SYNOPSIS

Name of Sponsor:

Abbott Biologicals B.V.

Name of Finished Product:

Influvac® 2012/2013

Name of Active Ingredient:

A/California/7/2009 (H1N1)pdm09-like strain;
A/Victoria/361/2011 (H3N2)-like strain;
B/Wisconsin/1/2010-like strain.

Individual Study Table:

(For National Authority Use only)

Study Title:

Immunogenicity, Reactogenicity and Safety of the Trivalent Influenza Subunit Vaccine Influvac® for the Northern Hemisphere Season 2012/2013. An Open-Label, Baseline-Controlled Study in Two Age Groups: Adult Subjects ≥ 18 and ≤ 60 Years and Elderly Subjects ≥ 61 Years of Age.

Investigator:

PPD

Study Center:

PPD Germany.

Publication (Reference):

Not applicable.

Study Period:

02 JUL 2012 (first subject first visit) to
25 JUL 2012 (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 northern hemisphere season 2012/2013, three weeks after vaccination 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) in two groups: adults aged ≥ 18 and ≤ 60 years and elderly ≥ 61 years of age.

The safety objective was to collect evidence on the safety (unsolicited adverse events [AEs]) 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 and elderly ≥ 61 years of age. 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) for all vaccine strains and in addition for the B strain single radial hemolysis (SRH) titration. Subjects

were asked to record local and systemic reactions daily on a diary at home for 72 hours after vaccination. At Visit 2 (Day 8), the subjects returned to the study site and the diaries were collected. After three weeks (Visit 3, Day 22), the subjects returned to the study center for blood sampling for serology testing and assessment of safety and tolerability.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned 120 subjects, consented 126 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 2012/2013) given intramuscularly and containing approximately 15 mcg hemagglutinin for each strain:

- A/California/7/2009 (H1N1)pdm09-derived strain used reassortant virus NYMC X-181
- A/Victoria/361/2011 (H3N2)-derived strain used reassortant virus IVR-165
- B/Wisconsin/1/2010-like strain used reassortant virus NYMC BX-39 derived from B/Hubei-Wuijagang/158/2009

Batch number: 1082499-A01C.

Duration of Treatment:

Single dose on Day 1.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable.

Criteria for Evaluation

Efficacy:

The following serological parameters were to be derived separately for each strain and for each vaccination group:

- the pre-and post-vaccination seroprotection rates
- the proportion of subjects with seroconversion/significant increase in antihemagglutinin antibody titer
- the geometric mean fold increase.

Safety:

Spontaneously reported AEs were monitored throughout the study. Tolerability (reactogenicity and overall inconvenience), including local and systemic reactions, was recorded by the subjects on a diary 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

Adults aged ≥ 18 and ≤ 60 years

Sixty subjects were vaccinated, all of whom were included in the safety sample; 26 males and 34 females. Their mean age was 38.0 years (range 21-59 years).

Elderly aged ≥ 61 years

Sixty subjects were vaccinated, all of whom were included in the safety sample; 20 males and 40 females. Their mean age was 72.3 years (range 62-85 years).

Efficacy Results:

The efficacy sample comprised 118 subjects: 58 adults aged ≥ 18 and ≤ 60 years and 60 elderly aged ≥ 61 years. For two adult subjects (3.3%), Day 1 and/or Day 22 titers were missing. For one subject, no Day 22 serum sample was available because the subject dropped out after Day 8 due to personal reasons (lack of time), while the Day 1 titers could not be determined due to aspecific agglutination; and for one subject, no Day 22 serum sample was available because the subject dropped out after Day 8 due to personal reasons (lack of time). These two subjects were therefore excluded from the efficacy sample.

The following tables summarize the serology results for both age groups and for both the HI titers (all strains) and the SHR titers (B strain only).

Serology: Summary Results for All Strains, HI Titers, 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:	100% (93.8%, 100%)	100% (93.8%, 100%)	89.7% (78.8%, 96.1%)
Proportion:	58/58	58/58	52/58
Seroconversion or 4-fold increase			
Percentage:	87.9% (76.7%, 95.0%)	81.0% (68.6%, 90.1%)	74.1% (61.0%, 84.7%)
Proportion:	51/58	47/58	43/58
MFI			
Geometric mean:	29.8 (19.6, 45.1)	19.1 (12.2, 29.8)	15.0 (10.1, 22.3)
n:	58	58	58

Note(s): 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 the B Strain, SRH Titers, Adults Aged ≥ 18 and ≤ 60 Years (Day 22 Results, Post-vaccination Data)

Efficacy Sample

	B - like (N=58)
Seroprotection	
Percentage:	96.6% (88.1%, 99.6%)
Proportion:	56/58
Seroconversion/significant increase	
Percentage:	81.0% (68.6%, 90.1%)
Proportion:	47/58
MFI	
Geometric mean:	5.6 (4.2, 7.5)
n:	58

Note(s): 95% confidence limits are given between brackets
CHMP Criteria for Healthy Subjects between 18 and 60 Years of Age:
Seroprotection: > 70%
Seroconversion/significant Increase: > 40%
MFI: > 2.5

Serology: Summary Results for All Strains, HI Titers, 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:	98.3% (91.1%, 100%)	90.0% (79.5%, 96.2%)	70.0% (56.8%, 81.2%)
Proportion:	59/60	54/60	42/60
Seroconversion or 4-fold increase			
Percentage:	60.0% (46.5%, 72.4%)	55.0% (41.6%, 67.9%)	43.3% (30.6%, 56.8%)
Proportion:	36/60	33/60	26/60
MFI			
Geometric mean:	9.6 (6.2, 14.9)	7.3 (5.0, 10.6)	4.8 (3.5, 6.6)
n:	60	60	60

Note(s): 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

Serology: Summary Results for the B Strain, SRH Titers, Elderly Aged ≥ 61 Years (Day 22 Results, Post-vaccination Data)

Efficacy Sample

	B - like (N=60)
Seroprotection	
Percentage:	83.3% (71.5%, 91.7%)
Proportion:	50/60
Seroconversion/significant increase	
Percentage:	66.7% (53.3%, 78.3%)
Proportion:	40/60
MFI	
Geometric mean:	3.9 (3.0, 5.1)
n:	60

Note(s): 95% confidence limits are given between brackets
CHMP Criteria for Healthy Subjects >= 61 Years of Age:
Seroprotection: > 60%
Seroconversion/significant Increase: > 30%
MFI: > 2.0

Three weeks after vaccination, Influvac® 2012/2013 induced an adequate antibody response in the studied populations, fulfilling the CHMP requirement for influenza vaccine immunogenicity.

Three weeks after vaccination, the three strains showed an increase in antibody levels, measured by HI method for all strains and by SRH method for the B Strain. For both methods, all three criteria were met for the specified serological parameters for influenza vaccines in adults aged ≥ 18 and ≤ 60 years and in elderly aged ≥ 61 years.

Safety Results:

There were no deaths and there were no other serious AEs during the study.

Adults aged ≥ 18 and ≤ 60 years

During the 72 hours after vaccination, 25 subjects (41.7%) reported any local reaction and 13 subjects (21.7%) reported any systemic reaction. Tenderness (pain or discomfort upon touch) and pain were the most frequent local reactions (26.7% and 21.7%, respectively); headache (16.7%) and fatigue (13.3%) were the most frequent systemic reactions.

Forty-seven subjects (78.3%) reported no inconvenience after vaccination, 11 subjects (18.3%) reported mild inconvenience and one subject (1.7%) each reported moderate or severe inconvenience.

Ten subjects (16.7%) reported 25 treatment emergent AEs (TEAEs). One subject was reported with one severe AE (wrist fracture). The following AEs were reported in more than one subject: fatigue, chills, headache and hyperhidrosis (three subjects) and vaccination site pain (two subjects). No other AE was reported in more than one subject. Seventeen TEAEs in three subjects were assessed as related to the vaccination by the investigator.

Elderly aged ≥ 61 years

During the 72 hours after vaccination, eight subjects (13.3%) reported any local reaction and nine subjects (15.0%) reported any systemic reaction. Tenderness (pain or discomfort upon touch) was the most frequent local reaction (10.0%); headache and increased sweating (both 8.3%) were the most frequent systemic reactions.

Fifty-four subjects (90.0%) reported no inconvenience after vaccination, four subjects (6.7%) reported mild inconvenience, two subjects (3.3%) reported moderate inconvenience and no subjects reported severe inconvenience.

Six subjects (10.0%) reported seven TEAEs. No severe AEs were observed. No AE was reported in more than one subject. One TEAE in one subject was assessed as related to the vaccination by the investigator.

Conclusion:

The results of this study indicate that Influvac® 2012/2013 induced an adequate antibody response in the studied populations, fulfilling the CHMP requirement for influenza vaccine immunogenicity. All three CHMP criteria were met for all three strains in the Influvac® 2012/2013 vaccine, for both age groups.

Influvac® 2012/2013 was safe and well tolerated in this study.