Report on the Deliberation Results

March 8, 2018

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Shingrix for Intramuscular Injection
Non-proprietary Name	Dried Recombinant Herpes Zoster Vaccine (Derived from Chinese Hamster Ovary Cells)
Applicant	Japan Vaccine Co., Ltd.
Date of Application	April 18, 2017

Results of Deliberation

In its meeting held on March 2, 2018, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product, and the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Review Report

February 13, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Shingrix for Intramuscular Injection
Non-proprietary Name	Dried Recombinant Herpes Zoster Vaccine (Derived from Chinese Hamster Ovary Cells)
Applicant	Japan Vaccine Co., Ltd.
Date of Application	April 18, 2017
Dosage Form/Strength	A lyophilized drug product containing 50 μg of varicella zoster virus glycoprotein E (VZV gE) as active ingredient per 0.5 mL when 1 vial of the product is reconstituted with the full volume of accompanying adjuvant for reconstitution
Application Classification	Prescription drug, (1) Drug(s) with a new active ingredient
Items Warranting Special Mention	None
Reviewing Office	Office of Vaccines and Blood Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prevention of herpes zoster, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The safety of the product under routine use should be further evaluated in post-marketing surveillance.

Indication(s)	Prevention of herpes zoster
Dosage and Administration	The antigen preparation is reconstituted with the full volume of accompanying adjuvant for reconstitution, and the usual dosage is 0.5 mL administered intramuscularly twice at intervals of 2 months to adults aged ≥50 years.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

January 4, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Shingrix for Intramuscular Injection
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Applicant	Japan Vaccine Co., Ltd.
Date of Application	April 18, 2017
Dosage Form/Strength	A lyophilized drug product containing 50 μg of varicella zoster virus glycoprotein E (VZV gE) as active ingredient per 0.5 mL when 1 vial of the product is reconstituted with the full volume of accompanying adjuvant for reconstitution
Proposed Indication(s)	Prevention of herpes zoster and postherpetic neuralgia
Proposed Dosage and Administration	The antigen preparation is reconstituted with the full volume of accompanying adjuvant for reconstitution, and the usual dosage is 0.5 mL administered intramuscularly twice at intervals of 2 to 6 months.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

The varicella zoster virus (VZV) causes chickenpox as the primary infection, then is latent in the ganglion until reactivated by a decrease of cellular immune function due to stimuli such as aging, fatigue, stress, malignant tumor, use of immunosuppressant, causing herpes zoster (HZ) on the skin in the region of nerve distribution (*Clin Infect Dis* 2010;51:197-213, *J Infect Dis* 2008;197:825-35, *N Engl J Med* 2013;369:255-63).

Patients with herpes zoster develop paresthesia, pain, and itching as early symptoms on one side in the region of nerve distribution, and the symptoms last for several days to a week. Edematous erythema then appears in the same area, with a swath of numerous blisters. The blisters become pustules or blood blisters in 2 to 3 days, break in 4 to 5 days, becoming erosive and forming a scab, which falls off in about 3 weeks, and the condition heals. In the elderly, postherpetic neuralgia (PHN) reportedly occurs in about 20% of patients after herpes zoster heals (*J Epidemiol* 2015;25:617-25). The symptoms of neuralgia are sometimes extremely severe, and pain management can be difficult, so the burden on the patient is high.

The incidence rate of herpes zoster in Japan has been reported as 2.06 to 2.85 cases per 1,000 person-years at <50 years of age and 5.30 to 8.25 cases per 1,000 person-years at ≥50 years in a large-scale epidemiological study conducted in Miyazaki prefecture since 1997 (*J. JOCD* 2012;29:799-804). Approximately 600,000 individuals are estimated to develop herpes zoster each year, and 1 out of 3 persons develop herpes zoster by age 80 years (*IASR* 2013;34:298-300). The development of a herpes zoster vaccine was selected as a priority by the R&D and Production/Distribution Subcommittee of the Immunization and Vaccine Section Meeting in the Health Sciences Council (the fifth meeting), held in October 2013.

In Japan, the additional indication of "prevention of herpes zoster in persons aged ≥50 years" was approved in March 2016 for the previously approved drug product of dried live attenuated varicella vaccine "Biken." However, since this is a live attenuated vaccine, administration to patients with a disease apparently causing abnormal immune function or who are undergoing treatment that causes immunosuppression is regarded as inappropriate.

Shingrix is a recombinant subunit vaccine which is produced using Chinese hamster ovary (CHO) cells and has VZV glycoprotein E (VZV gE) as the active ingredient. It contains $AS01_B$ as an adjuvant, which is a liposomal formulation of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and purified Quillaja saponin (QS-21). Shingrix was approved in Canada and the United States in October 2017. In Europe, approval applications were filed in November 2016 and are currently under review.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The drug product is a vaccine that has purified gE antigen as the active ingredient, obtained by culturing CHO[redacted] cells which carry the gene for the VZV gE antigen. $AS01_B$, which contains MPL and QS-21, is used as an adjuvant.

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The gE antigen gene is the gene for the transmembrane glycoprotein VZV gE, cloned from VZV genomic deoxyribonucleic acid (DNA) derived from a patient with varicella, from which the genes encoding the transmembrane domain and the C-terminal domain on the cytoplasmic side have been deleted. The gE antigen gene was inserted into the expression vector by gene recombination technology. The resulting gene expression construct was introduced into CHO[redacted] cells, and a cell line which highly expressed gE antigen was isolated. The master cell bank (MCB) and working cell bank (WCB) were sequentially prepared from this cell line.

Characterization and purity tests were conducted during the preparation of MCB and WCB, and for CAL, according to ICH Q5A (R1), Q5B, and Q5D. The results confirmed genetic stability during the manufacturing period. Other than the endogenous retrovirus-like particles known to be present in rodent cell lines, no viral and non-viral adventitious agents were detected within the tested attributes.

The MCB and WCB are stored in liquid nitrogen. There is no plan to update the MCB, and the WCB is updated as necessary.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of cell thawing, preculture, culture, antigen production, clarification, [redacted] chromatography, low pH treatment, [redacted] chromatography, [redacted] chromatography, ultrafiltration, nanofiltration, and filtration. The drug substance is stored at ≤−45°C in a polyethylene terephthalate glycol (PETG) container. The critical steps are antigen production, [redacted] chromatography, low pH treatment, [redacted] chromatography, [redacted] chromatography, ultrafiltration, nanofiltration, and filtration.

Process validation of the manufacturing process of the drug substance is conducted at commercial scale.

2.1.3 Safety evaluation of adventitious agents

No animal- or human-derived raw materials other than the host CHO[redacted] cell line are used in the manufacturing process of the drug substance. Carboxypeptidase B from porcine pancreas and trypsin from New Zealand bovine pancreas are used in MCB preparation, and trypsin from porcine pancreas is used as a raw material of biological origin in WCB preparation.

Carboxypeptidase B and trypsin used in the MCB preparation process were used in the production of [redacted], that is [redacted], contained in the culture medium of the MCB. Detailed information on the inactivation or removal of pathogens in the production of these raw materials of biological origin has not been obtained, but it meets the specifications in the "Handling of Drugs etc. Produced from Master Cell Banks or Master Seeds That Do Not Meet the Standards for Biological Ingredients" (Administrative Notification dated March 27, 2009) [see Section 2.R.1]. The trypsin used in the WCB preparation step has been confirmed to meet the biological origin standards. Trypsin of non-animal origin will be used the next time the WCB is renewed.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process, as shown in Table 1.

Table 1. Viral clearance index

Clearance process	X-MuLV	Sindbis virus	SV40	PPV	MMV
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low pH treatment	[redacted]	[redacted]	Not conducted	Not conducted	Not conducted
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nanofiltration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total clearance index	≥13.68	≥11.95	11.39	4.52	≥9.03

2.1.4 Manufacturing process development

The main changes in the manufacturing processes of the drug substance in the development process are shown in Table 2 (as manufacturing processes A, B, C, D, E, and F [a proposed commercial process]). In association with each change in the manufacturing process, the comparability of the quality of the drug substance before and after each change was confirmed.

The drug products produced from the drug substances manufactured by Process A was used in Study EXPLO-CRD-004, by Process B in Study ZOSTER-003, by Process C in Studies ZOSTER-010, ZOSTER-001, and ZOSTER-023, and by Process D in Studies ZOSTER-006, ZOSTER-022, ZOSTER-015, ZOSTER-026, ZOSTER-032, and ZOSTER-033.

Table 2. Main changes in the manufacturing process of drug substance

Manufacturing process	Changes
Process A to Process B	- Preparation of [redacted] - Change in storage temperature of [redacted]
Process B to Process C	- Scale-up of [redacted] - Addition of [redacted]
Process C to Process D	- Scale-up of [redacted] - Change in storage temperature of [redacted]
Process D to Process E	- Discontinuation of [redacted]
Process E to Process F	- Change of manufacturing site

2.1.5 Characterization

2.1.5.1 Structure, physicochemical properties and biological properties

Characteristic analyses shown in Table 3 were conducted on the drug substance.

Table 3. Outline of characteristic analyses

Items		
Structure	Primary structure	Peptide map, Edman degradation (N-terminal analysis), [redacted] HPLC ([redacted])
	Higher order structure	Total reflection Fourier transform infrared spectroscopy (secondary structure), MS (disulfide bond), fluorescence spectrum
	Glycan structure /amino acid modification	[redacted] chromatography (N-linked glycan structure, O-linked glycan structure, neutral and amino sugar content, and sialic acid content), MS ([redacted]-linked glycan structure)
Physicochemical properties		SDS-PAGE (Coomassie stain, silver stain), western blot, capillary electrophoresis (isoelectric point), MS (average molecular weight), [redacted] HPLC ([redacted] content), ultracentrifugal analysis, multi-angle light scattering detection (average molecular weight, polydispersity, average inertia radius)
Biological properties (antigenicity)		ELISA (specific activity)

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characteristic analyses, A and B were regarded as product-related impurities. It was confirmed that product-related impurity A is always lower than the limit of quantitation in the drug substance, and that [redacted] is suppressed by adding [redacted] to the drug product. Product-related impurity B has been confirmed to be within a certain range in the manufacturing process. There is no molecular species which is regarded a product-related substance.

2.1.5.3 Process-related impurities

Proteins and DNA which are derived from the host cell, bacterial endotoxins, [redacted], and [redacted], which are process-related impurities, have all been confirmed to be permanently removed in the manufacturing process.

2.1.6 Control of drug substance

The drug substance specifications have been set for description, identification (ELISA), pH, purity (SDS-PAGE), bacterial endotoxins, host-derived protein content ([redacted]), [redacted] ([redacted] HPLC) and quantification methods (protein content, specific activity [ELISA]).

2.1.7 Stability of drug substance

Stability tests of the drug substance are shown in Table 4.

Table 4. Stability tests of drug substance

	Manufacturing process	No. of lots	Storage conditions	Test period	Storage form
Long-term storage tests	Process E	3	−45 [redacted]°C Dark place	60 months	PETG container with high density polyethylene cap
	Process F	3		24 months[a]	
Stress test	Process E	3	[redacted]°C Dark place	[redacted] days	
	Process F	3		[redacted] days	

a: To be continued up to 60 months

Under the long-term condition, time-dependent changes were not observed throughout the test period, and the drug substance met the specifications.

Based on the above, a shelf life of 60 months was proposed for the drug substance when stored at ≤−45°C in a PETG container with a high density polyethylene cap.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product consists of gE lyophilized drug product and $AS01_B$ drug product, an adjuvant for reconstitution. They are combined for injection at the time of use.

2.2.2 gE lyophilized drug product

The gE lyophilized drug product contains 50 μg of gE antigen per vial as the active ingredient. The drug product contains purified sucrose, polysorbate 80, sodium dihydrogen phosphate, and dipotassium phosphate as excipients. The primary container is a glass vial (3 mL) with a [redacted] rubber stopper, and the secondary container is a paper box.

2.2.2.1 gE lyophilized drug product manufacturing process

The manufacturing process of gE lyophilized drug product consists of gE final bulk preparation, filling, and lyophilization, followed by labeling, packaging, and storage processes. The critical steps are [redacted] and [redacted].

Process validation of the manufacturing process of gE lyophilized drug product is conducted at actual production scale.

2.2.2.2 Manufacturing process development of gE lyophilized drug product

The main changes in the manufacturing process of gE lyophilized drug product during development are shown in Table 5 (as Processes a, b, c, d, and e [proposed commercial process]). In association with each change in the manufacturing process, the comparability of the quality of the drug substance before and after each change was confirmed.

The drug products manufactured by Process a was used in Study EXPLO-CRD-004, by Process b in Study ZOSTER-003, by Process c in Studies ZOSTER-010, ZOSTER-001, and ZOSTER-023, and by Process d in Studies ZOSTER-006, ZOSTER-022, ZOSTER-015, ZOSTER-026, ZOSTER-032, and ZOSTER-033.

Table 5. Main changes in the manufacturing process of gE lyophilized drug product

Manufacturing process	Change
Process a to Process b	- Addition of [redacted] - Change in [redacted] - Changes in the storage temperature of [redacted], fill volume of [redacted], and storage temperature of [redacted]
Process b to Process c	- Scale-up of [redacted] - Addition of [redacted] ([redacted]) - Change in the storage container material for [redacted] - Addition of [redacted]
Process c to Process d	- Scale-up of [redacted]
Process d to Process e	- Scale-up of [redacted]

2.2.2.3 Control of gE lyophilized drug product

The gE lyophilized drug substance specifications have been set for description, identification (ELISA), osmotic pressure ratio, pH, water content, bacterial endotoxin, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, [redacted] content, [redacted] content, and quantification methods (protein content, relative titer). In addition, the proposed specifications for the gE lyophilized drug product following reconstitution with $AS01_B$ include description, extractable volume, foreign insoluble matter, and abnormal toxicity.

2.2.2.4 Stability of gE lyophilized drug product

The stability tests of gE lyophilized drug product are shown in Table 6.

Table 6. Stability tests of gE lyophilized drug product

	Drug substance manufacturing process	Drug product manufacturing process	No. of lots	Storage conditions	Test period	Storage form
Long-term storage test	Process D	Process d	Inverted: 3 lots[a]	2-8°C Dark place	60 months	Glass vial/ [redacted] rubber stopper
	Process E	Process d	Inverted: 3 lots		36 months[b]	
	Process F	Process e	Inverted: 3 lots		24 months[b]	
Accelerated test	Process E	Process d	Inverted: 3 lots	[redacted]°C	[redacted] days	
	Process F	Process e	Inverted: 3 lots	Dark place	[redacted] days	
Stress test	Process D	Process d	Inverted: 3 lots	[redacted]°C	[redacted] months	
	Process E	Process d	Inverted: 3 lots	Dark place	[redacted] days	
	Process F	Process e	Inverted: 3 lots		[redacted] days	

a: Some test items have not been implemented
b: To be continued up to 60 months

Under the long-term condition, time-dependent changes were not observed throughout the test period, and the drug substance met the specifications. Photostability is not tested.

Based on the above, a shelf life of 36 months was proposed for the gE lyophilized drug substance when stored in a glass vial (3 mL) at 2-8°C (avoid freezing), protected from light.

2.2.3 $AS01_B$ drug product

The $AS01_B$ drug product is a solution for dissolving the gE lyophilized drug product and is an adjuvant containing 50 μg of MPL and 50 μg of QS-21 in 0.5 mL. It contains liposome comprising of DOPC and

cholesterol as a base, to which anhydrous sodium hydrogen phosphate, potassium dihydrogen phosphate, and sodium chloride are added. The primary container is a glass vial (3 mL) with a [redacted] rubber stopper, and the secondary container is a paper box.

2.2.3.1 $AS01_B$ drug product manufacturing process

The manufacturing process of $AS01_B$ drug product consists of manufacturing of [redacted], manufacturing of [redacted], $AS01_B$ final bulk preparation, filling, labeling, packaging, and storage processes. The critical steps are [redacted], [redacted], [redacted], and [redacted].

Process validation of the manufacturing process of $AS01_B$ drug product is conducted at commercial scale.

2.2.3.2 Safety evaluation of adventitious agents in $AS01_B$ drug product

No raw materials of biological origin are used in the manufacturing process of $AS01_B$ drug product. Although casamino acids derived from bovine milk are used in the MPL manufacturing process, the raw materials have been confirmed to conform to biological origin standards.

2.2.3.3 Manufacturing process development of $AS01_B$ drug product

The main changes in the manufacturing processes of $AS01_B$ drug product during development are shown in Table 7 (as Processes 1, 2, 3, 4, 5, 6, and 7 [proposed commercial process]).

The drug products manufactured by Process 1 was used in Studies EXPLO-CRD-004 and ZOSTER-003, by Process 2 in Studies ZOSTER-001, ZOSTER-010, and ZOSTER-023, by Process 4 in Studies ZOSTER-006 and ZOSTER-022, and by Process 5 in Studies ZOSTER-004, ZOSTER-007, ZOSTER-026, ZOSTER-032, and ZOSTER-033.

In association with each change in the manufacturing process, the comparability of the quality of $AS01_B$ drug product before and after each change was confirmed.

Table 7. Main changes in the manufacturing process of $AS01_B$ drug product

Manufacturing process	Change
Process 1 to Process 2	- Change in [redacted]
Process 2 to Process 3	- Change in [redacted]
Process 3 to Process 4	- Storage condition of [redacted], Change in [redacted]
Process 4 to Process 5	- Scale-up of [redacted] - Change in the condition of [redacted]
Process 5 to Process 6	- Scale-up of [redacted] - Storage condition of [redacted], Change in the storage container for [redacted]
Process 6 to Process 7	- Scale-up of [redacted] - Change in the storage condition of [redacted]

2.2.3.4 Control of $AS01_B$ drug product

The $AS01_B$ drug product specifications have been set for description, osmotic pressure ratio, pH, particle diameter, polydispersity index, purity test ([redacted], [redacted]), foreign insoluble matter, insoluble particulate matter, sterility, [redacted], MPL content, QS-21 content, [redacted], and [redacted].

2.2.3.5 Stability of $AS01_B$ drug product

The stability tests of $AS01_B$ drug product are shown in Table 8.

Table 8. Stability tests of $AS01_B$ drug product

	Manufacturing process	No. of lots	Storage conditions	Test period	Storage form
Long-term storage test	Process 5	Inverted: 3 lots	2-8°C Dark place	48 months[a]	Glass vial/ [redacted] rubber stopper
	Process 6	Inverted: 3 lots		36 months[a]	
	Process 7	Inverted: 3 lots		24 months[a]	
Accelerated test	Process 5	Inverted: 3 lots	[redacted]°C Dark place	[redacted] days	
	Process 6	Inverted: 3 lots		[redacted] days	
	Process 7	Inverted: 3 lots		[redacted] days	
Stress test	Process 5	Inverted: 3 lots	[redacted]°C Dark place	[redacted] days	
	Process 6	Inverted: 3 lots		[redacted] days	
	Process 7	Inverted: 3 lots		[redacted] days	

a: To be continued up to 60 months

Under the long-term condition, time-dependent changes were not observed throughout the test period, and the drug substance met the specifications. Photostability is not tested.

Based on the above, a shelf life of 36 months was proposed for $AS01_B$ drug product when stored in a glass vial (3 mL) at 2-8°C (avoid freezing), protected from light, taking also account of the shelf life of gE lyophilized drug product.

2.R Outline of the review conducted by PMDA

PMDA determined from the submitted data and the following investigation that the quality of drug substance and drug product is properly controlled.

2.R.1 Raw materials of biological origin

PMDA determined that safety has been secured against adventitious agents, because adventitious agents in the carboxypeptidase B and trypsin used in the MCB preparation step were ruled out by control tests of MCB, and sufficient virus clearance ability is observed in the manufacturing process of the drug substance. PMDA concluded that the raw materials of biological origin can be used as they were determined to conform to the “Handling of Drugs etc. Produced from Master Cell Banks or Master Seeds That Do Not Meet the Standards for Biological Ingredients” (Administrative Notification dated March 27, 2009).

2.R.2 Novel excipients

Since the excipients QS-21 and DOPC that are included in the drug product have no record of use as excipients, and cholesterol has not been used for muscular injection, QS-21, DOPC and cholesterol are classified as novel excipients.

2.R.2.1 Specifications, test methods and stability

PMDA has concluded that cholesterol conforms to the Japanese Pharmacopoeia and that there is no quality issues. In addition, PMDA concluded that no particular issues were raised in the specifications, test methods, and stability of QS-21 and DOPC on the basis of the submitted data.

2.R.2.2 Safety

From the data submitted, PMDA found that transient local irritancy was observed at the current amount of each excipients used, but it was within the acceptable range for an adjuvant, and the possibility of safety problems was extremely small. Since the purpose of QS-21 is only to activate immunity for vaccines to prevent infectious diseases, it was concluded appropriate not to handle it as a precedent for general use.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The results of a primary pharmacodynamics study (immunogenicity study using mice) and a safety pharmacology study using rats have been submitted for Shingrix. Drug substance manufactured by process B [see Section 2.1.4] was used in the immunogenicity study, and Shingrix produced from the drug substance manufactured by process B [see Section 2.1.4] was used in the safety pharmacology study.

3.1 Primary pharmacodynamics

3.1.1 Immunogenicity study (CTD 4.2.1.1, Study 20[redacted]0384)

Live attenuated varicella vaccine (about 1×10^4 pfu) was subcutaneously administered to mice (12 females/group) to sensitize them to VZV. Five weeks after the live attenuated varicella vaccine was administered, 50 μL each of gE antigen alone (5 μg as VZV gE), gE antigen (5 μg as VZV gE) supplemented with 1 of 6 adjuvants ($AS01_B$, AS[redacted], AS[redacted], AS[redacted], AS[redacted], AS[redacted] [Table 9]), or saline was administered intramuscularly (with 4-week interval, 2 times in total) (a total of 96 animals in 8 groups), and anti-gE antibody titer in serum was measured by ELISA 14 days and 29 days after the second administration. In the results, the groups administered gE antigen to which adjuvant had been added exhibited significantly higher anti-gE antibody titer than the group administered gE antigen alone both 14 and 29 days after the second administration ($P < 0.05$). In order to evaluate cellular immune response, the spleen was excised 33 days after the second administration and the ratio of gE-specific CD4-positive T-cells producing cytokines (IFN-γ/IL-2) was determined by the intracellular cytokine staining method. The ratio of gE-specific CD4-positive T cells tended to be higher in the groups administered gE antigen to which $AS01_B$ was added than in the groups administered gE antigen to which other adjuvant was added, suggesting greater induction of cellular immune response.

These results confirmed the suitability of adding $AS01_B$ as an adjuvant, and that anti-gE antibody and cellular immune response are highly inducible by administration of Shingrix and $AS01_B$.

Table 9. List of added adjuvants

Adjuvant added	Components and their content			
	MPL (μg)	QS-21 (μg)	DOPC (μg)	Oil-in-water emulsion (μL)
$AS01_B$	5	5	100	—
AS[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AS[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AS[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AS[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AS[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.2 Secondary pharmacodynamics

No such studies have been conducted.

3.3 Safety pharmacology (CTD 4.2.1.3, Study [redacted] 0006/062657)

Rats (4 males/group) were given 1 mL/kg of Shingrix containing 100 μg of VZV gE per 0.5 mL (about 140 times the expected clinical dose on a body weight basis), or 1 mL/kg of saline as a negative control, by a single intravenous administration (a total of 8 animals in 2 groups). Respiratory parameters (respiratory rate, tidal volume, and minute ventilation) and cardiovascular parameters (blood pressure, heart rate, and electrocardiogram) were evaluated at 10 minute intervals from 0 to 150 minutes after administration. The results showed no effects by Shingrix on the respiratory system or cardiovascular system.

In repeated dose toxicity studies in rabbits (CTD 4.2.3.2, Study [redacted]6721 and Study [redacted]20094), evaluation of clinical signs and behavior observation, hematology and clinical chemistry examinations, autopsy, organ weight measurement, and histopathological examination were conducted. All results showed no effect on the central nervous system, respiratory system nor cardiovascular system attributable to Shingrix [see Section 5.2].

3.4 Pharmacodynamic drug interactions

No such studies have been conducted.

3.R Outline of the review conducted by PMDA

PMDA asked the applicant to explain the significance of the induction of antibody production against gE antigen and cellular immune response that were observed in the immunogenicity test.

The applicant explained as follows: From the following reports on the relationship between induction of antibody production against gE antigen and cellular immune response and the prevention of HZ, a certain vaccine efficacy against HZ is considered to be expected.

- Along with early induction of VZV-specific cellular immune response, reduced incidence of HZ has been observed when hematopoietic stem cell transplant recipients are vaccinated with inactivated varicella vaccine (*N Engl J Med* 2002;347:26-34), suggesting a relationship between cellular immune response and prevention of HZ.
- Correlation between VZV-specific cellular immune response and anti-VZV antibody titer has been confirmed (*J Infect Dis* 2015;211:600-12).

PMDA accepted the applicant's explanation and concluded that there were no particular issues in safety pharmacology.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

No such studies have been conducted.

5. Toxicity and Outline of the Review Conducted by PMDA

Repeated-dose toxicity studies, reproductive and developmental toxicity studies, and local tolerance studies were conducted, using Shingrix produced from the drug substance manufactured by Process B and Process D [see Section 2.1.4].

5.1 Single-dose toxicity

The acute toxicity of Shingrix was evaluated in local tolerance studies (Study [redacted]6812/02 and Study [redacted]9912/05), and the results are described in "Section 5.6 Local tolerance." These studies showed no death or changes in clinical signs attributable to Shingrix.

5.2 Repeated-dose toxicity

5.2.1 Repeated intramuscular administration in rabbits (CTD 4.2.3.2, Study [redacted]6721)

Rabbits (New Zealand White [NZW], 10 males and 10 females/group) were given 0.5 mL of Shingrix containing 100 μg of VZV gE (about 33 times the expected clinical dose on a body weight basis), adjuvant ($AS01_B$), or saline intramuscularly (at 2-week intervals, a total of 3 times) (a total of 60 animals in 3 groups). No animals died in any group, and no clinical signs related to administration of Shingrix were observed. Transient hematological changes (high value for fibrinogen, high value for total protein, and low value for albumin/globulin ratio), which are considered to be caused by inflammation or immunoreaction, were observed in the Shingrix and adjuvant groups. Necropsy 3 days after the final administration revealed high popliteal lymph node weight and, as histopathological changes, mixed inflammatory cell infiltration of the gastrocnemius muscle and activation of the popliteal lymph node in the Shingrix administration group, but reversibility was observed in all findings at necropsy 28 days after the final administration. Slightly stronger changes observed in the Shingrix group than in the adjuvant group were presumed to result from immunoreaction in the presence of the antigen being added to that caused by administration of the adjuvant.

5.2.2 Repeated subcutaneous or intramuscular administration in rabbits (CTD 4.2.3.2, Study [redacted]20094)

Rabbits (NZW, 10 males and 10 females/group) were given 0.5 mL of Shingrix (about 15 times the expected clinical dose on a body weight basis), adjuvant ($AS01_B$), or saline subcutaneously or intramuscularly (at 2-week intervals, a total of 4 times) (a total of 100 animals in 5 groups). No animals died in any group, and no clinical signs related to administration of Shingrix were observed. Transient hematologic changes (high levels of fibrinogen and CRP), which are considered to be caused by inflammation or immunoreaction, were observed in both the subcutaneous and intramuscular administration groups of Shingrix or adjuvant. Necropsy 28 days (male) or 29 days (female) after the final administration revealed high popliteal lymph node weight in the Shingrix subcutaneous and intramuscular administration groups. Histopathological changes were inflammatory cell infiltration at the administration site in both the Shingrix subcutaneous and intramuscular administration groups at necropsy 3 days after the final administration of Shingrix, and its frequency was higher in intramuscular group. Reversibility was observed for the change at the administration site at necropsy 28 days (male) or 29 days (female) after the final administration, but activation of lymph nodes, which is considered to be caused by immunoreaction, was observed. Slightly stronger changes observed in the Shingrix group than in the adjuvant group were presumed to result from immunoreaction in the presence of the antigen being added to that caused by administration of the adjuvant.

5.3 Genotoxicity

No such studies have been conducted.

5.4 Carcinogenicity

No such studies have been conducted.

5.5 Reproductive and developmental toxicity

5.5.1 Male fertility in rats (CTD 4.2.3.5, Study [redacted]0004)

Rats (CD, 22 males/group) were given 0.1 mL of the Shingrix (about 25 times the expected clinical dose on a body weight basis), adjuvant ($AS01_B$), or saline intramuscularly (3 times: 42, 28, and 14 days before mating with females) (a total of 66 animals in 3 groups). Males were necropsied after 9 weeks from the initial dose. Mated females were caesarean sectioned on day 14 of gestation, and uterine contents were examined. Transient oedema at the administration site was observed in the adjuvant group and the Shingrix group, but no deaths were observed in any group, and there were no clinical signs or effects on reproductive performance due to Shingrix administration.

5.5.2 Pre- and post-natal development in rats (CTD 4.2.3.5, Study [redacted]0005)

Rats (CD, 44 females/group) were given 0.2 mL of the Shingrix (about 81 times the expected clinical dose on a body weight basis), adjuvant ($AS01_B$), or saline intramuscularly (28 and 14 days before mating) (a total of 132 animals in 3 groups). In addition, each test substance was administered to animals after mating (40 rats/group) on days 3, 8, 11 and 15 of gestation. Embryo-fetal development was

evaluated at caesarean section (20 animals/group) on day 20 of gestation, and the animals that delivered (20 animals/group) were given the test substance on day 7 after delivery. Pups were evaluated for survival and development until day 25 after birth. Transient oedema at the administration site was observed in the adjuvant and Shingrix groups, but no deaths were observed in dams. There were no clinical signs or effects on reproductive performance, embryo-fetal development, or pups due to the Shingrix administration.

5.6 Local tolerance

5.6.1 Local tolerance of intramuscular administration in rabbits (CTD 4.2.3.6, Study [redacted]6812/02)

Rabbits (NZW, 3 males and 3 females/group) were given 0.5 mL of the Shingrix containing 100 μg of VZV gE, adjuvant ($AS01_B$), or saline in a single intramuscular administration (a total of 18 animals in 3 groups). Injection site was assessed by the Draize method at 3, 24, 48 and 72 hours after administration, and histopathological examination of the administration site was conducted at necropsy on day 3 after administration of the test substance. There were no deaths and no abnormalities in clinical signs or macroscopic findings. Histopathological examination of the administration site revealed slight mononuclear cell infiltration in the adjuvant group, and slight or mild mononuclear cell infiltration in the Shingrix group.

5.6.2 Local tolerance of subcutaneous administration in rabbits (CTD 4.2.3.6, Study [redacted]9912/05)

Rabbits (NZW, 3 males and 3 females/group) were given 0.5 mL of Shingrix, adjuvant ($AS01_B$), or saline in a single subcutaneous administration (a total of 18 animals in 3 groups). Injection site was assessed by the Draize method at 3, 24, 48 and 72 hours after administration, and histopathological examination of the administration site was conducted at necropsy on day 3 after administration of the test substance. No abnormalities in clinical signs or macroscopic findings were observed, other than subcutaneous bleeding associated with puncture that was seen occasionally in all groups. Histopathological examination of the administration site showed mild epidermal thickening and mild to moderate diffuse mixed inflammatory cell infiltration in the adjuvant group, and mild epidermal hyperplasia and mild to severe diffuse mixed inflammatory cell infiltration in the Shingrix group. Recovery was not evaluated in the local tolerance study, but the same findings, which were observed at the administration site in the repeated dose toxicity study (Study [redacted]20094), were confirmed to be reversible [see Section 5.2.2].

5.R Outline of the review conducted by PMDA

Based on the results of nonclinical studies, PMDA concluded that there is no particular problem regarding the toxicity of Shingrix.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

No such studies have been conducted.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

Results of 9 clinical studies were submitted as evaluation data on efficacy and safety. In addition, results of 7 clinical studies were submitted as reference data. Table 10 outlines the submitted clinical studies, and Table 11 shows the investigational product used in each study.

Table 10. Outline of clinical studies

Phase	Name of study	Country/ Region	Design	Subjects	No. of subjects enrolled	Dosage and administration	Objectives
Evaluation data							
Global study (in and outside Japan)							
III	ZOSTER-006	Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, Mexico, Korea, Spain, Sweden, Taiwan, UK, USA	Randomized, Observer-blind	Adults aged ≥50 years	Shingrix group: 8,068 subjects Placebo group: 8,077 subjects	Shingrix or saline 0.5 mL administered intramuscularly at 0 and 2 months	Efficacy, safety, immunogenicity
III	ZOSTER-022	Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, Mexico, Korea, Spain, Sweden, Taiwan, UK, USA	Randomized, Observer-blind	Adults aged ≥70 years	Shingrix group:7,408 subjects Placebo group: 7,406 subjects	Shingrix or saline 0.5 mL administered intramuscularly at 0 and 2 months	Efficacy, safety, immunogenicity
Japan study							
III	ZOSTER-032	Japan	Randomized, Open-label	Adults aged ≥50 years	Shingrix Subcutaneous vaccination group: 30 subjects Intramuscular vaccination group: 30 subjects	Subcutaneous group: Shingrix 0.5 mL administered subcutaneously at 0 and 2 months Intramuscular group: Shingrix 0.5 mL administered intramuscularly at 0 and 2 months	Safety, immunogenicity
Foreign or global study (outside Japan only)							
I/ II	EXPLO-CRD-004	Belgium	Randomized, Open-label	Adults aged 18-30 years Adults aged 50-70 years	(age 18-30 years) gE group: 10 subjects gEVAR group: 10 subjects (age 50-70 years) VAR group: 45 subjects gE group: 45 subjects gEVAR group: 45 subjects	gE group: HZ/su 0.7 mL administered intramuscularly at 0 and 2 months gEVAR group: HZ/su 0.7 mL and VARILRIX 0.5 mL administered intramuscularly and subcutaneously, respectively, at 0 and 2 months VAR group: VARILRIX 0.5 mL administered subcutaneously at 0 and 2 months	Safety, immunogenicity
II	ZOSTER-003	Czech Republic, Germany, Netherlands, Sweden	Randomized, Single-blind	Adults aged ≥60 years	gE251B group: 164 subjects gE501B group: 167 subjects gE1001B group: 165 subjects SgE1B group: 165 subjects gE100/S group: 54 subjects	gE251B group: gE251B 0.5 mL administered intramuscularly at 0 and 2 months gE501B group: gE501B 0.5 mL administered intramuscularly at 0 and 2 months gE1001B group: gE1001B 0.5 mL administered intramuscularly at 0 and 2 months SgE1B group: saline 0.5 mL administered intramuscularly at 0 months; gE1001B 0.5 mL administered intramuscularly at 2 months	Safety, immunogenicity (investigation of antigen amount and vaccination schedule)

Phase	Name of study	Country/ Region	Design	Subjects	No. of subjects enrolled	Dosage and administration	Objectives
						gE100/S group: gE100/S 0.5 mL administered intramuscularly at 0 and 2 months	
II	ZOSTER-024 (EXT-003)	Czech Republic, Germany, Netherlands, Sweden	Open-label	Adults aged ≥60 years	Shingrix group: 129 subjects	Same as ZOSTER-003	Safety, immunogenicity
II	ZOSTER-010	Czech Republic, Spain, USA	Randomized, Observer-blind	Adults aged ≥50 years	Shingrix group: 150 subjects gE/AS01E group: 149 subjects gE/S group: 73 subjects Saline group: 38 subjects	Shingrix, gE/AS01E, gE/S or saline 0.5 mL administered intramuscularly at 0 and 2 months	Safety, immunogenicity (investigation of adjuvant dose)
III	ZOSTER-026	USA, Estonia	Randomized, Open-label	Adults aged ≥50 years	Shingrix 2-month interval vaccination group: 119 subjects 6-month interval vaccination group: 119 subjects 12-month interval vaccination group: 116 subjects	2-month interval vaccination group: Shingrix 0.5 mL administered intramuscularly at 0 and 2 months 6-month interval vaccination group: Shingrix 0.5 mL administered intramuscularly at 0 and 6 months 12-month interval vaccination group: Shingrix 0.5 mL administered intramuscularly at 0 and 12 months	Safety, immunogenicity (investigation of vaccination schedule)
I	ZOSTER-023	Australia	Open-label	Adults aged 18-30 years and 50-69 years	Shingrix group: (age 18-30) 10 subjects (age 50-69) 10 subjects	Shingrix 0.5 mL administered intramuscularly at 0 and 2 months	Safety, immunogenicity
Reference data							
Foreign or global study (Outside Japan only)							
I/ II	ZOSTER-018/019 (EXT EXPLO-CRD-004 M30/M42)	Belgium	Open-label	Adults aged 18-30 years Adults aged 50-70 years	**ZOSTER-018** gE group: (age 18-30) 4 subjects (age 50-70) 30 subjects **ZOSTER-019** gE group: (age 18-30) 3 subjects (age 50-70) 20 subjects	Same as EXPLO-CRD-004	Safety, immunogenicity
II	ZOSTER-011/012/013 (EXT-003 Y1/Y2/Y3)	Czech Republic, Germany, Netherlands, Sweden	Single-blind	Adults aged ≥60 years	**ZOSTER-011** gE251B group: 156 subjects gE501B group: 159 subjects gE1001B group: 159 subjects SgE1B group: 161 subjects gE100/S group: 50 subjects **ZOSTER-012** gE251B group: 150 subjects gE501B group: 155 subjects gE1001B group: 154 subjects SgE1B group: 157 subjects gE100/S group: 49 subjects **ZOSTER-013** gE251B group: 147 subjects gE501B group: 147 subjects gE1001B group: 150 subjects SgE1B group: 154 subjects gE100/S group: 47 subjects	Same as ZOSTER-003	Safety, immunogenicity
III	ZOSTER-004	Canada, Germany, USA	Randomized, Open-label	Adults aged ≥50 years	Simultaneous vaccination group: 413 subjects Control group: 415 subjects	Simultaneous vaccination group: FLU-D-QIV 0.5 mL administered intramuscularly at 0 months; Shingrix 0.5 mL administered intramuscularly at 0 and 2 months Control group: FLU-D-QIV 0.5 mL administered intramuscularly at 0 months; Shingrix 0.5 mL administered intramuscularly at 2 and 4 months	Safety, immunogenicity

Phase	Name of study	Country/ Region	Design	Subjects	No. of subjects enrolled	Dosage and administration	Objectives
I/ II	ZOSTER-001	USA	Randomized, Observer-blind	Autologous hematopoietic stem cell transplant recipients aged ≥18 years	Shingrix 3 vaccinations group: 30 subjects gE/AS01E group: 29 subjects Shingrix 2 vaccinations group: 31 subjects Placebo group: 30 subjects	Shingrix 3 vaccinations group: Shingrix 0.5 mL administered intramuscularly at 0, 1 and 3 months gE/AS01E group: gE/AS01E 0.5 mL administered intramuscularly at 0, 1 and 3 months Shingrix 2 vaccinations group: saline 0.5 mL at 0 months and Shingrix 0.5 mL at 1 and 3 months administered intramuscularly Placebo group: saline 0.5 mL administered intramuscularly at 0, 1 and 3 months	Safety, immunogenicity
I/ II	ZOSTER-015	Germany, UK, USA	Randomized, Observer-blind	HIV-infected persons aged ≥18 years	Shingrix group: 74 subjects Placebo group: 49 subjects	Shingrix or saline 0.5 mL administered intramuscularly at 0, 2 and 6 months	Safety, immunogenicity
III	ZOSTER-007 (Interim)	Belgium, Canada, USA	Randomized, Double-blind	Adults aged ≥50 years	Shingrix Lot A group: 218 subjects Lot B group: 217 subjects Lot C group: 216 subjects	Shingrix 0.5 mL administered intramuscularly at 0 and 2 months	Safety, immunogenicity
III	ZOSTER-033	Canada, Russia	Uncontrolled, Open-label	Adults aged ≥50 years with history of HZ	Shingrix group: 96 subjects	Shingrix 0.5 mL administered intramuscularly at 0 and 2 months	Safety, immunogenicity

Table 11. List of investigational products

Investigational product	Composition
gE251B	Vaccine containing VZV gE 25 μg and $AS01_B$ in 0.5 mL
gE501B or Shingrix	Vaccine containing VZV gE 50 μg and $AS01_B$ in 0.5 mL
gE1001B	Vaccine containing VZV gE 100 μg and $AS01_B$ in 0.5 mL
gE/AS01E	Vaccine containing VZV gE 50 μg and $AS01_E$ (half amount of $AS01_B$) in 0.5 mL
gE/S	Vaccine containing VZV gE 50 μg and saline in 0.5 mL
gE100/S	Vaccine containing VZV gE 100 μg and saline in 0.5 mL
HZ/su	Vaccine containing VZV gE 50 μg and $AS01_B$ in 0.7 mL
VARILRIX®	Live attenuated varicella vaccine (GlaxoSmithKline Biologicals)
FLU-D-QIV	Fluarix® Quadrivalent inactivated seasonal influenza HA vaccine (GlaxoSmithKline Biologicals)

7.1 Phase III studies

7.1.1 Global phase III study (CTD 5.3.5.1.5, Study ZOSTER-006; study period, August 2010 to July 2015)

A multi-center, randomized, observer-blind, parallel-group study was conducted at 268 facilities in and out of Japan to investigate the efficacy of Shingrix in prevention of HZ in adults aged ≥50 years (target number of subjects, 7,990 in the Shingrix group and 7,990 in the placebo group).

The study drug was administered intramuscularly twice, at 0 and 2 months, at a dose of 0.5 mL.

Subjects were randomized, and all 15,405 subjects (7,695 in the Shingrix group and 7,710 in the placebo group) who received the study drug at least once (total vaccinated cohort, TVC) were included in the safety analysis. Subjects who were assigned to “diary card subset” (Shingrix group, 4,457 subjects; placebo group, 4,464 subjects) were the diary card TVC, in which specified local reactions (injection

site pain, injection site redness, injection site swelling) and specified general adverse events (fatigue, gastrointestinal disorder, headache, myalgia, chills, pyrexia) were analyzed up to 6 days after each administration of study drug. Among the 15,411 TVC subjects (Shingrix group, 7,698 subjects; placebo group, 7,713 subjects) at the time of the final efficacy analysis cutoff date (July 1, 2014), 14,759 subjects (Shingrix group, 7,344 subjects; placebo group, 7,415 subjects), excluding 652 subjects who did not receive 2 administrations were regarded as the modified total vaccinated cohort (mTVC) and were included in the primary efficacy analysis population.

The primary endpoint was the number of patients with confirmed HZ and was evaluated during the period from 1 month after the second study drug administration to the cut-off date of the final efficacy analysis (median follow-up, 3.1 years). Subjects who met the definition in Table 12 were considered as confirmed cases of HZ. The number of subjects who developed confirmed HZ cases was 6 in the Shingrix group and 210 in the placebo group. The lower limit of the two-sided 95% confidence interval (CI) for HZ prevention was above the pre-defined evaluation criterion (25%), and the efficacy of Shingrix was confirmed (Table 13).

Table 12. Definition of definitively diagnosed HZ

HZ confirmed subject	"HZ suspected subject" is defined as new unilateral rash accompanied by pain (including allodynia, pruritus, and other sensations) and no alternative diagnosis. The "HZ suspected subject" is referred to as "HZ confirmed subject" when they meet either of the followings: • in whom the presence of VZV DNA is detected by real-time Polymerase Chain Reaction (PCR) in rash lesion samples • in whom definitive diagnosis by PCR cannot be confirmed, but is determined to have confirmed HZ by HZ Ascertainment Committee[a] based on clinical data

a: Comprised of physicians with HZ expertise but not participating as investigators

Table 13. Vaccine efficacy against HZ (mTVC, final efficacy analysis)

Group	No. of subjects analyzed	No. of subjects with HZ	Incidence rate[a] (/1,000 person-years)	Vaccine efficacy (%)[b, c] [two-sided 95% CI]
Shingrix	7,344	6	0.3	97.16 [93.72, 98.97]
Placebo	7,415	210	9.1	—

a: No. of subjects with HZ per observed person-years
b: Vaccine efficacy (%) = {1 − (HZ incidence in Shingrix group/HZ incidence in placebo group)} × 100
c: Poisson regression model with treatment group, age (50-59 years, 60-69 years, ≥70 years), and region as factors, and observation period (logarithm) as offset variable

At the end of study (EOS), the number of subjects who developed confirmed HZ in the Shingrix group and the placebo group was 9 and 254, respectively, and the vaccine efficacy against HZ [95% CI] was 96.50 [93.25, 98.46].

Regarding safety, specified local reaction, specified general adverse events, and specified adverse reactions that developed up to 6 days after each administration of study drug in the diary card TVC are shown in Tables 14 and 15. All specified local reactions were collected as adverse reactions.

Table 14. Specified local reactions (diary card TVC)

Event	Shingrix group				Placebo group			
	After first vaccination (N = 4,359)		After second vaccination (N = 4,207)		After first vaccination (N = 4,361)		After second vaccination (N = 4,224)	
	n	%	n	%	n	%	n	%
Injection site pain	3,120	71.6	2,807	66.7	352	8.1	258	6.1
Injection site redness	1,225	28.1	1,151	27.4	40	0.9	24	0.6
Injection site swelling	810	18.6	762	18.1	31	0.7	17	0.4

Table 15. Specified general adverse events and specified general adverse reactions (diary card TVC)

After first vaccination								
Event	Shingrix group (N = 4,346)				Placebo group (N = 4,362)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Myalgia	1,446	33.3	1,231	28.3	377	8.6	265	6.1
Fatigue	1,395	32.1	1,153	26.5	531	12.2	355	8.1
Headache	1,112	25.6	891	20.5	511	11.7	341	7.8
Chills	632	14.5	539	12.4	166	3.8	104	2.4
Pyrexia[a]	500	11.5	420	9.7	65	1.5	38	0.9
Gastrointestinal disorder	465	10.7	317	7.3	263	6.0	141	3.2
After second vaccination								
Event	Shingrix group (N = 4,205)				Placebo group (N = 4,222)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Myalgia	1,474	35.1	1,314	31.2	274	6.5	197	4.7
Fatigue	1,456	34.6	1,270	30.2	379	9.0	279	6.6
Headache	1,249	29.7	1,107	26.3	340	8.1	219	5.2
Chills	947	22.5	838	19.9	128	3.0	88	2.1
Pyrexia[a]	645	15.3	571	13.6	72	1.7	40	0.9
Gastrointestinal disorder	495	11.8	392	9.3	183	4.3	91	2.2

a: ≥37.5°C

Besides the specified local reactions and specified general adverse events shown in Tables 14 and 15, the incidence of nonspecified adverse events that occurred by 29 days after each vaccination were 45.9% (3,534 of 7,695 subjects) in the Shingrix group and 31.5% (2,426 of 7,710 subjects) in the placebo group. The incidence of nonspecified adverse reactions was 28.6% (2,199 of 7,695 subjects) in the Shingrix group and 5.7% (439 of 7,710 cases) in the placebo group. Adverse events observed in ≥1% of subjects in either group are shown in Table 16, together with the incidence of adverse reaction.

Table 16. Nonspecified adverse events and adverse reaction observed in ≥1% of subjects in either group (safety analysis population)[a]

Event	Shingrix group (N = 7,695)				Placebo group (N = 7,710)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Injection site pain	1,390	18.1	1,389	18.1	104	1.3	104	1.3
Pyrexia[b]	562	7.3	536	7.0	37	0.5	12	0.2
Injection site redness	493	6.4	492	6.4	10	0.1	10	0.1
Headache	492	6.4	363	4.7	256	3.3	74	1.0
Injection site swelling	401	5.2	401	5.2	6	0.1	6	0.1
Nasopharyngitis	282	3.7	40	0.5	328	4.3	21	0.3
Myalgia	257	3.3	232	3.0	46	0.6	15	0.2
Chills	237	3.1	225	2.9	18	0.2	11	0.1
Fatigue	213	2.8	189	2.5	48	0.6	30	0.4
Injection site pruritus	151	2.0	148	1.9	12	0.2	12	0.2
Malaise	147	1.9	137	1.8	17	0.2	6	0.1
Arthralgia	138	1.8	76	1.0	94	1.2	12	0.2
Upper respiratory tract infection	137	1.8	9	0.1	108	1.4	7	0.1
Pain	123	1.6	102	1.3	17	0.2	5	0.1
Back pain	117	1.5	28	0.4	102	1.3	8	0.1
Cough	107	1.4	10	0.1	106	1.4	4	0.1
Oropharyngeal pain	103	1.3	27	0.4	97	1.3	10	0.1
Dizziness	90	1.2	56	0.7	42	0.5	19	0.2
Nausea	80	1.0	69	0.9	36	0.5	16	0.2
Pain in extremity	78	1.0	22	0.3	54	0.7	3	0.0

a: For subjects who were not included in the diary card TVC, events collected in subjects in the diary card TVC as specified local reactions or specified general systemic adverse events were also collected as nonspecified adverse events.
b: ≥37.5°C

All serious adverse events were collected until 1 year after the second vaccination. However, serious adverse events leading to death and serious adverse events considered to be related to the investigational drug were collected until discontinuation or completion of the study. Of adverse events that led to death, there were 281 events in 208 subjects in the Shingrix group and 287 events in 221 subjects in the placebo group [see Section 7.R.8.1 for the observed events], but relationship to the study drug was ruled out in each case. There were 2,277 serious adverse events reported in 1,458 subjects (1,136 events in 727 subjects in the Shingrix group and 1,141 events in 731 subjects in the placebo group), but except for 3 events in 3 subjects in the Shingrix group (immune thrombocytopenic purpura, musculoskeletal chest pain, nervous system disorder) and 8 events in 7 subjects in the placebo group (2 cases of rheumatoid arthritis, immune thrombocytopenic purpura, deafness neurosensory, IVth nerve paralysis, mononeuritis, syncope, hypotension), causal relationship with the study drug was ruled out. The outcome was recovery in all 3 events in 3 subjects in the Shingrix group in which causal relationship with the study drug was not ruled out. There were 658 serious adverse events leading to treatment discontinuation in 462 subjects (317 events in 227 subjects in the Shingrix group, 341 events in 235 subjects in the placebo group), but a causal relationship to the study drug was denied for all events except for 1 event (mononeuritis) in 1 subject in the placebo group. Recovery was reported for mononeuritis for which causal relationship with the study drug was not ruled out.

7.1.2 Global phase III study (CTD 5.3.5.1.6, Study ZOSTER-022; study period, August 2010 to July 2015)

A multi-center, randomized, observer-blind, parallel-group study was conducted to investigate the efficacy of Shingrix in preventing HZ and PHN in adults aged ≥70 years (target number of subjects, 7,256 in the Shingrix group and 7,256 in the placebo group) at 267 facilities in and out of Japan.

The study drug was administered intramuscularly twice, at 0 and 2 months, at a dose of 0.5 mL.

All 13,900 subjects[1] (6,950 in the Shingrix group and 6,950 in the placebo group) who were randomized and received the study drug at least once (TVC) were included in the safety analysis. Among them, 13,163 subjects, excluding 737 who did not receive 2 vaccinations, were regarded as mTVC (6,541 in the Shingrix group, 6,622 in the placebo group), and were included in the primary efficacy analysis population. Subjects who were assigned to "diary card subset" (512 in the Shingrix group, 513 in the placebo group) were included in the diary card TVC, in which specified local reactions (injection site pain, injection site redness, injection site swelling) and specified general adverse events (fatigue, gastrointestinal disorder, headache, myalgia, chills, pyrexia) were analyzed up to 6 days after each administration of study drug.

The primary endpoint was the number of subjects who developed confirmed HZ[2], which was evaluated during the period from 1 month after the second study drug administration to the cut-off date (April 21, 2015) of the final efficacy analysis (median follow-up of 3.9 years). Subjects who met the definition in Table 12 were considered to have confirmed HZ. The number of subjects who developed confirmed HZ was 23 in the Shingrix group and 223 in the placebo group. The lower limit of two-sided 95% CI for HZ prevention was above the pre-defined criterion for evaluation (10%), and the efficacy of Shingrix was confirmed (Table 17).

Table 17. Vaccine efficacy against HZ (mTVC)

Group	No. of subjects analyzed	No. of subjects with HZ	Incidence rate[a] (/1,000 person-years)	Vaccine efficacy (%)[b, c] [two-sided 95% CI]
Shingrix	6,541	23	0.9	89.79 [84.29, 93.66]
Placebo	6,622	223	9.2	—

a: No. of subjects with HZ per observed person-years
b: Vaccine efficacy (%) = {1 − (incidence of HZ in the Shingrix group/ incidence of HZ in the placebo group)} × 100
c: Poisson regression model with treatment group, age (70-79 years, ≥80 years) and region as factors, and observation period (logarithm) as offset variable

1 The patient enrollment was completed earlier than planned on the basis of a blinded review of study data collected by October 15, 2014.

2 The co-primary endpoint at the time of planning was the number of subjects who developed HZ and the number of subjects who developed PHN. However, the number of subjects who developed PHN was demoted to a descriptive secondary endpoint because collection of subjects who developed PHN was much delayed than initially predicted.

Regarding safety, specified local reaction, specified general adverse events, and specified general adverse reactions that developed up to 6 days after each administration of study drugs are shown in Tables 18 and 19. All specified local reactions were collected as adverse reactions.

Table 18. Specified local reactions (diary card TVC)

Event	Shingrix group				Placebo group			
	After first vaccination (N = 502)		After second vaccination (N = 492)		After first vaccination (N = 504)		After second vaccination (N = 491)	
	n	%	n	%	n	%	n	%
Injection site pain	297	59.2	282	57.3	26	5.2	23	4.7
Injection site redness	143	28.5	137	27.8	3	0.6	3	0.6
Injection site swelling	85	16.9	68	13.8	2	0.4	0	0

Table 19. Specified general adverse events and specified general adverse reactions (diary card TVC)

After first vaccination								
Event	Shingrix group (N = 501)				Placebo group (N = 503)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Myalgia	106	21.2	91	18.2	27	5.4	16	3.2
Fatigue	104	20.8	85	17.0	56	11.1	34	6.8
Headache	72	14.4	58	11.6	42	8.3	27	5.4
Pyrexia[a]	39	7.8	31	6.2	9	1.8	4	0.8
Chills	38	7.6	32	6.4	17	3.4	12	2.4
Gastrointestinal disorder	25	5.0	16	3.2	28	5.6	14	2.8
After second vaccination								
Event	Shingrix group (N = 492)				Placebo group (N = 489)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Fatigue	122	24.8	105	21.3	39	8.0	30	6.1
Myalgia	113	23.0	94	19.1	18	3.7	16	3.3
Headache	76	15.4	63	12.8	26	5.3	20	4.1
Chills	59	12.0	47	9.6	11	2.2	9	1.8
Pyrexia[a]	38	7.7	35	7.1	6	1.2	2	0.4
Gastrointestinal disorder	37	7.5	26	5.3	19	3.9	13	2.7

a: ≥37.5°C

Besides the specified local reactions and specified general adverse events shown in Tables 18 and 19, the incidence of nonspecified adverse events that occurred by 29 days after each vaccination were 55.5% (3,859 of 6,950 subjects) in the Shingrix group and 32.6% (2,263 of 6,950 subjects) in the placebo group. The incidence of nonspecified adverse reactions was 41.1% (2,853 of 6,950 subjects) in the Shingrix group and 7.6% (529 of 6,950 subjects) in the placebo group. Adverse events observed in ≥1% of subjects in any group are shown with the incidence of the adverse reactions in Table 20.

Table 20. Nonspecified adverse events and nonspecified adverse reactions observed in ≥1% in any group (safety analysis population)[a]

Event	Shingrix group (N = 6,950)				Placebo group (N = 6,950)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Injection site pain	1,975	28.4	1,973	28.4	148	2.1	148	2.1
Injection site redness	864	12.4	864	12.4	27	0.4	27	0.4
Injection site swelling	613	8.8	613	8.8	16	0.2	16	0.2
Pyrexia[b]	475	6.8	443	6.4	39	0.6	19	0.3
Headache	462	6.6	366	5.3	189	2.7	93	1.3
Fatigue	309	4.4	270	3.9	92	1.3	53	0.8
Chills	279	4.0	273	3.9	17	0.2	14	0.2
Myalgia	221	3.2	199	2.9	59	0.8	28	0.4
Nasopharyngitis	210	3.0	35	0.5	210	3.0	15	0.2
Injection site pruritus	166	2.4	165	2.4	23	0.3	23	0.3
Nausea	117	1.7	98	1.4	33	0.5	16	0.2
Arthralgia	114	1.6	55	0.8	77	1.1	13	0.2
Malaise	107	1.5	100	1.4	26	0.4	18	0.3
Cough	102	1.5	9	0.1	104	1.5	8	0.1
Upper respiratory tract infection	94	1.4	7	0.1	74	1.1	4	0.1
Back pain	94	1.4	17	0.2	84	1.2	10	0.1
Dizziness	92	1.3	54	0.8	71	1.0	28	0.4
Injection site warmth	91	1.3	91	1.3	4	0.1	4	0.1
Diarrhoea	84	1.2	32	0.5	58	0.8	14	0.2
Pain	81	1.2	68	1.0	17	0.2	4	0.1
Pain in extremity	77	1.1	28	0.4	53	0.8	7	0.1

a: Events collected as specified local reactions or specified general adverse events for subjects in the diary card TVC were collected as nonspecified adverse events in subjects not included in the diary card TVC.
b: ≥37.5°C

All serious adverse events were collected until 1 year after the second vaccination. However, serious adverse events leading to death and serious adverse events for which a causal relationship to the study drug was classified as "related" were collected until discontinuation or completion of the study. Of adverse events that led to death, 577 events were reported in 426 subjects in the Shingrix group and 599 events in 459 subjects in the placebo group [see Section 7.R.8.2 for the reported events)], but causal relationship to the study drug was denied for all the events except for 1 event in 1 subject in the Shingrix group (neutropenic sepsis). A total of 4,081 serious adverse events were reported in 2,367 subjects (1,908 events in 1,153 subjects in the Shingrix group and 2,173 events in 1,214 subjects in the placebo group). However, a causal relationship to the study drug was denied except for 16 events (lymphadenitis, acute myocardial infarction, colitis ulcerative, acute pancreatitis, administration site erythema, administration site pain, chills, pyrexia, allergic granulomatous angiitis, arthritis bacterial, erysipelas, herpes zoster oticus, neutropenic sepsis, acute myeloid leukaemia, Guillain-Barre syndrome, and eczema) in 12 subjects in the Shingrix group and 8 events (polymyalgia rheumatica, adenocarcinoma gastric, cerebral infarction, cerebrovascular accident, Guillain-Barre syndrome, consciousness disturbed, syncope, and glomerulonephritis) in 8 subjects in the placebo group. The outcome of 16 events in 12 subjects for whom causal relationship to the study drug could not be ruled out was recovery or improving except for 3 events (allergic granulomatous angiitis, acute myeloid leukaemia, and neutropenic sepsis) in 2 subjects [see Section 7.R.3.1.2 for details]. A total of 1,365 serious adverse events leading to treatment discontinuation were reported in 941 subjects (648 events in 455 subjects in the Shingrix group, 717 events in 486 subjects in the placebo group). A causal relationship to the study drug was

denied in all the events except for 6 events in 3 subjects in the Shingrix group (acute myocardial infarction, administration site erythema, administration site pain, chills, pyrexia, and acute myeloid leukaemia). The outcomes of the 6 events in 3 subjects in which a causal relationship to the study drug could not be ruled out were reported as "resolved" except for acute myeloid leukaemia which was unresolved [see Section 7.R.3.1.2 for details].

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package and review policy

The applicant explained the structure of the clinical data package for this application as follows.

The HZ vaccine efficacy of Shingrix was examined in adults aged ≥50 years in Study ZOSTER-006 and in adults aged ≥70 years in Study ZOSTER-022, with the number of subjects who developed clinically confirmed HZ as primary endpoint. In addition, the vaccine efficacy of Shingrix on PHN, an HZ-associated complication, was evaluated as a secondary endpoint in Study ZOSTER-006 and Study ZOSTER-022 because PHN is considered as an important medical problem for the following reasons: the incidence and burden of disease are higher than those of other complications; well-established preventive method or fundamental treatment are unavailable; and PHN is refractory after sequelae develops due to the progress of nerve degeneration. The vaccine efficacy of Shingrix on PHN in subjects aged ≥70 would be evaluated by pooling data from subjects aged ≥70 years in Study ZOSTER-006 and the data from Study ZOSTER-022, when HZ vaccine efficacy, the primary endpoint of Study ZOSTER-006 and Study ZOSTER-022, is confirmed. The PHN vaccine efficacy was evaluated using mTVC, not limited to the study population who developed HZ. The results of analysis on PHN, which is an HZ-associated complication after the onset of HZ, may overlap with HZ vaccine efficacy. However, in consideration of the disease burden of PHN, the medical benefit of reducing the incidence of PHN in the overall group is considered to be significant, regardless of the onset of HZ, and the efficacy of Shingrix against PHN can be appropriately evaluated.

The safety of Shingrix was evaluated based on the Japanese and non-Japanese clinical studies submitted as evaluation data, focusing on the Study ZOSTER-006 and Study ZOSTER-022 in which HZ vaccine efficacy was examined.

PMDA considers as follows:

The efficacy of Shingrix against HZ is evaluated based on the 2 global studies (Study ZOSTER-006, Study ZOSTER-022) in which the HZ vaccine efficacy was evaluated. However, because PHN is a complication associated with HZ, the PHN vaccine efficacy is properly evaluated from the number of patients who developed PHN after onset of HZ (*Cochrane Database of Systematic Reviews* 2011;3:CD007795). Therefore, PMDA considers that the method presented by the applicant does not adequately evaluate the vaccine efficacy of Shingrix on PHN after onset of HZ.

The safety of Shingrix was evaluated based on the results of Japanese and non-Japanese clinical trials

which were regarded as evaluation data, focusing on the 2 global studies which included Japanese subjects.

7.R.2 Efficacy

7.R.2.1 Efficacy against herpes zoster

Regarding the efficacy against HZ, PMDA considers that vaccine efficacy of Shingrix has been confirmed by the incidence rate of HZ (per 1,000 person-years) from 1 month after the second administration of the study drug in subjects aged ≥50 years in Study ZOSTER-006 and in subjects aged ≥70 years in Study ZOSTER-022 [see Tables 13 and 17], and that the efficacy against HZ can be expected.

Regarding the efficacy in Japanese subjects, HZ occurred in 2 of 276 subjects in the Shingrix group and 11 of 285 subjects in the placebo group in Study ZOSTER-006. The incidence rate of HZ was 1.8 cases per 1,000 person-years in the Shingrix group and 9.7 cases per 1,000 person-years in the placebo group, and the vaccine efficacy [95% CI] was 81.44 [14.93, 98.00] (analysis at EOS). In Study ZOSTER-022, HZ occurred in 1 of 237 subjects in the Shingrix group and 22 of 244 subjects in the placebo group. The incidence rate of HZ was 1.1 cases per 1,000 person-years in the Shingrix group and 24.1 cases per 1,000 person years in the placebo group, and the vaccine efficacy [95% CI] was 99.55 [72.49, 99.98], which was similar to the results of the overall population in the both studies.

7.R.2.2 Efficacy against HZ-associated complications

PMDA concluded that the occurrence of various complications after Shingrix vaccination should be confirmed, because HZ-associated complications including PHN are clinically important events in the prognosis of HZ.

The applicant's explanation about the efficacy against HZ-associated complications:
PHN was defined by "the presence of HZ-associated severe 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash" in Study ZOSTER-006 and Study ZOSTER-022. In each study, the vaccine efficacy against PHN was evaluated as a secondary endpoint by comparing the incidence rate of PHN in the Shingrix (per 1,000 person-years) and placebo groups. As shown in Table 21, the incidence rate of PHN in the Shingrix group was lower than that in the placebo group in subjects aged ≥50 years and ≥70 years.

Table 21. Vaccine efficacy against PHN (mTVC: EOS)

Study	Group	No. of subjects analyzed	No. of subjects with PHN	Incidence rate[a] (/1,000 person-years)	Vaccine efficacy (%)[b] [two-sided 95% CI]
ZOSTER-006 (aged ≥50 years)	Shingrix	7,340	0	0	100 [77.11, 100][c]
	Placebo	7,413	18	0.6	—
ZOSTER-022 (aged ≥70 years)	Shingrix	6,541	4	0.2	85.49 [58.52, 96.30][d]
	Placebo	6,622	28	1.1	—

a: No. of PHN cases per observed person-years
b: Vaccine efficacy (%) = {1 − (PHN incidence in Shingrix group / PHN incidence in placebo group)} × 100
c: Poisson regression model with treatment group, age (50-59 years, 60-69 years, ≥70 years), and region as factors, and observation period (logarithm) as offset variable
d: Poisson regression model with treatment group, age (70-79 years, ≥80 years), and region as factors, and observation period (logarithm) as offset variable

In addition, PHN occurred in 4 of 8,250 subjects in the Shingrix group and 36 of 8,346 subjects in the placebo group in the pooled analysis of the results of subjects aged ≥70 years in Study ZOSTER-006 and the results of Study ZOSTER-022. The incidence rate (per 1,000 person-years) was 0.1 cases per 1,000 person-years in the Shingrix group and 1.2 cases per 1,000 person-years in the placebo group, and the PHN vaccine efficacy [95% CI] was 88.78 [68.70, 97.10].

Although the number of subjects was extremely limited, the incidence of PHN in subjects who developed HZ in the 2 studies was as shown in Table 22.

Table 22. Incidence of PHN in subjects who developed HZ (Study ZOSTER-006 and Study ZOSTER-022: EOS)

	Shingrix group				Placebo group			
	No. of subjects in mTVC	No. of subjects with HZ	No. of subjects with PHN	Incidence % [95% CI]	No. of subjects in mTVC	No. of subjects with HZ	No. of subjects with PHN	Incidence % [95% CI]
ZOSTER-006 (aged ≥50 years)	7,340	9	0	0 [0, 33.63]	7,413	254	18	7.09 [4.25, 10.97]
ZOSTER-022 (aged ≥70 years)	6,541	23	4	17.39 [4.95, 38.78]	6,622	223	28	12.56 [8.51, 17.63]

HZ-associated complications other than PHN (herpes zoster vasculitis, disseminated disorder, eye disorder, neurological disorder, visceral disease, stroke) occurred in 0 of 7,340 subjects in the Shingrix group and 6 of 7,413 subjects in the placebo group (4 events of disseminated disorder, 1 event of herpes zoster vasculitis, and 1 event of eye disorder) in Study ZOSTER-006, and in 1 of 6,541 subjects in the Shingrix group (eye disorder) and 10 of 6,622 subjects in the placebo group (6 events of eye disorder, 3 events of neurological disorder, and 2 events of disseminated disorder) in Study ZOSTER-022, showing fewer occurrences of events in the Shingrix group than the placebo group in both studies. The occurrence of herpes zoster-related complications other than PHN in subjects who developed HZ was 0 of 9 subjects in the Shingrix group and 6 of 254 subjects in the placebo group in Study ZOSTER-006, and 1 of 23 subjects in the Shingrix group and 10 of 223 subjects in the placebo group in Study ZOSTER-022.

PMDA considers that the occurrences of PHN and HZ-associated complications were lower in the Shingrix group than in the placebo group in Study ZOSTER-006 and Study ZOSTER-022, suggesting that the incidences of HZ-associated complications including PHN decreased as Shingrix suppressed the development of HZ. However, it is difficult to evaluate the vaccine efficacy of Shingrix on HZ-associated complications such as PHN only in subjects who developed HZ according to the results of these studies in which the number of subjects who developed HZ was small. Therefore, PMDA concluded that the efficacy of Shingrix against HZ-associated complications including PHN was unknown at present.

7.R.3 Safety

The applicant explained the safety of Shingrix as follows.

7.R.3.1 Safety results in clinical studies

7.R.3.1.1 Adverse events in clinical studies

The incidences of specified local reactions and specified general reactions observed up to 6 days after each vaccination in the Shingrix group and the placebo group in Study ZOSTER-006 and Study ZOSTER-022 were compared (Tables 14, 15, 18, and 19). In the Shingrix group, the incidences of specified local reactions were high, and injection site pain was the most frequent. The incidence of general adverse reactions tended to be higher in the Shingrix group than in the placebo group, and incidences of fatigue, headache, and myalgia were high. For adverse events and adverse reactions shown in Tables 14 and 15, the incidences of Grade 3 events are shown in Tables 23 to 26. All adverse events observed in the Shingrix group were confirmed to be resolved or resolving.

Table 23. Incidences of Grade 3[a] specified local reactions in Study ZOSTER-006 (diary card TVC)

Event	Shingrix group				Placebo group			
	After first vaccination (N = 4,359)		After second vaccination (N = 4,207)		After first vaccination (N = 4,361)		After second vaccination (N = 4,224)	
	n	%	n	%	n	%	n	%
Injection site pain	159	3.6	185	4.4	6	0.1	10	0.2
Injection site redness	82	1.9	56	1.3	0	0	0	0
Injection site swelling	28	0.6	18	0.4	0	0	0	0

a: Grade 3 is defined as follows:
For injection site pain, adverse event which prevents normal, daily activities.
For injection site redness, diameter is >100 mm.
For injection site swelling, diameter is >100 mm.

Table 24. Incidence of Grade 3[a] specified general adverse events and specified general adverse reactions in Study ZOSTER-006 (diary card TVC)

After first vaccination								
Event	Shingrix group (N = 4,346)				Placebo group (N = 4,362)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Fatigue	109	2.5	85	2.0	29	0.7	21	0.5
Myalgia	104	2.4	87	2.0	21	0.5	14	0.3
Chills	69	1.6	60	1.4	3	0.1	2	0
Headache	67	1.5	54	1.2	20	0.5	14	0.3
Gastrointestinal disorders	30	0.7	19	0.4	12	0.3	6	0.1
Pyrexia	7	0.2	6	0.1	1	0	0	0
After second vaccination								
Event	Shingrix group (N = 4,205)				Placebo group (N = 4,222)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Myalgia	160	3.8	144	3.4	13	0.3	8	0.2
Fatigue	157	3.7	138	3.3	18	0.4	15	0.4
Chills	139	3.3	129	3.1	9	0.2	6	0.1
Headache	105	2.5	96	2.3	13	0.3	6	0.1
Gastrointestinal disorder	33	0.8	27	0.6	14	0.3	6	0.1
Pyrexia	8	0.2	8	0.2	5	0.1	2	0

a: Grade 3 is defined as follows:
For pyrexia, fever is >39.0°C
For others, the severity of adverse event is comparable to that prevents usual daily activities.

Table 25. Incidence of Grade 3[a] specified local reactions in Study ZOSTER-022 (diary card TVC)

Event	Shingrix group				Placebo group			
	After first vaccination (N = 502)		After second vaccination (N = 492)		After first vaccination (N = 504)		After second vaccination (N = 491)	
	n	%	n	%	n	%	n	%
Injection site pain	12	2.4	12	2.4	1	0.2	0	0
Injection site redness	9	1.8	15	3.0	0	0	0	0
Injection site swelling	2	0.4	7	1.4	0	0	0	0

a: Grade 3 is defined as follows:
For injection site pain, adverse event which prevents normal, daily activities.
For injection site redness, diameter is >100 mm.
For injection site swelling, diameter is >100 mm.

Table 26. Incidence of Grade 3[a] specified general adverse events and specified general adverse reactions in Study ZOSTER-022 (diary card TVC)

After first vaccination								
Event	Shingrix group (N = 501)				Placebo group (N = 503)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Fatigue	8	1.6	6	1.2	4	0.8	2	0.4
Myalgia	6	1.2	5	1.0	2	0.4	1	0.2
Gastrointestinal disorder	3	0.6	1	0.2	2	0.4	0	0
Headache	2	0.4	1	0.2	4	0.8	2	0.4
Chills	1	0.2	1	0.2	1	0.2	1	0.2
Pyrexia[a]	0	0	0	0	2	0.4	0	0
After second vaccination								
Event	Shingrix group (N = 492)				Placebo group (N = 489)			
	Adverse event		Adverse reaction		Adverse event		Adverse reaction	
	n	%	n	%	n	%	n	%
Fatigue	9	1.8	9	1.8	0	0	0	0
Myalgia	7	1.4	6	1.2	0	0	0	0
Chills	5	1.0	5	1.0	1	0.2	1	0.2
Headache	4	0.8	3	0.6	0	0	0	0
Gastrointestinal disorder	3	0.6	2	0.4	1	0.2	0	0
Pyrexia[a]	0	0	0	0	2	0.4	0	0

a: Grade 3 is defined as follows:
For pyrexia, fever is >39.0°C
For others, the severity of adverse event is comparable to that prevents usual daily activities.

Regarding safety in Japanese subjects, the occurrences of specified local reactions, specified general adverse events, and specified general adverse reactions observed in Japanese subjects in Study ZOSTER-006 and Study ZOSTER-022 are shown in Tables 27 to 30. As with the results of the overall population, the incidence of injection site pain tended to be higher among the specified local reactions in the Japanese subjects of Shingrix group, and the incidence of specified general adverse reactions was high in the order of myalgia, fatigue, and headache. All Grade 3 events were transient, and recovery was confirmed.

Table 27. Incidence of specified local reactions in Japanese subjects of Study ZOSTER-006 (diary card TVC)

Event		Shingrix group				Placebo group			
		After first vaccination (N = 158)		After second vaccination (N = 151)		After first vaccination (N = 158)		After second vaccination (N = 156)	
		n	%	n	%	n	%	n	%
Injection site pain	Overall	134	84.8	123	81.5	18	11.4	14	9.0
	Grade 3[a]	2	1.3	6	4.0	0	0	0	0
Injection site redness	Overall	112	70.9	90	59.6	7	4.4	4	2.6
	Grade 3[a]	19	12.0	12	7.9	0	0	0	0
Injection site swelling	Overall	91	57.6	64	42.4	5	3.2	0	0
	Grade 3[a]	8	5.1	3	2.0	0	0	0	0

a: Grade 3 is defined as follows:
For injection site pain, adverse event which prevents normal, daily activities.
For injection site redness, diameter is >100 mm.
For injection site swelling, diameter is >100 mm.

Table 28. Incidence of specified general adverse events and specified general adverse reactions in Japanese subjects of Study ZOSTER-006 (diary card TVC)

After first vaccination									
Event		Shingrix group (N = 158)				Placebo group (N = 158)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%
Myalgia	Overall	77	48.7	67	42.4	16	10.1	12	7.6
	Grade 3[a]	1	0.6	1	0.6	0	0	0	0
Fatigue	Overall	72	45.6	67	42.4	12	7.6	10	6.3
	Grade 3[a]	5	3.2	4	2.5	0	0	0	0
Headache	Overall	49	31.0	46	29.1	9	5.7	6	3.8
	Grade 3[a]	1	0.6	0	0	0	0	0	0
Chills	Overall	32	20.3	29	18.4	2	1.3	1	0.6
	Grade 3[a]	1	0.6	1	0.6	0	0	0	0
Pyrexia	Overall	26	16.5	24	15.2	1	0.6	1	0.6
	Grade 3[a]	0	0	0	0	0	0	0	0
Gastrointestinal disorder	Overall	17	10.8	12	7.6	9	5.7	3	1.9
	Grade 3[a]	1	0.6	1	0.6	0	0	0	0
After second vaccination									
Event		Shingrix group (N = 151)				Placebo group (N = 157)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%
Myalgia	Overall	63	41.7	59	39.1	13	8.3	10	6.4
	Grade 3[a]	5	3.3	5	3.3	0	0	0	0
Fatigue	Overall	56	37.1	49	32.5	11	7.0	8	5.1
	Grade 3[a]	7	4.6	6	4.0	0	0	0	0
Headache	Overall	50	33.1	47	31.1	8	5.1	3	1.9
	Grade 3[a]	3	2.0	3	2.0	0	0	0	0
Chills	Overall	41	27.2	40	26.5	2	1.3	1	0.6
	Grade 3[a]	6	4.0	6	4.0	0	0	0	0
Pyrexia	Overall	33	21.9	30	19.9	1	0.6	0	0
	Grade 3[a]	0	0	0	0	0	0	0	0
Gastrointestinal disorder	Overall	20	13.2	19	12.6	4	2.5	2	1.3
	Grade 3[a]	1	0.7	1	0.7	0	0	0	0

a: Grade 3 is defined as follows:
For pyrexia, fever is >39.0°C
For others, adverse event which prevents normal, daily activities.

Table 29. Incidence of specified local reactions in Japanese subjects of Study ZOSTER-022 (diary card TVC)

Event		Shingrix group				Placebo group			
		After first vaccination (N = 28)		After second vaccination (N = 27)		After first vaccination (N = 29)		After second vaccination (N = 29)	
		n	%	n	%	n	%	n	%
Injection site redness	Overall	20	71.4	22	81.5	0	0	0	0
	Grade 3[a]	4	14.3	7	25.9	0	0	0	0
Injection site pain	Overall	18	64.3	20	74.1	2	6.9	2	6.9
	Grade 3[a]	0	0	0	0	0	0	0	0
Injection site swelling	Overall	17	60.7	13	48.1	0	0	0	0
	Grade 3[a]	1	3.6	4	14.8	0	0	0	0

a: Grade 3 is defined as follows:
For injection site pain, adverse event which prevents normal, daily activities.
For injection site redness, diameter is >100 mm.
For injection site swelling, diameter is >100 mm.

Table 30. Incidence of specified general adverse events and specified general adverse reactions in Japanese subjects of Study ZOSTER-022 (diary card TVC)

After first vaccination									
Event		Shingrix group (N = 28)				Placebo group (N = 29)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%
Myalgia	Overall	11	39.3	10	35.7	1	3.4	0	0
	Grade 3[a]	0	0	0	0	0	0	0	0
Fatigue	Overall	7	25.0	6	21.4	3	10.3	2	6.9
	Grade 3[a]	0	0	0	0	0	0	0	0
Headache	Overall	6	21.4	5	17.9	3	10.3	2	6.9
	Grade 3[a]	0	0	0	0	0	0	0	0
Gastrointestinal disorder	Overall	3	10.7	3	10.7	3	10.3	2	6.9
	Grade 3[a]	0	0	0	0	0	0	0	0
Chills	Overall	3	10.7	2	7.1	2	6.9	1	3.4
	Grade 3[a]	0	0	0	0	0	0	0	0
Pyrexia	Overall	2	7.1	2	7.1	1	3.4	1	3.4
	Grade 3[a]	0	0	0	0	0	0	0	0
After second vaccination									
Event		Shingrix group (N = 27)				Placebo group (N = 29)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%
Myalgia	Overall	14	51.9	11	40.7	0	0	0	0
	Grade 3[a]	0	0	0	0	0	0	0	0
Fatigue	Overall	12	44.4	11	40.7	1	3.4	1	3.4
	Grade 3[a]	0	0	0	0	0	0	0	0
Headache	Overall	9	33.3	9	33.3	2	6.9	1	3.4
	Grade 3[a]	0	0	0	0	0	0	0	0
Chills	Overall	5	18.5	4	14.8	0	0	0	0
	Grade 3[a]	0	0	0	0	0	0	0	0
Pyrexia	Overall	4	14.8	4	14.8	0	0	0	0
	Grade 3[a]	0	0	0	0	0	0	0	0
Gastrointestinal disorder	Overall	3	11.1	3	11.1	1	3.4	0	0
	Grade 3[a]	0	0	0	0	0	0	0	0

a: Grade 3 is defined as follows:
For pyrexia, fever is >39.0°C
For others, adverse event which prevents normal, daily activities.

In Study ZOSTER-006 and Study ZOSTER-022, the observation period started from the day of first study vaccination to the end of follow-up period (April 21, 2015, i.e. 4.2 years after the final administration of the study drug), and 10 Japanese subjects died in the Shingrix group and 8 in the placebo group in Study ZOSTER-006, and 16 in the Shingrix group and 20 in the placebo group in Study ZOSTER-022, but a causal relationship to study drug was denied for all events. Serious adverse events were reported in 29 Japanese subjects in the Shingrix group and 31 in the placebo group in Study ZOSTER-006, and 53 in the Shingrix group and 42 in the placebo group in Study ZOSTER-022. Although serious adverse event for which a causal relationship to the study drug could not be not ruled out was not reported in the Shingrix groups, 2 subjects reported serious adverse events (immune thrombocytopenic purpura, rheumatoid arthritis, in 1 subject each) in the placebo group of Study ZOSTER-006, and 1 subject reported serious adverse event (gastric adenocarcinoma) in the placebo group of Study ZOSTER-022. Immune thrombocytopenic purpura and gastric adenocarcinoma were confirmed to be resolved or resolving. Adverse events that led to study drug discontinuation were reported in 11 subjects in the Shingrix group and 9 in the placebo group in Study ZOSTER-006, and 17 in the Shingrix group and 22 in the placebo group in Study ZOSTER-022. Among these events, a causal

relationship to the study drug could not be not ruled out in 1 subject (myalgia) in the Shingrix group in Study ZOSTER-006, but the event was confirmed to recover.

Based on the above results, no particular safety issue was found in Japanese subjects who received Shingrix.

7.R.3.1.2 Serious adverse events and adverse reactions

In the clinical studies of the evaluation data for Shingrix (Studies ZOSTER-006, ZOSTER-022, ZOSTER-032, ZOSTER-003, ZOSTER-026, ZOSTER-024, ZOSTER-010, hereinafter referred to as "7 studies in evaluation data"), 15,110 subjects were vaccinated with Shingrix (excluding different dosage and administration of study vaccine). Among these subjects, 281 adverse events leading to death were reported in 208 subjects in Study ZOSTER-006, 577 events in 426 subjects in Study ZOSTER-022, 8 events in 6 subjects in Study ZOSTER-003 and its follow-up studies (up to Study ZOSTER-024), 1 event in 1 subject in Study ZOSTER-026, and 1 event in 1 subject in Study ZOSTER-010. However, a causal relationship to Shingrix was denied for all events except for 1 event (neutropenic sepsis) in 1 subject in Study ZOSTER-022. In the 15,110 subjects who were vaccinated with Shingrix, 1,136 serious adverse events were reported in 727 subjects in Study ZOSTER-006, 1,908 events in 1,153 subjects in Study ZOSTER-022, 1 event in 1 subject in Study ZOSTER-032, 84 events in 52 subjects in Study ZOSTER-003 and its follow-up studies (up to Study ZOSTER-024), 6 events in 5 subjects in Study ZOSTER-026, and 13 events in 10 subjects in Study ZOSTER-010. Among these, 3 serious adverse reactions (immune thrombocytopenic purpura, musculoskeletal chest pain, and nervous system disorder) were reported in 3 subjects in Study ZOSTER-006, and 16 events (lymphadenitis, acute myocardial infarction, colitis ulcerative, pancreatitis acute, administration site erythema, administration site pain, chills, pyrexia, allergic granulomatous angiitis, arthritis bacterial, erysipelas, herpes zoster oticus, neutropenic sepsis, acute myeloid leukaemia, Guillain-Barre syndrome, and eczema) in 12 subjects in Study ZOSTER-022, but recovery or improvement was confirmed in all cases except for 3 events (allergic granulomatous angiitis, neutropenic sepsis, and acute myeloid leukaemia) in 2 subjects in Study ZOSTER-022. Allergic granulomatous angiitis in 1 subject developed 320 days after the second vaccination and was in a chronic condition at the end of the study. Because this event occurred long time after the study vaccination, the applicant concludes that the possibility of Shingrix being associated with the event is extremely low. Acute myeloid leukaemia and neutropenic sepsis in 1 subject (the same subject for whom a causal relationship of the study drug to death could not be ruled out) developed 75 days and 97 days after the first vaccination, respectively, and death occurred thereafter (98 days after the vaccination). The subject had had idiopathic thrombocytopenia over a long period of time and subsequently developed acute myeloid leukaemia. Therefore, the applicant concluded that neutropenic sepsis occurred as a result of chemotherapy for acute myeloid leukaemia.

7.R.3.1.3 Noteworthy adverse events and adverse reactions

The applicant raised and explained about shock, anaphylaxis, and potential immune-mediated disease (pIMD) as important potential risks as follows:

For other vaccines, anaphylaxis or other hypersensitivities to single or multiple vaccine components are regarded as notable adverse events. In clinical studies with Shingrix, subjects were excluded from the study if they have a history of hypersensitivity to the components of Shingrix. In Study ZOSTER-006 and Study ZOSTER-022, adverse events of "hypersensitivity, narrow term" in standardised MedDRA queries (SMQ) occurred up to 29 days after the administration of study drug in 380 subjects (2.6%) in the Shingrix group and 349 subjects (2.4%) in the placebo group. The incidences of rash, dermatitis, and eczema were high, and raised no particular safety concerns. Although 1 subject in the Shingrix group was reported to develop a non-serious anaphylactic reaction associated with the study drug in Study ZOSTER-006, the event did not conform to the definition of anaphylaxis when evaluated according to the Brighton Collaboration's Definitions and Guidelines for Anaphylaxis (*Vaccine* 2007;25:5675-84).

The applicant examined pIMD that includes autoimmune or immune-mediated inflammatory diseases as events of special interest, because a vaccine that contains an adjuvant such as $AS01_B$ may affect the adjustment of the immune mechanism and harm immune reaction. In Study ZOSTER-006 and Study ZOSTER-022, pIMD was reported in 179 subjects (1.2%) in the Shingrix group and 202 subjects (1.4%) in the placebo group during the entire post-vaccination follow-up period. pIMD that is concluded as related to the study drug was reported in 16 subjects (0.1%) (rheumatoid arthritis and psoriasis in 2 subjects each; immune thrombocytopenic purpura, thrombocytopenia, colitis ulcerative, acute pancreatitis, allergic granulomatous angiitis, reactive arthritis, polymyalgia rheumatica, Guillain-Barre syndrome, myasthenic syndrome, alopecia areata, dermatitis exfoliative, and hypersensitivity vasculitis in 1 subject each) in the Shingrix group and 18 subjects (0.1%) (polymyalgia rheumatica in 3 subjects; rheumatoid arthritis and Sjogren's syndrome in 2 subjects each; immune thrombocytopenic purpura, uveitis, colitis ulcerative, inclusion body myositis, Guillain-Barre syndrome, IVth nerve paralysis, mononeuritis, glomerulonephritis, erythema nodosum, psoriasis, and Behcet's syndrome in 1 subject each) in the placebo group. The incidence of pIMD was similar between the Shingrix group and the placebo group, showing no clinically significant difference between the two groups. However, the US FDA's Vaccines and Related Biological Products Advisory Committee pointed out a difference in the incidence of gout or gouty arthritis between the Shingrix group and the placebo group as nonspecific adverse events that occurred up to 29 days after study vaccination (27 subjects [0.18%] in the Shingrix group; 8 subjects [0.05%] in the placebo group) from the pooled analysis of safety results in Study ZOSTER-006 and Study ZOSTER-022. The studies were reviewed in response to the notion. The results revealed that serious adverse events related to gout were reported in 5 subjects (0.03%) in the Shingrix group and 1 subject (0.01%) in the placebo group during the period from the first vaccination to 365 days after the final vaccination, but none of these events were considered to be related to study drug. Although it is difficult to determine gout and gouty arthritis as identified risks of Shingrix from the currently available information, gout will be added to pIMD that requires monitoring at the use of Shingrix based on the difference in the incidence between Shingrix group and placebo group, and information will be continued to be collected and risk will be evaluated. The risks of using Shingrix in patients receiving treatment with immune checkpoint inhibitors for immunostimulation were also

examined, but no assessable information has been obtained in previous clinical studies. In addition to regular pharmacovigilance activities, the applicant plans to design a post-marketing drug use-results survey that enables collection of safety information when Shingrix is administered to patients who are receiving immune checkpoint inhibitors, because Shingrix may be administered to patients aged ≥50 years with cancer.

PMDA's views on the tolerability of Shingrix as follows:
Tolerability of Shingrix is accepted because i) all severe adverse events reported after Shingrix vaccination in Study ZOSTER-006 and Study ZOSTER-022 were confirmed to be resolved or resolving, ii) serious adverse reactions reported after Shingrix vaccination in the 7 studies in evaluation data were confirmed to be resolved or resolving, except for 3 events (allergic granulomatous angiitis that developed 320 days after the second vaccination in 1 subject; acute myeloid leukaemia that developed in 1 subject with long-standing idiopathic thrombocytopenia and neutropenic sepsis that is considered to have developed as a result of chemotherapy for acute myeloid leukaemia in the same subject) in 2 subjects in Study ZOSTER-022 for which causal relationship with Shingrix was unclear, and iii) the incidences of hypersensitivity such as anaphylaxis and pIMD were similar between the Shingrix group and placebo group.

Based on the above results, PMDA concluded the safety of Shingrix to be tolerable.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of Shingrix is as follows:
At the initial infection of VZV, varicella develops and the VZV persists in neurons of the dorsal root and cerebral ganglion. HZ is an endogenously derived disease that develops by the reactivation of latent VZV. Typically, a painful rash appears along a single dermatome and heals in 2 to 4 weeks, and scar and pigment changes may remain. The pain persists for a median duration of 2 weeks, and a very severe pain may cause dysfunction or hinder the patient's daily activities. Individuals whose cellular immunity has decreased due to aging, disease or medical intervention have been shown to have a high risk of developing HZ (*N Engl J Med* 2013;369:255-63). Over 60% of those who develop HZ are aged ≥50 years. Known HZ-associated complications include PHN, Ramsay-Hunt syndrome, VZV encephalitis, and meningitis. PHN, a neuropathic pain, develops in 10% to 30% of patients with HZ (*BMJ Open* 2014;4:e004833, *N Engl J Med* 2014;371:1526-33). PHN usually resolves within a year in about 70% to 80% of patients, but sometimes persists for several years, greatly affecting the quality of life for the elderly (*BMC Public Health* 2015;15:193). Antiviral drugs (such as aciclovir) are used to treat HZ and other complications, but there is no established treatment for PHN, and administration of antidepressants is recommended *(J. Clin. Therap. Med.* 2012;28:161-73). ZOSTAVAX, a live attenuated vaccine, is currently marketed outside Japan as a preventive vaccine for HZ. In Japan, the dry live attenuated varicella vaccine "Biken" which contains the same attenuated live VZV (Oka strain) as ZOSTAVAX as the active ingredient was approved in March 2016 for the indication of "preventing herpes zoster in persons aged ≥50 years." Both the live attenuated vaccine ZOSTAVAX and dry live attenuated varicella

vaccine “Biken” are contraindicated for adults with immunosuppression or immunodeficiency because there is a risk of rash or disseminated disorder from the virus contained in the vaccine. Shingrix is a recombinant protein product and does not contain infectious viral particles, so it is considered to be suitable for vaccinating adults and the elderly with reduced immune function, who are considered at high risk of developing HZ. The results of Study ZOSTER-006 and Study ZOSTER-022 demonstrated the vaccine efficacy of Shingrix against HZ in adults aged ≥50 years. Suppression of HZ-associated complications is also expected with Shingrix vaccination by preventing the onset of HZ. From the above, introducing Shingrix in Japan is considered to have significance. The efficacy and safety of Shingrix in patients with confirmed or suspected immunosuppression/immunodeficiency (condition with diseases such as malignant tumor and HIV infection, immunosuppressive therapy or cytotoxic therapy [cancer chemotherapy, organ transplant etc.]) are not examined in Study ZOSTER-006 and Study ZOSTER-022, in which the efficacy of Shingrix was confirmed. However, no safety issues have been found in subjects aged ≥50 years in clinical studies currently being conducted (Studies ZOSTER-001, ZOSTER-015, etc.) in patients aged ≥18 years who have decreased immune function (such as patients with cellular immune dysfunction due to autologous hematopoietic stem cell transplantation, solid organ transplantation, HIV infection, and malignant tumors).

PMDA’s views on the positioning of Shingrix are as follows:
In Japan, the incidence rate of HZ reportedly increases with age from the age of 50 years (*J. JOCD* 2012;29:799-804), and main recipients of Shingrix vaccination are presumably similar in herpes zoster prevention with a live attenuated vaccine. Shingrix has been confirmed to prevent HZ in adults aged ≥50 years and is positioned as a new option in the prevention of HZ as the first recombinant herpes zoster vaccine in Japan. In light of the medical need for preventing herpes zoster in patients with confirmed or suspected immunosuppression or immunodeficiency, it is desirable for the applicant to respond appropriately if new findings are obtained in the current clinical study results.

7.R.5 Indications

PMDA’s views on the indications of Shingrix are as follows:
As described in Section 7.R.2.1, the results of Study ZOSTER-006 and Study ZOSTER-022 showed vaccine efficacy of Shingrix against HZ. However, as described in Sections 7.R.1 and 7.R.2.2, vaccine efficacy of Shingrix against PHN is unknown at present as it should be evaluated in patients with HZ and has not been evaluated. Therefore, it is not appropriate to state prevention of PHN in the indication of Shingrix.

Based on the above consideration, PMDA concluded that “prevention of herpes zoster” is appropriate for the indication of Shingrix.

7.R.6 Dosage and administration

The applicant explained the rationale for setting dosage and administration as follows.

7.R.6.1 Amount of antigen

The amount of antigen was examined in Study ZOSTER-003 in adults aged ≥60 years. The safety and immunogenicity of 2 administrations of Shingrix (gE251B, gE501B, and gE1001B) containing 3 dose levels of gE antigen (25, 50, and 100 μg) were examined, together with 1 administration of Shingrix containing 100 μg of gE antigen (gE1001B), and 2 administrations of study drug not containing $AS01_B$ (gE100/S). The safety of 2 administrations of Shingrix showed no difference between the 3 dose levels, and all the doses were considered tolerable. Regarding immunogenicity, the geometric mean (GM) of the frequency of gE-specific CD4-positive T-cells producing more than 1 type of cytokine was evaluated for the cell mediated immunity (CMI) response at 1 month after the final administration of the study drug, and geometric mean concentration (GMC) of anti-gE antibody was evaluated for humoral immune response (Table 31). In the results, CMI response was higher in all dose groups in which Shingrix was administered twice than the SgE1B group in which gE1001B was administered once and the gE100/S group using investigational drug not containing $AS01_B$. Although the response tended to be higher in gE1001B group than the gE501B group, they were similar, and the response in both groups were higher than the gE251B group. On the other hand, humoral immune response was highest in the gE1001B group. CMI response is considered important for suppressing VZV reactivation (*J Infect Dis* 2009;200:1068-77). Emphasizing the result of CMI response, the amount of gE antigen in Shingrix was set at 50 μg, as the minimum tolerable dose at which CMI response can be expected.

Table 31. gE-specific CMI response and humoral immune response 1 month after second administration of study drug in Study ZOSTER-003 (ATP immunogenicity analysis population)

Treatment group	gE antigen (μg)	Adjuvant	gE-specific CMI response			Humoral immune response	
			No. of subjects analyzed	Frequency of gE-specific CD4-positive T-cells producing ≥2 types of cytokines (median)[a]	GM[b]	No. of subjects analyzed	Anti-gE antibody GMC (EU/mL) [95% CI]
gE251B	25	$AS01_B$	151	1751.75	9.02	155	9315.3 [8283.2, 10476.1]
gE501B	50	$AS01_B$	148	1755.39	9.81	156	12898.0 [11681.2, 14241.6]
gE1001B	100	$AS01_B$	144	1792.20	11.54	151	15626.5 [14030.3, 17404.3]
SgE1B	100[c]	$AS01_B$	148	524.87	4.21	153	6287.2 [5372.0, 7358.3]
gE100/S	100[d]	None	47	468.30	3.34	49	4298.3 [3220.0, 5737.7]

a: Frequency of gE-specific CD4-positive cells producing ≥2 types of cytokines (CD40L, IFNγ, IL-2, and TNFα) per million CD4-positive T-cells

b: Geometric mean of odds ratio of frequency of CD4-positive T-cells producing ≥2 types of cytokines (CD40L, IFNγ, IL-2, and TNFα) per million CD4-positive T-cells with and without gE antibody stimulation

c: First administration of saline, second administration of gE1001B

d: 2 administrations of gE100/S

7.R.6.2 Number and intervals of vaccinations

The number of vaccinations was assessed as follows: In Study ZOSTER-003, the GMC of anti-gE antibodies (EU/mL) and median value of gE-specific CMI response[3] at 2 months after the first vaccination in the Shingrix group were 4139.4 and 382.57, respectively, and those at 1 month after the second vaccination were higher at 12898.0 and 1755.39. In Study EXPLO-CRD-004, the GMC of anti-

[3] Frequency of gE-specific CD4- or CD8-positive cells producing ≥2 types of cytokines (CD40L, IFNγ, IL-2, and TNFα) per million CD4- or CD8-positive T-cells

gE antibodies (EU/mL) and median value of gE-specific CMI response at 2 months after the first vaccination in the gE group were 4844.2 and 402.00, respectively, and those at 1 month after the second vaccination were higher at 14816.8 and 2323.00. Two vaccinations of Shingrix resulted in a higher humoral immune response and gE-specific CMI response compared to single vaccination; therefore, it was concluded that 2 vaccinations were appropriate.

The interval between vaccinations was assessed as follows: Immunogenicity was evaluated in Study ZOSTER-026 by 2 vaccinations at intervals (6 months or 12 months) longer than the interval (2 months) used in Studies ZOSTER-006 and ZOSTER-022 in which the efficacy of Shingrix was confirmed, in order to examine the possibility of vaccination intervals with flexibility to improve vaccination compliance and the immunization rate. The vaccine antibody response rate for the anti-gE antibody (percentage of subjects who became antibody-positive[4]) [two-sided 97.5% CI] was examined at 1 month after the second Shingrix vaccination in the groups vaccinated twice at a 6-month or 12-month interval (6-month interval group, 12-month interval group), and the antibody response rates were 96.5 [90.4, 99.2] and 94.5 [87.6, 98.3], respectively. In either vaccination groups, the lower limit of two-sided 97.5% CI for the antibody response rates was above the pre-defined criterion (60%). Then, GMC of anti-gE antibody in the 6-month interval group and the 12-month interval group were compared with that in the 2-month interval group (2 vaccinations at a 2-month interval). As a result, the upper limit of two-sided 97.5% CI of GMC ratio fell below the pre-defined non-inferiority limit (1.5) in the 6-month interval vaccination group only, and noninferiority of the 6-month interval vaccination group to the 2-month interval vaccination group was demonstrated (Table 32).

Table 32. Comparison of GMC of anti-gE antibody1 month after second administration of study drug at 6-month interval or 12-month interval with 2-month interval in Study ZOSTER-026 (ATP immunogenic subject population)

	Vaccination group	No. of subjects analyzed	Adjusted GMC [Two-sided 97.5% CI]	Adjusted GMC ratio [Two-sided 97.5% CI]
Comparison of 2-month interval and 6-month interval	2-month interval vaccination group	118	44352.6 [39208.5, 50171.5]	—
	6-month interval vaccination group	114	38137.8 [33642.5, 43233.7]	1.16 [0.98, 1.39][a]
Comparison of 2-month interval and 12-month interval	2-month interval vaccination group	118	44201.0 [37183.6, 52542.7]	
	12-month interval vaccination group	110	37019.9 [30945.7, 44286.3]	1.19 [0.93, 1.53][b]

a: 2-month interval vaccination group/6-month interval vaccination group
b: 2-month interval vaccination group/12-month interval vaccination group
Covariance analysis model with logarithmically converted antibody concentration before vaccination as a continuous covariate, vaccination group and age group (50-59 years, 60-69 years, ≥70 years) as fixed effects

Regarding safety, onset of specified local reactions, specified general adverse events, and specified general adverse reactions up to 6 days after the study vaccination are shown in Tables 33 and 34. The

[4] Among subjects who were antibody-negative before vaccination, those who had an anti-gE antibody concentration at least 4 times the cutoff value (4 × 97 mIU/mL) after vaccination with Shingrix, and among subjects who were antibody-positive before vaccination, those with an anti-gE antibody concentration after vaccination with Shingrix more than 4 times that before vaccination

incidences of nonspecified adverse events up to 29 days after each study vaccination in the 2-month interval vaccination group, 6-month interval vaccination group, and 12-month interval vaccination group were 22.7% (27 of 119 subjects), 22.7% (27 of 119 subjects), and 19.8% (23 of 116 subjects), respectively. Based on the occurrence of serious adverse events including deaths during the study period and of adverse events that led to discontinuation of the study treatment [see Section 7.R.8.6], all of the vaccination intervals examined were considered to be tolerable.

Based on the above, the vaccination interval was set at 2 to 6 months after the initial vaccination.

Table 33. Incidence of specified local reactions in Study ZOSTER-026 (TVC)

		2-month interval vaccination group				6-month interval vaccination group				12-month interval vaccination group			
		After first vaccination (N = 119)		After second vaccination (N = 118)		After first vaccination (N = 119)		After second vaccination (N = 117)		After first vaccination (N = 115)		After second vaccination (N = 111)	
		n	%	n	%	n	%	n	%	n	%	n	%
Injection site pain	Overall	84	70.6	71	60.2	77	64.7	83	70.9	80	69.6	87	78.4
	Grade 3[a]	1	0.8	6	5.1	0	0	6	5.1	2	1.7	10	9.0
Injection site redness	Overall	37	31.1	28	23.7	39	32.8	27	23.1	32	27.8	37	33.3
	Grade 3[a]	0	0	2	1.7	0	0	0	0	1	0.9	0	0
Injection site swelling	Overall	17	14.3	15	12.7	23	19.3	9	7.7	25	21.7	24	21.6
	Grade 3[a]	0	0	0	0	0	0	0	0	0	0	0	0

a: Grade 3 is defined as follows:
For injection site pain, adverse event which prevents normal, daily activities.
For injection site redness, diameter is >100 mm.
For injection site swelling, diameter is >100 mm.

Table 34. Incidence of specified general adverse events and specified general adverse reactions in Study ZOSTER-026 (TVC)

First vaccination													
Event		2-month interval vaccination group (N = 119)				6-month interval vaccination group (N = 119)				12-month interval vaccination group (N = 115)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%	n	%	n	%
Myalgia	Overall	43	36.1	36	30.3	38	31.9	33	27.7	46	40.0	40	34.8
	Grade 3[a]	2	1.7	2	1.7	2	1.7	2	1.7	0	0	0	0
Fatigue	Overall	42	35.3	37	31.1	50	42.0	49	41.2	46	40.0	38	33.0
	Grade 3[a]	3	2.5	3	2.5	1	0.8	1	0.8	0	0	0	0
Headache	Overall	35	29.4	31	26.1	39	32.8	31	26.1	34	29.6	26	22.6
	Grade 3[a]	1	0.8	1	0.8	1	0.8	1	0.8	0	0	0	0
Chills	Overall	25	21.0	22	18.5	25	21.0	22	18.5	29	25.2	26	22.6
	Grade 3[a]	1	0.8	1	0.8	0	0	0	0	0	0	0	0
Gastro-intestinal disorder	Overall	22	18.5	19	16.0	17	14.3	14	11.8	17	14.8	12	10.4
	Grade 3[a]	3	2.5	3	2.5	1	0.8	1	0.8	0	0	0	0
Pyrexia	Overall	21	17.6	19	16.0	22	18.5	21	17.6	14	12.2	13	11.3
	Grade 3[a]	1	0.8	0	0	0	0	0	0	0	0	0	0
Second vaccination													
Event		2-month interval vaccination group (N = 118)				6-month interval vaccination group (N = 117)				12-month interval vaccination group (N = 111)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%	n	%	n	%
Myalgia	Overall	48	40.7	46	39.0	42	35.9	39	33.3	43	38.7	38	34.2
	Grade 3[a]	5	4.2	4	3.4	2	1.7	2	1.7	3	2.7	2	1.8
Fatigue	Overall	43	36.4	41	34.7	46	39.3	41	35.0	59	53.2	56	50.5
	Grade 3[a]	4	3.4	3	2.5	4	3.4	1	0.9	4	3.6	4	3.6
Headache	Overall	36	30.5	32	27.1	27	23.1	22	18.8	37	33.3	33	29.7
	Grade 3[a]	2	1.7	1	0.8	3	2.6	1	0.9	5	4.5	5	4.5
Chills	Overall	25	21.2	24	20.3	23	19.7	20	17.1	35	31.5	31	27.9
	Grade 3[a]	3	2.5	2	1.7	3	2.6	2	1.7	3	2.7	3	2.7
Pyrexia	Overall	20	16.9	19	16.1	16	13.7	16	13.7	26	23.4	24	21.6
	Grade 3[a]	0	0	0	0	0	0	0	0	2	1.8	2	1.8
Gastro-intestinal disorder	Overall	14	11.9	14	11.9	5	4.3	5	4.3	12	10.8	10	9.0
	Grade 3[a]	0	0	0	0	1	0.9	1	0.9	1	0.9	1	0.9

a: Grade 3 is defined as follows
For pyrexia, fever is >39.0°C
For others, adverse event which prevents normal, daily activities.

7.R.6.3 Route of vaccination

The Advisory Committee on Immunization Practices (ACIP) recommends intramuscular administration for vaccines containing adjuvants to reduce adverse reactions after vaccination (*MMWR Recom Rep* 2011;60:1-64). Shingrix was developed as a vaccine for intramuscular administration, and its efficacy and safety have been confirmed. In the Japanese Study ZOSTER-032, the safety of 2 subcutaneous or intramuscular administrations (0, 2 months) of Shingrix in adults aged ≥50 years was evaluated (Table 35 and Table 36), and specified local adverse events of Grade 3 were more common in the subcutaneous group. These local reactions were transient and not serious adverse events, but intramuscular administration is the recommended route for Shingrix vaccination rather than subcutaneous administration.

Table 35. Incidence of specified local reactions in Study ZOSTER-032 (TVC)

		Intramuscular administration				Subcutaneous administration			
		After first vaccination (N = 30)		After second vaccination (N = 29)		After first vaccination (N = 30)		After second vaccination (N = 30)	
		n	%	n	%	n	%	n	%
Injection site pain	Overall	26	86.7	21	72.4	28	93.3	25	83.3
	Grade 3[b]	0	0	0	0	2	6.7	1	3.3
Injection site redness	Overall	11	36.7	12	41.4	23	76.7	23	76.7
	Grade 3[b]	1	3.3	1	3.4	12	40.0	12	40.0
Injection site swelling	Overall	7	23.3	11	37.9	22	73.3	20	66.7
	Grade 3[b]	1	3.3	1	3.4	8	26.7	6	20.0
Vaccination site movement impairment[a]	Overall	7	23.3	11	37.9	10	33.3	16	53.3
	Grade 3[b]	0	0	0	0	1	3.3	0	0
Injection site pruritus[a]	Overall	6	20.0	8	27.6	19	63.3	15	50.0
	Grade 3[b]	0	0	0	0	0	0	0	0

a: Event defined as a specified local reaction only in Study ZOSTER-032

b: Grade 3 is defined as follows:

For vaccination site movement impairment, injection site pruritus, injection site pain: adverse event which prevents normal, daily activities.

For injection site redness, diameter is >100 mm.

For injection site swelling, diameter is >100 mm.

Table 36 Incidence of specified general adverse events and specified general adverse reactions in Study ZOSTER-032 (TVC)

First vaccination								
		Intramuscular administration (N = 30)				Subcutaneous administration (N = 30)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%
Fatigue	Overall	12	40.0	12	40.0	14	46.7	14	46.7
	Grade 3[a]	0	0	0	0	0	0	0	0
Headache	Overall	8	26.7	8	26.7	11	36.7	11	36.7
	Grade 3[a]	0	0	0	0	0	0	0	0
Gastrointestinal disorder	Overall	4	13.3	4	13.3	2	6.7	2	6.7
	Grade 3[a]	0	0	0	0	0	0	0	0
Chills	Overall	3	10.0	3	10.0	3	10.0	3	10.0
	Grade 3[a]	1	3.3	1	3.3	0	0	0	0
Pyrexia	Overall	2	6.7	2	6.7	3	10.0	3	10.0
	Grade 3[a]	0	0	0	0	0	0	0	0
Myalgia	Overall	1	3.3	1	3.3	2	6.7	2	6.7
	Grade 3[a]	0	0	0	0	1	3.3	1	3.3
Second vaccination									
		Intramuscular administration (N = 29)				Subcutaneous administration (N = 30)			
		Adverse event		Adverse reaction		Adverse event		Adverse reaction	
		n	%	n	%	n	%	n	%
Headache	Overall	10	34.5	10	34.5	11	36.7	11	36.7
	Grade 3[a]	2	6.9	2	6.9	0	0	0	0
Fatigue	Overall	9	31.0	9	31.0	16	53.3	16	53.3
	Grade 3[a]	1	3.4	1	3.4	0	0	0	0
Chills	Overall	6	20.7	6	20.7	6	20.0	6	20.0
	Grade 3[a]	0	0	0	0	0	0	0	0
Pyrexia	Overall	6	20.7	6	20.7	5	16.7	5	16.7
	Grade 3[a]	0	0	0	0	0	0	0	0
Myalgia	Overall	3	10.3	3	10.3	5	16.7	5	16.7
	Grade 3[a]	1	3.4	1	3.4	0	0	0	0
Gastrointestinal disorder	Overall	3	10.3	3	10.3	5	16.7	5	16.7
	Grade 3[a]	1	3.4	1	3.4	0	0	0	0

a: Grade 3 is defined as follows
Pyrexia: >39.0°C
Others: Adverse event of severity that prevents ordinary daily activities

7.R.6.4 Vaccination subjects

In the global studies that confirmed the efficacy, the target population was subjects aged ≥50 years in Study ZOSTER-006 and aged ≥70 years in Study ZOSTER-022. Therefore, Shingrix is described as a vaccine for individuals aged ≥50 years.

PMDA considers as follows:

Because the relationship between immunogenicity and a vaccine efficacy against HZ is unclear, ability to conclude the appropriateness of dosage and administration on the basis of immunogenicity results such as gE-specific CMI and anti gE antibody titer is limited. However, from the results of Study ZOSTER-006 and Study ZOSTER-022, in which Shingrix with 50 μg of gE antigen was administered twice at a 2-month interval, the vaccine efficacy of Shingrix against HZ was confirmed and the tolerability of the dosage and administration was confirmed, and PMDA concluded that the proposed dosage and administration is acceptable. However, it is not considered appropriate to set the vaccination interval up to 6 months based only on the results of immunogenicity, which is not clearly related to vaccine efficacy against HZ. However, considering that a second vaccination in a 2-month interval can be difficult, and that administration up to 6 months after the first vaccination is acceptable from the

safety viewpoint on the basis of immunogenicity and tolerability results in Study ZOSTER-026, PMDA concluded that it is acceptable to include the description in a PRECAUTION of package insert. The incidence rate of HZ in Japan is largely constant at all ages <50 years at 2.06 to 2.85 cases per 1,000 person-years, compared to 5.30 cases per 1,000 person-years at 50 to 59 years of age, 7.14 cases per 1,000 person-years at 60 to 69 years of age, and 8.25 cases per 1,000 person-years at 70 to 79 years of age (*J. JOCD* 2012;29:799-804). Considering the clinical positioning of Shingrix [see Section 7.R.4], the proposed dosage and administration of ≥50 years of age is acceptable.

As discussed above, PMDA concluded that the dosage and administration statement of Shingrix as shown below is acceptable.

[Dosage and Administration]
The antigen preparation is reconstituted with the full volume of accompanying adjuvant for reconstitution, and the usual dosage is 0.5 mL administered intramuscularly twice at intervals of 2 months to adults aged ≥50 years.

7.R.7 Post-marketing investigations

The applicant is planning to conduct a use-results survey to examine the safety of Shingrix in routine clinical practice (target sample size of 1,500 subjects). Currently, a global study (Study ZOSTER-049) is ongoing to investigate the safety for up to 10 years after Shingrix vaccination, vaccine efficacy against HZ, and continuation of immunogenicity in patients from Study ZOSTER-006 and Study ZOSTER-022, and the study is intended to be continued as a post-marketing clinical study.

PMDA's view is as follows:
Although the clinical studies of Shingrix provide experiences in a wide range of patients, including those with underlying disease, it is necessary to collect post-marketing safety information on the use of Shingrix under the routine clinical practice as planned by the applicant. This is because after its launch, Shingrix is expected to be used in patients with malignant tumors and immunocompromised patients who were not included in the clinical studies. The applicant's post-marketing surveillance plan, etc., based on comments from the Expert Discussion, is described in Review Report (2).

7.R.8 Adverse events observed in clinical studies

Details of deaths, serious adverse events, and adverse events that led to treatment discontinuation in Study ZOSTER-006 [see Section 7.1.1] and Study ZOSTER-022 [see Section 7.1.2] are provided in Sections 7.R.8.1 and 7.R.8.2. Details of deaths, serious adverse events, and adverse events that led to treatment discontinuation in adult subjects aged ≥50 years vaccinated with Shingrix or HZ/su [see Table 11] in Study EXPLO-CRD-004 and its follow-up Studies ZOSTER-018/019, Study ZOSTER-003 and its follow-up studies ZOSTER-011/012/013/024, Study ZOSTER-010, Study ZOSTER-026, and Study ZOSTER-032 are provided in Sections 7.R.8.3 to 7.R.8.7. No deaths, serious adverse events, or adverse events that led to treatment discontinuation from the study were reported in Study ZOSTER-023.

7.R.8.1 Study ZOSTER-006 (Global phase III study)

During the period from the day of the first study vaccination to 1 year after the second study vaccination, 79 adverse events leading to death occurred in 55 subjects in the Shingrix group (adverse events occurring at least twice were: pneumonia [6], myocardial infarction [4], pancreatic carcinoma [3], cerebrovascular accident [3], acute myocardial infarction [2], completed suicide [2]), and 80 adverse events leading to death occurred in 60 subjects in the placebo group (adverse events occurring at least twice were: acute myocardial infarction [6], sepsis [4], cardiac failure [3], road traffic accident [3], myocardial infarction [2], death [2], sudden death [2], pneumonia [2], intrahepatic bile duct cancer [2], colon cancer [2], hepatic neoplasm malignant [2], cerebral haemorrhage [2], cerebral infarction [2], cerebrovascular accident [2], completed suicide [2], renal failure [2], circulatory collapse [2]). A total of 905 serious adverse events occurred in 594 subjects in the Shingrix group (adverse events occurring at least twice were: pneumonia [32], atrial fibrillation [21], myocardial infarction [17], cardiac failure congestive [14], cerebrovascular accident [14], coronary artery disease [11], chest pain [11], heart failure [10], chronic obstructive pulmonary disease [9], cellulitis [8], urinary tract infection [8], osteoarthritis [8], breast cancer [8], syncope [8], acute myocardial infarction [7], ankle fracture [7], radius fracture [7], prostate cancer [7], transient ischaemic attack [7], hypertension [7], anaemia [6], myocardial ischaemia [6], cholecystitis acute [6], cholelithiasis [6], femur fracture [6], colon cancer [6], asthma [6], arrhythmia [5], gastritis [5], pancreatitis acute [5], cholecystitis [5], osteomyelitis [5], pyelonephritis [5], invasive ductal breast carcinoma [5], cerebral infarction [5], acute coronary syndrome [4], angina pectoris [4], atrial flutter [4], coronary artery stenosis [4], vertigo [4], diarrhoea [4], pancreatitis [4], diverticulitis [4], gastroenteritis [4], femoral neck fracture [4], toxicity to various agents [4], upper limb fracture [4], osteonecrosis [4], basal cell carcinoma [4], pancreatic carcinoma [4], headache [4], suicide attempt [4], calculus ureteric [4], skin ulcer [4], iron deficiency anaemia [3], supraventricular tachycardia [3], diverticulum [3], gastric ulcer [3], gastrointestinal haemorrhage [3], inguinal hernia [3], asthenia [3], appendicitis [3], gangrene [3], respiratory tract infection [3], fibula fracture [3], joint dislocation [3], meniscal injury [3], rib fracture [3], tibia fracture [3], dehydration [3], hyperlipidaemia [3], intraductal proliferative breast lesion [3], lung adenocarcinoma [3], lung neoplasm malignant [3], dizziness [3], depression [3], benign prostatic hyperplasia [3], cystocele [3], pulmonary embolism [3], respiratory failure [3], deep vein thrombosis [3], disseminated intravascular coagulation [2], angina unstable [2], atrioventricular block second degree [2], bradycardia [2], cardiac failure chronic [2], cardiac valve disease [2], intracardiac thrombus [2], sinus node dysfunction [2], stress cardiomyopathy [2], cataract [2], abdominal pain [2], intestinal obstruction [2], oesophagitis [2], peptic ulcer perforation [2], small intestinal obstruction [2], malaise [2], non-cardiac chest pain [2], hypersensitivity [2], bronchitis [2], clostridium difficile colitis [2], erysipelas [2], gastroenteritis viral [2], pneumonia mycoplasmal [2], sepsis [2], staphylococcal infection [2], upper respiratory tract infection [2], upper respiratory tract infection bacterial [2], urosepsis [2], wound infection [2], chemical poisoning [2], facial bones fracture [2], fall [2], head injury [2], hip fracture [2], humerus fracture [2], procedural pain [2], snake bite [2], spinal compression fracture [2], subdural haematoma [2], tendon rupture [2], diabetes mellitus [2], hypoglycaemia [2], hyponatraemia [2], type 2 diabetes mellitus [2], arthropathy [2], back pain [2],

spondylolisthesis [2], adenocarcinoma of colon [2], invasive papillary breast carcinoma [2], lung cancer metastatic [2], malignant melanoma [2], metastases to lung [2], plasma cell myeloma [2], diabetic neuropathy [2], sciatica [2], seizure [2], completed suicide [2], somatoform disorder [2], acute renal failure [2], diabetic nephropathy [2], tubulointerstitial nephritis [2], dyspnoea [2], hypoxia [2], pleural effusion [2], diabetic vascular disorder [2], hypertensive crisis [2], hypotension [2], orthostatic hypotension [2], peripheral arterial occlusive disease [2], peripheral artery stenosis [2], peripheral venous disease [2], thrombophlebitis [2]), and 910 serious adverse events occurred in 591 subjects in the placebo group (adverse events occurring at least twice were: pneumonia [20], coronary artery disease [17], myocardial infarction [16], acute myocardial infarction [15], cardiac failure [15], chest pain [12], osteoarthritis [11], cholelithiasis [10], pulmonary embolism [10], hypertension [10], sepsis [9], urinary tract infection [9], myocardial ischaemia [8], inguinal hernia [8], colon cancer [8], prostate cancer [8], cerebrovascular accident [8], syncope [8], cardiac failure congestive [7], pancreatitis acute [7], radius fracture [7], intervertebral disc protrusion [7], asthma [7], atrial fibrillation [6], cholecystitis [6], appendicitis [6], cellulitis [6], diverticulitis [6], hip fracture [6], breast cancer [6], cerebral infarction [6], transient ischaemic attack [6], chronic obstructive pulmonary disease [6], cataract [5], lower respiratory tract infection [5], femoral neck fracture [5], road traffic accident [5], respiratory failure [5], anaemia [4], angina unstable [4], retinal detachment [4], gastritis [4], haemorrhoids [4], large intestine polyp [4], cholecystitis acute [4], bronchitis [4], gastroenteritis [4], ankle fracture [4], head injury [4], laceration [4], type 2 diabetes mellitus [4], bladder cancer [4], invasive ductal breast carcinoma [4], lung neoplasm malignant [4], dizziness [4], epilepsy [4], depression [4], urinary retention [4], deep vein thrombosis [4], peripheral arterial occlusive disease [4], angina pectoris [3], atrial flutter [3], vertigo [3], colitis ischemic [3], gastric ulcer [3], hiatus hernia [3], intestinal obstruction [3], small intestinal obstruction [3], bile duct stone [3], erysipelas [3], post procedural infection [3], pyelonephritis [3], femur fracture [3], lower limb fracture [3], multiple injuries [3], spinal osteoarthritis [3], bladder neoplasm [3], gastric cancer [3], renal cancer [3], ischaemic stroke [3], seizure [3], subarachnoid haemorrhage [3], psychotic disorder [3], acute renal failure [3], renal failure [3], pleural effusion [3], aortic aneurysm [3], aortic stenosis [3], haematoma [3], hypertensive crisis [3], orthostatic hypotension [3], acute coronary syndrome [2], aortic valve stenosis [2], atrioventricular block complete [2], bradycardia [2], cardiac arrest [2], cardiac failure acute [2], abdominal pain [2], constipation [2], enteritis [2], gastric ulcer haemorrhage [2], gastrointestinal haemorrhage [2], gastrooesophageal reflux disease [2], ileus [2], irritable bowel syndrome [2], death [2], pain [2], sudden death [2], clostridium difficile infection [2], lobar pneumonia [2], osteomyelitis [2], peritonitis [2], pyelonephritis acute [2], septic shock [2], upper respiratory tract infection [2], urosepsis [2], comminuted fracture [2], contusion [2], fall [2], hand fracture [2], humerus fracture [2], ligament sprain [2], multiple fractures [2], post procedural haemorrhage [2], wound [2], dehydration [2], diabetes mellitus [2], hyperglycaemia [2], hyponatraemia [2], type 1 diabetes mellitus [2], foot deformity [2], rotator cuff syndrome [2], spinal stenosis [2], adenocarcinoma gastric [2], intrahepatic bile duct cancer [2], intraductal proliferative breast lesion [2], lipoma [2], metastases to liver [2], metastases to lymph nodes [2], pancreatic carcinoma [2], plasma cell myeloma [2], renal neoplasm [2], cerebral haemorrhage [2], radiculopathy [2], completed suicide [2], chronic kidney disease [2], nephrolithiasis [2], renal cyst [2], benign prostatic hyperplasia [2], pleurisy [2], pneumonia aspiration

[2], arteriosclerosis [2], circulatory collapse [2], hypotension [2], intermittent claudication [2], varicose vein [2]). Among these, there were 3 events for which a causal relationship to Shingrix could not be ruled out occurred in 3 subjects (immune thrombocytopenic purpura [1], musculoskeletal chest pain [1], and nervous system disorder [1]), but recovery was observed in all the events.

After ≥1 year since the second study vaccination, 231 serious adverse events occurred in 177 subjects (among these, 202 events in 156 subjects[5] were adverse events leading to death) in the Shingrix group, and 231 serious adverse events occurred in 174 subjects (among these, 207 events in 163 subjects[6] were adverse events leading to death) in the placebo group, but a causal relationship to Shingrix was denied in all events.

During the study period, 347 adverse events leading to study drug discontinuation occurred in 257 subjects in the Shingrix group, and 359 adverse events leading to study drug discontinuation occurred in 253 subjects in the placebo group. Among these, a causal relationship to Shingrix could not be ruled out for 21 events in 21 subjects (injection site pain [8], myalgia [2], headache [2], injection site reaction [1], injection site swelling [1], hypersensitivity [1], malaise [1], fatigue [1], cerebral ischaemia [1], arthralgia [1], asthenia [1], urticarial [1]), but outcome was recovery in all cases except for myalgia [1] and cerebral ischaemia [1] (reported as "dizziness due to cerebral ischaemia") which did not resolve and injection site pain [1] whose outcome was unknown. All of the events, including those whose outcome was not recovered or unknown, were non-serious.

7.R.8.2 Study ZOSTER-022 (Global phase III study)

During the period from the day of the first study vaccination to 1 year after the second study vaccination, 142 adverse events leading to death occurred in 98 subjects in the Shingrix group (adverse events occurring at least twice were: lung neoplasm malignant [7], acute myocardial infarction [5], myocardial infarction [5], pneumonia [5], cardiac failure [4], cerebrovascular accident [4], atrial fibrillation [3], cardiac arrest [3], sudden death [3], prostate cancer [3], arrhythmia [2], cardiac failure congestive [2], coronary artery disease [2], death [2], multi-organ failure [2], sepsis [2], urinary tract infection [2], gastric cancer [2], ovarian cancer [2], subarachnoid haemorrhage [2], renal failure [2]), and 147 adverse events leading to death occurred in 108 subjects in the placebo group (adverse events occurring at least twice were: cardiac failure [9], myocardial infarction [7], multi-organ failure [6], acute myocardial infarction [4], cardiac arrest [4], metastases to liver [4], pancreatic carcinoma [4], cerebrovascular accident [4], cardio-respiratory arrest [3], death [3], colon cancer [3], anaemia [2], arteriosclerosis coronary artery [2], intestinal obstruction [2], pneumonia [2], septic shock [2], urinary tract infection [2], urosepsis [2], adenocarcinoma [2], endometrial adenocarcinoma [2], gastric cancer [2], hepatic cancer [2], lung cancer metastatic [2], metastases to bone [2], cerebral haemorrhage [2], cerebral infarction [2], respiratory failure [2], decubitus ulcer [2]). A causal relationship to the study drug was denied in all events, except for 1 event of neutropenic sepsis in 1 subject [see Section 7.R.3.1.2 for

[5] Including 3 subjects whose adverse events were reported within 1 year of the second study vaccination.
[6] Including 2 subjects whose adverse events were reported within 1 year of the second study vaccination.

details]. A total of 1,434 serious adverse events occurred in 888 subjects in the Shingrix group (adverse events occurring at least twice were: pneumonia [53], atrial fibrillation [43], urinary tract infection [32], coronary artery disease [27], osteoarthritis [26], cardiac failure [25], cerebrovascular accident [25], myocardial infarction [24], transient ischaemic attack [22], chest pain [20], prostate cancer [19], chronic obstructive pulmonary disease [18], hypertension [18], acute myocardial infarction [16], cardiac failure congestive [16], angina pectoris [13], cholelithiasis [13], sepsis [13], cerebral infarction [12], acute renal failure [12], pulmonary embolism [12], lung neoplasm malignant [11], femur fracture [10], syncope [10], benign prostatic hyperplasia [9], cellulitis [8], dehydration [8], hypertension crisis [8], angina unstable [7], cataract [7], cholecystitis [7], bronchitis [7], gastroenteritis [7], urosepsis [7], fall [7], subdural haematoma [7], hypokalaemia [7], anaemia [6], atrial flutter [6], ileus [6], cholecystitis acute [6], hip fracture [6], rib fracture [6], hypoglycaemia [6], spinal stenosis [6], renal failure [6], deep vein thrombosis [6], peripheral arterial occlusive disease [6], iron deficiency anaemia [5], myocardial ischaemia [5], sinus node dysfunction [5], inguinal hernia [5], intestinal obstruction [5], pancreatitis acute [5], appendicitis [5], diverticulitis [5], radius fracture [5], spinal compression fracture [5], type 2 diabetes mellitus [5], intervertebral disc protrusion [5], basal cell carcinoma [5], bladder cancer [5], breast cancer [5], colon cancer [5], nephrolithiasis [5], respiratory failure [5], hypotension [5], arrhythmia [4], bradycardia [4], cardiac arrest [4], cholangitis [4], cystitis [4], erysipelas [4], lobar pneumonia [4], pneumonia bacterial [4], pyelonephritis acute [4], concussion [4], contusion [4], head injury [4], tendon rupture [4], toxicity to various agents [4], polymyalgia rheumatica [4], gastric cancer [4], sciatica [4], depression [4], chronic kidney disease [4], pleural effusion [4], pneumonia aspiration [4], aortic aneurysm [4], coronary artery stenosis [3], supraventricular tachycardia [3], tachycardia [3], vertigo [3], colitis ischaemic [3], constipation [3], diverticulum [3], gastric ulcer [3], gastrooesophageal reflux disease [3], large intestine perforation [3], large intestine polyp [3], sudden death [3], postoperative abscess [3], pyelonephritis [3], staphylococcal infection [3], tuberculosis [3], wound infection [3], ankle fracture[3], humerus fracture [3], joint dislocation [3], meniscus injury [3], patella fracture [3], upper limb fracture [3], rotator cuff syndrome [3], spinal osteoarthritis [3], adenocarcinoma of colon [3], bladder neoplasm [3], renal cell carcinoma [3], ischaemic stroke [3], haematuria [3], urinary retention [3], haemoptysis [3], acute coronary syndrome [2], atrioventricular block complete [2], cardiac failure chronic [2], cardiac valve disease [2], congestive cardiomyopathy [2], extrasystoles [2], mitral valve incompetence [2], tricuspid valve incompetence [2], ventricular tachycardia [2], vertigo positional [2], optic ischaemic neuropathy [2], abdominal hernia [2], abdominal pain upper [2], gastric ulcer haemorrhage [2], gastritis [2], gastrointestinal haemorrhage [2], haemorrhoids [2], incarcerated inguinal hernia [2], nausea [2], oesophageal spasm [2], pancreatitis [2], rectal haemorrhage [2], umbilical hernia [2], upper gastrointestinal haemorrhage [2], death [2], multi-organ failure [2], pyrexia [2], bile duct stone [2], endocarditis [2], gastroenteritis viral [2], infective exacerbation of chronic obstructive airways disease [2], liver abscess [2], septic shock [2], sinusitis [2], urinary tract infection bacterial [2], viral infection [2], facial bones fracture [2], femoral neck fracture [2], foot fracture [2], hand fracture [2], joint injury [2], ligament sprain [2], lumbar vertebral fracture [2], pelvic fracture [2], pubis fracture [2], tibia fracture [2], diabetes mellitus [2], gout [2], hyponatraemia [2], back pain [2], bursitis [2], gouty arthritis [2], musculoskeletal pain [2], rheumatoid arthritis [2], spondyloarthropathy [2], adenocarcinoma gastric [2],

bladder cancer recurrent [2], hepatocellular carcinoma [2], invasive ductal breast cancer [2], lymphoma [2], metastases to liver [2], metastases to lung [2], metastases to peritoneum [2], oesophageal carcinoma [2], ovarian cancer [2], prostate cancer recurrent [2], rectal adenocarcinoma [2], thyroid cancer [2], transitional cell carcinoma [2], amyotrophic lateral sclerosis [2], cerebral haemorrhage [2], cerebrovascular disorder [2], dementia [2], Alzheimer-type dementia [2], epilepsy [2], generalised tonic-clonic seizure [2], hypoaesthesia [2], lacunar infarction [2], seizure [2], subarachnoid haemorrhage [2], delirium [2], renal cyst [2], urethral stenosis [2], acute pulmonary oedema [2], asthma [2], dyspnoea [2], respiratory distress [2], eczema [2], internal haemorrhage [2], orthostatic hypotension [2]), and 1,647 serious adverse events occurred in 934 subjects in the placebo group (adverse events occurring at least twice were: atrial fibrillation [54], pneumonia [47], cardiac failure [32], hypertension [27], myocardial infarction [26], cardiac failure congestive [23], coronary artery disease [23], urinary tract infection [21], chest pain [20], cerebrovascular accident [20], syncope [19], cholecystitis [17], osteoarthritis [17], acute myocardial infarction [16], anaemia [15], transient ischaemic attack [15], cholelithiasis [14], femur fracture [14], prostate cancer [14], cellulitis [13], cerebral infarction [13], pulmonary embolism [13], bladder cancer [12], acute renal failure [12], myocardial ischaemia [11], diverticulitis [11], chronic obstructive pulmonary disease [11], inguinal hernia [10], deep vein thrombosis [9], arrhythmia [8], bradycardia [8], pancreatitis [8], gastroenteritis [8], urosepsis [8], chronic kidney disease [8], renal failure [8], pleural effusion [8], angina unstable [7], ventricular tachycardia [7], cataract [7], abdominal pain [7], ileus [7], bronchitis [7], sepsis [7], rib fracture [7], dehydration [7], benign prostatic hyperplasia [7], aortic stenosis [7], acute coronary syndrome [6], angina pectoris [6], coronary artery stenosis [6], sinus node dysfunction [6], gastric ulcer [6], gastritis [6], multi-organ failure [6], erysipelas [6], humerus fracture [6], type 2 diabetes mellitus [6], spinal stenosis [6], hypertension crisis [6], cardio-respiratory arrest [5], intestinal obstruction [5], pancreatitis acute [5], cholangitis [5], appendicitis [5], lobar pneumonia [5], ankle fracture [5], contusion [5], femoral neck fracture [5], radius fracture [5], subdural haematoma [5], back pain [5], spinal osteoarthritis [5], colon cancer [5], dizziness [5], subarachnoid haemorrhage [5], respiratory failure [5], haematoma [5], hypotension [5], peripheral arterial occlusive disease [5], iron deficiency anaemia [4], atrial flutter [4], cardiac arrest [4], vertigo [4], retinal detachment [4], diarrhoea [4], gastric ulcer haemorrhage [4], gastrointestinal haemorrhage [4], large intestine polyp [4], small intestinal obstruction [4], chest discomfort [4], non-cardiac chest pain [4], cholecystitis acute [4], pyelonephritis [4], septic shock [4], facial bones fracture [4], fall [4], pelvic fracture [4], tendon rupture [4], upper limb fracture [4], hypoglycaemia [4], hyponatraemia [4], intervertebral disc protrusion [4], lung neoplasm malignant [4], malignant melanoma [4], metastases to lung [4], pancreatic carcinoma [4], ischaemic stroke [4], sciatica [4], tubulointerstitial nephritis [4], uterine prolapse [4], asthma [4], dyspnoea [4], diabetic foot [4], arteriosclerosis [4], orthostatic hypotension [4], aortic valve stenosis [3], atrioventricular block [3], atrioventricular block second degree [3], palpitations [3], vestibular disorder [3], hypothyroidism [3], diverticulum [3], rectal haemorrhage [3], death [3], bile duct stone [3], clostridium difficile colitis [3], peritonitis [3], upper respiratory tract infection [3], concussion [3], head injury [3], laceration [3], post procedural haemorrhage [3], pubis fracture [3], tibia fracture [3], diabetes mellitus [3], adenocarcinoma [3], adenocarcinoma of colon [3], basal cell carcinoma [3], bladder neoplasm [3], breast cancer [3], hepatic cancer [3], metastases to bone

[3], renal cell carcinoma [3], cerebral haemorrhage [3], depression [3], epistaxis [3], pulmonary oedema [3], arteriosclerosis coronary artery [2], atrioventricular block complete [2], cardiac failure chronic [2], heart valve incompetence [2], ischaemic cardiomyopathy [2], mitral valve incompetence [2], tachycardia [2], ventricular fibrillation [2], abdominal hernia [2], abdominal pain upper [2], chronic gastritis [2], constipation [2], diverticulum intestinal [2], gastrointestinal angiodysplasia [2], gastrooesophageal reflux disease [2], haematochezia [2], incarcerated umbilical hernia [2], retroperitoneal haemorrhage [2], umbilical hernia [2], upper gastrointestinal haemorrhage [2], device dislocation [2], peripheral swelling [2], cholangitis acute [2], hepatic cirrhosis [2], drug hypersensitivity [2], arthritis infective [2], bronchopneumonia [2], empyema [2], Escherichia sepsis [2], gastroenteritis viral [2], oesophageal candidiasis [2], orchitis [2], post procedural infection [2], postoperative wound infection [2], respiratory tract infection [2], vestibular neuronitis [2], wound infection [2], craniocerebral injury [2], foot fracture [2], hip fracture [2], joint injury [2], lumbar vertebral fracture [2], meniscus injury [2], muscle rupture [2], toxicity to various agents [2], wrist fracture [2], cachexia [2], decreased appetite [2], diabetes mellitus inadequate control [2], hyperglycaemia [2], hypokalaemia [2], malnutrition [2], osteoporosis [2], rotator cuff syndrome [2], systemic lupus erythematosus [2], trigger finger [2], B-cell lymphoma [2], bladder transitional cell carcinoma [2], Bowen's disease [2], breast cancer metastatic [2], colon neoplasm [2], endometrial adenocarcinoma [2], gastric cancer [2], invasive ductal breast carcinoma [2], invasive lobular breast carcinoma [2], lung adenocarcinoma [2], lung cancer metastatic [2], meningioma [2], metastases to central nervous system [2], non-Hodgkin's lymphoma [2], non-small cell lung cancer stage IV [2], rectal cancer [2], squamous cell carcinoma [2], squamous cell carcinoma of skin [2], balance disorder [2], cerebellar haemorrhage [2], dementia [2], epilepsy [2], haemorrhagic stroke [2], lacunar infarction [2], lumbar radiculopathy [2], parkinsonism [2], presyncope [2], delirium [2], major depression [2], bladder perforation [2], bladder prolapse [2], haematuria [2], nephrolithiasis [2], prerenal failure [2], urethral stenosis [2], urinary retention [2], prostatic obstruction [2], prostatitis [2], acute respiratory failure [2], hypoxia [2], pneumothorax [2], decubitus ulcer [2], skin necrosis [2], intermittent claudication [2], thrombosis [2]). Among these, a causal relationship to Shingrix could not be ruled out in 16 events of 12 subjects (lymphadenitis [1], acute myocardial infarction [1], colitis ulcerative [1], pancreatitis acute [1], administration site erythema [1], administration site pain [1], chills [1], pyrexia [1], allergic granulomatous angiitis [1], arthritis bacterial [1], erysipelas [1], herpes zoster oticus [1], neutropenic sepsis [1], acute myeloid leukaemia [1], Guillain-Barre syndrome [1], and eczema [1]). All the events resolved or were resolving, except for allergic granulomatous angiitis and acute myeloid leukaemia which remained unresolved, neutropenic sepsis which led to death, and herpes zoster oticus which resolved with sequelae. After the patient with herpes zoster oticus was hospitalized for treatment, dizziness and tinnitus persisted, and the outcome was concluded to be recovery with sequelae of inner ear disorder. However, the event was considered to be caused by VZV that was a latent infection from before the Shingrix vaccination because the onset was the day after the first vaccination with Shingrix. [See Section 7.R.3.1.2 for allergic granulomatous angiitis, neutropenic sepsis, and acute myeloid leukaemia.]

After ≥1 year since the second study vaccination, 474 serious adverse events occurred in 354 subjects (among these, 435 events in 332 subjects[7] were adverse events leading to death) in the Shingrix group, and 526 serious adverse events occurred in 380 subjects (among these, 452 events in 351 subjects were adverse events leading to death) in the placebo group, but causal relationship to Shingrix was denied in all events.

During the study period, 692 adverse events leading to study drug discontinuation occurred in 499 subjects in the Shingrix group, and 732 adverse events leading to study drug discontinuation occurred in 501 subjects in the placebo group. Among these, a causal relationship to Shingrix could not be ruled out for 26 events in 23 subjects (injection site pain [7], chills [2], injection site swelling [2], myalgia [2], papule [2], acute myocardial infarction [1], administration site erythema [1], administration site pain [1], malaise [1], pyrexia [1], cellulitis [1], oral herpes [1], vaccination complication [1], acute myeloid leukaemia [1], headache [1], and erythema [1]). The outcome was recovery in all events except for 1 event each of acute myeloid leukaemia, papule, and erythema which remained unresolved, and 1 event of vaccination complication that resolved with sequelae. The papule, erythema, and vaccination complication (reported as worsening of Parkinson's disease) were non-serious [see Section 7.R.3.1.2 for unresolved acute myeloid leukaemia]. The vaccination complication occurred in a patient with Parkinson's disease before Shingrix administration, and was observed on the day of the first vaccination with Shingrix. The complication may have been natural deterioration, and causal relationship to Shingrix is unclear.

7.R.8.3 Study EXPLO-CRD-004 and its follow-up Study ZOSTER-018/019 (Foreign phase I/II study)

During the period from the day of the first study vaccination to 1 year after the second study vaccination, no adverse events leading to death occurred. Four serious adverse events occurred in 3 subjects in the gE group in which subjects aged 50 to 70 years received only HZ/su (mitral valve incompetence [1], back pain [1], intervertebral disc disorder [1], and uterine leiomyoma [1]), and a causal relationship to the study drug was denied in all these events. No serious adverse events occurred after ≥1 year since the second study vaccination.

There were no adverse events that led to treatment discontinuation during the study period.

7.R.8.4 Study ZOSTER-003 and follow-up Studies ZOSTER-011/012/013/024 (Foreign multinational phase II study)

During the period from the day of the first study vaccination to 1 year after the second study vaccination, 2 adverse events leading to death occurred in 1 subject (metastases to bone [1], metastases to liver [1]) in the Shingrix group. A total of 28 serious adverse events occurred in 22 subjects (spinal stenosis [2], angina pectoris [1], atrioventricular block first degree [1], Meniere's disease [1], colitis ulcerative [1], duodenal ulcer [1], gastric ulcer [1], inguinal hernia [1], subileus [1], cholecystitis [1], allergy to

[7] Including 4 subjects whose adverse events were reported within 1 year of the second study vaccination.

arthropod bite [1], ankle fracture [1], contusion [1], meniscus injury [1], rib fracture [1], breast cancer [1], metastases to bone [1], metastases to liver [1], carotid artery stenosis [1], cerebral ischaemia [1], drop attacks [1], syncope [1], chronic obstructive pulmonary disease [1], circulatory collapse [1], hypertension [1], orthostatic hypotension [1], and peripheral arterial occlusive disease [1]), but causal relationship to Shingrix was denied in all events, including the events which led to death.

After ≥1 year since the second study vaccination, 56 serious adverse events occurred in 37 subjects (among these, 6 events in 5 subjects were adverse events leading to death), but a causal relationship to Shingrix was denied in all these events.

Excluding a subject who was not enrolled into the subsequent study because of death occurred between completion of the study and the enrollment to the follow-up study, 3 adverse events leading to study drug discontinuation occurred in 3 subjects in the Shingrix group (death [1], circulatory collapse [1], and asthenia [1]), but causal relationship to Shingrix was denied in all these events.

7.R.8.5 Study ZOSTER-010 (Foreign multinational phase II study)

During the period from the day of the first study vaccination to 1 year after the second study vaccination, 1 adverse event leading to death occurred in 1 subject (myocardial infarction) in the Shingrix group, but a causal relationship to the study drug was denied. In the same period, 13 serious adverse events occurred in 10 subjects in the Shingrix group (atrial fibrillation [1], bradycardia [1], myocardial infarction [1], myocardial ischaemia [1], sinus node dysfunction [1], ileus [1], pancreatic mass [1], chest pain [1], pneumonia [1], bladder cancer [1], cerebrovascular disorder [1], pulmonary embolism [1], and respiratory failure [1]), but causal relationship to the study drug was denied in all these events. No serious adverse events occurred after ≥1 year since the second study vaccination. Two adverse events leading to study drug discontinuation (myocardial infarction, malaise) occurred in 2 subjects in the Shingrix group, but a causal relationship to the study drug was denied except for 1 event (malaise) in 1 subject. The event (malaise), for which causal relationship could not be ruled out, was non-serious and recovered.

7.R.8.6 Study ZOSTER-026 (Foreign multinational phase III study)

During the period from the day of the first study vaccination to 1 year after the second study vaccination, 1 adverse event leading to death (cerebral haemorrhage) occurred in 1 subject in the Shingrix 2-month interval vaccination group, and 1 adverse event leading to death (cardiovascular disorder) occurred in 1 subject in the Shingrix 12-month interval vaccination group. Causal relationship to the study drug was denied in both events. Six serious adverse events (diverticulum [1], large intestinal stenosis [1], arthralgia [1], cerebral haemorrhage [1], tubulointerstitial nephritis [1], and hypertension [1]) occurred in 5 subjects in the Shingrix 2-month interval vaccination group; 17 serious adverse events (cerebral infarction [2], acute myocardial infarction [1], atrial fibrillation [1], atrial flutter [1], bradycardia [1], coronary artery disease [1], ventricular extrasystoles [1], cholecystitis acute [1], femur fracture [1], osteoarthritis [1], colon cancer [1], prostate cancer [1], carotid artery disease [1], nephrolithiasis [1],

respiratory failure [1], and hidradenitis [1]) occurred in 9 subjects in the Shingrix 6-month interval vaccination group; and 15 serious adverse events (anaemia [1], cardiovascular disorder [1], diverticulum [1], inguinal hernia [1], Mallory-Weiss syndrome [1], varices oesophageal [1], Helicobacter gastritis [1], injury [1], dyslipidaemia [1], osteoarthritis [1], colorectal adenocarcinoma [1], lung neoplasm malignant [1], prostate cancer [1], psychotic disorder [1], and venous thrombosis limb [1]) occurred in 12 subjects in the Shingrix 12-month interval vaccination group. A causal relationship to the study drug was denied in all events. No serious adverse events occurred after ≥1 year since the second study vaccination. One adverse event leading to study drug discontinuation (cerebral haemorrhage) occurred in 1 subject in the Shingrix 2-month interval vaccination group; 2 adverse events leading to study drug discontinuation (colon cancer [1], prostate cancer [1]) occurred in 2 subjects in the Shingrix 6-month interval vaccination group; and 1 adverse event leading to study drug discontinuation (cardiovascular disorder) occurred in 1 subject in the in Shingrix 12-month interval vaccination group, but a causal relationship to Shingrix was denied in all events.

7.R.8.7 Study ZOSTER-032 (Japanese phase III study)

During the period from the day of the first study vaccination to 1 year after the second study vaccination, no adverse event leading to death was reported. Two serious adverse events (finger deformity [1], chronic obstructive pulmonary disease [1]) occurred in 2 subjects in the Shingrix subcutaneous vaccination group, and 1 serious adverse event (spinal compression fracture) occurred in 1 subject in the Shingrix intramuscular vaccination group, but causal relationship with the study drug was denied in all events. There were no adverse events that led to study drug discontinuation.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently in progress, and the results and PMDA's conclusions are reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently in progress, and the results and PMDA's conclusions are reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Shingrix has vaccine efficacy against herpes zoster as shown in Section 7.R.5, and that Shingrix has acceptable safety in view of its benefits.

PMDA has concluded that Shingrix may be approved if Shingrix is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 13, 2018

Product Submitted for Approval

Brand Name	Shingrix for intramuscular injection
Non-proprietary Name	Dried recombinant Herpes Zoster Vaccine (Derived from Chinese Hamster Ovary Cells)
Applicant	Japan Vaccine Co., Ltd.
Date of Application	April 18, 2017

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in "7.R.2 Efficacy," "7.R.5 Indications," and "7.R.6 Dosage and administration" of the Review Repot (1).

PMDA conducted an additional review of the following issues and took necessary actions.

1.1 Safety

The PMDA's conclusions that are presented in Review Report (1) were supported by expert advisors. The following comments were raised at the Expert Discussion:

- Among the adverse events reported in Study ZOSTER-006 and Study ZOSTER-022, the incidence of Grade 3 adverse events, defined as "adverse event which prevents normal, daily activities," was ≥10 times higher in the Shingrix group than in the placebo group, and such events were reported to persist for a certain period. Given that Shingrix will also be administered to healthy recipients, and that $AS01_B$ contained in Shingrix is a novel adjuvant, the tolerability needs to be carefully examined in light of the benefits obtained by Shingrix vaccination and the risks of Shingrix, in addition to the safety evaluation of Shingrix in Review Report (1).

- The incidence rate of pIMD in clinical studies is similar between the Shingrix group and placebo group, and there is no evidence at present that Shingrix vaccination increases the risk of pIMD.

However, given that $AS01_B$ is considered to largely contribute to the vaccine efficacy of Shingrix against HZ, as shown in Study ZOSTER-006 and Study ZOSTER-022, post-marketing pharmacovigilance activities on pIMD is important.

On the basis of the above comments from the expert advisors, PMDA asked the applicant for further information on the occurrence of Grade 3 adverse events in clinical studies, the latest information on the safety of Shingrix including pIMD, and discussion on the tolerability of Shingrix while taking its benefits into account.

The applicant's explanation was as follows:
For Grade 3 adverse events, defined as "adverse events which prevents normal, everyday activities," in the diary card TVC of Study ZOSTER-006 and Study ZOSTER-022, detailed information such as reasons for classifying adverse events as Grade 3 had not been collected. Therefore, information on visits to medical institution by individual subject was examined. As a result, the proportion of subjects with Grade 3 adverse events who visited medical institution in the Shingrix group was 2.0% (9 of 459 subjects) in subjects with specified local reactions and 3.9% (18 of 465 subjects) in subjects with specified general adverse reactions, and that in the placebo group was 11.8% (2 of 17 subjects) in subjects with specified local reactions and 9.5% (7 of 74 subjects) in subjects with specified general adverse reactions. Visiting medical institution was not considered necessary in most cases.

The applicant also examined the time required until resolution of Grade 3 specified adverse events (specified local reactions and specified general adverse events) occurred within 6 days after study vaccination. The time until resolution of Grade 3 specified adverse events is shown in Table 37 and Table 38, and most events are confirmed to be resolved within 7 days. The duration of specified adverse events regardless of severity averaged 3.0 to 3.9 days (median: 3.0 days for any event) for specific local reactions and 1.7 to 3.0 days (median: 1.0-2.0 days) for specified general adverse events in the Shingrix group. Specified local reactions and specified general adverse reactions observed in clinical studies, including Grade 3 events, were considered to be caused by immune response to Shingrix, but all events were transient.

The Grade 3 adverse events reported with Shingrix vaccination were compared with the results of clinical studies using other vaccines in Japanese adults. Although there is a limitation to the comparability of the data, a large difference was not noted in the time from the onset to recovery for the Grade 3 event (injection site pain) that tended to occur at high incidence with Shingrix (Prevenar 13 Suspension Liquid for Injection, Review Report 2014, *J. Clin. Therap. Med.* 2014;30:963-74).

Table 37. Time required until resolution of specified local reactions occurred within 6 days after study vaccination in Study ZOSTER-006 and Study ZOSTER-022 (diary card TVC)

After first vaccination								
Event	Group	No. of subjects analyzed	No. of subjects with Grade 3 event	Time from onset of Grade 3 event to resolution				
				Median value [Minimum, Maximum] (days)	No. of subjects by time from onset to resolution			
					<7 days	8-10 days	11-20 days	21-50 days
Injection site pain	Shingrix	4,861	171	4.0 [1.0, 41.0]	156	6	8	1
	Placebo	4,865	7	4.0 [1.0, 8.0]	6	1	0	0
Injection site redness	Shingrix	4,861	91	6.0 [2.0, 41.0]	66	14	8	3
	Placebo	4,865	0	—	—	—	—	—
Injection site swelling	Shingrix	4,861	30	5.0 [2.0, 14.0]	25	4	1	0
	Placebo	4,865	0	—	—	—	—	—
After second vaccination								
Event	Group	No. of subjects analyzed	No. of subjects with Grade 3 event	Time from onset of Grade 3 event to resolution				
				Median value [Minimum, Maximum] (days)	No. of subjects by time from onset to resolution			
					<7 days	8-10 days	11-20 days	21-50 days
Injection site pain	Shingrix	4,699	196[a]	4.0 [1.0, 17.0]	185	5	6	0
	Placebo	4,715	9[a]	7.0 [2.0, 16.0]	7	0	2	0
Injection site redness	Shingrix	4,699	71	4.0 [2.0, 23.0]	62	5	3	1
	Placebo	4,715	0	—	—	—	—	—
Injection site swelling	Shingrix	4,699	25	4.0 [1.0, 10.0]	22	3	0	0
	Placebo	4,715	0	—	—	—	—	—

a: Excluding subjects for whom the time until resolution of the Grade 3 specified local reaction is unknown.

Table 38. Time required until resolution of specified general adverse reactions occurred within 6 days after study vaccination in Study ZOSTER-006 and Study ZOSTER-022 (diary card TVC)

After first vaccination								
Event	Group	No. of subjects analyzed	No. of subjects with Grade 3 event	Time from onset of Grade 3 event to resolution				
				Median value [Minimum, Maximum] (days)	No. of subjects by time from onset to resolution			
					<7 days	8-10 days	11-20 days	21-100 days
Fatigue	Shingrix	4,847	91	4.0 [1.0, 70.0]	81	4	4	2
	Placebo	4,865	23	6.0 [1.0, 30.0]	19	1	2	1
Gastrointestinal disorder	Shingrix	4,847	20	3.0 [1.0, 11.0]	19	0	1	0
	Placebo	4,865	6	4.5 [1.0, 7.0]	6	0	0	0
Headache	Shingrix	4,847	55	3.0 [1.0, 60.0]	50	1	3	1
	Placebo	4,865	16	3.5 [1.0, 55.0]	13	1	1	1
Myalgia	Shingrix	4,847	92	4.0 [1.0, 59.0]	85	3	3	1
	Placebo	4,865	15	7.0 [3.0, 54.0]	11	2	0	2
Chills	Shingrix	4,847	61	2.0 [1.0, 11.0]	59	1	1	0
	Placebo	4,865	3	2.0 [1.0, 3.0]	3	0	0	0
Pyrexia	Shingrix	4,847	6	3.0 [1.0, 7.0]	6	0	0	0
	Placebo	4,865	0	—	—	—	—	—
After second vaccination								
Event	Group	No. of subjects analyzed	No. of subjects with Grade 3 event	Time from onset of Grade 3 event to resolution				
				Median value [Minimum, Maximum] (days)	No. of subjects by time from onset to resolution			
					<7 days	8-10 days	11-20 days	21-100 days
Fatigue	Shingrix	4,697	147	3.0 [1.0, 40.0]	139	4	3	1
	Placebo	4,711	14[a]	5.0 [1.0, 15.0]	13	0	1	0
Gastrointestinal disorder	Shingrix	4,697	29	3.0 [1.0, 10.0]	28	1	0	0
	Placebo	4,711	6	2.0 [1.0, 4.0]	6	0	0	0
Headache	Shingrix	4,697	99	3.0 [1.0, 41.0]	95	1	1	2
	Placebo	4,711	6	4.0 [2.0, 7.0]	6	0	0	0
Myalgia	Shingrix	4,697	149[a]	3.0 [1.0, 13.0]	143	4	2	0
	Placebo	4,711	8	5.5 [2.0, 7.0]	8	0	0	0
Chills	Shingrix	4,697	134	2.0 [1.0, 41.0]	132	1	0	1
	Placebo	4,711	7	2.0 [1.0, 6.0]	7	0	0	0
Pyrexia	Shingrix	4,697	8	2.5 [1.0, 6.0]	8	0	0	0
	Placebo	4,711	2	3.0 [1.0, 5.0]	2	0	0	0

a: Excluding subjects for whom the time until resolution of the Grade 3 specified general adverse reaction is unknown.

In the latest Development Safety Update Report (DSUR) on Shingrix (data lock point on November 28, 2017), the incidence of pIMD in the cumulative data of clinical studies in development phase was 1.2% (364 of 30,691 subjects) in Shingrix groups and 1.6% (296 of 17,239 subjects) in placebo groups. The incidence of pIMD concluded to be related to the study drug was 23 subjects (0.07%) in the Shingrix groups and 19 subjects (0.1%) in the placebo groups. In the information obtained up to date, the incidence of pIMD is comparable between Shingrix groups and placebo groups, similar to the results in Study ZOSTER-006 and Study ZOSTER-022 [see Section "7.R.3.1.3 Noteworthy adverse events and adverse reactions"]. Besides Shingrix vaccination, pIMD are suspected to be associated with patient background factors. Therefore, there is no clear information that suggests an association of Shingrix vaccination with the development of pIMD.

The above discussions and safety results of clinical studies [see Sections "7.1 Phase III Studies," "7.R.3 Safety" and "7.R.8 Adverse events observed in clinical studies"] have raised no particular safety concern on Shingrix.

, i.e. the target disease of Shingrix vaccine, and

On the other hand, the incidence of HZ and occurrence of pain or PHN in patients with HZ (such as duration of pain) were examined based on the epidemiological information in Japan and the results of Study ZOSTER-006 and Study ZOSTER-022. The incidence rate of HZ in Japan has been reported as 4.2 cases per 1,000 person-years (5.2 cases per 1,000 person-years for age 50-59 years; 7.0 cases per 1,000 person-years for age 60-69 years; and 7.8 cases per 1,000 person-years for age 70-79 years) in a long-term prospective epidemiology study in Miyazaki prefecture conducted from 1995 to 2006 (*J Med Virol* 2009;81:2053-8). A prospective cohort study (SHEZ study) conducted from 2008 to 2009 reported the incidence rate as 10.9 cases per 1,000 person-years in adults aged ≥50 years, and as 12.6 cases per 1,000 person-years in adults aged 70 to 79 years (*J Epidemiol* 2015;25:617-25). During the period of HZ rash, acute local pain occurs in up to 90% of individuals with normal immune function (*Pain* 2007;128:189-90), and the median duration is 2 weeks (*Vaccine* 2006;24:1308-14). HZ-associated pain may be very severe, causing dysfunction or interfering with daily activities, and PHN or HZ-associated complications may also develop. According to the above-mentioned SHEZ study, 19.7% of HZ patients aged ≥50 years develop PHN in Japan when PHN is defined as pain that persists for ≥3 months after onset of HZ (*J Epidemiol* 2015;25:617-25). The incidence of HZ, the duration of HZ-associated pain, and the occurrence of PHN in subjects who developed HZ in Study ZOSTER-006 and Study ZOSTER-022 are shown in Table 39. According to the epidemiological data in Japan and the results of the placebo group in clinical studies, severe pain may occur and persist for > 2 weeks when HZ develops in patients who are not vaccinated with Shingrix. In addition, a certain proportion of such patients may develop PHN or other HZ-associated complications that cause pain, persisting for > 3 months. In the clinical studies, HZ developed in subjects who received Shingrix and PHN subsequently developed. However, the incidence of HZ was lower than the placebo group, and the duration of pain associated with HZ showed no tendency to be longer than the placebo group. Based on a detailed discussion on the disadvantages of HZ and the safety of Shingrix that includes Grade 3 adverse events, the benefit of Shingrix vaccination, that is, to reduce the expected risk of developing HZ, is considered to outweigh the possible risks, and Shingrix is considered tolerable. The safety of Shingrix will continue to be monitored through pharmacovigilance activities, by focusing on the incidence of pIMD, which is a potential risk, and unknown adverse reactions not reported in clinical trials, and the risk/benefit balance will be evaluated.

Table 39. Incidence of HZ, duration of HZ-associated pain, and occurrence of PHN in Study ZOSTER-006 and Study ZOSTER-022 (mTVC: EOS)

Study (age of subjects)	Group	No. of subjects in mTVC	No. of subjects with HZ	HZ incidence rate (/1,000 person-years)	Duration of HZ-associated pain (days)		No. of subjects with PHN (% of PHN in HZ)
					Mean	Median value [Minimum, Maximum]	
ZOSTER-006 (≥50 years)	Shingrix	7,340	9	0.3	20.6	11.0 [3.0, 78.0]	0
	Placebo	7,413	254	8.9	30.2	15.0 [1.0, 464.0]	18 (7.09%)
ZOSTER-022 (≥70 years)	Shingrix	6,541	23	0.9	34.6	13.5 [1.0, 162.0]	4 (17.39%)
	Placebo	6,622	223	9.2	48.5	19.0 [1.0, 834.0]	28 (12.56%)

PMDA accepted the applicant's explanation and concluded that the safety of Shingrix to be tolerable. Shingrix has an aspect as a vaccine rather than herd immunity against infection of VZV, and the main purpose of Shingrix is to acquire personal immunity to prevent onset of HZ that is caused by the revitalization of VZV accompanied by lowered immunity due to aging, disease, etc. The need and appropriateness of Shingrix vaccination to each individual patient should be carefully determined. In particular, it is important to fully explain the possible risks of Shingrix vaccination, the expected benefits, and the availability of other options to vaccine recipients.

1.2 Risk management plan (draft)

PMDA concluded that a post-marketing survey is needed to examine the safety of Shingrix in routine clinical settings as described in Section "7.R.7 Post-marketing investigations" in the Review Report (1), and the conclusion was supported by the expert advisors. However, the following comments were raised at the Expert Discussion on how to respond after its market launch.

- $AS01_B$ is a novel adjuvant, and although large-scale clinical studies are being conducted, safety information on the Japanese is limited. Therefore, a post-marketing drug use-results survey in routine clinical settings needs to be conducted in as many Japanese patients as possible to examine the safety. In addition, post-marketing information including the risks of pIMD and anaphylaxis also needs to be collected continuously.
- Information should be collected on the use of Shingrix in patients with malignant tumors who were not enrolled in the clinical studies (in particular, patients who are using immune checkpoint inhibitors such as human PD-1 antibody).
- The target recipients of Shingrix vaccination are "adults aged ≥50 years" and are in an age group that often suffer from or are diagnosed with various disorders including so-called "lifestyle-related diseases." Presumably, it would be difficult to determine whether events occurring after Shingrix vaccination are adverse reactions or a sickness not related to Shingrix. When monitoring the post-marketing safety of Shingrix, it is important to gather detailed information on patients who developed adverse reactions and carefully evaluate them.

Taking account of the above comments from the expert advisors, PMDA instructed the applicant: a) to provide adequate information on the risks and benefits of Shingrix so that vaccine recipients and healthcare professionals can properly decide the necessity and the appropriateness of the Shingrix vaccination; b) to conduct post-marketing pharmacovigilance activities; and c) to reconsider the target number of patients in the use-results survey. The applicant responded that the target number of patients in the use-results survey is set to 7,500 patients (15,000 vaccinations) to collect more safety information in Japanese, so that safety information will also be obtained from patient population that was not included in the clinical studies. PMDA accepted the applicant's response, considering that it is possible to examine safety information in the number of Japanese patients comparable to that of the global studies.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for Shingrix should include the safety and efficacy specifications presented in Table 40, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 41 and Table 42.

Table 40. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	・ Shock, anaphylaxis ・ Potential immune-mediated disease (pIMD)	・ None
Efficacy specification		
・ Long-term efficacy and immunogenicity		

Table 41. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・ Early post-marketing phase vigilance ・ Drug use-results survey ・ Post-marketing clinical study (subjects from Study ZOSTER-006 and Study ZOSTER-022)[a]	・ Information provision by early post-marketing phase vigilance

a: Replaced with post-marketing clinical study after approval of Shingrix

Table 42. Outline of use-results survey (draft)

Objective	To identify safety problems or questions on Shingrix in routine clinical use
Survey method	Central registration system
Subjects	Patients receiving Shingrix vaccination for the first time
Observation period	30 days after each vaccination
Planned sample size	7,500 patients (15,000 vaccinations)
Main survey items	Patient characteristics (underlying disease, medical history, history of allergy, immune abnormalities, etc.), information on Shingrix vaccination (route of administration, etc.), information during observation period (drugs used, etc.), adverse events reported after Shingrix vaccination, etc.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion on the results of GCP on-site inspection

The new drug application data (CTD 5.3.5.1.5, CTD 5.3.5.1.6, CTD 5.3.5.1.8) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted, as it

was determined that the clinical studies were conducted according to GCP as a whole. Although it did not have a large effect on the overall evaluation, the heads of the medical institutions concerned were notified of the following as a matter to be improved because it was observed at some medical institutions.

Matter for improvement

Medical institutions

- Faults in the operation of the Institutional Review Board (non-compliance with the conditions of deliberation and expedited review)

3. Overall Evaluation

As a result of its review, PMDA concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs. The product is classified as a biological product.

Indication

Prevention of herpes zoster

Dosage and Administration

The antigen preparation is reconstituted with the full volume of accompanying adjuvant for reconstitution, and the usual dosage is 0.5 mL administered intramuscularly twice at intervals of 2 months to adults aged ≥50 years.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ACIP	The Advisory Committee on Immunization Practices
AS	Adjuvant system
ATP	According-To-Protocol
CAL	Cells at the limit of *in vitro* cell age used for production
CHO	Chinese hamster ovary
CI	Confidence interval
[redacted]	[redacted]
CMI	Cell mediated immunity
CRP	C-reactive protein
DOPC	Dioleoyl phosphatidylcholine
Drug product	Drug product that contains varicella zoster virus glycoprotein E
DSUR	Development Safety Update Report
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
FDA	Food and Drug Administration, US
GCP	Good Clinical Practice
gE	Glycoprotein E
GMC	Geometric mean concentration
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HZ	Herpes zoster
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN-γ	Interferon gamma
IL-2	Interleukin 2
MCB	Master cell bank
MMV	Minute mouse virus
MPL	3-*O*-desacyl-4'-monophosphoryl Lipid A
MS	Mass spectrometry
mTVC	Modified total vaccinated cohort
NZW	New Zealand White
PCR	Polymerase Chain Reaction
PD-1	Programmed cell death 1
PETG	Polyethylene terephthalate glycol
PHN	postherpetic neuralgia
pIMD	Potential immune-mediated disease
PMDA	Pharmaceuticals and Medical Devices Agency
PPV	Porcine parvovirus
QS-21	QS-21 Stimulon® (Quillaja saponaria Molina fraction 21)
[redacted]	[redacted]
SDS-PAGE	Sodium dodecyl sulfate -polyacrylamide gel electrophoresis
Shingrix	Shingrix for Intramuscular Injection
SMQ	Standardized MedDRA Query
SV40	Simian virus 40
TNFα	Tumor Necrosis Factor alpha
TVC	total vaccinated cohort
VZV	Varicella zoster virus
WCB	Working cell bank
X-MuLV	Xenotropic murine leukemia virus