## SYNOPSIS

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|---|---|---|
| **Name of Sponsor/Company:**<br>Solvay Pharmaceuticals | **Individual Study Table** | **(For National Authority Use only)** |
| **Name of Finished Product:**<br>Influvac® 2007/2008 | | |
| **Name of Active Ingredient:**<br>A/Wisconsin/67/2005 ($H_3N_2$)-like strain;<br>A/Solomon Islands/3/2006 ($H_1N_1$)-like strain;<br>B/Malaysia/2506/2004-like strain. | | |

**Title of Study:**
Immunogenicity and Reactogenicity of the Trivalent Influenza Subunit Vaccine Influvac® for the Season 2007/2008. An Open, Baseline-controlled Multi-center Study in Two Groups of Healthy Subjects: Adult Subjects ≥ 18 and ≤ 60 Years and Elderly Subjects ≥ 61 Years of Age. Week 3 Results

**Investigators:**
PPD

**Study Centers:**
PPD Belgium PPD
PPD Germany PPD

**Publication (Reference):**
Not applicable

| **Study Period:** | **Phase of Development:** |
|---|---|
| 14 JUN 2007 (First Subject First Visit) –<br>07 JUL 2007 (Last Subject Last Visit) | IIIa |

**Objectives:**
The primary objective of this study was to determine the immunogenicity of the trivalent influenza subunit vaccine Influvac® for the season 2007/2008, in two groups of healthy subjects: adult subjects aged ≥ 18 and ≤ 60 years and elderly subjects ≥ 61 years of age. The safety objective was to collect data on the safety and tolerability (reactogenicity and overall inconvenience) of Influvac®.

**Methodology:**
This was an open, baseline controlled study in two groups of healthy subjects: adults PPD and elderly PPD. Subjects were screened within 14 days prior to Visit 1 (Day 1) or at Visit 1 (Day 1). Eligible subjects were vaccinated at Visit 1 (Day 1) after blood sampling for baseline hemagglutination inhibition (HI) antibody titration. Subjects were asked to record local and systemic reactions daily on a questionnaire at home for 72 hours after vaccination. After two weeks (Visit 2, Day 15) and three weeks (Visit 3, Day 22), the subjects returned to the study center for blood sampling and assessment of safety and tolerability. This report concerns the analysis of the Week 3 results. The Week 2 clinical study report (Day 15 results) was issued on 12 JUL 2007.

**Number of Subjects (Planned, Consented, Randomized and Analyzed):**
Planned 120 subjects, consented 121, vaccinated 120, analyzed safety 120 (59 adults aged ≥ 18 and ≤ 60 years and 61 elderly aged ≥ 61 years), analyzed efficacy 119 (59 adults aged ≥ 18 and ≤ 60 years and 60 elderly aged ≥ 61 years).

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**Diagnosis and Main Criteria for Inclusion:**
Healthy adults and elderly subjects who had not been vaccinated against influenza in the six months previous to study entry.

**Test Product, Dose and Mode of Administration, Batch Number:**
A single 0.5 mL dose of Influvac® 2007/2008 vaccine given intramuscularly and containing approximately 15 mcg hemagglutinin for each strain:
- A/Wisconsin/67/2005 ($H_3N_2$)-like strain;
- A/Solomon Islands/3/2006 ($H_1N_1$)-like strain;
- B/Malaysia/2506/2004-like strain

Batch number: M01A.

**Duration of Treatment:**
Single dose on Day 1.

**Reference Therapy, Dose and Mode of Administration, Batch Number:**
Not applicable.

**Criteria for Evaluation:**
Primary Efficacy:
Serological parameters according to the Committee for Medicinal Products for Human Use (CHMP) Note for Guidance on Harmonization of Requirements for Influenza Vaccines (CPMP/BWP/214/96 1997), derived from the observed HI titers:
- The pre-and post-vaccination protection rates
- The proportion of subjects with seroconversion or at least a four-fold increase in HI titer
- The mean fold increase (MFI)

Safety and Tolerability:
Spontaneously reported adverse events were monitored throughout the study. Tolerability (reactogenicity and overall inconvenience), including local and systemic reactions, was recorded by the subjects on a questionnaire during the first 72 hours after vaccination.

**Statistical Methods:**
Serological results were evaluated according to the criteria specified in the CHMP Note for Guidance (CPMP/BWP/214/96 1997). All analyses were performed by age group. Safety and tolerability (reactogenicity and overall inconvenience) were summarized by means of absolute and relative frequencies and by the duration of the local and systemic reactions.

**Summary – Conclusions**
This report presents the Week 3 immunogenicity results and the safety results up to Week 3 inclusive.
Adults aged ≥ 18 and ≤ 60 years
Fifty-nine subjects were vaccinated, all of whom were included in the safety sample; 25 males and 34 females. Their mean age was 42.4 years (range 18-60 years).

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Elderly aged ≥ 61 years

Sixty-one subjects were vaccinated and included in the safety sample; 22 males and 39 females. Their mean age was 68.0 years (range 61-77 years).

**Efficacy Results:**

The efficacy sample comprised 119 subjects: 59 adults aged ≥ 18 and ≤ 60 years and 60 elderly aged ≥ 61 years. One subject was excluded from the efficacy sample due to missing Day 22 HI titer data.

The following tables summarize the serology results.

Serology: Summary Results for All Strains, ≥ 18 and ≤ 60 Years of Age (Day 22 Results, Post-vaccination Data)

Efficacy Sample

| | A (H3N2) - like (N= 59) | A (H1N1) - like (N= 59) | B - like (N= 59) |
|---|---|---|---|
| Seroprotection | | | |
| Percentage: | 100% (94%~100%) | 97% (88%~100%) | 80% (67%~89%) |
| Proportion: | 59/59 | 57/59 | 47/59 |
| Seroconversion or 4-fold increase | | | |
| Percentage: | 41% (28%~54%) | 64% (51%~76%) | 41% (28%~54%) |
| Proportion: | 24/59 | 38/59 | 24/59 |
| MFI | | | |
| Geometric mean: | 5.0 ( 3.3~7.6) | 11.8 ( 7.4~18.9) | 4.9 ( 3.1~7.7) |

95% confidence limits are given between brackets

CHMP Criteria for Healthy Subjects between 18 and 60 Years of Age:

| | |
|---|---|
| Seroprotection: | > 70% |
| Seroconversion/4-fold Increase: | > 40% |
| MFI: | > 2.5 |

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Serology: Summary Results for All Strains, ≥ 61 Years of Age (Day 22 Results, Post-vaccination Data)

Efficacy Sample

| | A (H3N2) - like (N= 60) | A (H1N1) - like (N= 60) | B - like (N= 60) |
|---|---|---|---|
| Seroprotection | | | |
| Percentage: | 100% (94%~100%) | 88% (77%~95%) | 77% (64%~87%) |
| Proportion: | 60/60 | 53/60 | 46/60 |
| Seroconversion or 4-fold increase | | | |
| Percentage: | 57% (43%~69%) | 80% (68%~89%) | 40% (28%~53%) |
| Proportion: | 34/60 | 48/60 | 24/60 |
| MFI | | | |
| Geometric mean: | 7.4 ( 5.0~11.1) | 23.7 (16.4~34.3) | 5.7 ( 3.6~8.9) |

95% confidence limits are given between brackets

CHMP Criteria for Healthy Subjects >= 61 Years of Age:

| | |
|---|---|
| Seroprotection: | > 60% |
| Seroconversion/4-fold Increase: | > 30% |
| MFI: | > 2.0 |

Three weeks after vaccination the three vaccine strains showed an adequate increase in antibody levels that met all three criteria for the specified serological parameters for influenza vaccines in adults aged ≥ 18 and ≤ 60 years and in elderly aged ≥ 61 years (as described in the CHMP Note for Guidance).

**Safety Results:**

Adults aged ≥ 18 and ≤ 60 years

During the 72 hours after vaccination, 15 subjects (25.4%) reported any local reaction and two subjects (3.4%) reported any systemic reaction. The most frequent local reaction was pain at the slightest pressure (12%); headache was the most frequent systemic reaction (3%).
Fifty-eight subjects (98.3%) reported no inconvenience after vaccination, one subject (1.7%) reported mild inconvenience, none of the subjects rated the inconvenience as moderate or severe.
Seven subjects (11.9%) reported 11 treatment emergent adverse events. None of these events was serious. No severe adverse events were observed. The only adverse event reported in more than one subject was injection site pain (n=3; 5.1%); the relationship to the vaccine of these events was considered probable.

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Elderly aged ≥ 61 years

During the 72 hours after vaccination, 11 subjects (18.3%) reported any local reaction and fourteen subjects (23.3%) reported any systemic reaction. The most frequent local reaction was pain at the slightest pressure (12%); headache was the most frequent systemic reaction (17%).

Fifty-six subjects (93.3%) reported no inconvenience after vaccination, four subjects (6.7%) reported mild inconvenience and no subjects reported moderate or severe inconvenience.

Eight subjects (13.1%) reported nine treatment emergent adverse events. Two of these events were serious and severe; coronary artery disease and transient ischaemic attack. The event of coronary artery disease (unrelated to the vaccine) led to withdrawal of the subject from the study. No other serious or severe adverse events were observed. No adverse event was reported in more than one subject.

**Conclusion:**

The Week 3 results of this study indicate that Influvac® 2007/2008 induced an adequate antibody response in the studied populations, fulfilling the CHMP requirement for immunogenicity. This is consistent with observations in previous years. All three CHMP criteria were fulfilled for all three strains in the Influvac® 2007/2008 vaccine, for both age groups.

Influvac® 2007/2008 was safe and well tolerated in this study.