Sponsor

Novartis Vaccines and Diagnostics S.r.l.

Generic Drug Name

MF-59-adjuvanted inactivated subunit influenza vaccine

Trial Indication(s)

Prophylaxis of Influenza

Protocol Number

V70P3

Protocol Title

A phase III, randomized, controlled, observer-blind, single-center study to compare immunogenicity and safety of an MF59-adjuvanted inactivated subunit influenza vaccine (Fluad®) to those of a non-adjuvanted inactivated subunit influenza vaccine, when administered to adults affected by chronic diseases.

Clinical Trial Phase

Phase III

Study Start/End Dates

29-Nov-2006 to 06-May-2007

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

Subjects were randomly allocated in a 1:1 ratio, to receive a single intramuscular (IM) injection of Fluad or Agrippal. Blood was collected for serological assays before vaccination, at day 1, and after vaccination, at day 22. Subjects were observed at the site for 30 minutes after injection to be evaluated for any immediate reactions. All subjects were instructed to complete a diary card to record solicited local (i.e., ecchymosis, erythema, induration, swelling and pain at injection site) and solicited systemic reactions (i.e., chills, malaise, myalgia, arthralgia, headache, sweating, and fatigue) and axillary temperature for each of the 7 days following vaccination. All adverse events (AEs) necessitating a physician's visit or consultation and/or leading to premature study discontinuation were collected for 3 weeks following vaccination. All serious adverse events (SAEs) were collected in the six months follow-up and data was reconciled at day 181 (visit 3).

Centers

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Objectives:

Immunogenicity To compare the immune response to Fluad® with inactivated subunit virus influenza vaccine to A/H3N2 vaccine strain (primary objective), and B and A/H1N1 vaccine strains (secondary objective), as measured by HI assay at day 22 in subjects with underlying chronic disease(s).
Safety: To evaluate the safety of a single IM injection of the two influenza vaccines.

Test Product (s), Dose(s), and Mode(s) of Administration

Fluad®, MF59-adjuvanted inactivated subunit influenza vaccine (Lot: 068002, Expiry date: 08/2007, containing the purified viral envelope-glycoproteins neuraminidase (NA) and hemagglutinin (HA), derived from three strains [including 15 µg of the HA of the strains A/New Caledonia/20/99 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, B/Malaysia/2506/2004-like] recommended for the influenza season 2006-2007 in the Northern Hemisphere. A single 0.5mL dose of Fluad was administered into the deltoid muscle, preferably of the non-dominant arm.

Statistical Methods

Immunogenicity:
The null hypothesis associated with the primary immunogenicity objective was that the 2-sided 95% Confidence interval (CI) for the ratio of A/H3N2 post-vaccination GMTs between Fluad and the non-adjuvanted subunit influenza vaccine would include 1.

Assuming 150 evaluable subjects for Fluad and 150 for the non-adjuvanted inactivated subunit influenza vaccine, an underlying ratio of GMTs at day 22 equal to 1.50 and a standard deviation of 0.5 (for the log_{10} transformation), the power to reject the null hypothesis is 85%.

Safety:

The accuracy of the sample size, as measured by the 95% CI, depends on the observed percentage reporting solicited reactions, as well as unsolicited AEs.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

Individuals eligible for enrollment in this study were male and female who:

1. were 18 to 60 years of age adult volunteers, mentally competent, willing and able to give written informed consent prior to study entry;
2. were able to comply with all the study requirements
3. were suffering from at least one of these chronic diseases:
   a. moderate to severe hypertension
   b. moderate to severe congestive heart failure
   c. chronic obstructive pulmonary disease (COPD) or moderate to severe asthma
   d. moderate to severe hepatic or renal insufficiency
   e. arteriosclerotic disease or insulin dependent diabetes mellitus

Exclusion criteria:

Individuals not eligible to be enrolled in the study were those:

1. who were hypersensitive to ovalbumin, chicken protein, chicken feathers, influenza viral protein, neomycin or polymyxin or any other component of the vaccine;
2. who had a history of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine;
3. who had a known or suspected (or have a high risk of developing) impairment/ alteration of immune function (excluding that normally associated with advanced age) resulting from (for example):
   a. receipt of immunosuppressive therapy (any parenteral or oral cortical steroid or cancer chemotherapy/radiotherapy) within the past 60 days and for the full length of the study;
   b. receipt of immunostimulants;
   c. receipt of parenteral immunoglobulin preparation, blood products and/or plasma derivates within the past 3 months and for the full length of the study;
   d. suspected or known HIV infection or HIV-related disease;

4. who had a known or suspected history of drug or alcohol abuse;
5. who were pregnant, or women able to bear children but not willing to practice acceptable contraception for the first three weeks of the duration of the trial;

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Participant Flow Table

Summary of Study Terminations

	Number (%) of subjects	
Vaccine group	**Fluad**	**Agrippal**
Enrolled	181	180
Completed study	179 (99%)	178 (99%)
Premature withdrawals	2 (1%)	2 (1%)
AE or Death	0	1 (<1%)
Withdrawal of consent	0	1 (<1%)
Lost to follow-up	1 (<1%)	0
Protocol deviation/violation	1 (<1%)	0

Baseline Characteristics

Demography and Baseline Characteristics – Enrolled Population

Variable	Fluad	Agrippal
	N=181	N=180
Mean Age (yrs ± SD)	49.2 ± 10.0	49.7 ± 9.2
Male/Female (%)	106/75 (59%/41%)	89/91 (49%/51%)
Ethnicity – N (%):		
Asian	1 (<1%)	0
Black	2 (1%)	1 (<1%)
Caucasian	178 (98%)	177 (98%)
Hispanic	0	2 (1%)
Mean Weight (kg ± SD):	78.84 ± 15.75	77.07 ± 16.03
Mean Height (cm ± SD):	170.1 ± 8.4	167.3 ± 9.1
Body Mass Index:(± SD):	27.20 ± 4.84	27.45 ± 4.92
Previously Vaccinated:	71 (39%)	67 (37%)
Moderate to Severe Hypertension - N (%):	132 (73%)	134 (74%)
Moderate to Severe Congestive Heart Failure - N (%):	10 (6%)	13 (7%)
COPD or Moderate to Severe Asthma - N (%):	45 (25%)	40 (22%)
Moderate to Severe Hepatic or Renal Insufficiency - N (%):	11 (6%)	15 (8%)
Arteriosclerosis or Diabetes Mellitus - N (%):	8 (4%)	10 (6%)

Summary of Efficacy

Geometric Mean HI Titers Against A/H3N2 Vaccine Strain Post Vaccination (Day 22) – PP Population

	Fluad	Agrippal	Fluad/Agrippal GMT ratio (95% CI)
	N= 163	N=156	
Post Vaccination GMT (95% CI)	351 (269-457)	159 (121-208)	2.21 (1.52-3.23)

Summary of CHMP Criteria[a] Met After Vaccination with Fluad or Agrippal – PP Population

Serological Criteria to meet CPMP/BWP/214/96 requirements	A/H3N2		A/H1N1		B-antigen	
	Fluad	Agrippal	Fluad	Agrippal	Fluad	Agrippal
	N=163	N=156	N=163	N=156	N=163	N=156
Seroprotection[b] >70%	+	+	+	+	-	-
GMR[c] >2.5	+	+	+	+	+	+
Seroconversion[d] or significant increase[e] >40%	+	+	+	+	+	+

[a] CHMP criteria for 18-60 year old healthy adults were used in assessing immunogenicity for subjects under evaluation, [b] Seroprotection is defined as an HI titer ≥ 40; [c] GMR = ratios of day 22/day 1 geometric mean HI titers; [d] Seroconversion is defined as negative pre-vaccination serum (i.e., HI titer <10) and post-vaccination HI titer ≥ 40; [e] Significant increase is defined at least a 4-fold increase from non-negative (≥ 10) pre-vaccination HI titer.

Summary of Safety

Safety Results

Overview of Subjects With Solicited Reactions

Type of Reaction	Number (%) of Subjects with Solicited Reactions	
	Fluad N=180	Agrippal N=179
Any reaction	112 (62)	78 (44)
Local reaction	89 (49)	50 (28)
Systemic reaction	89 (49)	50 (28)
Other reactions	23 (13)	11 (6)

Table 6: Overview of Subjects With Other Adverse Events (days 1 - 22)

Type of Reaction	Number (%) of Subjects with AEs	
	Fluad N=180	Agrippal N=179
Any AE	32 (18%)	36 (20%)
At least possibly related AE	4 (2%)	4 (2%)
Serious AEs	0	1 (1%)
AEs leading to discontinuation	0	1 (1%)
At least possibly related serious AE	0	0
Death	0	0

Table 7: Overview of Subjects With Other Adverse Events (days 23 to Study Termination)

Type of Reaction	Number (%) of Subjects with AEs	
	Fluad N=180	Agrippal N=179
Any AE	2 (1%)	1 (1%)
At least possibly related AE	0	0
Serious AEs	2 (1%)	1 (1%)
AEs leading to discontinuation	0	0
At least possibly related serious AE	0	0
Death	0	0

Other Relevant Findings

None

Publication

Baldo V, Baldovin T, Angiolelli G, et al. Immunogenicity and safety of an MF59®-adjuvanted and a non-adjuvanted inactivated subunit influenza vaccine in adults affected by chronic diseases. J Clin Trials 2012;2:112

Date of Clinical Trial Report

04 Feb 2009