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 REPEVAX®	Volume	
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)	Page	

TITLE OF STUDY

A randomised, comparative, multicentre clinical trial of the immunogenicity and safety of Tdap-IPV vaccine (REPEVAX®) and a tetanus monovalent vaccine in healthy adults 18 years of age and older

Study Identification Number: RPV02C

EudraCT Number: 2008-008724-32

COORDINATING INVESTIGATORS

France: Pr. Henri LAURICHESSE, MD, Clermont-Ferrand, France

Germany: Dr. Ulrich ZIMMERMANN, MD, Heilbronn, Germany

STUDY CENTRES

Nine (9) active centres, 4 in France and 5 in Germany.

PUBLICATION (REFERENCE)

Not applicable

STUDIED PERIOD	5 months	**PHASE OF DEVELOPMENT**
First Visit First Subject:	06 July 2009	Phase 3b
Last Visit Last Subject:	08 December 2009	

OBJECTIVES

PRIMARY OBJECTIVE

To demonstrate that a booster dose of Tdap-IPV vaccine is as immunogenic as a booster dose of Tetanus monovalent vaccine in terms of anti-tetanus seroprotection rate defined as the percentage of subjects with an anti-tetanus antibody titre >=0.1 IU/mL (measured by Enzyme-Linked ImmunoSorbent Assay [ELISA]) 10 days after vaccination.

The primary hypothesis was that a booster dose of Tdap-IPV vaccine was non-inferior to a booster dose of Tetanus monovalent vaccine in terms of anti-tetanus seroprotection rate 10 days after vaccination. The non-inferiority of Tdap-IPV vaccine (Group 1) compared to Tetanus monovalent vaccine (Group 2) was demonstrated if the lower bound of the two-sided 95% Confidence Interval around the difference in anti-tetanus seroprotection rates (Group 1 – Group 2) was greater than -10% (i.e. the non-inferiority margin).

Name of Sponsor/Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table Referring to Part of the Dossier** Volume Page	*(For National Authority Use only)*
Name of Finished Product REPEVAX®		
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)		

SECONDARY OBJECTIVES

Immunogenicity:

- To describe the Geometric Mean Titre (GMT) for tetanus antibodies in both groups at Day 0, Day 10 and Day 28 and the seroprotection rate at Day 28.

Safety:

- To describe the safety profile of the two vaccines.

METHODOLOGY

Randomised, open-label, comparative, multi-centre study

Visit 1 Day 0	**Visit 2** Day 10 *Visit 1 + 10 days* *(± 1 days)*	**Visit 3** Day 28 *Visit 1 + 28 days* *(+ 7 days)*
✓ Informed consent form ✓ Blood Sample 1 ✓ Vaccination ✓ Record of immediate safety	✓ Blood Sample 2 ✓ Record of Safety	✓ Blood Sample 3 ✓ Record of Safety

Total of 28 days (+7 days) follow-up in each group: REPEVAX group (Group 1) and Tetanus monovalent group (Group 2).

NUMBER OF SUBJECTS (PLANNED AND ANALYSED)

- ***Planned:*** 456 randomised subjects (228 subjects per group) to reach 410 evaluable subjects (205 per group)
- ***Actual:*** 456 randomised subjects (N = 223 in REPEVAX Group and N = 233 in Tetanus monovalent Group)

Table 1: Disposition of Subjects

	REPEVAX Group	**Tetanus monovalent Group**	**All**
Screened (a)			458
Randomised	223 (100%)	233 (100%)	456 (100%)
Vaccinated	223 (100%)	233 (100%)	456 (100%)
Completed	220 (98.7%)	232 (99.6%)	452 (99.1%)
Withdrawn	3 (1.3%)	1 (0.4%)	4 (0.9%)
- Consent withdrawn	0	1 (0.4%)	1 (0.2%)
- Lost to follow-up	3 (1.3%)	0	3 (0.7%)

Name of Sponsor/Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table Referring to Part of the Dossier** Volume Page	*(For National Authority Use only)*
Name of Finished Product REPEVAX®		
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)		

%: percentage based on the number of randomised subjects (a) subjects who signed the informed consent form, 2 screening failures related to inclusion /exclusion criteria

- ***Analysed:*** refer to Table 2

Table 2: Description of analysis sets

	REPEVAX Group	**Tetanus monovalent Group**	**All**
Randomised	223	233	456
Full Analysis Set (a)	222 (99.6%)	232 (99.6%)	454 (99.6%)
Per Protocol Set			
- Day-10 Per Protocol Set (b)	183 (82.1%)	199 (85.4%)	382 (83.8%)
- Day-28 Per Protocol Set (c)	175 (78.5%)	195 (83.7%)	370 (81.1%)
Safety Analysis Set (d)	222 (99.6%)	232 (99.6%)	454 (99.6%)

%: percentage based on the number of randomised subjects,
(a) All randomised subjects who received one of the study vaccines and with a post-vaccination immunogenicity evaluation. Subjects were analysed in the group to which they were randomised,
(b) Consisted of all randomised subjects excluding subjects with protocol violation(s) which may interfere with the immunogenicity evaluation post-vaccination at Day 10,
(c) Consisted of all randomised subjects excluding subjects with protocol violation(s) which may interfere with the immunogenicity evaluation post-vaccination at Day 28,
(d) The Safety Analysis Set was defined as all subjects who received one of the study vaccines and who had safety follow-up data. Subjects were analysed according to the study vaccine they actually received.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Adults of both gender 18 years of age and above who received the last booster with a T-containing vaccine 5 to 10 years (included) prior to the administration of the study vaccine (documented by written evidence) having signed an informed consent form prior to any study procedure and without any significant underlying illness or immunodeficiency.

TEST VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

REPEVAX®, suspension for injection in pre-filled syringe

Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)

Active ingredients: 1 dose (0.5 mL) contains:

- Diphtheria Toxoid .....Not less than 2 IU* (2 Lf)
- Tetanus Toxoid .....Not less than 20 IU* (5 Lf)
- Pertussis Antigens
  - Pertussis Toxoid.....2.5 micrograms
  - Filamentous Haemagglutinin .....5 micrograms

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 REPEVAX®	Volume	
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)	Page	

- Pertactin.....3 micrograms
- Fimbriae Types 2 and 3.....5 micrograms

- Poliomyelitis Virus Type 1** (inactivated) .....40 D antigen units
- Poliomyelitis Virus Type 2** (inactivated) .....8 D antigen units
- Poliomyelitis Virus Type 3** (inactivated) .....32 D antigen units
- Adsorbed on aluminium phosphate.....1.5 mg (0.33 mg Al)

* As lower confidence limit (p = 0.95) of activity measured according to the assay described in the European Pharmacopoeia.
** Produced in Vero cells.

Batch number: D0250-2 (expiry date: 28 February 2011)

REFERENCE VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Tetanus monovalent vaccine, suspension for injection in a pre-filled syringe

Active ingredients: 1 dose (0.5 mL) contains:

- Tetanus Toxoid .....≥40 IU
- Adsorbed on aluminium hydroxyde.....0.6 mg Al

Batch number: D5465-1 (expiry date: 31 July 2011)

DURATION OF FOLLOW-UP

The maximum duration of follow-up for each subject was 35 days.

CRITERIA FOR EVALUATION

IMMUNOGENICITY

Primary endpoint:

The anti-tetanus seroprotection rate (percentage of subjects with anti-tetanus antibody titre (ELISA) >=0.1 IU/mL) 10 days after vaccination.

Secondary endpoints:

- The anti-tetanus seroprotection rate (antibody titre ≥ 0.1 IU/mL ELISA) at Day 28 post-vaccination,
- The anti-tetanus GMT at Day 10 and Day 28 post-vaccination.

SAFETY

The percentage of subjects reporting the following adverse events:

- From Day 0 to Day 7: immediate (at least 20 min) reactions, solicited injection-site reactions,

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 REPEVAX®	Volume	
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)	Page	

systemic reactions and unsolicited adverse events,
- From Day 0 to Visit 3: serious adverse events.

STATISTICAL METHODS

IMMUNOGENICITY

The immunogenicity analyses were performed for the main analysis on the per protocol set (subjects without protocol deviations that may interfere with immune responses) and for the supportive analyses on the full analysis set (subjects with any post-vaccination immunological evaluation).

Primary analysis

The primary objective of the study was to demonstrate that a booster dose of Tdap-IPV vaccine (Group 1) was at least as immunogenic as a booster dose of Tetanus monovalent vaccine (Group 2) in terms of anti-tetanus seroprotection rate (antibody titre >=0.1 IU/ml ELISA), 10 days after vaccination.

The non-inferiority of Group 1 compared to Group 2 was tested as follows: the Group 1 seroprotection rate was considered as non-inferior to the Group 2 seroprotection rate if the two-sided 95% Confidence Interval around the difference in rates (Group 1 – Group 2) excluded a decrease of 10% or more (*i.e.* the lower bound of the CI was greater than -10%). This was similar testing the statistical hypotheses as follows: H0: Group 1 - Group 2 <=-0.1 *versus* H1: Group 1 - Group 2 >-0.1.

Secondary analysis

Descriptive statistics were provided for each group including the GMT (and two-sided 95% CI) at Day 10 and at Day 28, and the seroprotection rate (and two-sided 95% CI) at Day 28 post-vaccination.

SAFETY

An overall summary of rates of adverse events as well as rates of both injection-site adverse reactions and systemic adverse events were provided. Intensity, time to onset, duration and relationship to vaccination (for systemic adverse events) were described for all adverse events. Specific description was provided for serious adverse events.

SUMMARY - CONCLUSIONS

DEMOGRAPHY:

The 2 groups were comparable in terms of age, weight, height and BMI. The gender ratio (Male/Female) was numerically higher in the REPEVAX Group than in the Tetanus monovalent Group (0.72 and 0.52, respectively).

The mean (+/-SD) time since last booster T-containing vaccine was 7.3 (+/-1.5) years with comparable

Name of Sponsor/Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table Referring to Part of the Dossier** Volume Page	*(For National Authority Use only)*
Name of Finished Product REPEVAX®		
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)		

time in the 2 groups.

IMMUNOGENICITY RESULTS: refer to Table 3, Table 4 and Table 5

Primary objective

According to the Day-10 Per Protocol Set, the non-inferiority of the REPEVAX Group compared to the Tetanus monovalent vaccine Group was demonstrated in terms of seroprotection rate (estimated of the difference of 1.01%[95%CI -1.18; 3.59]) at Day 10 after vaccination (Table 3). Supportive analyses on the Full Analysis Set provided similar results.

Table 3: Day-10 seroprotection rate to Tetanus & non-inferiority analysis of seroprotection rates to Tetanus - Day-10 Per Protocol Set

	REPEVAX Group (N=183)	**Tetanus monovalent Group (N=199)**	**Estimate of the difference (a)**	**Non-inferiority (b)**
Seroprotection rate (>=0.1 IU/mL)				
n subjects (%)	183 (100%)	197 (99.0%)	**1.01 %**	**Yes**
[95% CI]	[98.0;100]	[96.4;99.9]	[**-1.18** ; 3.59]	

(a) REPEVAX Group - Tetanus monovalent Group
(b) The REPEVAX Group seroprotection rate was considered as non-inferior to the Tetanus monovalent Group seroprotection rate if the lower bound of the 95% CI is greater than -10%

Secondary objectives

On Day-10 Per Protocol Set, the pre-vaccination Geometric Mean Titres (GMTs) and the anti-tetanus seroprotection rates were similar prior to vaccination in both groups. On Day 10 post-vaccination GMTs and Geometric Mean Titre Ratios (GMTRs) were higher in the REPEVAX Group than in the Tetanus monovalent Group, based on the non-overlapping of the 95% confidence intervals (CI) (Table 4).

Table 4: Pre- and Day-10 post-vaccination GMT, GMTR and seroprotection rate to Tetanus {IU/mL - ELISA} - Day-10 Per Protocol Set

	REPEVAX Group (N=183)		**Tetanus monovalent Group (N=199)**	
	Day 0	**Day 10**	**Day 0**	**Day 10**
Anti-Tetanus titres (IU/mL)				
GMT	1.5	**12.1**	1.5	**6.6**
[95% CI]	[1.3;1.7]	[10.7;13.7]	[1.3;1.7]	[5.7;7.6]
Seroprotection rate (>=0.1 IU/mL)				
n subjects (%)	181 (98.9%)	183 (**100%**)	193 (97.0%)	197 (**99.0%**)
[95% CI]	[96.1;99.9]	[98.0;100]	[93.6;98.9]	[96.4;99.9]

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 REPEVAX®	Volume	
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)	Page	

Ratio Post / Pre-vaccination		
GMTR	**7.9**	**4.5**
[95% CI]	[6.8;9.3]	[3.9;5.2]

On Day-28 Per Protocol Set, the seroprotection rate was 100% in both groups. The Day-28 post-vaccination GMTs and GMTR were higher in the REPEVAX Group than in the Tetanus monovalent Group, based on the non-overlapping of the 95% confidence interval (CI) (Table 5). Similar results were observed on the Full analysis set.

Table 5: Pre- and Day-28 post-vaccination GMT, GMTR and seroprotection rate to Tetanus {IU/mL - ELISA} - Day-28 Per Protocol Set

	REPEVAX Group (N=175)		**Tetanus monovalent Group (N=195)**	
	Day 0	**Day 10**	**Day 0**	**Day 10**
Anti-Tetanus titres (IU/mL)				
GMT	1.5	**10.5**	1.4	**7.0**
[95% CI]	[1.3;1.7]	[9.3;11.8]	[1.2;1.7]	[6.3;7.7]
Seroprotection rate >=0.1 IU/mL				
n subjects (%)	173 (98.9%)	175 (**100%**)	189 (96.9%)	195 (**100%**)
[95% CI]	[95.9;99.9]	[97.9;100]	[93.4;98.9]	[98.1;100]
Ratio Post / Pre-vaccination				
GMTR		**6.8**		**4.8**
[95% CI]		[5.8;8.1]		[4.1;5.6]

SAFETY RESULTS:

No adverse event led to withdrawal of subjects.

One Serious Adverse Event (SAE) was reported in a 25-year-old female who developed an episode of multiple sclerosis 35 days after being vaccinated with a booster dose of REPEVAX. The subject had terminated her study follow-up at Day 28 post-vaccination. Two hypotheses were evoked by the investigator, either a long-standing multiple sclerosis which relapsed after vaccination or the first clinical manifestations of multiple sclerosis which occurred after vaccination. The patient's neurologist and immunologist assessed the relationship to study vaccine as unknown, Health Authorities as doubtful and the investigator as probable.

The rates of subjects with at least one adverse event between Day 0 and Day 7 were comparable in the 2 groups: 81.5% in the REPEVAX Group and 79.7% in the Tetanus monovalent Group. Adverse events were mainly of mild or moderate intensity and lasted less than 8 days. Only one injection-site induration in the Tetanus monovalent Group lasted more than 14 days (21 days). One event of cough considered as

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 REPEVAX®	Volume	
Name of Active Ingredients Diphtheria, Tetanus, Pertussis (acellular, components) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content)	Page	

related to REPEVAX® lasted more than 14 days (16 days).

About 75% of the subjects experienced an injection-site adverse reaction, most of them were solicited AEs. The rates were similar in both groups regarding injection-site reaction (erythema, pain and swelling: 17.6%, 74.3% and 19.8%, respectively in the REPEVAX Group and 19.8%, 72.8% and 20.7%, respectively in the Tetanus monovalent Group). Most of the solicited injection-site reactions started within 4 days after vaccination.

However, the rates of subjects with at least one systemic adverse event were numerically higher in the REPEVAX Group compared to the Tetanus monovalent Group: 47.7% and 39.7%, respectively. The rates of unsolicited adverse events were similar in both groups but the rates of vaccine-related solicited adverse events were numerically higher in the REPEVAX Group compared to the Tetanus monovalent Group (myalgia, headache, malaise, and pyrexia: 22.5%, 19.8%, 8.1%, and 2.3% in the REPEVAX Group and 14.2%, 11.6%, 2.2% and 0.4% in the Tetanus monovalent Group, respectively).

CONCLUSION

- The non-inferiority of REPEVAX® compared to Tetanus monovalent vaccine was demonstrated in terms of anti-tetanus seroprotection rates at Day 10 post-vaccination.
- The anti-tetanus GMTs and GMTRs were higher in the REPEVAX Group compared to the Tetanus monovalent Group at Day 10 and Day 28 post-vaccination.
- Even though the rates of subjects reporting a vaccine-related solicited systemic adverse event were numerically higher in the REPEVAX Group compared to the Tetanus monovalent Group, the safety profile in the REPEVAX Group was in-line with the Summary of Product Characteristics.

Consequently, these data can support the use of REPEVAX® for Tetanus prophylaxis in wound management in patients who received the last Tetanus-containing booster vaccine 5 to 10 years before the event.

DATE OF REPORT 16 December 2010