1. 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 Ingredients: Preparation of shingles (herpes zoster) vaccine (live)		

TITLE OF STUDY

An open-label, single-arm, phase IV study assessing the immunogenicity and safety of ZOSTAVAX® at minimum release specification approaching expiry potency in subjects ≥50 years old.
Study Identification Number: **ZTV02C**
EudraCT Number: **2007-006532-66**

COORDINATING INVESTIGATOR

Robert ARNOU, MD, Angers, France

STUDY CENTRES: Six centres in France

PUBLICATION: None

STUDY PERIOD (years)	**Phase of development**
First Visit First Subject:14-May-2008 First Visit Last Subject: 28-May-2008 Last Visit Last Subject: 25-June-2008	IV

OBJECTIVES

Primary objective

The **primary objective** was to demonstrate whether or not ZOSTAVAX® at minimum release specification approaching expiry potency elicits an acceptable Varicella-Zoster Virus (VZV) antibody fold rise (measured by gpELISA) from pre-vaccination to 4 weeks post-vaccination.
The **primary hypothesis** was that ZOSTAVAX® at minimum release specification approaching expiry potency elicits an acceptable geometric mean fold rise (GMFR) in VZV gpELISA antibody titres from pre-vaccination to 4 weeks post-vaccination. Acceptability was demonstrated if the lower bound of the two-sided 95% Confidence Interval (CI) on the GMFR from pre-vaccination to 4 weeks post-vaccination was >1.4. Success for the study required the above primary hypothesis to be met.

Secondary objective

The **secondary objective** was to describe the safety profile of ZOSTAVAX® at minimum release specification approaching expiry potency.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Adults of either gender, aged ≥50 years on day of signing informed consent, having a positive history of varicella (or residence for more than 30 years in a country with endemic VZV infection), affiliated to a health social security system, able to attend all scheduled visits and to comply with all study procedures and having signed the informed consent prior to any procedure. All women were to be post-menopausal at inclusion visit or to have a negative serum or urine pregnancy test.

TEST VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

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ZOSTAVAX®: shingles (herpes zoster) vaccine (live).

- **Presentation and mode of administration**: Powder and solvent for suspension for injection.
- **Dose**: 0.65 mL containing active ingredient, Varicella-zoster virus, Oka/Merck strain (live attenuated) not less than 19,400 Plaque Forming Units (PFU) produced in human diploid (MRC-5) cells
- **Route:** Subcutaneous injection
- **Storage**: Powder and solvent (+2.0°C to +8.0°C), in original package protected from light
- **Batch number**: 0656053 (expiry date: 14-November-2008, potency at release: 88,710 PFU/mL (*57,662 PFU/dose*).

REFERENCE VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Not applicable

METHODOLOGY AND VACCINATION SCHEDULE

This was an open-label, single arm and multicentre study.

Each investigator was instructed to recruit half of the subjects aged 50 to 59 years old and half of the subjects aged 60 years or more; therefore the study targeted an equal distribution between the above mentioned age groups.

DURATION OF FOLLOW-UP

One visit was performed within seven days before or at the time of vaccination and the last one between Day 28 and Day 35 after vaccination (Table 1).

CRITERIA FOR EVALUATION

Table 1: Schedule of immunogenicity and safety

Timing	**Visit 0** **Day-7 to Day 0**	**Visit 1** **Day 0**	**Visit 2** **Day 28 to Day 35**
Informed consent	**X** **(signed before any study procedure)**		
Vaccination		**ZOSTAVAX®**	
Immunogenicity assessment [1]	**Blood sample 1** **(pre-vaccination)**		**Blood sample 2** **(post-vaccination)**
Safety assessment [2]	**Record of safety**		

[1] Immune responses measured by gpELISA, [2] All subjects were kept under medical surveillance for 20 minutes post-vaccination to collect all immediate adverse events. Solicited injection-site adverse reactions were collected from Day 0 to Day 4 post-vaccination. Unsolicited injection-site adverse reactions and systemic adverse events were collected from Day 0 to Day 28 post-vaccination. Serious adverse events were collected throughout the study.

Immunogenicity

The primary evaluation criterion was the geometric mean fold rise (GMFR) of VZV antibody titres from pre- to post-vaccination. The secondary evaluation criterion was the post-vaccination geometric mean of VZV antibody titre (GMT).

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Safety

- From Day 0 to Day 4, solicited injection-site adverse reactions: erythema, swelling and pain.
- From Day 0 to Day 28, unsolicited injection-site adverse reactions (including erythema, swelling and pain starting from Day 5 to Day 28), and unsolicited systemic adverse events (herpes zoster, varicella and/or rash vesicular and other systemic adverse events).
- From Visit 1 to Visit 2: serious adverse events.

STATISTICAL METHODS

Primary analyses

The main analysis was performed on the Per Protocol Set (i.e. any subject without protocol deviation or condition which may interfere with the immunogenicity evaluation).

The acceptability of the GMFR from pre- to post-vaccination was tested in subjects providing pre- and post-vaccination antibody titres as follows:

The primary hypothesis was H_0: GMFR ≤ 1.4 vs. H_1: GMFR >1.4. Rejecting the null hypothesis (H_0) at the one-sided $\alpha = 0.025$ level corresponds to the lower bound of the two-sided 95% CI on the GMFR being >1.4. In that case the conclusion was that ZOSTAVAX® at minimum release specification approaching expiry potency elicits an acceptable VZV antibody fold rise.

The criterion for an acceptable VZV antibody response, that the 95% CI of the GMFR exceed 1.4, was based on regulatory agency request and clinical relevancy of the endpoint. The above hypothesis was tested using the Student's t distribution for paired samples on log-transformed data.

For supportive purpose, the main analysis was repeated on the Full Analysis Set (i.e. subjects with any immunogenicity evaluation).

Secondary analyses

Descriptive statistics on immunogenicity were performed on the Per Protocol Set and on the Full Analysis Set for all subjects and split by age classes (i.e. 50 to 59 years and 60 years or more). A safety analysis was performed on the Safety Analysis Set (subjects vaccinated and providing a safety follow-up).

NUMBER OF SUBJECTS (PLANNED AND ANALYSED)

- ***Planned:*** 96 subjects (86 evaluable subjects for the Per Protocol Set)
- ***Screened***: 97 subjects (for whom an informed consent has been signed)
- ***Vaccinated***: 96 subjects

All vaccinated subjects were included in the Included Set, Full Analysis Set and the Safety Set. Four subjects were identified as having protocol deviation(s) or condition(s) which may have interfered with the immunogenicity evaluation and were excluded from the Per Protocol Set.

SUMMARY – CONCLUSIONS

RESULTS – DEMOGRAPHY

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The mean age of the subjects was 62.2 years (minimum: 51; maximum: 82) with 50 subjects aged 50 to 59 years and 46 subjects aged 60 years or more. The sex-ratio (female/male) was 1.1.

The medical history of the subjects was as expected for this age group, including 54% of subjects with vascular disorders (mainly hypertension), 44% with metabolism and nutrition disorders (mainly hypercholesterolemia and diabetes mellitus), 41% with musculoskeletal and connective tissue disorders (mainly osteoarthritis), and 38% with psychiatric disorders (mainly depression). The prior and concomitant medications (at Visit 1) were linked to the medical history described above: 68% of the subjects received medication for the cardiovascular system, 43% for the nervous system, and 29% for alimentary tract and metabolism disorders.

RESULTS – IMMUNOGENICITY

- **Primary endpoints**

The GMFR as measured by gpELISA, from pre-vaccination to 4 weeks post-vaccination reached 3.1 with a two-sided 95% CI of [2.6; 3.8] on the Per Protocol Set. The lower bound of 95% CI of GMFR being greater than 1.4, it is concluded that ZOSTAVAX® at minimum release specification approaching expiry potency elicits an acceptable VZV antibody fold rise (Table 2).

Table 2: Primary endpoint – GMT and GMFR of VZV antibody titres {gpELISA units/mL} – Per Protocol Set (main analysis)

	N = 92
Pre-vaccination (BS1)	
GMT, [95% CI] (units/mL)	215.8, [178.1 ; 261.4]
Post-vaccination (BS2)	
GMT, [95% CI], (units/mL)	674.0, [565.4; 803.5]
Post/Pre-vaccination (BS2/BS1)	
GMFR, [95% CI]	**3.1,** [**2.6**; 3.8]
Acceptability	**Yes**

Lower bound of the two-sided 95% CI on the GMFR >1.4

The results observed on the Full Analysis Set lead to the same conclusion as the Per Protocol Set.

- **Secondary endpoint**

Whereas the GMTs at baseline were similar in both age subgroups (subjects 50 to 59 years of age and 60 years or above), the GMFR in the subgroup of younger subjects were numerically higher as compared to the subgroup of older subjects: 3.9 [95%CI: 2.9; 5.1] and 2.5 [95%CI: 1.9; 3.2], respectively. Despite a rather limited sample size, it is observed that the lower bounds of the 95% CI exceeded 1.4 in both age groups.

RESULTS - SAFETY

From Day 0 to Day 28, 57 subjects (59.4%) reported at least one adverse event. About 52% of the subjects reported an injection-site adverse reaction (ISR). All ISRs except four were solicited and all were reported within the first four days. The four unsolicited ISRs were pruritus. Out of the 100 reported ISRs, two (erythema and pain) were severe. The rate of subjects reporting at least one systemic adverse event was 22.9% and 8.3% of subjects experienced a vaccine-related systemic event.

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Twenty-seven systemic adverse events were reported by 22 subjects. Eight subjects reported nine vaccine-related systemic adverse events: keratitis (1), asthenia (2) and pyrexia (1), herpes zoster (1), headache (2) and paraesthesia (1), and rash vesicular (1). One of the asthenia was considered severe.

Two subjects presented with a rash of interest: one presented with a herpes zoster on day 5 which lasted 16 days, and one presented with a varicella-like rash on day 1 which lasted three days. Their intensity was moderate and mild, respectively. Both were considered vaccine-related. No lesion specimen was obtained to further investigate the viral strain involved.

No subject presented a serious adverse event during the study period. No adverse event led to withdrawal from the study (Table 3).

Table 3: Secondary endpoints – Global Summary of Safety – Safety Set

	N = 96 N vaccinated = 96 Nb Subj (%)	[95% CI]
Injection-site adverse reaction/ systemic adverse event from Day 0 to Day 28	**57 (59.4)**	**[48.9; 69.3]**
Injection-site adverse reaction/ vaccine-related systemic adverse event	52 (54.2)	[43.7; 64.4]
Injection-site adverse reaction from Day 0 to Day 28	**50 (52.1)**	**[41.6; 62.4]**
Solicited injection-site adverse reaction from Day 0 to Day 4	50 (52.1)	[41.6; 62.4]
Unsolicited injection-site adverse reaction from Day 0 to Day 28	4 (4.2)	[1.1; 10.3]
Systemic adverse event from Day 0 to Day 28	**22 (22.9)**	**[15.0; 32.6]**
Vaccine-related systemic adverse event from Day 0 to Day 28	8 (8.3)	[3.7; 15.8]
Rash of interest from Day 0 to Day 28	**2 (2.1)**	**[0.3; 7.3]**
Injection-site rash of interest from Day 0 to Day 28	0 (0.0)	[0.0; 3.8]
Non-injection-site rash of interest from Day 0 to Day 28	2 (2.1)	[0.3; 7.3]
Varicella/Varicella-like rash from Day 0 to Day 28	1 (1.0)	[0.0; 5.7]
Herpes zoster/Zoster-like rash from Day 0 to Day 28	1 (1.0)	[0.0; 5.7]
Serious adverse event from Day 0 to Visit 2	**0 (0.0)**	**[0.0; 3.8]**

* Nb subj: number of subjects presenting at least once the considered event, %: percentage of subjects presenting at least once the considered event

CONCLUSION

The data support the use of ZOSTAVAX® at minimum release specification approaching expiry potency. An acceptable VZV antibody fold rise (gpELISA) from pre-vaccination to 4 weeks post-vaccination was observed in subjects over 50 years of age. In addition ZOSTAVAX® at minimum release specification approaching expiry potency was well tolerated and similar to the known safety profile.

Date of the report: 12-March-2009