SYNOPSIS - WEEK 3 RESULTS

Name of Sponsor:
Solvay Biologicals B.V.

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
Influvac® 2008/2009

Name of Active Ingredient:
A/Brisbane/59/2007 (H1N1)-like strain;
A/Brisbane/10/2007 (H3N2)-like strain;
B/Florida/4/2006-like strain.

Study Title:
Immunogenicity, Reactogenicity and Safety of the Trivalent Influenza Subunit Vaccine Influvac® for the Season 2008/2009. An Open-label, Baseline-controlled, Multi-center Study in Two Groups: Adult Subjects ≥ 18 and ≤ 60 Years and Elderly Subjects ≥ 61 Years of Age. Week 3 Results

Investigators:
PPD

Study Centers:
PPD Belgium
PPD
Germany

Publication (Reference):
Not applicable

Study Period:
19 JUN 2008 (first subject first visit) to
17 JUL 2008 (last subject last visit)

Phase of Development:
Phase IIIa

Objectives:
The primary objective of this study was to determine the immunogenicity of the trivalent influenza subunit vaccine Influvac® for the season 2008/2009, in two groups of 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-label, baseline-controlled study in two groups of subjects: adults aged ≥ 18 and ≤ 60 years PPD and elderly ≥ 61 years of age PPD. After screening, 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 2 weeks (Visit 2, Day 15) and 3 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 23 JUL 2008.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned 120 subjects, consented 122 subjects, vaccinated 120 subjects, analyzed safety 120 (60 adults aged ≥ 18 and ≤ 60 years and 60 elderly aged ≥ 61 years), analyzed efficacy 118 (58 adults aged ≥ 18 and ≤ 60 years and 60 elderly aged ≥ 61 years).

Diagnosis and Main Criteria for Inclusion:
Adults and elderly subjects in good health who had not been vaccinated against influenza in the 6 months previous to study entry.

Test Product, Dose and Mode of Administration, Batch Number:
A single 0.5 mL dose of trivalent influenza subunit vaccine Influvac® (season 2008/2009) given intramuscularly and containing approximately 15 mcg hemagglutinin for each strain:

- A/Brisbane/59/2007 (H1N1)-like strain;
- A/Brisbane/10/2007 (H3N2)-like strain;
- B/Florida/4/2006-like strain.

Batch number: 1061757-610106.

Duration of Treatment:
Single dose on Day 1.

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

Criteria for Evaluation

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 seroprotection rates
- The proportion of subjects with seroconversion or at least a four-fold increase in HI titer
- The mean fold increase (MFI).

According to this guideline, the requirement for sufficient immunogenicity is that for both age groups, at least one of the following three criteria is met:

	adults	elderly
proportion of subjects achieving a HI antibody titer ≥ 40:	> 70%	> 60%
proportion of subjects with a seroconversion or at least a 4-fold increase:	> 40%	> 30%
MFI:	> 2.5	> 2.0

Safety:
Spontaneously reported adverse events (AEs) 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 influenza vaccine immunogenicity results and the safety results up to Week 3 inclusive.

Adults aged ≥ 18 and ≤ 60 years

Sixty subjects were vaccinated, all of whom were included in the safety sample; 32 males and 28 females. Their mean age was 41.1 years (range 23-59 years).

Elderly aged ≥ 61 years

Sixty subjects were vaccinated and included in the safety sample; 30 males and 30 females. Their mean age was 70.5 years (range 61-85 years).

Efficacy Results:

The efficacy sample comprised 118 subjects: 58 adults aged ≥ 18 and ≤ 60 years and 60 elderly aged ≥ 61 years. Two subjects were excluded from the efficacy sample due to missing Day 22 HI titer data: two subjects did not return for Visit 3 (Day 22). For an additional three subjects, serum samples agglutinated spontaneously with erythrocytes due to aspecific agglutination. As a result incomplete HI titer data was available for the efficacy analysis for these three subjects.

The following tables summarize the serology results.

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

Efficacy Sample

	A (H3N2) - like (N= 58)	A (H1N1) - like (N= 58)	B - like (N= 58)
Seroprotection			
Percentage:	97% (88%~100%)	100% (94%~100%)	98% (91%~100%)
Proportion:	56/58	57/57	56/57
Seroconversion or 4-fold increase			
Percentage:	89% (78%~96%)	82% (69%~91%)	66% (52%~78%)
Proportion:	49/55	45/55	37/56
MFI			
Geometric mean:	48.0 (30.9~74.7)	22.3 (14.5~34.4)	9.5 (5.9~15.3)

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

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

Efficacy Sample

	A (H3N2) - like (N= 60)	A (H1N1) - like (N= 60)	B - like (N= 60)
Seroprotection			
Percentage:	95% (86%~99%)	100% (94%~100%)	97% (88%~100%)
Proportion:	57/60	60/60	58/60
Seroconversion or 4-fold increase			
Percentage:	63% (50%~75%)	27% (16%~40%)	27% (16%~40%)
Proportion:	38/60	16/60	16/60
MFI			
Geometric mean:	8.1 (5.6~11.6)	2.5 (1.9~3.4)	2.5 (1.9~3.3)

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 the CHMP requirement for immunogenicity 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, ten subjects (16.9%) reported any local reaction and five subjects (8.5%) reported any systemic reaction. Pain at the slightest pressure (10%), ecchymosis (7%) and warmth (5%) were the only local reactions reported for more than two subjects; headache was the most frequent systemic reaction (7%).

All 59 subjects with data (100%) reported no inconvenience after vaccination.

Three subjects (5.0%) reported four treatment emergent AEs. None of these events was serious. No severe AEs were observed. No AE was reported in more than one subject.

Elderly aged ≥ 61 years

During the 72 hours after vaccination, six subjects (10.0%) reported any local reaction and three subjects (5.0%) reported any systemic reaction. Itching, redness, swelling and warmth (all 3%) were the only local reactions reported for more than one subject; none of the systemic reactions were reported for more than one subject.

Fifty-eight subjects (96.7%) reported no inconvenience after vaccination, two subjects (3.3%) reported mild inconvenience and no subjects reported moderate or severe inconvenience.

Six subjects (10.0%) reported eight treatment emergent AEs. None of these events was serious. No severe AEs were observed. No AE was reported in more than one subject.

Conclusion:

The Week 3 results of this study indicate that Influvac® 2008/2009 induced an adequate antibody response in the studied populations, fulfilling the CHMP requirement for influenza vaccine immunogenicity. This is consistent with observations in previous years.
Influvac® 2008/2009 was safe and well tolerated in this study.