SYNOPSIS

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/Solomon Islands/3/2006(H1N1)-like IVR-145 reass. A/Wisconsin/67/2005(H3N2)-like NYMC X-161 B reass. B/Malaysia/2506/2004	**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 2007/2008 Vaccination Season	
Study Number	FluvalAB-H-YL2007	
EudraCT Number	2007-002614-19	
Investigators and Study Centres:	**Principal investigator:** József Fűzi MD. District Doctor's Office, Dunakeszi	
Publication (reference):	Vajo, Z., Kosa, L., Szilvasy, I., Pauliny, Z., Bartha, K., Visontay, I., Jankovics, M., Kis, A. and Jankovics, I. (2008), Yearly licensing studies from 1997 to 2007 of the inactivated whole virus seasonal influenza vaccine fluval – a useful approach to pandemic vaccine development even in less well developed countries?. Influenza and Other Respiratory Viruses, 2: 221–228.	
Phase of development:	Phase IV	
Studied period **Date of first enrolment:** **Date of last completed:**	 11.09.2007 06.10.2007	
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.	

<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:

Page:</td><td rowspan="3">For National Authority use only</td></tr>
<tr><td>Name of Finished Product:
FluvalAB influenza vaccine (trivalent, seasonal)</td></tr>
<tr><td>Name of Active Ingredient:
A/Solomon Islands/3/2006(H1N1)-like IVR-145 reass.
A/Wisconsin/67/2005(H3N2)-like NYMC X-161 B reass.
B/Malaysia/2506/2004</td></tr>
<tr><td>Methodology:</td><td colspan="2">After physical examinations and blood sampling, 0.5 ml of the injection 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 influenza A/H1N1, A/H3N2 and B viruses by serology testing were taken at screening (Day 0) and at Day 21-28 after vaccination.
At Day 0 the following procedures were performed:
• recording demographic data and medical history,
• recording pre-existing conditions, concomitant medication,
• physical examination, vital signs (temperature, blood pressure, pulse rate),
• in case of females of childbearing age: pregnancy test,
• taking of blood samples from the cubital vein to test for specific antibodies against influenza A(H1N1), A(H3N2) and B viruses before vaccination,
• administration of 0.5 ml of the injection at one side into the deltoid muscle with a deep intramuscular injection. The injection is not repeated.
• documentation.
Control visit was performed at Day 21-28 after vaccination, in the course of which the following procedures were performed:
• recording of past history, AEs, concomitant medication used during the past 21 28 days,
• physical examination, vital signs (temperature, blood pressure, pulse rate),
• taking of blood samples from the cubital vein to test for specific antibodies against influenza A(H1N1), A(H3N2) and B viruses,
• documentation.</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 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.
Fifty (50) healthy adult volunteers of age between 18 and 60 years and fifty (50) healthy adult volunteers of age over 60 years were enrolled in the study. All 100 subjects entered the study and were vaccinated (ITT population). No subject has withdrawn his consent orally or in writing, and all 100 volunteers out of the 100 enrolled ones have reported themselves on the visit at Day 21-28. (PP population).</td></tr>
</table>

<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:

Page:</td><td rowspan="3">For National Authority use only</td></tr>
<tr><td>Name of Finished Product:
FluvalAB influenza vaccine (trivalent, seasonal)</td></tr>
<tr><td>Name of Active Ingredient:
A/Solomon Islands/3/2006(H1N1)-like IVR-145 reass.
A/Wisconsin/67/2005(H3N2)-like NYMC X-161 B reass.
B/Malaysia/2506/2004</td></tr>
<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 cortricosteroid 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>
</table>

<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:

Page:</td><td rowspan="3">For National Authority use only</td></tr>
<tr><td>Name of Finished Product:
FluvalAB influenza vaccine (trivalent, seasonal)</td></tr>
<tr><td>Name of Active Ingredient:
A/Solomon Islands/3/2006(H1N1)-like IVR-145 reass.
A/Wisconsin/67/2005(H3N2)-like NYMC X-161 B reass.
B/Malaysia/2506/2004</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/Solomon Islands/3/2006(H1N1)-like IVR-145 reass. A/Wisconsin/67/2005(H3N2)-like NYMC X-161 B reass. B/Malaysia/2506/2004
Active ingredient content: 3 x 15 μg HA / dos
Formulated: vaccine, 1 dos = 0.5 ml
Manufacturer of the study drug: Omninvest Ltd.
Production number: 4807
Registration number is: OGYI-T-8998.
Date of production: 2007.07.
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.</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, induration, redness, swelling, warmth;
• systemic reactions: headache, malaise, fever;
• 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 - AEs were calculated by simple descriptive statistics.</td></tr>
</table>

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/Solomon Islands/3/2006(H1N1)-like IVR-145 reass. A/Wisconsin/67/2005(H3N2)-like NYMC X-161 B reass. B/Malaysia/2506/2004	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*For National Authority use only*
Efficacy:	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.	
Statistical methods:	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 analysed 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).	

<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:

Page:</td><td rowspan="3">For National Authority use only</td></tr>
<tr><td>Name of Finished Product:
FluvalAB influenza vaccine (trivalent, seasonal)</td></tr>
<tr><td>Name of Active Ingredient:
A/Solomon Islands/3/2006(H1N1)-like IVR-145 reass.
A/Wisconsin/67/2005(H3N2)-like NYMC X-161 B reass.
B/Malaysia/2506/2004</td></tr>
<tr><td>Summary - Conclusions</td><td colspan="2"></td></tr>
<tr><td>Safety Results:</td><td colspan="2">Administration of FluvalAB influenza vaccine was well tolerated by all volunteers. The vaccine proved to be safe, no clinically significant changes in the physical condition or the vital signs of the volunteers were observed. No Severe Adverse Event was observed, no subject showed systemic adverse events. During the study two (2) adverse events were recorded at two (2) volunteers. Both adverse events were local reaction: one case of redness at injection site and one case of local pain at injection site. Both adverse events developed within 48 hours after vaccination. Both AEs were classified as mild. The relationship of these adverse events to the study drug was evaluated as probable. The subjects in word recovered within 24 hours after the redness developed without sequelae. The adverse events did not endanger the volunteers' safety. No medical intervention in consequence of the adverse events were necessary. The rate of volunteers with adverse event compared to the total number of volunteers is 2.0% (2/100).</td></tr>
<tr><td>Efficacy Results:</td><td colspan="2">Concerning immunogenicity, 21-28 days after immunization the study population in both age groups and in case of all three virus strains met all three CHMP efficacy criteria.
Overall summary chart on immunogenicity criteria and results in the study population:
<table>
<tr><th></th><th colspan="2">18-60 years</th><th colspan="2">Over 60 years</th></tr>
<tr><th></th><th>Criteria</th><th>Results</th><th>Criteria</th><th>Results</th></tr>
<tr><td>A(H1N1)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Seroconversion</td><td>> 40 %</td><td>52 % (+)</td><td>> 30 %</td><td>42 % (+)</td></tr>
<tr><td>Increase in GMT</td><td>> 2.5</td><td>5.4 (+)</td><td>> 2.0</td><td>3.0 (+)</td></tr>
<tr><td>Seropositivity</td><td>> 70 %</td><td>76 % (+)</td><td>> 60 %</td><td>68 % (+)</td></tr>
<tr><td>A(H3N2)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Seroconversion</td><td>> 40 %</td><td>52 % (+)</td><td>> 30 %</td><td>50 % (+)</td></tr>
<tr><td>Increase in GMT</td><td>> 2.5</td><td>3.9 (+)</td><td>> 2.0</td><td>3.1 (+)</td></tr>
<tr><td>Seropositivity</td><td>> 70 %</td><td>80 % (+)</td><td>> 60 %</td><td>68 % (+)</td></tr>
<tr><td>B</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Seroconversion</td><td>> 40 %</td><td>50 % (+)</td><td>> 30 %</td><td>42 % (+)</td></tr>
<tr><td>Increase in GMT</td><td>> 2.5</td><td>3.9 (+)</td><td>> 2.0</td><td>2.9 (+)</td></tr>
<tr><td>Seropositivity</td><td>> 70 %</td><td>76 % (+)</td><td>> 60 %</td><td>68 % (+)</td></tr>
</table>
(+) Met CPMP criteria</td></tr>
<tr><td>Conclusion</td><td colspan="2">On the basis of the results of the clinical study the FluvalAB influenza vaccine should consider safe and effective.</td></tr>
<tr><td>Date of Report</td><td colspan="2">08 June 2017</td></tr>
</table>