SYNOPSIS

Name of Sponsor:
Abbott Biologicals B.V. (formerly Solvay Biologicals B.V.)

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
Influenza Vaccine (surface antigen, inactivated, prepared in cell cultures)

Name of Active Ingredient:
15 mcg hemagglutinin (HA) per viral strain:
A/California/7/2009 (H1N1)-like strain.
A/Perth/16/2009 (H3N2)-like strain.
B/Brisbane/60/2008-like strain

Study Title:
Randomized, Double-blind, Active-controlled Trial to Assess the Safety and Immunogenicity of Solvay's Cell-derived Influenza Vaccine, Including Re-vaccination, in Elderly Subjects

Month 6, Year 2 Report

Investigator(s):
Twelve investigators

Study Center(s):
Twelve study centers in three countries: Czech Republic, Estonia and Lithuania

Publication (Reference):
Not applicable.

Study Period:
06 OCT 2010 (first subject first visit) to
28 APR 2011 (last subject last visit)

Phase of Development:
II

Objectives:
The primary objective was to demonstrate in elderly subjects (≥ 61 years of age), that three weeks after the first vaccination the cell-derived influenza vaccine met all three of the Committee for Medicinal Products for Human Use (CHMP) criteria for influenza vaccine immunogenicity for the three strains in the vaccine.

The secondary objectives were:

- *To assess in the elderly subjects one year following the initial vaccination, whether three weeks after re-vaccination with the cell-derived influenza vaccine all three CHMP criteria for influenza vaccine immunogenicity were met for all three strains in the vaccine.
- To assess in elderly subjects during the first year the long-term immunogenicity of the cell-derived influenza vaccine six months following the vaccination.

The safety objectives were:

- To assess in elderly subjects during the first year the safety and reactogenicity of the cell-derived influenza vaccine for up to six months following initial vaccination and compare to an egg-derived influenza vaccine (Influvac®).
- *To assess in elderly subjects one year following the initial vaccination, the safety and reactogenicity of re-vaccination with the cell-derived influenza vaccine for up to six months following re-vaccination.

* Indicates the objectives answered in this Year 2 report.

Methodology:

This was a randomized, double-blind, active-controlled, parallel group study in which at least three visits and one telephone call were planned during the first year and at least two additional visits and one telephone call were planned during the following year.

Information regarding the conduct of the first year of the study may be found in the Year 1 clinical study report.

In Year 1 of the study, 622 subjects were vaccinated (416 with cell-derived influenza vaccine and 206 with Influvac®). Of the 622 subjects who were vaccinated in Year 1, 575 continued into Year 2 (432 with cell-derived influenza vaccine and 143 with Influvac®).

Subjects who continued to participate in the second year of the study were screened again within 14 days prior to or at Year 2 Day 1 (Day 317). Screening included an assessment of any serious adverse events (SAEs) or new chronic illnesses (NCIs) since the Month 6-Visit, measurement of vital signs, physical examination, pre-vaccination assessments and a review of the inclusion and exclusion criteria.

At Year 2 Day 1 (Day 317), after a review of the inclusion and exclusion criteria, physical examination, collection of blood for immunogenicity laboratory assessments, measurement of vital signs, the subjects were randomized in a 3:1 ratio to receive cell-derived influenza vaccine or Influvac®, respectively. Following vaccination by intramuscular injection, subjects were observed for at least 30 minutes to monitor for any immediate adverse reactions and a daily diary, thermometer and ruler provided for daily reporting of solicited local and systemic reactions and overall inconvenience occurring during the first seven days after re-vaccination. A telephone call was scheduled to occur three days after re-vaccination to remind subjects to complete the daily diary.

Following vaccination and until the Year 2 Day 22-Visit (Day 338), subjects were instructed to immediately contact the Investigator by telephone in the event of the occurrence of symptoms or signs likely to predict influenza infection, at which time an extra visit was to be scheduled, preferably within 24 hours, but no later than 72 hours after the onset of symptoms. At these extra visits, body temperature was measured and a nasal and/or pharyngeal swab collected for the diagnosis of influenza infection.

The Year 2 Day 22-Visit (Day 338) was scheduled to occur three weeks after vaccination and included collection of the daily diary, assessment of adverse events (AEs), a symptom-directed physical examination if AEs were present and blood collection for immunogenicity assessments.

A telephone call was scheduled six months after re-vaccination (Year 2 Month 6-telephone

call; Day 485) and any additional SAEs and NCIs were recorded.

This clinical study report covers all data obtained from subjects participating in the second year of the study until their Year 2 Month 6-telephone call, inclusive. The Year 1 clinical study report covers all data obtained from subjects until their Month 6-Visit, inclusive, during the first year of the study.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Year 1: planned 600 subjects, consented 628 subjects, vaccinated 622 subjects (416 subjects to cell-derived influenza vaccine, 206 subjects to Influvac®), analyzed 622 subjects in the safety sample and 620 subjects in the full analysis (FA) sample.

Year 2: planned 480 subjects (assuming a drop-out rate of 20%), randomized 575 subjects (432 subjects to cell-derived influenza vaccine, 143 subjects to Influvac®), analyzed 575 subjects in the safety sample and 574 subjects in the FA sample.

Diagnosis and Main Criteria for Inclusion:
Subjects in good health being 61 years of age or older.

Test Product, Dose and Mode of Administration, Batch Number:

A single 0.5 mL dose of cell-derived influenza vaccine (containing 15 mcg of HA antigen per vaccine strain season 2010/2011 Northern Hemisphere) administered by intramuscular injection.

Lot batch number: 610497.

Duration of Treatment:

A single dose administered on Day 317 ± 7 days.

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

A single 0.5 mL dose of egg-derived influenza vaccine (Influvac®) (containing 15 mcg of HA antigen per virus strain season 2010/2011 Northern Hemisphere) administered by intramuscular injection.

Lot batch number: 610500.

Criteria for Evaluation

Immunogenicity:

The primary immunogenicity endpoints for the second year of the study were the serum hemagglutination inhibition (HI) antibody titers measured the same day as but prior to the second vaccination as well as three weeks after the second vaccination. From these measurements, seroprotection rates, seroconversion rates and mean fold increases (MFIs) were derived.

Safety:

During the seven days following the second vaccination: solicited local and systemic reactions (including body temperature) and overall inconvenience.

During the three weeks following the second vaccination: AEs other than those specifically solicited and concomitant medication.

Between three weeks and six months following the second vaccination: SAEs and NCIs.

Statistical Methods:

Unless stated otherwise, data were presented by the vaccination received during the second

year (cell-derived influenza vaccine or Influvac®), with 're-vaccination' defined as vaccination with a subunit influenza vaccine again in the second year. For the immunogenicity analysis, the primary sample was the Year 2 FA sample.

Immunogenicity:

Hemagglutination inhibition antibody titers were summarized by means of geometric mean titers, MFIs, seroprotection rates and seroconversion rates. These summary statistics were used to assess immunogenicity of the cell-derived influenza vaccine. To demonstrate immunogenicity of the cell-derived influenza vaccine, it was checked whether three weeks after the second study vaccination all three CHMP criteria for influenza vaccine immunogenicity were met for all three vaccine strains.

For the immunogenicity analysis, the primary sample was the Year 2 FA sample.

Safety:

Adverse events (serious and non-serious) and NCIs were coded using the Medical Dictionary for Regulatory Activities thesaurus (version 12.1). All AEs were reported by study year and study period. Only treatment-emergent AEs (TEAEs) were analyzed. For each local and systemic reaction, the occurrence, the severity and the duration were summarized, and exact two-sided 95% confidence intervals for the absolute incidences were calculated. Overall inconvenience was to be summarized by means of relative frequencies.

Safety and reactogenicity of re-vaccination with the cell-derived influenza vaccine one year following the initial vaccination was assessed by comparing subjects who received two doses of the cell-derived influenza vaccine to subjects who received Influvac® initially and the cell-derived influenza vaccine the following year. Proportions of subjects reporting any severe systemic reaction were compared between those re-vaccinated and those vaccinated for the first time with the cell-derived influenza vaccine, at the two-sided significance level 0.05. The same approach was used to compare the incidences of local and systemic reactions between those re-vaccinated and those vaccinated for the first time with the cell-derived influenza vaccine during the second year.

Concomitant medication, including coding data, were summarized per assigned treatment period for incidence per subject, for primary therapeutic subgroup (3rd level Anatomical Therapeutic Chemical code) and for generic name by therapeutic subgroup. The Year 2 safety sample was used for the analysis of the safety and reactogenicity data.

Summary - Conclusions

This report presents the Year 2 Day 22 immunogenicity results and the safety results from Year 2 Day 1 until Year 2 Month 6 inclusive.

A total of 575 elderly subjects were vaccinated in the second year of the study, all of whom were included in the safety sample (432 subjects in the cell-derived influenza vaccine group and 143 subjects in the Influvac® group). The mean age of subjects in the Year 2 safety sample was 69.8 years and 69.1 years in the cell-derived influenza vaccine and Influvac® vaccine groups, respectively. The majority of subjects randomized to receive either vaccination were female (59.5% and 58.0%, respectively). All subjects were white.

Immunogenicity Results:

For the Year 2 Day 22 analysis, the FA sample comprised 574 elderly subjects (431 subjects in the cell-derived influenza vaccine group and 143 subjects in the Influvac® group). The

Blind Data Review Committee noted only two major protocol violations (both in the cell-derived influenza vaccine group); because of the small number of major protocol deviations separate per-protocol analyses were not performed.

Year 2 baseline (Day 317) HI titers were low for each of the three vaccine strains for both vaccine groups. The following tables summarize the serology results.

Serology: Summary Results for All Strains, for the Cell-derived Influenza Vaccination (Year 2 Day 22 Results, Post-vaccination Data), FA Sample

	Strain		
	A (H3N2) - like (N=431)	A (H1N1) - like (N=431)	B - like (N=431)
Post-vaccination (Day 338)			
HI Titer			
Geometric mean:	174.4 (154.5~196.9)	15.4 (13.7~17.4)	16.2 (14.6~18.0)
n:	431	431	431
Seroprotection			
Percentage:	91.0% (87.8%~93.5%)	25.1% (21.0%~29.4%)	26.0% (21.9%~30.4%)
Proportion:	392/431	108/431	112/431
Seroconversion			
Percentage:	58.9% (54.1%~63.6%)	17.9% (14.4%~21.8%)	5.1% (3.2%~7.6%)
Proportion:	254/431	77/431	22/431
MFI			
Geometric mean:	6.6 (5.7~7.6)	2.1 (1.9~2.3)	1.4 (1.3~1.4)
n:	431	431	431

Note: 95% confidence limits are given between brackets

CHMP Criteria for Healthy Subjects greater than or equal to 61 Years of Age:
- Seroprotection: > 60%
- Seroconversion: > 30%
- Geometric Mean Fold Increase > 2

Serology: Summary Results for All Strains, for the Influvac® Vaccination (Year 2 Day 22 Results, Post-vaccination Data), FA Sample

	Strain		
	A (H3N2) - like (N=143)	A (H1N1) - like (N=143)	B - like (N=143)
Post-vaccination (Day 338)			
HI Titer			
Geometric mean:	210.9 (169.5~262.4)	54.0 (42.5~68.6)	22.4 (18.3~27.5)
n:	143	143	143
Seroprotection			
Percentage:	93.0% (87.5%~96.6%)	65.0% (56.6%~72.8%)	35.0% (27.2%~43.4%)
Proportion:	133/143	93/143	50/143
Seroconversion			
Percentage:	65.0% (56.6%~72.8%)	60.1% (51.6%~68.2%)	16.1% (10.5%~23.1%)
Proportion:	93/143	86/143	23/143
MFI			
Geometric mean:	8.5 (6.5~11.1)	7.7 (6.1~9.7)	1.9 (1.6~2.2)
n:	143	143	143

Note: 95% confidence limits are given between brackets

CHMP Criteria for Healthy Subjects greater than or equal to 61 Years of Age:
Seroprotection: > 60%
Seroconversion: > 30%
Geometric Mean Fold Increase > 2

Three weeks after the second vaccination, cell-derived influenza vaccine met all three CHMP criteria for influenza vaccine immunogenicity in elderly subjects for the A/H3N2-like strain (seroprotection, seroconversion and MFI) and one criterion for the A/H1N1-like strain (MFI); for the B-like strain none of the criteria were met. Influvac® met all three criteria for the A/H3N2-like and A/H1N1-like strains but none for the B-like strain.

The B-like strain was the only strain that was given in both years of the study. The B-like strain failed to meet the seroprotection and seroconversion criteria for the cell-derived influenza vaccine following the second study vaccination. This was similar to the serological response following the first study vaccination.

Safety Results:

No deaths or TEAEs leading to discontinuation were reported from Year 2 Day 1 up to the Year 2 Day 22-Visit. One death was reported from the Year 2 Day 22-Visit up to the Year 2 Month 6-telephone call (cardiac death [cell-derived influenza vaccine group]) which was considered to be unrelated to the vaccine.

Three (0.7%) subjects in the cell-derived influenza vaccine group and one (0.7%) subject in

the Influvac® group experienced at least one treatment-emergent serious adverse event (TESAE) from Year 2 Day 1 up to the Year 2 Day 22-Visit. The incidence of TESAEs from the Year 2 Day 22-Visit up to the Year 2 Month 6-telephone call was similar in both vaccination groups (2.5% and 3.5%, respectively) and the incidence of NCIs was lower in the cell-derived influenza vaccine group compared to the Influvac® group (3.9% and 7.0%, respectively). No TESAEs or NCIs were considered to be related to the vaccine.

The proportion of subjects reported with at least one TEAE up to the Year 2 Day 22-Visit of the study was similar in both the cell-derived influenza vaccine and Influvac® groups (6.3% and 4.9%, respectively). The incidence of related and severe TEAEs was low (both reported in 0.9% of subjects in the cell-derived influenza vaccine group and no subjects in the Influvac® group).

The most common TEAEs by preferred term (reported by two or more subjects in either vaccination group), regardless of causality, were: pyrexia (0.7% of subjects in the cell-derived influenza vaccine group and no subjects in the Influvac® group); hypertension (0.2% and 1.4% of subjects, respectively); and bronchitis, osteochondrosis, urinary tract infection, myalgia and cough (each reported in 0.5% and no subjects, respectively).

In the safety sample, 288 subjects were vaccinated in both Year 1 and Year 2 with cell-derived influenza vaccine and 144 subjects were vaccinated only in Year 2 with cell-derived influenza vaccine.

The proportion of subjects reported with at least one TEAE from Year 2 Day 1 up to the Year 2 Day 22-Visit of the study was the same in subjects vaccinated twice with cell-derived influenza vaccine compared to subjects vaccinated for the first time with cell-derived influenza vaccine (both 6.3%). There were no marked differences in the incidence of the most commonly reported TEAEs between the two subgroups.

The available data from Year 2 Day 1 up to the Year 2 Day 22-Visit and from the Year 2 Day 22-Visit up to the Year 2 Month 6-telephone call do not give rise to special concerns with respect to Guillain-Barré syndrome and autoimmune disorders.

The proportion of subjects reporting local reactions was similar in the cell-derived influenza vaccine and Influvac® groups (16.0% and 16.1% of subjects, respectively). The most frequent local reaction was tenderness (8.8% and 7.0% of subjects, respectively). The majority of reported local reactions in both groups had an onset during the first two days following vaccination and a duration of the reaction of one to three days. All local reactions were rated as mild or moderate in severity, with the majority rated as mild. No local reactions were judged to be severe in the cell-derived influenza vaccine or Influvac® groups.

The proportion of subjects reporting systemic reactions was also similar in the cell-derived influenza vaccine (19.3%) and Influvac® groups (18.9%). The most frequent systemic reaction was fatigue (11.1% and 11.2% of subjects, respectively). The majority of reported systemic reactions had an onset during the first three days following vaccination and a duration of the reaction of one to three days. A small number of systemic reactions lasted up to seven days, with fatigue reported as the most frequent (five and one subject in the cell-derived influenza vaccine and Influvac® groups, respectively). The majority of systemic reactions were rated as mild or moderate in severity, with most rated as mild. Four subjects in the cell-derived influenza vaccine group were reported with systemic reactions rated as severe. No systemic reactions in the Influvac® group were rated as severe.

It was investigated if subjects vaccinated with cell-derived influenza vaccine at both Year 1 and Year 2 had a higher risk of solicited local or systemic reactions compared to subjects vaccinated for the first time with cell-derived influenza vaccine at Year 2. The proportion of subjects that reported any local reaction was higher in subjects vaccinated twice with cell-derived influenza vaccine (18.1% versus 11.8%). The only local reaction interpreted as a potential safety signal was warmth which was reported at a higher frequency in subjects vaccinated twice with cell-derived influenza vaccine. Analysis of the relative risks showed that there were no apparent signals that suggest that being vaccinated twice with cell-derived influenza vaccine increases the risk of solicited systemic reactions compared to subjects being vaccinated for the first time with cell-derived influenza vaccine.

Four subjects reported fever (graded based on the highest recorded body temperature). Three subjects in the cell-derived influenza vaccine group reported a body temperature of $\geq 38^{o}$C and one subject in the Influvac® group reported a body temperature $> 38^{o}$C: no subjects reported a body temperature of > 39.0°C. None of the cases of fever were severe.

The majority of subjects in both vaccination groups did not experience any inconvenience after vaccination (94.9% in the cell-derived influenza vaccine group and 97.2% in the Influvac® group). If reported at all, inconvenience was generally mild, with a small proportion of subjects reporting moderate inconvenience after vaccination (0.7% in the cell-derived influenza vaccine group and no subjects in the Influvac® group). Only one (0.2%) subject in the cell-derived influenza vaccine group reported severe inconvenience.

Conclusion:

- Three weeks after the second study vaccination, in elderly subjects (≥ 61 years of age), the cell-derived influenza vaccine did not meet all three CHMP criteria for all three strains; for the A/H3N2-like strain three criteria were met, for the A/H1N1-like strain one criterion was met, and for the B-like strain none of the criteria were met.
- Subjects vaccinated twice with cell-derived influenza vaccine had a higher incidence of local reactions than subjects vaccinated for the first time with cell-derived influenza vaccine at Year 2. The only reaction interpreted as a potential safety signal was the local reaction, warmth, which was reported at a higher frequency in subjects vaccinated twice with cell-derived influenza vaccine than subjects vaccinated for the first time with cell-derived influenza vaccine at Year 2.
  In terms of the relative risk of any systemic reaction, there were no significant differences between subjects vaccinated twice with cell-derived influenza vaccine and subjects vaccinated for the first time with cell-derived influenza vaccine at Year 2.
- The cell-derived influenza vaccine and Influvac® were safe and generally well-tolerated in elderly subjects (≥ 61 years of age) from Year 2 Day 1 up to the Year 2 Month 6-telephone call. No notable differences in the reported safety parameters were observed between the vaccination groups.