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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

TITLE OF STUDY

An open-label, randomised, phase 3, comparative, multi-centre study of the immunogenicity and safety of a 1-dose regimen and different 2-dose regimens of a Zoster vaccine (Live), ZOSTAVAX®, in subjects >=70 years of age

Study Identification Number: X06-Z-305

EudraCT Number: 2007-000744-28

COORDINATING INVESTIGATOR(S)

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STUDY CENTRES

Twenty four (24) active centres in European Union, including Finland (6), Germany (13), Italy (2), Spain (2), and The Netherlands (1).

PUBLICATION (REFERENCE)

None

STUDIED PERIOD	20 months	**PHASE OF DEVELOPMENT**
First Visit First Subject:	26 October 2007	Phase 3
Last Visit Last Subject:	03 June 2009	
End of study:	15 September 2009	

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

OBJECTIVES

PRIMARY OBJECTIVE

Immunogenicity

The primary objective was to demonstrate that a second dose of ZOSTAVAX® elicits higher varicella-zoster virus (VZV) antibody titres than a first dose of ZOSTAVAX® whether given as a 0-1 month schedule or as a 0-3 month schedule in subjects >=70 years of age as measured at 4-week post-vaccination.

The hypothesis for the primary objective is that a second dose of ZOSTAVAX® would be superior to a first dose of ZOSTAVAX® in terms of VZV antibody GMT (gpELISA) at 4-week post-vaccination within at least one of the 2-dose vaccination schedules.

SECONDARY OBJECTIVES

Immunogenicity

The secondary objectives of immunogenicity were:

- To summarise the VZV antibody titres at 4-week post-vaccination after a 1-dose regimen and 4-week post-vaccination after each dose of each 2-dose regimen of ZOSTAVAX® administered to subjects >=70 years of age.
- To compare the VZV antibody titres at 12 months after completion of a 1-dose regimen with the VZV antibody titres at 12 months after completion of each 2-dose regimen of ZOSTAVAX® administered to subjects >=70 years of age.
- To summarise the VZV antibody titres at 24 and 36 months after completion of a 1-dose regimen and at 24 and 36 months after completion of each 2-dose regimen of ZOSTAVAX® administered to subjects >=70 years of age.

Safety

To assess the safety profile of a 1-dose regimen and the safety profile of each 2-dose regimen of ZOSTAVAX® administered to subjects >=70 years of age.

METHODOLOGY

It was an open-label, randomised, comparative, three-group, multicentre study with 2/3 of the subjects between 70 and 79 years of age and 1/3 of the subjects 80 years of age or more.

Subjects were randomised in a 1:1:1 ratio to receive:

- Group 1 (one-dose regimen): ZOSTAVAX® at Day 0 only
- Group 2 (0-1 month regimen): ZOSTAVAX® at Day 0 and Month 1 (Day 28 to Day 35)
- Group 3 (0-3 month regimen): ZOSTAVAX® at Day 0 and Month 3 (Day 81 to Day 97)

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

Table 1: Timing for Immunisation and Blood Sampling

	Visit 0	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
	Within 7 days before visit 1	**Month 0**	**Month 1** *4-week post-dose 1 (*28 to 42 days)	**Month 2** *4-week post-dose 2 (*28 to 42 days)	**Month 3**	**Month 4** *4-week post-dose 2* (110 to 140 days)	*Last dose + 12 months*	*Last dose + 24 months*	*Last dose + 36 months*
Group 1	BS1	**ZTV**	BS2				BS4	BS5	BS6
Group 2	BS1	**ZTV**	BS2 **ZTV**	BS3			BS4	BS5	BS6
Group 3	BS1	**ZTV**	BS2		**ZTV**	BS3	BS4	BS5	BS6

BS = Blood Sample, **ZTV**: ZOSTAVAX®

The study could be stopped at the time of the 24-month follow-up depending on the results of the 12-month post-last dose analysis. If there was no statistical evidence or clinical trend for superiority of any 2-dose regimen compared with the 1-dose regimen, Visits 7 and 8 were to be cancelled.

One or two analyses were planned for this study using the following split of the data:

- Data between Visit 0 and Visit 6 (12-month post-last dose)
- Data of Visit 7 (24-month post-last dose) and Visit 8 (36-month post-last dose).

The decision whether or not to pursue the follow-up at 24 months and at 36 months was to be taken following the comparison between groups of the 12-month post-last dose results.

The present Clinical Study Report displays the results of the Visit 0 to Visit 6 (12-month post-last dose) analysis as the study was stopped on 15 Sepember 2009, following results at 12-month post last dose.

Name of Sponsor/Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table Referring to Part of the Dossier** Volume	*(For National Authority Use only)*
Name of Finished Product ZOSTAVAX®		
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

NUMBER OF SUBJECTS (PLANNED AND ANALYSED)

Planned: 750 subjects (250 subjects per group)

Randomised: 759 subjects: Group 1 (N=253), Group 2 (N=255), Group 3 (N=251)

Higher rates of drop-out were observed in the 2-dose regimen groups (Groups 2 and 3) compared to the one-dose regimen (Group 1): roughly 10% in Groups 2 and 3 and 1% in Group 1 respectively (Table 2). It was mostly due to withdrawn consents (6.3% and 5.2% in Group 2 and Group 3, respectively) and adverse events (1.6% and 2.4% in Group 2 and Group 3, respectively).

Table 2: Disposition of Subjects

	Group 1 ***One-dose regimen***	**Group 2** ***0-1 month regimen***	**Group 3** ***0-3 month regimen***	**All**
N screened				**779**
N randomised	**253**	**255**	**251**	**759**
Finland	123 (48.6%)	122 (47.8%)	120 (74.8%)	365 (48.1%)
Germany	105 (41.5%)	105 (41.2%)	105 (41.8%)	315 (41.5%)
Italy	10 (4.0%)	12 (4.7%)	11 (4.4%)	33 (4.3%)
Spain	2 (0.8%)	3 (1.2%)	2 (0.8%)	7 (0.9%)
The Netherlands	13 (5.1%)	13 (5.1%)	13 (5.2%)	39 (5.1%)
N vaccinated	**253 (100.0%)**	**254 (99.6%)**	**250 (99.6%)**	**757 (99.7%)**
Received only one dose	253 (100.0%)	19 (7.5%)	29 (11.6%)	301 (39.7%)
Received two doses	-	235 (92.2%)	221 (88.0%)	456 (60.1%)
N completed V0-V5	**250 (98.8%)**	**229 (89.8%)**	**225 (89.6%)**	**704 (92.8%)**
N withdrawn V0-V5	**3 (1.2%)**	**26 (10.2%)**	**26 (10.4%)**	**55 (7.2%)**
N completed V6	**243 (96.0%)**	**220 (86.3%)**	**215 (85.7%)**	**678 (89.3%)**
N withdrawn V5-V6	**7 (2.8%)**	**9 (3.5%)**	**10 (4.0%)**	**26 (3.4%)**

V stands for Visit - Percentages are calculated based on the number of randomised subjects.

Name of Sponsor/Company Sanofi Pasteur MSD S.N.C.	**Individual Study Table Referring to Part of the Dossier** Volume	*(For National Authority Use only)*
Name of Finished Product ZOSTAVAX®		
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

Analysed: refer to Table 3

Table 3: Description of Analysis Sets

	Group 1 ***One-dose regimen***	**Group 2** ***0-1 month regimen***	**Group 3** ***0-3 month regimen***	**All**
Randomised Set	253	255	251	759
Full Analysis Set (FAS)	251 (99.2%)	242 (94.9%)	246 (98.0%)	739 (97.4%)
Per Protocol Set (PPS)	243 (96.0%)	203 (79.6%)	198 (78.9%)	644 (84.8%)
12-month Per Protocol Set (12-month PPS)	223 (88.1%)	189 (74.1%)	204 (81.3%)	616 (81.2%)
Post-dose 1 Safety Set	252 (99.6%)	249 (97.6%)	248 (98.8%)	749 (98.7%)
Post-dose 2 Safety Set		233 (91.4%)	220 (87.6%)	453 (89.5%)

Percentages are calculated based on the number of randomised subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Adults of either gender 70 years of age and above with a positive history of varicella (or residence for >30 years in a country with endemic VZV infection), having signed the informed consent form prior to any study procedure and without: prior herpes-zoster episode clinically diagnosed by a physician, receipt of varicella or zoster vaccine, exposure to varicella or herpes-zoster within a 4-week period prior to the first vaccination, significant underlying illness preventing completion of the study vaccination schedules and known active tuberculosis or immunodeficiency.

TEST VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS

- Name of finished product: ZOSTAVAX®
- Presentation and mode of administration:
  - Varicella-zoster virus, Oka/Merck strain, (live attenuated) not less than 19,400 PFU
  - Powder and solvent for suspension for subcutaneous administration
  - Dose: 0.65 mL
- Storage: +2°C to +8°C
- Batch number: 0656052 (expiry date 15 August 2008)

REFERENCE VACCINE(S), DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER(S)

Not applicable.

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

DURATION OF FOLLOW-UP

The maximum duration of the follow-up of the first part of the study for each subject was 12-month post-last dose. All subjects were followed until the end of the study (decision to not pursue the study after 12-month post-last dose results analysis was taken on 15 September 2009).

CRITERIA FOR EVALUATION

IMMUNOGENICITY

Primary endpoint:

4-week post-dose 1 and 4-week post-dose 2 VZV antibody titres (i.e. Geometric Mean Titre [GMT]) in Groups 2 and 3.

Secondary endpoints:

- VZV antibody titre (i.e. GMT):
  - 4-week post-dose 1 in Group 1
  - 12-month post-dose 1 in Group 1
  - 12-month post-dose 2 in Groups 2 and 3

- VZV antibody titre individual fold-rise (i.e. Geometric Mean Fold Rise, [GMFR])
  - 4-week post-dose 1 titre/pre-vaccination titre in all groups
  - 4-week post-dose 2 titre/pre-vaccination titre in Groups 2 and 3
  - 12-month post-dose 1 titre/pre-vaccination titre in Group 1
  - 12-month post-dose 2 titre/pre-vaccination titre in Groups 2 and 3.

All immunogenicity criteria were derived from the gpELISA assay results.

SAFETY

- From Day 0 to Day 4 following each dose: solicited injection-site adverse reactions (injection-site erythema, injection-site swelling and injection-site pain).
- From Day 0 to Day 28 following each dose: unsolicited injection-site adverse reactions, herpes-zoster/ varicella/ zoster-like rashes/ varicella-like rashes, other systemic adverse events, and serious adverse events (SAEs).
- From the first dose to Visit 6 or the last visit of the subject: deaths, vaccine-related SAEs and herpes-zoster/ varicella/ zoster-like rash/ varicella like-rash

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

STATISTICAL METHODS

IMMUNOGENICITY

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

Primary objective

The superiority of the second dose compared to the first dose was demonstrated within Group 2 (0-1 month regimen) and within Group 3 (0-3 month regimen) if the lower bound of the 2-sided 95% CI (adjusted for multiplicity) on the GMT ratio [GMT2/ GMT1] was greater than 1.2, where GMT2 is the GMT at 4-week post-dose 2 and GMT1 is the GMT at 4-week post-dose 1. GMT ratio (and their 95% CI) were estimated using an ANOVA model within Group 2 and within Group 3 on natural log-transformed data with repeated measurement on blood sample (i.e. post-dose 1 and post-dose 2), including country and age at inclusion as independent variable.

To control the overall Type I error at the 2-sided α of 0.05 (1-sided α of 0.025), the Hochberg adjustment step-up procedure was used to determine the overall study success.

An estimate was provided for the GMT ratio (GMT2/GMT1), together with the two-sided CI of the appropriate size determined through the Hochberg procedure.

Secondary objectives

To decide whether the follow-up at 24 months and at 36 months should continue, a comparison of 12-month post-last dose GMT between the groups was performed.

The GMT ratios [GMT12m (Group 2) / GMT12m (Group 1)] and [GMT12m (Group 3) / GMT12m (Group 1)], where GMT12m (Group 1), GMT12m (Group 2) and GMT12m (Group 3) are the 12-month post-last dose GMT in Groups 1, 2 and 3 respectively, and their two-sided 95% CI were estimated using an ANCOVA model on natural log-transformed data, including country, age at inclusion and group as independent variable and log-transformed baseline data (BS1) as covariate.

Descriptive statistics were provided, including the calculation of GMT (and their 95% CI) and GMFR (and their 95% CI) within each group after the first dose, after the second dose (when applicable) of ZOSTAVAX® and at each follow-up time point.

Within country and within age class (i.e. between 70 and 79 years of age versus 80 years of age or more) estimates and CI were provided.

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(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)		

SAFETY

After each dose, 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 rashes and SAEs.

An overall summary of deaths, vaccine-related SAEs and herpes-zoster/ varicella/ zoster-like rash/ varicella like-rash was provided at 12-month post-last dose for all groups.

SUMMARY – CONCLUSIONS (VISIT 0 TO VISIT 6)

***DEMOGRAPHY*: refer to Table 4.**

The 3 groups were comparable in terms of age at dose 1, classes of age (70-79 years, >=80 years), gender (Table 4), weight and height and body mass index. The median age was 71.7 and 81.9 years in 70-79 years and 80 years and above strata, respectively (*data not presented in Table*).

Table 4: Demographic Data – Randomised Set

		Group 1 *One-dose regimen* (N=253)	Group 2 *0-1 month regimen* (N=255)	Group 3 *0-3 month regimen* (N=251)	All (N=759)(a)
Age (Years) at dose 1	Mean (SD)	76.2 (5.5)	76.0 (5.4)	76.1 (5.3)	76.1 (5.4)
	Median	74.4	73.8	74.4	74.2
	Min ; Max	70.1 ; 93.6	70.1 ; 88.3	70.0 ; 92.8	70.0 ; 93.6
Age in classes					
70-79 years	n (%)	170 (67.2%)	168 (66.1%)	171 (68.4%)	509 (67.2%)
>=80 years	n (%)	83 (32.8%)	86 (33.9%)	79 (31.6%)	248 (32.8%)
Gender					
Male	n (%)	105 (41.5%)	117 (45.9%)	116 (46.2%)	338 (44.5%)
Female	n (%)	148 (58.5%)	138 (54.1%)	135 (53.8%)	421 (55.5%)

(a) Two subjects had missing data, the results are presented on 757 subjects

The medical history of the subjects was as expected for this age group, including 62% of subjects with vascular disorders (mainly hypertension [56%]), 42% with metabolism and nutrition disorder (mainly hypercholesterolemia [28%] and diabetes mellitus [9%]), 39% with musculoskeletal and connective tissue disorders (mainly osteoarthritis [18%] and osteoporosis [8%]), 27% with cardiac disorders (mainly coronary artery disease [10%] and arrhythmia [7%]).

The prior and concomitant medications (at Visit 1) were linked to the medical history described above: 69% of the subjects received medication for the cardiovascular system, 30% antithrombotic agents, 31% for alimentary tract and metabolism disorders, 26% for musculoskeletal system and 23% for nervous systems.

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

IMMUNOGENICITY RESULTS: refer to Tables 5, 6, 7 and 8.

- **Primary objective**

The superiority of the VZV antibody GMTs at 4-week post-dose 2 (GMT2) compared to the GMTs at 4-week post-dose 1 (GMT1) within Group 2 (0-1 month regimen) and within Group 3 (0-3 month regimen) was not demonstrated as the lower bounds of the 2-sided CI (adjusted for multiplicity) on the GMT ratio (GMT2/GMT1) were below 1.2. The upper bound of the 95%CI around the GMT ratio of Group 3 was below 1 (i.e. 0.85) showing a decrease of the VZV antibody titre post-dose 2 compared to the VZV antibody titre post-dose 1. (Table 5)

Table 5 : Superiority of 4-Week Post-Dose 2 GMT Compared to 4-Week Post-Dose 1 GMT of VZV Antibody Titres {gpELISA units/mL} in Groups 2 and 3 - ANOVA Model (a) - Per Protocol Set

	Group 2 ***0-1 month regimen*** **(N=203)**	**Group 3** ***0-3 month regimen*** **(N=198)**
GMT Post-dose 1 (GMT1)	**498.8**	**523.3**
[95% CI]	[438.7 ; 567.1]	[459.0 ; 596.7]
GMT Post-dose 2 (GMT2)	**555.3**	**410.5**
[95% CI]	[496.6 ; 620.9]	[363.1 ; 464.2]
GMT ratio (GMT2/GMT1)	**1.11**	**0.78**
[95% CI]	[1.02 ; 1.22]	[**0.73** ; 0.85]
Superiority (b)		**No**
[97.5%CI]	[**1.00** ; 1.24]	
Superiority (c)	**No**	
p-value (d)	0.948	>0.999

(a) The ANOVA models include country and age at first vaccination as independent variables

(b) Hochberg adjustment procedure, first step: superiority is achieved if the lower bound of the 2-sided 95% CI of the GMT ratio is greater than 1.2.

(c) Hochberg adjustment procedure, second step: superiority is achieved if the lower bound of the 2-sided 97.5% CI of the GMT ratio is greater than 1.2.

(d) One sided p-value for testing superiority (GMT2/GMT1 >1.2) to be compared to 0.025 or 0.0125 depending on the step of the Hochberg adjustment procedure.

Analyses on the FAS and without country and age as covariate provided similar results. Analyses by sub-group of ages showed the same trend. (Table 6)

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(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)		

Table 6: GMT of VZV Antibody Titres {gpELISA units/mL} at 4-Week Post-Dose 1 and 4-Week Post-Dose 2 by Age – Per Protocol Set

	70 to 79 years		80 years	
	Group 2 ***0-1 month regimen*** **(N=140)**	**Group 3** ***0-3 month regimen*** **(N=138)**	**Group 2** ***0-1 month regimen*** **(N=63)**	**Group 3** ***0-3 month regimen*** **(N=60)**
GMT Post-dose 1 (GMT1)	**509.7**	**506.6**	**475.4**	**564.1**
[95% CI]	[439.1 ; 591.6]	[435.8 ; 588.8]	[369.5 ; 611.7]	[430.6 ; 738.9]
GMT Post-dose 2 (GMT2)	**565.6**	**401.5**	**533.0**	**432.1**
[95% CI]	[494.5 ; 647.1]	[349.1 ; 461.7]	[434.8 ; 653.5]	[336.8 ; 554.4]
GMT ratio (GMT2/GMT1)	**1.11**	**0.79**	**1.12**	**0.77**
[95% CI]	[1.01 ; 1.22]	[0.73 ; 0.86]	[0.91 ; 1.37]	[0.65 ; 0.91]

- **Secondary objectives**

Based on the PPS, the VZV antibody GMTs at baseline were similar in the 3 groups. The GMFR from pre-vaccination to post-dose 1 were also similar in the three groups: 2.35, 2.37 and 2.29 in Group 1, Group 2 and Group 3, respectively. The GMFR from pre-vaccination to post-dose 2 was lower in Group 3 than in Group 2: 1.8 and 2.64, respectively with non-overlapping CIs. (Table 7)

Table 7: GMT and GMFR of VZV Antibody Titres {gpELISA units/mL} at 4-Week Post-Dose 1 and 4-Week Post-Dose 2 – Per Protocol Set

	N	**Group 1** ***One-dose regimen (N=243)***	**N**	**Group 2** ***0-1 month regimen (N=203)***	**N**	**Group 3** ***0-3 month regimen (N=198)***
GMT Pre-vaccination	242	**233.7**	203	**210.2**	198	**228.4**
[95% CI]		[207.1 ; 263.7]		[185.7 ; 238.0]		[199.2 ; 261.8]
GMT Post-Dose 1	243	**550.0**	203	**498.8**	198	**523.3**
[95% CI]		[489.2 ; 618.4]		[438.9 ; 566.9]		[458.7 ; 597.1]
GMT Post-Dose 2			203	**555.3**	198	**410.5**
[95% CI]				[496.8 ; 620.7]		[363.3 ; 463.9]
GMFR Post-Dose 1/Pre- vaccination	242	**2.35**	203	**2.37**	198	**2.29**
[95% CI]		[2.11 ; 2.62]		[2.11 ; 2.66]		[2.05 ; 2.57]
GMFR Post-Dose 2/Pre- vaccination			203	**2.64**	198	**1.80**
[95% CI]				[2.37 ; 2.95]		[1.63 ; 1.98]

On the 12-month PPS, the VZV antibody GMTs at 12-month post-last dose, after adjustment on baseline titres were similar in the 2-dose regimen groups. The estimates of 12-month post-last dose GMT ratio [Group 2/Group 1] and [Group 3/Group 1] were 1.06 and 1.08 respectively and 95% CI included 1.

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

(Table 8)

Table 8: Comparison of 12-Month Post-last Dose GMT of VZV Antibody Titres {gpELISA units/mL} – ANCOVA Model (a) – 12-Month Per Protocol Set

	Group 1 ***One-dose regimen*** **(N=223)**	**Group 2** ***0-1 month regimen*** **(N=189)**	**Group 3** ***0-3 month regimen*** **(N=204)**
GMT pre-vaccination [95% CI]	**241.6** [213.6 ; 273.2]	**217.0** [190.9 ; 246.7]	**227.2** [197.9 ; 260.9]
GMT 12-month post-last dose [95% CI]	**246.8** [230.9 ; 263.9]	**261.1** [242.8 ; 280.7]	**266.6** [248.6 ; 285.8]
GMT ratio (2-dose / one-dose regimen) [95% CI]		**1.06** [**0.96** ; 1.17]	**1.08** [**0.98** ; 1.19]

(a) The ANCOVA model includes country and age at first vaccination as independent variables and baseline antibody titre as covariate. The GMT 12-month post-last dose is the GMT adjusted from the ANCOVA model.

In addition, the GMFR from pre-vaccination to post last-dose were similar in the three groups: 1.06 (95% CI [0.99, 1.14]), 1.16 (95% CI [1.06, 1.26]) and 1.17 (95% CI [1.07, 1.27]).

SAFETY RESULTS:

Serious adverse events (SAEs)

All SAEs were assessed as unrelated to ZOSTAVAX®. During the Visit 0 to Visit 6 period, 22 SAEs were reported in 19 subjects. After Visit 6 and before the study was stopped (on 15 September 2009), 6 additional fatal non-vaccine related SAEs were reported by 5 subjects.

Withdrawal due to adverse event

During the Visit 0 to Visit 6 period, 22 adverse events led to the withdrawal of 17 subjects (10 subjects for SAE and 7 for non-serious adverse events). During the 28 days following vaccination, 15 adverse events (3 serious but non-vaccine-related and 12 non-serious vaccine-related) led to the withdrawal of 10 subjects. Among the 10 subjects withdrawn for SAE, death was reported for 7 subjects and other SAEs for 3.

Rashes of interest

Eight subjects reported rashes of interest during the Visit 0 to Visit 6 period. Within the 28 days following vaccination, 2 subjects (post-dose 1) presented with a herpes zoster-like rash (PCR negative for both) and 2 subjects (post-dose 2) presented with a varicella-like rash (PCR negative for one subject and no sample collected for the other). Outside the 28 days following vaccination, 3 other subjects presented with zoster-like rashes (PCR was negative for 2 subjects and no sample collected for the other) and 1 subject presented with a herpes zoster (no sample collected). Two additional subjects were diagnosed with a zoster after V6 and before the study was stopped. One of them was hospitalised due to a severe trigeminal herpes zoster, no sample was collected. The second one had a confirmed diagnosis with a wild type by

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

positive PCR. No varicella was reported.

Global safety results during the 28 days following the first dose (all 3 groups pooled)
In all, 57.8% of the subjects presented with at least one adverse event (i.e. injection-site adverse reaction or systemic adverse event) and 47.1% of the subjects experienced a vaccine-related adverse event. Injection-site adverse reactions were observed in 45.5% of the subjects and almost all were solicited. Systemic adverse events were reported by 28.0% of the subjects including 6.4% with at least one systemic adverse event assessed by the investigators as vaccine-related. Nine subjects reported a SAE, none was vaccine-related.

Global safety results during the 28 days following the second dose (Groups 2 and 3)
The rates of subjects presenting with at least one adverse event were similar regardless of the interval between doses (53.0% and 48.4% in Group 2 and Group 3 respectively). In both groups, 43% of subjects reported vaccine-related adverse events and 42% of the subjects reported injection-site adverse reactions. The rate of subjects with a systemic adverse event was numerically lower in Group 3 than in Group 2 (15.4% and 20.7%, respectively) but the rates of vaccine-related systemic adverse events were similar (2.7% and 3.4% respectively). Four subjects reported a SAE (two in Group 2 and two in Group 3). None was vaccine-related.

Adverse event risk differences between the second and the first dose (Groups 2 and 3)
Results were similar in each of the 2-dose regimen groups. In both groups, less subjects reported systemic adverse events after the second dose than after the first dose, however the rates of subjects reporting injection-site adverse reactions were similar between doses and between groups. Also, differences between doses were observed for unsolicited injection-site adverse reactions with a risk difference with opposite direction, -3.0% and 2.7% for Group 2 and Group 3, respectively. It should be noted that the reporting rates of unsolicited injection-site adverse reactions were also numerically different after the first dose between the two groups: 4.3% and 0.5% in Groups 2 and 3, respectively (post-dose 1, Post-Dose 2 Subset).

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 ZOSTAVAX®	Volume	
Name of Active Ingredient(s) Preparation of varicella-zoster virus, Oka/Merck strain, (live attenuated)	Page	

CONCLUSION

In this study:

- The superiority of the VZV antibody GMTs (in gpELISA units/mL) at 4-week post-dose 2 compared to the VZV antibody GMTs at 4-week post-dose 1 in both 2-dose regimen groups, 0-1 month regimen and 0-3 month regimen, was not demonstrated.
- The VZV antibody GMTs at 12-month post-second dose were similar in both 2-dose regimen groups and similar to the 12-month post-vaccination GMTs observed in subjects who received a single injection of ZOSTAVAX®.
- ZOSTAVAX® was generally well tolerated, either given as a 1-dose regimen or as a 2-dose regimen with an interval of one or three months between doses and the safety profile after the first dose was similar to the known safety profile.
- The rate of systemic adverse events was lower following the second dose of ZOSTAVAX® administered one or three months after the first dose than following the first dose.

Based on the above immunogenicity conclusions, the Sponsor made the decision on 15 September 2009 not to continue to study for the 24- and 36-month follow-up (Visits 7 and 8).

DATE OF REPORT 14 June 2010