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

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<tr><td>Name of Finished Product:
FluvalAB influenza vaccine (trivalent, seasonal)</td></tr>
<tr><td>Name of Active Ingredient:
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A/Uruguay/716/2007 (H3N2)-like NYMC X-175C reass. strain
B/Florida/4/2006 strain</td></tr>
<tr><td>Title of Study:</td><td colspan="2">Serological Study of FluvalAB Influenza Vaccine (Trivalent, Seasonal) Intended to Use in the 2008/2009 Vaccination Season</td></tr>
<tr><td>Study Number</td><td colspan="2">FluvalAB-H-YL2008</td></tr>
<tr><td>EudraCT Number</td><td colspan="2">2008-003655-74</td></tr>
<tr><td>Investigators and Study Centres:</td><td colspan="2">Principal investigator:
József Fűzi MD.
District Doctor's Office, Dunakeszi</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">

26.08.2008

20.09.2008</td></tr>
<tr><td>Objectives:</td><td colspan="2">• 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.</td></tr>
<tr><td>Methodology:</td><td colspan="2">After physical examinations and blood sampling, 0.5 ml of the vaccine was administered at one side into the deltoid muscle with a deep intramuscular injection.
Blood samples from the cubital vein to test for specific antibodies against A/H1N1, A/H3N2 and B viruses by serology testing were taken at screening (Day 0) and at Day 21-28 after vaccination.</td></tr>
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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 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 (60-60 per group) healthy volunteers of age over 18 years was permitted in this study. A total of 105 healthy volunteers (male and female) were selected for inclusion in the study, and screened prior to the vaccination. All 105 subjects entered the study and were vaccinated (ITT population). All 105 have reported themselves on the visit at Day 21-28. The data of all 105 subjects were available and evaluated at Day 21-28 (PP population).
Age group 18-60:
Screened: 52 healthy volunteers of full contractual capacity from both sexes. PP population: 52 persons. Treatment: 15 µg HA/strain/dos of FluvalAB trivalent influenza vaccine was administered once (at Day 0).
Age group >60:
Screened: 53 healthy volunteers of full contractual capacity from both sexes. PP population: 53 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, including 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 of the study;
• influenza vaccination within 6 month of 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 of vaccination;
• experimental drug therapy within 1 month prior to vaccination;
• alcohol or drug abuse.</td></tr>
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Name of Sponsor/Company: Omninvest Vaccine Manufacturing, Researching and Trading Ltd. **Name of Finished Product:** FluvalAB influenza vaccine (trivalent, seasonal) **Name of Active Ingredient:** A/Brisbane/59/2007 (H1N1)-like IVR-148 reass. strain A/Uruguay/716/2007 (H3N2)-like NYMC X-175C reass. strain B/Florida/4/2006 strain	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*For National Authority use only*

Test product, dose and mode of administration, batch number:	Study drug: FluvalAB influenza vaccine (trivalent, seasonal) Active ingredient: A/Brisbane/59/2007 (H1N1)-like IVR-148 reass. strain A/Uruguay/716/2007 (H3N2)-like NYMC X-175C reass. strain B/Florida/4/2006 strain Active ingredient content: 3 x 15 µg HA / dose Formulated: vaccine, 1 dose = 0.5 ml Manufacturer of the study drug: Omninvest Ltd. Batch No.: 5208 Registration number is: OGYI-T-8998. Date of production: 2008.07. 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 aluminium phosphate.
Duration of treatment	Single dose
Reference therapy, dose and mode of administration, batch number	-
Criteria for evaluation: **Safety:**	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, redness, 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.

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<tr><td>Efficacy:</td><td colspan="2">Serum antibody titres were measured by haemagglutinin inhibition (HI) test. The primary efficacy variable is the change of HI titres in time. HI antibody titres were determined at baseline on Day 0, and at Day 21-28 after vaccination. HI titres were used to calculate seroconversion rates, increase in geometric mean titres (GMTs), and seroprotection rates. 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, 18 to 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 >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 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.</td></tr>
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<tr><td>Statistical methods:</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.
Tolerability was analyzed in all ITT patients vaccinated. Immunogenicity was analysed using the data of all participants completing the study (PP population). In this clinical study there was no difference between ITT and PP populations.
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 variables were 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 seropositivity rate (% of subjects with titres >40).</td></tr>
<tr><td>Summary - Conclusions

Safety Results:</td><td colspan="2">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. Two (2) volunteers had 2 adverse events. The relationships of these cases to the study drug were evaluated as "probable". These AEs were local reactions and were classified as mild. Beyond these no other or further AEs were registered.</td></tr>
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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 sexes and both age groups.

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 %	**58 % (+)**	> 30 %	**53 % (+)**
Increase in GMT	> 2.5	**3.8 (+)**	> 2.0	**4.7 (+)**
Seropositivity	> 70 %	**73 % (+)**	> 60 %	**62 % (+)**
A(H3N2)				
Seroconversion	> 40 %	**48 % (+)**	> 30 %	**51 % (+)**
Increase in GMT	> 2.5	**3.5 (+)**	> 2.0	**3.4 (+)**
Seropositivity	> 70 %	**85 % (+)**	> 60 %	**77 % (+)**
B				
Seroconversion	> 40 %	**67 % (+)**	> 30 %	**57 % (+)**
Increase in GMT	> 2.5	**4.2 (+)**	> 2.0	**4.2 (+)**
Seropositivity	> 70 %	**71 % (+)**	> 60 %	**66 % (+)**

(+) Met CPMP criteria

Conclusion	**The immunogenicity of the Study Drug met all three CPMP criteria 21-28 days after immunization. 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