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:

Page:</td><td rowspan="3">For National Authority use only</td></tr>
<tr><td>Name of Finished Product:
Fluval P monovalent influenza vaccine</td></tr>
<tr><td>Name of Active Ingredient:
A/California/7/2009 (H1N1)</td></tr>
<tr><td>Title of Study:</td><td colspan="2">Tolerability and Immunogenicity Study of Fluval P Monovalent Influenza Vaccine in Children and Adolescents</td></tr>
<tr><td>Study Number</td><td colspan="2">FLUVAL P-H-07</td></tr>
<tr><td>EudraCT Number</td><td colspan="2">2009-014807-30</td></tr>
<tr><td>Investigators and Study Centres:</td><td colspan="2">Investigator:
Éva Szabó MD.
Chief Physician, Head of Department
"Csolnoky Ferenc" Veszprém County Hospital
Center for Pediatrics</td></tr>
<tr><td>Publication (reference):</td><td colspan="2">None</td></tr>
<tr><td>Phase of development:</td><td colspan="2">Interventional, prevention, randomized, single-blind, controlled</td></tr>
<tr><td>Studied period

Date of first enrolment:

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

31.08.2009

01.10.2009</td></tr>
<tr><td>Objectives:</td><td colspan="2">Primary Objective:
• To assess tolerability/safety (incidence of adverse events) of the study drug.
Secondary Objectives:
• To assess the efficacy (immunogenicity) of the study drug by serology testing of blood samples taken at Day 21-28 after immunization in groups and in age groups.
• To assess the efficacy of the study drug by optional epidemiological follow-up of the participants until the end of the influenza season.
• To assess the immunogenicity of the study drug by optional cross-reactive immunity tests performed with non-homologous influenza A and B virus strains.</td></tr>
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A/California/7/2009 (H1N1)</td></tr>
<tr><td>Methodology:</td><td colspan="2">After physical examinations, just prior to vaccination, two Vacuette tubes of venous blood sample were taken from each trial subject, for base-line titration of circulating anti-HA antibodies. Immediately thereafter, children of 3-12 years of age received 0.25 ml vaccine, while adolescents of 12-18 years of age received 0.5 ml vaccine by deep intramuscular injection into the deltoid muscle. The injection was not repeated. The vaccinated persons were observed for 2 hours after the injection.
This was a single blind study, the Investigator was not inform study subjects whether they were vaccinated with Fluval P or Fluval AB vaccine, but in the course of visits at Day 21-28 after vaccination the blinding were revoked.
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.
Adverse events and serious adverse events were monitored by telephone follow-up on Days 1., 2., 3., 7. and 10. after vaccination, and during control visit at Day 21-28. after vaccination.</td></tr>
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Name of Active Ingredient: A/California/7/2009 (H1N1)		

Number of patients (planned and analysed):

Fifty-eight volunteers were enrolled in this study (28 children of 3-12 years of age and 30 adolescents of 12-18 years of age). The subjects enrolled in this study were randomly assigned in a 1:1:1 ratio to one of the vaccine groups below.

Group 1:
Ten children (of 3-12 years of age), and 10 adolescents (of 12-18 years of age) from both sexes were enrolled and vaccinated.
Treatment: Vaccination with Fluval P monovalent influenza vaccine with 6 μg HA/0.5 ml active ingredient content and aluminium phosphate gel adjuvant.
Dose: 0.25 ml (total 3 μg HA) in age group 3-12 years, and 0.5 ml (total 6 μg HA) in age group 12-18 years, single dose.

Group 2:
Nine children (of 3-12 years of age), and 10 adolescents (of 12-18 years of age) from both sexes were enrolled and vaccinated.
Treatment: Fluval AB trivalent influenza vaccine with 15 μg HA/0.5ml/strain active ingredient content and aluminium phosphate gel adjuvant.
Dose: 0.25 ml (total 3x7.5 μg HA) in age group 3-12 years, and 0.5 ml (total 3x15 μg HA) in age group 12-18 years, single dose.

Group 3:
Nine children (of 3-12 years of age), and 10 adolescents (of 12-18 years of age) from both sexes were enrolled and vaccinated.
Treatment: Fluval AB Novo trivalent influenza vaccine with 6 μg HA/0.5ml/strain active ingredient content and aluminium phosphate gel adjuvant.
Dose: 0.25 ml (total 3x3 μg HA) in age group 3-12 years, and 0.5 ml (total 3x6 μg HA) in age group 12-18 years, single dose.

Actual number of subjects enrolled in the study:

Vaccine Age group	Group 1: Fluval P	Group 2: Fluval AB	Group 3: Fluval AB Novo	Total
3-12 years	10	9	9	28
12-18 years	10	10	10	30
Total	20	19	19	58

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<tr><td>Name of Active Ingredient:
A/California/7/2009 (H1N1)</td></tr>
<tr><td>Diagnosis and main criteria for inclusion:</td><td colspan="2">Inclusion Criteria:
• Children aged 3 to 12 years, adolescents aged 12 to 18 years, both sexes;
• 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;
• Femal volunteers 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 adolescent participants aged 12 to 18 years and the legitimate representative of all volunteers to understand and comply with planned study procedures;
• Adolescent participants aged 12 to 18 years and the legitimate representative of all volunteers provide written informed consent prior to initiation of study procedures;
• Absence of existence of any exclusion criteria.
Exclusion Criteria:
• Pregnancy or breast feeding or positive urine pregnancy test at baseline prior to vaccination;
• Known allergy to eggs or other components of the vaccine (in particular mercury);
• History of Guillain-Barré syndrome;
• Active neoplasm;
• Immunosuppressive therapy in the preceding 36 months;
• Concomitant corticosteroid therapy, including high-dose inhaled corticosteroids;
• Immunoglobulin (or similar blood product) therapy within 3 months prior to vaccination;
• Documented HIV, HBV or HCV infection;
• Chronic illness that, in the opinion of the investigator, may interfere with the evaluation of the immunoresponse;
• Acute febrile respiratory illness within one week prior to vaccination;
• Vaccine therapy within 4 weeks prior to vaccination;
• Influenza vaccination within 6 months prior to vaccination;
• Experimental drug therapy within 1 month prior to vaccination;
• Past or current psychiatric disease of the volunteer or the legitimate representative that upon judgement of the investigator may have effect on the objective decision-making of the volunteer or the legitimate representative;
• Alcohol or drug abuse of the participant or the legitimate representative.</td></tr>
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<tr><td>Name of Active Ingredient:
A/California/7/2009 (H1N1)</td></tr>
<tr><td>Test product, dose and mode of administration, batch number:</td><td colspan="2">Study drug: Fluval P monovalent influenza vaccine
Active ingredient: A/California/7/2009 (H1N1)
Active ingredient content: 6 µgHA / 0.5 mL
Formulated: vaccine, 1 dose = 0.5 mL
Manufacturer of the study drug: Omninvest Ltd.
Lot No.: FL-P-K-01/09
The influenza A(H1N1) strain included in the vaccine was 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>
</table>

Name of Sponsor/Company: Omninvest Vaccine Manufacturing, Researching and Trading Ltd. **Name of Finished Product:** Fluval P monovalent influenza vaccine **Name of Active Ingredient:** A/California/7/2009 (H1N1)	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*For National Authority use only*

Reference therapy, dose and mode of administration, batch number

Study drug:	**Fluval AB Seasonal Trivalent Influenza Vaccine**
Active ingredient:	A/Brisbane/59/2007(H1N1)-like strain A/Brisbane/10/2007(H3N2)-like strain B/Brisbane/60/2008-like strain
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.:	5609
Registration number is:	OGYI-T-8998.

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.

Study drug:	**Fluval AB Novo Seasonal Trivalent Influenza Vaccine**
Active ingredient:	A/Brisbane/59/2007(H1N1)-like strain A/Brisbane/10/2007(H3N2)-like strain B/Brisbane/60/2008-like strain
Active ingredient content:	3 x 6 μgHA / 0.5 mL
Formulated:	vaccine, 1 dose = 0.5 mL
Manufacturer of the study drug:	Omninvest Ltd.
Lot No.:	FL-K-13/09

Fluval AB Novo 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.

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<tr><td>Name of Active Ingredient:
A/California/7/2009 (H1N1)</td></tr>
<tr><td>Criteria for evaluation:

Safety:</td><td colspan="2">According to Para. 2.4., 2.6., and 3.2. of CPMP/BWP/214/96 ("Note for Guidance on Harmonization of Requirements for Influenza Vaccines", 12 March 1997), adverse reactions for 3 days following vaccination, either local (induration, erythema, ecchymosis, pain) or general (fever, shivering, malaise, other side-effects) and any other adverse reactions lasting 2 days beyond vaccination were recorded and assessed.
The frequency of the following symptoms were especially assessed:
a) local reactions:
- indurations larger than 50 mm diameter and persisting for more than 3 days;
- ecchymosis.
b) general symptoms:
- temperature above 38oC for 24 hours or more;
- malaise;
- shivering.
Adverse events and serious adverse events were monitored by telephone follow-up on Days 1., 2., 3., 7. and 10. after vaccination, and during control visit at Day 21-28. after vaccination.</td></tr>
<tr><td>Efficacy:</td><td colspan="2">Immunogenicity related to HI was assessed according to the criteria defined in guideline CPMP/BWP/214/96:
(i) number of seroconversions* or significant** (i.e. >4-fold) increase in HI antibody titre;
(ii) mean geometric increase; and
(iii) the proportion of subjects achieving an HI titre >40.
For the purposes of calculation, HI results <10 (=undetectable) were expressed as 5.
In absence of adopted requirements for children and adolescents those specified for adults were considered.
According to CPMP/BWP/214/96 the following requirements have to be met in subjects of <60 years of age:
(i) seroconversion* rate should be > 40%,
(ii) increase in GMT should be > 2.5-fold, and
(iii) seroprotection rate should be > 70%.
* 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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Statistical methods:	Safety and tolerability have been analysed in all ITT patients vaccinated. Immunogenicity has been analysed in all subjects completing the control visit at Day 21-28 after vaccination. In the course of safety/tolerability assessment frequency, severity, mean time of appearance and duration of all local and systemic AEs were calculated in all groups by simple descriptive statistics according to CPMP/BWP/214/96: "Note for Guidance on Harmonization of Requirements for Influenza Vaccines", 12 March 1997, Para. 2.4., 2.6., and 3.2. Secondary objective of the study was to assess the efficacy of the study drugs in the subjects 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. HI titers were used to calculate seroconversion rates, seroprotection rates, and increase in geometric mean titers.	
Summary - Conclusions **Safety Results:**	Administration of Fluval P influenza vaccine with 6 μg HA/0.5ml, and administration of Fluval AB or Fluval AB Novo seasonal trivalent influenza vaccines proved to be safe and were well tolerated by the participants of the study. No clinically significant changes in the physical condition or vital signs of the volunteers were observed. No possibly or probably Fluval P vaccine related moderate and no Serious Adverse Event were observed. Fluval P vaccine related side effects were rare and mild. No medical intervention was necessary. No serious adverse events were observed in any of the groups.	

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Omninvest Vaccine Manufacturing, Researching and Trading Ltd.

Name of Finished Product:
Fluval P monovalent influenza vaccine

Name of Active Ingredient:
A/California/7/2009 (H1N1)

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Efficacy Results:

In **Group 1** administration of Fluval P pandemic influenza vaccine with 6 µg HA/0.5ml active ingredient content induced strong immune response against A/H1N1/09 swl. antigen to meet all three CPMP criteria for adults between 18 60 years of age 21-28 days after immunization in both age groups.

Immunogenicity criteria	Age group			
Antigen: A/H1N1/09 swl	children of 3-12 years		children of 12-18 years	
	Criteria	Result	Criteria	Result
Seroconversion	> 40 %	80.0 (+)	> 40 %	90.0 (+)
Increase in GMT	> 2.5	6.1 (+)	> 2.5	12.1 (+)
Seropositivity	> 70 %	80.0 (+)	> 70 %	90.0 (+)

Administration of Fluval P influenza vaccine in Group 1 has not induced significant immune response against seasonal A/H1N1, A/H3N2 and B antigens at day21-28.

Immunogenicity criteria	children of 3-12 years		children of 12-18 years	
	Criteria	Results	Criteria	Results
A(H1N1)				
Seroconversion	> 40 %	0.0	> 40 %	0.0
Increase in GMT	> 2.5	1.2	> 2.5	1.3
Seropositivity	> 70 %	30.0	> 70 %	40.0
A(H3N2)				
Seroconversion	> 40 %	0.0	> 40 %	20.0
Increase in GMT	> 2.5	1.2	> 2.5	1.6
Seropositivity	> 70 %	60.0	> 70 %	50.0
B				
Seroconversion	> 40 %	10.0	> 40 %	0.0
Increase in GMT	> 2.5	1.2	> 2.5	1.0
Seropositivity	> 70 %	10.0	> 70 %	0.0

(+) Met CPMP criteria for adults between 18-60 years of age.

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Name of Active Ingredient: A/California/7/2009 (H1N1)		

In **Group 2** administration of Fluval AB seasonal influenza vaccine with 15 µg HA/strain/0.5ml active ingredient content induced strong immune response against seasonal A/H1N1, A/H3N2 and B antigens to meet all three CPMP criteria for adults between 18-60 years of age 21-28 days after immunization in both age groups in case of all strains with the exception of strain B and age group 3-12 years where the seropositivity rate was just 66.7% instead of the required >70%. However, seroconversion rate and GMT ratio was above 40% and 2.5 respectively, meeting thus CPMP criteria on seasonal flu vaccines in case of this strain and age group as well.

Immunogenicity criteria	**children of 3-12 years**		**children of 12-18 years**	
	Criteria	**Results**	**Criteria**	**Results**
A(H1N1)				
Seroconversion	> 40 %	77.8 (+)	> 40 %	80.0 (+)
Increase in GMT	> 2.5	5.4 (+)	> 2.5	6.5 (+)
Seropositivity	> 70 %	100.0 (+)	> 70 %	100.0 (+)
A(H3N2)				
Seroconversion	> 40 %	66.7 (+)	> 40 %	70.0 (+)
Increase in GMT	> 2.5	6.9 (+)	> 2.5	4.6 (+)
Seropositivity	> 70 %	88.9 (+)	> 70 %	90.0 (+)
B				
Seroconversion	> 40 %	66.7 (+)	> 40 %	80.0 (+)
Increase in GMT	> 2.5	7.4 (+)	> 2.5	6.1 (+)
Seropositivity	> 70 %	66.7	> 70 %	90.0 (+)

Administration of Fluval AB seasonal influenza vaccine in Group 2 has not induced significant immune response against A/H1N1/09 swl. antigen at Day 21-28.

Immunogenicity criteria	**Age group**			
Antigen: A/H1N1/09 swl	**children of 3-12 years**		**children of 12-18 years**	
	Criteria	**Result**	**Criteria**	**Result**
Seroconversion	> 40 %	0.0	> 40 %	0.0
Increase in GMT	> 2.5	1.1	> 2.5	1.1
Seropositivity	> 70 %	0.0	> 70 %	0.0

(+) Met CPMP criteria for adults between 18-60 years of age.

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In **Group 3** administration of Fluval AB Novo seasonal influenza vaccine with 6 µg HA/strain/0.5ml active ingredient content induced strong immune response against seasonal A/H1N1, A/H3N2 and B antigens to meet all three CPMP criteria for adults between 18-60 years of age 21-28 days after immunization in both age groups in case of all strains with the exception of strain B and age group 3-12 years where the seropositivity rate was just 66.7% instead of the required >70%. However, seroconversion rate and GMT ratio was above 40% and 2.5 respectively, meeting thus CPMP criteria on seasonal flu vaccines in case of this strain and age group as well.

Immunogenicity criteria	**children of 3-12 years**		**children of 12-18 years**	
	Criteria	**Results**	**Criteria**	**Results**
A(H1N1)				
Seroconversion	> 40 %	77.8 (+)	> 40 %	80.0 (+)
Increase in GMT	> 2.5	8.0 (+)	> 2.5	7.5 (+)
Seropositivity	> 70 %	100.0 (+)	> 70 %	90.0 (+)
A(H3N2)				
Seroconversion	> 40 %	66.7 (+)	> 40 %	80.0 (+)
Increase in GMT	> 2.5	4.0 (+)	> 2.5	8.6 (+)
Seropositivity	> 70 %	77.8 (+)	> 70 %	90.0 (+)
B				
Seroconversion	> 40 %	66.7 (+)	> 40 %	80.0 (+)
Increase in GMT	> 2.5	5.9 (+)	> 2.5	5.3 (+)
Seropositivity	> 70 %	66.7 (+)	> 70 %	80.0 (+)

Administration of Fluval AB Novo seasonal influenza vaccine in Group 3 have not induced significant immune response against A/H1N1/09 swl. antigen at 21-28.

Immunogenicity criteria	**Age group**			
Antigen: A/H1N1/09 swl	**children of 3-12 years**		**children of 12-18 years**	
	Criteria	**Result**	**Criteria**	**Result**
Seroconversion	> 40 %	0.0	> 40 %	0.0
Increase in GMT	> 2.5	1.0	> 2.5	1.2
Seropositivity	> 70 %	0.0	> 70 %	0.0

(+) Met CPMP criteria for adults between 18-60 years of age.

Conclusion	In summary, administration of Fluval P pandemic influenza vaccine induced strong immune response against pandemic A/H1N1/09 swl. antigen, and Fluval AB and Fluval AB Novo seasonal influenza vaccines induced strong immune response against seasonal A/H1N1, A/H3N2 and B antigens, but they could not induce at the same time significant cross-protection immunity against the seasonal A/H1N1, A/H3N2 and B antigens or the pandemic A/H1N1/09 swl. antigen respectively.
Date of Report	08 June 2017