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: An open, phase I/II study to evaluate the safety, reactogenicity and immunogenicity of GSK Biologicals' 11PCV combined with adjuvant AS02V given as a 2-dose vaccination in adults aged 18-40 years old.

Principal Investigator:
This study was conducted by one investigator in Belgium: Prof. Dr. [redacted] Belgium.

Study Centre(s):
[redacted] Belgium.

Publication (reference):
Not published as of October 2007.

Study period:	**Clinical phase:**
Study Initiation Date: 01 June 2006 Study Completion Date: 06 October 2006	**I/II**

Objectives:
Primary:

- To assess in healthy adult subjects the safety and reactogenicity of the 11PCV adjuvanted with AS02V, given as a 2-dose vaccination 3 months apart.
- To evaluate the B-cell memory response to 11 polysaccharides in all subjects, before vaccination 1, 1 month post vaccination 1, 2 weeks and 1 month post vaccination 2.

Exploratory:

- To evaluate the B-cell memory response to NTHi protein D in all subjects, before vaccination 1, 1 month post vaccination 1, 2 weeks and 1 month post vaccination 2.
- To evaluate the T-cell response to NTHi protein D in all subjects, before vaccination 1, 1 month post vaccination 1, 2 weeks and 1 month post vaccination 2.

Study design:
This was an open blinded, non-randomized study with a single group containing 10 subjects. The subjects received two doses vaccination of the GSK Biologicals' 11PCV combined with adjuvant AS02V at Month 0 and Month 3. Blood samples were taken at Months 0, 1, 3, 3.5, and 4 (5 blood samples in total).

Number of subjects:
Planned: 10 subjects in one group
Enrolled: 10 subjects in one group
Completed: 10 subjects in one group
Safety: Total vaccinated cohort - 10 subjects in one group
Immunogenicity: Total vaccinated cohort - 10 subjects in one group

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Diagnosis and criteria for inclusion:
The subjects were adults aged between 18 and 40 years old in good general health at the time of the first vaccine dose and that had never been vaccinated with the 23-valent pneumococcal polysaccharide vaccine or any other vaccination against *Streptococcus pneumoniae.*

Study vaccine, dose, mode of administration, lot no:
Vaccination schedule/site:
At Day 0 and Month 3, all subjects received one dose of the 11PCV adjuvanted candidate vaccine via an intramuscular injection into the deltoid muscle of the non-dominant arm.
Vaccine composition/ dose/ lot number:
The GSK Biologicals' adjuvanted 11-valent pneumococcal conjugate vaccine (11PCV/AS02V) was composed as followed:

- **11PCV** (lot number: DSPNA024A) containing:
  Protein D carrier: 1 µg of each PS for serotypes 1, 3, 5, 6B, 7F, 9V, 14 and 23F and 3 µg for serotype 4 conjugated to PD.
  Tetanus toxoid carrier with AH spacer: 3 µg of capsular PS of serotypes 18C conjugated to TTAH.
  Diphtheria toxoid: 3 µg of capsular PS of serotype 19F conjugated to DT.
- **AS02V** (500µl) (lot number: DA2VA002A) containing:
  MPL and QS21, and oil in water emulsion.
- No preservative.

Reference vaccine, dose and mode of administration, lot no.:
No reference vaccines were administered in this study.

Duration of treatment:
The duration of study was approximately 4 months from the first vaccination for each subject.

Criteria for evaluation:
Immunogenicity:

- The frequency of PS-specific memory B cells measured in vitro by B-cell ELISPOT assay for 11 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) in all subjects before vaccination 1, one month post vaccination 1, 2 weeks and one month post vaccination 2.
- The frequency of protein D specific B-cell memory was measured by in vitro cultivated memory B-cells (measured by B-cell ELISPOT) in all subjects before vaccination 1, one month post vaccination 1, 2 weeks and one month post vaccination 2.
- The cell-mediated immunity was assessed by the determination of the frequency of CD4+ and CD8+ T-Cells to NTHi protein D by the intracellular cytokine staining assay (ICS) in all subjects before vaccination 1, one month post vaccination 1, 2 weeks and one month post vaccination 2.

Safety:
Occurrence, intensity and relationship to vaccination of

- Any solicited local and general signs and symptoms during a 7-day follow up period (i.e. day of vaccination and 6 subsequent days) after each vaccine dose.
- Unsolicited local and general signs and symptoms during a 31-day follow up period (i.e. day of vaccination and 30 subsequent days) after each vaccine dose.

Occurrence and relationship to vaccination of all serious adverse events (SAEs) occurring throughout the study period.

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Statistical methods:

Analyses were performed as per protocol. As none of the subjects were eliminated from the ATP cohorts, all statistical analyses were performed on the Total vaccinated cohort.

Analysis of immunogenicity

The primary analysis for immunogenicity was performed on the Total Vaccinated cohort.

ELISPOT data

Frequency of PS-specific plasma cells and NTHi protein D-specific plasma cells were summarized at each assessed time point.

ICS data

At each assessed time point, the following parameters were tabulated per treatment group:
the frequency of protein D specific CD4/CD8 T-lymphocytes per 10^6 producing at least

- two different cytokines (IL-2, IFN-γ, TNF-α, CD40L)
- IL-2 and another cytokine (IFN-γ, TNF-α, CD40L)
- IFN-γ and another cytokine (IL-2, TNF-α, CD40L)
- TNF-α and another cytokine (IL-2, IFN-γ, CD40L)
- CD40L and another cytokine (IL-2, IFN-γ, TNF-α).

Analysis of safety.

The primary analysis for safety was performed on the Total Vaccinated cohort.
The following adverse events were tabulated per treatment group:

- The percentage of subjects with at least one local adverse event (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any adverse event during the solicited follow-up period, with exact 95% CI after each vaccine dose and overall.
- The percentage of doses followed by at least one local adverse event (solicited and unsolicited), by at least one general adverse event (solicited and unsolicited) and by any adverse event, over the whole vaccination course, with exact 95% CI.
- The percentage of subjects reporting each individual solicited local and general adverse event during the solicited follow-up period, with exact 95% CI.
- The percentage of doses followed by each individual solicited local and general adverse event, over the whole vaccination course, with exact 95% CI.
- The percentage of subjects with at least one report of unsolicited adverse event classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after each vaccination, with exact 95% CI.

Similar tabulations were done for grade 3 adverse events and/or for adverse events with relationship to vaccination. Serious adverse events and withdrawals due to adverse events were described in detail.

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Summary:

Demography Results:

The mean age at the first time of vaccination was 24.9 years old, there were more male subjects than female subjects and the population was of white/Caucasian origin.

Immunogenicity Results:

The first vaccination induced a 2-7 fold increase in PS-specific responses in most serotypes. An increase was observed post vaccination dose 2 versus post dose 1, for all serotypes. A peak response was observed at 15 days post dose 2 (Month 3.5) and then generally the memory B cell response waned 1 month post dose 2 (Month 4).

The frequency of protein D-specific memory B cells pre vaccination (Month 0) was low. The first vaccination induced a low response. The second vaccination induced a boost of the response, which peaked at Month 3.5 and then decreased at Month 4.

The frequency of NTHi protein D-specific CD4 T-lymphocytes pre vaccination was low. The first vaccination increased slightly the response at Month 1. The second vaccination induced a transient further increase of the response at Month 3.5 which then waned at Month 4. No CD8 response was detected.

Safety Results:

The safety analysis was performed on the Total vaccinated cohort.

The vaccine formulation was safe.

Pain was the most frequent solicited local symptom. Overall, 100% of subjects reported pain, 40% of subjects reported swelling and 30% reported redness. 2/10 subjects reported grade 3 pain lasting less than 2 days after each dose, 1 subject reported grade 3 swelling after each dose lasting less than 2 days and 1 subject reported grade 3 redness after dose 1.

The most frequent solicited general symptoms reported (overall/subject) were headache (90%) followed by myalgia, malaise and fatigue (all 80%). Few subjects report grade 3 general symptoms: 1 reported grade 3 fever, 1 reported grade 3 headache and 1 reported grade 3 myalgia.

No increase in incidence rates of solicited symptoms was seen after the second dose compared to the first dose.

7 subjects reported unsolicited adverse events with a causal relationship to vaccination. The most frequently report unsolicited adverse event was chills that were reported by 30% of subjects.

Only one subject reported a grade 3 unsolicited adverse event (chills) after dose 1, that was reported as causally related to vaccination.

Serious Adverse Events:

[redacted]

No subjects died from a SAE.

Withdrawals due to adverse events/serious adverse events:

No subjects withdrew from the study due to SAEs and AEs.

Pregnancies:

No pregnancies occurred during the trial.

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Conclusion(s):

This study was performed to assess the safety of an adjuvanted conjugate pneumococcal polysaccharide vaccine in young healthy adults and to validate an ELISPOT assay to measure the B Memory response to the polysaccharides. Additional testing was also performed.

All subjects reported pain at the injection site but the other symptoms were less frequently reported and few were grade 3. Only 2/10 subjects reported grade 3 pain after each dose, all lasting 2 days or less. No subject withdrew from the study. The vaccine formulation was safe.

The first vaccination induced a 2-7 fold increase in PS-specific responses in most serotypes. An increase was observed post vaccination dose 2 versus post dose 1, for all serotypes. A peak response was observed at 15 days post dose 2 and then generally the memory B cell response waned 1 month post dose 2.

The memory B cell and CD4+ T cell responses to protein D were weak but also maximum at 2 weeks post second vaccination.

Date of report: October 2007