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® and VAXIGRIP®	Volume	
Name of Active Ingredient(s) REPEVAX®: Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content) VAXIGRIP®: Influenza vaccine (split virion, inactivated)	Page	

TITLE OF STUDY

An open-label, randomised, multicentre study to evaluate the immunogenicity and safety of a booster dose of diphtheria, tetanus, acellular pertussis and inactivated poliomyelitis adsorbed vaccine (REPEVAX®) administered concomitantly versus non-concomitantly with an influenza vaccine (VAXIGRIP®) to subjects of 60 years of age and older

Study Identification Number: RPV03C

EudraCT Number: 2010-021068-13

COORDINATING INVESTIGATORS

FRANCE: Gaëtan GAVAZZI, MD, Centre Hospitalier Universitaire A. Michallon, Grenoble

GERMANY: Ulrich ZIMMERMANN, Hospital, Heilbronn

STUDY CENTRE(S)

12 centres in France and 8 in Germany enrolled subjects in the study.

PUBLICATION (REFERENCE)

Not applicable.

STUDIED PERIOD	11 months	**PHASE OF DEVELOPMENT**
First Visit First Subject:	01 October 2010	Phase 3b
Last Visit Last Subject:	28 March 2011	
End of study:	29 August 2011 (serology results available)	

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OBJECTIVES

PRIMARY OBJECTIVES

- To demonstrate that REPEVAX® administered concomitantly with VAXIGRIP® in subjects 60 years of age and older was at least as immunogenic as REPEVAX® administered alone.

and

- To demonstrate that VAXIGRIP® administered concomitantly with REPEVAX® in subjects 60 years of age and older was at least as immunogenic as VAXIGRIP® administered alone.

Hypothesis

The first co-primary hypothesis was that REPEVAX® administered concomitantly with VAXIGRIP® (Group 1) in subjects 60 years of age and older was non-inferior to REPEVAX® administered alone (Group 2) in term of immune responses.

The non-inferiority of Group 1 compared to Group 2 was demonstrated if:

- The lower bound of the 2-sided 95% confidence interval (CI) around the difference in anti-tetanus seroprotection rates (Group 1–Group 2) was greater than -5% (i.e. excluding a decrease of 5% or more).

and

- The lower bounds of the 2-sided 95% CI around the difference in diphtheria and poliomyelitis type 1, 2 & 3 seroprotection rates (Group 1–Group 2) were greater than -10% (i.e. excluding a decrease of 10% or more).

and

- The lower bounds of the 2-sided 95% CI around the difference of the post-vaccination percentage of subjects with antibody titre ≥5 enzyme-linked immunosorbent assay (ELISA) unit (EU)/mL for each of the pertussis components (Pertussis toxoid [PT], Filamentous haemagglutinin [FHA], Pertactin [PRN] and Fimbriae types 2 and 3 [FIM2&3]) (Group 1–Group 2) were greater than -10% (i.e. excluding a decrease of 10% or more).

The second co-primary hypothesis was that VAXIGRIP® administered concomitantly with REPEVAX® (Group 1) in subjects 60 years of age and older was non-inferior to VAXIGRIP® administered alone (Group 2) in term of immune responses.

- The non-inferiority of Group 1 compared to Group 2 was demonstrated if the lower bound of the 2-sided 95% CI around the post-vaccination geometric mean of antibody titres (GMT) ratio (GMT Group 1/GMT Group 2) was greater than 2/3 for each of the 3 strains: A/H1N1, A/H3N2, and B (i.e. excluding a 1.5 decrease or more).

Success of the study required that all the above hypotheses were met.

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SECONDARY OBJECTIVES

The secondary objectives of this study were descriptive, thus no formal hypothesis was tested.

Immunogenicity

- To describe the immune responses to REPEVAX® and VAXIGRIP® when administered concomitantly or not in subjects 60 years of age and older.
- To describe the immune response of VAXIGRIP® according to European Medicines Agency (EMA) criteria in subjects 60 years of age and older (Note for Guidance, 1997: 28).

Safety

- To describe the safety of REPEVAX® and VAXIGRIP® when administered concomitantly or not in subjects 60 years of age and older.

METHODOLOGY

Open-label, randomised (ratio 1:1), 2-parallel-group, comparative and multi-centre study.

Table 1. Study Flow Chart

	Visit 1 (Day 0)	**Visit 2** 28 to 35 days after visit 1	**Visit 3** 28 to 35 days after visit 2
Group 1	Blood sample 1 **REPEVAX® + VAXIGRIP®**	Blood sample 2	
Group 2	Blood sample 1 **VAXIGRIP®**	Blood sample 2 **REPEVAX®**	Blood sample 3

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NUMBER OF SUBJECTS (PLANNED AND ANALYZED)

Planned (total number of subjects to be randomised): 954 subjects (477 per group).

Screened (informed consent form signed): 974 subjects.

Randomised: 954 subjects (Group 1: 478, Group 2: 476).

Table 2. Disposition of Subjects

	Group 1 REPEVAX® and VAXIGRIP® concomitantly	**Group 2 REPEVAX® after VAXIGRIP**	**All**
N screened (a) N screening failures			974 20
N randomised N withdrawn between randomisation and vaccination Non compliance with protocol	478 2 (0.4%) 2 (0.4%)	476 0 (0%) 0 (0%)	954 2 (0.2%) 2 (0.2%)
N vaccinated - REPEVAX® - VAXIGRIP®	476 (99.6%) 476 (99.6%) 476 (99.6%)	476 (100%) 463 (97.3%) 476 (100%)	952 (99.8%) 939 (98.4%) 952 (99.8%)
N withdrawn after vaccination - Between study vaccines administration (b) Adverse event (c) Non compliance with protocol Consent withdrawn - After the 2nd study vaccination Other (d)	0 (0%) 0 (0%) 0 (0%)	14 (2.9%) 13 (2.7%) 6 (1.3%) 1 (0.2%) 6 (1.3%) 1 (0.2%) 1 (0.2%)	14 (1.5%) 1 (0.1%) 1 (0.1%)
N completed	476 (99.6%)	462 (97.1%)	938 (98.3%)

Percentages are calculated based on the number of randomised subjects
(a) Subjects who signed informed consent form.
(b) Group 2 only.
(c) See text on safety results.
(d) Planned hip surgery

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Analysed: Please, refer to the following table.

Table 3. Analysis Sets of Subjects

	Group 1 REPEVAX® and VAXIGRIP® concomitantly	**Group 2 REPEVAX® after VAXIGRIP**	**All**
Randomised Set	478	476	954
Full Analysis Set (a) (b)	474 (99.2%)	468 (98.3%)	942 (98.7%)
Per Protocol Set (PPS) - VAXIGRIP® PPS (VPPS) - REPEVAX® PPS (RPPS)	 463 (96.9%) 452 (94.6%)	 448 (94.1%) 423 (88.9%)	 911 (95.5%) 875 (91.7%)
Safety Set (a) - Safety Set Post-VAXIGRIP® - Safety Set Post-REPEVAX®	476 (99.6%)	476 (100%) 472 (99.2%) 459 (96.4%)	

Percentages are calculated based on the number of randomised subjects.
(a) For the FAS and Safety Sets: 4 subjects randomised in Group 2 received REPEVAX® and VAXIGRIP® concomitantly. and were therefore analysed in Group 1
(b) One subject randomised in Group 2 received REPEVAX® first and then VAXIGRIP®. The subject was analysed in Group 2 according to the vaccine he received.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Adults aged ≥60 years at Visit 1 with at least 1 documented booster dose with a tetanus- and diphtheria-containing vaccine between 5 and 15 years before Visit 1, no receipt of a booster dose with a tetanus- or diphtheria- or poliomyelitis-containing vaccine within the last 5 years before Visit 1, and no medical condition or treatment that could affect the immune system.

TEST VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

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

Presentation: suspension for injection in prefilled syringe

Dose: 1 dose (0.5 mL)

Route of administration: intramuscular (preferred injection site: deltoid muscle)

Storage: +2°C to +8°C

Batch number: E0427-1 (expiry date: 27 February 2012)

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CONCOMITANT VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

VAXIGRIP®: Influenza vaccine (split virion, inactivated)*

Presentation: suspension for injection in prefilled syringe

Dose: 1 dose (0.5 mL)

Route of administration: intramuscular (preferred injection site: deltoid muscle)

Storage: +2°C to +8°C

Batch number: G9838-1 (expiry date: 31 May 2011)

** Influenza vaccine strains: A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), B/Brisbane/60/2008 in accordance with the World Health Organisation (WHO) recommendations (Northern Hemisphere) and European Union decision for the 2010/2011 season*

DURATION OF FOLLOW-UP

The total follow-up was to be of 28 to 35 days in Group 1 and 56 to 70 days in Group 2.

CRITERIA FOR EVALUATION

IMMUNOGENICITY

Primary endpoints

REPEVAX®

- The post-vaccination seroprotection rate for diphtheria defined as the percentage of subjects with antibody titre ≥0.1 international unit (IU)/mL (seroneutralisation [SN]).
- The post-vaccination seroprotection rate for tetanus defined as the percentage of subjects with antibody titre ≥0.1 IU/mL (ELISA).
- The post-vaccination percentage of subjects with antibody titre ≥5 EU/mL (ELISA) for each of the pertussis components (PT, FHA, PRN, and FIM2&3).
- The post-vaccination seroprotection rate for poliomyelitis types 1, 2 & 3 defined as the percentage of subjects with antibody titre ≥8 (1/dil) (SN).

VAXIGRIP®

- The post-vaccination geometric mean of anti-haemagglutinin (anti-HA) antibody titres (GMT) for each of the 3 strains: A/H1N1, A/H3N2 and B (haemagglutination inhibition assay [HI method]).

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Secondary endpoints

REPEVAX®

- The post-vaccination GMC to diphtheria (IU/mL) (SN).
- The post-vaccination geometric mean of antibody concentration (GMC) to tetanus (IU/mL) (ELISA).
- The post-vaccination GMC (EU/mL) and the geometric mean of individual post/pre-antibody concentration ratio (GMCR) to pertussis components (PT, FHA, PRN and FIM2&3) (ELISA).
- The post-vaccination GMT to poliomyelitis type 1, 2 & 3 (1/dil) (SN).

VAXIGRIP®

For each of the 3 influenza strains (A/H1N1, A/H3N2, and B):

- The post-vaccination seroprotection rate, i.e. percentage of subjects with a post-vaccination anti-HA ≥40 (1/dil) (HI method).
- The seroconversion and/or significant increase rate, i.e. percentage of subjects with a post-vaccination anti-HA ≥40 (1/dil) when pre-vaccination anti-HA was <10 (1/dil) or with a ≥4-fold increase in anti-HA from pre- to post-vaccination when pre-vaccination anti-HA was ≥10 (1/dil) (HI method).
- The geometric mean of individual post/pre-antibody titre ratio (GMTR) (HI method).

SAFETY

The safety endpoints were the percentage of subjects with the following adverse events (AEs):

From Day 0 to Day 7 following each REPEVAX® vaccination:

- Solicited injection-site adverse reactions
  - Injection-site erythema.
  - Injection-site swelling.
  - Injection-site pain.
- Solicited systemic adverse reactions
  - Fever (body temperature ≥38.0°C).
  - Headache.
  - Malaise.
  - Myalgia.

From Day 0 to Day 28 following each REPEVAX® and/or VAXIGRIP® vaccination

- Unsolicited injection-site adverse reactions.
- Unsolicited Systemic AEs.

From Visit 1 to the last visit of the concerned subject:

- Serious adverse events (SAEs).

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STATISTICAL METHODS

IMMUNOGENICITY

Primary objectives

REPEVAX®:

The statistical criterion for the demonstration of non-inferiority corresponded to the lower bound of the 2-sided 95% CI of the post-vaccination seroprotection rate difference (Group 1 – Group 2) being greater than -10% for diphtheria and poliomyelitis type 1, 2 & 3 and being greater than -5% for tetanus

The statistical criterion for the demonstration of non-inferiority corresponded to the lower bound of the 2-sided 95% CI around the difference in the post-vaccination percentage of subjects with antibody titre ≥5 EU/mL (Group 1 – Group 2) being greater than -10% for each pertussis components (PT, FHA, PRN and FIM2&3)

The CIs around the seroprotection rate / post-vaccination percentage of subjects with pertussis antibody titre ≥5 EU/mL differences were calculated using the Wilson Score method without continuity correction.

VAXIGRIP®:

The statistical criterion for the demonstration of non-inferiority corresponded to the lower bound of the 2-sided 95% CI of the post-vaccination GMT ratio (GMT Group 1/GMT Group 2) being greater than 2/3.

For each strain, a covariance analysis (ANCOVA) model with the baseline level (log10 transformed) as covariate, the vaccine group as fixed effect and the (log10-transformed) post-vaccination as response was set up. Geometric mean titre ratios together with their 2-sided 95% CI were based on the above model.

Secondary objectives

Descriptive summaries for each group including reverse cumulative distribution curves (RCDC)

SAFETY

Descriptive safety profile for each group.

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SUMMARY – CONCLUSIONS

DEMOGRAPHY AND OTHER BASELINE CHARACTERISTICS:

Please refer to Tables 4, 5, and 6.

Table 4. Demographic Data and Other Baseline Characteristics - Randomised Set

		REPEVAX® and VAXIGRIP® concomitantly (N=478)	**REPEVAX® after VAXIGRIP® (N=476)**	**All (N=954)**
Age (years) at Visit 1	Mean (SD)	68.78 (6.22)	68.78 (6.51)	68.78 (6.36)
	Min. ; Max.	60.0 ; 88.6	60.0 ; 92.4	60.0 ; 92.4
	>65 years	292 (61.1%)	292 (61.3%)	584 (61.2%)
Gender	Male	220 (46.0%)	197 (41.4%)	417 (43.7%)
	Female	258 (54.0%)	279 (58.6%)	537 (56.3%)
Weight (kg)	Mean (SD)	77.6 (15.0)	76.6 (15.8)	77.1 (15.4)
	Min. ; Max.	41 ; 135	43 ; 140	41 ; 140
Height (cm)	Mean (SD)	167.1 (9.3)	166.2 (8.9)	166.6 (9.1)
	Min. ; Max.	146 ; 196	141 ; 191	141 ; 196

Max.: maximum; Min.: minimum; SD: standard deviation

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Table 5. Prior Diphtheria, Tetanus, Pertussis and Poliomyelitis Vaccinations – Randomised Set

	REPEVAX® and VAXIGRIP® concomitantly (N=478)	**REPEVAX® after VAXIGRIP® (N=476)**
Prior diphtheria vaccination		
Nb. of subjects with at least 1 boost dose from 5 to 15 years prior to study vaccination	469 (98.1%)	465 (97.7%)
Time since last vaccination (years)	n=471	n=467
Mean (SD)	8.05 (2.47)	8.31 (2.58)
Min. ; Max.	4.9 ; 15.7	1.4 ; 15.9
Nb. of doses received in the last 15 years		
1	356 (75.6%)	349 (74.7%)
2	61 (13.0%)	49 (10.5%)
3	45 (9.6%)	63 (13.5%)
More than 3	9 (1.9%)	6 (1.3%)
Prior tetanus vaccination		
Nb. of subjects with at least 1 boost dose from 5 to 15 years prior to study vaccination	474 (99.2%)	473 (99.4%)
Time since last vaccination (years)	n=476	n=475
Mean (SD)	7.99 (2.44)	8.35 (2.59)
Min. ; Max.	4.3 ; 15.7	0.7 ; 15.9
Nb. of tetanus doses received in the last 15 years		
1	342 (71.8%)	345 (72.6%)
2	63 (13.2%)	60 (12.6%)
3	57 (12.0%)	60 (12.6%)
More than 3	14 (2.9%)	10 (2.1%)
Prior poliomyelitis vaccination		
Nb. of subjects with at least 1 boost dose from 5 to 15 years prior to study vaccination	338 (70.7%)	318 (66.8%)
Time since last vaccination (years)	n=344	n=321
Mean (SD)	8.12 (2.60)	8.46 (2.69)
Min. ; Max.	2.0 ; 15.7	1.4 ; 15.9
Nb. of polio doses received in the last 15 years		
1	261 (75.9%)	250 (77.9%)
2	53 (15.4%)	34 (10.6%)
3	22 (6.4%)	29 (9.0%)
More than 3	8 (2.3%)	8 (2.5%)
Prior pertussis vaccination		
Nb. of subjects with at least 1 boost dose from 5 to 15 years prior to study vaccination	2 (0.4%)	0 (0%)

Max.: maximum; Min.: minimum; Nb.: number; SD: standard deviation

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Table 6. Prior Influenza Vaccinations – Randomised Set

	REPEVAX® and VAXIGRIP® concomitantly (N478)	**REPEVAX® after VAXIGRIP® (N=476)**
Nb. of subjects with at least 1 prior influenza vaccination, excluding H1N1 pandemic vaccine, within the 3 last years prior to study vaccination	247 (51.7%)	272 (57.1%)
Time since last vaccination (years) Mean (SD) Min. – Max.	n=247 1.16 (0.36) 0.8 ; 3.0	n=272 1.20 (0.46) 0.5 ; 3.0
Nb. of subjects with a prior vaccination with a H1N1 pandemic vaccine prior to study vaccination	83 (17.4%)	91 (19.1%)

Max.: maximum; Min.: minimum; Nb.: number; SD: standard deviation

IMMUNOGENICITY RESULTS

The primary objectives were met for REPEVAX®:

- The post-vaccination seroprotection rates for ***diphtheria*** (85.4% vs. 87.5%), ***tetanus*** (100% vs. 100%), ***poliomyelitis type 1*** (99.8% vs. 100%) ***poliomyelitis type 2*** (100% vs. 100%) ***poliomyelitis type 3*** (99.3% vs. 99.8%) were non-inferior when REPEVAX® was administered concomitantly to VAXIGRIP® compared to when REPEVAX® was administered after VAXIGRIP® (see Tables 7 and 8).
- The post-vaccination percentage of subjects with antibody titre ≥5 EU/mL for ***pertussis PT*** (94.3% vs. 98.1%) ***pertussis FHA*** (99.8% vs. 100%) ***pertussis PRN*** (97.3% vs. 96.0%) ***pertussis FIM2&3*** (91.7% vs. 89.5%) were non-inferior when REPEVAX® was administered concomitantly to VAXIGRIP® compared to when REPEVAX® was administered after VAXIGRIP® (see Tables 9 and 10).

Results related to the immune responses following REPEVAX® were similar in the Full Analysis Set (FAS) and when stratification by country and age class was used.

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Table 7. Seroprotection Rate for Diphtheria, Tetanus and Poliomyelitis Type 1, 2 and 3 – REPEVAX® Per Protocol Set

	REPEVAX® and VAXIGRIP® concomitantly (N=463)		**REPEVAX® after VAXIGRIP® (N=448)**	
	Pre-vaccination	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
Diphtheria ≥0.1 IU/mL [95% CI]	n=452 205 (45.4%) [40.8%;50.0%]	n=451 385 (85.4%) [81.8%;88.3%]	n=423 217 (51.3%) [46.5%;56.0%]	n=423 370 (87.5%) [84.0%;90.3%]
Tetanus ≥0.1 IU/mL [95% CI]	n=443 425 (95.9%) [93.7%;97.4%]	n=444 444 (100%) [99.1%;100%]	n=420 398 (94.8%) [92.2%;96.5%]	n=423 423 (100%) [99.1%;100%]
Poliomyelitis type 1 ≥8 (1/dil) [95% CI]	n=433 419 (96.8%) [94.6%;98.1%]	n=433 432 (99.8%) [98.7%;99.9%]	n=408 397 (97.3%) [95.2%;98.5%]	n=423 423 (100%) [99.1%;100%]
Poliomyelitis type 2 ≥8 (1/dil) [95% CI]	n=433 415 (95.8%) [93.5%;97.4%]	n=433 433 (100%) [99.1%;100%]	n=408 397 (97.3%) [95.2%;98.5%]	n=423 423 (100%) [99.1%;100%]
Poliomyelitis type 3 ≥8 (1/dil) [95% CI]	n=433 408 (94.2%) [91.6%;96.1%]	n=433 430 (99.3%) [98.0%;99.8%]	n=408 382 (93.6%) [90.8%;95.6%]	n=423 422 (99.8%) [98.7%;99.9%]

CI: confidence interval; dil: dilution; IU: international unit

Table 8. Non-Inferiority Analysis of Post-Vaccination Seroprotection Rates for Diphtheria, Tetanus and Poliomyelitis Type 1, 2 and 3 – REPEVAX® Per Protocol Set

	Estimate of the difference	**[95%CI]**	**Non-inferiority (a)**
Diphtheria seroprotection rate Group 1 - Group 2	-2.1%	[-6.6%;2.5%]	Yes
Tetanus seroprotection rate Group 1 - Group 2	0%	[-0.9%;0.9%]	Yes
Poliomyelitis type 1 seroprotection rate Group 1 - Group 2	-0.2%	[-1.3%;0.7%]	Yes
Poliomyelitis type 2 seroprotection rate Group 1 - Group 2	0%	[-0.9%;0.9%]	Yes
Poliomyelitis type 3 seroprotection rate Group 1 - Group 2	-0.5%	[-1.8%;0.7%]	Yes

Group 1: REPEVAX® and VAXIGRIP® concomitantly; Group 2: REPEVAX® after VAXIGRIP®.
CI: confidence interval
(a) Non-inferiority was achieved as the lower bound of the 2-sided 95%CI of the difference was greater than -10% for diphtheria and poliomyelitis type 1, 2 & 3 and greater than -5% for tetanus

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Name of Finished Product REPEVAX® and VAXIGRIP®	Volume	
Name of Active Ingredient(s) REPEVAX®: Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content) VAXIGRIP®: Influenza vaccine (split virion, inactivated)	Page	

Table 9. Percentage of Subjects with an Antibody Titre ≥5 EU/mL for Each Pertussis Component (PT, FHA, PRN and FIM2&3) – REPEVAX® Per Protocol Set

	REPEVAX® and VAXIGRIP® concomitantly (N=463)		**REPEVAX® after VAXIGRIP® (N=448)**	
	Pre-vaccination	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
PT antibody ≥5 EU/mL [95% CI] (≥5 EU/mL)	n=442 295 (66.7%) [62.2%;71.0%]	n=436 411 (94.3%) [91.7%;96.1%]	n=410 280 (68.3%) [63.6%;72.6%]	n=415 407 (98.1%) [96.2%;99.0%]
FHA antibody ≥5 EU/mL [95% CI] (≥5 EU/mL)	n=448 436 (97.3%) [95.4%;98.5%]	n=446 445 (99.8%) [98.7%;99.9%]	n=417 403 (96.6%) [94.4%;98.0%]	n=422 422 (100%) [99.1%;100%]
PRN antibody ≥5 EU/mL [95% CI] (≥5 EU/mL)	n=446 241 (54.0%) [49.4%;58.6%]	n=443 431 (97.3%) [95.3%;98.4%]	n=419 210 (50.1%) [45.4%;54.9%]	n=423 406 (96.0%) [93.7%;97.5%]
FIM2&3 antibody ≥5 EU/mL [95% CI] (≥5 EU/mL)	n=436 156 (35.8%) [31.4%;40.4%]	n=444 407 (91.7%) [88.7%;93.9%]	n=415 127 (30.6%) [26.4%;35.2%]	n=418 374 (89.5%) [86.2%;92.1%]

CI: confidence interval; EU: enzyme-linked immunosorbent assay (ELISA) unit

Table 10. Non-Inferiority Analysis of Percentage of Subjects with a Post-Vaccination Antibody Titre ≥5 EU/mL for Each Pertussis Component (PT, FHA, PRN and FIM2&3) – REPEVAX® Per Protocol Set

	Estimate of the difference	**[95%CI]**	**Non-inferiority (a)**
Percentage of subjects with a post-vaccination antibody titre ≥5 EU/mL for PT pertussis Group 1 - Group 2	-3.8%	[-6.6%;-1.2%]	Yes
Percentage of subjects with a post-vaccination antibody titre ≥5 EU/mL for FHA pertussis Group 1 - Group 2	-0.2%	[-1.3%;0.7%]	Yes
Percentage of subjects with a post-vaccination antibody titre ≥5 EU/mL for PRN pertussis Group 1 - Group 2	1.3%	[-1.2%;3.9%]	Yes
Percentage of subjects with a post-vaccination antibody titre ≥5 EU/mL for FIM2&3 pertussis Group 1 - Group 2	2.2%	[-1.7%;6.2%]	Yes

Group 1: REPEVAX® and VAXIGRIP® concomitantly; Group 2: REPEVAX® after after VAXIGRIP®.
CI: confidence interval; EU: enzyme-linked immunosorbent assay (ELISA) unit
(a) Non-inferiority was achieved as the lower bound of the 2-sided 95%CI was greater than -10%

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® and VAXIGRIP®	Volume	
Name of Active Ingredient(s) REPEVAX®: Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine (adsorbed, reduced antigen(s) content) VAXIGRIP®: Influenza vaccine (split virion, inactivated)	Page	

The primary objectives were met for VAXIGRIP®:

- The post-vaccination GMTs of anti-HA for ***strain A/California (H1N1)***, ***strain A/Perth (H3N2)***, and ***strain B/Brisbane*** were 177, 291, and 305 (1/dil), respectively, when REPEVAX® and VAXIGRIP® were administered concomitantly, and 189, 338, and 308 (1/dil) when VAXIGRIP® was administered alone (see Table 11).
- The post-vaccination GMTs of anti-HA for ***strain A/California (H1N1)***, ***strain A/Perth (H3N2)***, and ***strain B/Brisbane*** were non-inferior when VAXIGRIP® was administered concomitantly to REPEVAX® compared to when VAXIGRIP® was administered alone (see Table 12).

Results related to the immune responses following VAXIGRIP® were similar in the FAS and when stratification by country and age class was used.

Table 11. GMT of Anti-HA for A/California (H1N1), A/Perth (H3N2) and B/Brisbane {HI Method 1/dil} – VAXIGRIP® Per Protocol Set

	REPEVAX® and VAXIGRIP® concomitantly (N=463)		**REPEVAX® after VAXIGRIP® (N=448)**	
	Pre-vaccination	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
Anti-HA for A/California (H1N1) GMT [95% CI]	n=463 16 [14;18]	n=463 177 [153;205]	n=447 16 [14;18]	n=448 189 [163;218]
Anti-HA for A/Perth (H3N2) GMT [95% CI]	n=463 32 [27;36]	n=463 291 [255;333]	n=448 34 [30;40]	n=448 338 [296;385]
Anti-HA for B/Brisbane GMT [95% CI]	n=463 81 [70;93]	n=463 305 [275;340]	n=448 81 [71;94]	n=448 308 [276;344]

CI: confidence interval; GMT: geometric mean of antibody titres

Table 12. Non-Inferiority Analysis of GMT Post-Vaccination Anti-HA for A/California (H1N1), A/Perth (H3N2) and B/Brisbane {HI Method 1/dil} – ANCOVA Model – VAXIGRIP® Per Protocol Set

	GMT post-vaccination (Group 1)	**GMT post-vaccination (Group 2)**	**Post-vaccination GMT ratio (Group 1/Group 2)**	**[95%CI]**	**Non-inferiority (a)**
Anti-HA for A/California (H1N1)	176	189	0.9	[0.8;1.1]	Yes
Anti-HA for A/Perth (H3N2)	296	332	0.9	[0.7;1.1]	Yes
Anti-HA for B/Brisbane	306	308	1.0	[0.9;1.1]	Yes

Within the secondary immunogenicity objectives, EMA criteria for VAXIGRIP® were met in both groups.

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SAFETY RESULTS:

Please refer to Table 13.

During the follow-up period (Day 0 to Day 28), after vaccination, a similar percentage of subjects reported at least 1 injection-site reaction at the REPEVAX® injection-site when REPEVAX® was administered concomitantly to VAXIGRIP® (48.3%, including solicited injection-site reactions that occurred between Day 0 and Day 7: erythema, 9.6%; pain, 45.4%; swelling, 10.0%) or when REPEVAX® was administered after VAXIGRIP® (49.5%, including solicited injection-site reactions that occurred between Day 0 and Day 7: erythema, 8.3%; pain, 46.4%; swelling, 9.4%). A similar percentage of subjects reported at least 1 solicited systemic AE when REPEVAX® was administered concomitantly to VAXIGRIP® (40.8%, including solicited systemic AEs that occurred between Day 0 and Day 7: headache, 13.8%; malaise, 7.7%; myalgia, 19.4%; pyrexia, 1.5%) or when REPEVAX® was administered after VAXIGRIP® (40.3%, including solicited systemic AEs that occurred between Day 0 and Day 7: headache, 13.5%; malaise, 6.5%; myalgia, 17.0%; pyrexia, 0.9%). In addition, 24.0% and 19.8% of subjects reported at least 1 systemic AE that was considered by the investigator to be related to vaccination when REPEVAX® and VAXIGRIP® were administered concomitantly and when REPEVAX® was administered after VAXIGRIP®, respectively. No subject was withdrawn from the study due to an AE considered by the investigator to be related to REPEVAX®.

Fewer subjects reported at least 1 injection-site reaction at the VAXIGRIP® injection site when VAXIGRIP® was administered concomitantly to REPEVAX® (8.3%) than when VAXIGRIP® was administered alone (12.1%). Six subjects were withdrawn due to an AE following VAXIGRIP®. Two AEs were considered as serious and unrelated to VAXIGRIP® according to the investigator: 1 subject presented with severe pulmonary embolism 27 days after vaccination, and 1 subject had a tonsil phlegmon of moderate intensity, 32 days after vaccination. For the remaining 4 non-SAEs leading to withdrawal following VAXIGRIP®, according to the investigator, 1 AE (a case of mild exanthema of the mouth occurring 1 day after vaccination) was considered as related to VAXIGRIP® and the other 3 AEs (1 case of uveitis of moderate intensity occurring 15 days after vaccination, 1 case of 'heart hurry' of moderate intensity occurring 8 days after vaccination, and 1 case of mild itching occurring 5 days after vaccination) were considered as not related to VAXIGRIP®.

Thirteen (13) subjects reported 19 SAEs; none of these SAEs was considered by the investigator to be related to either REPEVAX® or VAXIGRIP®.

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Table 13. Global Summary of Safety – Safety Set

	REPEVAX® and VAXIGRIP® concomitantly (N=480)	**VAXIGRIP® (N=472)**	**REPEVAX® (N=459)**
	N (%)	**N (%)**	**N (%)**
AE from Day 0 to Day 28	308 (64.2%)	156 (33.1%)	293 (63.8%)
Vaccine-related AE from Day 0 to Day 28	267 (55.6%)	85 (18.0%)	250 (54.5%)
Injection-site adverse reaction at REPEVAX® injection site from Day 0 to Day 28	232 (48.3%)		227 (49.5%)
- Solicited injection-site adverse reaction at REPEVAX® injection site from Day 0 to Day 7	231 (48.1%)		222 (48.4%)
Injection site erythema	46 (9.6%)		38 (8.3%)
Injection site pain	218 (45.4%)		213 (46.4%)
Injection site swelling	48 (10.0%)		43 (9.4%)
- Unsolicited injection-site adverse reaction at REPEVAX® injection-site from Day 0 to Day 28	9 (1.9%)		12 (2.6%)
Injection-site adverse reaction at VAXIGRIP® injection site from Day 0 to Day 28	40 (8.3%)	57 (12.1%)	
Systemic AE from Day 0 to Day 28	196 (40.8%)	127 (26.9%)	185 (40.3%)
- Solicited systemic AE after REPEVAX® from Day 0 to Day 7	138 (28.8%)		119 (25.9%)
Headache	66 (13.8%)		62 (13.5%)
Malaise	37 (7.7%)		30 (6.5%)
Myalgia	93 (19.4%)		78 (17.0%)
Pyrexia	7 (1.5%)		4 (0.9%)
- Unsolicited systemic AE from Day 0 to Day 28	96 (20.0%)	127 (26.9%)	102 (22.2%)
Vaccine-related systemic AE from Day 0 to Day 28	115 (24.0%)	37 (7.8%)	91 (19.8%)
Serious AE from vaccination to next visit	4 (0.8%)	3 (0.6%)	6 (1.3%)
- Vaccine-related serious AE	0	0	0
Withdrawal due to AE following vaccination	0 (0%)	6 (1.3%)	0

AE: adverse event; N: number of subjects presenting at least once the considered event

CONCLUSION

These data support the concomitant administration of REPEVAX® with VAXIGRIP® in adults of 60 year-old or more as they demonstrated that (a) both vaccines can be administered concomitantly without impairing the immune response to each vaccine and (b) the safety profile of REPEVAX® when administered concomitantly with VAXIGRIP® is in accordance with its Summary of Product Characteristics (SmPC).

DATE OF REPORT 09 January 2012