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 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>Title of Study:</td><td colspan="2">A Randomized, Active Controlled, Double-blind, Multi-Centre Study to Evaluate Safety and Immunogenicity of One Dose of FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccine Containing 6µgHA of Seasonal A/H1N1, A/H3N2 and B Influenza Antigens in Non-elderly Adult and Elderly Subjects</td></tr>
<tr><td>Study Number</td><td colspan="2">FluvalAB-H-15</td></tr>
<tr><td>EudraCT Number</td><td colspan="2">2011-003314-16</td></tr>
<tr><td>Investigators and Study Centres:</td><td colspan="2">Coordinating Investigator:
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District Doctor's Office, Budapest XIII.
Péter VAJER MD, general practitioner,
District Doctor's Office, Biatorbágy
Tibor HRUTKA MD, general practitioner,
District Doctor's Office, Vecsés</td></tr>
<tr><td>Publication (reference):</td><td colspan="2">None</td></tr>
<tr><td>Phase of development:</td><td colspan="2">Phase III</td></tr>
<tr><td>Studied period

Date of first enrolment:

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

Oct. 24, 2011

March 21, 2012</td></tr>
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Objectives:	**Immunogenicity objectives:** To assess - immunogenicity of one 0.5 mL intramuscular (IM) injection of FAB-6011 trivalent influenza vaccine containing 6µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens, as measured by haemagglutination inhibition (HI) test 21 days and 120 days after vaccination in compliance with the requirements of the current European Union recommendations as determined in CPMP/BWP/214/96. - non-inferiority of one 0.5 mL IM injection of FAB-6011 trivalent influenza vaccine containing 6µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens against FLUVAL AB trivalent influenza vaccine containing 15µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens in terms of post-immunization geometric mean titers (GMTs) as measured by HI test 21 days and 120 days after vaccination. **Safety and Tolerability Objectives:** To evaluate the safety of the administration of one 0.5 mL IM injection of FAB-6011 trivalent influenza vaccine containing 6µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens.	
Methodology:	Subjects were randomly assigned in a 1:1 ratio to one of the following vaccine groups, and vaccinated as follows: **Group 1:** one 0.5 mL injection of FAB-6011 trivalent influenza vaccine containing 6µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens; **Group 2:** one 0.5 mL injection of FLUVAL AB trivalent influenza vaccine containing 15µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens. The subjects were enrolled into two subgroups according to their age (18-60 years and over 60 years). Control visits at Day 21 and Day 120 were planned to collect blood samples for HI test to assess immunogenicity and to record adverse events to assess safety of the vaccination.	

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<tr><td>Number of patients (planned and analysed):</td><td colspan="2">
The planned enrolment was minimum 1106 and maximum 1232 subjects (with minimum 225 and maximum 504 subjects aged 18-60 years and minimum 328 and maximum 728 subjects aged over 60 years) overall. This headcount ensures a statistical power of 80%.
Group 1: 252 subjects aged 18-60 years /Group 1A/ and 364 subjects aged over 60 years /Group 1E/;
Group 2: 252 subjects aged 18-60 years /Group 2A/ and 364 subjects aged over 60 years /Group 2E/).
Actually 1206 subjects were enrolled in the study, randomly assigned to two vaccine groups, and vaccinated by double-blind medication (ITT population). The data of these 1206 subjects were included in the safety evaluation.
Out of the 1206 subjects vaccinated 1179 subjects attended both Visit 2 at Day 21 and Visit 3 at Day 120 (PP population).
<table>
<tr><th colspan="4">Actual number of subjects completing the study</th></tr>
<tr><th rowspan="2">Age group</th><th colspan="3">Vaccine group</th></tr>
<tr><th>Group 1:
FAB-6011
influenza vaccine.
(6 µgHA/0.5mL)</th><th>Group 2:
FluvalAB
influenza vaccine.
(15 µgHA/0.5mL)</th><th>Total</th></tr>
<tr><td>18-60 years</td><td>241</td><td>237</td><td>478</td></tr>
<tr><td>over 60 years</td><td>347</td><td>354</td><td>701</td></tr>
<tr><td>Total</td><td>588</td><td>591</td><td>1179</td></tr>
</table>
The data of these 1179 subjects were included in the immunogenicity evaluation.
</td></tr>
<tr><td>Diagnosis and main criteria for inclusion:</td><td colspan="2">
Subjects eligible for enrolment into this study were:
• male and female adult volunteers aged 18 years or older,
• mentally competent,
• able to understand and comply with all study requirements,
- willing and able to give written informed consent prior to initiation of study procedures,
- in good health (as determined by clinical judgement of the investigator on the basis of medical history and existing medical condition) or are in stable medical condition.
• Female subjects aged 18 to 60 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.
• Absence of existence of any exclusion criteria.
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<tr><td>Test product, dose and mode of administration, batch number:</td><td colspan="2">Name: Fluval AB-like influenza vaccine
Active ingredient content: 6 µgHA/strain/0.5ml seasonal A/H1N1, A/H3N2 and B influenza antigens each) with aluminium phosphate gel adjuvant.
Code in the study: FAB-6011
Method of administration: i.m. injection
Doses administered: 0.5mL
Manufacturer: Omninvest Kft. (H-2097 Pilisborosjenö, Fö utca 7.)</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">Name: Fluval AB influenza vaccine
Active ingredient content: 15 µgHA/strain/0.5ml
Code in the study: FluvalAB
MA number: OGYI-T-8998 (registered by the National Institute of Pharmacy, Hungary)
Method of administration: i.m. injection
Doses administered: 0.5mL
Manufacturer: Omninvest Kft. (H-2097 Pilisborosjenö, Fö utca 7.)</td></tr>
<tr><td>Criteria for evaluation:

Safety:</td><td colspan="2">Safety and tolerability data are assessed in comparison with two study vaccine.
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 – and the study termination visit at Day 120) either judged as related or not to vaccination by the investigator, were recorded.</td></tr>
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Efficacy:	Immunogenicity study objectives were assessed in compliance with CHMP requirements concerning seasonal influenza vaccines as determined in CPMP/BWP/214/96 guideline. According to this guideline, at least one of the following requirements should be meet as measured by HI test 3 weeks after vaccination: • Adult subjects between **18 and 60 years** (i.e. ≥18 and <60): - number of seroconversions* or significant increase in antibody titer* >40%, - increase in geometric mean titres >2.5, - the proportion of subjects achieving an HI titer ≥40 should be >70%. • Elderly subjects aged 60 years and over (i.e., ≥60): - number of seroconversions1 or significant increase in antibody titer2 >30%, - increase in geometric mean titres >2.0, - the proportion of subjects achieving an HI titer ≥40 should be >60%. * Seroconversion is defined as negative (<10) pre-vaccination serum and post-vaccination titer ≥40. ** Significant increase in antibody titer is defined as at least a fourfold increase from non-negative (≥10) pre-vaccination serum. Non-inferiority is concluded if the lower limit of the 95% two-sided confidence interval for $\log(GMT_6) - \log(GMT_{15})$ is greater than -0.405.	
Statistical methods:	Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age at enrolment are calculated overall and by age group. Distributions of subjects by sex and previous influenza vaccination are summarized overall and by age group. According to this guideline, at least one of the following Immunogenicity objectives according to CHMP requirements was analysed descriptively in both study vaccine. At the non-inferiority assessment of the study vaccines the null hypothesis stated that the lower limit of the two-sided 95% confidence interval for the ratio of geometric mean titers measured 21 days and 120 days after vaccination in Group 1 (6μgHA) and Group 2 (15μgHA) is below 1/1.5. Interim analysis was planned by the study protocol by not performed during the study. Number and percentage of subjects with at least one (systemic and local) adverse event or adverse reaction occurred between Day 0 and the study termination visit at Day 120 was calculated.	
Summary - Conclusions **Safety Results:**	Administration of both the investigational and the reference vaccines was well tolerated by the study subjects. No serious and no severe possibly or probably related adverse event was observed. Both the investigational and the reference vaccines proved to be safe, no vaccine-related clinically significant changes in the physical condition or vital signs of the volunteers were observed. Significant difference between safety profiles of the investigational and the reference vaccines could not be established.	

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Efficacy Results:

Summary of results according to CPMP/BWP/214/96 criteria

A.G.	Strain	CPMP criteria		Vaccine Group 6µgHA		Vaccine Group 15µgHA	
				Day 21	Day 120	Day 21	Day 120
18-60	A/H1N1	SC	≥ 40 %	66 %	47 %	69 %	51 %
		GMTR	≥ 2.5	5.4	3.7	6.1	4.1
		SP	≥ 70 %	93 %	83 %	95 %	87 %
	A/H3N2	SC	≥ 40 %	65 %	51 %	69 %	54 %
		GMTR	≥ 2.5	5.4	3.8	5.5	3.8
		SP	≥ 70 %	99 %	95 %	99 %	96 %
	B	SC	≥ 40 %	67 %	50 %	75 %	56 %
		GMTR	≥ 2.5	5.2	3.4	5.5	3.4
		SP	≥ 70 %	90 %	75 %	90 %	79 %
60+	A/H1N1	SC	≥ 30 %	68 %	51 %	68 %	51 %
		GMTR	≥ 2.0	5.5	3.8	5.2	3.8
		SP	≥ 60 %	83 %	72 %	83 %	72 %
	A/H3N2	SC	≥ 30 %	60 %	38 %	58 %	40 %
		GMTR	≥ 2.0	4.5	3.0	4.4	2.9
		SP	≥ 60 %	95 %	92 %	97 %	94 %
	B	SC	≥ 30 %	56 %	42 %	64 %	50 %
		GMTR	≥ 2.0	4.0	2.7	4.2	3.0
		SP	≥ 60 %	76 %	66 %	82 %	74 %

Furthermore, a non-inferiority analysis demonstrated that on the basis of Para. III.B.1.a. of Guidance for Industry of U.S. Department of Health and Human Services, Food and Drug Administration on Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (May 2007) FAB-6011 trivalent seasonal influenza vaccine containing 6 µgHA/strain/0.5mL antigen is non inferior in terms of HI titers and seroconversion rates at post-immunisation days 21-28 and 110-120 to FluvalAB 15 µgHA/strain/0.5mL vaccine.

Conclusion

In summary, on the basis of the results of the present clinical study the Fluval AB-like influenza vaccine of 6 µgHA/strain/0.5mL antigen content is safe and effective, and non inferior to FluvalAB seasonal influenza vaccine of 15 µgHA/strain/0.5mL antigen content.

Date of Report	20 December 2016