SYNOPSIS

Name of Sponsor/Company: Omninvest Vaccine Manufacturing, Researching and Trading Ltd. **Name of Finished Product:** Fluval AB Influenza Vaccine (trivalent, seasonal) **Name of Active Ingredient:** Influenza A/Brisbane/59/2007(H1N1)-like IVR-148 reass. strain, Influenza A/Uruguay/716/2007(H3N2)-like NYMC X-175C reass. strain, Influenza B/Brisbane/60/2008 strain	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*For National Authority use only*
Title of Study:	Serological Study of FluvalAB Influenza Vaccine (Trivalent, Seasonal) Intended to Use in the 2009/2010 Vaccination Season	
Study Number	FluvalAB-H-YL2009	
EudraCT Number	2009-012555-22	
Investigators and Study Centres:	**Principal investigator:** József Fűzi MD District Doctor's Office, Dunakeszi	
Publication (reference):	None	
Phase of development:	Phase IV	
Studied period **Date of first enrolment:** **Date of last completed:**	 17.08.2009 10.09.2009	
Objectives:	- to assess the immunogenicity of the hemagglutinin of the vaccine strains (i.e. the titre and frequency of anti-HA antibody responses) in humans by serology testing of blood taken at Day 21-28 after immunization; - to assess tolerability (incidence of adverse reactions) of the study drug in humans.	
Methodology:	In this open label, uncontrolled, one center immunogenicity and tolerability study subjects were enrolled in two groups according to age (18-60 years and ≥60 years) and assigned to the following vaccine group: **Group 1:** Single injection of Fluval AB suspension for injection. All adverse events were collected during the period of Visit 1 (Day 0) to Visit 2 (between Day 21 and Day 28). Serum samples for immunogenicity assays were collected immediately before immunization on Visit 1 (Day 0) and on Visit 2 (between Day 21 and Day 28) in all subjects. Immunogenicity was evaluated by HI test.	

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<tr><td>Number of patients (planned and analysed):</td><td colspan="2">The sample size (min. 50 subjects of age between 18 and 60 years, and min. 50 subjects of age over 60 years) was determined in accordance with point 2.2., Chapter "E" ("Clinical Trial Related to Yearly Licencing of Influenza Vaccine") of guideline CPMP/BWP/214/96.
Enrolment of up to 120 healthy volunteers of age over 18 years was permitted in this study. A total of 120 healthy volunteers (male and female) were selected for inclusion in the study, and screened prior to the vaccination. All 120 subjects entered the study and were vaccinated (ITT population). All 120 have reported themselves on the visit at Day 21-28. The data of all 120 subjects were available and evaluated at Day 21-28 (PP population).
Age group 18-60:
Screened: 55 healthy volunteers of full contractual capacity from both sexes.
PP population: 55 persons.
Treatment: 15 µg HA/strain/dos of FluvalAB trivalent influenza vaccine was administered once (at Day 0).
Age group >60:
Screened: 65 healthy volunteers of full contractual capacity from both sexes.
PP population: 65 persons.
Treatment: 15 µg HA/strain/dos of FluvalAB trivalent influenza vaccine was administered once (at Day 0).</td></tr>
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<tr><td>Diagnosis and main criteria for inclusion:</td><td colspan="2">Inclusion Criteria:
• Healthy adult volunteers aged over 18 years, both sexes;
• Full contractual capacity of the participants;
• Are in good health (as determined by vital signs and medical history);
• Negative urine or serum pregnancy test for females of childbearing potential. If the subject is female and of childbearing potential, she must use an acceptable contraception method and not become pregnant for the duration of the study.
• Are able to understand and comply with planned study procedures;
• Signed informed consent prior to initiation of study procedures;
• Absence of existence of any exclusion criteria.
Exclusion Criteria:
• Known allergy to eggs OR other components of the vaccine (in particular mercury);
• History of Guillain-Barré syndrome;
• Pregnancy OR breast feeding OR positive pregnancy test prior to vaccination;
• Immunosuppressive therapy in the preceding 36 months;
• Active neoplasm (i.e. requiring any form of anti-neoplastic therapy);
• Concomitant corticosteroid therapy, including inhaled corticosteroids. Local corticosteroid or corticosteroid nasal spray are permitted.
• Psychiatric illness and/or concomitant psychiatric drug therapy that may have effect on full contractual capacity of the participant;
• Immunoglobulin (or similar blood product) therapy within 3 months prior to vaccination;
• Vaccine therapy within 4 weeks prior to the study;
• Influenza vaccination within 6 months prior to the study;
• Chronic illness that, in the opinion of the investigator, may interfere with the evaluation of the immune response;
• Documented HIV, HBV or HCV infection;
• Acute febrile respiratory illness within one week prior to vaccination;
• Experimental drug therapy within 1 month prior to vaccination;
• Alcohol or drug abuse.</td></tr>
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<tr><td>Test product, dose and mode of administration, batch number:</td><td colspan="2">Study drug: FluvalAB influenza vaccine (trivalent, seasonal)
Active ingredient: Influenza A/Brisbane/59/2007(H1N1)-like IVR-148 reass. strain, Influenza A/Uruguay/716/2007(H3N2)-like NYMC X-175C reass. strain, Influenza B/Brisbane/60/2008 strain
Active ingredient content: 3 x 15 µg HA / dose
Formulated: vaccine, 1 dose = 0.5 ml
Manufacturer of the study drug: Omninvest Ltd.
Registration number is: OGYI-T-8998.
Date of production: 2009.07.

FluvalAB is a trivalent influenza vaccine against seasonal flu. The influenza A(H1N1), A(H3N2) and B strains included in the vaccine were grown in embryonic hen egg, formaldehyde-inactivated, purified and concentrated, and absorbed to aluminum phosphate.</td></tr>
<tr><td>Duration of treatment</td><td colspan="2">Single dose</td></tr>
<tr><td>Reference therapy, dose and mode of administration, batch number</td><td colspan="2">-</td></tr>
<tr><td>Criteria for evaluation:

Safety:</td><td colspan="2">Tolerability evaluation was based on monitoring of adverse events (AEs) and clinically significant changes in physical status and vital signs.
Tolerability parameters were:
• local reactions: pain at injection site, erythema, swelling, induration, ecchymosis;
• systemic reactions: fever, headache, malaise, myalgia, shivering;
• clinically significant changes in physical status and vital signs: skin, mucous membranes, BP, heart rate, lungs, abdomen, liver, extremities, neurology.
Frequency, mean time of appearance and duration of all local and systemic adverse reactions were calculated by simple descriptive statistics.</td></tr>
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Efficacy:	The measures of immunogenicity, collected for all evaluable subjects completing the study on Day 0, and between Day 21 and Day 28 after vaccination by using HI test. Immunogenicity measures were assessed in comparison to so-called CHMP criteria specified in CPMP/BWP/214/96. In order to confirm protective immunogenicity, at least one of the following three requirements had to be met in subjects aged 18 to 60 years: i. number of seroconversions or significant increase in antihaemagglutinin antibody titre should be >40%; ii. mean geometric increase should be >2.5; iii. the proportion of subjects achieving an HI titre ≥40 should be >70%, and or at least one of the following three requirements have to be met in subjects aged over 60 years: i. number of seroconversions or significant increase in antihaemagglutinin antibody titre should be >30%; ii. mean geometric increase should be >2.0; iii. the proportion of subjects achieving an HI titre ≥40 should be >60% Antibody titrations were done in duplicate; pre- and post-vaccination sera were titrated simultaneously. The titre assigned to each sample was the geometric mean of two independent determinations. * Seroconversion is defined as negative pre-vaccination serum (<10) / post-vaccination titer ≥ 40. ** Significant increase in antibody titer is defined as at least a fourfold increase from non-negative (≥10) pre-vaccination serum.	
Statistical methods:	Safety and tolerability were analysed using the data of all participants vaccinated (ITT-population). Immunogenicity was analysed using the data of all participants completing the study (PP-population). For demography descriptive statistics was performed. For adverse events the number and proportion of patient(s) reporting adverse event were assessed by type of AE, severity, relationship to study medication and by outcome. For efficacy the primary efficacy variable was the change in HI titres gained from serology testings of blood. The HI endpoints were the variables recommended for interpandemic influenza vaccines: the proportion of people seroconverting or displaying a four-fold titre increase post-to-pre-vaccination, the post-to-pre-vaccination GMT ratio; and post-vaccination seroprotectivity rate (% of subjects with HI titres ≥40)	
Summary - Conclusions **Safety Results:**	Administration of the vaccine was well tolerated by all participants of the study. The study vaccine proved to be safe, no clinically significant changes in the physical condition or vital signs of the volunteers were observed. No Severe AEs were observed. No subject showed systemic adverse events. Three (3) volunteers had four (4) AEs. These cases were evaluated as "probable". Three cases were pain at injection site developed within 24 hours after vaccination, one case was redness at injection site. Beyond these no other or further AEs were registered.	

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Efficacy Results:

Primary objective of the study was to assess the efficacy of the study drug in humans by serology testing of blood taken at Day 21-28 after immunization. In this respect changes in HI titres were considered as primary efficacy parameter.

Geometric mean of HI titres against both A/H1N1, A/H3N2, and B antigens significantly increased 21-28 days after immunization in both age groups and both sexes.

The percentage of seropositive (= post-vaccination titres of ≥1:40) individuals was over 70% in age group below 60 years and over 60% in age group above 60 years.

The rate of seroconversion was above 40% in the age group below 60 years and above 30% in age group above 60 years.

Efficacy criteria met CPMP immunogenicity criteria with respect of all 3 antigens in case of results at Day 21-28 after vaccination.

	18-60 years		**Over 60 years**	
	Criteria	**Results**	**Criteria**	**Results**
A(H1N1)				
Seroconversion	> 40 %	**65.5% (+)**	> 30 %	**47.7% (+)**
Increase in GMT	> 2.5	**3.6 (+)**	> 2.0	**4.1 (+)**
Seropositivity	> 70 %	**72.7% (+)**	> 60 %	**61.5% (+)**
A(H3N2)				
Seroconversion	> 40 %	**65.5% (+)**	> 30 %	**55.4%**
Increase in GMT	> 2.5	**3.0 (+)**	> 2.0	**3.0 (+)**
Seropositivity	> 70 %	**76.4% (+)**	> 60 %	**64.6% (+)**
B				
Seroconversion	> 40 %	**54.6% (+)**	> 30 %	**56.9 (+)**
Increase in GMT	> 2.5	**3.0 (+)**	> 2.0	**2.9 (+)**
Seropositivity	> 70 %	**78.2 (+)**	> 60 %	**63.1 (+)**

+) Met CPMP criteria

Conclusion

The immunogenicity of the Study Drug met all three CPMP criteria 21-28 days after immunization in both age groups. The Study Drug was well tolerated. On the basic of the study the FluvalAB vaccine (trivalent, seasonal) is safe and effective.

Date of Report

08 June 2017