI(D21)	125	3.2	2.6	3.8
	FluLD	PI(D21)	513	4.5	4.1	5.0
B/Malaysia	**Flu**	PI(D21)	125	1.6	1.4	1.7
	FluLD	PI(D21)	513	2.1	1.9	2.2

Seroconversion factor defined as the fold increase in serum HI GMT on Day 21 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 at Day 21

Safety Results: Number (%) of subjects with unsolicited adverse events during the 30-day post-vaccination period (Total Vaccinated cohort).

Most Frequent Adverse Events - On-Therapy- (occurring within Days 0-29 following vaccination)	**Flu Group N = 133**	**FluLD Group N = 545**
Subjects with any AE(s), n (%)	31 (23.3)	121 (22.2)
Subjects with any grade 3 AE(s), n (%)	1 (0.8)	9 (1.7)
Subjects with any related AE(s), n (%)	4 (3.0)	34 (6.2)
Nasopharyngitis	13 (9.8)	33 (6.1)
Bronchitis	1 (0.8)	8 (1.5)
Cough	2 (1.5)	6 (1.1)

Injection site pruritus	1 (0.8)	7 (1.3)
Nausea	1 (0.8)	7 (1.3)
Dizziness	1 (0.8)	6 (1.1)
Diarrhea	1 (0.8)	4 (0.7)
Pharyngolaryngeal pain	1 (0.8)	4 (0.7)
Chills	1 (0.8)	3 (0.6)
Injection site warmth	1 (0.8)	3 (0.6)
Pneumonia	1 (0.8)	3 (0.6)
Sinusitis	-	4 (0.7)
Abdominal pain upper	2 (1.5)	-
Blepharitis	1 (0.8)	-
Cystitis	1 (0.8)	-
Dental operation	1 (0.8)	-
Eye inflammation	1 (0.8)	-
Herpes zoster	1 (0.8)	-
Hypertension	1 (0.8)	-
Musculoskeletal stiffness	1 (0.8)	-
Pain	1 (0.8)	-
Pulmonary embolism	1 (0.8)	-
Pyrexia	1 (0.8)	-
Skin irritation	1 (0.8)	-
Tooth infection	1 (0.8)	-

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 adverse event was not reported in the particular group or that the adverse event was reported in the particular group but did not fall within the pre-defined counting rule of 10 most frequent events for that group
Grade 3 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 (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	**Flu Group N = 133**	**FluLD Group N = 545**
Subjects with any SAE(s), n (%) [n assessed by investigators as related]	1 (0.8) [0]	2 (0.4) [0]
Cholelithiasis	0 (0.0) [0]	1 (0.2) [0]
Pancreatitis	0 (0.0) [0]	1 (0.2) [0]
Pneumonia	1 (0.8) [0]	0 (0.0) [0]
Pulmonary embolism	1 (0.8) [0]	0 (0.0) [0]
Sudden death	0 (0.0) [0]	1 (0.2) [0]
Fatal SAEs	**Flu Group N = 133**	**FluLD Group N = 545**
Subjects with fatal SAE(s), n (%) [n assessed by investigators as related]	0 (0.0) [0]	1 (0.2) [0]
Sudden death	0 (0.0) [0]	1 (0.2) [0]

Conclusion: Across groups, pain and redness at the injection site were the most frequently reported solicited local symptoms while fatigue and muscle aches were the most frequently reported solicited general in the FluLD Group, fatigue and headache were the most frequently reported solicited general in the Flu Group.
Unsolicited AEs were reported by 31 subjects (23.3%) and 121 (22.2%) in the Flu Group and FluLD Group, respectively; for 1 subject (0.8%) in the Flu Group and 9 subjects (1.7%) in the FluLD Group, the reported AEs were rated as Grade 3, while unsolicited AEs reported by 4 (3.0%) subjects in the Flu Group and 34 subjects (6.2%) in the FluLD Group were considered by the investigators to be related to the study vaccination. SAEs were reported for 1 subject in the Flu Group and 2 subjects in the FluLD Group; one SAE in the FluLD Group was fatal. None of the SAEs reported were considered by the investigators as related to the study vaccination.

Date updated: 04-September-2014