SYNOPSIS

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

Title of the study	A double-blind comparative and randomised study in healthy adults of safety, tolerability, and immunogenicity of PNEUMOVAX® II formulated with either all new process polysaccharides or all current process polysaccharides Study Identification Number: U05-PnPS-403 EudraCT number: 2005-002789-12	
Principal investigator	Stuart J MAIR, MBChB, DRCOG, DCPSA (United Kingdom)	
Study centre	Inveresk Clinical Research Unit, Riccarton, Edinburgh (United Kingdom)	
Publication	Not applicable	
Study period	First Visit First Subject: 27-October-2005 Last Visit Last Subject: 13-January-2006	**Phase of development** Phase IV
Objectives	**Primary objective** To compare the post-vaccination geometric mean titres (GMT) of antibody to pneumococcal serotypes 3 and 8 in recipients of PNEUMOVAX® II formulated with all new process polysaccharides to the same antibody responses in recipients of PNEUMOVAX® II formulated with all current process polysaccharides. **Study hypothesis** was that post-vaccination GMT of antibody to serotypes 3 and 8 elicited by new process PNEUMOVAX® II are non-inferior to that elicited by the current process PNEUMOVAX® II. **Secondary objective** To assess the safety and tolerability of PNEUMOVAX® II formulated with all new process polysaccharides.	
Methodology	Randomised, double-blind, single site. Healthy adults randomised 1:1 to two study groups to receive: **Group 1**: new process PNEUMOVAX® II or **Group 2**: current process PNEUMOVAX® II.	

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

Number of subjects (planned and analysed)

Planned: 220 subjects (110 subjects per group)
Randomised: 220 subjects (Group 1: 111 subjects, Group 2: 109 subjects)

Table 1: Disposition of Subjects

	Group 1 new process PNEUMOVAX® II	**Group 2 current process PNEUMOVAX® II**
n vaccinated	111 (100%)	109 (100%)
n completed	110 (99.1%)	109 (100%)
n withdrawn	1 (0.9%) [1]	-
Adverse event	1 (0.9%) [1]	-
Serious adverse event	1 (0.9%) [1]	-
Death	-	-
Vaccine-related serious adverse event	-	-

[1] Ankle fracture, not related to the study vaccine (subject 194)

Table 2: Analysis Sets

	Group 1 new process PNEUMOVAX® II	**Group 2 current process PNEUMOVAX® II**	**All**
Randomised Set [1]	111	109	220
Full Analysis Set (FAS) [2]	109 (98.2%)	109 (100%)	218 (99.1%)
Per Protocol Set (PPS) [3]	106 (95.5%)	108 (99.1%)	214 (97.3%)
Safety Set [4]	111 (100%)	109 (100%)	220 (100%)

[1] All randomised subjects

[2] All randomised subjects who received a study vaccine dose and with at least one post-vaccination immunogenicity evaluation; 2 subjects were excluded for missing post-vaccination immunogenicity evaluation in Group 1

[3] All randomised subjects excluding those with protocol violation which might interfere with the immunogenicity evaluation; 5 subjects were excluded for post-vaccination immunogenicity evaluation either missing or outside time window in Group 1; 1 subject was excluded for post-vaccination immunogenicity evaluation outside time window in Group 2

[4] All subjects who received a study vaccine dose and who had safety follow-up data

Diagnosis and main criteria for inclusion

Healthy, immunocompetent, adults ≥ 50 years having signed the informed consent form, not previously immunised with any pneumococcal vaccine, and without known allergy to any component of the study vaccines.

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

Test/ Reference vaccine, dose and mode of administration, batch numbers

Table 3: Vaccines Characteristics

	Group 1 **new process** **PNEUMOVAX® II**	**Group 2** **current process** **PNEUMOVAX® II**
	23 pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F	
Presentation	vial containing 0.5 mL of solution for injection	
Dose	each 0.5 mL dose contains 25 µg of each serotype	
Route	intramuscular injection in the deltoid region	
Storage	+2°C to +8°C	
Batch numbers	1103P (expiry 03-June-2007)	0884P (expiry 13-February-2007)

Vaccination schedule

Group 1: one dose of new process PNEUMOVAX® II
Group 2: one dose of current process PNEUMOVAX® II.

Follow-up duration

First blood sample at Visit 1 (Day 0) and second blood sample at Visit 2 (Day 28 ± 7 days)

Evaluation criteria

Immunogenicity
One-month post-vaccination antibody titres to pneumococcal serotypes 3 and 8 measured by Enzyme-Linked Immunosorbent Assay (ELISA).

Safety

Table 4: Safety Criteria

Visit 1 **Day 0**	**Day 4**	**Day 14**	**Visit 2** **Day 28**
Solicited injection-site adverse reactions [(1)]			
Solicited systemic adverse events [(2)]			
Unsolicited [(3)] injection-site adverse reactions			
Unsolicited [(3)] systemic adverse events			
Serious adverse events			

[(1)] Injection site erythema, injection site induration, and injection site pain
[(2)] Pyrexia (oral temperature ≥ 37.8°C), asthenia, chills, headache and pain (body aches)
[(3)] Events spontaneously reported

Statistical methods

Immunogenicity

The primary objective of this study was to show that for serotypes 3 and 8, the post-vaccination GMT elicited by the new process PNEUMOVAX® II is non-inferior to that elicited by the current process PNEUMOVAX® II. The criterion for success for each serotype was that the lower bound of the one-sided 97.5% CI around the ratio of post-vaccination GMT [GMT_{new} (Group 1)/ $GMT_{current}$ (Group 2)] was > 0.5 (i.e. excluding a decrease of 2.0-fold or more).

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

The secondary immunogenicity analyses described the responses to serotypes 3 and 8 by group as:

1) the percentage and CI of subjects with a ≥ 2-fold increase from pre- to post-vaccination of individual titres,
2) the geometric mean of individual titres ratio post-/ pre-vaccination (GMTR) and CI,
3) the post-vaccination reverse cumulative distribution curves, and the percentage and CI of subjects with post-vaccination antibody titres ≥ 0.5 µg/mL, ≥ 1.0 µg/mL, and ≥ 5.0 µg/mL.

To assess the ratio of the post-vaccination GMT for each serotype, the pre- and post-vaccination titre was log-transformed. An estimate of the difference between groups was obtained from a covariance analysis (ANCOVA) with log transformed post-vaccination titre as the dependent variable, and group and log transformed pre-vaccination titre as independent variables. The estimate of the difference was back transformed to obtain the ratio of the post-vaccination GMT. Using the pre-vaccination titre as a covariate was equivalent to a GMT fold-rise approach in that the variability due to baseline titre was employed to improve the precision of the estimate of vaccine effects.

Safety

The secondary objective of this study was to present an overall summary of adverse events with separate summaries of injection-site adverse reactions and systemic adverse events. For each type of adverse event, number of adverse events, number and proportion of subjects were calculated according to the MedDRA primary system organ class and preferred term. For quantitative data, mean and standard deviation, median, minimum and maximum were displayed.

SUMMARY – CONCLUSIONS

DEMOGRAPHY

Table 5: Demographic and Other Baseline Characteristics – Randomised Set

	Group 1 new process PNEUMOVAX® II N = 111	**Group 2 current process PNEUMOVAX® II N = 109**
Sex		
Male	49 (44.1%)	50 (45.9%)
Female	62 (55.9%)	59 (54.1%)
Age (years) at Vaccination		
Mean (SD)	58.4 (4.9)	58.0 (5.3)
Median	57.9	57.6
Minimum - Maximum	50.1;71.9	50.1;81.2
Body mass index (kg/m²)		
Mean (SD)	27.0 (3.9)	26.8 (4.4)
Median	26.7	26.5
Minimum - Maximum	19.7;38.9	18.2;41.7

The two groups were comparable with respect to these characteristics. The results on the FAS and PPS were comparable to those on the Randomised Set.

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

IMMUNOGENICITY

Primary endpoint:

Table 6: Comparison Between Groups of Post-vaccination Geometric Mean of Titres to Pneumococcal serotypes 3 and 8 (µg/mL – ELISA) – Adjustment on Baseline (ANCOVA) – PPS

	Group 1 new process PNEUMOVAX® II N = 106	Group 2 current process PNEUMOVAX® II N = 108	Group 1 / Group 2 Adjusted ratio N = 214	Non-inferiority
Serotype 3				
GMT (1)	1.40	1.24	1.13	Yes
[95% CI] (2)	[1.21;1.63]	[1.07;1.43]	[0.92;1.39]	
Serotype 8				
GMT (1)	10.78	9.72	1.11	Yes
[95% CI] (2)	[9.10;12.77]	[8.22;11.50]	[0.87;1.41]	

(1) Post-vaccination GMT were adjusted on pre-vaccination level
(2) The one-sided 97.5% CI is similar to a two-sided 95% CI when considering only one bound.
The lower bounds of the 95% two-sided CI of the post-vaccination GMT ratio [GMT_{new} (Group 1)/ $GMT_{current}$ (Group 2)] were >0.5 therefore it was concluded that for both serotypes 3 and 8, the post-vaccination GMT elicited by the new process were non-inferior (similar) to that elicited by the current process

The analysis without adjustment on pre-vaccination titres and the results on the FAS provided comparable results to those on the PPS.

Secondary endpoints:

Table 7: Percentage of Subjects with a ≥ 2-fold Increase (with Confidence Intervals) of Antibody Titres to Pneumococcal Serotypes 3 and 8 – PPS

	Group 1 new process PNEUMOVAX® II N = 106	Group 2 current process PNEUMOVAX® II N= 108
Serotype 3		
≥ 2-fold increase pre-to post-vaccination	50 (47.2%)	38 (35.2%)
[95% CI]	[37.4;57.1]	[26.2;45.0]
Serotype 8		
≥ 2-fold increase pre-to post-vaccination	90 (84.9%)	87 (80.6%)
[95% CI]	[76.6;91.1]	[71.8;87.5]

The results on the FAS were comparable to those on the PPS.

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

Table 8: Geometric Mean Fold Increase of Individual Antibody Titres to Pneumococcal Serotypes 3 and 8 (µg/mL – ELISA) – PPS

	Group 1 **new process PNEUMOVAX® II** **N = 106**	**Group 2** **current process PNEUMOVAX® II** **N = 108**
	Ratio **post-/ pre-vaccination**	**Ratio** **post-/ pre-vaccination**
Serotype 3		
GMTR	2.01	1.79
[95% CI]	[1.72;2.36]	[1.49;2.14]
Serotype 8		
GMTR	6.66	5.86
[95% CI]	[5.39;8.21]	[4.78;7.19]

The results on the FAS were comparable to those on the PPS.

For each serotype, the post-vaccination distribution for the 2 groups overlap almost completely and the 2 groups were comparable with respect to percentages of subjects with post-vaccination antibody titres ≥0.5 µg/mL, ≥1.0 µg/mL, and ≥5.0 µg/mL.

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

SAFETY

The following Tables 9, 10 and 11 summarise all reported adverse events by group. Safety follow-up was obtained for all subjects who were enrolled in the study.

Table 9: Global Summary of Safety – Safety Set

	Group 1 **new process PNEUMOVAX® II** **N = 111** **n vaccinated = 111**	**Group 2** **current process PNEUMOVAX® II** **N = 109** **n vaccinated = 109**
	n (%)	**n (%)**
Any injection-site adverse reaction or systemic adverse event from **Day 0 to Day 14**	77 (69.4%)	68 (62.4%)
Any injection-site adverse reaction or vaccine-related systemic adverse event from **Day 0 to Day 14**	74 (66.7%)	66 (60.6%)
Any injection-site adverse reaction [(1)] from **Day 0 to Day 14**	62 (55.9%)	60 (55.0%)
Any systemic adverse event [(1)] from **Day 0 to Day 14**	44 (39.6%)	31 (28.4%)
Any vaccine-related systemic adverse event from Day 0 to Day 14	38 (34.2%)	24 (22.0%)
Any serious adverse event from **Day 0 to Visit 2**	1 (0.9%) [(2)]	-
Any vaccine-related serious adverse event from **Day 0 to Visit 2**	-	-
Any death from **Day 0 to Visit 2**	-	-
Any withdrawal due to an adverse event from **Day 0 to Visit 2**	1 (0.9%) [(2)]	-
Any withdrawal due to a vaccine-related adverse event from **Day 0 to Visit 2**	-	-

n (%) = number of subjects presenting the event considered at least once (percentage of subjects presenting the event at least once); percentages are calculated with regard to the number of subjects vaccinated

[(1)] Solicited and unsolicited combined

[(2)] Hospitalisation for an ankle fracture of severe intensity at Day 29 post-vaccination leading to withdrawal from the study and assessed by the investigator as unrelated to the study vaccine (subject 194)

As shown in Table 9, overall comparable event rates were observed across groups while the data suggested a higher incidence of systemic adverse events in Group 1 versus Group 2.

There were no vaccine-related serious adverse events and no premature discontinuations due to vaccine-related adverse events.

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

Table 10: Injection-Site Adverse Reactions – Day 0 to Day 14 – Safety Set

	Group 1 new process PNEUMOVAX® II N = 111 n vaccinated = 111	**Group 2 current process PNEUMOVAX® II N = 109 n vaccinated = 109**
	n (%)	**n (%)**
Any **solicited** injection-site adverse reaction from **Day 0 to Day 4**	60 (54.1%)	58 (53.2%)
Injection site erythema	20 (18.0%)	9 (8.3%)
Injection site induration	14 (12.6%)	7 (6.4%)
Injection site pain	56 (50.5%)	57 (52.3%)
Any **unsolicited** injection-site adverse reaction from **Day 0 to Day 14**(1)	11 (9.9%)	5 (4.6%)

n (%) = number of subjects presenting the event considered at least once (percentage of subjects presenting the event at least once); percentages are calculated with regard to the number of subjects vaccinated

(1) May include Injection site erythema, injection site induration or injection site pain starting from Day 5 to Day 14

As shown in Tables 9 and 10, the vast majority of injection-site adverse reactions were solicited and occurred from Day 0 to Day 4. A comparable frequency of injection-site adverse reactions was observed overall across groups. More cases of injection site erythema and injection site induration were reported in subjects in Group 1. Injection-site adverse reactions were mainly of mild intensity and lasted 1 to 6 days in both groups.

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

Table 11: Systemic Adverse Events – Day 0 to Day 14 – Safety Set

	Group 1 new process PNEUMOVAX® II N = 111 n vaccinated = 111	**Group 2 current process PNEUMOVAX® II N = 109 n vaccinated = 109**
	n (%)	**n (%)**
Any **solicited** systemic adverse event from **Day 0 to Day 4**	35 (31.5%)	20 (18.3%)
Any solicited vaccine-related systemic adverse event from **Day 0 to Day 4**	35 (31.5%)	20 (18.3%)
Pyrexia (oral temperature ≥ 37.8°C)	-	-
Asthenia	14 (12.6%)	9 (8.3%)
Chills	8 (7.2%)	4 (3.7%)
Headache	17 (15.3%)	14 (12.8%)
Pain (body aches)	18 (16.2%)	7 (6.4%)
Any **unsolicited** systemic adverse event from **Day 0 to Day 14** (1)	20 (18.0%)	19 (17.4%)
Any unsolicited vaccine-related systemic adverse event from **Day 0 to Day 14**	12 (10.8%)	11 (10.1%)

n (%) = number of subjects presenting the event considered at least once (percentage of subjects presenting the event at least once); percentages are calculated with regard to the number of subjects vaccinated.

(1) May include pyrexia (oral temperature ≥ 37.8°C), asthenia, chills, headache or pain (body aches) starting from Day 5 to Day 14

As shown in Tables 9 and 11, the majority of systemic adverse events were solicited and occurred from Day 0 to Day 4. Although comparable frequency of unsolicited systemic adverse events (reported from Day 0 to Day 14) was observed overall across groups, the data suggested a higher incidence in Group 1 for several solicited systemic adverse events. Solicited systemic adverse events were mainly of mild intensity and lasted 1 to 6 days in both groups.

Name of Sponsor/ Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table referring to part of the dossier**	*(For National Authority use only)*
Name of Finished Product PNEUMOVAX® II Pneumococcal Polysaccharide Vaccine	Volume	
Name of Active Ingredients Twenty-three (23) pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Page	

SUMMARY – CONCLUSIONS

CONCLUSIONS

Immunogenicity after vaccination with new process PNEUMOVAX®II was non-inferior (similar) to that of the current process as demonstrated by the post-vaccination geometric mean titres for both serotypes 3 and 8. This conclusion is supported by the finding of generally comparable proportions of subjects exhibiting a ≥2-fold increase in antibody titres from pre- to post-vaccination for both serotypes.

New and current process PNEUMOVAX®II were both well tolerated. There were no vaccine-related serious adverse events and no premature discontinuations due to vaccine-related adverse events. Although differences were observed in the incidences of several solicited injection-site adverse reactions and several solicited systemic adverse events when compared to the current process PNEUMOVAX® II, the overall incidence of adverse events was comparable. Solicited adverse events were mainly of mild intensity and lasted 1 to 6 days. These adverse events appeared to be clinically acceptable with comparable intensity and duration to those observed with the current process PNEUMOVAX® II.

Date of the report 31-January-2007