SYNOPSIS

Name of Sponsor/Company: Omninvest Vaccine Manufacturing, Researching and Trading Ltd. **Name of Finished Product:** Fluval AB suspension for injection **Name of Active Ingredient:** seasonal A/H1N1, A/H3N2 and B influenza antigens	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*For National Authority use only*
Title of Study:	Tolerability and Immunogenicity Study of Fluval AB Suspension for Injection (trivalent, seasonal influenza vaccine, active ingredient content: 15 µgHA/strain/0.5mL) for the Use in the Season 2013/2014 in Adult and Elderly Subjects	
Study Number	FluvalAB-H-YL2013	
EudraCT Number	2013-002153-30	
Investigators and Study Centres:	**Principal Investigator:** Ferenc TAMÁS MD, general practitioner, District Doctor's Office, Pilisvörösvár **Investigators:** Ágnes HASITZ MD, general practitioner, District Doctor's Office, Szentendre Judit SIMON MD, general practitioner, District Doctor's Office, Budapest VIII.	
Publication (reference):	None	
Phase of development:	Phase IV.	
Studied period **Date of first enrolment:** **Date of last completed:**	 22.08.2013 17.09.2013	
Objectives:	**Immunogenicity Objective:** To assess immunogenicity of a single intramuscular (IM) injection of Fluval AB suspension for injection (trivalent, seasonal influenza vaccine, active ingredient content: 15 µgHA/0.5mL of seasonal A/H1N1, A/H3N2 and B influenza antigens each), as measured by haemagglutination inhibition (HI) test. **Safety and Tolerability Objectives:** To evaluate safety and tolerability (incidence of adverse events) of a single IM injection of Fluval AB suspension for injection.	

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Methodology:	In this open label, uncontrolled, multi-centre immunogenicity and tolerability study subjects were enrolled in two groups according to age (18-59 years and ≥60 years) and assigned to the following vaccine group: Group 1: Single injection of Fluval AB suspension for injection. Subjects were observed for 30 minutes after the injection on Visit 1 (Day 0) for any immediate reactions. All subjects were requested to complete a diary card to record local reactions (injection site pain, erythema, swelling, induration and ecchymosis) and systemic reactions (fever, shivering, headache, malaise, fatigue, sweating, nausea, myalgia and arthralgia) started on the day of vaccination on Visit 1 (Day 0) until 7 (seven) days following that. 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.	
Number of patients (planned and analysed):	The sample size (min. 50 subjects of age between 18 and 59 years, and min. 50 subjects of age at and 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. Enrollment of up to 120 healthy volunteers of age over 18 years was permitted in this study. A total of 120 healthy volunteers (males and females) were selected for inclusion in the study, and screened prior to vaccination. All 120 subjects entered the study and were vaccinated (ITT population). 119 subjects attended the control visit at Day 21-28. The data of 119 subjects were available and evaluated at Day 21-28 (PP population). **Age group 18-59:** Enrolled: 60 healthy volunteers of full contractual capacity from both sexes. Treatment: 15 µgHA/strain/0.5mL of Fluval AB trivalent influenza vaccine was administered once at Day 0. PP population: 59 persons. **Age group ≥60:** Enrolled: 60 healthy volunteers of full contractual capacity from both sexes. Treatment: 15 µgHA/strain/0.5mL of Fluval AB trivalent influenza vaccine was administered once at Day 0. PP population: 60 persons.	

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Diagnosis and main criteria for inclusion:	**Inclusion Criteria:** • Adult persons aged 18 to 59 years, elderly persons aged ≥60 years from both sexes, mentally competent; • Were in good health (as determined by vital signs and existing medical condition) or were in stable medical condition. Subjects were not excluded with known adequately treated clinically significant organ or systemic diseases (e.g. asthma or diabetes), such that, in the opinion of the investigator, the significance of the disease did not compromise the subject's participation in the study; • Female volunteers aged 18-59 years (i.e. participants of childbearing potential) with a negative result from the urine pregnancy test prior to vaccination who agreed to use an acceptable contraception method or abstinence throughout the trial and not become pregnant for the duration of the study. • Capability of participants to understand and comply with planned study procedures; • Participants provided written informed consent (IC) prior to initiation of study procedures; • Absence of existence of any exclusion criteria. **Exclusion Criteria:** • Pregnancy, breast feeding or positive urine pregnancy test at baseline prior to vaccination. Female subjects who were able to bear children but were not willing to use an acceptable contraception method for the duration of the study. • Known hypersensitivity to eggs, chicken protein, thiomersal, formaldehyde, gentamycin, ciprofloxacin, neomycin, vancomycin or any other component of the vaccine; • History of Guillain-Barré syndrome; • History of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine; • Serious disease, such as cancer, autoimmune disease, advanced arteriosclerotic disease, complicated diabetes mellitus, acute or progressive hepatic disease, acute or progressive renal disease, congestive heart failure; • Immunosuppressive therapy within 36 months prior to vaccination; • Concomitant corticosteroid therapy, including high-dose inhaled corticosteroids; • Receipt of immunostimulants; • Receipt of parenteral immunoglobulin, blood products and/or plasma derivate within 3 months prior to vaccination; • Suspected or known HIV, HBV or HCV infection; • Acute disease and/or axillary temperature ≥37^{o}C within 3 days prior to vaccination; • Vaccine therapy within 4 weeks prior to vaccination; • Influenza vaccination (any kind) within 6 months prior to vaccination; • Experimental drug therapy within 4 weeks prior to vaccination; • Concomitant participation in another clinical study; • Any condition which, in the opinion of the investigator, may interfere with the evaluation of the study; • Past or current psychiatric disease of the volunteer that upon judgement of the investigator could have effect on the objective decision-making of the volunteer; • Alcohol or drug abuse of the participant.	

<table>
<tr><td>Name of Sponsor/Company:
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Fluval AB suspension for injection</td></tr>
<tr><td>Name of Active Ingredient:
seasonal A/H1N1, A/H3N2 and B influenza antigens</td></tr>
<tr><td>Test product, dose and mode of administration, batch number:</td><td colspan="2">Study drug: FluvalAB influenza vaccine (trivalent, seasonal)
Active ingredient: A/California/7/2009(H1N1)-like virus A/Victoria/361/2011, A/Texas/50/2012(H3N2)-like virus B/Massachusetts/2/2012 (wild type)-like virus
Active ingredient content: 3 x 15 µgHA / 0.5 mL
Formulated: vaccine, 1 dose = 0.5 mL
Manufacturer of the study drug: Omninvest Ltd.
Lot No.: FL-KL-01/13
Registration number is: OGYI-T-8998.
Date of production: June of 2013

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 embryonated hen egg, inactivated by formaldehyde, purified and concentrated, and absorbed to aluminium phosphate gel.</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">Safety criteria include data from the physical examination and observed local and systemic reactions and adverse events.
Any other indicators of reactogenicity, all adverse events occurring during the study (between study Day 21 and Day 28) either judged as related or not to vaccination by the investigator, were recorded.
Number and percentage of subjects with at least one local reaction between Day 0 and Day 21-28.
Number and percentage of subjects with at least one systemic reaction between Day 0 and Day 21-28.
Number and percentage of subjects with at least one adverse reaction between Day 0 and Day 21-28.</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 with respect to criteria specified in CPMP/BWP/214/96. According to CPMP/BWP/214/96, following serological assessments should be considered for each strain in adult subjects, **aged between 18 and 59 years**, and at least one of the assessments should meet the indicated requirements: - number of seroconversions* or significant increase* in antihaemagglutinin antibody titre should be >40%; - mean geometric increase should be >2.5; - the proportion of subjects achieving an HI titre ≥40 should be >70%, and the following serological assessments should be considered for each strain in adult subjects, aged at and **over 60 years**, and at least one of the assessments should meet the indicated requirements: - number of seroconversions* or significant increase* in antihaemagglutinin antibody titre should be >30%; - mean geometric increase should be >2.0; - the proportion of subjects achieving an HI titre ≥40 should be >60% * 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 titers 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 titer increase post-to-pre-vaccination, the post-to-pre-vaccination GMT ratio; and post-vaccination seroprotectivity rate (% of subjects with HI titers ≥40).	

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Summary - Conclusions

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 0 (before immunization) and Day 21-28 (after immunization). In this respect changes in HI titers were considered as primary efficacy parameter.
Geometric mean of HI titers (GMT) against all three (A/H1N1, A/H3N2, and B) antigens significantly increased 21-28 days after immunization in both age groups and both sexes.
The rate of seroconversion was well above 40% in age group of 18-60 years and well above 30% in age group over 60 years.
The Geometric Mean HI Titer Ratio (GMTR) was well above 2.5 in age group of 18-60 years and well above 2.0 in age group over 60 years.
The percentage of seroprotected (= post-vaccination titers ≥40) individuals was well above 70% in age group of 18-60 years and well above 60% in age group over 60 years.

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

	18 - 59 years		**≥ 60 years**	
	Criteria	**Results**	**Criteria**	**Results**
A(H1N1)				
Seroconversion	> 40 %	**59 % (+)**	> 30 %	**67 % (+)**
Increase in GMT	> 2.5	**3.1 % (+)**	> 2.0	**3.2 % (+)**
Seroprotectivity	> 70 %	**95 % (+)**	> 60 %	**97 % (+)**
A(H3N2)				
Seroconversion	> 40 %	**69 % (+)**	> 30 %	**70 % (+)**
Increase in GMT	> 2.5	**3.6 % (+)**	> 2.0	**3.9 % (+)**
Seroprotectivity	> 70 %	**100 % (+)**	> 60 %	**100 % (+)**
B				
Seroconversion	> 40 %	**54 % (+)**	> 30 %	**65 % (+)**
Increase in GMT	> 2.5	**3.6 % (+)**	> 2.0	**4.3 % (+)**
Seroprotectivity	> 70 %	**80 % (+)**	> 60 %	**78 % (+)**

(+) Met CPMP criteria

Conclusion

Immunogenicity of the Study Drug met all three CPMP criteria in respect of all three virus strains 21-28 days after immunization in both age groups.
The Study Drug was safe and well tolerated.
On the basis of the results of the study Fluval AB influenza vaccine (trivalent, seasonal) is safe and effective.

Date of Report

20 December 2016