**Sponsor:** Novartis Vaccines and Diagnostics

**Investigational Product:** FLUVIRIN® [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur]

**Indication:** Prophylaxis: Influenza

**Protocol Number:** V78_08S

**Protocol Title:** A Phase III, multicenter, uncontrolled, open label study to evaluate safety and immunogenicity of FLUVIRIN® [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur], Formulation 2010/2011, when administered to adult and elderly subjects

**Phase of Development:** Phase III

**Study Period:**

Date of first enrolment: 05 JUL 10

Date of last visit: 27 JUL 10

**Methodology:**

All volunteers received a single 0.5 mL dose of Fluvirin into the deltoid muscle of (preferably) the non-dominant arm on day 1. Prior to vaccination on day 1 (Visit 1), the study staff queried each female of childbearing potential to determine the date of her last menstrual period and the subject's commitment to use a birth control from day 1 up to and including the three weeks following vaccination. To be eligible for this study, all females of childbearing potential were required to have a negative urine pregnancy test to receive study vaccination. Blood samples, approx. 10 mL, for the determination of antibody titers were drawn on day 1 prior to vaccination and on day 22 (-1/+5 days) (end of individual study participation).
Subjects were contacted by phone on day 5 (+2) after vaccination to ensure that local and systemic reaction data were collected on the Subject's Diary Card and also to determine the subject's clinical status.
After immunization, subjects were observed for approximately 30 minutes for any immediate reactions. Each subject was instructed to complete a diary card for on the immunization day and three days thereafter to collect local (ecchymosis, erythema, induration, swelling and pain at the injection site) and systemic (chills/shivering, malaise, myalgia, arthralgia, headache, sweating, fatigue and fever [i.e., axillary temperature ≥ 38°C]) reactions. All adverse events (solicited and unsolicited) were collected during day 1 to 4. All adverse events necessitating a physician's visit or consultation and/or leading to premature study discontinuation and all serious adverse events were collected throughout the trial.

Serology testing was performed by HI test and by SRH test.

Subjects were informed that in the event of severe inter-current infection (i.e., any severe flu-like symptoms) during the study period until day 22, he/she had to contact the Investigator who would take a nasal and/or pharyngeal swab for the diagnosis of influenza or any other respiratory infection of viral origin. For confirmatory purposes, specimens were planned to be analyzed via Quick test and RT-PCR or culture.

**Number of Subjects (planned and analyzed):**

Approximately 126 subjects were planned to be enrolled, of which 63 in the non-elderly adult age group (aged 18 to 60) and 63 in the elderly age group (aged 61 and older). In the non-elderly adult age group, not more than approximately half of the subjects should have been aged between 41 and 60 years. The sample size (126) allowed for up to 13 non evaluable subjects per age group.

In total 144 subjects were actually enrolled, all of the 144 subjects were included in the safety analysis and 136 subjects in the immunogenicity analysis (per protocol set).

**Study Centers:**

One center in Germany.

**Publication (reference) and/or ClinicalTrials.gov National Clinical Trial (NCT) Number:**

NCT01161264

**Objectives:**

Immunogenicity:

Primary

To evaluate the antibody response to each influenza vaccine antigen, as measured by Hemagglutination Inhibition (HI) at 21 days post immunization in non-elderly adult and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96). Antibodies may be additionally quantified using the Single Radial Hemolysis (SRH) test for confirmation purposes (Note for Guidance on Harmonization of Requirements for Influenza Vaccines. CPMP/BWP/214/96: 12 March 1997).

Safety:

To evaluate safety of a single IM (intramuscular) dose of the subunit influenza vaccine Fluvirin in non-elderly adult and elderly subjects in compliance with the requirements of the current EU recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96).

**Test Product, Dose, Mode of Administration, Lot Number:**

A single 0.5 mL dose of FLUVIRIN®, influenza subunit vaccine for the Northern Hemisphere (NH) influenza season 2010/2011 was administered IM. Lot Number: 112078.

**Duration of Study:**

Each subject participated approximately for 3 weeks after enrolment into the study.

**Reference Therapy, Dose, Mode of Administration, Lot Number:**

None.

**Statistical Methods:**

There was no statistical null hypothesis associated with the immunogenicity objective. Statistical analysis was carried out descriptively.

This study is in compliance with the sample size requirements of the current Committee for Medicinal Products for Human Use (CHMP) guideline on harmonization of requirements for influenza vaccines (CPMP/BWP/214/96).

**Diagnosis and Main Criteria for Inclusion and Exclusion:**

The study population consisted of healthy male and female adults who were ≥18 years of age, mentally competent, willing and able to give informed consent prior to study entry. They were eligible if they did not receive any seasonal or pandemic influenza vaccine or did not have a laboratory confirmed seasonal or pandemic influenza disease within the past 6 months.

**Criteria for Evaluation:**

Immunogenicity

Seroprotection rate, geometric mean ratio (GMR) and rate of seroconversion or significant increase were determined by HI and SRH and assessed according to CPMP/BWP/214/96. In non- elderly adult subjects aged 18 to 60 years at least one of the assessments was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: i.e., seroprotection rate > 70%; seroconversion or significant increase rate > 40%;·post-/pre-vaccination GMR > 2.5. In elderly subjects aged 61 years and older at least one of the following assessments was to meet the indicated requirements (CPMP/BWP/214/96) for each strain: i.e., seroprotection rate > 60%; seroconversion or significant increase rate > 30%; post/pre- vaccination GMR > 2.0.

Safety

Safety was assessed in accordance with available safety data on influenza vaccines.

**Results:**

**Table 1: Overview of Subject Populations**

| | Number (%) of Subjects | | |
|---|---|---|---|
| | **18-60 YOA** | **≥61 YOA** | **TOTAL** |
| | **N = 76** | **N = 68** | **N = 144** |
| Population | | | |
| Enrolled | 76 (100%) | 68 (100%) | 144 (100%) |
| Immunogenicity (FAS) | 76 (100%) | 67 (99%) | 143 (99%) |
| Immunogenicity (PPS) | 75 (99%) | 61 (90%) | 136 (94%) |
| Exposed | 76 (100%) | 68 (100%) | 144 (100%) |
| Safety | 76 (100%) | 68 (100%) | 144 (100%) |
| Safety After Study Day 4 | 76 (100%) | 68 (100%) | 144 (100%) |

FAS: full analysis set; PPS: per protocol set; YOA: years of age.

**Table 2: Summary of Study Terminations - All Enrolled Set**

| | Number (%) of Subjects | | |
|---|---|---|---|
| | **18-60 YOA** | **≥61 YOA** | **TOTAL** |
| | **N = 76** | **N = 68** | **N = 144** |
| Completed | 75 (99%) | 65 (96%) | 140 (97%) |
| Completed protocol | 75 (99%) | 65 (96%) | 140 (97%) |
| Premature withdrawal | 1 (1%) | 3 (4%) | 4 (3%) |
| Protocol deviations/violation | 1 (1%) | 2 (3%) | 3 (2%) |
| Unable to classify | 0 | 1 (1%) | 1 (<1%) |

YOA: years of age.

**Table 3: Demography and Baseline Characteristics by Priming Status – All Enrolled Set**

| | 18-60 YOA N=76 | ≥ 61 YOA N=68 | TOTAL N=144 |
|---|---|---|---|
| Age (Years): | 28.2 ± 9.8 | 66.9 ± 4.6 | 46.5±20.9 |
| Gender | | | |
| Male | 37 (49%) | 28 (41%) | 65 (45%) |
| Female | 39 (51%) | 40 (59%) | 79 (55%) |
| Child Bearing Potential | | | |
| No | 5 (7%) | 41 (60%) | 46 (32%) |
| Yes | 34 (45%) | 0 | 34 (24%) |
| Not Available | 37 | 27 | 64 |
| Pregnancy Test: | | | |
| Negative | 34 (45%) | 0 | 34 (24%) |
| Not Applicable | 5 (7%) | 41 (60%) | 46 (32%) |
| Not Available | 37 | 27 | 64 |
| Ethnic Origin: | | | |
| Caucasian | 76 (100%) | 68 (100%) | 144 (100%) |
| Weight (kg): | 74.59 ± 13.62 | 77.65 ± 14.99 | 76.04 ± 14.32 |
| Height (cm): | 173.9 ± 9.6 | 169.8 ± 8.8 | 172.0 ± 9.4 |
| Body Mass Index | 24.59±3.72 | 26.86±4.21 | 25.66±4.10 |
| Previous Seasonal. Vaccination | | | |
| No | 30 (39%) | 15 (22%) | 45 (31%) |
| Unknown | 12 (16%) | 1 (1%) | 13 (9%) |
| Yes | 34 (45%) | 52 (76%) | 86 (60%) |
| Previous. Pandemic. Vaccination | | | |
| No | 73 (96%) | 65 (96%) | 138 (96%) |
| Yes | 3 (4%) | 3 (4%) | 6 (4%) |
| Met Entry Criteria | | | |
| No | 1 (1%) | 2 (3%) | 3 (2%) |
| Yes | 75 (99%) | 66 (97%) | 141 (98%) |

Categorical parameters: N (%), non-categorical parameters: Mean ± Std; YOA: years of age.

**Table 4: Vaccine Immunogenicity Assessed by HI Assay - Per Protocol Set**

| | | 18-60 YOA (N=75) | | | | | | | ≥ 61 YOA (N=61) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Strains** | | **A(H1N1)** | | **A(H3N2)** | | **B** | | | **A(H1N1)** | | **A(H3N2)** | | **B** | | |
| **PREVACCINATION (Day 1)** | | | | | | | | | | | | | | | |
| | | **n/N[1]** | **%** | **n/N** | **%** | **n/N** | **%** | | **n/N** | **%** | **n/N** | **%** | **n/N** | **%** | |
| **GMT[2]** | | 29 | | 35 | | 12 | | | 14 | | 47 | | 21 | | |
| **95% CI[3]** | | 20% - 44% | | 25% - 49% | | 9.37% - 15% | | | 11% - 18% | | 32% - 69% | | 15% - 28% | | |
| **Seroprotection rate[4]** | | 29/75 | 39 | 36/75 | 48 | 13/75 | 17 | | 7/61 | 11 | 37/61 | 61 | 23/61 | 38 | |
| **95% CI** | | 28% - 51% | | 36% - 60% | | 10% - 28% | | | 5% - 22% | | 47% - 73% | | 26% - 51% | | |
| **POSTVACCINATION (Day 22)** | | | | | | | | | | | | | | | |
| | **CHMP[8]** | **n/N** | **%** | **n/N** | **%** | **n/N** | **%** | **CHMP[8]** | **n/N** | **%** | **n/N** | **%** | **n/N** | **%** | |
| **Seroconversion rate[5]** | | 25/27 | 93 | 12/12 | 100 | 21/34 | 62 | | 14/21 | 67 | 9/9 | 100 | 3/15 | 20 | |
| **Significant increase in antibody titers[6]** | | 37/48 | 77% | 48/63 | 76% | 10/41 | 24% | | 24/40 | 60% | 33/52 | 63% | 3/46 | 7% | |
| **Seroconversion rate or significant** | **>40%** | 62/75 | **83%** | 60/75 | **80%** | 31/75 | **41%** | **>30%** | 38/61 | **62%** | 42/61 | **69%** | 6/61 | 10% | |
| **95% CI** | | 72% - 90% | | 69% - 88% | | 30% - 53% | | | 49% - 74% | | 56% - 80% | | 4% - 20% | | |
| **GMT** | | 749 | | 411 | | 46 | | | 122 | | 367 | | 33 | | |
| **95% CI** | | 522% - 1075% | | 312% - 541% | | 37% - 58% | | | 79% - 188% | | 277%- 486% | | 24% - 44% | | |
| **GM Increase[7]** | **>2.5** | **25** | | **12** | | **3.89** | | **<2.0** | **8.43** | | **7.73** | | 1.56 | | |
| **95% CI** | | 16% - 40% | | 8.15% - 17% | | 2.98% - 5.09% | | | 5.63% - 13% | | 5.35% - 11% | | 1.3% - 1.87% | | |

| | | 18-60 YOA (N=75) | | | | | | | ≥ 61 YOA (N=61) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Seroprotection rate** | **>70%** | 70/75 | **93 %** | 73/75 | **97 %** | 52/75 | 69 % | **>60%** | 46/61 | **75 %** | 60/61 | **98 %** | 34/61 | 56 % |
| **95% CI** | | 85% - 98% | | 91% - 100% | | 58% - 79% | | | 63% - 86% | | 91% - 100% | | 42% - 68% | |

**Bold:** CHMP criteria met; YOA: years of age.

[1] n/N: responders (n) as part of number of subjects of the (sub-) population (N).

[2] GMT: geometric mean titer.

[3] 95% CI: 95% confidence interval.

[4] Seroprotection rate: proportion of subjects with a protective titer (titer ≥ 40).

[5] Seroconversion rate: proportion of subjects with antibody increase from < 10.

[6] Significant increase: proportion of subjects with an antibody titer of ≥10 prevaccination and at least 4-fold antibody increase postvaccination.

[7] GM increase = Geometric mean increase.

[8] CHMP criteria- Committee for Medicinal Products for Human Use.

**Table 5: Vaccine Immunogenicity Assessed by SRH Assay - Per Protocol Set**

| | | 18-60 YOA (N=75) | | | | | | | ≥ 61 YOA (N=61) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Strains** | | **A(H1N1)** | | **A(H3N2)** | | **B** | | | **A(H1N1)** | | **A(H3N2)** | | **B** | | |
| **PREVACCINATION (Day 1)** | | | | | | | | | | | | | | | |
| | | **n/N[1]** | **%** | **n/N** | **%** | **n/N** | **%** | | **n/N** | **%** | **n/N** | **%** | **n/N** | **%** | |
| **GMA[2]** | | 12 | | 8.35 | | 26 | | | 9.38 | | 8.91 | | 37 | | |
| **95% CI[3]** | | 9.23% - 16% | | 6.84% - 10% | | 21% - 31% | | | 7.06% - 12% | | 7.06% - 11% | | 29% - 46% | | |
| **Seroprotection rate[4]** | | 26/75 | 35 | 11/75 | 15 | 40/75 | 53 | | 17/61 | 28 | 11/61 | 18 | 41/61 | 67 | |
| **95% CI** | | 24% - 47% | | 8% - 25% | | 41% - 65% | | | 17% - 41% | | 09% - 30% | | 54% - 79% | | |
| **POSTVACCINATION (Day 22)** | | | | | | | | | | | | | | | |
| | **CHMP[8]** | **n/N** | **%** | **n/N** | **%** | **n/N** | **%** | **CHMP** | **n/N** | **%** | **n/N** | **%** | **n/N** | **%** | |
| **Seroconversion rate[5]** | | 30/33 | 91 | 26/36 | 72 | 2/3 | 67 | | 26/34 | 76 | 17/30 | 57 | 2/4 | 50 | |
| **Significant increase in antibody titers[6]** | | 32/42 | 76% | 31/39 | 79% | 51/72 | 71% | | 19/27 | 70% | 24/31 | 77% | 21/57 | 37% | |
| **Seroconversion rate or significant increase** | **> 40%** | 62/75 | **83%** | 57/75 | **76%** | 53/75 | **71%** | **> 30%** | 45/61 | **74%** | 41/61 | **67%** | 23/61 | **38%** | |
| **95% CI[3]** | | 72% - 90% | | 65% - 85% | | 59% - 81% | | | 61% - 84% | | 54% - 79% | | 26% - 51% | | |
| **GMA[2]** | | 83 | | 45 | | 70 | | | 53 | | 36 | | 57 | | |
| **95% CI[3]** | | 71% - 97% | | 37% - 55% | | 62% - 78% | | | 40% - 69% | | 30% - 43% | | 49% - 68% | | |
| **GM Increase[7]** | **> 2.5** | **6.85** | | **5.39** | | **2.73** | | **> 2.0** | **5.64** | | **4.02** | | 1.55 | | |
| **95% CI[3]** | | 5.13% - 9.15% | | 4.18% - 6.95% | | 2.23% - 3.34% | | | 4.09% - 7.77% | | 3.18% - 5.09% | | 1.33% - 1.82% | | |
| **Seroprotection rate[4]** | **> 70%** | 71/75 | **95** | 63/75 | **84** | 72/75 | **96** | **> 60%** | 53/61 | **87** | 46/61 | **75** | 56/61 | **92** | |
| **95% CI[3]** | | 87% - 99% | | 74% - 91% | | 89% - 99% | | | 76% - 94% | | 63% – 86% | | 82% - 97% | | |

**Bold**: CHMP criteria met; YOA: years of age.

[1] n/N: responders (n) as part of number of subjects of the (sub-) population (N).

[2] GMA: geometric mean area.

[3] 95% CI: 95% confidence interval.

[4] Seroprotection rate: proportion of subjects with a pre- or post-vaccination area $\geq$ 25 $mm^2$.

[5] Seroconversion rate: proportion of subjects with negative pre- vaccination serum and a postvaccination serum area $\geq$ 25 $mm^2$.

[6] Significant increase: proportion of subjects with at least a 50% increase in area from positive pre-vaccination serum.

[7] GM increase = Geometric mean increase.

[8] CHMP: Committee for Medicinal Products for Human Use.

**Table 6: Overview of Solicited Reactions – Safety Set**

| | Number (%) of Subjects With Solicited Reactions | | |
|---|---|---|---|
| | **18-60 YOA** | **≥ 61 YOA** | **TOTAL** |
| | **N=76** | **N=68** | **N=144** |
| Any[1] | 51 (67) | 22 (32) | 73 (51) |
| Local | 39 (51) | 11 (16) | 50 (35) |
| Systemic | 35 (46) | 16 (24) | 51 (35) |

YOA: years of age.

[1] Number and percent of subjects with one or more local and systemic reactions. Hence, number and percent of local and systemic reactions may not sum to number and percent of subjects with any reactions.

**Table 7: Overview of Solicited Local Reactions (1-4 Days Post-Vaccination) – Safety Set**

| | | Number (%) of Subjects With Injection Site Reactions | | |
|---|---|---|---|---|
| | | **18-60 YOA** | **≥ 61 YOA** | **TOTAL** |
| | | **N=76** | **N=68** | **N=144** |
| Ecchymosis (mm) | Any | 1 (1) | 3 (4) | 4 (3) |
| | >50 mm | 0 | 0 | 0 |
| Erythema (mm) | Any | 2 (3) | 3 (4) | 5 (3) |
| | >50 mm | 0 | 1 (1) | 1 (1) |
| Induration (mm) | Any | 9 (12) | 1 (1) | 10 (7) |
| | >50 mm | 2 (3) | 0 | 2 (1) |
| Swelling (mm) | Any | 8 (11) | 2 (3) | 10 (7) |
| | >50 mm | 2 (3) | 1 (1) | 3 (2) |
| Pain | Any | 37 (49) | 9 (13) | 46 (32) |
| | Severe | 0 | 0 | 0 |

YOA: years of age.

Note: The numbers (N) in the header is the total number of subjects with documented reactions.

Categorization of Erythema, Swelling, Ecchymosis and Induration: none (diameter < 10 mm), mild (diameter 10-25 mm), moderate (diameter 26-50 mm) and severe (diameter > 50 mm).

**Table 8: Overview of Solicited Systemic Reactions (1-4 Days Post-Vaccination) – Safety Set**

| | | Number (%) of Subjects With Systemic Reactions | | |
|---|---|---|---|---|
| | | **18-60 YOA N=76** | **≥ 61 YOA N=68** | **TOTAL N=144** |
| Chills/Shivering | Any | 2 (3) | 0 | 2 (1) |
| | Severe | 0 | 0 | 0 |
| Malaise | Any | 4 (5) | 3 (4) | 7 (5) |
| | Severe | 0 | 0 | 0 |
| Myalgia | Any | 12 (16) | 6 (9) | 18 (13) |
| | Severe | 0 | 0 | 0 |
| Arthralgia | Any | 5 (7) | 1 (1) | 6 (4) |
| | Severe | 0 | 0 | 0 |
| Headache | Any | 18 (24) | 7 (10) | 25 (17) |
| | Severe | 0 | 1 (1) | 1 (1) |
| Sweating | Any | 4 (5) | 2 (3) | 6 (4) |
| | Severe | 0 | 0 | 0 |
| Fatigue | Any | 17 (22) | 9 (13) | 26 (18) |
| | Severe | 0 | 1 (1) | 1 (1) |
| Fever (≥ 38°C ) | Yes | 0 | 0 | 0 |

YOA: years of age.
Note: The numbers (N) in the header is the total number of subjects with documented reactions.

**Table 9: Overview of Other AEs – Safety Set**

| | Number (%) of Subjects with Adverse Events | | |
|---|---|---|---|
| | **18-60 YOA N=76** | **≥ 61 YOA N=68** | **TOTAL N=144** |
| Any AEs | 7 (9) | 6 (9) | 13 (9) |
| At least possibly related AEs | 6 (8) | 6 (9) | 12 (8) |
| SAEs | 0 | 0 | 0 |
| At least possibly related SAEs | 0 | 0 | 0 |
| AEs leading to discontinuation | 0 | 0 | 0 |
| Death | 0 | 0 | 0 |

AE: adverse events; SAE: serious adverse events; YOA: years of age..

| **Table 10:** | **Number (Percentages) of Subjects with Serious Adverse Events by Preferred Term, sorted by System Organ Class** |
|---|---|
| None reported | |

| **Table 11:** | **Number (Percentages) of Subjects with Unsolicited Adverse Events Reported in > 5 % of Subjects by Preferred Term sorted by System Organ Class** |
|---|---|
| None reported | |

**Conclusion:**

In this prospective clinical trial involving 76 non-elderly adults (18 – 60 years) and 68 elderly subjects (≥ 61 years of age), immunogenicity, safety and tolerability of the trivalent subunit influenza vaccine FLUVIRIN were investigated. The vaccine contained purified viral envelope-glycoproteins, neuraminidase and hemagglutinin of the virus strains selected for 2010/2011 according to WHO recommendations (i.e., A/California/7/09 (H1N1)-like strain; A/Perth/16/09 (H3N2)-like strain; B/Brisbane/60/08-like strain). The vaccine was injected into the deltoid muscle.

FLUVIRIN fulfilled the CHMP requirement that at least one of the CHMP criteria was met measured with SRH assay for each strain in both adult and elderly subjects. In particular, for the 2 A-strains in non-elderly adults and elderly subjects, all three CHMP criteria were met. For the B/Brisbane/60/2008-like strain, in non-elderly adults all 3 CHMP criteria were met. In the elderly subjects, 2 out of 3 CHMP criteria were met (GMR criterion was not met). Since the CHMP Guidance (CPMP/BWP/214/96) considers both the HI and SRH method acceptable to evaluate the immune response to seasonal influenza vaccines and since the HI assay was known to be less sensitive against the B strain the SRH results presented above may more accurately reflect the B antibody responses.

Overall, the incidences of solicited local and systemic reactions reported were comparable with incidences seen with other influenza vaccines. As expected more local and systemic reactions were reported in the non-elderly adult than in the elderly population. No subject reported any SAE and no AE led to a premature withdrawal from the study.

Thus, FLUVIRIN [Influenza Vaccine (Surface Antigen, Inactivated) Ph.Eur], formulation 2010-2011, was well tolerated and can be considered protective, and complies with the CHMP criteria for the approval of influenza vaccines.

**Date of Clinical Trial Report:** **09 AUG 10**