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/Brisbane/59/2007 (H1N1)-like strain;
A/Brisbane/10/2007 (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 Revaccination, in Elderly Subjects

Month 6, Year 1 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:
30 NOV 2009 (first subject first visit) – 09 JUL 2010 (last subject six month 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 revaccination 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 revaccination with the cell-derived influenza vaccine for up to six months following revaccination.

* Indicates the objectives answered in this Month 6, Year 1 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. Once informed consent was obtained, subjects were screened within 14 days prior to or at Visit 1 (Day 1). Screening included a medical history, measurement of vital signs (body temperature, heart rate and blood pressure), physical examination, prevaccination assessments and a review of the inclusion and exclusion criteria.

On Visit 1 (Day 1), after a review of the inclusion and exclusion criteria, physical examination, collection of venous blood for baseline clinical safety and immunogenicity laboratory assessments, and measurement of vital signs, subjects were randomized in a 2:1 ratio to receive cell-derived influenza vaccine or egg-derived influenza vaccine (Influvac®), respectively. Following vaccination by intramuscular injection, subjects were observed for at least 30 minutes to monitor for any immediate adverse reactions (appropriate medical treatment and supervision were readily available in case of an anaphylactic event), and a daily diary, thermometer and ruler were provided for daily reporting of solicited local and systemic reactions and overall inconvenience that occurred during the first seven days after vaccination. A telephone call was scheduled to occur three days after vaccination to remind subjects to complete the daily diary.

Following vaccination and until the Month 6-Visit (Day 169; Visit 3), subjects were instructed to immediately contact the investigator by telephone in the event of the occurrence of symptoms or signs requiring diagnostic testing for influenza, 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 was collected for the diagnosis of influenza infection.

Visit 2 (Day 22-Visit) 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 and clinical safety laboratory assessments.

Visit 3 (Month 6-Visit) was scheduled to occur six months after vaccination, when any additional serious adverse events (SAEs), new chronic illnesses (NCIs), intercurrent vaccinations and concomitant medications that could have compromised the immune response were recorded and a blood sample was collected for immunogenicity assessments.

This clinical study report covers all data obtained from subjects until their Month 6-Visit. A follow-up report will cover all additional data obtained from subjects participating in the second

year of the study until their Day 485 telephone call.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned 600 subjects, consented 628 subjects, vaccinated 622 subjects (416 subjects to cell-derived influenza vaccine, 206 subjects to Influvac®). Analyzed at Day 22: 622 (416 subjects to cell-derived influenza vaccine, 206 subjects to Influvac®) subjects in the safety sample, 620 (414 subjects to cell-derived influenza vaccine, 206 subjects to Influvac®) subjects in the full analysis (FA) sample. Analyzed at Month 6: 622 subjects in the safety sample, 615 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 2009/2010 Northern Hemisphere) administered by intramuscular injection.

Final lot batch number: 610400.

Duration of Treatment:

During the first year: a single dose administered on the Day 1 visit. A second dose will be administered during the second year on the Day 317-Visit.

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 2009/2010 Northern Hemisphere) administered by intramuscular injection.

Final lot batch number: 610381.

Criteria for Evaluation

Immunogenicity:

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

Safety:

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

During the three weeks following the first vaccination: AEs other than those specifically solicited, concomitant medication and clinical safety laboratory parameters.

From three weeks following the first vaccination: SAEs and NCIs.

Statistical Methods

Immunogenicity:

Hemagglutination inhibition antibody titers were summarized by means of geometric mean titers (GMTs), geometric MFIs, seroprotection rates and seroconversion rates. These summary

statistics were used to assess immunogenicity of the cell-derived influenza vaccine, including long-term (Month 6) immunogenicity. To demonstrate immunogenicity of the cell-derived influenza vaccine, it was checked whether at the Day 22-Visit, all three CHMP criteria for influenza vaccine immunogenicity were met for all three strains of the vaccine.

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

Safety:

Adverse events (serious and non-serious) and NCIs were coded using the Medical Dictionary for Regulatory Activities thesaurus. 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 (CIs) for the absolute incidences were calculated. Overall inconvenience was quantified by treatment period by means of the relative distribution of the severity scores.

Clinical safety laboratory variables, including changes from baseline, were summarized. A frequency table was presented for clinically significant or markedly abnormal values. Shift tables were presented according to the reference ranges (low, normal or high). For the Day 22 data, frequencies of markedly abnormal values were compared between the cell-derived influenza vaccine and Influvac® group using the Double False Discovery Rate method to control the false positive rate.

Vital signs data summaries included mean values of absolute values and changes from baseline, as well as frequency tables of marked abnormalities.

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 safety sample was used for the analysis of the safety and reactogenicity data.

Summary - Conclusions

This report presents the immunogenicity results and the safety results up to Month 6 inclusive.

A total of 622 elderly subjects were vaccinated, all of whom were included in the safety sample (416 subjects in the cell-derived influenza vaccine group and 206 subjects in the Influvac® group). The mean age of subjects in the safety sample was 68.8 years and 69.3 years in the cell-derived influenza vaccine and Influvac® vaccination groups, respectively. Most subjects fell in to the ≥ 61 to ≤ 64 years and/or ≥ 65 to ≤ 69 age categories. The majority of subjects randomized to receive either vaccination were female (57.0% and 63.6%, respectively). All subjects were white.

Immunogenicity Results:

For the Day 22 analysis, the FA sample comprised 620 elderly subjects (414 subjects in the cell-derived influenza vaccine group and 206 subjects in the Influvac® group).

Baseline HI titers were low for each of the three vaccine strains for both vaccination groups. The following tables summarize the serology results.

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

	Strain		
	A (H3N2) - like (N=414)	A (H1N1) - like (N=414)	B - like (N=414)
Post-vaccination (Day 22)			
HI Titer			
Geometric mean:	147.9 (125.1~174.9)	46.3 (40.6~52.7)	23.6 (20.7~27.0)
n:	414	414	414
Seroprotection			
Percentage:	81.6% (77.6%~85.3%)	59.7% (54.8%~64.4%)	38.2% (33.5%~43.0%)
Proportion:	338/414	247/414	158/414
Seroconversion			
Percentage:	62.8% (57.9%~67.5%)	42.5% (37.7%~47.4%)	28.0% (23.7%~32.6%)
Proportion:	260/414	176/414	116/414
MFI			
Geometric mean:	9.4 (8.0~11.1)	4.3 (3.8~4.9)	3.0 (2.6~3.4)
n:	414	414	414

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 (Day 22 Results, Post-vaccination Data), FA Sample

	Strain		
	A (H3N2) - like (N=206)	A (H1N1) - like (N=206)	B - like (N=206)
Post-vaccination (Day 22)			
HI Titer			
Geometric mean:	229.9 (187.5~281.7)	73.4 (61.4~87.7)	30.8 (25.8~36.8)
n:	206	206	206
Seroprotection			
Percentage:	91.3% (86.5%~94.7%)	75.7% (69.3%~81.4%)	48.1% (41.1%~55.1%)
Proportion:	188/206	156/206	99/206
Seroconversion			
Percentage:	71.4% (64.7%~77.4%)	55.3% (48.3%~62.3%)	37.4% (30.8%~44.4%)
Proportion:	147/206	114/206	77/206
MFI			
Geometric mean:	12.8 (10.3~16.0)	6.5 (5.4~7.9)	3.9 (3.3~4.6)
n:	206	206	206

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 vaccination, cell-derived influenza vaccine did not meet the CHMP criteria for influenza vaccine immunogenicity in elderly subjects (≥ 61 years of age). The CHMP criteria were met for seroprotection for one of the three vaccine strains, seroconversion for two of the three vaccine strains and for MFI for all three vaccine strains. The serological results of Influvac® met the CHMP criteria for two of the three vaccine strains for seroprotection, and for all three vaccine strains for seroconversion and for MFI.

After six months, the post-vaccination HI antibody titers for the cell-derived influenza vaccine group showed a moderate increase from baseline for all three vaccine strains: 69.2 at Month 6 versus 17.1 at baseline for the A/H3N2-like vaccine strain, 28.5 versus 11.3 for the A/H1N1-like vaccine strain and 16.1 versus 8.4 for the B-like vaccine strain. Similar results were observed for the Influvac® group. The seroprotection rates at the Month 6-Visit for the cell-derived influenza vaccine group met the CHMP criterion for one of the three vaccine strains (the A/H3N2-like strain).

Safety Results:

No deaths, SAEs or TEAEs leading to discontinuation were reported up to the Day 22-Visit.

Two deaths were reported from the Day 22-Visit up to the Month 6-Visit: one in the cell-derived influenza vaccine group (on Day 95; sudden death) and one in the Influvac® group (on Day 56; congestive cardiac failure). Both deaths were considered unrelated to study vaccine.

The proportion of subjects reported with at least one treatment-emergent SAE or NCI from the Day 22-Visit up to the Month 6-Visit was similar between the cell-derived influenza vaccine and Influvac® groups (10.8% and 12.6%, respectively). Throughout the study, no TESAEs or NCIs were considered by the Investigator to be related to the vaccine.

The proportion of subjects reported with at least one TEAE up to the Day 22-Visit of the study was low and similar between the cell-derived influenza vaccine and Influvac® groups (7.0% and 6.3%, respectively), as was the proportion of subjects with at least one related TEAE (0.7% and 1.9% of subjects, respectively). No severe TEAEs were reported in either vaccination group.

The most common TEAEs by preferred term (reported by > 1% of subjects in either vaccination group), regardless of causality, were increased blood creatine phosphokinase (0.7% of subjects in the cell-derived influenza vaccine group and 1.0% of subjects in the Influvac® group), hypertension (0.2% and 1.0% of subjects, respectively) and diarrhea (no subjects and 1.0% of subjects, respectively).

The available data through Day 22 and from Day 22 to Month 6 do not give rise to special concerns with respect to Guillain-Barré syndrome or other autoimmune disorders.

The incidence of local reactions was slightly higher in the cell-derived influenza vaccine group (22.4%) than the Influvac® group (18.0%). The most frequent local reaction was tenderness (8.2% and 7.8% 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. Almost all local reactions were rated as mild or moderate in severity, with the majority rated as mild. Only one subject (cell-derived influenza vaccine group) was reported with a severe reaction (swelling). No subjects in the Influvac® group were reported with any local reaction rated as severe.

The incidence of systemic reactions was slightly higher in the cell-derived influenza vaccine group (30.1%) than the Influvac® group (26.2%). The most frequent systemic reactions were fatigue (18.3% and 12.1% of subjects, respectively) and headache (15.4% and 12.1% of subjects, respectively). The majority of reported systemic reactions in both vaccination groups had an onset during the first three days following vaccination and a duration of the reaction of one to three days. Almost all systemic reactions were rated as mild or moderate in severity, with the majority rated as mild. In the cell-derived influenza vaccine group, three subjects were reported with systemic reactions rated as severe (fatigue, headache and shivering/chills) compared to one subject in the Influvac® group (headache).

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 above 38°C (all in the range of 38.0 - 38.4°C) and one subject in the Influvac® group reported a body temperature above 38°C (in the range of 38.5 - 39.0°C): no subjects reported a body

temperature of > 39.0°C. None of the cases of fever were severe or lasted longer than two days.

The majority of subjects in both vaccination groups did not experience any inconvenience after the first vaccination (93.0% in the cell-derived influenza vaccine group and 93.7% in the Influvac® group). No subjects reported severe inconvenience. If reported at all, inconvenience was generally mild, with a small proportion of subjects reporting moderate inconvenience after either vaccination (1.0% in the cell-derived influenza vaccine group and 0.5% in the Influvac® group).

No clinically significant differences were observed in the mean changes from baseline in laboratory parameters or vital signs between the two vaccination groups.

Conclusion:

- Three weeks after vaccination, in elderly subjects (≥ 61 years of age), the serological results of cell-derived influenza vaccine met the CHMP criterion for seroprotection for the A/H3N2-like vaccine strain; for seroconversion for the A/H3N2-like and A/H1N1-like vaccine strains; and for MFI for all three vaccine strains.
  Three weeks after vaccination, the serological results of Influvac® met all three of the CHMP criteria for the A/H3N2-like and A/H1N1-like vaccine strains, while the B-like vaccine strain met the CHMP criteria for seroconversion and for MFI.
- Long-term immunogenicity of the cell-derived influenza vaccine was apparent six months after vaccination, with GMTs which remained above the pre-vaccination levels and with one of the three vaccine strains maintaining seroprotection (the A/H3N2-like vaccine strain).
- The cell-derived influenza vaccine and Influvac® were safe and generally well-tolerated in elderly subjects (≥ 61 years of age). No notable differences in the reported safety parameters were observed between the vaccine groups, except that the incidence of local or systemic reactions was slightly higher in the cell-derived influenza vaccine group compared to the Influvac® group.