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Study No.: 110028
Title: A phase I/II, observer-blind, randomized, active-controlled trial to evaluate the safety and immunogenicity of an investigational vaccination regimen
Rationale: The aim of this study was to assess safety and immunogenicity of an investigational vaccination regimen when compared to GlaxoSmithKline (GSK) Biologicals' H5N1 A/Vietnam/1194/04 antigen manufactured in its Dresden facility (by the <i>Fluarix</i> ® manufacturing process). GSK Biologicals' H5N1 A/Vietnam/1194/04 antigen manufactured in its Dresden facility (Flu H5N1)
Phase: I/II
Study Period: 28 July 2007 to 21 March 2008
Study Design: Observer-blind, randomized (1:2:2:2:2), multi-center, active-controlled five-arm trial. Data from the group receiving the currently registered vaccines are presented. Data from the investigational vaccine regimen, which is not yet approved or marketed, are not reported at this time.
Centers: 10 centers: 7 in the United States and 3 in Canada.
Indication: Immunization against influenza disease caused by influenza A virus potential pandemic subtype (H5N1).
Treatment: The study groups were as follows: <ul style="list-style-type: none"> • Flu Group: Subjects received two doses of Flu H5N1 vaccine at Day 0 and Day 21 • Four groups received an investigational vaccination regimen Flu H5N1 vaccine was administered intramuscularly in the deltoid region of the non-dominant (Day 0) or dominant (Day 21) arm.
Objectives: <i>Only objectives related to the licensed vaccine are presented.</i> <ul style="list-style-type: none"> • To demonstrate the immunogenicity of the Flu H5N1 vaccine. Criteria for Evaluation: The criteria for evaluation of this objective consisted of the Geometric Mean Titer (GMT) and the seroconversion rate (SCR). <ul style="list-style-type: none"> • To describe the safety of the Flu H5N1 vaccine in terms of solicited local and general events, unsolicited adverse events (AEs), and serious adverse events (SAEs).
Primary Outcome/Efficacy Variables: <i>Only outcome variables related to the licensed vaccine are presented.</i> Immunogenicity: <ul style="list-style-type: none"> • Vaccine-homologous virus antibody response in subjects receiving 2 doses of vaccine, as demonstrated by the hemagglutination-inhibition (HI) antibody titer at Day 42. Safety: <ul style="list-style-type: none"> • The occurrence of specifically-solicited local and general signs and symptoms during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each dose of vaccine and overall per subject considering both post-immunization periods. • The occurrence of unsolicited AEs during a 21-day follow-up period after the first vaccination and 21 days after the second vaccination (Day 0 to 21 pre-dose and Day 21 post-dose to Day 42 intervals), as well as overall (Day 0 through Day 84). • The occurrence of SAEs, medically-attended events, and new onset chronic diseases (NOCDs) during the entire study period (Day 0 to 182).
Secondary Outcome/Efficacy Variables: <i>Only outcome variables related to the licensed vaccine are presented.</i> <ul style="list-style-type: none"> • Vaccine-homologous virus antibody response at 21 days following receipt of a first dose of vaccine. • Persistence of this response through approximately 6 months (182 days), as demonstrated by the vaccine-homologous virus HI antibody titer at Day 182.
Statistical Methods: The analyses were performed on the Total Vaccinated Cohort and the According-To-Protocol (ATP) cohort for immunogenicity <ul style="list-style-type: none"> • The Total Vaccinated Cohort included all subjects who received at least one dose of vaccine for whom any post-vaccination data were available. • The ATP Cohort for immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria,

complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom a complete set of immunogenicity data required for the primary outcome variables analyses were available. This implied that all subjects in the ATP Cohort for immunogenicity had at least Day 0 and 42 HI titer results for the A/Indonesia/5/05 virus.

Analysis of immunogenicity:

The analysis was based on the ATP Cohort for immunogenicity.

For subjects between 18 and 64 years of age, the lower bound of the 95% confidence interval (CI) for the percent of subjects achieving seroconversion for vaccine-homologous virus HI antibody (SCR*) should meet or exceed 40%, and the lower bound of the 95% CI for the percent of subjects achieving a vaccine-homologous virus HI antibody reciprocal titer \geq 40 (SPR**) should meet or exceed 70%.

The GMTs of vaccine-homologous virus HI antibody titers, SCR at Days 21 and 182 and SPR at Days 0, 21 and 182 with their two-sided 95% CI were also calculated.

*SCR is defined as the percentage of vaccinees who had either a prevaccination reciprocal titer $<$ 10 and a post-vaccination reciprocal titer \geq 40 or a prevaccination reciprocal titer \geq 10 and at least a 4-fold increase in post vaccination titer on the specified study day.

** SPR at Days 0, 21 and 182, defined as the percentage of vaccinees with a serum HI antibody reciprocal titer \geq 40 on the specified study day.

Analysis of safety

The analysis was based on the Total Vaccinated Cohort.

The percentage of subjects reporting each individual solicited local and general symptom during the 7-day (Day 0-6) solicited follow-up period after vaccination was tabulated with 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The proportion of subjects with at least one report of unsolicited AEs classified by the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and reported up to 21 days (Day 0 -20) after the first or after the second vaccination as well as overall (Day 0 through Day 84) was tabulated. The occurrence of SAEs, Medically-Attended AEs and NOCDs during the entire the study period was tabulated according to MedDRA preferred terms.

Study Population: Healthy adults 18 to 64 years of age, inclusive were enrolled in the study. Subjects with significant uncontrolled illness (medical or psychological), blood pressure abnormalities, cancer diagnosis and/or treatment within 3 years, immunosuppressive or immunodeficient conditions, or coagulation disorders were to be excluded from the study. Additionally, female subjects were not to be pregnant, nursing, or lactating; subjects of child bearing potential were to have a history of reliable contraceptive practices. Receipt of systemic glucocorticoids within 1 month, any other cytotoxic or immunosuppressive drug within 6 months, any non-influenza vaccines or investigational or non-registered products (drugs or vaccines) within 30 days, and any immunoglobulins or blood products within 3 months of study enrollment also were exclusionary criteria.

Number of subjects		Flu Group
Planned, N		150
Randomized, N (Total Vaccinated Cohort)		151
Completed to visit Day 42, n (%)		151 (100)
Completed to visit Day 182, n (%)		148 (98.0)
Total Number Subjects Withdrawn, n (%)		3 (2.0)
Withdrawn due to Adverse Events, n (%)		0(0.0)
Withdrawn due to Lack of Efficacy, n (%)		Not applicable
Withdrawn for other reasons, n (%)		3 (2.0)
Demographics		Flu Group
N (Total Vaccinated Cohort)		151
Females:Males		100:51
Mean Age, years (SD)		38.7 (11.25)
White - Caucasian / European heritage, n (%)		133 (88.1)

Primary Efficacy Results: Seroconversion for A/Indonesia/5/05 antibody at Days 21 and 42 (ATP cohort for immunogenicity)

Group	Pre-vacc status	N	Seroconversion							
			Day 21				Day 42*			
			n	%	95% CI		n	%	95% CI	
					LL	UL			LL	UL
Flu Group	S-	139	63	45.3	36.9	54	134	96.4	91.8	98.8
	S+	1	1	100	2.5	100	1	100	2.5	100

	Total	140	64	45.7	37.3	54.3	135	96.4	91.9	98.8				
<p>S- = seronegative subjects (antibody titer < 1:10 for A/Indonesia/5/05 antibody) prior to vaccination S+ = seropositive subjects (antibody titer ≥ 1:10 for A/Indonesia/5/05 antibody) prior to vaccination Total = subjects either seropositive or seronegative at pre-vaccination N = number of subjects with both pre- and post-vaccination results available n (%) = number (percentage) of responders 95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit * Primary Efficacy Variable</p>														
Primary Efficacy Results: Seropositivity rates and GMTs for A/Indonesia/5/05 antibodies (ATP cohort for immunogenicity)														
Antibody	Group	Timing	N	≥ 1:10				≥ 1:40				GMT*		
				n	%	95% CI		n	%	95% CI		value	95% CI	
						LL	UL			LL	UL		LL	UL
A/Indonesia/5/05	Flu Group	PRE	140	1	0.7	0	3.9	0	0	0	2.6	5	5	5.1
		Day 21	140	83	59.3	50.7	67.5	64	45.7	37.3	54.3	23.5	18.3	30.3
		Day 42*	140	136	97.1	92.8	99.2	135	96.4	91.9	98.8	480.3	390.5	590.7
		Day182	138	91	65.9	57.4	73.8	68	49.3	40.7	57.9	26.1	20.7	32.8
<p>Seroprotection = A/Indonesia/5/05antibody titer ≥ 1:40 N = number of subjects with available results n (%) = number (percentage) of subjects with titer within the specified range 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = Blood sample taken before vaccination Day 21 = Day 21 Post Dose 1 Day 42 = Day 42 Post Dose 1 Day 182 = Day 182 Post Dose1 * Primary Efficacy Variable</p>														
Primary Efficacy Results: Incidence of solicited local symptoms reported during the 7-day post-vaccination period (Day 0-6) following each dose and across doses (Total Vaccinated cohort)														
Symptom	Intensity	Flu Group												
		N	n	%	95 % CI									
					LL	UL								
Dose 1														
Pain	Any	151	131	86.8	80.3	91.7								
	Grade 3	151	6	4	1.5	8.4								
Redness	≥20 mm	151	7	4.6	1.9	9.3								
	>100 mm	151	0	0	0	2.4								
Swelling	≥20 mm	151	15	9.9	5.7	15.9								
	>100 mm	151	0	0	0	2.4								
Dose 2														
Pain	Any	147	123	83.7	76.7	89.3								
	Grade 3	147	5	3.4	1.1	7.8								
Redness	≥20 mm	147	5	3.4	1.1	7.8								
	>100 mm	147	0	0	0	2.5								
Swelling	≥20 mm	147	12	8.2	4.3	13.8								
	>100 mm	147	0	0	0	2.5								
Across Doses														
Pain	Any	151	139	92.1	86.5	95.8								
	Grade 3	151	10	6.6	3.2	11.8								
Redness	≥20 mm	151	9	6	2.8	11								
	>100 mm	151	0	0	0	2.4								
Swelling	≥20 mm	151	21	13.9	8.8	20.5								
	>100 mm	151	0	0	0	2.4								
<p>Any = occurrence of any solicited local symptom regardless of their intensity grade Grade 3 pain = significant pain at rest; prevented normal activities as assessed by inability to attend/do work or school N = number of subjects with at least one documented dose n (%) = number (percentage) of subjects reporting at least once the symptom</p>														

95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit						
Primary Efficacy Results: Incidence of solicited general symptoms reported during the 7-day post-vaccination period (Day 0-6) following each dose and across doses (Total Vaccinated cohort)						
Symptom	Intensity	Flu Group				
		N	n	%	95 % CI	
					LL	UL
Dose 1						
Fatigue	Any	151	42	27.8	20.8	35.7
	Grade 3	151	2	1.3	0.2	4.7
	Related	151	38	25.2	18.5	32.9
Headache	Any	151	45	29.8	22.6	37.8
	Grade 3	151	3	2	0.4	5.7
	Related	151	40	26.5	19.6	34.3
Joint pain at other location	Any	151	29	19.2	13.3	26.4
	Grade 3	151	1	0.7	0	3.6
	Related	151	28	18.5	12.7	25.7
Muscle aches	Any	151	64	42.4	34.4	50.7
	Grade 3	151	0	0	0	2.4
	Related	151	59	39.1	31.2	47.3
Shivering	Any	151	9	6	2.8	11
	Grade 3	151	1	0.7	0	3.6
	Related	151	7	4.6	1.9	9.3
Sweating	Any	151	9	6	2.8	11
	Grade 3	151	2	1.3	0.2	4.7
	Related	151	8	5.3	2.3	10.2
Temperature (Oral)	≥38 °C	151	1	0.7	0	3.6
	≥39 °C	151	0	0	0	2.4
	Related	151	1	0.7	0	3.6
Dose 2						
Fatigue	Any	147	48	32.7	25.2	40.9
	Grade 3	147	2	1.4	0.2	4.8
	Related	147	44	29.9	22.7	38
Headache	Any	147	45	30.6	23.3	38.7
	Grade 3	147	4	2.7	0.7	6.8
	Related	147	44	29.9	22.7	38
Joint pain at other location	Any	147	38	25.9	19	33.7
	Grade 3	147	2	1.4	0.2	4.8
	Related	147	37	25.2	18.4	33
Muscle aches	Any	147	60	40.8	32.8	49.2
	Grade 3	147	3	2	0.4	5.8
	Related	147	56	38.1	30.2	46.5
Shivering	Any	147	22	15	9.6	21.8
	Grade 3	147	0	0	0	2.5
	Related	147	19	12.9	8	19.4
Sweating	Any	147	18	12.2	7.4	18.7
	Grade 3	147	1	0.7	0	3.7
	Related	147	17	11.6	6.9	17.9
Temperature (Oral)	≥38 °C	147	11	7.5	3.8	13
	≥39 °C	147	0	0	0	2.5
	Related	147	10	6.8	3.3	12.2
Across doses						
Fatigue	Any	151	67	44.4	36.3	52.7
	Grade 3	151	4	2.6	0.7	6.6
	Related	151	62	41.1	33.1	49.3

Headache	Any	151	66	43.7	35.7	52
	Grade 3	151	6	4	1.5	8.4
	Related	151	64	42.4	34.4	50.7
Joint pain at other location	Any	151	53	35.1	27.5	43.3
	Grade 3	151	3	2	0.4	5.7
	Related	151	52	34.4	26.9	42.6
Muscle aches	Any	151	86	57	48.7	65
	Grade 3	151	3	2	0.4	5.7
	Related	151	79	52.3	44	60.5
Shivering	Any	151	27	17.9	12.1	24.9
	Grade 3	151	1	0.7	0	3.6
	Related	151	23	15.2	9.9	22
Sweating	Any	151	24	15.9	10.5	22.7
	Grade 3	151	3	2	0.4	5.7
	Related	151	23	15.2	9.9	22
Temperature (Oral)	≥38 °C	151	12	7.9	4.2	13.5
	≥39 °C	151	0	0	0	2.4
	Related	151	11	7.3	3.7	12.7

Any = occurrence of any solicited general symptom regardless of their intensity grade or relationship to vaccination
Grade 3 headache, fatigue, joint pain at other location, muscle aches, shivering and sweating = Prevented normal everyday activities as assessed by inability to attend/do work or school, or required intervention of a physician/healthcare provider

Related = general symptom assessed by the investigator to be causally related to the study vaccination

N = number of subjects with an administered dose

n (%) = number (percentage) of subjects reporting at least once the symptom

95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Secondary Outcome Variable(s): Vaccine response for A/Indonesia/5/05 antibody at Day 182 (ATP cohort for immunogenicity)

Group	Pre-vacc status	N	Vaccine response			
			n	%	95% CI	
					LL	UL
Flu Group	S-	137	67	48.9	40.3	57.6
	S+	1	0	0	0	97.5
	Total	138	67	48.6	40	57.2

S- = seronegative subjects (antibody titer < 1:10 for A/Indonesia/5/05) prior to vaccination

S+ = seropositive subjects (antibody titer ≥ 1:10 for A/Indonesia/5/05) prior to vaccination

Total = subjects either seropositive or seronegative at pre-vaccination

Vaccine response defined as:

For initially seronegative subjects, antibody titer ≥ 1:40 at Day 182

For initially seropositive subjects, antibody titer at Day 182 ≥ 4 fold the pre-vaccination antibody titer

N = number of subjects with both pre- and post-vaccination results available

n (%) = number (percentage) of responders

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Safety results: Most frequent unsolicited AEs experienced by study participants after first and second vaccination (Total Vaccinated cohort)

Most frequent adverse events - On-Therapy (occurring within Day 0 - 20 following vaccination)	Flu Group N = 151
Subjects with any AE(s), n (%)	73 (48.3)
Nausea	7 (4.6)
Pharyngolaryngeal pain	10 (6.6)
Headache	13 (8.6)
Nasopharyngitis	7 (4.6)
Lymphadenopathy	6 (4)

Detail of rule: > 30 subjects/treatment group and > 3 groups: display the most frequent 5 events in each treatment group

Safety results: Most frequent unsolicited AEs experienced by study participants (Days 0-84) (Total Vaccinated cohort)

Most frequent adverse events – On-Therapy	Flu Group N = 151
Subjects with any AE(s), n (%)	81 (53.6)
Nasopharyngitis	9 (6)
Headache	13 (8.6)
Nausea	7 (4.6)
Pharyngolaryngeal pain	10 (6.6)
Upper respiratory tract infection	7 (4.6)
Lymphadenopathy	7 (4.6)
Detail of rule: > 30 subjects/treatment group and > 3 groups: display the most frequent 5 events in each treatment group	
Safety results: Number (%) of subjects with medically attended AEs (Day 0-182) (Total Vaccinated cohort)	
Most frequent adverse events - On-Therapy (occurring within Day 0 - 182 following vaccination)	Flu Group N = 151
Subjects with any AE(s), n (%)	28 (18.5)
Sinusitis	3 (2)
Lymphadenopathy	2 (1.3)
Ear infection	2 (1.3)
Pyrexia	2 (1.3)
Skin laceration	2 (1.3)
Detail of rule: > 30 subjects/treatment group and > 3 groups: display the most frequent 5 events in each treatment group	
Safety results: Number (%) of subjects with NOCDs (Day 0-182) (Total Vaccinated cohort)	
Most frequent NOCDs - On-Therapy (occurring within Day 0 - 182 following vaccination)	Flu Group N = 151
Subjects with any NOCD(s), n (%)	0 (0)
Safety results: Number (%) of subjects with serious adverse events (Day 0-182) (Total Vaccinated cohort)	
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]	
All SAEs	Flu Group N = 151
Subjects with any SAE(s), n (%) [n assessed by investigator as related]	2 (1.3) [0]
Ovarian cyst	1 (0.7) [0]
Pulmonary embolism	1 (0.7) [0]
Uterine leiomyoma	1 (0.7) [0]
Fatal SAEs	Flu Group N = 151
Subjects with fatal SAE(s), n (%) [n assessed by investigator as related]	0 (0) [0]

Conclusion:

At Day 42, 96.4% of subjects seroconverted for A/Indonesia/5/05 antibodies and the GMT for A/Indonesia/5/05 antibodies was 480.3. Across doses, pain and muscle aches were the most frequent solicited local and general symptoms, respectively.

During the 21-day follow-up period after each vaccine dose and between Day 0 and Day 84, unsolicited AEs were reported by 73 (48.3%) and 81 (53.6%) subjects in Flu Group, respectively. Up to Day 182, medically-attended AEs, NOCDs and SAEs were reported by 28 (18.5%), 0 (0%) and 2 (1.3%) subjects, respectively. None of the SAEs were assessed by investigators as related to the vaccination. No fatal SAEs were reported up to Day 182.

Publications: None

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