22 October 2015
EMA/837681/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zostavax

International non-proprietary name: shingles (herpes zoster) vaccine (live)

Procedure No. EMEA/H/C/000674/X/0085

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

°C	Celsius degree
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance Model
BS	Blood Sample
CI	Confidence Interval
CMI	Cell Mediated Immunity
CSR	Clinical Study Report
ELISPOT	Enzyme-Linked ImmunoSpot
EMA	European Medicines Agency
ERA	Environmental Risk assessment
FAS	Full Analysis Set
GCP	Good Clinical Practices
GMC	Geometric Mean Count
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titre
gpELISA	Glycoprotein Enzyme-Linked ImmunoSorbent Assay
HZ	Herpes Zoster
IFN-γ	Interferon gamma
IM	Intramuscular
IMP	Investigational Medicinal Product
LDA	Longitudinal Data Analysis
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
PCR	Polymerase Chain Reaction
PEI	Paul-Ehrlich-Institut
PFU	Plaque-forming units
PHN	Post-Herpetic Neuralgia
PPS	Per Protocol Set
PT	Preferred Term
RCDC	Reverse Cumulative Distribution Curve
RSI	Request for supplementary Information
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class from MedDRA
SPS	Shingles Prevention Study
VZV	Varicella-Zoster Virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi Pasteur MSD SNC submitted on 26 May 2005 an application for extension of a Marketing Authorisation to the European Medicines Agency (EMA) for Zostavax. The MAH applied for a new route of administration: intramuscularly use.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008, Annex I 2.(e) Change or addition of a new route of administration.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMA decision P/0309/2014 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice/Protocol Assistance

The applicant did not seek any scientific advice or Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

Rapporteur: Jan-Mueller-Berghaus Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

- The application was received by the EMA on 19 December 2014.
- The procedure started on 22 January 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2015.
- The PRAC Assessment Report was circulated to all PRAC members on 27 April 2015.

- During the meeting on 18-21 May 2015, the CHMP agreed on a List of Questions to be sent to the applicant. The final List of Questions was sent to the applicant on 21 May 2015.
- The applicant submitted the responses to the CHMP List of Questions on 20 August 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 September 2015.
- During the meeting on 16-19 October 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation for a new route of administration of Zostavax.

2. Scientific discussion

2.1. Introduction

Zostavax is an attenuated live virus vaccine containing varicella-zoster virus strain OKA/Merck. It is a sterile lyophilized preparation supplied with water for injection as diluent. Following reconstitution each 0.5 ml dose contains a minimum of 19,400 PFU (plaque-forming units) of Oka/Merck varicella virus.

Zostavax is indicated for prevention of herpes zoster (HZ) and herpes zoster-related post-herpetic neuralgia (PHN) in individuals 50 years of age or older. Currently, the vaccine has to be administered by subcutaneous (SC) injection preferably in the deltoid region.

None of the Zostavax studies conducted during the clinical development assessed the safety, tolerability and immune response of Zostavax administered by intramuscular (IM) route. With this application, the final CSR of study ZTV03C was provided to seek approval for the administration of Zostavax by the IM route.

On 3 July 2014, in view of the submission of the new route of administration application, the Applicant submitted under Article 13 of Regulation (EC) No 1901/2006 as amended, the request for a product-specific waiver for all paediatric subjects. The Paediatric Committee (PDCO) of the EMA agreed to grant a product-specific waiver for all subsets of the paediatric population and the condition 'prevention of varicella-zoster reactivation' in accordance with Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients (EMA decision P/0309/2014, 24 November 2014).

The waiver applies to:

• all subsets of the paediatric population from birth to less than 18 years of age;

• for powder and solvent for suspension for injection, subcutaneous use, intramuscular use;

• on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subsets.

2.2. Quality aspects

N/A

2.3. Non-clinical aspects

N/A

2.3.1. Environmental Risk assessment

The same ERA for Zostavax which was included in the dossier of the initial marketing authorisation application was submitted and assessed for the approval of the IM administration as an additional route of vaccination. The CHMP agreed that the risk of attenuated zoster vaccine live to the environment is low. Minimal viral shedding has been associated with attenuated viruses and the shedding of vaccine virus has been rarely linked to disease transmission. The newly proposed IM route of administration in addition to the already established SC administration of Zostavax does not change the environmental risk of this live zoster vaccine. CHMP therefore agreed that the current ERA is appropriate.

2.4. Clinical aspects

2.4.1. Introduction

Study ZTV03C was an open-label randomised, comparative, two-arm, multicentre study to assess the immunogenicity and safety of Zostavax administered either by the SC or IM routes of administration in subjects 50 years of age and older.

The efficacy of Zostavax was previously demonstrated in Protocol 004, also known as the Shingles Prevention Study (SPS), a randomised, double-blind, placebo-controlled, multicentre efficacy study in adults ≥ 60 years of age. The protective efficacy of a single dose of Zostavax against HZ was 51% (95% CI: [44 to 58%]). The indication was extended to subjects 50–59 years of age by demonstrating non-inferior immunogenicity (Variation II/003). The VZV-antibody responses measured by gpELISA at 6 weeks post vaccination (titre and fold-rise vs. pre-vaccination titres) were accepted as surrogates of efficacy.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Types of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Study Vaccine(s): Dosing Schedule; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of vaccination Period	Study Status; Type of Report
Immuno-genicity and safety	ZTV03C EudraCT Number: 2009-012458-19	5.3.5.4	**Co-primary objectives:** • 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** • To evaluate the immunogenicity as measured by VZV antibody titres (gpELISA) at 4 weeks following ZOSTAVAX® administered by IM or SC route.	Phase 3, open-label, randomised, comparative, 2 arms, multicentre study conducted in 10 centres (7 in Germany and 3 in Spain).	**ZOSTAVAX®:** preparation of shingles (herpes zoster) vaccine live **Dose:** 0.65 mL containing not less than 19,400 Plaque-forming Units (PFU) of Varicella-zoster virus, Oka/Merck strain (live, attenuated). **Route**: intramuscular (IM) or subcutaneous (SC) injection in the deltoid region of upper arm (preferably in non-dominant arm).	354 subjects Group 1 (IM route): 177 Group 2 (SC route): 177	Healthy subjects of either gender aged ≥50 years on day of vaccination.	FVFS: 20 June 2011 LVLS: 15 October 2012	Complete; Full
			• 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. • To describe the safety profile of ZOSTAVAX® administered by IM or SC route.						
FVFS: First visit of the first subject; LVLS: Last visit of the last subject									

2.4.2. Pharmacokinetics

N/A

2.4.3. Pharmacodynamics

N/A

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

N/A

2.5.2. Main 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)

Study ZTV03C was an open-label, randomised, comparative, two-arm, multicentre study to evaluate the immunogenicity and safety of Zostavax when administered by intramuscular route or subcutaneous route to subjects ⩾50 years of age. The study was conducted in 10 centres in Germany and Spain from June 2012 to October 2012. The entire study period was 16 months (from First Visit First Subject to Last Visit Last Subject). Subjects were expected to participate for 28 to 35 days. The maximum individual follow-up period for safety and immunogenicity was 35 days post-vaccination.

Methods

Study Participants

Eligible for enrolment were subjects of either sex aged 50 years or older on the day of vaccination, who had a history of varicella or who have resided for more than 30 years in a country with endemic VZV infection, able to attend all scheduled visits and to comply with all study procedures. Subjects with a history of clinically diagnosed HZ were excluded. Furthermore, immunocompromised and subjects with thrombocytopenia or any other coagulation disorder that would contraindicate intramuscular injection were not enrolled. A full list of inclusion and exclusion criteria is provided in the Clinical Study Report (CSR).

The CHMP noted that inclusion and exclusion criteria were adequately chosen. The age of the studied subjects (≥ 50 years) reflect the target population.

Treatments

All subjects received one dose of 0.65 ml Zostavax. The route of administration was the deltoid region of the upper arm, either IM or SC. The CHMP noted that all participants received the currently approved Zostavax.

The administered dose for all participants and the provided pharmaceutical form was in accordance with the approved SmPC.

Objectives

Primary objectives

Two co-primary objectives were defined:

- To demonstrate that Zostavax administered by IM route is non-inferior to Zostavax administered by SC route in terms of 4-week post-vaccination antibody titres (gpELISA) to 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

Immunogenicity:

- To evaluate the 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 IFN-γ- ELISPOT at 4 weeks following Zostavax administered by IM or SC route.

Safety:

- To describe the safety profile of Zostavax administered by IM or SC route.

Two co-primary hypotheses were tested.

The hypothesis for the first co-primary objective was that Zostavax administered by IM route is non-inferior to Zostavax administered by SC route in terms of VZV antibody titres as measured by gpELISA at 4 weeks post-vaccination.

The hypothesis for the second co-primary objective was that Zostavax administered by IM route induces an acceptable VZV antibody Geometric Mean Fold Rise (GMFR) as measured by gpELISA from pre- to 4-week post-vaccination.

Success for the study required that both co-primary hypotheses were met.

No formal hypothesis was tested for the secondary immunogenicity and safety objectives.

Outcomes/endpoints

The primary immunogenicity endpoints were:

- The 4-week post-vaccination VZV antibody Geometric Mean Titre (GMT) in both groups;
- The VZV antibody GMFR from pre- to 4-week post-vaccination in the IM Group.

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.

The safety endpoints were the percentage of subjects with the following AEs:

- 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
  - Varicella, Varicella-like rashes, Herpes zoster (or shingles) and Zoster-like rashes
  - Other systemic AEs
- From Day 0 to Visit 2 (i.e. Day 28 to Day 35):
  - Serious adverse events (SAEs)

Following the release of the results for the group comparison for injection site reactions a post-hoc analysis was performed to explore the relation between age of participants and rates of injection site reactions for both vaccine routes.

Sample size

354 subjects were randomised to two vaccine groups (IM and IC administration of Zostavax, 177 per group). A subset of 228 participants (115 in the IM and 113 in the SC vaccine group) was randomised to the Interferon gamma (IFN-γ) Enzyme-Linked ImmunoSpot (ELISPOT) group for assessment of cell mediated immunity (CMI).

Randomisation

Subjects were allocated in a 1:1 ratio by permuted block randomisation with blocks of 4 or 6. The randomisation was stratified by ELISPOT subset status (ELISPOT versus non ELISPOT site) and age with 3 strata (50- 59, 60- 69 and ≥ 70 years of age). Randomisation was performed through the electronic case report form. The CHMP noted that the method of randomisation is acceptable for the study design.

Blinding (masking)

The study is open-label but immunogenicity assays were performed by laboratory staff blinded to the vaccine group.

Statistical methods

The statistical analysis was performed using the SAS software version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA).

The main immunogenicity analysis was performed on the Per Protocol Set (PPS) and a second supportive analysis on the Full Analysis Set (FAS). Two PPS (PPS and ELISPOT PPS) and two FAS (FAS and ELISPOT FAS) were defined.

- PPS: all randomised subjects who had received the study vaccine and had at least one valid immunogenicity evaluation for VZV antibody;

- ELISPOT PPS: randomised subjects of the ELISPOT subset who had received the study vaccine and had at least one valid immunogenicity evaluation for VZV INF-γ ELISPOT count;
- FAS: randomised subjects who had received the study vaccine and had any immunogenicity evaluation for VZV antibody;
- ELISPOT FAS: randomised subjects of the ELISPOT subset who had received the study vaccine and had any immunogenicity evaluation for VZV INF-γ ELISPOT count.

Immunogenicity

Two statistical hypotheses were tested for assessing the two co-primary immunogenicity endpoints.

The first hypothesis was that Zostavax administered by IM route is non-inferior to Zostavax administered by SC route in terms of VZV antibody titres as measured by gpELISA at 4 weeks post-vaccination. Non-inferiority was demonstrated if the two-sided 95% CI around the 4-week post-vaccination GMT ratio (IM/SC) excludes a 1.5 decrease or more (i.e. the lower bound of the two-sided 95% CI being > 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 second hypothesis was that Zostavax administered by IM route induces an acceptable VZV antibody Geometric Mean Fold Rise (GMFR) as measured by gpELISA from pre-to 4-week post-vaccination. Acceptability was demonstrated if the two-sided 95% CI around the GMFR from pre- to 4-week post-vaccination excludes fold-rise less or equal to 1.4 (i.e. the lower bound of the two-sided 95% CI being > 1.4). This hypothesis was tested using the Student's t distribution for paired samples on log-transformed data.

Success for the study required that both co-primary hypotheses were met.

The secondary immunogenicity objectives were descriptive. No formal hypothesis was tested. Descriptive immunogenicity statistics included gpELISA GMT and GMFR (with two-sided 95% CI) in both groups and IFN-γ ELISPOT GMC and GMFR (with two-sided 95% CI) in both groups of the ELISPOT subset.

Adjustment of covariates

The statistical analysis for the demonstration of non-inferiority of VZV antibodies in the IM vaccination group compared with the SC vaccination group included age at vaccination and pre-vaccination titres as a covariate. gpElisa GMT (IM Group/SC Group) and associated 95% CIs were calculated using a longitude data analysis model (LDA). In addition a sensitivity analysis was performed to evaluate the effect of the choice of the covariates on the comparison of both vaccination routes in terms of 4-week post-vaccination VZV antibody titres by gpELISA. The gpELISA GMT ratio and associated 95% CIs were estimated based on two alternative models: an analysis of variance model (ANOVA) including group and an analysis of covariance model (ANCOVA) adjusting for pre-vaccination titres and age at vaccination in years.

Safety

Safety results were descriptive. No formal hypothesis was tested. The safety analysis was performed on the Safety Analysis Set (SAS) that included all subjects who received the study vaccine and who had safety follow-up data. AEs were presented according to administration route. Risk differences and two-sided 95% CIs for IM and SC route were provided for injection site and systemic AEs with an incidence $\geq$ 2.2%. P-values corresponding to tests of significance of the risk differences were provided for solicited injections site AEs.

The CHMP noted that the applied statistical methods were adequate. The non-inferiority margin chosen for the first immunogenicity hypothesis was commonly used in the Zostavax clinical development. The criterion for an acceptable VZV GMFR is the same as was used to compare the efficacy and immunogenicity in subjects 50-59 years of age (ZEST study) with the initial pivotal shingles prevention study. The criterion was found acceptable at that time, and it remains acceptable.

Results

Disposition of subjects

A total of 359 subjects was screened and signed informed consent within two recruitment periods. One of the screened participants was lost to follow up before randomisation and 4 participants met exclusion criteria. 354 participants were randomised equally to the two vaccination groups. One participant randomised to the IM route vaccination group and included in the ELISPOT subset was withdrawn before vaccination due to history of HZ. Thus, 353 subjects were vaccinated (176 in the IM Group and 177 in the SC Group). All vaccinated subjects completed the study. For one subject of Group 2 (SC administration) the blood sample for immunity assessment scheduled for Visit 2 was not drawn due to non-compliance with GCP.

Table 1. Disposition of subjects in study

	Group 1 - IM route	Group 2 - SC route	All
	n (%)	n (%)	n (%)
N screened (a)			359
Screening failures			*5 (b)*
N randomised	177	177	354
N vaccinated	176 (99.4%)	177 (100%)	353 (99.7%)
N withdrawn before vaccination	1 (0.6%)	0	1 (0.3%)
Other reason	1 (0.6%)	0	1 (0.3%)
N completed	176 (99.4%)	177 (100%)	353 (99.7%)
N withdrawn after vaccination	0	0	0

Percentages are calculated based on the number of randomised subjects
(a) Informed consent form signed
(b) 1 subject lost to follow-up and 4 non respect of inclusion / exclusion criteria

For the ELISPOT subset 228 subjects were screened and randomised (115 in the IM group and 113 in the SC group). Only one subject randomised to the ELISPOT t subset of Group 1 was withdrawn due to history of HZ. Of the participants, 174 (49.2%) were included in 7 centres in Germany and 180 (50.8%) in Spain. Participants randomised to the ELISPOT subset were recruited in one German and in all Spanish sites.

The CHMP noted that subjects were equally randomised to the two vaccination groups and the number of subjects in the ELISPOT subset was comparable between both groups (115 versus 113) subjects. Drop-outs were very rare in the study (0.6%). Only one randomised subject (in Group 1) was not vaccinated due to a history of HZ. All vaccinated subjects completed the study.

Recruitment

An amendment of clinical study protocol (Amendment 3) was issued following a 10-month temporary halt of the subject recruitment due to a manufacturing investigation on the IMP opened by the MAH. Consequences of the manufacturing investigations were that a new batch of Zostavax was used in the clinical trial period following the halt of the study and participants were recruited within two recruitment periods. 201 participants were screened and signed informed consent during the first recruitment period from 20 June

2011 to 24 August 2011 and 158 subjects during the second recruitment period from 11 June 2012 to 12 September 2012 following the 10-month halt. Raw estimates of the post-vaccination GMT ratio and two-sided 95% CI were calculated within each of the two recruitment periods. Results were evaluated in term of consistency between the recruitment periods. Consistency was shown.

The Applicant was requested during the procedure to outline the manufacturing investigation on the IMP leading to a halt of the study and the implementation of a new batch of Zostavax. Further, the Applicant was requested to outline the methods for showing consistency of data collected in the two recruitment periods and to provide the data.

The MAH provided detailed information regarding the investigation which led to the temporary halt of study ZTV03C. After the conclusion of the investigation and the corrective actions, the trial was restarted with a new lot of vaccine (due to the expiry of the initially investigated lot).

For the second question, the MAH outlined the methods used (sensitivity analysis) to show consistency of data collection in the two recruitment periods and provided the tabulated data. Immunogenicity data evaluated in the clinical trial were calculated within each of the two recruitment periods. CHMP agreed that the provided immunogenicity data for each recruitment period are comparable.

Conduct of the study

Baseline data

The mean age was 62.6 years in both vaccination groups with a range between 50.0 and 90.5 years. The number of subjects included in the three different age strata (50-59 years, 60-69 years and ≥ 70 years) was comparable between the two groups. The majority of enrolled subjects were between 50-59 years in both vaccination groups (overall 46.0% of subjects). 31.4% of all randomised subjects were between 60 and 69 years of age and 22.6% were ≥ 70 years of age. Slightly more females than males were randomised (55.1% versus 44.9%).

The two vaccination groups were overall comparable regarding the medical history of included subjects. The most frequently reported underlying medical conditions by SOC in both vaccination groups were vascular disorders (most frequent hypertension) reported from 52.3% of subjects, metabolism and nutrition disorders (most frequent hypercholesterolemia) by 42.7% of all subjects and musculoskeletal and connective tissue disorders (most frequent osteoarthritis) by 42.1% of all subjects. The two vaccination groups were generally comparable regarding the use of specific medication within 28 days prior to study vaccination (81.9% of subjects in each vaccination group). Of note, one subject in the IM vaccination group received tetanus vaccine during the study.

The CHMP noted that the two vaccine groups were balanced with respect to age, gender, heights, weight, underlying medical conditions and use of medication 28 days prior to vaccination. Demographic data of the randomised set and the ELISPOT subset were also comparable.

Numbers analysed

One subject randomised to the IM vaccination group and the ELISPOT subset was not vaccinated due to history of HZ, thus the FAS and the safety set included 353 subjects. Another subject in the IM vaccination group received immunosuppressive therapy prior to vaccination and was therefore excluded from the PPS. Thus 352 subjects were included in the PPS for evaluation of immunogenicity.

Table 2. Description of Immunogenicity Analysis Set (Source: CSR, Page 62)

	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 Randomised Subset (a)	**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%)
Percentages are calculated based on the number of randomised subjects (a) Subjects from sites 07 to 10			

The CHMP noted that the number of protocol deviations and subjects excluded from PPS (randomised and ELISPOT set) was low in the study.

Outcomes and estimation

Immunogenicity results

Humoral immune response was evaluated by measuring VZV specific gpELISA. In a subset of participants CMI was assessed by VZV IFN-γ ELISPOT.

CHMP noted that both assays used to evaluate the immunogenicity were previously employed in the pivotal efficacy shingles prevention study (SPS, Protocol 004) and in the studies to extend the age indication to subjects aged 50–59 years (P010, P011; ref to variation II/003). Although there is no definite cut-off value, gp-antibody titres and fold rise of titres were accepted as surrogates for vaccine efficacy in terms of protection against HZ and post-herpetic neuralgia PHN. CMI plays a critical role in protection against HZ. However, it is unknown what CMI response is predictive for (long term) protection.

The primary immunogenicity analysis was performed on the PPS and a second supportive analysis on the FAS. Results were generally comparable in both sets.

The first co-primary objective pertained to the GMT as measured by the VZV gpELISA (Table 3). Non-inferiority was demonstrated as the lower bound of the two-sided 95% CI around the gpELISA GMT ratio (IM/SC route) is greater than 2/3 (i.e. 0.67).

Table 3. Non-Inferiority Analysis of 4-Week Post-Vaccination VZV Antibody Titres (gpELISA units/mL)-IM Route Versus SC Route-Per Protocol Set (Source: CSR, Page 67)

	Group 1 - IM route (N=175)	Group 2 - SC route (N=177)
n	175	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 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. n: number of subjects with available data		

For the second formal NI tested criterion, non-inferiority was demonstrated if the two-sided 95% CI around the GMFR from pre-to 4-week post-vaccination was > 1.4. As shown by the results given in Table 4 non-inferiority of the intramuscular compared to the subcutaneous route of administration was demonstrated because the GMFR (Post-/Pre-vaccination) was 2.7 and the lower bound of the 2-sided 95% CI was 2.4.

Table 4. Pre-and 4-Week Post-Vaccination GMT and GMFR of VZV Antibody Titres (gpELISA units/mL) for IM Route-Per Protocol Set (Source: CSR, Page 68)

	Group 1 - IM route (N=175)	
	Pre-vaccination	**Post-vaccination**
n	175	168
GMT	144.6	395.3
95% CI	[125.3;166.9]	[350.6;445.6]
n		168
GMFR (Post/Pre-vaccination)		**2.7**
95% CI		**[2.4**;3.0]
Acceptability (a)		Met
(a) Acceptability is demonstrated if the lower bound of the two-sided 95% CI is >1.4.		
n: number of subjects with available data		

The CHMP noted that both pre-defined formal non-inferiority criteria were met, indicating that both routes of administration have similar immunogenicity. Of note, for the GMT evaluation a time interval of 4 weeks post vaccination was investigated as in the efficacy trials conducted in subjects 50-59 years (i.e. ZEST study) while in the initial SPS efficacy trial a 6-week interval was assessed.

Immunogenicity stratified by age

Immunogenicity data were provided for the overall study population and by age stratum. No difference in the antibody responses were reported for the pre-and 4-week post-vaccination GMTs and GMFRs in both vaccination groups (Table 5). Results for PPS and FAS were consistent.

Table 5. Pre-and 4-Week Post-Vaccination GMT and GMFR of VZV Antibody Titres (gpELISA units/ml) -Per Protocol Set (Source: CSR, Page 147)

	Group 1 - IM route (N=175)		Group 2 - SC route (N=177)	
	Pre-vaccination	**Post-vaccination**	**Pre-vaccination**	**Post-vaccination**
VZV gpELISA antibody				
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]
Median	142.6	369.4	164.0	354.9
Min. ; Max.	2.7 ; 1806.9	41.6 ; 2980.9	1.9 ; 1719.2	22.3 ; 2497.2
Missing data	0	7	1	4
n		168		172
GMFR (Post/Pre-vaccination)		2.7		2.5
95% CI		[2.4;3.0]		[2.2;2.8]
Median		2.4		2.2
Min. ; Max.		0.7 ; 48.5		0.7 ; 35.9
Missing data		7		5

GMTs and GMFRs were provided for the three age strata implemented in the study (Table 6). No significant differences in the antibody responses between the two vaccination groups were observed across age strata.

Table 6. Pre- and post-vaccination GMT and GMFR of VZV antibody titres (gpELISA units/ml) by age stratum - Per Protocol Set (Source: CSR, Page 149)

	Group 1 - IM route (N=175)		Group 2 - SC route (N=177)	
	Pre-vaccination	Post-vaccination	Pre-vaccination	Post-vaccination
VZV gpELISA antibody by age stratum				
50 to 59 years old				
n	79	74	82	79
GMT	133.9	446.1	164.8	454.1
95% CI	[108.9;164.7]	[368.1;540.6]	[134.3;202.3]	[390.1;528.5]
Missing data	0	5	0	3
n		74		79
GMFR (Post/Pre-vaccination)		3.2		2.8
95% CI		[2.7;3.9]		[2.3;3.4]
Missing data		5		3
60 to 69 years old				
n	56	55	54	54
GMT	154.5	394.7	158.7	338.6
95% CI	[117.4;203.3]	[321.1;485.2]	[121.4;207.4]	[273.1;419.8]
Missing data	0	1	1	1
n		55		53
GMFR (Post/Pre-vaccination)		2.5		2.2
95% CI		[2.0;3.1]		[1.8;2.6]
Missing data		1		2
>=70 years old				
n	40	39	40	40
GMT	153.4	314.8	147.7	356.3
95% CI	[112.8;208.5]	[250.7;395.3]	[108.1;201.9]	[268.9;471.9]
Missing data	0	1	0	0
n		39		40
GMFR (Post/Pre-vaccination)		2.1		2.4
95% CI		[1.8;2.5]		[1.9;3.0]
Missing data		1		0

CMI results

Pre-and 4-week post-vaccination IFN-γ Elispot GMCs and the IFN-γ Elispot and GMFR (4-week post-vaccination/ pre-vaccination) were comparable between the two groups. Results for PPS and FAS were consistent. CMI results are provided in Table 7 and Table 8 below.

Table 7. Pre and post vaccination GMC and GMFR of VZV INF-gamma ELISPOT counts - ELISPOT Per Protocol Set (Source: CSR, Page 155)

	Group 1 - IM route (N=111)		Group 2 - SC route (N=111)	
	Pre-vaccination	Post-vaccination	Pre-vaccination	Post-vaccination
VZV INF-gamma ELISPOT counts				
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]
Median	81.0	238.0	86.0	250.0
Min. ; Max.	0.5 ; 511.0	15.0 ; 1280.0	0.5 ; 404.0	7.0 ; 981.0
Missing data	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]
Median		2.7		2.6
Min. ; Max.		0.8 ; 724.0		0.6 ; 148.0
Missing data		18		21

Table 8. Pre and post vaccination GMC and GMFR of VZV INF-gamma ELISPOT counts - ELISPOT Full Analysis Set (Source: CSR, Page 156)

	Group 1 - IM route (N=113)		Group 2 - SC route (N=111)	
	Pre-vaccination	Post-vaccination	Pre-vaccination	Post-vaccination
VZV INF-gamma ELISPOT counts				
n	101	108	96	108
GMC	64.3	217.0	58.4	197.8
95% CI	[49.6;83.4]	[182.1;258.6]	[42.6;80.2]	[164.4;238.0]
Median	81.0	262.0	86.0	252.0
Min. ; Max.	0.5 ; 511.0	15.0 ; 1280.0	0.5 ; 404.0	7.0 ; 981.0
Missing data	12	5	15	3
n		96		93
GMFR (Post/Pre-vaccination)		3.2		3.3
95% CI		[2.7;3.8]		[2.7;4.2]
Median		2.7		2.6
Min. ; Max.		0.8 ; 724.0		0.6 ; 148.0
Missing data		17		18

Ancillary analyses

N/A

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

N/A

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The study was designed to assess whether the immune response following IM administration of Zostavax is non-inferior to the immune response after the SC administration.

Of note, while the proof of efficacy of Zostavax was not an objective of the study, the efficacy of Zostavax was previously demonstrated in Protocol 004, also known as the Shingles Prevention Study (SPS), a randomised, double-blind, placebo-controlled, multicentre efficacy study in adults ≥ 60 years of age (pivotal study for the initial marketing authorisation application). It was shown that the protective efficacy of a single dose of Zostavax against HZ was 51% (95% CI: [44 to 58%]). In June 2007, the indication was subsequently extended from subjects 60 years old down to subjects 50–59 years of age by demonstrating non-inferiority of immunogenicity (ref to variation II/003). The immunogenicity data presented in that application (II03) were derived from an integrated report, which analysed combined immunogenicity data from two clinical studies, Protocol 010 and Protocol 011. These data showed that ZOSTAVAX induces a VZV antibody response in subjects 50 to 59 years of age that is non-inferior to that in subjects ≥ 60 years of age, and thereby provided an immunological bridge to the vaccine efficacy demonstrated in the SPS study in subjects ≥ 60 years of age. At that time, the CHMP agreed that VZV antibody response measured by gpELISA at 4 or 6 weeks post-vaccination (titre and fold-rise from pre-vaccination) in individuals vaccinated with ZOSTAVAX equally correlate with the reduction of HZ and thus represent an indirect measurement of the vaccine effect against HZ, and can be used for bridging immunogenicity to efficacy in clinical studies (surrogates of efficacy).

Study ZTV03C was overall well conducted and had a low drop-out rate and balanced vaccination groups. One limitation of the design could have been the open-label design due to the two different routes of administration. However, the laboratory staff performing the immunogenicity assays was not aware of the route of administration as the immunogenicity assays were performed on blinded samples.

Participants were recruited within two recruitment periods because of a 10-month temporary halt due to manufacturing investigation on the vaccine. Raw estimates of the post-vaccination GMT ratio and two-sided 95% CI were calculated within each of the two recruitment periods. Results were evaluated in terms of consistency between the recruitment periods and consistency was shown. Immunogenicity data for PPS and FAS were provided. Results for both sets were comparable.

Two formal co-primary objectives were defined to demonstrate that Zostavax IM administration is non-inferior to SC administration in terms of 4-week post-vaccination GMTS, and elicits an acceptable GMFR of antibody titres measured by gpELISA.

Efficacy data and additional analyses

Both pre-defined formal non-inferiority and acceptability criteria were met in the submitted study.

The descriptive analysis showed that gpElisa GMTs (pre- and post-vaccination) and GMFRs are comparable between the IM and the SC vaccination Group.

GMCs pre-and post-vaccination and GMFR obtained using the INF-γ ELISPOT assay in a subset of 222 subjects (111 in each group, PPS) were comparable between the two groups, although INF-γ ELISPOT results were not provided by age stratum.

In summary, the immunogenicity data showed that the immune response elicited by IM vaccination of Zostavax is comparable to that elicited by SC administration. Non-inferiority of the intramuscular compared to the subcutaneous route of administration was shown.

2.5.4. Conclusions on the clinical efficacy

CHMP agreed that the provided clinical data support the administration of Zostavax via the intramuscular route, in addition to the subcutaneous route.

2.6. Clinical safety

A secondary objective of study ZTV03C was to assess the safety profile of Zostavax administered by IM or SC route. Safety results were descriptive. No formal hypothesis was tested. The safety analysis was performed on the Safety Analysis Set (SAS) that included all subjects who received the study vaccine and who had safety follow-up data.

Patient exposure

Of the enrolled 354 subjects one subject randomised to the IM vaccination group was withdrawn before vaccination due to history of HZ. All other subjects received one dose of Zostavax and were included into the SAS.

Adverse events

The following adverse events (AEs) were recorded:

- Solicited injection site AEs (injection site erythema, injection site swelling, injection site pain) from Day 0 to Day 4;
- Unsolicited injection site AEs from Day 0 to Day 28;
- Systemic AES from Day 0 to Day 28;
- Varicella (VZ)/VZ-like or herpes zoster (HZ)/HZ-like rash from Day 0 to Day 28;
- Oral temperature each time the subject felt febrile;
- Serious adverse events (SAEs) during the entire study period, i.e. from Day 0 until the 4-week post-vaccination blood sample collection at Day 28 to Day 35.

Adverse events were assessed for causality and graded for intensity by a 3-point scale (mild/moderate/severe). AEs were classified according to preferred term (PT) and system organ class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA).

Summary of AEs

The proportion of subjects who reported at least one AE was smaller in the IM compared with the SC vaccination group. This is mainly due to a higher incidence of injection site adverse events in the SC group. The percentage of subjects reporting at least one systemic AE was comparable between IM and SC

vaccination group. Three subjects experienced SAEs, none were considered vaccine-related by the investigator. No AE led to study withdrawal. No deaths were reported during the study. The safety results are summarised in Table 9 below.

Table 9. Global Summary of Safety-Safety Analysis Set (Source: CSR, Page 78)

	Group 1 - IM route (N=176)		Group 2 - SC route (N=177)	
	n (%)	95% CI	n (%)	95% CI
AE from Day 0 to Day 28	**83 (47.2%)**	**[39.6%;54.8%]**	**123 (69.5%)**	**[62.1%;76.2%]**
Vaccine-related AE from Day 0 to Day 28	68 (38.6%)	[31.4%;46.3%]	118 (66.7%)	[59.2%;73.6%]
ISR from Day 0 to Day 28	**60 (34.1%)**	**[27.1%;41.6%]**	**114 (64.4%)**	**[56.9%;71.4%]**
Solicited ISR from Day 0 to Day 4	58 (33.0%)	[26.1%;40.4%]	110 (62.1%)	[54.6%;69.3%]
Injection-site erythema	28 (15.9%)	[10.8%;22.2%]	93 (52.5%)	[44.9%;60.1%]
Injection-site pain	45 (25.6%)	[19.3%;32.7%]	70 (39.5%)	[32.3%;47.2%]
Injection-site swelling	24 (13.6%)	[8.9%;19.6%]	66 (37.3%)	[30.1%;44.9%]
Unsolicited ISR from Day 0 to Day 28	9 (5.1%)	[2.4%;9.5%]	14 (7.9%)	[4.4%;12.9%]
Systemic AE from Day 0 to Day 28	**41 (23.3%)**	**[17.3%;30.2%]**	**40 (22.6%)**	**[16.7%;29.5%]**
Vaccine-related AE from Day 0 to Day 28	12 (6.8%)	[3.6%;11.6%]	13 (7.3%)	[4.0%;12.2%]
Injection-site rash of interest from Day 0 to Day 28	**0**	**[0%;2.1%]**	**0**	**[0%;2.1%]**
Non injection-site rash of interest from Day 0 to Day 28	**1 (0.6%)**	**[<0.1%;3.1%]**	**0**	**[0%;2.1%]**
Herpes zoster, zoster-like rash from Day 0 to Day 28	1 (0.6%)	[<0.1%;3.1%]	0	[0%;2.1%]
SAE at any time post-vaccination	**1 (0.6%)**	**[<0.1%;3.1%]**	**2 (1.1%)**	**[0.1%;4.0%]**
Vaccine-related SAE at any time post-vaccination	0	[0%;2.1%]	0	[0%;2.1%]
Withdrawal due to an AE at any time post-vaccination	**0**	**[0%;2.1%]**	**0**	**[0%;2.1%]**

n (%): number (percentage) of subjects presenting at least once the considered event
95% CI: two-sided 95% CI of the percentage
of subjects presenting at least once the considered event is calculated using the exact binomial method.
AE: Adverse Event; ISR: Injection-Site adverse Reaction, SAE: Serious Adverse Event

Injection site AEs

The proportion of subjects reporting at least one injection site AE was approximately twice as high in the SC vaccination group compared with the IM vaccination group (Table 10). The most frequently reported injection site AEs in both vaccination groups were injection site pain, injection site swelling and injection site erythema. The proportion of subjects reporting injection site erythema, swelling, pain and pruritus was lower in the IM vaccination group. The difference was statistically significant (Table 9). The only injection site AE that was slightly more frequently observed in the IM vaccination group was injection site haematoma. However, the frequency of injection site haematoma was generally low in both groups.

Table 10. Number (%) of subjects with injection site adverse reactions from Day 0 to Day 28-SAS (Source: CSR, Page 165)

	Group 1 IM route (N=176)		Group 2 SC route (N=177)	
	n AE	n (%)	n AE	n (%)
Injection-site adverse reaction from Day 0 to Day 28	106	60 (34.1%)	247	114 (64.4%)
Solicited injection-site adverse reactions from Day 0 to Day 4	97	58 (33.0%)	229	110 (62.1%)
Injection site erythema	28	28 (15.9%)	93	93 (52.5%)
Injection site pain	45	45 (25.6%)	70	70 (39.5%)
Injection site swelling	24	24 (13.6%)	66	66 (37.3%)
Other injection-site adverse reaction from Day 0 to Day 28 (a)	9	9 (5.1%)	18	14 (7.9%)
Injection site pruritus	3	3 (1.7%)	13	11 (6.2%)
Injection site haematoma	2	2 (1.1%)	1	1 (0.6%)
Injection site erythema	1	1 (0.6%)	1	1 (0.6%)
Injection site induration	1	1 (0.6%)	1	1 (0.6%)
Injection site pain	1	1 (0.6%)	0	0
Injection site reaction	1	1 (0.6%)	0	0
Injection site swelling	0	0	1	1 (0.6%)
Injection site warmth	0	0	1	1 (0.6%)

n AE: number of episodes of the considered event
n (%): number (percentage) of subjects presenting at least once the considered event
(a) Including injection site erythema, pain and swelling from Day 5 to Day 28

Table 11. Comparison of IM route and SC route on the percentages of subjects with injection site AES (incidence >= 2.2% in at least one group)-SAS (Source: CSR, Page 166).

	Group 1 IM route (N=176)		Group 2 SC route (N=177)				
	N subj (%)	95%CI	N subj (%)	95%CI	Risk difference (%)	95%CI	p-value
Injection-site adverse reaction	60 (34.1%)	[27.1%;41.6%]	114 (64.4%)	[56.9%;71.4%]	-30.3	[-39.9;-20.1]	
Solicited injection-site adverse reaction from Day 0 to Day 4	58 (33.0%)	[26.1%;40.4%]	110 (62.1%)	[54.6%;69.3%]	-29.2	[-38.8;-18.9]	
Injection site erythema	28 (15.9%)	[10.8%;22.2%]	93 (52.5%)	[44.9%;60.1%]	-36.6	[-45.4;-27.2]	<0.001
Injection site pain	45 (25.6%)	[19.3%;32.7%]	70 (39.5%)	[32.3%;47.2%]	-14.0	[-23.5;-4.2]	0.005
Injection site swelling	24 (13.6%)	[8.9%;19.6%]	66 (37.3%)	[30.1%;44.9%]	-23.7	[-32.3;-14.8]	<0.001
Other injection-site adverse reaction from Day 0 to Day 28 (a)	9 (5.1%)	[2.4%;9.5%]	14 (7.9%)	[4.4%;12.9%]	-2.8	[-8.4;2.5]	
Injection site pruritus	3 (1.7%)	[0.4%;4.9%]	11 (6.2%)	[3.1%;10.8%]	-4.5	[-9.3;-0.5]	

n (%): number (percentage) of subjects presenting at least once the considered event
(a) Including injection site erythema, pain and swelling from Day 5 to Day 28

Injection site AEs by maximum intensity, day of onset and duration

The majority of injection site AEs was graded as mild to moderate in both vaccination groups. The only injection site AEs graded as severe were pain (2 subjects in the SC group), erythema (2 subjects in the IM and 3 subjects in the SC vaccination group) and swelling (1 subject in the IM and 4 subjects in the SC vaccination group). Grading for injection site swelling was missing in one subject of the IM vaccination group.

Most of subjects in both vaccination groups reported injection site AEs from Day 0 to Day 4 (33.0% in the IM and 62.1% in the SC vaccination group). Only few subjects reported injection site AEs from Day 0 to Day 28 (5.1% versus 7.9%, respectively).

The majority of subjects in both vaccination groups reported injection site AEs lasting 1-7 days. Only few reported duration up to 14 days or longer.

Injection site AEs by age stratum

Risk differences for solicited injection site AEs and pruritus were provided for the three age strata.

In line with results from previous Zostavax studies local reactogenicity was generally higher in younger subjects than in the older ones in the SC vaccination group of the submitted study. Overall, 65.9% of subjects 50 to 59 years of age, 72.7% of subjects 60 to 69 years of age and 50.0% of subjects 70 years and older reported at least one injection site AE. This could not be observed in the IM vaccination group of study ZTV03C were the proportion of subjects of 70 years and older reporting at least one injection site AE was higher than in subjects 60 to 69 years of age (37.5% versus 19.6%). In subjects 50 to 59 years of age 46.3% reported at least one injection site AE.

In the age stratum 50 to 59 years of age, the proportion of subjects reporting injection site erythema (46.3% versus 65.9%, risk difference [RD]-33.7 [95% CI -46.8;-19.1] and swelling (18.8% versus 41.5%, RD-22.7 [95% CI -36.0;-8.7]) was significantly lower in the IM than in the SC vaccination group.

In the age stratum 60 to 69 years of age, the proportion of subjects reporting injection-site erythema (12.5% versus 63.6%, RD -22.7 [-36.0;-8.7], injection site pain (8.9% versus 36.4%, RD -27.4 [95% CI -42.1;-12.4]), injection site swelling (8.9% versus 45.5%, RD -36.5 [95% CI -51.1;-20.8]) and injection site pruritus (0% versus 9.1%, RD -9.1 [95% CI -19.6;-2.3]) was statistically significant lower in the IM group compared with the SC group.

In the age stratum $\geq$ 70 years old, there was a statistically significant difference between IM and SC vaccination group only for the incidence of injection-site erythema (12.5% versus 35.0%, RD -22.5% [95% CI: -40.3;-3.9]).

The CHMP noted that local reactogenicity was significantly lower in subjects receiving Zostavax by IM route compared with subjects vaccinated by SC route.

Systemic adverse events

The proportion of subjects reporting at least one systemic adverse event was comparable in both vaccination groups (23.3% in the IM and 22.6% in the SC vaccination group). The most frequently reported systemic AEs by SOC were infection and infestations (mainly nasopharyngitis and oral herpes) nervous system disorders (mainly headache), skin and subcutaneous tissue disorders (mainly erythema and pruritus) and musculoskeletal and connective tissue disorders mainly myalgia).

Table 12. Summary of systemic adverse events from Day 0 to Day 28-SAS (Source: CSR, Page 177)

	Group 1 IM route (N=176)				Group 2 SC route (N=177)			
	All		Vaccine-related		All		Vaccine-related	
	n AE	n (%)	n AE	n (%)	n AE	n (%)	n AE	n (%)
Systemic adverse events from Day 0 to Day 28	61	41 (23.3%)	21	12 (6.8%)	62	40 (22.6%)	21	13 (7.3%)
Cardiac disorders	0	0	0	0	2	1 (0.6%)	0	0
Arrhythmia	0	0	0	0	2	1 (0.6%)	0	0
Eye disorders	0	0	0	0	4	4 (2.3%)	1	1 (0.6%)
Conjunctival haemorrhage	0	0	0	0	1	1 (0.6%)	0	0
Diplopia	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Eye pain	0	0	0	0	1	1 (0.6%)	0	0
Scintillating scotoma	0	0	0	0	1	1 (0.6%)	0	0
Gastrointestinal disorders	6	3 (1.7%)	5	2 (1.1%)	3	3 (1.7%)	0	0
Abdominal pain upper	0	0	0	0	1	1 (0.6%)	0	0
Diarrhoea	3	2 (1.1%)	3	2 (1.1%)	0	0	0	0
Dyspepsia	1	1 (0.6%)	0	0	0	0	0	0
Gastritis	0	0	0	0	1	1 (0.6%)	0	0
Lip swelling	1	1 (0.6%)	1	1 (0.6%)	0	0	0	0
Oral discomfort	1	1 (0.6%)	1	1 (0.6%)	0	0	0	0
Tongue ulceration	0	0	0	0	1	1 (0.6%)	0	0
General disorders and administration site conditions	4	4 (2.3%)	0	0	4	4 (2.3%)	2	2 (1.1%)
Adverse drug reaction	1	1 (0.6%)	0	0	0	0	0	0

	Group 1 IM route (N=176)				Group 2 SC route (N=177)			
	All		Vaccine-related		All		Vaccine-related	
	n AE	n (%)	n AE	n (%)	n AE	n (%)	n AE	n (%)
Chest pain	0	0	0	0	1	1 (0.6%)	0	0
Chills	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Hernia obstructive	1	1 (0.6%)	0	0	0	0	0	0
Malaise	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Oedema peripheral	2	2 (1.1%)	0	0	0	0	0	0
Pyrexia	0	0	0	0	1	1 (0.6%)	0	0
Infections and infestations	12	10 (5.7%)	3	2 (1.1%)	13	13 (7.3%)	4	4 (2.3%)
Bacterial infection	0	0	0	0	1	1 (0.6%)	0	0
Herpes simplex ophthalmic	1	1 (0.6%)	0	0	0	0	0	0
Nasopharyngitis	2	2 (1.1%)	0	0	3	3 (1.7%)	1	1 (0.6%)
Oral herpes	3	2 (1.1%)	3	2 (1.1%)	3	3 (1.7%)	2	2 (1.1%)
Pharyngitis	1	1 (0.6%)	0	0	2	2 (1.1%)	0	0
Rhinitis	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Tinea manuum	1	1 (0.6%)	0	0	0	0	0	0
Tinea pedis	2	2 (1.1%)	0	0	0	0	0	0
Upper respiratory tract infection	1	1 (0.6%)	0	0	0	0	0	0
Urinary tract infection	1	1 (0.6%)	0	0	3	3 (1.7%)	0	0
Injury, poisoning and procedural complications	7	6 (3.4%)	0	0	3	3 (1.7%)	0	0

Arthropod bite	2	2 (1.1%)	0	0	1	1 (0.6%)	0	0
Arthropod sting	1	1 (0.6%)	0	0	0	0	0	0
Incision site haematoma	0	0	0	0	1	1 (0.6%)	0	0
Ligament sprain	1	1 (0.6%)	0	0	1	1 (0.6%)	0	0
Muscle strain	1	1 (0.6%)	0	0	0	0	0	0
Post-traumatic pain	1	1 (0.6%)	0	0	0	0	0	0
Sunburn	1	1 (0.6%)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	7	7 (4.0%)	1	1 (0.6%)	3	3 (1.7%)	1	1 (0.6%)
Arthralgia	1	1 (0.6%)	0	0	1	1 (0.6%)	0	0
Back pain	1	1 (0.6%)	0	0	1	1 (0.6%)	0	0
Muscle spasms	1	1 (0.6%)	0	0	0	0	0	0
Myalgia	2	2 (1.1%)	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)
Neck pain	1	1 (0.6%)	0	0	0	0	0	0
Rotator cuff syndrome	1	1 (0.6%)	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	2	2 (1.1%)	0	0
Basal cell carcinoma	0	0	0	0	1	1 (0.6%)	0	0
Pyogenic granuloma	0	0	0	0	1	1 (0.6%)	0	0
Nervous system disorders	8	8 (4.5%)	4	4 (2.3%)	12	11 (6.2%)	8	8 (4.5%)
Dizziness	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Dysaesthesia	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Headache	7	7 (4.0%)	3	3 (1.7%)	8	7 (4.0%)	4	4 (2.3%)
Migraine	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Presyncope	1	1 (0.6%)	1	1 (0.6%)	0	0	0	0
Somnolence	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Psychiatric disorders	1	1 (0.6%)	0	0	0	0	0	0
Depression	1	1 (0.6%)	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3	1 (0.6%)	3	1 (0.6%)	5	4 (2.3%)	2	2 (1.1%)
Cough	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)	1	1 (0.6%)
Epistaxis	0	0	0	0	1	1 (0.6%)	0	0
Oropharyngeal pain	1	1 (0.6%)	1	1 (0.6%)	3	2 (1.1%)	1	1 (0.6%)
Rhinorrhoea	1	1 (0.6%)	1	1 (0.6%)	0	0	0	0
Skin and subcutaneous tissue disorders	12	11 (6.3%)	5	4 (2.3%)	6	6 (3.4%)	2	2 (1.1%)
Dermatitis contact	1	1 (0.6%)	0	0	0	0	0	0
Eczema	1	1 (0.6%)	0	0	1	1 (0.6%)	0	0
Erythema	2	2 (1.1%)	0	0	0	0	0	0

	Group 1 IM route (N=176)				Group 2 SC route (N=177)			
	All		Vaccine-related		All		Vaccine-related	
	n AE	n (%)	n AE	n (%)	n AE	n (%)	n AE	n (%)
Hidradenitis	1	1 (0.6%)	0	0	0	0	0	0
Hyperkeratosis	0	0	0	0	1	1 (0.6%)	0	0
Neurodermatitis	1	1 (0.6%)	1	1 (0.6%)	0	0	0	0
Pigmentation disorder	1	1 (0.6%)	1	1 (0.6%)	0	0	0	0
Pruritus	1	1 (0.6%)	0	0	2	2 (1.1%)	1	1 (0.6%)
Pruritus generalised	0	0	0	0	1	1 (0.6%)	1	1 (0.6%)
Rash	1	1 (0.6%)	0	0	0	0	0	0
Rash vesicular	1	1 (0.6%)	1	1 (0.6%)	0	0	0	0
Skin ulcer	0	0	0	0	1	1 (0.6%)	0	0
Urticaria	2	1 (0.6%)	2	1 (0.6%)	0	0	0	0
Surgical and medical procedures	0	0	0	0	1	1 (0.6%)	0	0
Tooth extraction	0	0	0	0	1	1 (0.6%)	0	0
Vascular disorders	1	1 (0.6%)	0	0	4	4 (2.3%)	1	1 (0.6%)
Deep vein thrombosis	0	0	0	0	2	2 (1.1%)	0	0
Essential hypertension	1	1 (0.6%)	0	0	0	0	0	0
Hypotension	0	0	0	0	2	2 (1.1%)	1	1 (0.6%)

n AE: number of episodes of the considered event
n (%): number (percentage) of subjects presenting at least once the considered event

The risk difference between IM and SC group was calculated for all systemic AEs (vaccine related and unrelated) and for systemic AEs with an incidence greater or equal to 2.2% in at least one group. No significant difference could be observed. Headache was the only systemic AE reported with an incidence ≥ 2.2%.

Table 13. Comparison of IM Route and SC Route on the Percentages of Subjects With Systemic AEs (Incidence ⩾ 2.2% in At Least One Group)-SAS (Source: CSR, Page 86)

	Group 1 - IM route (N=176)	Group 2 - SC route (N=177)	Risk difference
	n (%) 95% CI	n (%) 95% CI	(%) 95% CI
Systemic AEs from Day 0 to Day 28	41 (23.3%) [17.3%;30.2%]	40 (22.6%) [16.7%;29.5%]	0.7 [-8.1;9.5]
Headache	7 (4.0%) [1.6%;8.0%]	7 (4.0%) [1.6%;8.0%]	0.0 [-4.5;4.5]
Vaccine-related systemic AEs from Day 0 to Day 28	12 (6.8%) [3.6%;11.6%]	13 (7.3%) [4.0%;12.2%]	-0.5 [-6.2;5.1]
Vaccine-related headache	3 (1.7%) [0.4%;4.9%]	4 (2.3%) [0.6%;5.7%]	-0.6 [-4.2;2.9]

n (%): number (percentage) of subjects presenting at least once the considered event
AE: Adverse event

Vaccine-related systemic AEs

The proportion of subjects reporting vaccine related systemic AEs was comparable between the two vaccination groups (6.8% in the IM versus 7.3% in the SC group) as illustrated in Table 11. Specific vaccine-related AEs were reported by a comparable number of subjects in both vaccination groups. The most frequent reported vaccine-related AEs were headache (1.7% of subjects in the IM versus 2.3% in the SC

vaccination group), oral herpes (1.1% of subjects in each group), and diarrhoea (1.1% of subjects in the IM and no subject in the SC vaccination group).

VZ/VZ-like and HZ/HZ-like rashes

Overall, only one subject (in the IM vaccination group) reported a VZ-like rash at the right thoracic dermatome. Rash occurred at Day 12 following vaccination, was of mild intensity and lasted 6 days. Specimen for PCR testing was not obtained as the subject was not seen by a physician.

Systemic adverse events by intensity

Systemic AEs were mainly of mild to 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 IM vaccination group
- Dysaesthesia, headache and somnolence, all in 1 subject (0.6%) from the SC vaccination group

The CHMP noted that the proportion of subjects reporting at least one systemic AE was comparable in the two vaccination groups. AEs were reported at about equal frequencies in both groups. No difference in the reporting of vaccine-related systemic AEs could be observed in the two groups. The safety profile of Zostavax was comparable for both vaccination groups. No safety signals regarding systemic AEs could be observed in the study.

Serious adverse event/deaths/other significant events

During the entire study period three subjects reported an SAE.

- 1 subject (hernia obstructive) in the IM vaccination group
- 2 subjects (humerus fracture and deep vein thrombosis) in the SC vaccination group

None of the reported SAEs were considered vaccine related by the investigators.

No deaths were reported during the entire study period.

Laboratory findings

No clinical laboratory parameters have been analysed for the scope of this study.

Immunological events

Only sporadic cases of AEs considered vaccine related by the investigators and indicating an immunological event were recorded.

- IM vaccination group: one case of worsening neurodermatitis, two cases of urticaria;
- SC vaccination group: one case of pruritus, one case of generalised pruritus.

No medical conditions considered potentially indicative of autoimmune disorders could be identified from the AE listings.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not assessed in the submitted study.

Discontinuation due to adverse events

No subject was discontinued due to AEs.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

One of the secondary objectives of study ZTV03C was to assess the safety profile of Zostavax administered to subjects ⩾ 50 years of age either by IM or SC route. No formal hypothesis was tested for safety. Safety data were collected from 353 subjects during a safety follow-up period of a maximum of 35 days post-vaccination.
The incidence of all solicited injection-site adverse reactions (erythema, pain, and swelling) was statistically significantly lower in the IM vaccination group (15.9%, 25.6%, and 13.6%, respectively) compared with the SC vaccination group (52.5%, 39.5% and 37.3%, respectively). The risk difference was: -36.6%, [95% CI: -45.4;-27.2] for erythema, -14.0% [95% CI: -23.5;-4.2] for pain and -23.7% [95% CI: -32.3;-14.8] for swelling. The finding of lower local reactogenicity in subjects vaccinated by IM route is in line with the data in published literature.
The incidence of systemic AEs related and unrelated to the vaccine was comparable between the two vaccination groups.
No vaccine-related SAEs were reported and no subject was withdrawn due to AEs.
The safety data showed that Zostavax was generally well tolerated by subjects of both vaccination groups and the safety profile was comparable to the known safety profile of Zostavax.
The frequency of injection site reactions following administration of Zostavax is lower when administered by IM route compared with the SC administration.
From the safety database all the adverse reactions reported in the clinical trial have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

IM injection is a common route of administration for many vaccines in Europe. Both routes of administration are comparable regarding systemic safety and tolerability, and of note the local reactogenicity is significantly lower following IM vaccination. This has been previously described for other vaccines.

The safety data provided in the CSR of the submitted study support the administration of Zostavax using either the SC or the IM route.

2.7. Risk Management Plan

N/A

2.8. Pharmacovigilance

Pharmacovigilance system

N/A

2.9. Product information

Sections 4.8 and 5.1 of the SmPC are being updated to inform about the results of Zostavax administered either by SC or IM route. The IM route of administration was added in section 4.2. The PL was updated accordingly.

The MAH was requested during the procedure to revise the SmPC to be more concise, particularly regarding sections 4.8 and 5.1 and to implement the latest version of the QRD template and the SmPC guideline. Please refer to the attached Product Information, which includes all the proposed changes. These changes were reviewed by the CHMP and the QRD group and were considered acceptable.

2.9.1. User consultation

N/A

2.9.2. Labelling exemptions

N/A

3. Benefit-Risk Balance

Non-inferiority of the immune response elicited after the intramuscular compared to the subcutaneous route of administration was demonstrated. The immunogenicity data showed that the immune response elicited by IM vaccination of Zostavax is comparable to that elicited by SC administration by meeting both the pre-defined formal non-inferiority criteria. The descriptive analysis showed that gpElisa GMTs (pre- and post-vaccination) and GMFRs are comparable between the IM and the SC vaccination group.

The reviewed safety data showed that Zostavax was generally well tolerated by subjects of both vaccination groups and the safety profile was comparable to the known safety profile of Zostavax. In addition, the frequency of injection site reactions following administration of Zostavax is significantly lower when administered by IM route compared with the SC administration.

In conclusion CHMP agreed that the safety and immunogenicity data generated by study ZTV03C support the administration of Zostavax using either the SC or the IM route, but the IM administration could be preferable because of the lower frequency of injection site reactions.

The overall benefit/risk profile of Zostavax remains positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Zostavax in the prevention of herpes zoster ("zoster" or shingles) and herpes zoster-related post-herpetic neuralgia (PHN) in individuals 50 years of age or older is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

Obligation to complete post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.