SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Omninvest Vaccine Manufacturing, Researching and Trading Ltd.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

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<tr><td>Name of Finished Product:
FluvalAB influenza vaccine (trivalent, seasonal)</td></tr>
<tr><td>Name of Active Ingredient:
A/California/7/2009(H1N1)-like virus
A/Perth/16/2009(H3N2)-like virus
B/Brisbane/60/2008-like virus</td></tr>
<tr><td>Title of Study:</td><td colspan="2">Serological Study of FluvalAB Influenza Vaccine (Trivalent, Seasonal) Intended to Use in the 2011/2012 Vaccination Season</td></tr>
<tr><td>Study Number</td><td colspan="2">FluvalAB-H-YL2011</td></tr>
<tr><td>EudraCT Number</td><td colspan="2">2011-002158-30</td></tr>
<tr><td>Investigators and Study Centres:</td><td colspan="2">Investigators:
Ferenc TAMÁS MD
District Doctor’s Office, Pilisvörösvár

László SINKA MD
Fourmed Medical Center, Veszprém</td></tr>
<tr><td>Publication (reference):</td><td colspan="2">None</td></tr>
<tr><td>Phase of development:</td><td colspan="2">Phase IV</td></tr>
<tr><td>Studied period

Date of first enrolment:

Date of last completed:</td><td colspan="2">

26.07.2011

24.08.2011</td></tr>
<tr><td>Objectives:</td><td colspan="2">Immunogenicity objective:
To assess immunogenicity of a single intramuscular (IM) injection of Fluval AB influenza vaccine (trivalent, seasonal, active ingredient content: 15 µgHA/0.5 mL of seasonal A/H1N1, A/H3N2 and B influenza antigens each), as measured by haemagglutination inhibition (HI) test.

Safety and tolerability objective:
To evaluate safety and tolerability (incidence of adverse events) of a single intramuscular injection of Fluval AB influenza vaccine.</td></tr>
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<tr><td>Methodology:</td><td colspan="2">In this uncontrolled, open, multi-center immunogenicity and tolerability study subjects were enrolled into 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 influenza vaccine (trivalent, seasonal, active ingredient content: 15 µgHA/0.5mL).
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 (pain at injection site, erythema, swelling, induration and ecchymosis) and systemic reactions (fever, shivering, headache, malaise, fatigue, sweating, nausea, myalgia and arthralgia) and auxillary temperature starting on the day of vaccination and for each of the 7 (seven) days following that.
All adverse events were collected during the period of Visit 1 (Day 0) to Visit 2 (between Days 21. and 28.).
Serum samples for immunogenicity assay were collected immediately before immunization on Visit 1 (Day 0) and on Visit 2 (between Days 21. and 28.) in all subjects. Immunogenicity was evaluated by HI test in all subjects.</td></tr>
<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.
Enrollment of up to 120 healthy volunteers of age over 18 years was permitted in this study. A total of 121 healthy volunteers (male and female) were selected for inclusion in the study, and screened prior to vaccination. All 121 subjects entered the study and were vaccinated (ITT population). 121 subjects attended the control visit at Day 21-28. The data of all 121 subjects were available and evaluated at Day 21-28 (PP population).
Age group 18-60:
Screened: 60 healthy volunteers of full contractual capacity from both sexes.
PP population: 60 persons.
Treatment: 15 µgHA/strain/0.5mL of FluvalAB trivalent influenza vaccine was administered once (at Day 0).
Age group >60:
Screened: 61 healthy volunteers of full contractual capacity from both sexes.
PP population: 61 persons.
Treatment: 15 µgHA/strain/0.5mL of FluvalAB trivalent influenza vaccine was administered once (at Day 0).</td></tr>
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Diagnosis and main criteria for inclusion:	**Inclusion Criteria:** • Adults aged 18 to 60 years, elderly persons aged over 60 years, both sexes, mentally competent; • Are in good health (as determined by vital signs and existing medical condition) or are in stable medical condition. Subjects will not be 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 will not compromise the subject's participation in the study; • Female volunteers aged 18-60 years (i.e. participants of childbearing potential) with a negative result from the urine pregnancy test prior to vaccination who agrees 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 aged above 18 years provide written informed consent 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 are able to bear children but 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 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 the past 36 months; • Concomitant corticosteroid therapy, including high-dose inhaled corticosteroids; • Receipt of immunostimulants, • Receipt of parenteral immunoglobulin, blood products and/or plasma derivates within the past 3 months; • Suspected or HIV, HBV or HCV infection; • Acute disease and/or axillary temperature ≥37oC within the past 3 days; • Vaccine therapy within the past 4 weeks; • Influenza vaccination (any kind) within the past 6 months; • Experimental drug therapy within the past 4 weeks; • 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 may have effect on the objective decision-making of the volunteer; • Alcohol or drug abuse of the participant.	

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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: A/California/7/2009(H1N1)-like virus
A/Perth/16/2009(H3N2)-like virus
B/Brisbane/60/2008-like virus
Active ingredient content: 3 x 15 µgHA / dose
Formulated: vaccine, 1 dose = 0.5 mL
Manufacturer of the study drug: Omninvest Ltd.
Registration number is: OGYI-T-8998.
Lot No.: FL-K-04/11
Date of production: 2011.07.

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 embryonated hen egg, formaldehyde-inactivated, 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 0, Day 7and the study termination visit at Day 21-28) 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 7. after immunization.
Number and percentage of subjects with at least one systemic reaction between Day 0 and Day 7. after immunization.
Number and percentage of subjects with at least one adverse event 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 in comparison to so-called CHMP 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 60**, 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 over 60**, 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, as well as immunogenicity were analysed using the data of all participants completing the study. 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 titres ≥40).	
Summary - Conclusions **Safety Results:**	Administration of the vaccine was well tolerated by the 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. All related adverse events occurred during the study recovered completely without medical intervention. No severe or serious AE was observed.	

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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 0 (before immunization) and Day 21-28 after immunization. In this respect changes in HI titres were considered as primary efficacy parameter.
Geometric mean of HI titres (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 titre 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 titres ≥1:40) 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 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 %	**64 % (+)**	> 30 %	**57 % (+)**
Increase in GMT	> 2.5	**4.3 (+)**	> 2.0	**3.3 (+)**
Seroprotectivity	> 70 %	**100 % (+)**	> 60 %	**98 % (+)**
A(H3N2)				
Seroconversion	> 40 %	**69 % (+)**	> 30 %	**65 % (+)**
Increase in GMT	> 2.5	**5.0 (+)**	> 2.0	**4.1 (+)**
Seroprotectivity	> 70 %	**98 % (+)**	> 60 %	**100 % (+)**
B				
Seroconversion	> 40 %	**57 % (+)**	> 30 %	**65 % (+)**
Increase in GMT	> 2.5	**3.9 (+)**	> 2.0	**3.4 (+)**
Seroprotectivity	> 70 %	**92 (+)**	> 60 %	**83 (+)**

+) Met CPMP criteria

Conclusion

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 basis of the results of the study FluvalAB influenza vaccine (trivalent, seasonal) is safe and effective.

Date of Report

08 June 2017