SYNOPSIS

Name of Sponsor/Company: Omninvest Vaccine Manufacturing, Researching and Trading Ltd. **Name of Finished Product:** Fluval AB suspension for injection **Name of Active Ingredient:** A/California/7/2009(H1N1) derived NYMC X-179A reass. strain A/Perth/16/2009(H3N2)-like A/Victoria/210/2009(H3N2) derived NYMC X-187 reass. strain B/Brisbane/60/2008 derived NYMC BX-35 reass. strain	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	*For National Authority use only*
Title of Study:	A Randomized, Double-blind, Multi-Center Study to Evaluate Safety and Immunogenicity of One Dose of Four FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccines Containing 3.5µgHA, 6µgHA, 9µgHA or 15µgHA of Seasonal A/H1N1, A/H3N2 and B Influenza Antigens in Non-elderly Adult and Elderly Subjects	
Study Number	FluvalAB-H-14	
EudraCT Number	2011-003166-32	
Investigators and Study Centres:	**Coordinating Investigator:** József FŰZI MD, general practitioner, District Doctor's Office, **Investigators:** Ágnes HASITZ, MD, general practitioner, District Doctor's Office, Szentendre Judit SIMON MD, general practitioner, District Doctor's Office Budapest VIII. Péter TORZSA MD, general practitioner, District Doctor's Office, Budapest XIII.	
Publication (reference):	None	
Phase of development:	Phase III	
Studied period **Date of first enrolment:** **Date of last completed:**	 Sept. 05, 2011 Oct. 17, 2011	
Objectives:	**Immunogenicity objectives** *Primary immunogenicity objectives* a) To assess immunogenicity of one 0.5 mL intramuscular (IM) injection of four FLUVAL AB-like trivalent influenza vaccines containing either 3.5µgHA, 6µgHA, 9µgHA or 15µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens, as measured by haemagglutination inhibition (HI) test 21 days after vaccination in compliance with the requirements of the current European Union recommendations as determined in CPMP/BWP/214/96.	

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Objectives (cont.):	b) To determine dose-effect relationship between one 0.5 mL IM injection of four FLUVAL AB-like trivalent influenza vaccines containing either 3.5µgHA, 6µgHA, 9µgHA or 15µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens and immune response provoked 21 days after vaccination in terms of pre- and post-immunization HA titers as measured by HI test. *Secondary immunogenicity objectives* a) To assess immunogenicity of one 0.5 mL IM injection of four FLUVAL AB-like trivalent influenza vaccines containing either 3.5µgHA, 6µgHA, 9µgHA or 15µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens, as measured by HI test 14 days after vaccination in compliance with the requirements of the current European Union recommendations as determined in CPMP/BWP/214/96. b) To find the highest dose of FLUVAL AB-like trivalent influenza vaccine among 3.5µgHA, 6µgHA and 9µgHA the response of which differs from that of dose 15µgHA in terms of post-immunization HA titers as measured by HI test 21 days after vaccination. c) To find the highest dose of FLUVAL AB-like trivalent influenza vaccine among 3.5µgHA, 6µgHA and 9µgHA the response of which differs from that of dose 15µgHA in terms of post-immunization HA titers as measured by HI test 14 days after vaccination. d) To find the highest dose of FLUVAL AB-like trivalent influenza vaccine among 3.5µgHA, 6µgHA and 9µgHA the response of which differs from that of dose 15µgHA in terms of the percentage of subjects achieving seroconversion[1] or significant increase in antibody titer[2] at day 21 after vaccination. e) To find the highest dose of FLUVAL AB-like trivalent influenza vaccine among 3.5µgHA, 6µgHA and 9µgHA the response of which differs from that of dose 15µgHA in terms of the percentage of subjects achieving seroconversion[1] or significant increase in antibody titer[2] at day 14 after vaccination. [1)] Seroconversion is defined as negative (<10) pre-vaccination serum and post-vaccination titer ≥40. [2)] Significant increase in antibody titer is defined as at least a fourfold increase from non-negative (≥10) pre-vaccination serum. f) To find the highest dose of FLUVAL AB-like trivalent influenza vaccine among 3.5µgHA, 6µgHA and 9µgHA the response of which differs from that of dose 15µgHA in terms of Day 21/Day 0 geometric mean titer ratios (GMTRs) as determined by HI. g) To find the highest dose of FLUVAL AB-like trivalent influenza vaccine among 3.5µgHA, 6µgHA and 9µgHA the response of which differs from that of dose 15µgHA in terms of Day 14/Day 0 geometric mean titer ratios (GMTRs) as determined by HI. **Safety and tolerability objective** To evaluate the safety of the administration of one 0.5 mL IM injection of four FLUVAL AB-like trivalent influenza vaccines containing either 3.5µgHA, 6µgHA, 9µgHA or 15µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens.	

<table>
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A/Perth/16/2009(H3N2)-like
A/Victoria/210/2009(H3N2) derived NYMC X-187 reass. strain
B/Brisbane/60/2008 derived NYMC BX-35 reass. strain</td></tr>
<tr><td>Methodology:</td><td colspan="2">In this randomized, double-blind, multi-centre study, subjects were randomly assigned in 1:1:1:1 ratio to one of the following vaccine groups, and were vaccinated as follows:
Group 1: one 0.5mL injection of FAB-3511 trivalent influenza vaccine containing 3.5µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens;
Group 2: one 0.5mL injection of FAB-6011 trivalent influenza vaccine containing 6µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens;
Group 3: one 0.5mL injection of FAB-9011 trivalent influenza vaccine containing 9µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens;
Group 4: one 0.5mL injection of FLUVAL AB trivalent influenza vaccine containing 15µgHA of seasonal A/H1N1, A/H3N2 and B influenza antigens.
Subjects were enrolled into two subgroups according to their age (18-60 years and over 60 years).
Subjects were observed for 30 minutes after vaccination for any immediate reactions. All subjects were instructed to complete a diary card to record local reactions (ecchymosis, erythema, induration, swelling and pain at injection site) and systemic ones (chills, malaise, myalgia, arthralgia, nausea, headache, sweating, fatigue and potential indicators of oculo-respiratory syndrome) and axillary temperature starting on the day of vaccination (Day 0, Visit 1) and for each of the 7 days following the immunization.
All adverse events will be collected during days 0 to 21 (Day 21, Visit 3).</td></tr>
<tr><td>Number of patients (planned and analysed):</td><td colspan="2">The planned enrolment was 256 subjects overall (with 128 subjects aged 18-60 years and 128 subjects aged over 60 years).
Group 1: one 0.5 mL injection of FAB-3511 trivalent influenza vaccine (Group 1A: subjects aged 18-60 years, Group 1E: subjects aged over 60 years);
Group 2: one 0.5 mL injection of FAB-6011 trivalent influenza vaccine (Group 2A: subjects aged 18-60 years, Group 2E: subjects aged over 60 years);
Group 3: one 0.5 mL injection of FAB-9011 trivalent influenza vaccine (Group 3A: subjects aged 18-60 years, Group 3E: subjects aged over 60 years);
Group 4: one 0.5 mL injection of FLUVAL AB trivalent influenza vaccine (Group 4A: subjects aged 18-60 years, Group 4E: subjects aged over 60 years).</td></tr>
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Number of patients cont.

Actually 256 healthy volunteers (male and female) were selected for inclusion in the study, and screened prior to vaccination. All 256 subjects entered the study and were vaccinated (ITT population). Their data were used for safety evaluation of the study. 254 subjects attended the last control visit at Day 21-28. Their data were used for immunogenicity evaluation of the study (PP population).

Table 1: Number of subjects completing the study (PP population)

Age group	Vaccine group				
	Group 1: FAB-3511 infl. vaccine. (3.5µgHA/dose)	Group 2: FAB-6011 infl. vaccine. (6µgHA/dose)	Group 3: FAB-9011 infl. vaccine. (9µgHA/dose)	Group 4: FluvalAB infl. vaccine. (15µgHA/dose)	Total
18-60 years	31	30	31	34	126
60+ years	31	33	32	32	128
Total	62	63	63	66	254

Diagnosis and main criteria for inclusion:

Inclusion criteria:

- 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 were in stable medical condition. Subjects were not 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 would not compromise the subject's participation in the study.
- 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.

Test product, dose and mode of administration, batch number:

Vaccine A:

Name:	Fluval AB-like influenza vaccine
Active ingredient content:	3.5 µgHA/strain/0.5ml
Code in the study:	FAB-3511
Lot number:	FL-K-01/11
Manufacturer:	Omninvest Kft.
Date of manufacturing:	June 2011
Date of expiry:	31 August 2012

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	Vaccine B: Name: Fluval AB-like influenza vaccine Active ingredient content: 6 µgHA/strain/0.5ml Code in the study: FAB-6011 Lot number: FL-K-02/11 Manufacturer: Omninvest Kft. Date of manufacturing: June 2011 Date of expiry: 31 August 2012	
Test product (Cont.)	**Vaccine C:** Name: Fluval AB-like influenza vaccine Active ingredient content: 9 µgHA/strain/0.5ml Code in the study: FAB-9011 Lot number: FL-K-03/11 Manufacturer: Omninvest Kft. Date of manufacturing: June 2011 Date of expiry: 31 August 2012	
Duration of treatment	Single dose	
Reference therapy, dose and mode of administration, batch number	**Vaccine D:** 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) Lot number: FL-K-04/11 Method of administration: i.m. injection Doses administered: 0.5mL Manufacturer: Omninvest Kft. (H-2097 Pilisborosjenö, Fö utca 7.) Date of manufacturing: June 2011 Date of expiry: 31 August 2012	
Criteria for evaluation: **Safety:**	Number and percentage of subjects with at least one local reaction between Day 0 and Day 7 after vaccination. Number and percentage of subjects with at least one systemic reaction between Day 0 and Day 7 after vaccination. Number and percentage of subjects with at least one adverse event between Day 0 and the study termination visit at Day 21. Safety and tolerability were assessed in accordance with available safety data on	

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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: • Non-elderly adult subjects between 18 and 60 years (i.e. ≥18 and <60): - number of seroconversions[1] or significant increase in antibody titer[2] >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%. 1) Seroconversion is defined as negative (<10) pre-vaccination serum and post-vaccination titer ≥40. 2) Significant increase in antibody titer is defined as at least a fourfold increase from non-negative (≥10) pre-vaccination serum. Serum samples were assessed by means of strain-specific HI test.	
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. GMTs measured at Day 21 and Day 14, separately for each age group. According to CHMP 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 14 days and 21 days after vaccination in Group 1 (6µgHA) and Group 2 (15µgHA) is below 1/1.5. *Secondary immunogenicity objectives "b)" and "c)"* It was assumed that GMT3.5 ≤ GMT6 ≤ GMT9 ≤ GMT15.A step-down Dunnett test procedure was performed on 21 and 14 post-vaccination day GMTs comparing Group 4 (15µgHA) to Groups 1, 2 and 3 (3.5µgHA, 6µgHA and 9µgHA).	

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Statistical methods (Cont.):	That means, the ordered null hypotheses according to the closure principle was: H01: log(GMT9) – log(GMT15) ≥ 0 and log(GMT6) – log(GMT15) ≥ 0 and log(GMT3.5) – log(GMT15) ≥ 0 H02: log(GMT9) – log(GMT15) ≥ 0 and log(GMT6) – log(GMT15) ≥ 0 and log(GMT3.5) – log(GMT15) < 0 H03: log(GMT9) – log(GMT15) ≥ 0 and log(GMT6) – log(GMT15) < 0 and log(GMT3.5) – log(GMT15) < 0 Alternative hypothesis if H03 was rejected: H13: log(GMT9) – log(GMT15) < 0 and log(GMT6) – log(GMT15) < 0 and log(GMT3.5) – log(GMT15) < 0 Secondary immunogenicity objective "b)" concerned the A one-sided alpha value of 5% was used. The null hypotheses stated that the lower limits of the Dunnett-adjusted two-sided 90% simultaneous confidence intervals for percentages are greater than or equal to zero, that is the percentage in Groups 1, 2 or 3 is equal to or higher than that in Group 4. H0,3.5: Seroconversion3.5 - Seroconversion15 ≥ 0 H0,6: Seroconversion6 - Seroconversion15 ≥ 0 H0,9: Seroconversion9 - Seroconversion15 ≥ 0 H1, 3.5: Seroconversion3.5 - Seroconversion15 < 0 H1, 6: Seroconversion6 - Seroconversion15 < 0 H1, 9: Seroconversion9 - Seroconversion15 < 0 Secondary immunogenicity objective "d)" concerned the percentages at Day 21, secondary immunogenicity objective "e)" concerned the percentages at Day 14, separately for each age group. A one-sided alpha value of 5% was used. *Secondary immunogenicity objectives "f)" and "g)"* GMTR means geometric mean ratio, that is, the geometric mean of the fold rise of titers between Day 0 and Day 21 or Day 14. It was assumed that GMTR3.5 ≤ GMTR6 ≤ GMTR9 ≤ GMTR15. A step-down Dunnett test procedure was performed on 21 and 14 post-vaccination day GMTRs comparing Group 4 (15µgHA) to Groups 1, 2 and 3 (3.5µgHA, 6µgHA and 9µgHA). That means, the ordered null hypotheses according to the closure principle was: H01: log(GMTR9) – log(GMTR15) ≥ 0 and log(GMTR6) – log(GMTR15) ≥ 0 and log(GMTR3.5) – log(GMTR15) ≥ 0 H02: log(GMTR9) – log(GMTR15) ≥ 0 and log(GMTR6) – log(GMTR15) ≥ 0 and log(GMTR3.5) – log(GMTR15) < 0 H03: log(GMTR9) – log(GMTR15) ≥ 0 and log(GMTR6) – log(GMTR15) < 0 and log(GMTR3.5) – log(GMTR15) < 0 Alternative hypothesis if H03 was rejected: H13: log(GMTR9) – log(GMTR15) < 0 and log(GMTR6) – log(GMTR15) < 0 and log(GMTR3.5) – log(GMTR15) < 0	

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<tr><td>Statistical methods (Cont.):</td><td colspan="2">Secondary immunogenicity objective "f)" concerned the GMTRs measured at Day 21, secondary immunogenicity objective "g)" concerned the GMTRs measured at Day 14, separately for each age group.

Statistical power considerations
Secondary immunogenicity objective “b)” was considered for statistical power calculations.
A sample size of 32 per age group per vaccine group can give the power of 70% to detect a 2-fold difference in the ratio of GMTs between vaccine groups 1-2-3 and Group 4 with one-sided alpha value 10% assuming a geometric standard deviation of 3.17 (estimated geometric standard deviation of 21-day post-vaccination titers among the 3 different strains measured at a previous study containing the same virus strains as the current study vaccines (FluvalAB-H-YL2010, sponsored by Omninvest Ltd.).
No interim analysis of data from this trial was planned and performed.
Number and percentage of subjects with at least one (systemic and local) adverse event or adverse reaction occurred between Day 7 and the study termination visit Day21 in all vaccine groups was calculated.</td></tr>
<tr><td>Summary - Conclusions

Safety Results:</td><td colspan="2">Administration of all investigational vaccines was well tolerated by the participants of the study. All investigational vaccines proved to be safe; no clinically significant changes in the physical condition or vital signs of the volunteers were observed. All possibly or probably related adverse events (i.e. adverse reactions) occurred during the study were mild, or some of them moderate, and recovered completely in a few days without medical intervention and sequelae. No severe or serious adverse reaction was observed. No statistically significant difference was found in frequency of adverse reactions occurred in Groups 1, 2, or 3 compared to Group 4.</td></tr>
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Efficacy Results:

A descriptive statistical analysis showed that all four vaccines of 3.5, 6, 9, and 15µgHA/strain/0.5mL active ingredient content fulfill all three CHMP immunogenicity criteria for the evaluation of seasonal influenza vaccines as determined in CPMP/BWP/214/96 guideline in terms of all three virus strains and both age groups in case of both 14 days and 21 days after vaccination (Table 2, 3 and 4).

Table 2: Proportion of Subjects Seroconverted[1] or Showing Significant Titre Increase[2]

Age group	Virus strain	at Day 14				at Day 21			
		Group 1 3.5µgHA	Group 2 6µgHA	Group 3 9µgHA	Group 4 15µgHA	Group 1 3.5µgHA	Group 2 6µgHA	Group 3 9µgHA	Group 4 15µgHA
18-60	A/H1N1	61%	53%	58%	62%	68%	60%	58%	65%
	A/H3N2	42%	57%	55%	71%	45%	57%	65%	74%
	B	48%	57%	42%	59%	55%	60%	45%	62%
60+	A/H1N1	58%	58%	53%	59%	55%	61%	53%	63%
	A/H3N2	48%	61%	53%	59%	48%	64%	59%	63%
	B	42%	42%	47%	47%	45%	49%	47%	53%

1) Seroconversion is defined as negative (<10) pre-vaccination serum and post-vaccination titer ≥40.
2) Significant increase in antibody titer is defined as at least a fourfold increase from non-negative (≥10) pre-vaccination serum.

Table 3: Increase in Post-Vaccination Geometric Mean Titres

Age group	Virus strain	Day 14 / Day 0				Day 21 /Day 0			
		Group 1 3.5µgHA	Group 2 6µgHA	Group 3 9µgHA	Group 4 15µgHA	Group 1 3.5µgHA	Group 2 6µgHA	Group 3 9µgHA	Group 4 15µgHA
18-60	A/H1N1	3.9	3.2	4.9	4.2	4.0	3.5	5.1	4.4
	A/H3N2	3.5	4.1	4.2	4.4	3.6	4.0	4.5	4.5
	B	4.3	3.3	4.1	4.2	4.7	3.4	4.1	4.3
60+	A/H1N1	3.5	4.1	4.9	4.8	3.3	4.5	4.8	5.0
	A/H3N2	3.2	4.4	4.4	4.8	3.1	4.7	4.7	5.1
	B	2.7	3.5	3.6	3.6	2.7	3.7	3.6	3.6

Table 4: Proportion of Subjects Seroprotected (achieving an HI titre of ≥40)

Age group	Virus strain	at Day 14				at Day 21			
		Group 1 3.5µgHA	Group 2 6µgHA	Group 3 9µgHA	Group 4 15µgHA	Group 1 3.5µgHA	Group 2 6µgHA	Group 3 9µgHA	Group 4 15µgHA
18-60	A/H1N1	94%	97%	100%	97%	94%	100%	97%	97%
	A/H3N2	90%	100%	97%	100%	90%	100%	100%	100%
	B	84%	97%	87%	100%	94%	97%	87%	100%
60+	A/H1N1	94%	91%	91%	97%	94%	94%	91%	100%
	A/H3N2	97%	97%	100%	97%	97%	97%	100%	97%
	B	81%	91%	88%	84%	81%	94%	88%	84%

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Efficacy Results (Cont.):	As far as dose-effect relationship between vaccines of 3.5, 6, 9, and 15µgHA/strain/0.5mL active ingredient content is concerned, there is little evidence of a tendency of increasing immunogenicity effect with increasing active ingredient content in terms of post-immunziation GMTs, rate of seroconversion or significant increase of antibody titres and GMTRs.	
Conclusion	All four study drugs were well tolerated by the participants. On the basis of the actual number of participants in the certain vaccine groups, no statistically significant difference was found in frequency of adverse reactions occurred in Fluval AB-like influenza vaccines of 3.5, 6, or 9µgHA/strain/0.5mL antigen content were administered compared to Fluval AB influenza vaccine of 15µgHA/strain/0.5mL antigen content was administered. All four vaccines of 3.5, 6, 9, and 15µgHA/strain/0.5mL active ingredient content fulfill all three CHMP immunogenicity criteria for the evaluation of seasonal influenza vaccines as determined in CPMP/BWP/214/96 guideline in terms of all three virus strains and both age groups in case of both 14 days and 21 days after vaccination. The results of the evaluation suggest that vaccines of 6 and 9µgHA/strain/0.5mL active ingredient content are on the plateau of the dose-response curve and do not significantly differ from that of vaccine of 15µgHA/strain/0.5mL active ingredient content, while for vaccine of 3.5µgHA/strain/0.5mL active ingredient content there is weaker evidence for that. **In summary, on the basis of the results of the present study all four Fluval AB-like influenza vaccines are safe and effective.**	
Date of Report	20 December 2016	