SYNOPSIS

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 ZOSTAVAX®		
Name of Active Ingredient Varicella-zoster virus, Oka/Merck strain (live, attenuated)		

TITLE OF STUDY

An open-label, randomised, comparative, multicentre study of the immunogenicity and safety of ZOSTAVAX® when administered by intramuscular route or subcutaneous route to subjects ≥50 years of age.

Study Identification Number: ZTV03C

EudraCT Number: 2009-012458-19

COORDINATING INVESTIGATORS

- **Germany**: Prof. Thomas WEINKE, MD, Klinikum Ernst von Bergmann, Postdam
- **Spain:** Dr. Javier DIEZ-DOMINGO, MD, Centro Superior de Investigación en Salud Pública (CSISP), Valencia

STUDY CENTRES

10 active centres, in Germany and Spain.

PUBLICATION (REFERENCE)

Not applicable

STUDIED PERIOD	16 months (between FVFS and LVLS)	**PHASE OF DEVELOPMENT**
First Visit First Subject:	20 June 2011	Phase 3
Last Visit Last Subject:	15 October 2012	

OBJECTIVES

PRIMARY OBJECTIVE

The two co-primary objectives were:

- To demonstrate that ZOSTAVAX® administered by intramuscular (IM) route is non-inferior to ZOSTAVAX® administered by subcutaneous (SC) route in terms of 4-week post-vaccination antibody titres as measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) to varicella-zoster virus (VZV) in subjects ≥50 years of age.
- To demonstrate that ZOSTAVAX® administered by IM route induces an acceptable fold-rise of VZV antibody titres (gpELISA) from pre- to 4-week post-vaccination in subjects ≥50 years of age.

SECONDARY OBJECTIVES

The secondary immunogenicity objectives of this study were:

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- To evaluate the immunogenicity as measured by VZV antibody titres (gpELISA) at 4 weeks following ZOSTAVAX® administered by IM or SC route.
- To evaluate the immune response as measured by a second assay, the VZV Interferon-gamma (IFN-γ)-ELISPOT at 4 weeks following ZOSTAVAX® administered by IM or SC route.

The secondary safety objective of this study was to describe the safety profile of ZOSTAVAX® administered by IM or SC route.

METHODOLOGY

Open-label, randomised, comparative, 2 arms, multicentre study. Randomisation was stratified by ELISPOT subset status (ELISPOT site or non-ELISPOT site) and age with 3 strata: 50-59, 60-69, ≥70 years.

During the conduct of the trial the enrolment was monitored to make sure that no single age stratum dominated enrolment. The stratum 50-59 and the stratum ≥70 years had to not exceed one half and one third of the total sample, respectively.

Table 1. Study Schedule

Timing	**Visit 0** **Day -7 to Day 0**	**Visit 1** **Day 0**	**Visit 2** **Day 28 to Day 35**
Informed consent	Signed before any study procedure		
Vaccination		ZOSTAVAX® IM or SC route according to randomisation	
Immunogenicity assessment (a)	Blood sample 1 (pre-vaccination)		Blood sample 2 (4-week post-vaccination)
Safety assessment (b)	Record of safety		

(a) Immune responses measured by gpELISA in all subjects and IFN-γ-ELISPOT in the ELISPOT subset
(b) All subjects were kept under medical surveillance for at least 20 minutes post-vaccination to collect all immediate adverse events. Solicited injection-site adverse reactions (injection-site erythema, injection-site swelling and injection-site pain) were collected from Day 0 to Day 4 post-vaccination. Unsolicited injection-site adverse reactions and systemic adverse events and rashes of interest (i.e. Varicella, Varicella-like rashes, Herpes zoster (or shingles) and Herpes zoster-like rashes) were collected from Day 0 to Day 28 post-vaccination. Serious adverse events were collected throughout the study.

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NUMBER OF SUBJECTS (PLANNED AND ANALYSED)

Planned*:*

- Total to be randomised: 354 subjects (177 subjects per group)
- Total evaluable: 318 subjects (159 subjects per group)
- Total to be randomised in the ELISPOT subset: 228 subjects (114 subjects per group)
- Total evaluable in the ELISPOT subset: 160 subjects (80 subjects per group)

Estimated proportion of non-evaluable subjects: 10% for gpELISA and 30% in the ELISPOT subset.

Analysed: refer to Table 2.

Table 2. Analysis Sets of Subjects

	Group 1 - IM route	**Group 2 - SC route**	**All**
Randomised Set	177	177	354
Full Analysis Set	176 (99.4%)	177 (100%)	353 (99.7%)
Per Protocol Set	175 (98.9%)	177 (100%)	352 (99.4%)
ELISPOT (a) Randomised Subset	115	113	228
ELISPOT Full Analysis Set	113 (98.3%)	111 (98.2%)	224 (98.2%)
ELISPOT Per Protocol Set	111 (96.5%)	111 (98.2%)	222 (97.4%)
Safety Set	176 (99.4%)	177 (100%)	353 (99.7%)

Percentages are calculated based on the number of randomised subjects
(a) Subjects from sites 07 to 10.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Subject of either gender aged ≥50 years on day of vaccination, Varicella history-positive or residence for >30 years in a country with endemic VZV infection, able to attend all scheduled visits and to comply with all study procedures.

TEST VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

- **Name of finished product:** ZOSTAVAX®, preparation of shingles (herpes zoster) vaccine live
- **Presentation and mode of administration:** Powder and solvent for suspension for IM or SC injection in the deltoid region of upper arm (preferably in non-dominant arm).
- **Dose:** 0.65 mL containing not less than 19,400 Plaque-forming Units (PFU) of Varicella-zoster virus, Oka/Merck strain (live, attenuated).
- **Storage:** +2°C to +8°C
- **Batch numbers:** WL00040507 and WL00046785

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REFERENCE VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

- Not applicable

DURATION OF FOLLOW-UP

Subjects were followed up for a maximum of 35 days post-vaccination.

CRITERIA FOR EVALUATION

IMMUNOGENICITY

- **Primary endpoints:** The two primary immunogenicity endpoints were:
    - The 4-week post-vaccination VZV antibody Geometric Mean of Titre (GMT) in both groups,
    - The VZV antibody Geometric Mean Fold Rise (GMFR) from pre- to 4-week post-vaccination in the IM Group.
- **Secondary endpoints:** The secondary immunogenicity endpoints were:
    - The VZV antibody GMFR from pre- to 4-week post-vaccination in the SC Group,
    - The 4-week post-vaccination VZV IFN-γ ELISPOT Geometric Mean Count (GMC) in both groups of the ELISPOT subset,
    - The VZV IFN-γ ELISPOT GMFR from pre- to 4-week post-vaccination in both groups of the ELISPOT subset.

SAFETY

The safety assessment included:

- From Day 0 to Day 4: solicited injection-site adverse reactions: erythema, swelling, pain,
- From Day 0 to Day 28:
    - unsolicited injection-site adverse reactions,
    - rashes of interest (i.e. Varicella, Varicella-like rashes, Herpes zoster [or shingles] and Herpes zoster-like rashes), and
    - other systemic adverse events (AEs),
- From Day 0 to Visit 2: Serious adverse events (SAEs).

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STATISTICAL METHODS

IMMUNOGENICITY

Primary objective analyses

Immunogenicity was evaluated using a Per Protocol approach (main analysis) and a Full Analysis approach (supportive analysis).

- The 4-week post-vaccination gpELISA GMT in the IM Group was considered as non-inferior to the 4-week post-vaccination gpELISA GMT in the SC Group if the lower bound of the two-sided 95% CI around the gpELISA GMT ratio (GMT(Group 1)/GMT(Group 2)) was greater than 2/3 (i.e. ruling out a 1.5-fold decrease or more). This was similar to testing H0: GMT(Group 1)/GMT(Group 2) $\leq$2/3 versus H1: GMT(Group 1)/GMT(Group 2) >2/3.

This hypothesis was tested using a Longitudinal Data Analysis model including pre and post-vaccination log-transformed titres as response variables and age at vaccination, group and visit (pre- and post-vaccination) as covariate.

- The gpELISA GMFR in the IM Group was considered as acceptable if the lower bound of its two-sided 95% CI was greater than 1.4. This was similar to testing H0: GMFR(Group 1) $\leq$1.4 versus H1: GMFR(Group 1) >1.4.

This hypothesis was tested using the Student's t distribution for paired samples on log-transformed data.

Secondary objectives analyses

Descriptive statistics were performed including:

- gpELISA GMT and GMFR (and two-sided 95% CI) in both groups,
- IFN-γ ELISPOT GMC and GMFR (and two-sided 95% CI) in both groups of the ELISPOT subset.

SAFETY

A descriptive analysis of the safety profile was provided for each of the two administration routes.

SUMMARY – CONCLUSIONS

DEMOGRAPHY

The 2 groups were comparable in terms of age, gender, weight and height. On the Randomised Set, the mean age of the 354 subjects was 62.6 years [range: 50.0; 90.5], 44.9% were male. 46.0%, 31.4% and 22.6% of the participants belonged to 50-59 years stratum, 60-69 years stratum and $\geq$ 70 years stratum, respectively. Demographic data of the ELISPOT Randomised Subset were comparable to the demographic data of the Randomised Set.

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IMMUNOGENICITY RESULTS

The two co-primary immunogenicity objectives were met:

- ZOSTAVAX® administered by IM route was non-inferior to ZOSTAVAX® administered by SC route in terms of 4-week post-vaccination VZV antibody titres (gpELISA) in subjects ≥50 years of age since the lower bound of the 2-sided 95% CI around the estimated GMT ratio IM/SC is greater than 0.67 (see Table 3).
- ZOSTAVAX® administered by IM route induced an acceptable fold-rise of VZV antibody titres (gpELISA) from pre- to 4-week post-vaccination in subjects ≥50 years of age since the lower bound of the 2-sided 95% CI around the estimated GMFR using the IM route is >1.4 (see Table 4)

Both results were similar for the Full Analysis Set.

Table 3. Non-Inferiority Analysis of 4-Week Post-Vaccination VZV Antibody Titres {gpELISA units/mL} - IM Route versus SC Route - Per Protocol Set

	Group 1 - IM route (N=175)	**Group 2 - SC route (N=177)**
Estimated GMT (a)	402.7	384.9
Estimated GMT ratio IM/SC [95% CI] (a)	**1.05 [0.93**;1.18]	
p-value (a)	**<0.001**	
Non-inferiority (b)	**Met**	

(a) The 4-week post-vaccination estimated responses, GMT ratio (IM/SC), 95% CI and p-value are based on a longitudinal regression model adjusting for pre-vaccination titres and age at vaccination in years.
(b) Non-inferiority is achieved if the lower bound of the 2-sided 95% CI for the GMT ratio is greater than 2/3.

Table 4. Pre and 4-Week Post-Vaccination GMT and GMFR of VZV Antibody Titres {gpELISA units/mL} - Per Protocol Set

	Group 1 - IM route (N=175)		**Group 2 - SC route (N=177)**	
	Pre-vaccination	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
n	175	168	176	173
GMT	144.6	395.3	158.9	391.7
95% CI	[125.3;166.9]	[350.6;445.6]	[137.9;183.1]	[348.9;439.7]
n		168		172
GMFR (Post/Pre-vaccination)		**2.7**		2.5
95% CI		[**2.4**;3.0]		[2.2;2.8]
Acceptability (a)		**Met**		*Not applicable*

(a) Acceptability is demonstrated if the lower bound of the two-sided 95% CI is >1.4.

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Secondary objectives

- *VZV antibody (gpELISA)*

On the Per Protocol Set (PPS), the GMTs at baseline were comparable in the 2 groups as well as the GMFR (post-vaccination/pre-vaccination titre) (refer to Table 4). Similar results were observed on the Full Analysis Set.

The 4-week post-vaccination GMTs and GMFRs were comparable between Group 1 (IM route) and Group 2 (SC route) within each age strata (50 to 59 years, 60 to 69 years, 70 years and older). The 4-week post-vaccination GMTs and the GMFRs were numerically higher in 50 to 59 years stratum as compared to 60 to 69 years, and 70 years and older strata.

- *VZV IFN-γ-ELISPOT*

On the ELISPOT Per Protocol Set, the pre- and 4-week post-vaccination GMCs and the GMFR of IFN-γ ELISPOT counts were comparable between the 2 groups (Table 5). Similar results were observed on the ELISPOT Full Analysis Set.

Table 5: Pre and 4-Week Post-Vaccination GMC and GMFR of VZV INF-γ ELISPOT Counts - ELISPOT Per Protocol Set

	Group 1 - IM route (N=111)		**Group 2 - SC route (N=111)**	
	Pre-vaccination	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
n	101	103	96	105
GMC	64.3	**209.8**	58.4	**195.7**
95% CI	[49.6;83.4]	[175.2;251.3]	[42.6;80.2]	[161.9;236.6]
Missing data (a)	10	8	15	6
n		93		90
GMFR (Post/Pre-vaccination)		**3.3**		**3.4**
95% CI		[2.8;3.9]		[2.7;4.3]
Missing data (a)		18		21

IFN-γ = Interferon-gamma, ELISPOT = Enzyme-linked immunospot,
the ELISPOT count is the number of spot-forming cells per 10^6 PBMC, PBMC = Peripheral blood mononuclear cells.
(a) Missing data for pre-vaccination time point are mainly due to samples not being stored frozen, and therefore, not evaluable. Missing data for post-vaccination time points are due to protocol deviations and thus results were excluded from the analyses.

SAFETY RESULTS.

Within the 28 days following ZOSTAVAX® administration:

- The percentage of subjects reporting at least one AE (overall and those considered as vaccine related by the investigator) was lower in Group 1 (IM route) than in Group 2 (SC route):

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- All AE: 47.2% [95% CI: 39.6;54.8] and 69.5% [95% CI: 62.1;76.2], respectively
- Vaccine-related AE: 38.6% [95% CI: 31.4;46.3] and 66.7% [95% CI: 59.2;73.6], respectively

- The percentage of subjects reporting at least one injection site reaction (ISR) was lower in Group 1 (IM route) than in Group 2 (SC route): 34.1% [95% CI: 27.1;41.6] and 64.4% [95% CI: 56.9;71.4], respectively.
- The percentages of subjects reporting at least one systemic AE (overall and those considered as vaccine related by the investigator) were comparable between Group 1 (IM route) and Group 2 (SC route):
  - All: 23.3% [95% CI: 17.3%;30.2%] and 22.6%[95% CI: 16.7%;29.5%], respectively
  - Vaccine-related: 6.8% [95% CI: 3.6%;11.6%] and 7.3%[95% CI: 4.0%;12.2%] , respectively.
- For all ISRs solicited within the 4 days following ZOSTAVAX® administration, the incidence was significantly lower in Group 1 (IM route) than in Group 2 (SC route):
  - Injection-site erythema: 15.9% and 52.5%, respectively and risk difference: -36.6%, [95% CI: -45.4;-27.2]
  - Injection-site pain: 25.6% and 39.5%, respectively, and risk difference: -14.0% [95% CI: -23.5;-4.2]
  - Injection-site swelling: 13.6% and 37.3%, respectively, and risk difference: -23.7% [95% CI: -32.3;-14.8]
- For unsolicited AEs collected within the 28 days following ZOSTAVAX® administration:
  - The incidence of injection-site pruritus was statistically lower in Group 1 (IM route) than in Group 2 (SC route): 1.7% and 6.2%, respectively and risk difference: -4.5% [95% CI: -9.3;-0.5]
  - The incidence of headache considered as vaccine related by the investigator was comparable in Group 1 (IM route) and in Group 2 (SC route): 1.7% and 2.3%, respectively and risk difference: -0.6% [95% CI: -4.2;2.9].

All the risk differences remained statistically significant after adjustment for multiplicity (multiple comparisons).

ISRs were mainly mild (<5 cm in size or defined as awareness of sign or symptom but easily tolerated) or moderate (≥5 to <10 cm in size or defined as discomfort enough to cause interference with usual activity) in intensity. Few subjects reported severe (≥10 cm or defined as incapacitating with inability to work or do usual activity) ISRs:

- Erythema: 2 (1.1%) in Group 1 (IM route) and 3 (1.7%) in Group 2 (SC route)
- Pain: 2 (1.1%) in Group 2 (SC route)

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- Swelling: 1 (0.6%) in Group 1 (IM route) and 4 (2.3%) in Group 2 (SC route).

ISRs were mainly reported within the 4 days following ZOSTAVAX® administration and lasted less than 8 days.

Systemic AEs were mainly mild or moderate in intensity. Four subjects reported severe systemic AEs considered as vaccine-related by the investigator:

- Diarrhoea and pigmentation disorder in 1 subject (0.6%) from Group 1 (IM route)
- Dysaesthesia, headache and somnolence in 1 subject each (0.6%) from Group 2 (SC route).

The systemic AEs considered as vaccine related by the investigator were mainly reported within the 4 days following ZOSTAVAX® administration and lasted less than 4 days.

One subject reported in Group 1 (IM route) a zoster like rash (right thoracic dermatome) of mild intensity that occurred on day 12 after ZOSTAVAX® administration and lasted 6 days. No specimen was obtained for PCR testing.

No subject was withdrawn due to an AE at any time after ZOSTAVAX® administration. No deaths were reported. Three subjects reported an SAE: 1 subject (Hernia obstructive) in Group 1 (IM route) and 2 subjects (Humerus fracture and Deep vein thrombosis) in Group 2 (SC route). None were assessed as vaccine related by the investigator.

CONCLUSION

In this study, in subjects ≥50 years of age,

- The geometric mean of the VZV gpELISA antibody titres at 4-week post-vaccination induced by ZOSTAVAX® administered by the IM route was similar (non-inferior) to that induced by ZOSTAVAX® administered by the SC route.
- The GMFR of the VZV gpELISA antibody titres from pre-vaccination to 4-week post-vaccination induced by ZOSTAVAX® administered by the IM route was acceptable (lower bound of its two-sided 95% CI was greater than 1.4).
- The GMC of VZV IFN-γ ELISPOT at 4-week post-vaccination and the GMFR of VZV IFN-γ ELISPOT from pre-vaccination to 4-week post-vaccination were comparable by IM and SC route.
- ZOSTAVAX® was generally well tolerated, either given by IM route or SC route and the safety profile of SC route group was comparable to the known safety profile. While systemic adverse events (overall and vaccine-related) were reported with comparable rates, the rates of injection-site reactions were lower in the group receiving the vaccine by IM route compared to the group receiving the vaccine by SC route. Statistically significant differences were identified for injection-site erythema, pain, swelling and pruritus.

DATE OF REPORT 18 July 2013