SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** 11PCV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : A phase I/II, randomized, observer blinded study to evaluate and compare the safety, reactogenicity and immunogenicity of various formulations of the GlaxoSmithKline Biologicals' adjuvanted 11-valent pneumococcal conjugate vaccine versus the licensed single-dose 23-valent pneumococcal polysaccharide vaccine and GlaxoSmithKline Biologicals' aluminium-based 10-valent pneumococcal conjugate vaccine, in healthy elderly subjects.

Study: 106072 (STREP-ELD-011 EXT010 Y1)

Rationale for the annex report: In the primary report 106068 (STREP-ELD-010) dated 05 November 2007 the safety, reactogenicity, and immunogenicity of the GSK Biologicals candidate 11PCV combined with different adjuvants (AS01B, AS01E, or AS02V) in healthy adults aged 65 years or above were assessed. The safety profile and the immune response to one and two doses of these vaccines formulations were evaluated in comparison to 23PPV and GSK Biologicals 10 valent pneumococcal conjugate vaccine adjuvanted with $AlPO_4$.

In order to evaluate the persistence of the immune response induced by two doses of 11PCV combined with different adjuvants (AS01B, AS01E, or AS02V), blood samples were taken at Month 12 in a cohort of subjects. Immunogenicity results were presented up to Month 4 in the primary report 106068 (STREP-ELD-010). ELISA results up to Month 12 are presented separately in this annex report. Safety results from Month 4 to Month 12 are also presented in this annex report, for subjects enrolled in study STREP ELD-010. OPA, haematological, and biochemistry results will be presented in a second annex report.

As no adjuvant effect was observed on T-cell response in study STREP ELD-010, the following immunological tests were not performed at Month 12 (study STREP ELD 011):

- The frequency of gamma class immunoglobulin (IgG) polysaccharides (PS) specific plasma cells generated by in vitro cultivated memory B-cells, measured by enzyme-linked immunospot (ELISPOT)
- The frequency of IgG protein D-specific plasma cells generated by in vitro cultivated memory B cells, measured by ELISPOT.
- The frequencies of cluster differentiation 4+ and 8+ (CD4+ and CD8+) T cells with antigen-specific interleukin-2 (IL-2), interferon-γ (IFN-γ), tumour necrosis factors-α (TNF-α), and/or cluster of differentiation 40 ligand (CD40L) secretion/expression to protein D as determined by intracellular cytokine staining.

Principal investigator:

- Prof. Dr. [redacted] Belgium)
- Dr. [redacted] Finland).
- Dr. [redacted] Sweden).

Study centre(s):

This study was conducted in one centre (Belgium). ELISA data at Month 12 were assessed for the Belgian site: [redacted] Belgium.

In Sweden and Finland, the reporting of the SAEs during the 9 months period after the last vaccine dose were not done through active collection at Visit 5, as this Visit 5 did not take place for subjects in Sweden and Finland. Only SAEs which were spontaneously reported by the subjects were collected and reported.

Serious adverse events (SAEs) from Month 4 to 12 were assessed for the three centres:

- [redacted] Belgium.
- [redacted] Finland.
- [redacted] Sweden.

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Publication (reference): Not published as of September 2008.		
Study period: Study initiation date (Year 1): 10-May-2007 Study completion date (Year 1): 19-June-2008 Data Lock point: 25-July-2008 (note: database will be locked for a second time after the OPA results are available)		**Clinical phase: I/II**

Objectives:

Objectives at Month 12 are only evaluated in subjects of the Belgian site.
The objectives of the primary study can be found in the primary study report 106068 (STREP-ELD-010).

The study objectives covered in this annex report are:

- To evaluate the humoral immune response at Month 12 in each group.
- To evaluate the humoral immune response to carrier proteins at Month 12, in the 11PCV/AS01B, 11PCV/AS01E, 11PCV/AS02V, and 10PCV/$AlPO_4$ groups.
- To evaluate safety and reactogenicity in the 11PCV/AS01B, 11PCV/AS01E, 11PCV/AS02V, 10PCV/$AlPO_4$, and 23PPV groups

The following objectives pertaining to Month 12 will be assessed in a second annex report.

- To evaluate the safety as measured by haematological and biochemical parameters in each group.

As it was decided to perform only the ELISA and OPA testings, the following secondary objectives will not be assessed:

- To evaluate the B-cell memory response to 4 polysaccharides in all subjects and to 11 polysaccharides in 10 subjects per group at Month 12.
- To evaluate the B-cell memory response to non typable *Haemophilus influenzae* (NTHi) protein D at Month 12 in a subset of subjects (all subjects minus PS B-cell memory subset) of the 11PCV/AS01B, 11PCV/AS01E, 11PCV/AS02V and, 10PCV/$AlPO_4$ groups.
- To evaluate the T-cell response to NTHi protein D at Month 12, in a subset of subjects (all subjects minus PS B-cell memory subset) of the 11PCV/AS01B, 11PCV/AS01E, 11PCV/AS02V, and 10PCV/$AlPO_4$ groups.

Study design:

This was a phase I/II, observer blind, multicentre, multicountry, randomized controlled study with five parallel groups.

- 11PCV/AS01B group: GSK Biologicals 11PCV combined with adjuvant AS01B.
- 11PCV/AS01E group: GSK Biologicals 11PCV combined with adjuvant AS01E.
- 11PCV/AS02V group: GSK Biologicals 11PCV combined with adjuvant AS02V.
- 23PPV group: 23PPV (control)
- 10PCV/$AlPO_4$ group: GSK Biologicals 10PCV adjuvanted with $AlPO_4$ (control)

In the 4 groups receiving GSK Biologicals' vaccines, each subject received 2 doses of vaccine at Month 0 and 3. For the group receiving 23PPV, subjects received 1 dose of vaccine at Month 0 and 1 dose of placebo at Month 3. Blood samples were taken at Months 0, 1, 3, and 4 (results for these blood samples were presented in the primary study report 106068 [STREP-ELD-010]). One additional blood sample was collected at Month 12 for subjects enrolled at the Belgian site.

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Number of subjects:
Planned: In this annex report, only subjects enrolled in the Belgian site were assessed, except for the SAEs. In the primary study 106068 (STREP-ELD-010), 108 subjects were enrolled in the Belgian site.
Enrolled and completed: 107 in total (20 subjects / 11PCV/AS01B; 21 subjects / 11PCV/AS01E; 21 subjects / 11PCV/AS02V; 23 subjects / 10PCV/$AlPO_4$; 22 subjects / 23PPV).
Safety (Total Vaccinated cohort [TVC]) and *Immunogenicity* (According-to-Protocol [ATP]): 107 in total (20 subjects / 11PCV/AS01B; 21 subjects / 11PCV/AS01E; 21 subjects / 11PCV/AS02V; 23 subjects / 10PCV/$AlPO_4$; 22 subjects / 23PPV).

Diagnosis and criteria for inclusion:
Elderly subjects aged between 65 and 85 years old, in good general health at the time of the first vaccination. Subjects that had never been vaccinated with the 23PPV or any other vaccine against *Streptococcus pneumoniae*. See primary report 106068 (STREP-ELD-010) for details.

Study vaccine, dose, mode of administration, lot no.:
No vaccine was given during the follow-up period, see the primary report 106068 (STREP-ELD-010) for the details regarding the vaccination schedule and composition.

Duration of treatment:
The subject follow-up duration was approximately 12 months for each subject in the Belgian site and 4 months in the other sites. Therefore only Belgian sites contributed to this annex report. However late SAE reporting from non Belgian sites have also been included in this report.

Criteria for evaluation:
Immunogenicity:
The following immunogenicity results were discussed in this annex report:

- IgG antibody concentration against the different serotypes out of the 11 present in the vaccine was measured by ELISA with a cut-off of 0.05 µg/mL. The criteria were: post vaccination concentration IgG ≥ 5 µg/mL and fold increase Post/Pre ≥ 2 for at least 6 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) at Month 12 for the 11PCV formulations and one month after dose 1 for the 23PPV group. The IgG antibody concentration to serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F was determined for all groups at Month 12.
- The anti-protein D, anti-tetanus and anti-diphtheria toxoid IgG antibody concentrations were determined by ELISA (cut-off of 100 EL.U/mL for the anti-protein D and 0.1 IU/mL for the two others) at Month 12 in all groups except the 23PPV group.

Safety:
Recording of SAEs during the entire study period. In Sweden and Finland, the reporting of the SAEs during the 9 months period after the last vaccine dose were not done through active collection at Visit 5, as this Visit 5 did not take place for subjects in Sweden and Finland. Only SAEs which were spontaneously reported by the subjects were collected and reported. Furthermore, SAEs occurring from Month 4 to Month 12 at the Belgian site were recorded.

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Statistical methods:
Analyses were performed as per protocol and the study reporting and analysis plan.
The analysis of safety was performed on the TVC, the analysis of immunogenicity was performed on the ATP cohort for immune persistence.

- The TVC included all subjects vaccinated in study STREP-ELD-010 from the Belgium site.
- The ATP cohort for analysis of immune persistence included all subjects included in the ATP cohort for analysis of immunogenicity in study STREP-ELD-010, who were evaluable (i.e. complying with the procedures defined in the protocol, with no elimination criteria at Month 12) and for whom assay data concerning immunogenicity endpoint measures were available.

Immunogenicity:
Percentage of responders, seropositivity rates, and geometric mean concentrations (GMC) with 95% confidence interval (95% CI) for ELISA data were tabulated per group and per serotype/antigen, overall and by the age randomization factor (< 70 years old or ≥ 70 years old).
Safety:
SAEs recorded from Month 4 to 12 were tabulated and classified by Medical Directory for Regulatory Activities (MedDRA) primary system organ class and preferred term. The percentage of subjects with at least one SAE was tabulated per group, with exact 95% CI (for Belgian site only).

Changes in planned analysis: As no adjuvant effect was observed on T-cell response in study STREP-ELD-010, the cell mediated immunity tests were not performed at Month 12 (study STREP-ELD-011). OPA, haematological, and biochemistry results for samples taken at Month 12 will be presented in a second annex report.

Protocol Amendments: See primary report for details (Amendment: 01-June-2007).

Results:
Demography:
Demographic data are presented in Supplement 1. At Month 12, the mean age was 68.2 years (range: 65 to 80 years), the mean body mass index (BMI) was 26.7 kg/m^2. There were approximately the same number of male and female subjects and the population was mainly of Caucasian origin. The demographic profile of the 5 groups was comparable with respect to mean age and gender.
Table 1 presents the number of subjects in each analysis cohort. A total of 108 subjects were enrolled in the Belgian site of the primary phase (STREP-ELD-010). Of these, 107 subjects participated in the secondary phase for blood sampling at Month 12. All these 107 subjects were included in the ATP cohort for immune persistence.

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Table 1: Number of subjects enrolled into the persistence analysis as well as the number excluded from ATP analyses with reasons for exclusion.

	Total		11AS01B	11AS01E	11ASO2V	10AlPO$_4$	23 PPV
Title (Belgian site only)	n	%	n	n	n	n	n
Total vaccinated cohort	108	100	21	21	21	23	22
Total enrolled at Month 12 visit	107	99	20*	21	21	23	22
ATP cohort for immune persistence	107	99	20*	21	21	23	22

11AS01B = 11PCV combined with AS01B
11AS01E = 11PCV combined with AS01E
11AS02V = 11PCV combined with AS02V
10AlPO$_4$ = 10PCV combined with AlPO$_4$
23PPV = 23-valent pneumococcal polysaccharide vaccine
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the ATP cohort relative to the Total vaccinated cohort
* [redacted]

Immunogenicity: (1 year after the vaccination in the primary phase):
Analysis of immunogenicity was performed on the ATP cohort for immune persistence.

Immunogenicity to pneumococcal serotypes in all groups
Table 2 presents the number and percentage of responders to each serotype and, the number and percentage of responders to at least 6 serotypes out of the 11 tabulated per group, with exact 95% CI. A subject was considered to be a responder for a particular serotype if post vaccination the anti-PS antibody concentration was ≥ 5 µg/mL and there was a fold increase Post/Pre ≥ 2.
The highest percentages of responders at Month 12 were observed for the serotypes 14, 18C, and 19F (42.9 - 60.9%, 52.4 - 95.2%, and 47.4 - 68.4%, respectively). The serotypes 1, 4, 5, 6B, 7F, 9V, and 23F had moderate percentages of responders and 3 subjects responded for serotype 3.
A decrease in the percentage of responders to at least 6 serotypes of the 11 was observed from Month 4 to Month 12, in the 5 groups. At Month 12, percentage of responders to at least 6 serotypes of the 11 was 5% for group 11AS01B, 28.6% for group 11AS01E, 19.1% for group 11AS02V, 26.1% for 10AlPO$_4$, and 18.2% for group 23PPV.

The percentage of responders to each serotype and the number and percentage of responders to at least 6 serotypes out of the 11 tabulated per group and by age categories (< 70 years old, ≥ 70 years old) is presented in Supplement 2.

Table 3 presents GMCs and seropositivity rates for anti-PS antibodies against 13 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F, 6A, 19A) tabulated per group, with 95% CI.
At Month 12, most subjects (91.3% to 100%, depending on the serotype) were seropositive for each of the 13 serotypes. GMCs were lower at Month 12 with respect to Month 4 for all vaccine groups and serotypes.

The GMCs and seropositivity rates for anti-PS antibodies against 13 serotypes tabulated per group and by age categories (< 70 years old, ≥ 70 years old) are presented in Supplement 3.

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Immunogenicity to carrier proteins
GMCs and seropositivity rates for anti-protein D, anti-tetanus, and anti-diphtheria toxoid antibodies were tabulated per group, with 95% CI, overall in Tables 4, 5, and 6 and by age categories (< 70 years old, ≥ 70 years old) in Supplements 4, 5, and 6.

At Month 4, 95.5 to 100% of subjects were seropositive for anti-protein D antibodies. At Month 12, 73.9 to 90% of subjects were seropositive for anti-protein D antibodies. GMCs and seropositivity rates for anti-protein D antibodies were immunologically similar between the three 11PCV formulation groups and the $10AlPO_4$ group.

At Month 4, 100% of subjects were seropositive for anti-tetanus toxoid antibodies. At Month 12, 81 to 100% of subjects were seropositive for anti-tetanus toxoid antibodies. GMCs and seropositivity rates for anti-tetanus toxoid antibodies were immunologically similar between the three 11PCV formulation groups and the $10AlPO_4$ group.

At Month 4, 57.1 to 85% of subjects were seropositive for anti- diphtheria toxoid antibodies. At Month 12, 52.2 to 71.4% of subjects were seropositive for anti- diphtheria toxoid antibodies. GMCs and seropositivity rates for anti- diphtheria toxoid antibodies were immunologically similar between the three 11PCV formulation groups and the $10AlPO_4$ group.

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Table 2: Percentage of responders (ELISA) to each serotype and to at least 6 serotypes out of the 11 (ATP cohort for immune persistence)

				Post ≥ 5 μg/mL and Post / Pre ≥ 2			
						95% CI	
Serotypes	Group	Time	N	n	%	LL	UL
S Pneu. 1 IgG	11AS01B	Month 4	20	2	10.00	1.23	31.70
		Month 12	20	1	5.00	0.13	24.87
	11AS01E	Month 4	21	8	38.10	18.11	61.56
		Month 12	21	4	19.05	5.45	41.91
	11AS02V	Month 4	21	5	23.81	8.22	47.17
		Month 12	21	4	19.05	5.45	41.91
	10AlPO$_4$	Month 4	23	8	34.78	16.38	57.27
		Month 12	23	4	17.39	4.95	38.78
	23PPV	Month 4	22	12	54.55	32.21	75.61
		Month 12	22	10	45.45	24.39	67.79
S Pneu. 3 IgG	11AS01B	Month 4	17	0	0.00	0.00	19.51
		Month 12	17	1	5.88	0.15	28.69
	11AS01E	Month 4	21	1	4.76	0.12	23.82
		Month 12	21	0	0.00	0.00	16.11
	11AS02V	Month 4	19	0	0.00	0.00	17.65
		Month 12	18	0	0.00	0.00	18.53
	10AlPO4	Month 4	21	0	0.00	0.00	16.11
		Month 12	22	0	0.00	0.00	15.44
	23PPV	Month 4	21	5	23.81	8.22	47.17
		Month 12	21	2	9.52	1.17	30.38
S Pneu. 4 IgG	11AS01B	Month 4	20	5	25.00	8.66	49.10
		Month 12	19	3	15.79	3.38	39.58
	11AS01E	Month 4	21	12	57.14	34.02	78.18
		Month 12	21	9	42.86	21.82	65.98
	11AS02V	Month 4	21	7	33.33	14.59	56.97
		Month 12	21	5	23.81	8.22	47.17
	10AlPO$_4$	Month 4	23	10	43.48	23.19	65.51
		Month 12	23	9	39.13	19.71	61.46
	23PPV	Month 4	22	8	36.36	17.20	59.34
		Month 12	22	7	31.82	13.86	54.87

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				Post ≥ 5 µg/mL and Post / Pre ≥ 2			
						95% CI	
Serotypes	Group	Time	N	n	%	LL	UL
S Pneu. 5 IgG	11AS01B	Month 4	20	10	50.00	27.20	72.80
		Month 12	20	7	35.00	15.39	59.22
	11AS01E	Month 4	21	12	57.14	34.02	78.18
		Month 12	21	7	33.33	14.59	56.97
	11AS02V	Month 4	21	11	52.38	29.78	74.29
		Month 12	21	6	28.57	11.28	52.18
	$10AlPO_4$	Month 4	23	13	56.52	34.49	76.81
		Month 12	23	10	43.48	23.19	65.51
	23PPV	Month 4	21	11	52.38	29.78	74.29
		Month 12	21	9	42.86	21.82	65.98
S Pneu. 6B IgG	11AS01B	Month 4	20	5	25.00	8.66	49.10
		Month 12	20	3	15.00	3.21	37.89
	11AS01E	Month 4	21	6	28.57	11.28	52.18
		Month 12	21	3	14.29	3.05	36.34
	11AS02V	Month 4	21	9	42.86	21.82	65.98
		Month 12	21	4	19.05	5.45	41.91
	$10AlPO_4$	Month 4	23	7	30.43	13.21	52.92
		Month 12	23	4	17.39	4.95	38.78
	23PPV	Month 4	22	5	22.73	7.82	45.37
		Month 12	22	3	13.64	2.91	34.91
S Pneu. 7F IgG	11AS01B	Month 4	19	12	63.16	38.36	83.71
		Month 12	19	7	36.84	16.29	61.64
	11AS01E	Month 4	21	12	57.14	34.02	78.18
		Month 12	21	9	42.86	21.82	65.98
	11AS02V	Month 4	21	10	47.62	25.71	70.22
		Month 12	21	7	33.33	14.59	56.97
	$10AlPO_4$	Month 4	22	11	50.00	28.22	71.78
		Month 12	22	8	36.36	17.20	59.34
	23PPV	Month 4	21	11	52.38	29.78	74.29
		Month 12	21	9	42.86	21.82	65.98
S Pneu. 9V IgG	11AS01B	Month 4	19	4	21.05	6.05	45.57
		Month 12	19	3	15.79	3.38	39.58
	11AS01E	Month 4	21	13	61.90	38.44	81.89
		Month 12	21	9	42.86	21.82	65.98
	11AS02V	Month 4	21	11	52.38	29.78	74.29
		Month 12	21	5	23.81	8.22	47.17
	$10AlPO_4$	Month 4	23	9	39.13	19.71	61.46
		Month 12	23	7	30.43	13.21	52.92

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				Post ≥ 5 µg/mL and Post / Pre ≥ 2			
						95% CI	
Serotypes	Group	Time	N	n	%	LL	UL
	23PPV	Month 4	22	7	31.82	13.86	54.87
		Month 12	22	5	22.73	7.82	45.37
S Pneu. 14 IgG	11AS01B	Month 4	19	13	68.42	43.45	87.42
		Month 12	19	11	57.89	33.50	79.75
	11AS01E	Month 4	21	12	57.14	34.02	78.18
		Month 12	21	9	42.86	21.82	65.98
	11AS02V	Month 4	21	14	66.67	43.03	85.41
		Month 12	21	12	57.14	34.02	78.18
	$10AlPO_4$	Month 4	23	14	60.87	38.54	80.29
		Month 12	23	14	60.87	38.54	80.29
	23PPV	Month 4	21	12	57.14	34.02	78.18
		Month 12	21	11	52.38	29.78	74.29
S Pneu. 18C IgG	11AS01B	Month 4	20	20	100.00	83.16	100.00
		Month 12	20	18	90.00	68.30	98.77
	11AS01E	Month 4	21	20	95.24	76.18	99.88
		Month 12	21	20	95.24	76.18	99.88
	11AS02V	Month 4	20	20	100.00	83.16	100.00
		Month 12	20	19	95.00	75.13	99.87
	$10AlPO_4$	Month 4	23	22	95.65	78.05	99.89
		Month 12	23	15	65.22	42.73	83.62
	23PPV	Month 4	21	13	61.90	38.44	81.89
		Month 12	21	11	52.38	29.78	74.29
S Pneu. 19F IgG	11AS01B	Month 4	15	12	80.00	51.91	95.67
		Month 12	15	8	53.33	26.59	78.73
	11AS01E	Month 4	19	16	84.21	60.42	96.62
		Month 12	19	13	68.42	43.45	87.42
	11AS02V	Month 4	18	14	77.78	52.36	93.59
		Month 12	18	10	55.56	30.76	78.47
	$10AlPO_4$	Month 4	20	14	70.00	45.72	88.11
		Month 12	20	10	50.00	27.20	72.80
	23PPV	Month 4	19	14	73.68	48.80	90.85
		Month 12	19	9	47.37	24.45	71.14
S Pneu. 23F IgG	11AS01B	Month 4	19	4	21.05	6.05	45.57
		Month 12	19	2	10.53	1.30	33.14
	11AS01E	Month 4	21	6	28.57	11.28	52.18
		Month 12	21	2	9.52	1.17	30.38
	11AS02V	Month 4	20	8	40.00	19.12	63.95
		Month 12	20	6	30.00	11.89	54.28

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				Post ≥ 5 μg/mL and Post / Pre ≥ 2			
						95% CI	
Serotypes	Group	Time	N	n	%	LL	UL
	10AlPO4	Month 4	23	7	30.43	13.21	52.92
		Month 12	23	6	26.09	10.23	48.41
	23PPV	Month 4	22	8	36.36	17.20	59.34
		Month 12	22	4	18.18	5.19	40.28
At least 6 out of 11	11AS01B	Month 4	20	6	30.00	11.89	54.28
		Month 12	20	1	5.00	0.13	24.87
	11AS01E	Month 4	21	11	52.38	29.78	74.29
		Month 12	21	6	28.57	11.28	52.18
	11AS02V	Month 4	21	9	42.86	21.82	65.98
		Month 12	21	4	19.05	5.45	41.91
	10AlPO4	Month 4	23	10	43.48	23.19	65.51
		Month 12	23	6	26.09	10.23	48.41
	23PPV	Month 4	22	7	31.82	13.86	54.87
		Month 12	22	4	18.18	5.19	40.28

11AS01B = 11PCV combined with AS01B
11AS01E = 11PCV combined with AS01E
11AS02V = 11PCV combined with AS02V
10AlPO4 = 10PCV combined with AlPO4
23PPV = 23-valent pneumococcal polysaccharide vaccine
N = number of subjects with available results
n/% = number/percentage of responders (post vaccination anti-PS antibody concentration ≥ 5μg/mL and fold increase Post/Pre (day 0) ≥ 2)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

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Table 3: Seropositivity rates and GMCs (ELISA) for anti-polysaccharides antibodies against 13 serotypes (ATP cohort for immune persistence)

				≥ 0.05 µg/mL				GMC				
						95% CI			95% CI		Titres	
Antibody	Group	Timing	N	n	%	LL	UL	Value	LL	UL	Min	Max
S Pneu. 1 IgG	11AS01B	Month 4	20	20	100	83.2	100	1.55	1.05	2.29	0.30	7.54
		Month 12	20	20	100	83.2	100	0.92	0.59	1.44	0.19	6.16
	11AS01E	Month 4	21	21	100	83.9	100	2.81	1.46	5.39	0.23	23.23
		Month 12	21	21	100	83.9	100	1.73	0.97	3.09	0.13	8.71
	11AS02V	Month 4	21	21	100	83.9	100	2.72	1.62	4.56	0.28	17.02
		Month 12	21	21	100	83.9	100	1.63	0.98	2.73	0.16	8.32
	$10AlPO_4$	Month 4	23	23	100	85.2	100	1.94	1.03	3.69	0.15	24.19
		Month 12	23	23	100	85.2	100	1.24	0.65	2.37	0.09	17.33
	23PPV	Month 4	22	22	100	84.6	100	5.31	2.42	11.68	0.13	62.90
		Month 12	22	22	100	84.6	100	3.66	1.66	8.10	0.15	50.24
S Pneu. 3 IgG	11AS01B	Month 4	20	20	100	83.2	100	0.83	0.57	1.20	0.16	2.80
		Month 12	20	20	100	83.2	100	0.50	0.28	0.91	0.07	20.44
	11AS01E	Month 4	21	21	100	83.9	100	0.99	0.64	1.53	0.28	5.10
		Month 12	21	21	100	83.9	100	0.64	0.40	1.02	0.15	4.48
	11AS02V	Month 4	21	21	100	83.9	100	1.20	0.78	1.86	0.14	9.29
		Month 12	20	20	100	83.2	100	0.72	0.41	1.28	0.07	10.10
	$10AlPO_4$	Month 4	22	18	81.8	59.7	94.8	0.20	0.11	0.38	<0.05	2.76
		Month 12	23	21	91.3	72.0	98.9	0.21	0.12	0.35	<0.05	2.57
	23PPV	Month 4	22	22	100	84.6	100	2.28	1.24	4.21	0.08	26.42
		Month 12	22	21	95.5	77.2	99.9	1.41	0.73	2.74	<0.05	17.52
S Pneu. 4 IgG	11AS01B	Month 4	20	20	100	83.2	100	3.72	2.13	6.52	0.80	187.18
		Month 12	19	19	100	82.4	100	1.65	0.90	3.03	0.32	48.59
	11AS01E	Month 4	21	21	100	83.9	100	5.85	3.45	9.93	0.95	32.18
		Month 12	21	21	100	83.9	100	3.55	2.14	5.89	0.65	14.88
	11AS02V	Month 4	21	21	100	83.9	100	4.24	2.50	7.20	1.00	50.42
		Month 12	21	21	100	83.9	100	2.21	1.26	3.86	0.31	37.37
	$10AlPO_4$	Month 4	23	23	100	85.2	100	5.05	3.09	8.27	0.38	46.48
		Month 12	23	23	100	85.2	100	3.38	2.06	5.56	0.19	20.67

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				≥ 0.05 µg/mL				GMC				
						95% CI			95% CI		Titres	
Antibody	Group	Timing	N	n	%	LL	UL	Value	LL	UL	Min	Max
	23PPV	Month 4	22	22	100	84.6	100	2.77	1.41	5.45	0.15	47.88
		Month 12	22	22	100	84.6	100	1.95	1.02	3.75	0.08	18.03
S Pneu. 5 IgG	11AS01B	Month 4	20	20	100	83.2	100	4.72	2.31	9.65	0.37	66.85
		Month 12	20	20	100	83.2	100	2.20	1.03	4.71	0.10	33.29
	11AS01E	Month 4	21	21	100	83.9	100	5.48	2.84	10.56	0.30	51.18
		Month 12	21	21	100	83.9	100	3.14	1.78	5.53	0.37	24.42
	11AS02V	Month 4	21	21	100	83.9	100	4.53	2.48	8.28	0.24	71.74
		Month 12	21	21	100	83.9	100	2.21	1.20	4.07	0.16	37.41
	$10AlPO_4$	Month 4	23	23	100	85.2	100	6.77	3.03	15.13	0.14	120.55
		Month 12	23	23	100	85.2	100	3.63	1.59	8.26	0.08	87.72
	23PPV	Month 4	22	22	100	84.6	100	5.27	2.20	12.67	0.35	348.79
		Month 12	22	22	100	84.6	100	3.56	1.48	8.56	0.20	199.12
S Pneu. 6B IgG	11AS01B	Month 4	20	20	100	83.2	100	2.07	1.10	3.89	0.12	16.27
		Month 12	20	19	95.0	75.1	99.9	1.42	0.70	2.90	<0.05	11.47
	11AS01E	Month 4	21	21	100	83.9	100	3.16	1.98	5.07	0.36	16.25
		Month 12	21	21	100	83.9	100	2.12	1.32	3.38	0.29	8.85
	11AS02V	Month 4	21	21	100	83.9	100	2.83	1.48	5.42	0.06	15.12
		Month 12	21	21	100	83.9	100	1.77	0.90	3.49	0.06	9.57
	$10AlPO_4$	Month 4	23	22	95.7	78.1	99.9	2.60	1.19	5.67	<0.05	32.84
		Month 12	23	22	95.7	78.1	99.9	1.71	0.81	3.61	<0.05	26.05
	23PPV	Month 4	22	22	100	84.6	100	1.63	0.79	3.37	0.10	76.71
		Month 12	22	21	95.5	77.2	99.9	1.00	0.47	2.16	<0.05	27.49
S Pneu. 7F IgG	11AS01B	Month 4	20	20	100	83.2	100	7.02	3.77	13.05	0.97	193.92
		Month 12	20	20	100	83.2	100	4.23	2.35	7.62	0.59	121.67
	11AS01E	Month 4	21	21	100	83.9	100	7.04	4.25	11.66	0.43	37.89
		Month 12	21	21	100	83.9	100	4.12	2.52	6.74	0.33	19.82
	11AS02V	Month 4	21	21	100	83.9	100	4.76	3.01	7.52	0.52	28.63
		Month 12	21	21	100	83.9	100	3.00	1.89	4.77	0.29	13.27
	$10AlPO_4$	Month 4	23	23	100	85.2	100	4.65	2.57	8.41	0.13	72.04
		Month 12	23	23	100	85.2	100	2.81	1.58	4.98	0.11	30.69
	23PPV	Month 4	22	22	100	84.6	100	5.41	2.50	11.70	0.29	157.59
		Month 12	22	22	100	84.6	100	4.05	1.94	8.44	0.35	109.16
S Pneu. 9V IgG	11AS01B	Month 4	20	20	100	83.2	100	2.58	1.61	4.13	0.57	20.40
		Month 12	20	20	100	83.2	100	2.03	1.35	3.05	0.45	9.48
	11AS01E	Month 4	21	21	100	83.9	100	6.59	4.29	10.14	0.73	38.57
		Month 12	21	21	100	83.9	100	4.09	2.87	5.83	0.83	23.58
	11AS02V	Month 4	21	21	100	83.9	100	3.90	1.85	8.23	0.11	47.12
		Month 12	21	21	100	83.9	100	2.68	1.40	5.13	0.07	23.00

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				≥ 0.05 µg/mL				GMC				
						95% CI			95% CI		Titres	
Antibody	Group	Timing	N	n	%	LL	UL	Value	LL	UL	Min	Max
	10AlPO4	Month 4	23	23	100	85.2	100	3.60	2.05	6.32	0.30	45.43
		Month 12	23	23	100	85.2	100	2.67	1.59	4.50	0.31	35.03
	23PPV	Month 4	22	22	100	84.6	100	3.45	1.69	7.05	0.16	40.18
		Month 12	22	22	100	84.6	100	2.92	1.47	5.79	0.13	33.96
S Pneu. 14 IgG	11AS01B	Month 4	20	20	100	83.2	100	10.44	6.19	17.61	0.64	49.32
		Month 12	20	20	100	83.2	100	8.42	5.11	13.86	0.80	33.33
	11AS01E	Month 4	21	21	100	83.9	100	13.49	7.39	24.62	1.69	225.56
		Month 12	21	21	100	83.9	100	11.25	6.69	18.90	1.77	105.70
	11AS02V	Month 4	21	21	100	83.9	100	14.17	9.52	21.10	4.13	58.16
		Month 12	21	21	100	83.9	100	10.66	7.53	15.10	3.28	34.29
	10AlPO4	Month 4	23	23	100	85.2	100	10.31	5.62	18.93	0.73	126.49
		Month 12	23	23	100	85.2	100	7.57	4.22	13.58	0.38	71.26
	23PPV	Month 4	22	22	100	84.6	100	20.95	10.51	41.75	0.63	154.95
		Month 12	22	22	100	84.6	100	16.50	8.63	31.53	0.54	117.87
S Pneu. 18C IgG	11AS01B	Month 4	20	20	100	83.2	100	25.05	14.41	43.54	5.42	598.10
		Month 12	20	20	100	83.2	100	18.37	10.77	31.31	3.17	395.46
	11AS01E	Month 4	21	21	100	83.9	100	36.21	22.09	59.34	3.13	328.35
		Month 12	21	21	100	83.9	100	24.32	15.70	37.67	2.98	126.46
	11AS02V	Month 4	21	21	100	83.9	100	50.95	37.13	69.92	14.85	217.42
		Month 12	21	21	100	83.9	100	28.31	19.60	40.90	4.57	169.42
	10AlPO4	Month 4	23	23	100	85.2	100	18.56	11.36	30.34	3.46	157.85
		Month 12	23	23	100	85.2	100	12.11	7.12	20.59	2.44	235.99
	23PPV	Month 4	22	22	100	84.6	100	8.59	4.63	15.93	0.72	90.88
		Month 12	22	22	100	84.6	100	6.28	3.55	11.12	0.76	80.96
S Pneu. 19F IgG	11AS01B	Month 4	20	20	100	83.2	100	20.47	8.24	50.88	0.28	385.18
		Month 12	20	20	100	83.2	100	10.69	4.90	23.31	0.23	116.07
	11AS01E	Month 4	21	21	100	83.9	100	22.01	12.24	39.56	0.73	131.49
		Month 12	21	21	100	83.9	100	10.22	5.91	17.67	0.74	66.79
	11AS02V	Month 4	21	21	100	83.9	100	25.44	12.79	50.61	1.51	459.05
		Month 12	21	21	100	83.9	100	11.80	6.32	22.04	0.75	174.84
	10AlPO4	Month 4	23	23	100	85.2	100	10.85	5.31	22.18	0.38	393.07
		Month 12	23	23	100	85.2	100	6.00	3.09	11.65	0.28	178.79
	23PPV	Month 4	22	22	100	84.6	100	10.79	5.65	20.60	0.50	268.06
		Month 12	22	22	100	84.6	100	6.45	3.53	11.79	0.32	69.11
S Pneu. 23F IgG	11AS01B	Month 4	20	20	100	83.2	100	2.42	1.33	4.41	0.17	38.38
		Month 12	20	20	100	83.2	100	1.51	0.84	2.72	0.13	28.03
	11AS01E	Month 4	21	21	100	83.9	100	4.57	2.66	7.86	0.19	37.38
		Month 12	21	21	100	83.9	100	2.74	1.64	4.56	0.23	26.24

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				≥ 0.05 µg/mL				GMC				
						95% CI			95% CI		Titres	
Antibody	Group	Timing	N	n	%	LL	UL	Value	LL	UL	Min	Max
	11AS02V	Month 4	21	21	100	83.9	100	4.58	2.39	8.76	0.21	41.53
		Month 12	21	21	100	83.9	100	2.92	1.59	5.37	0.10	18.95
	10AlPO$_4$	Month 4	23	23	100	85.2	100	3.61	2.13	6.13	0.22	33.85
		Month 12	23	23	100	85.2	100	2.83	1.69	4.76	0.20	43.13
	23PPV	Month 4	22	21	95.5	77.2	99.9	1.98	0.85	4.63	<0.05	33.89
		Month 12	22	21	95.5	77.2	99.9	1.31	0.58	2.95	<0.05	30.74
S Pneu. 19A IgG	11AS01B	Month 4	20	20	100	83.2	100	7.03	3.26	15.14	0.15	73.37
		Month 12	20	20	100	83.2	100	4.98	2.43	10.24	0.21	53.68
	11AS01E	Month 4	21	21	100	83.9	100	8.79	5.45	14.17	0.79	76.95
		Month 12	21	21	100	83.9	100	6.65	4.37	10.12	1.03	53.82
	11AS02V	Month 4	21	21	100	83.9	100	6.71	3.70	12.18	0.89	94.03
		Month 12	21	21	100	83.9	100	5.18	3.04	8.81	0.96	50.60
	10AlPO$_4$	Month 4	23	23	100	85.2	100	4.14	2.37	7.24	0.22	25.93
		Month 12	23	23	100	85.2	100	3.36	1.92	5.86	0.22	34.63
	23PPV	Month 4	22	22	100	84.6	100	7.50	4.60	12.25	1.26	100.11
		Month 12	22	22	100	84.6	100	5.55	3.46	8.91	1.01	66.07
S Pneu. 6A IgG	11AS01B	Month 4	20	20	100	83.2	100	1.55	0.76	3.13	0.06	46.79
		Month 12	20	20	100	83.2	100	1.64	0.87	3.11	0.06	21.25
	11AS01E	Month 4	21	21	100	83.9	100	2.15	1.21	3.80	0.19	25.69
		Month 12	21	21	100	83.9	100	2.01	1.04	3.89	0.14	14.98
	11AS02V	Month 4	21	21	100	83.9	100	1.83	1.12	3.00	0.15	8.25
		Month 12	21	21	100	83.9	100	1.65	0.88	3.11	0.06	9.70
	10AlPO$_4$	Month 4	23	23	100	85.2	100	1.76	0.89	3.48	0.10	19.51
		Month 12	23	23	100	85.2	100	1.74	0.84	3.60	0.05	21.50
	23PPV	Month 4	22	21	95.5	77.2	99.9	1.23	0.51	3.00	<0.05	52.80
		Month 12	22	21	95.5	77.2	99.9	1.20	0.48	2.99	<0.05	28.49

11AS01B = 11PCV combined with AS01B
11AS01E = 11PCV combined with AS01E
11AS02V = 11PCV combined with AS02V
10AlPO$_4$ = 10PCV combined with AlPO$_4$
23PPV = 23-valent pneumococcal polysaccharide vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration ≥ 0.05 µg/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum

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Table 4: Seropositivity rates and GMCs (ELISA) for anti-protein D antibodies (ATP cohort for immune persistence)

				≥ 100 ELU/mL				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	Value	LL	UL	Min	Max
HI NTHI.PD AB	11AS01B	Month 4	18	18	100	81.5	100	995.5	680.8	1455.7	393.0	5624.0
		Month 12	20	18	90.0	68.3	98.8	366.6	228.0	589.2	<100.0	1620.0
	11AS01E	Month 4	18	18	100	81.5	100	640.8	433.1	948.0	156.0	5041.0
		Month 12	21	18	85.7	63.7	97.0	291.0	179.1	472.5	<100.0	2874.0
	11AS02V	Month 4	20	20	100	83.2	100	732.0	548.1	977.6	237.0	1821.0
		Month 12	19	17	89.5	66.9	98.7	298.2	193.7	458.9	<100.0	1731.0
	$10AlPO_4$	Month 4	22	21	95.5	77.2	99.9	705.9	421.1	1183.3	<100.0	13658.0
		Month 12	23	17	73.9	51.6	89.8	340.9	177.9	653.2	<100.0	10764.0

11AS01B = 11PCV combined with AS01B
11AS01E = 11PCV combined with AS01E
11AS02V = 11PCV combined with AS02V
$10AlPO_4$ = 10PCV combined with $AlPO_4$
23PPV = 23-valent pneumococcal polysaccharide vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum

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Table 5: Seropositivity rates and GMCs (ELISA) for anti-tetanus toxoid antibodies (ATP cohort for immune persistence)

				≥ 0.1 IU/mL				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	Value	LL	UL	Min	Max
C TETANI. TOX IgG	11AS01B	Month 4	20	20	100	83.2	100	2.4	1.5	4.0	0.3	11.3
		Month 12	20	20	100	83.2	100	1.0	0.5	1.9	0.1	8.0
	11AS01E	Month 4	21	21	100	83.9	100	3.0	1.8	5.0	0.2	18.0
		Month 12	21	20	95.2	76.2	99.9	1.3	0.7	2.4	<0.1	9.5
	11AS02V	Month 4	21	21	100	83.9	100	3.7	1.7	8.0	0.1	54.8
		Month 12	21	17	81.0	58.1	94.6	1.6	0.6	4.1	<0.1	35.8
	$10AlPO_4$	Month 4	23	23	100	85.2	100	2.5	1.4	4.3	0.1	16.4
		Month 12	23	22	95.7	78.1	99.9	1.4	0.7	2.6	<0.1	10.2

11AS01B = 11PCV combined with AS01B
11AS01E = 11PCV combined with AS01E
11AS02V = 11PCV combined with AS02V
$10AlPO_4$ = 10PCV combined with $AlPO_4$
23PPV = 23-valent pneumococcal polysaccharide vaccine
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum

Table 6: Seropositivity rates and GMCs (ELISA) for anti-diphteria toxoid antibodies (ATP cohort for immune persistence)

				≥ 0.1 IU/mL				GMC				
						95% CI						
Antibody	Group	Timing	N	n	%	LL	UL	Value	LL	UL	Min	Max
C DIPHT. TOX IgG	11AS01B	Month 4	20	17	85.0	62.1	96.8	0.5	0.2	1.2	<0.1	44.2
		Month 12	19	11	57.9	33.5	79.7	0.3	0.1	0.6	<0.1	18.0
	11AS01E	Month 4	21	12	57.1	34.0	78.2	0.2	0.1	0.5	<0.1	4.4
		Month 12	21	11	52.4	29.8	74.3	0.2	0.1	0.3	<0.1	2.7
	11AS02V	Month 4	21	16	76.2	52.8	91.8	0.4	0.2	0.7	<0.1	3.3
		Month 12	21	15	71.4	47.8	88.7	0.2	0.1	0.4	<0.1	1.1
	$10AlPO_4$	Month 4	23	17	73.9	51.6	89.8	0.3	0.1	0.5	<0.1	3.6
		Month 12	23	12	52.2	30.6	73.2	0.2	0.1	0.3	<0.1	2.3

11AS01B = 11PCV combined with AS01B
11AS01E = 11PCV combined with AS01E
11AS02V = 11PCV combined with AS02V
$10AlPO_4$ = 10PCV combined with $AlPO_4$
23PPV = 23-valent pneumococcal polysaccharide vaccine

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GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum

Safety /reactogenicity:

Serious adverse events:

SAEs that occurred from Month 4 to 12 were recorded for the Belgian subjects. A list of SAEs is presented in Supplement 7. All subjects were followed for SAEs during the entire study period.
4 subjects reported 4 SAEs, (1 subject in the 23 PPV group, 1 subject in the 11AS01B group, 1 subject in the 11AS01E group, and 1 subjects in the 11AS02V group), none of which were considered to be causally related to vaccination.

[redacted]

In Finland and Sweden accounting for 227 vaccinated subjects, late SAEs were reported after the visit at Month 4. These late SAEs are presented in Supplement 8.
5 subjects reported 6 SAEs, (1 subject in the 23 PPV group, 2 subjects in the 11AS01E group, and 2 subjects in the $10AlPO_4$ group), none of which were considered to be causally related to vaccination.

[redacted]

Conclusions:

Due to the small sample size, data provided in this annex report should be interpreted with caution. All analyses were descriptive. Results suggest that the highest percentages of responders at Month 12 were observed for the pneumococcal serotypes 14, 18C, and 19F. The serotypes 1, 4, 5, 6B, 7F, 9V, and 23F had moderate percentages of responders. At Month 12, percentage of responders to at least 6 serotypes of the 11 was 5% for group 11AS01B, 28.6% for group 11AS01E, 19.1% for group 11AS02V, 26.1% for $10AlPO_4$, and 18.2% for group 23PPV.

At Month 12, most subjects (91.3% to 100%, depending on the serotype) were seropositive for anti-PS antibodies against 13 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F, 6A, 19A).

Seropositivity rates for anti-protein D antibodies, anti-tetanus toxoid antibodies, anti-diphtheria toxoid antibodies were immunologically similar between the three 11PCV groups and the $10AlPO_4$ group.

In Belgium, 4 subjects out of 107 reported 4 SAEs and in Finland and Sweden, 5 subjects out of 227 reported 6 SAEs. None of these SAEs were considered to be causally related to vaccination.

Date of report: 01 October 2008.

SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** 11PCV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study : A phase I/II, randomized, observer blinded study to evaluate and compare the safety, reactogenicity and immunogenicity of various formulations of the GlaxoSmithKline Biologicals' adjuvanted 11-valent pneumococcal conjugate vaccine versus the licensed single-dose 23-valent pneumococcal polysaccharide vaccine and GlaxoSmithKline Biologicals' aluminium-based 10-valent pneumococcal conjugate vaccine, in healthy elderly subjects.
Study: 106072 (STREP-ELD-011 EXT 010 Y1)

Rationale for the Annex Report 2: The primary study STREP-ELD-010 (106068) was conducted in three centres (Belgium, Sweden and Finland). In the primary report of this study, dated 05 November 2007, the safety, reactogenicity, and immunogenicity up to Month 4 (i.e. 1 month Post-vaccination) of the GSK Biologicals candidate 11-valent pneumococcal conjugate vaccine (11PCV) combined with different adjuvants (AS01B, AS01E, or AS02V) in healthy adults aged 65 years or above were assessed. The safety profile and the immune response to one and two doses of these formulations were evaluated in comparison to 23-valent pneumococcal polysaccharide vaccine (23PPV) and GSK Biologicals 10-valent pneumococcal conjugate vaccine adjuvanted with $AlPO_4$.

Study 106072 (STREP-ELD-011 EXT 010 Y1) was the Month 12 (i.e. 9 months Post-vaccination) follow-up of the study 106068 (STREP-ELD-010) in one centre (Belgium). In order to evaluate the persistence of the immune response induced by two doses of 11PCV combined with different adjuvants (AS01B, AS01E, or AS02V), blood samples were taken at Month 12 in a cohort of subjects. Enzyme-linked immunosorbant assay (ELISA) results up to Month 12 were presented for this cohort in the Annex Report 1. Safety results in terms of Serious Adverse Events (SAEs) reporting from Month 4 to Month 12 for all subjects enrolled in study STREP-ELD-010 (106068) were also presented in the Annex Report 1 (See STREP-ELD-011 EXT 010 Y1 [106072] Annex 1 Report for details). In Sweden and Finland, the reporting of the SAEs during the 9 months period after the last vaccine dose was not done through active collection at Visit 5 (Month 12 visit, i.e. 9 months Post-vaccination), as this Visit 5 did not take place for these subjects. Only SAEs which were spontaneously reported by the subjects were collected and reported.

The results of opsonophagocytic activity (OPA), haematological and biochemical results, for samples taken at Month 12 (i.e. 9 months Post-vaccination) are now presented in this second Annex Report.

As no adjuvant effect was observed on T-cell response in study STREP-ELD-010 (106068), the following immunological tests planned per protocol were not performed at Month 12 (study STREP-ELD-011 EXT 010 Y1[106072]):

- The frequency of gamma class immunoglobulin (IgG) polysaccharides (PS) specific plasma cells generated by in vitro cultivated memory B-cells, measured by enzyme-linked immunospot (ELISPOT)
- The frequency of IgG protein D-specific plasma cells generated by in vitro cultivated memory B cells, measured by ELISPOT.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** 11PCV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- The frequencies of cluster differentiation 4^+ and 8^+ ($CD4^+$ and $CD8^+$) T cells with antigen-specific interleukin-2 (IL-2), interferon-γ (IFN-γ), tumour necrosis factors-α (TNF-α), and/or cluster of differentiation 40 ligand (CD40L) secretion/expression to protein D as determined by intracellular cytokine staining.

Principal investigator for the study:
- Prof. Dr. [redacted] Belgium)

Study centre:
The STREP-ELD-011 EXT 010 Y1(106072) study was conducted in one centre (Belgium):
- [redacted] Belgium

Publication (reference):
Not published as of 13 May 2009

Study period: Study initiation date: 10 May 2007 Study completion date: 18 September 2007 Data lock point: 02 March 2009	**Clinical phase: I/II**

Objectives:
The objectives of the primary study can be found in the primary study report 106068 (STREP-ELD-010).

The study objectives covered in the Annex Report 1 can be found in Annex 1 study report 106072 (STREP-ELD-011 EXT 010 Y1).

The objectives pertaining to Month 12 and reported in this Annex 2 report were:

- To evaluate the safety as measured by routine haematological and biochemical parameters in each group.
- To evaluate humoral immune response at Month 12 in each group.

Study design:
This primary study was a phase I/II, observer blind, multicentre, multicountry, randomized controlled study with five parallel groups.
- 11PCV/AS01B group: GSK Biologicals 11PCV combined with adjuvant AS01B.
- 11PCV/AS01E group: GSK Biologicals 11PCV combined with adjuvant AS01E.
- 11PCV/AS02V group: GSK Biologicals 11PCV combined with adjuvant AS02V.
- 23PPV group: 23PPV (*Pneumovax* 23, control)
- 10PCV/$AlPO_4$ group: GSK Biologicals 10PCV adjuvanted with $AlPO_4$ (control)

In the 4 groups receiving GSK Biologicals' vaccines, each subject received 2 doses of vaccine at Month 0 and 3. For the group receiving 23PPV, subjects received 1 dose of vaccine at Month 0 and 1 dose of placebo at Month 3. Blood samples were taken at Months 0, 1, 3, and 4 (results for these blood samples were presented in the primary study report 106068 [STREP-ELD-010]). One additional blood sample was collected at Month 12 for subjects enrolled at the Belgian site.

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Number of subjects:
Planned: In this annex report, only subjects enrolled in the Belgian site were assessed. In the primary study 106068 (STREP-ELD-010), 108 subjects were enrolled in the Belgian site and participated to the STREP-ELD-011 EXT 010 Y1 follow-up study.
Enrolled and completed: 107 in total (20 subjects in 11PCV/AS01B; 21 subjects in 11PCV/AS01E; 21 subjects in 11PCV/AS02V; 23 subjects in 10PCV/$AlPO_4$; 22 subjects in 23PPV).
Safety (Total Vaccinated cohort [TVC]) and *Immunogenicity* (According-to-Protocol [ATP]): 107 in total (20 subjects in 11PCV/AS01B; 21 subjects in 11PCV/AS01E; 21 subjects in 11PCV/AS02V; 23 subjects in 10PCV/$AlPO_4$; 22 subjects in 23PPV).

Diagnosis and criteria for inclusion:
Elderly subjects aged between 65 and 85 years old, in good general health at the time of the first vaccination. Subjects that had never been vaccinated with the 23PPV or any other vaccine against *Streptococcus pneumoniae*. See primary report 106068 (STREP-ELD-010) for details.

Study vaccine, dose, mode of administration, lot no.:
No vaccine was given during the follow-up period, see the primary report 106068 (STREP-ELD-010) for the details regarding the vaccination schedule and composition.

Duration of treatment:
The subject follow-up duration was approximately 12 months for each subject in the Belgian site.

Criteria for evaluation:
The following results were discussed in this Annex Report 2:
Immunogenicity:
The opsonophagocytic activity titres against pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) was determined in all groups, at Month 12 (i.e. 9 months Post-vaccination). The cut-off value for the OPA assay was 8 dilutions for 50% killing.
Safety:
Hematological and biochemical levels within or outside the normal ranges at Month 12.

Statistical methods:
Analyses were performed as per protocol.
For OPA data, seropositivity rates and the geometric mean titres (GMTs) with 95% confidence interval (CI) were tabulated per group and per serotype, at the assessed time point.
In addition, stratified analyses by age group (< 70 year olds versus ≥ 70 year olds) were performed.
For each laboratory parameter, the number and percentage of subjects with levels below, within and above normal range were tabulated per group, at the assessed time point. The number and percentage of subjects in each study group who fell into the categories (below, within and above normal range) at any assessment were cross-tabulated with their baseline category.
Haematological and biochemical levels of each laboratory parameter were summarized per group.

Changes in planned analysis:
As no adjuvant effect was observed on T-cell response in study STREP-ELD-010 (106068), the cell-mediated immunity test were not performed at Month 12 (STREP-ELD-011 EXT 010 Y1 [106072]).

Protocol Amendments
See primary report for details (Amendment: 01 June 2007)

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** **Name of active substance:** 11PCV	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Results

Demography

See Annex 1 STREP-ELD-011 EXT 010 Y1 (106072) for details

Immunogenicity:

Opsonophagocytic activity

- Geometric mean titres (GMTs) and seropositivity rates for opsonophagocytic antibody titres against 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) were tabulated per group, with 95% CI, overall in Supplement 1 and by age categories (<70 years old, ≥ 70 years old) in Supplement 2.
- At Month 12, depending on the serotype, 55 to 100% of the subjects had antibody titres≥1:8, with the exception of the serotype 3 (8.7% of the subjects with antibody titres ≥1:8) in the 10PCV group whose vaccine did not contain this serotype.
- Overall, GMTs tended to decrease from Month 4 (i.e. 1 month Post-vaccination) to Month 12 (i.e. 9 months Post-vaccination). As in the primary phase, GMTs tended to be superior for serotype 18C and to a lesser extent for serotype 19F, when comparing the 11PCV formulations groups to the 23PPV group. The anti-18C GMT was 7-12 fold higher, whilst the anti-19F GMT was 1.5-2.7 fold higher. When compared to the 10PCV group, the GMT of the 11PCV vaccine formulation groups also tended to be higher for serotypes 18C and 19F. For the other serotypes, GMTs remained in the same range across all groups.

Safety

Serious Adverse Events

See Annex 1 STREP-ELD-011 EXT 010 Y1 (106072) for details on Serious Adverse Events until Month 12.

Haematology / Biochemistry

- Refer to the Supplement 3 for the distribution of haematology and biochemistry with respect to normal ranges Post Dose 2 (Month 12).
- Refer to the Supplement 4 for the change from baseline for haematology and biochemistry with respect to normal range.
- Refer to Supplement 5 for the haematological and biochemical levels in the study centre.
- No clinically significant increase in the haematology and biochemistry levels was observed at Month 12. Overall, these levels remained in the same ranges across all groups.

Conclusions:

- Overall, the results at Month 12 indicated that the opsonophagocytic activity persisted whilst decreasing from Month 4 to Month12. For the Serotype 18C and to a lesser extent serotype 19F, persistence was better in the 11 PCV groups than in the two control groups (10PCV and 23PPV).
- No clinically significant increase in the haematology and biochemistry levels was observed at Month 12. Overall, these levels remained in the same ranges across all groups.

Date of Annex Report 2: 13 May 2009