EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/447929/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Shingrix

International non-proprietary name: herpes zoster vaccine (recombinant, adjuvanted)

Procedure No. EMEA/H/C/004336/II/0022

Marketing authorisation holder (MAH) GlaxoSmithkline Biologicals SA

Note

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

Table of contents

List of abbreviations

Ab	Antibody
AE	Adverse Event
AID	Auto-immune disease
AML	Acute Myeloid Leukemia
ART	Antiretroviral therapy
$AS01_B$	Adjuvant System containing 50 µg MPL, 50 µg QS-21, and liposomes
ATP	According-To-Protocol
AUC	Area under the curve
CBER	Center for Biologics Evaluation and Research
CD4	Cluster of differentiation marker 4
CD40L	Cluster of differentiation marker 40 ligand
CDC	Centers for Disease Control and Prevention
CDP	Clinical Development Program
CDQA	Clinical Development Quality Assurance
CHMP	Committee for Medicinal Products for Human Use
CFC	Cells Flow Cytometry
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
cPRA	Calculated Panel-Reactive Antibody
CMI	Cell-mediated Immunity
COPD	chronic obstructive pulmonary disease
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
EEA	European Economic Area
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EQ-5D	Euro-QoL 5 Dimension
EU	European Union
GCP	Good Clinical Practice
gE	Glycoprotein E
GM	Geometric Mean
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline Biologicals SA
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HSCT	Hematopoietic stem cell transplant
HZ	Herpes Zoster
HZAC	HZ Adjudication Committee

Ab	Antibody
HZ/su	The Herpes Zoster subunit vaccine *(50 µg gE/* $AS01_B$), also called $gE/AS01_B$. Recombinant subunit (su) vaccine for the prevention of HZ consisting of Varicella Zoster Virus (VZV) glycoprotein E (gE: 50 µg) as antigen and an Adjuvant System ($AS01_B$)
IBD	Inflammatory bowel disease
IC	Immunocompromised
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	Interferon gamma
IM	Intramuscular
IL-2	Interleukin 2
IR	Incidence rate
iSRC	Internal Safety Review Committee
LL	Lower Limit
MAA	Marketing Authorization Application
mIU	milli International Unit
MPL	3-*O*-desacyl-4'-monophosporyl Lipid A
mTVC	modified Total Vaccinated Cohort, i.e., TVC for efficacy with subjects excluded who did not receive 2 doses of HZ/su or who developed a confirmed HZ case prior to 1 month post Dose 2
NHBCL	Non-Hodgkin B Cell Lymphoma
NHTCL	Non-Hodgkin T Cell Lymphoma
NOAD	New onset of autoimmune disease
PBMC	Peripheral blood mononuclear cell
PBRER	Periodic Benefit Risk Evaluation Report
PCR	Polymerase Chain Reaction
PHN	Postherpetic neuralgia
pIMD	Potential Immune-Mediated Disease
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q	Quartile
QoL	Quality of Life
QS-21	*Quillaja saponaria* Molina fraction 21 ((Licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA)
RA	Rheumatoid arthritis
RMP	Risk Management Plan
RR	Relative Risk
SA	Scientific Advice
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard Deviation

Ab	Antibody
SF-36	Short form-36 (MOS SF-36)
SmPC	Summary of Product Characteristics
TNF-α	Tumor Necrosis Factor alpha
TVC	Total Vaccinated Cohort
UK	United Kingdom
UL	Upper Limit
US	United States
VE	Vaccine efficacy
VRR	Vaccine Response Rate
VZV	Varicella Zoster Virus
YOA	Years of Age
ZBPI	Zoster Brief Pain Inventory

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithkline Biologicals SA submitted to the European Medicines Agency on 16 December 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new population for Shingrix: adults 18 years of age or older at increased risk of Herpes Zoster supported by the clinical studies ZOSTER-002 (MEA 001), ZOSTER-039 (MEA 002), ZOSTER-041 (MEA 003), ZOSTER-028 (MEA 004), ZOSTER-001 and ZOSTER-015.
As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated in order to delete a warning and to add new safety and efficacy information. The Package Leaflet is updated in accordance. The RMP version 2.1 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0222/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0222/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Derogation of market exclusivity

Not applicable.

Scientific advice

The MAH received Scientific Advice EMEA/H/SA/997/4/2018/II. One question of this SA addressed the

evaluation of Shingrix in individuals with underlying autoimmune disease; a second part concerned the question, whether the clinical data package generated in subjects ≥18 years of age is sufficient to support the submission of an application for the extension of the Shingrix indication to adults ≥18 years of age. The CHMP stated that the amount of data in healthy young individuals is too limited and some further data on safety, and particularly local and systemic reactogenicity, from healthy young adults should be provided in any application to allow use from 18 years without any qualification. Within this submission, the applicant now decided to only seek licensure for the use in adults 18 years of age or older at increased risk of HZ.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christophe Focke Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	16 December 2019
Start of procedure:	1 February 2020
CHMP Rapporteur Assessment Report	30 March 2020
CHMP Co-Rapporteur Assessment Report	30 March 2020
PRAC Rapporteur Assessment Report	3 April 2020
PRAC members comments	6 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 April 2020
Request for supplementary information (RSI)	30 April 2020
PRAC Rapporteur Assessment Report	30 June 2020
PRAC members comments	1 July 2020
Updated PRAC Rapporteur Assessment Report	2 July 2020
CHMP Rapporteur Assessment Report	9 July 2020
PRAC Outcome	9 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur Assessment Report	16 July 2020
Opinion	23 July 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Herpes Zoster (HZ), commonly known as shingles, is caused by the reactivation of latent varicella zoster virus (VZV). Primary VZV infection results in varicella (chickenpox), after which VZV becomes latent in neurons of the dorsal root and cranial nerve ganglia. Following a variable period of latency, VZV can reactivate to produce infectious virus. This virus can travel to the skin and re-infect it, causing HZ. The lifetime risk of HZ is estimated to be 10-30%. HZ is thought to be associated with a decline in cell mediated immunity (CMI) due to aging or to an immunosuppressive illness or treatment.

HZ typically presents as an acute, painful, vesicular eruption distributed along a single dermatome. The most common complication of HZ is postherpetic neuralgia (PHN), defined as pain that persists beyond 90 days after the onset of the zoster rash. This pain is often chronic and debilitating and difficult to treat effectively. Other less frequent HZ complications include HZ ophthalmicus (HZO), neurological complications such as VZV encephalitis and meningitis, and disseminated HZ. Ramsay Hunt syndrome rarely occurs but is a common cause of facial nerve paralysis. An increased risk of stroke up to 3 months after a HZ episode has also been described.

Epidemiological evidence confirms that the risk of HZ increases dramatically in adults ≥18 YOA who are immunodeficient or immunosuppressed due to disease or therapy, placing them at a risk comparable to and in many instances far exceeding the risk seen in the general adult population ≥50 YOA. Immunocompromised (IC) individuals are not only at increased risk for the development of HZ but also develop more severe HZ than immunocompetent person, including persistent post-HZ pain and PHN complications. In IC patients, the HZ rash tends to be more severe and its duration prolonged. Cutaneous dissemination, visceral involvement (including varicella pneumonitis and hepatitis), VZV retinitis and acute retinal necrosis, meningoencephalitis, and chronic progressive encephalitis have been reported in IC patients. Chronic HZ may also occur in IC patients. Even if most HZ cases occur in older adults, IC patients therefore contribute substantially to the public health burden.

Beside immunosuppression, many chronic conditions such as diabetes, asthma, COPD, cardiovascular diseases, renal diseases are associated with an increased risk of HZ. PHN also appears to be more severe and persistent in diabetic patients.

Epidemiology and risk factors

Seroprevalence

In Europe, most Varicella Zoster Virus (VZV) infections occur in childhood with a rapid acquisition of antibodies to VZV and by 15–19 years most individuals are seropositive (ECDC 2014). Overall, more than 89% of young adults (20-29 years old) are seropositive to VZV in EU. Therefore, most adults 50 years and older is at risk for the development of HZ.

Overall disease incidence

The overall incidence rate (IR) of HZ in Europe, North America and Asia-Pacific is about 3 to 5 cases per 1000 person-years (PY) (Kawai, 2014).

The most common complication of HZ is PHN. About 5 to 30% of people who get HZ will experience PHN (depending of the type of study design and age distribution of study populations). Other less frequent HZ complications include HZ ophthalmicus (HZO) which occurs in 10% to 15% of HZ patients (Johnson 2014, Kawai 2014). Other complications are less frequent.

Disease incidence by risk factor

Age

The incidence of HZ increases markedly as of the age of 50, with two-thirds of HZ cases occurring in adults ≥ 50 years of age (Yawn 2007, Kawai 2014). The incidence increases with age from about 1-4 per 1,000 PY in adults aged 40–50 years, 7-8 per 1,000 PY in 60-70 years old, up to 10 per 1,000 PY after 80 years of age (YOA) (Pinchinat 2013).

Altered immunocompetence

Although most HZ cases occur in older adults, immunocompromised patients have a much greater risk of HZ compared to immunocompetent individuals of the same age (O'Connor 2013).

Table 1 summaries the incidence of HZ in the overall population and among particular IC populations. Among adults ≥18 YOA with IC conditions, patients who undergo HCT show the highest risk for HZ among the IC conditions. In addition to the underlying disease, the immunosuppressive cancer therapy may also be a risk factor for developing HZ in patients with haematological malignancies.

Patients with autoimmune disease are also at increased risk of HZ reactivation. In addition to the risk autoimmune disease may independently pose, most of these conditions are managed with immunosuppressive therapies that impair T cell immunity likely contributing to the increased rates of HZ seen in this population (Chakravarty, 2017) (Table 1).

Disease-induced immunosuppression has been proposed as a mechanism for increasing the risk of HZ in patients with other chronic diseases that directly affect CMI like HIV as well as those with less well defined mechanism of immunosuppression like type II diabetes mellitus (Table 1). In people living with HIV under highly active antiretroviral therapy (ART), HZ incidence has declined over time but remains higher than the rates reported in the general population (Moanna2013).

Table 1. Summary of the HZ incidence in various populations

Population	HZ incidence
Overall population	
Overall	3 to 5 cases per 1000 PY
18-49 YOA	3.4 cases per 1000 PY
≥65 YOA	8.4 cases per 1000 PY
Patients ≥18 YOA who undergo HSCT	
Overall	37 to 60 cases per 1,000 PY
First year following autologous HSCT	8% to 28%
Other adults at risk	
Solid organ transplant recipients	8 to 20 cases per 1000 PY
Hematologic cancers, overall	29 to 31 cases per 1000 PY
Malignant lymphoma	Hazard ratios of 8.4 (6.7, 10.6)
Oesophageal cancer and brain tumors	Hazard ratios 4.0 (2.1, 7.8) and 3.7 (2.4, 5.7)
Auto-immune diseases, overall	3 to 38 cases per 1000 PY
systemic lupus erythematosus	6 to 37 per 1,000 PY

rheumatoid arthritis	8 to 16 per 1,000 PY
inflammatory bowel disease	4 to 11 cases per 1000 PY
psoriasis	5 to 9 cases per 1000 PY
HIV, prior to introduction of highly active ART	32 cases per 1000 PY
Diabetes mellitus	3 to 13 cases per 1000 PY

Asano-Mori 2008; Mao 2018; Sahoo 2017; Schröder 2017; Schuchter 1989; Offidani 2001; Barton 2001; Kamber 2015; Koc 2000; Steer 2000; Kroger 2011; Chen 2014; Habel 2013; Pergam 2011; Hata 2011; Chakravarty 2017; Winthrop 2014; Gilbert 2017; Gilbert 2019; Moanna 2013; Kwon 2016; Guinee 1985; Sorensen 2011; Sandherr 2006; Anaissie 1988; Hata 2002; Nucci 2009; Sorensen 2009; Chanan-Khan 2008; Kim 2008; Ohguchi 2009; Yi 2010; Rusthoven 1988; Wade 2006; Sandherr 2006; Mattiuzzi 2003; Borba 2010; Chen 2017; Hu 2016; Khan 2018; Smitten 2007; Veetil 2013; Yun 2016; Zisman 2016.

Other risk factors

Other important risk factors described in the literature are co-morbidities such as renal diseases, COPD, asthma, and cardiovascular diseases. Other non-medical factors such as a recent physical trauma, stress, sleep disturbance, depression, recent weight loss, family history of HZ, female gender and Afro-American ethnicity are also associated with an increased risk of HZ (Marin 2016, Kawai 2017, Marra 2020).

Results from a recent meta-analysis based on 88 studies, excluding studies that used immunosuppressive medications, are summarized below (Marra 2020) and confirmed previous results observed in the meta-analysis performed by Kawai in 2017.

Table 2. Summary the Relative Risk of HZ occurrence in subjects with co-morbidities and non-medical risk factors

Population	RR (95% CI)
Chronic renal disease	1.29 (1.10-1.51)
COPD	1.41 (1.28-1.55)
Cardiovascular conditions	1.34 (1.17-1.54)
Asthma	1.24 (1.16-1.31)
Depression	1.23 (1.11-1.36)
Physical trauma	2.01 (1.39-2.91)
Psychological stress	1.47 (1.03-2.10)
Family history	2.48 (1.70-3.60)
Sex (women)	1.19 (1.14-1.24)
Race (black)	0.69 (0.56-0.85)

Management

Treatment

The main existing treatment options are:

Therapeutic measures for the management of HZ and acute HZ pain

In immunocompetent adults, antiviral therapy has been shown to decrease the duration of the HZ rash and the severity of pain associated with the rash, in particular in patients who received treatment within 72 hours after the onset of rash. Therefore, antiviral therapies, such as acyclovir, famciclovir and valacyclovir are used in the acute phase of infection with the main aims of reducing and/or stopping viral replication, which is thought to play a role in relieving pain and shortening duration of symptoms (Dworkin 2007b).

A variety of approaches have also been used with varying degrees of success for control of acute HZ pain, including acetaminophen, non-steroidal anti-inflammatory agents, tricyclic antidepressants, opioids, anticonvulsants, capsaicin, and topical anesthetics (Dworkin 2007b).

Therapeutic measures for the management of chronic pain

A recent Cochrane review, which considered all randomized controlled trials of antiviral treatment given within 72 hours after the onset of HZ for preventing PHN, showed that oral acyclovir does not reduce the incidence of PHN, while there is insufficient evidence to determine the effect of other antiviral treatments (Chen 2014). Furthermore, the addition of systemic glucocorticoids to antiviral drugs during the acute phase of HZ does not reduce the incidence of PHN (Wood 1994, Whitley 2010).

Treatment of PHN is aimed to control symptoms, as no disease-modifying therapy is currently available (van Wijck 2006). Treatment may involve topical therapy (lidocaine or capsaicin as first-line treatment for mild pain) and systemic therapy, generally with anti-epileptic drugs gabapentin and pregabalin, or tricyclic antidepressants (Johnson 2014). Conflicting evidences exist on the use of potent opioids (such as oxycodone) and tramadol in treating PHN (McNicol 2013, Johnson 2014, Finnerup 2015). Therefore opioids, including tramadol, should generally be considered as third-line drugs for treatment of PHN after consultation with a specialist and should be prescribed only with close monitoring.

Preventative option for the management of HZ

Vaccination for HZ prevention is available to decrease HZ and PHN in individuals over 50 years of age.

A live-attenuated VZV vaccine (Zostavax®,Merck & Co) has been licensed in several countries since 2006 and, in EU, is recommended for use in immunocompetent adults ≥50 yrs to prevent HZ and PHN. This vaccine is contraindicated in immunosuppressed or immunodeficient individuals due to concerns of possible vaccine-associated disseminated disease.

Other inactivated vaccines have been evaluated in IC populations. A heat inactivated VZV vaccine (V212, Merck & Co) was shown to reduce the incidence of HZ by 63.8% in autologous HSCT recipients ≥18 YOA, also after 4 doses (Winston, 2017).

Unmet medical need

Currently, Shingrix is indicated in adults ≥50 YOA, with no contraindication for use in the IC subjects.

In support of the initial MAA, data from 2 Phase I/II clinical studies conducted in 135 adults ≥18 YOA, of whom 73 were ≥50 YOA, with autologous HSCT or HIV infection (studies ZOSTER-001 and ZOSTER-015, respectively) were provided showing that Shingrix was immunogenic and well-tolerated in IC subjects either by disease or treatment. A statement that there are limited data available on the use of Shingrix in IC adults ≥50 YOA is included in the section 4.4 ”Special warnings and precautions for use” of the SmPC with additional information in Pharmacodynamics section since at the time of the MAA, data were limited.

There is also an unmet medical need in a wide range of adults ≥18 YOA at increased risk of HZ, i.e. individuals with underlying medical conditions or treatments predisposing them to HZ. This includes patients chronically using immunosuppressive medications (e.g., oncology patients and transplant recipients), patients with autoimmune diseases or other relevant chronic conditions (e.g., rheumatoid arthritis, IBD, COPD, cardiovascular diseases, renal disease, systemic lupus erythematosus, asthma, Type 2 diabetes mellitus, HIV), as well as subjects with congenital immunodeficiencies.

As described above, epidemiological evidence confirms that the risk of HZ increases in adults ≥18 YOA with those conditions, placing them at a risk comparable to and in many instances exceeding the risk seen in the general adult population ≥50 YOA. This wide spectrum of IC/conditions altering the immune status in adults illustrates the medical need for prevention through vaccination.

Currently, Shingrix is indicated for prevention of HZ and PHN in adults ≥50 YOA. The MAH proposes to amend the indication for Shingrix to include adults 18 years of age or older at increased risk of HZ to address the unmet medical need for HZ prevention in that population.

The claimed indication is for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in:

- adults 50 years of age or older.
- adults 18 years of age or older at increased risk of HZ.

2.1.2. About the product

The GlaxoSmithKline Biologicals SA (GSK) adjuvanted (AS01B) Herpes zoster (HZ) vaccine, also referred to as HZ/su (su for 'subunit') has demonstrated >90% efficacy in preventing HZ in adults ≥50 YOA, including in the subpopulation of adults aged 70 years and older. Consequently it, has been approved under the tradename *Shingrix* in Canada, the United States (US), the European Economic Area (EEA), Japan, Australia and China. In all 6 countries/regions, *Shingrix* is indicated for prevention of HZ in adults ≥50 years of age (YOA). In the EEA and Australia, *Shingrix* is also indicated for prevention of post-herpetic neuralgia (PHN) in the same population.

The vaccine is to be administered according to a 2-dose schedule, consisting of 2 injections given 2-6 months apart.

The glycoprotein E (gE) antigen contained in *Shingrix* is produced by recombinant DNA technology in Chinese Hamster Ovary cells and is provided in a lyophilized form (white powder) in monodose vials (50 µg/dose). The AS01B (liquid) Adjuvant System, which is a GSK proprietary Adjuvant System, is provided in separate monodose vials (0.5 mL/dose). The content of the AS01B vial is used to reconstitute the content of the gE vial prior to intramuscular injection of *Shingrix*.

The AS01B Adjuvant System contains 50 µg of each of the immune-enhancers Quillaja saponaria Molina fraction 21 (QS-21) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) combined with liposomes:

- QS-21 (licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, US corporation) is a natural saponin molecule (triterpene glycoside) purified from the bark of Quillaja saponaria Molina tree.
- MPL (GSK North America, US) consists of a chemically detoxified form of the parent lipopolysaccharide from the Gram-negative bacterium Salmonella minnesota.
- The liposomes consist of dioleoylphosphatidylcholine and cholesterol.

The pharmaceutical form of the reconstituted vaccine is a liquid suspension for injection appearing opalescent, colorless to pale brownish.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

To support this extension of indication, the MAH executed a specific clinical development program (CDP) of 4 pivotal phase II/III clinical studies in adults ≥18 YOA with the following severe immunocompromising conditions: autologous hematopoietic stem cell transplant (HSCT) recipients (ZOSTER-002), hematologic malignancy patients (ZOSTER-039), renal transplant recipients (ZOSTER-041), and solid tumor patients (ZOSTER-028). In these studies, a total of 1,452 subjects received at least one dose of Shingrix. Shingrix has also been studied in two supportive phase I/II clinical studies (ZOSTER-001 and ZOSTER-015) in 135 adults ≥18 YOA with autologous HSCT (N=61) or Human Immunodeficiency Virus (HIV) infection (N=74). The data from these two studies were presented in the initial MAA.

These studies were multi-country studies conducted worldwide. In all 4 pivotal studies, HZ/su was administered according to a 2-dose flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose.

In these studies, 1,452 IC subjects ≥18 YOA were exposed to at least one dose of Shingrix.

The proposal for SmPC update was formally discussed with EMA at a CHMP Scientific Advice (SA) procedure (31 January 2019).

The Company discussed with the Authorities at the time the following rationale for the proposed indication claim targeting the general population ≥18 YOA:

The CHMP considered the rationale for extension of the indication as valid: '*While the risk of HZ in otherwise healthy young adults is very low, this does not preclude an indication in adults ≥18 years of age, as the decision to use the vaccine is made based on recommendations of public health bodies and/or the clinical status of the individual'*.

It should be noted that the CHMP expressed a concern regarding the use of the adjuvant in the younger adult population: '*Some further data on safety, and particularly local and systemic reactogenicity, from healthy young adults should be provided in any application to allow use from 18 years without any qualification. In the absence of this, available data may, subject to assessment, support an indication in immunocompromised patients from 18 years of age*'. Based on this CHMP assessment, the Company proposes an extension of the indication to adults ≥18 YOA at increased risk of HZ.

2.1.4. General comments on compliance with GCP

The MAH claims that all trials were approved by Independent Ethics Committees (IECs) and conducted in accordance with the principles of Good Clinical Practice (GCP) and all applicable regulatory requirements, including the Declaration of Helsinki. Written informed consent was obtained from all subjects as per GCP requirements. Whenever potential issues with regard to the conduct of a study were identified, either via site monitoring activities or brought to GSK's attention by other oversight mechanisms, these issues were investigated and appropriate corrective and where possible preventive actions were taken as considered appropriate for GCP and protocol compliance.

All studies except ZOSTER-015 were audited by GSK's R&D Global Quality Compliance-Clinical Development Quality Assurance (CDQA) department, and/or external Audit Groups who performed independent audits on behalf of GSK.

According to the MAH, there were no significant audit findings that impacted the validity of the data collected. The MAH also claims that during the conduct of the all the studies, there were no significant deviations from GCP compliance identified by the MAH, with the exception of two relevant audit findings which occurred in ZOSTER-002 are described below. The MAH considers that there is no impact on the validity of the data.

During the conduct of ZOSTER-002, important GCP issues related to lack of evidence of Principal Investigator oversight and documentation deficiencies were detected and investigated during 2 for-cause audits of ZOSTER-002. The internal audits were conducted by GSK: (i) At one United Kingdom site. This site enrolled 5 out of the 1846 subjects included in the study; (ii) At one site in New Zealand. This site enrolled 3 out of the 1846 subjects included in the study. There was no evidence of impact on the validity of the data.

2.2. Non-clinical aspects

The GlaxoSmithKline Biologicals SA (GSK) adjuvanted (AS01B) Herpes zoswter (HZ) vaccine, also referred to as HZ/su (su for 'subunit') and gE/AS01B (research code), has been approved under the tradename Shingrix in Canada, the United States (US), the European Economic Area (EEA), Japan, Australia and China. One dose of HZ/su contains 50 µg of gE, as active ingredient, adjuvanted with AS01B including 50 µg of

each immunoenhancer [3-O-desacyl-4'-monophosphoryl lipid A (MPL) and Quillaja saponaria Molina fraction 21 (QS-21)] formulated in liposomes [1000 µg dioleoyl phosphatidylcholine (DOPC) and 250µg cholesterol by dose].

With this application the Company aims to extend the indication of Shingrix to adults ≥18 YOA in order to address the unmet medical need for HZ prevention in adults at increased risk of HZ due to an immunodeficiency or immunosuppression caused by disease or underlying therapy.

The dossier for Marketing Authorization Application (MAA)/ Biologics License Application (BLA) included nonclinical pharmacology and toxicity studies conducted with gE/AS01B that were complemented by nonclinical pharmacology, biodistribution and toxicity studies with the AS01B Adjuvant System as well as with the QS-21 and MPL immunoenhancer components of this Adjuvant System family. In particular, toxicity studies that were conducted with the gE/AS01B, AS01B alone, MPL and QS-21 were included. Nonclinical development followed guidelines that were in effect at the time of study conception and conduct which included: CPMP Note for Guidance on preclinical, pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95), the Guideline on adjuvants in vaccines for human use EMEA/CHMP/VEG/134716/2004), the WHO Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (WHO, 2013), the FDA Guidance for Industry: Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications (FDA, 2006) and the WHO Guideline on Nonclinical Evaluation of Vaccines (WHO, 2005).

The HZ/su vaccine candidate and the AS01B formulation were tested at the highest used clinical dose ("full human dose") in alignment with above mentioned guidelines. QS-21 (and MPL) were tested at doses greater than the full human dose in agreement with ICH harmonised tripartite guideline: detection of toxicity to reproduction. For medicinal products & toxicity to male fertility S5(R2). Current Step 4 version, parent Guideline dated 24 June 1993 (Addendum dated 9 November 2000 incorporated in November 2005).

The proposed extended indication would include women of childbearing potential. Of note, reproductive toxicity studies were included in the initial submission even though they were not relevant for the target population in the original indication (≥ 50 years of age). The CHMP raised concerns regarding the reproductive toxicity, specifically after administration of QS-21. The conclusion on the adjuvant component QS-21 was that it potentially induces treatment related adverse findings including kidney and great blood vessel malformations in rabbits but not in rats, at doses considered sufficiently in excess over the therapeutic dose to not raise concern. The CHMP recommended that, in case of extension of the target population to women of childbearing potential, the Company should consider testing the vaccine/adjuvant system in a second species in an embryo-fetal development (EFD) study.

Following the recommendations of CHMP, an additional reproductive toxicity study that would provide new data on potential effects of AS01 in rabbits has been performed and submitted with this application.

2.2.1. Introduction

This assessment pertains to the submitted results from the developmental and reproductive toxicity (DART) study after administration of AS01B in rabbits as well as additional background data allowing interpretation of malformations that occurred in rabbits after administration of QS-21 (**Table 3**).

Table 3: Overview of available DART studies

Product / Study type	gE/AS01$_B$	AS01$_B$	QS-21	MPL*
Pre-, peri- and post-natal reproductive toxicity in rat	X	X	X	
Pre-, peri- and post-natal reproductive toxicity in rabbit		X	X	
Embryo-fetal development in rat				X
Embryo-fetal development in rabbit				X
Pre-and post-natal development in rat				X

Studies shaded in grey are new or have new background data which are submitted as part of this variation. All other studies/data were part of the original filing. * all studies for MPL were performed by subcutaneous administration. Studies for gE/AS01$_B$, AS01$_B$ and QS-21 followed the clinical IM route of administration.

2.2.2. Toxicology

Reproduction toxicity

Reproductive toxicity studies submitted in the original MAA

The EPAR for Shingrix (EMA/88588/2018) summarizes the available reproductive toxicity studies (please refer to section 2.3.4 Toxicology – Reproduction studies).

In order to support this EOI, that will include women of childbearing potential, the MAH has submitted a developmental toxicity study (including teratogenicity and postnatal investigations) of RSVPreF3 or ASO1B by intramuscular injection in rabbits.

Developmental toxicity study (including teratogenicity and postnatal investigations) of RSVPreF3 or ASO1B by intramuscular injection in rabbits (study number 20152506, GLP)

The objectives of this study were to detect adverse effects of RSVPreF3 vaccine or AS01B (not part of the RSVPreF3 vaccine) on fertility, EFD and early postnatal development in female pregnant NZW rabbits. One group of rabbits received a viral antigen (RSVPreF3) that is not relevant for the assessment of effects of gE/AS01 or AS01B; however, the group can serve as control and results can be informative for the overall interpretation of the study.

To this end, 3 groups of 48 rabbits received RSVPReF3, AS01B or control article formulation at the dose levels shown in the table below by intramuscular injection in the morning hours on DS1 (28 days prior to mating), DS15 (14 days prior to mating), on GD3, GD11, GD16 and GD24 and after natural delivery on LD7 (as applicable, see treatment schedule below). From the 48 rabbits per group, 24 animals were allocated either to the caesarean section cohort or to the natural delivery cohort, based on computer-generated randomisation scheme balanced by body weights.

Table 4: Overview of the developmental toxicity study 20152506

Group	Test Material	Dose (µg/injection)	Number of Females	
			Assigned to Cesarean-Sectioning	Assigned to Natural Delivery
1	Control	0 (Control Article)	24	24
2	RSVPreF3	120[a]	24	24
3	$AS01_B$	50[b]	24	24

a. This dose was expected to give an approximate 20X dose multiple assuming a 3kg average rabbit weight and a 60 kg average human weight.

b. The dose of $AS01_B$ [50 µg of a saponin molecule (QS-21) and 50 µg of 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)] was selected because it is the highest clinical dose used for the licensed Shingrix vaccine and other vaccine candidates in development.

The dose of AS01B in 0.5 mL was selected because it is the highest clinical dose used for the licensed Shingrix vaccine and other vaccine candidates in development. Unless otherwise noted, study rabbits were euthanized on GD 29 (caesarean section cohort) or LD 35 (natural delivery cohort).

During the study, clinical condition, bodyweight, food consumption, gestation length and parturition observations, and macroscopic pathology investigations were recorded for F0 females. Fetuses from the embryo-fetal phase of the study were examined macroscopically at necropsy and subsequently by detailed internal visceral examination or skeletal examination. For offspring in the postnatal phase of the study, clinical condition and survival, sex ratio, bodyweight, pre-weaning reflex development and macropathology observations were recorded.

Mortality

There were no treatment-related deaths. Three rabbits in the AS01B group were found dead on GD 31, LD 28, and LD 30.

The cause of death was not apparent for the 3 found dead animals. The incidence of mortality during the gestation phase (1 female out of 24 died on GD 31) is within the historical control data (HCD) range for this type of study. Upon review of the scientific literature, it is reported that female rabbits in the last week of pregnancy and the first week of lactation have higher mortality rates than nonpregnant females [Rosell, 2016]. In the 2 rabbits that were found dead at the end of the lactation period, there were body weight losses and food consumption decrease within the week of being found dead. HCD collected during the prenatal and embryofetal development stages (HCD for the post-partum lactation period is not available) show that incidental maternal toxicity has occurred at a range of 0- 2 does/group. No literature was identified describing the incidence of maternal mortality during the later postpartum phase, however, mortality in conjunction with reduced food intake and indigestion has been reported [Harcourt-Brown, 2002; McInnes, 2012], as well as other conditions in periparturient does that are linked to anorexia and mortality [Rosell, 2016].

Based on the weight of evidence and the inconsistency between the previous dose and the time of death (7-23 days), these deaths were considered incidental and unlikely related to AS01B.

Embryofetal survival, fetal weight and gravid uterine weight

No treatment related effects on numbers of corpora lutea, implantations, resorptions, live and dead foetuses per litter, sex ratio, fetal body weight, gravid uterine weight or placental morphology.

The mean number of live fetuses/litter was slightly lower in the AS01B group (7.7) vs controls (8.3) but was not considered treatment-related as it was not statistically significant and within historical control (mean 8.8, range 7.0-10.1). Also, the post-implantation loss was slightly higher in AS01B groups vs controls (4.23 vs control value of 2.02) but was not considered treatment-related as not statistically significant, nor

did this higher postimplantation loss translate to lower numbers of live fetuses/litter and both were within historical control ranges for this laboratory, mean of 3.5, range of 0.8-22.9.

Fetal examinations C-section cohort

In the AS01B group, one fetus had a small eye and one multiply malformed fetus (domed head, hindlimbs malrotated, protruding tongue, distended abdomen, brain misshapen, small lungs, bent long bones (humerus/radius/ulna/femur/ tibia/fibula/metatarsal, and frontal/mandible/supraoccipital misshapen) was noted in a different litter.

In controls, there were 3 fetuses in 1 litter with large adrenal glands (also 2 other foetuses in this same litter had supernumerary lumbar vertebrae), 2 fetuses in 1 litter with fused thoracic centrum (one of these fetuses also had a branched rib, the other fetus had a fused thoracic arch).

Fetuses with malformations occurred in all groups including controls. All malformations and variations that were observed were considered unrelated to treatment because: 1) the abnormality was limited to a single fetus; 2) the abnormality occurred at a similar incidence in the control group; and/or 3) the litter and/or fetal incidence was within the range of the historical control data for the Testing Facility.

There were no treatment-related effects on natural delivery or litter observations.

Values for the numbers of does delivering litters, the duration of gestation, averages for implantation sites per delivered litter, does with stillborn and liveborn kits, the gestation index (number of does with one or more liveborn kits/number of pregnant rabbits), dams with all kits dying, kits found dead or presumed cannibalized, viability and lactation indices, surviving kits per litter, percentage of male kits per litter, live litter size at weighing, and kit weights per litter were all comparable among the groups including controls.

In the F1 generation, there were no treatment-related clinical signs or effects on reflex and physical development, macroscopic observations at scheduled euthanasia and brain weights. Early deaths of kits and the number of surviving kits/litter were comparable across 3 dose groups; therefore, the early deaths were not considered treatment related.

In conclusion, intramuscular injection of female rabbits with the full human dose of AS01B, 28 and 14 days before pairing, on gestation days 3, 11, 16, and 24, and on day 7 of lactation, was well tolerated. AS01B produced no adverse effects on female fertility, embryo-fetal or pre- and post-natal survival, growth or development of the offspring up to Day 35 of age.

Additional background data

The Applicant provided new background data in this submission that support that the findings observed in foetuses of female rabbits administered QS-21 at a high dose (200 µg/animal) in one developmental and reproductive toxicity study (AB14898) are background findings and not evidence of QS-21-mediated foetal damage.

These data are summarized as follows:

- In study AB14898, IM administration of QS-21 at 200 µg/animal/occasion to rabbits 28 and 14 days before the start of mating and on gestation days 3, 8, 11, 15 and 24 and on day 7 of lactation induced a significant maternal mean body weight loss associated with reduced mean food consumption at the end of the gestation period which is interpreted as minimal maternal toxicity consistent with expectations of ICH S5(R2) for the dose setting of the high dose group and related to this, lower mean foetal weight was noted at this dose level. Based on the absence of findings in the mid dose level, the NOAEL was considered to be a dose of 100 µg/rabbit (corresponding to 30 µg /kg BW considering a BW of 3.3 kg for rabbits).

Other DART studies that were conducted in rats or rabbits with test articles that contained QS-21 did not reveal evidence of developmental toxicity in rats (HEY0005, HEY0020, Segal, 2017) or rabbits (20152506). Doses used in those studies overlapped when calculated on a bodyweight basis.

- In order to consider a developmental toxicity signal as test-article related, a distinct embryologic abnormality needs to occur at a higher incidence than the background incidence and the abnormality needs to be consistent between foetuses. The malformations that occurred more than once in the high dose group of study AB14898 were (i) malpositioned and/ or malformed kidneys, and (ii) "great vessels malformations". The former findings were genetically linked to one male and both malformations fall within the reported historical background as evidenced by information from the Contract Research Organization provided in this submission (AB14898 accessory document -1,3,4). The likelihood of clustered malformations within one dose group was enhanced by a mating scheme that linked a limited number of males to one dose group, rather than allowing mating across dose groups (AB14898 accessory document -2).

- An incidental accumulation of findings in one dose group has been observed in historical control data (HCD), the highest number of affected litters were comparable to the 6 litters observed for study AB14898 (4 litters in HCD 2010-2012 –AB14898 Pre clinical study report, 5 litters in HCD 2014-2016- AB14898 accessory document -3 and 6 litters in HCD 2016-2017- AB14898 accessory document -4).

2.2.3. Ecotoxicity/environmental risk assessment

As mentioned in the scope of EMA's "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr1, 1 June 2006), inactivated vaccines, such as Shingrix, are exempted from an environmental risk assessment due to the nature of their constituents.

2.2.4. Discussion on non-clinical aspects

The new developmental toxicity study (including teratogenicity and postnatal investigations) of ASO1B by intramuscular injection in rabbits and the additional information provided in this application support the conclusion that there is no safety concern with regards to female fertility, embryo-fetal or pre- and post-natal survival, growth or development of the offspring, after administration of gE/AS01B, AS01B, QS-21 in rats and after administration of AS01B, QS-21 in rabbits, under the conditions of the respective studies.

Findings in the low dose group (20 µg of QS-21), including malpositioned kidneys, great vessel malformation and total litter losses, may be considered incidental based on the historical control data provided by the Applicant. Based on the absence of findings in study AB14898 in the mid dose level, the NOAEL for QS-21 was set at a dose of 100 µg/rabbit (corresponding to 30 µg /kg BW considering a BW of 3.3 kg for rabbits). As direct comparison to human doses is not possible given the particular experimental design of reproductive toxicity studies for vaccines, repeated dosing of a full human dose in absence of adverse findings is considered an acceptable safety margin. Adverse findings in previous studies were not observed in the new developmental toxicity study (including teratogenicity and postnatal investigations) of ASO1B by intramuscular injection in rabbits.

2.2.5. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Herpes zoster vaccine (recombinant, adjuvanted).

From a non-clinical point of view, this type II variation application is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 5: Tabular overview of all studies submitted

Study ID (eTrack No)	Study countries	Study design Objectives*	Population (age) Vaccination schedule	Study groups	Number of subjects	
					ATP cohort for Immune-genicity**	TVC
Pivotal studies						
ZOSTER-002 (115523)	Australia, Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Germany, Greece, Hong-Kong, Israel, Italy, Japan, Malaysia, the Netherlands, New Zealand, Panama, Poland, Romania, South Korea, Russian Federation, South Africa, Spain, Taiwan, Turkey, UK, US	Phase III, randomized, observer-blind, placebo-controlled efficacy study. Event (confirmed HZ cases)-driven analysis with a minimum follow-up of at least 12 months post last vaccination (actual median follow-up time for efficacy of 21 months). Primary objective: VE in preventing HZ. Secondary objectives: VE in terms of: Reducing total duration of severe 'worst' HZassociated pain. Reducing confirmed HZ-associated complications. Preventing PHN. Immunogenicity in terms of humoral immune responses to gE in a sub-cohort of subjects at Months 0, 1, 2, 13, and 25. Safety and reactogenicity up to study end.	Autologous HSCT recipients ≥18 YOA. Two subgroups by underlying disease (minimization factor used in randomization algorithm): MM Other diagnoses, including NHBCL, Hodgkin lymphoma, NHTCL, AML, solid organ malignancies, etc. 2 doses (Month 0 and Month 1 to 2) with the first dose administered within 50 to 70 days after transplant	1) HZ/su: 2 doses of HZ/su 2) Placebo: 2 doses of Placebo	82 76	922 (TVC)a 870 (mTVC)b 924 (TVC)a 851 (mTVC)b
ZOSTER-028 (116427)	Canada, Czech Republic, France, South Korea, Spain, UK	Phase II/III, randomized, observer-blind, placebo-controlled study. Duration of follow-up: 12 months post last vaccination. Co-primary objectives: Immunogenicity with respect to humoral immune responses (anti-gE Abs) in terms of GMC ratio in the PreChemo group at Month 2.	Adults ≥18 YOA with solid tumors treated with chemotherapy as: PreChemo Group, receiving first vaccination 8-30 days prior to the start of a chemotherapy cycle, and second vaccination at the start of a	1) HZ/su: 2 doses of HZ/su: a) PreChemo Group b) OnChemo Group 2) Placebo: 2 doses of Placebo: a) PreChemo	87 65 22 98 78	117 90 27 115 91

		▯ Safety and reactogenicity up to 30 days post last vaccination. Secondary objectives: ▯ Immunogencity with respect to humoral immune responses (anti-gE Abs): ▯ VRR to HZ/su in the PreChemo group at Month 2. ▯ GMC ratio in all subjects at Month 2. ▯ VRR to HZ/su in all subjects at Month2 ▯ Humoral immune responses to gE in all subjects at Months 0, 1, 2, 6, and 13. ▯ Immunogencity with respect to CMI responses (gEspecific CD4+ T-cell frequencies) in the CMI sub-cohort (PreChemo groups only) ▯ GM ratio at Month 2. ▯ VRR to HZ/su at Month 2. ▯ gE-specific CD4+ T-cell frequencies at Months 0, 1, 2, and 13. ▯ Safety from 30 days post last vaccination until study end.	chemotherapy cycle ▯ OnChemo Group, receiving first and second vaccination at the start of a chemotherapy cycle 2 doses (Month 0 and Month 1 to 2)	Group b) OnChemo Group	20	24
ZOSTER-039 (116428)	Australia, Belgium, Canada, Czech Republic, Finland, France, Hong Kong, Italy, New Zealand, Pakistan, Panama, Poland, Russian Federation, Singapore, South Korea, Spain, Sweden, Taiwan, Turkey, UK, US	Phase III, randomized, observer-blind, placebo-controlled study. Duration of follow-up: 12 months post last vaccination. Co-primary objectives: ▯ Safety and reactogenicity up to 30 days post last vaccination. ▯ Immunogenicity with respect to humoral immune responses (anti-gE Abs) in subjects with hematologic malignancies excluding subjects with NHBCL and CLL: ▯ VRR to HZ/su at Month 2. ▯ GMC ratio at Month 2. Secondary objectives: ▯ Safety from 30 days post last vaccination until study end. ▯ Immunogenicity with respect to humoral immune responses (anti-gE Abs): ▯ VRR to HZ/su in subjects with hematologic malignancies excluding subjects with NHBCL at Month 2. ▯ GMC ratio in subjects with hematologic malignancies excluding subjects with NHBCL at Month 2. ▯ Humoral immune responses to gE for the entire study	Adults ≥18 YOA with hematologic malignancies Stratified into 3 subgroups by underlying disease: ▯ NHBCL ▯ CLL ▯ MM and other diseases, i.e., MM, NHTCL, Hodgkin lymphoma and other hematologic malignancies 2 doses (Month 0 and Month 1 to 2) with administration at 10 days before or after chemotherapy or at 10 days to 6 months after completion of chemotherapy course	1) HZ/su: 2 doses of HZ/su 2) Placebo: 2 doses of Placebo	217 198	283 (TVC)a 259 (mTVC)b 279 (TVC)a 256 (mTVC)b

		population and by underlying disease strata at Months 0, 1, 2, and 13. Immunogenicity with respect to CMI responses (gE-specific CD4+ T-cell frequencies) in the CMI subcohort and by underlying disease strata at Months 0, 1, 2, and 13. Incidence of confirmed HZ cases until study end.				
ZOSTER-041 (116886)	Belgium, Canada, Czech Republic, Finland, Italy, Panama, South Korea, Spain, Taiwan	Phase III, randomized, observer-blind, placebo-controlled study. Duration of follow-up: 12 months post last vaccination. Co-primary objectives: Immunogenicity with respect to humoral immune responses (anti-gE Abs) in terms of VRR to HZ/su at Month 2. Safety and reactogenicity from first vaccination up to 30 days post last vaccination. Secondary objectives: Immunogenicity with respect to humoral immune responses (anti-gE Abs): GMC ratio at Month 2. Humoral immune responses to gE at Months 0, 1, 2, 7, and 13. Immunogenicity with respect to CMI responses (gEspecific CD4+ T-cell frequencies) in the CMI sub-cohort: VRR to HZ/su at Month 2. GM ratio at Month 2. gE-specific CD4+ T-cell frequencies at Months 0, 2, and 13. Safety from 30 days post last vaccination until study end.	Renal transplant recipients ≥18 YOA 2 doses (Month 0 and Month 1 to 2) with the first dose administered within 4 to 18 months after transplant.	1) HZ/su: 2 doses of HZ/su 2) Placebo: 2 doses of Placebo	121 119	132 132
Supportive studies						
ZOSTER-001	US	Phase I/IIa, randomized, observer-blind, placebo-controlled study. Duration of follow-up: 12 months post last vaccination. Co-primary objectives: Safety and reactogenicity, including hematology and biochemistry parameters up to study end. Immunogenicity with respect to CMI (CD4+ T cells) and humoral immune responses to gE at Month 4. Secondary objectives: Immunogenicity with respect to CMI (CD4+ T-cells) and	Phase I/IIa, randomized, observer-blind, placebo-controlled study. Duration of follow-up: 12 months post last vaccination. Co-primary objectives: Safety and reactogenicity, including hematology and	1) gE/AS01B3: 3 doses of HZ/su 2) gE/AS01E3: 3 doses of gE/AS01E 3) gE/AS01B2: 1 dose of placebo at Month 0 + 2 doses of HZ/su at Months 1 and 3	29 26 27 24	30 29 31 30

		humoral immune responses to gE and VZV at Months 1, 2, 3, 4, and 15. Descriptive assessment of HZ and its complications.		4) Placebo: 3 doses of placebo		
ZOSTER-015 (112673)	Germany, UK, US	Phase I/IIa, randomized, observer-blind, placebo-controlled study. Duration of follow-up: 12 months post last vaccination. Primary objectives: • Safety and reactogenicity, including hematology and biochemistry parameters and worsening of HIV condition, up to study end. • Immunogenicity with respect to humoral immune responses (anti-gE Abs) and CMI responses (CD4+ Tcell frequencies) at Month 7. Secondary objectives: • Immunogenicity with respect to humoral immune responses (anti-gE Abs) and CMI responses (CD4+ T-cell frequencies) at Months 0, 1, 2, 3, 6, 7, and 18.	HIV-infected adults ≥18 YOA Divided into 3 cohorts by HIV statusc: • ART High CD4 cohort • ART Low CD4 cohort • Non-ART High CD4 cohort 3 doses (Months 0, 2, and 6)	1) gE/AS01B: 3 doses of HZ/su 2) Placebo: 3 doses of Placebo	54 37	74 49

* This table presents all primary objectives and the secondary objectives related to the data presented in the Summary of Clinical Efficacy and the Summary of Clinical Safety. A list of all objectives can be found in the respective CSRs in Module 5.
** For the pivotal studies, numbers are presented for the ATP cohort for 'humoral' immunogenicity
a ZOSTER-002: TVC used for safety analysis.
b mTVC used for efficacy analysis (post-hoc in ZOSTER-039)
c In ZOSTER-015, subjects were divided into 3 cohorts by HIV status. As foreseen in the protocol, due to differential recruitment rates observed for the ART Low CD4 and the non-ART
High CD4 cohorts, portions of the subjects planned for enrolment in these 2 cohorts were reassigned to the ART High CD4 cohort during the study.
Abs = antibodies; MM and other diseases = Multiple Myeloma, Non-Hodgkin T-cell Lymphoma, Hodgkin Lymphoma and Other Haematologic Malignancies; CLL = Chronic Lymphocytic; Leukaemia; NHBCL = Non-Hodgkin B-cell Lymphoma; NHTCL = Non-Hodgkin T-Cell Lymphoma; HL = Hodgkin Lymphoma; AML = Acute Myeloid Leukemia.

Design

Pivotal Studies

One Phase II/III study and three Phase III studies support the HZ/su application in adults ≥18 YOA at increased risk of HZ:

- **ZOSTER-002** evaluated the efficacy, immunogenicity, reactogenicity and safety of HZ/su in autologous HSCT recipients ≥18 YOA.
- **ZOSTER-028** evaluated the immunogenicity, reactogenicity and safety of HZ/su in adults ≥18 YOA with solid tumors and receiving chemotherapy.
- **ZOSTER-039** evaluated the immunogenicity, reactogenicity and safety of HZ/su in adults ≥18 YOA with hematologic malignancies who were vaccinated during a cancer therapy course or after the full cancer therapy course.
- **ZOSTER-041** evaluated the immunogenicity, reactogenicity and safety of HZ/su in renal transplant recipients ≥18 YOA.

These were multi-country studies conducted worldwide. In all 4 pivotal studies, HZ/su was administered according to a 2-dose flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose.

Supportive Studies

In addition, 2 Phase I/II studies in adults ≥18 YOA with autologous HSCT (ZOSTER-001) and HIV infection (ZOSTER-015) support the schedule selection in the IC CDP and the extension of indication.

- **ZOSTER-015** evaluated the immunogenicity, reactogenicity and safety of HZ/su in HIV infected adults ≥18 YOA and provides additional safety and immunogenicity data in support of the proposed indication.
- **ZOSTER-001** evaluated the safety and immunogenicity of HZ/su when administered as 2 doses or 3 doses, and supported the selection of the 2-dose schedule of HZ/su for use in the Phase II/III studies in IC populations.

Study populations:

Study populations of ZOSTER-002 and ZOSTER-039 are described in detail in the clinical efficacy section. Study populations of ZOSTER-028 and ZOSTER-041 are described below in this section.

Blinding:

The studies were conducted in an observer-blind manner because the HZ/su and Placebo vaccines differed in their preparation method and appearance. Therefore, HZ/su and Placebo were prepared and administered only by authorized medical personnel not involved in any of the clinical study evaluation assays. The blinding was maintained until study end. Of note for ZOSTER-015, the investigators and investigative staff could have become aware of treatment allocation (inadvertent unblinding) with respect to some data included in the Month 7 CSR.

Randomization and treatment allocation:

All studies were conducted in a randomized manner. Treatment allocation for eligible subjects at the study site was performed using a central randomization system on the internet (SBIR) based on a minimization algorithm. Randomization was performed using several minimization factors aiming to ensure comparability of baseline characteristics between the two study groups. A randomization list was generated at GSK using a SAS program and was used to number the vaccines. A treatment number uniquely identified the vaccine dose to be administered to a subject. The vaccine doses were distributed to each study center, respecting the randomization block size.

In ZOSTER-028, subjects were stratified to the PreChemo group (first vaccination 8-30 days prior to the start of a chemotherapy cycle) or the OnChemo group (first vaccination at the start of a chemotherapy cycle) according to a 4:1 ratio. In both groups, the second vaccination was administered 1 to 2 months after the first vaccination and on the first day of a subsequent chemotherapy cycle.

Treatments:

In the pivotal studies, the vaccine was administered IM according to a flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose. The standard route was IM injection in the deltoid of the non-dominant arm.

All the studies used the final selected HZ/su formulation, i.e. 50 µg gE adjuvanted with AS01B.

Throughout this report, the GSK HZ vaccine is referred to as either Shingrix or HZ/su. Note that in ZOSTER-015, the vaccine has been referred to as gE/AS01B.

In ZOSTER-015, 3 vaccine doses were administered IM according to a 0, 2, 6-months schedule.

In all studies, the control group received placebo injections (lyophilized sucrose reconstituted with saline [NaCl] solution).

Study duration:

All subjects in the studies (except ZOSTER-001) were followed up for at least 12 months post last vaccination. In ZOSTER-002, the median follow-up for safety and efficacy was approximately 29 months and 21 months, respectively. In ZOSTER-028, ZOSTER-039 and ZOSTER-041, the study duration for each subject was 13 to 15 months. In ZOSTER-015, the study duration was approximately 18 months.

2.3.2. Pharmacokinetics

Pharmacokinetic studies including bioavailability and bioequivalence studies are usually not required for vaccines (EMA guidelines, EMEA/CHMP/VWP/164653/2005, EMEA/CHMP/VEG/134716/2004). Pharmacokinetic studies were not conducted during the clinical development of the candidate vaccine which was deemed acceptable at the initial MAA.

2.3.3. Immunogenicity

Mechanism of action

By combining the VZV specific antigen (gE) with an adjuvant system (AS01B), Shingrix is designed to induce antigen-specific cellular and humoral immune responses in individuals with pre-existing immunity against VZV.

Non-clinical data show that AS01B induces a local and transient activation of the innate immune system through specific molecular pathways. This facilitates the recruitment and activation of antigen presenting cells carrying gE-derived antigens in the draining lymph node, which in turn leads to the generation of gE-specific CD4+ T cells and antibodies. The adjuvant effect of AS01B is the result of interactions between MPL and QS-21 formulated in liposomes.

Immunogenicity Objectives and Endpoints

In ZOSTER-028, ZOSTER-039 and ZOSTER-041, with respect to primary and secondary confirmatory immunogenicity objectives, a hierarchical procedure was applied to control for Type I error. The objectives were assessed sequentially in order of ascending rank until an objective was not met. At this point, the evaluation proceeded with descriptive analyses of the remaining objectives. In ZOSTER-002, all immunogenicity objectives were non-confirmatory.

Table 6: Descriptive immunogenicity objectives and endpoints of the pivotal Studies.

Objective	Endpoint	ZOSTER-002	ZOSTER-028	ZOSTER-039	ZOSTER-041
Humoral immunity (secondary)					
Characterize anti-gE humoral immune responses at several time points (see Table 9)	Anti-gE humoral immune responses (anti-gE Ab concentrations and vaccine response for anti-gE Abs)	humoral immuno sub-cohort	all subjects	all subjects	all subjects
CMI (secondary or tertiairy)					
Characterize gE-specific CMI responses at several time points (see Table 9)	gE-specific CD4+ T-cell-mediated immune responses (frequencies of gE-specific CD4+ T-cells expressing ≥2 activation markers[a] and/or expressing each individual activation marker in addition to 1 other marker[a] [ZOSTER-002], and vaccine response for gE-specific CD4+ T-cells expressing ≥2 activation markers[a])	CMI sub-cohort[b]	CMI sub-cohort (PreChemo groups)	CMI sub-cohort	CMI sub-cohort

For confirmatory immunogenicity objectives, success criteria were defined for:

- **Humoral responses (ZOSTER-028, ZOSTER -039, and ZOSTER-041)**
  - (i) Vaccine response rate (VRR): The objective was met if the lower limit (LL) of the 95% confidence interval (CI) of the VRR for anti-gE enzyme-linked immunosorbent assay (ELISA) antibody (Ab) concentrations at Month 2 in the HZ/su vaccine group was at least 60%.
  - (ii) Geometric mean (GM) ratio: The objective was met if the LL of the 95% CI of the GM ratio (HZ/su over placebo) for anti-gE ELISA antibody concentrations at Month 2 was greater than 3.
- **Cellular responses (ZOSTER-028 and ZOSTER-041)**
  - (i) VRR: The objective was met if the lower limit of the 95% CI of the VRR for gE-specific CD4+ T-cell frequencies at Month 2 in the HZ/su vaccine group is at least 50%.
  - (ii) GM ratio (ZOSTER-028 for PreChemo group): The objective was met if the LL of the 95% CI of the GM ratio (HZ/su over placebo) in gE-specific CD4+ T-cell frequencies at Month 2 is greater than 1.

Results expression

- **Humoral immunogenicity**

Depending on the assays performed in each study, results were expressed in term of:

- Seropositivity rate with exact 95% CI, i.e., percentage of subjects with Ab concentration ≥assay cut-off value.
- GMC with 95% CI.
- VRR with exact 95% CI, i.e., percentage of subjects who had at least a 4-fold increase in the post Dose 2 anti-gE Ab concentration as compared to pre-vaccination anti-gE Ab concentration for subjects who were seropositive at baseline, or a 4-fold increase in the post Dose 2 anti-gE Ab concentration as compared to the anti-gE Ab cut-off value for seropositivity for subjects who were seronegative at baseline.
- Descriptive statistics of the fold increase over pre-vaccination (Mean, standard deviation [SD], Min, Q1, Median, Q3, Max).

- **Cellular immunogenicity**

Depending on the assays performed in each study, results were expressed in term of:

- VRR with exact 95% CI, i.e., a ≥2-fold increase in the frequency of CD4[2+] T-cells as compared to pre-vaccination frequencies (for subjects with pre-vaccination CD4[2+] T-cell ≥320 per 10^6 CD4 T-cells), or ≥2-fold increase as compared to the threshold of 320 per 10^6 CD4 T-cells (for subjects with pre-vaccination frequencies below the threshold).
- Descriptive statistics of the frequency of CD4[2+] T-cells (Mean, SD, Min, Q1, Median, Q3, Max).
- Descriptive statistics of the fold increase over pre-vaccination of gE-specific CD4[2+] T-cells (Mean, SD, Min, Q1, Median, Q3, Max).

Immunogenicity analysis (pivotal trials)

For all pivotal studies, the primary immunogenicity analysis was based on the according to protocol (ATP) cohort for humoral immunogenicity or CMI, as appropriate and the primary persistence analysis was based on the ATP cohort for humoral or CMI persistence, as appropriate.

The concept of **'Adapted ATP cohort for immunogenicity'** was used to denote that for each timepoint, the corresponding ATP cohort for immunogenicity/ATP cohort for persistence was used.

When the percentage of subjects excluded from either of these ATP cohorts (for Humoral Immunogenicity and for CMI) was greater than 5% in any treatment group, a second analysis based on the total vaccinated cohort (TVC) was performed to complement the ATP analysis.

In ZOSTER-028 and ZOSTER-039 studies, a first analysis of immunogenicity was performed on available data up to and including Month 2 (active phase), while the End of Study (EoS) analysis was performed when all study data up to and including Month 13 were available. Unless specified, results obtained during the active phase were similar to those obtained at the end of study.

Inferential analysis

Humoral immunogenicity

To evaluate anti-gE humoral immune responses at Month 2 following a 2-dose administration of HZ/su as compared to Placebo, a repeated measures model was used to assess the geometric mean concentration (GMC) fold increase over Placebo at Month 2.

For ZOSTER-028, ZOSTER-039 and ZOSTER-041, the model was used to assess the confirmatory objectives in terms of anti-gE humoral immune responses. The fixed-effect model included the visit by treatment interaction. Additionally, the model also included the first vaccination schedule (OnChemo/PreChemo) to assess the secondary confirmatory objective in ZOSTER-028 (in all subjects), and it included the underlying disease ("CLL" and "MM and other diseases") to assess the secondary confirmatory objective in ZOSTER-039 (in subjects with hematologic malignancies excluding subjects with NHBCL).

In ZOSTER-002, the analysis was an exploratory group comparison, and the fixed-effect model included treatment, and adjusted for age strata and underlying diseases ("MM" and "Other diagnoses, including NHBCL, Hodgkin Lymphoma, NHTCL, AML, solid organ malignancies, etc.").

A likelihood-based approach was used to analyze post-vaccination log-transformed anti-gE Ab concentrations (Month 1 to Month 2). The pre-vaccination log-transformed Ab concentration (Month 0) was included as a continuous covariate. Adjusted means and difference of means between HZ/su and Placebo were calculated together with 2-sided CIs and back-transformed to the original units to provide GMCs and GMC ratios over Placebo.

Cell-mediated immunogenicity

The evaluation of the CMI responses at Month 2 following a 2-dose administration of HZ/su as compared to Placebo was performed in terms of **gE-specific CD4[2+] T-cells**, defined as CD4 T-cells producing ≥2 activation markers from among IFN-γ, IL-2, TNF-α, and CD40L.

Geometric Means (GMs) for gE-specific CD4[2+] T-cells were calculated. These estimates better represent the net effect of the vaccines over the frequency of CD4[2+] T-cells as caused by the vaccine. The same model as described above was used to analyse the log-transformed ratio between induction frequency and background frequency of CD4[2+] T-cells. Least-squares means and difference of least-squares means were then back-transformed and used to provide estimates for the frequency difference divided by background ([induction-background] / background). The log-transformed ratios of these estimates between treatments were calculated together with CIs according to the Delta method (error propagation method). The CIs were calculated on the log scale and then back-transformed to the original units.

Descriptive analysis

The descriptive analyses performed to assess humoral immune responses and CMI responses in the pivotal studies were performed for the entire study population and by age stratum (18-49 YOA and ≥50 YOA). In addition, the following subgroup analyses were performed: by underlying disease (ZOSTER-002 and ZOSTER-039), by detailed underlying disease (ZOSTER-002), by duration between the first dose and the start of chemotherapy cycle (PreChemo/OnChemo, only humoral immunogenicity in ZOSTER-028), by timing of vaccination in relation to cancer therapy cycle (ZOSTER-039), and by type of immunosuppressive (IS) therapy (only humoral immunogenicity in ZOSTER-041).

Assays used to evaluate immunogenicity

All Phase I, II and III clinical studies with HZ/su evaluated vaccine-induced humoral immune responses measured by the ELISA, and CMI responses measured by Intracellular Cytokine Staining (ICS) (Table 7). All assays were validated for their used in the pivotal trials.

Table 7. Immunogenicity assays used in IC studies

Antigen	Assay type	Marker	Assay Method	Assay Unit	Assay Cut-off	Studies and time points
gE	Ab	Anti-gE antibodies	ELISA	mIU/mL	97	ZOSTER-002, Humoral Immunogenicity sub-cohort (Months 0, 1, 2, 13, 25a) ZOSTER-028, all subjects (Months 0, 1, 2, 6b, 13) ZOSTER-039, all subjects (Months 0, 1, 2, 13) ZOSTER-041, all subjects (Months 0, 1, 2, 7, 13)
					18	ZOSTER-015 (Months 0, 1, 2, 3, 6, 7, 18)
gE	ICS	CMI markers (IFN-γ, IL-2, TNF-α and CD40L)c	ICS	Frequency of gEspecific T-cells/ 106 T-cells	NA	ZOSTER-002, CMI sub-cohort (Months 0, 1, 2, 13, 25a) ZOSTER-028, CMI sub-cohort (Months 0, 1, 2, 13) ZOSTER-039, CMI sub-cohort (Months 0, 1, 2, 13) ZOSTER-041, CMI sub-cohort (Months 0, 2, 13) ZOSTER-015 (Months 0, 1, 2, 3, 6, 7, 18)

a If conditions for study end were met, the visit at Month 25 did not take place.

b The timing of this blood sampling was variable, depending on the subject's chemotherapy schedule and also on when vaccination was started in relation to their chemotherapeutic regimen. Blood sampling was to occur within Months 4 to 13, i.e., at the start of the last cycle of chemotherapy (if at least 2 months after the previous blood sampling at Month 2).
c CD4+ T-cells expressing at least 2 activation markers from among IFN-γ, IL-2, TNF- α and CD40L.

Serological Assay: Anti-gE ELISA

Principle

Anti-gE Ab concentrations were measured using an anti-gE ELISA, which allowed quantitative measurement of the humoral immune response induced by HZ/su. Serially diluted blood serum samples of subjects were added to microtiter wells pre-coated with VZV gE recombinant antigen. Secondary peroxidase-conjugated anti-human Abs were added, which bound to the primary human anti-gE Abs. After incubation of the microtiter wells with a chromogen substrate solution, the enzymatic reaction was stopped. Optical densities were recorded and anti-gE Ab concentrations were calculated from a standard curve. In February 2014, the assay cut-off was changed following additional validation experiments from 18 mIU/mL (used in ZOSTER-015) to 97 mIU/mL (used in the Phase II/III studies). The assay was performed on human serum at GSK's laboratory or another laboratory designated by GSK.

Validation

The validation documents of the assay used to measure anti-gE Ab in samples from the supportive and the pivotal studies were already submitted at the MAA, with the exception of the document VZVgEGSKMVR05 that was not found (both in the MAA documentation and in the documentation of the current submission). Description of the validation of the assay used for studies ZOSTER-001 and ZOSTER-015 are described in VZVgEGSKPCV02 and VZVgEGSKMVR03 whereas reports VZVgEGSKMVR04 and VZVgEGSKMVR05 described the updated validation results of the assay used for the pivotal studies.

Assay to evaluate CMI: gE ICS

Principle

Measurements of CMI responses were performed on thawed peripheral blood mononuclear cells (PBMCs) by intracellular cytokine staining (ICS) by a laboratory designated by GSK.

The gE ICS assay measures the frequency of gE-specific CD4+ T-cells in vitro. This assay provided information on the CD4+ T-cell concentration responding to culture medium or antigens (pool of overlapping peptides covering the entire sequence of the vaccine antigen gE) by producing activation markers involved in immunity such as IFN-γ, IL-2, TNF-α, and CD40L.

PBMCs isolated from whole blood samples of subjects were stimulated for 2 hours using culture medium (for evaluation of the nonspecific response), or with a pool of overlapping peptides covering the entire sequence of the vaccine antigen gE. Then, an intracellular block (brefeldin A) was added to inhibit activation marker secretion for a subsequent overnight incubation. Cells were then harvested, stained for surface markers (CD3, CD4 and CD8) and fixed. The fixed cells were then permeabilized and stained with antiactivation marker Abs, washed and analyzed by cytofluorometry to detect IFN-γ, IL-2, TNF-α or CD40L. Results are expressed in frequency of antigen-specific polypositive CD4+ T cells / 10^6 CD4+ T cells (where polypositive means a cell expressing at least two out of the four evaluated activation markers, CD4[2+]) after background subtraction.

Validation

The qualified assay method used in studies ZOSTER-001 and ZOSTER-015 was further validated for its used in the 4 pivotal studies.

Since the MAA, complement of validation for linearity and precision in the low range of response were performed, as recommended by CBER.

Precision experiments were performed on CMV clinical study or healthy donor samples (n=19) stimulated by a CMV gB pool of peptides. The choice of this antigen was guided by samples availability. CV ≤ 40% was used as validity criterion. Based on the results (n=342), the lower limit of precision (LLOP) was set at a frequency of 354 polypositive CD4+ T cells / 10^6 CD4+ T cells.

To evaluate the linearity focusing in the low gE-specific responses, stimulated PBMC of 3 samples (from study ZOSTER -003) were diluted in autologous non-stimulated PBMC using seven fractional dilutions, resulting in samples with target responses around 2000 (undiluted), 1000, 800, 600, 500, 400, 300, and 200 polypositive CD4+ T cells / 10^6 CD4+ T cells. Linearity was assumed if the 95% CI of the predicted DLi (deviation from linearity) was within the acceptance limits [0.50-2.00]. The observed DLis were obtained by dividing the corrected frequencies by the geometric mean of the frequencies observed for the non-diluted samples. Based on these three samples of low-specific gE responses, the lower limit of linearity (LLOL) was set at a frequency of 159 polypositive CD4+ T cells / 10^6 CD4+ T cells.

The lower limit of quantification (LLOQ) was therefore set at 354 polypositive CD4+ T cells / 10^6 CD4+ T cells for the ICS assay.

Based on the duplicates of the background values from the samples used for the precision evaluation, a cut-off of the assay has been set at 183 (percentile 95 of the distribution of delta background values).

Given that LLOL is below the cut-off, the assay is considered linear over the whole range from the cut-off up to the highest response evaluated.

The analytical range is determined from 183 (cut-off value) to 100000 (based on the literature) specific CD4+ T cells / 10^6 CD4+ T cells.

To ensure that issues occurring during the PBMCs preparation process do not interfere with assay results, a quality criterion has been set on PBMC viability upon thawing, which should be above 80%.

Standard operating procedures

SOP underwent various changes between the ICS of supportive study samples (SOP CLABSOP 046) and of pivotal study samples (SOP CLABSOP064 v4). Major changes are :

- Flow cytometer: FACSCANTO replaced by LSRII
- Fully adapted to 8 colors : add of a Live & dead marker and anti-human CD3 Ab (AF-700, clone UCHT1)
- Anti-human CD8 APC-Cy7 moAb replaced by anti-human CD8 APC-H7 moAb both being clone SK1
- Add of control on each run, on each plate.
- Details on live & dead marker preparation.

Dose response studies

The dose used was identical than the one used for immunocompetent subjects. Data supporting this choice was already submitted at initial MA (studies ZOSTER-001 and ZOSTER-015) and are briefly described under the section *Supporting studies*.

A flexible 2-dose schedule, with the second dose being administered 1 to 2 months after the first, was selected based on the results of study ZOSTER-001 (see section *Supportive studies*).

Main studies

ZOSTER -002

Study design and population are described in detail in Section 2.4.1 Clinical Efficacy.

Both humoral and cellular immune responses to the study vaccine were evaluated in a sub-cohort of subjects before vaccination (Month 0, Visit 1), one to two months post-dose 1 (Month 1, Visit 2), one month post-dose 2 (Month 2, Visit 3), and approximately 12 (Month 13, Visit 4) and 24 (Month 25, Visit 5) months post-dose 2. There was always a flexibility on the time intervals between visits, i.e. 30-60 days Visit 1 -> Visit 2, 30-48 days Visit 2 -> Visit 3, 335-425 days Visit 2 -> Visit 4, and 670-790 days Visit 2 -> Visit 5. The CMI sub-cohort was a subgroup of the Humoral Immunogenicity sub-cohort.

Anti-gE Ab concentrations were also determined at Month 0 and at Month 2, in all subjects with confirmed HZ and compared with matched controls for CoP assessment. Other assays may also be performed for this analysis, if deemed appropriate. Details regarding the CoP assessment and results are planned to be presented in a future report.

The primary analysis was based on the ATP cohort for analysis of humoral or CMI immunogenicity. Further analysis were conducted by age strata (18-49 YOA, ≥50 YOA) and by underlying diseases.

Results

1. Immunogenicity study population

There were 82 (out of 101, TVC for humoral immunogenicity) of the HZ/su group and 76 (out of 100, TVC for humoral immunogenicity) subjects of the Placebo group included in the ATP cohort for Humoral immunogenicity.
The ATP cohort for Humoral persistence at Month 13 included 54 subjects in the HZ/su and 47 subjects in the Placebo group, and, at Month 25, 39 subjects in the HZ/su and 30 subjects in the Placebo group.

There were 59 (out of 71, TVC for CMI immunogenicity) of the HZ/su group and 55 (out of 70, TVC for CMI immunogenicity) subjects of the Placebo group included in the ATP cohort for CMI.
The ATP cohort for CMI persistence at Month 13 included 42 subjects in the HZ/su and 35 subjects in the Placebo group, and, at Month 25, 35 subjects in the HZ/su and 23 subjects in the Placebo group.

The main reasons for exclusion were occurrence of a confirmed HZ episode or out of the blood sampling interval allowed for inclusion.

Table 8 summarizes the demographic characteristics for ATP cohort for humoral immunogenicity, which are overall representative of those of the TVC, of the CMI immunogenicity, and of those when stratified by age strata or by underlying diseases (multiple myeloma (MM) and other diagnoses). The mean age was 54.2 years and 56.5 years for the HZ/su and Placebo groups, and more male than female subjects were included in both groups. Percentages of subjects with geographical ancestry appeared to be overall similar in the HZ/su and Placebo groups.

Table 8. Summary of demographic characteristics (ATP cohort for humoral immunogenicity)

		HZ/su N = 82		Placebo N = 76		Total N = 158	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	54.2	-	56.5	-	55.3	-
	SD	11.8	-	9.9	-	11.0	-
	Median	57.0	-	59.0	-	58.0	-
	Minimun	18	-	30	-	18	-
	Maximun	70	-	74	-	74	-
Gender	Female	29	35.4	29	38.2	58	36.7
	Male	53	64.6	47	61.8	100	63.3
Ethnicity	American hispanic or latino	1	1.2	4	5.3	5	3.2
	Not american hispanic or latino	81	98.8	72	94.7	153	96.2

Geographic Ancestry	African Heritage / African American	3	3.7	1	1.3	4	2.5
	American Indian or Alaskan Native	0	0.0	0	0.0	0	00.0
	Asian - Central/South Asian Heritage	1	1.2	0	0.0	1	0.6
	Asian - East Asian Heritage	8	9.8	10	13.2	18	11.4
	Asian - Japanese Heritage	6	7.3	6	7.9	12	7.6
	Asian - South East Asian Heritage	2	2.4	0	0.0	2	1.3
	Native Hawaiian or Other Pacific Islande	0	0.0	0	0.0	0	00.0
	White - Arabic / North African Heritage	1	1.2	2	2.6	3	1.9
	White - Caucasian / European Heritage	59	72.0	56	73.7	115	72.8
	Other	2	2.4	1	1.3	3	1.9

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation

The median duration in days post-transplant to first was 61.0 for both HZ/su and placebo subjects (mTVC). The distribution of subjects receiving/not receiving IS treatment (classified by IS ingredient subclass) at least on day prior to HSCT up to blood sample 1 month post-dose 2 was similar between both groups (mTVC). The following ingredient subclasses of IS treatment were most frequently administered (by >20% of subjects in the HZ/su group): nitrogen and mustard analogues (96.3%), topoisomerase inhibitors (38.4%), pyrimidine analogues (33.1%) and nitrosoureas (32.0%). Post-transplant antineoplastic therapy with bortezomib was included as a separate minimization category because of the well-documented increased risk of HZ in persons treated with bortezomib.

2. Anti-gE specific humoral immune response

Overall, in autologous HCT recipients ≥18 YOA a strong anti-gE Ab response was elicited following a two dose-schedule of HZ/su (Month 2). From all timepoints evaluated, the highest immune responses were observed one month post-dose 2. The anti-gE Ab responses decreased one year post-dose 2 (Month 13) but persisted above pre-vaccination levels for up to two years post-dose 2 (Month 25) (Table 9).

Table 9. SPR and GMCs of anti-gE Ab ELISA at Months 0, 1, 2, 13 and 25 (adapted ATP cohort for humoral immunogenicity)

				≥ 97 mIU/mL				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-VZV gE antibody	HZ/su	PRE	82	78	95.1	88.0	98.7	762.8	568.6	1023.5	<97.0	23386.1
		PI(M1)	78	75	96.2	89.2	99.2	1844.2	1282.2	2652.4	<97.0	143121.1
		PII(M2)	82	82	100	95.6	100	12753.2	7973.0	20399.4	261.6	532820.0
		PII(M13)	54	53	98.1	90.1	100	3183.8	1869.8	5421.2	<97.0	255900.0
		PII(M25)	39	37	94.9	82.7	99.4	2819.0	1387.1	5729.1	<97.0	132826.2
	Placebo	PRE	76	68	89.5	80.3	95.3	555.0	404.3	761.8	<97.0	22841.7
		PI(M1)	71	63	88.7	79.0	95.0	556.6	407.3	760.6	<97.0	20846.7
		PII(M2)	76	66	86.8	77.1	93.5	443.8	330.8	595.4	<97.0	15941.1
		PII(M13)	45	36	80.0	65.4	90.4	503.6	307.8	824.1	<97.0	18960.8
		PII(M25)	28	23	82.1	63.1	93.9	527.0	274.3	1012.6	<97.0	22857.1

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13); PII(M25) = Post-vaccination Dose II (Month 25)

In the HZ/su group, the MGI over pre-vaccination was 2.49 (95% CI: 1.78 – 3.49), 16.72 (95% CI: 10.01 – 27.92), 4.51 (95% CI: 2.58 – 7.89) and 4.35 (95% CI: 1.89 – 9.99) at Months 1, 2, 13 and 25,

respectively. In the Placebo group, the MGI over pre-vaccination was not higher than 0.93 at any timepoint.

The highest VRR for anti-gE Ab concentrations was also observed one month post-dose 2 (67.1%, 95% CI 55.8-77.1). VRRs for anti-gE Ab concentrations at Months 13 (40.4%, 95% CI 27.0-54.9) and 25 (44.7%, 95% CI 28.6-61.7) were comparable. In the placebo group, it was not higher than 14.8% at any timepoint.

Adjusted GMs of anti-gE Ab concentrations at one month post-dose 2 were 11227.7 (95% CI:6769.6-18621.7) and 520.7 (95% CI:470.0-577.0) for HZ/su and placebo groups respectively, and the ratio for HZ/su group over Placebo group was 21.56 (95% CI: 12.91 – 36.01).

The results obtained for the 18-49 YOA and ≥50 YOA strata consistently showed high anti-gE immune responses in the HZ/su group that remained above pre-vaccination levels up to two years post-dose 2 (Table 10). The highest VRR for anti-gE Ab concentrations was also observed one month post-dose 2 for both groups (18-49 YOA: 57.7%, 95%CI 36.9-76.6 and ≥50 YOA: 71.4%, 95%CI 57.8-82.7). VRRs for anti-gE Ab concentrations at Months 13 and 25 were quite comparable. In the placebo group, it was not higher than 22.2 and 11.1% at any timepoint in the 18-49 YOA and ≥50 YOA strata, respectively.

Table 10. SPR and GMCs of anti-gE Ab ELISA at Months 0, 1, 2, 13 and 25 by age strata (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-VZVgE antibody	18-49 YOA	HZ/su	PRE	26	26	100	86.8	100	1011.0	629.7	1623.2	112.6	22550.3
			PI(M1)	25	25	100	86.3	100	2117.8	1033.6	4339.4	248.5	143121.1
			PII(M2)	26	26	100	86.8	100	12523.4	4950.7	31679.7	261.6	532820.0
			PII(M13)	19	19	100	82.4	100	3601.6	1361.2	9529.5	141.1	255900.0
			PII(M25)	14	13	92.9	66.1	99.8	1492.5	466.3	4777.1	<97.0	132826.2
		Placebo	PRE	17	14	82.4	56.6	96.2	360.4	190.8	680.9	<97.0	2398.9
			PI(M1)	16	14	87.5	61.7	98.4	398.0	216.7	731.0	<97.0	2678.2
			PII(M2)	17	14	82.4	56.6	96.2	321.2	178.0	579.8	<97.0	1625.2
			PII(M13)	11	8	72.7	39.0	94.0	250.8	104.5	602.0	<97.0	2471.7
			PII(M25)	9	7	77.8	40.0	97.2	351.7	106.9	1156.7	<97.0	4542.1
	≥50 YOA	HZ/su	PRE	56	52	92.9	82.7	98.0	669.3	460.2	973.5	<97.0	23386.1
			PI(M1)	53	50	94.3	84.3	98.8	1727.7	1123.2	2657.3	<97.0	45035.7
			PII(M2)	56	56	100	93.6	100	12861.3	7366.4	22455.0	266.3	422777.3
			PII(M13)	35	34	97.1	85.1	99.9	2977.6	1530.1	5794.6	<97.0	114820.4
			PII(M25)	25	24	96.0	79.6	99.9	4025.0	1597.6	10140.1	<97.0	116643.1
		Placebo	PRE	59	54	91.5	81.3	97.2	628.5	435.1	907.9	<97.0	22841.7
			PI(M1)	55	49	89.1	77.8	95.9	613.6	424.7	886.6	<97.0	20846.7
			PII(M2)	59	52	88.1	77.1	95.1	487.1	345.6	686.6	<97.0	15941.1
			PII(M13)	34	28	82.4	65.5	93.2	631.1	350.0	1137.7	<97.0	18960.8
			PII(M25)	19	16	84.2	60.4	96.6	638.3	274.4	1484.9	<97.0	22857.1

18-49 YOA = 18-49 years old subjects; ⩾50 YOA = ⩾50 years old subjects; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1)
PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13); PII(M25) = Post-vaccination Dose II (Month 25)

The results of the analyses by underlying diseases in autologous HSCT recipients consistently showed high anti-gE immune responses in the HZ/su group that persisted above pre-vaccination levels up to two

years post-dose 2 (Month 25) (Table 11). Underlying diseases were classified as (i) multiple myeloma or (ii) with all other diagnoses including non-Hodgkin B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin T-cell lymphoma, acute myeloid leukemia, solid organ malignancies, etc. Analyses by detailed underlying diseases are presented in Table 12.

Table 11. Seropositivity rates and Geometric Mean Concentrations (GMCs) of anti-gE Ab ELISA at Months 0, 1, 2, 13 and 25 by underlying disease (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-VZVgE antibody	Multiple myeloma	HZ/su	PRE	44	40	90.9	78.3	97.5	545.6	342.9	868.0	<97.0	23386.1
			PI(M1)	44	41	93.2	81.3	98.6	2393.4	1389.8	4121.7	<97.0	143121.1
			PII(M2)	44	44	100	92.0	100	24717.8	13979.1	43705.9	266.3	422777.3
			PII(M13)	29	28	96.6	82.2	99.9	3955.3	1743.9	8971.2	<97.0	137693.5
			PII(M25)	22	20	90.9	70.8	98.9	4369.9	1558.2	12255.2	<97.0	132826.2
		Placebo	PRE	42	35	83.3	68.6	93.0	427.6	267.6	683.1	<97.0	19865.5
			PI(M1)	39	33	84.6	69.5	94.1	406.9	263.1	629.3	<97.0	11422.0
			PII(M2)	42	34	81.0	65.9	91.4	318.6	213.3	475.9	<97.0	8384.4
			PII(M13)	26	18	69.2	48.2	85.7	399.3	187.9	848.3	<97.0	18960.8
			PII(M25)	16	12	75.0	47.6	92.7	507.0	171.5	1498.9	<97.0	22857.1
	Other diagnoses	HZ/su	PRE	38	38	100	90.7	100	1124.6	820.7	1541.0	226.9	22550.3
			PI(M1)	34	34	100	89.7	100	1316.1	836.1	2071.5	164.1	31001.7
			PII(M2)	38	38	100	90.7	100	5927.2	2885.4	12175.6	261.6	532820.0
			PII(M13)	25	25	100	86.3	100	2475.3	1230.6	4978.9	261.9	255900.0
			PII(M25)	17	17	100	80.5	100	1598.6	597.8	4275.2	105.3	116643.1
		Placebo	PRE	34	33	97.1	84.7	99.9	766.0	509.5	1151.5	<97.0	22841.7
			PI(M1)	32	30	93.8	79.2	99.2	815.3	529.0	1256.7	<97.0	20846.7
			PII(M2)	34	32	94.1	80.3	99.3	668.3	443.2	1007.8	<97.0	15941.1
			PII(M13)	19	18	94.7	74.0	99.9	692.0	379.8	1260.8	<97.0	16773.6
			PII(M25)	12	11	91.7	61.5	99.8	554.9	267.8	1149.9	<97.0	4542.1

Multiple myeloma = Subjects with an underlying diagnosis of multiple myeloma;Other diagnoses = Subjects with all other diagnoses (including non-Hodgkin B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin T cell lymphoma, acute myeloid leukemia [AML], solid organ malignancies, etc.); HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13); PII(M25) = Post-vaccination Dose II (Month 25)

Table 12. SPR and GMCs of anti-gE Ab ELISA at Months 0 and 2 by detailed underlying disease (mTVC)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-VZV gE antibody	MM	HZ/su	PRE	468	420	89.7	86.6	92.3	470.6	415.6	532.8	<97.0	320553.4
			PII(M2)	444	443	99.8	98.8	100	32549.3	27585.8	38405.7	<97.0	724073.4
		Placebo	PRE	459	415	90.4	87.3	92.9	461.9	410.9	519.3	<97.0	137146.7
			PII(M2)	440	373	84.8	81.1	88.0	361.7	318.4	410.8	<97.0	91401.5
	NHBCL	HZ/su	PRE	235	231	98.3	95.7	99.5	822.7	728.2	929.4	<97.0	30382.3
			PII(M2)	227	224	98.7	96.2	99.7	1378.4	1124.4	1689.8	<97.0	785870.9
		Placebo	PRE	242	238	98.3	95.8	99.5	843.4	748.8	950.0	<97.0	22841.7
			PII(M2)	226	216	95.6	92.0	97.9	761.2	663.8	872.8	<97.0	15941.1
	NHTCL	HZ/su	PRE	42	42	100	91.6	100	1221.7	853.2	1749.2	189.4	35974.1
			PII(M2)	40	40	100	91.2	100	11052.4	6179.4	19768.5	261.6	532820.0
		Placebo	PRE	39	37	94.9	82.7	99.4	827.9	591.0	1159.7	<97.0	4467.9
			PII(M2)	36	34	94.4	81.3	99.3	711.5	478.1	1059.1	<97.0	8890.7
	HL	HZ/su	PRE	74	72	97.3	90.6	99.7	1114.9	829.0	1499.5	<97.0	29730.5
			PII(M2)	68	67	98.5	92.1	100	22744.4	13849.0	37353.5	<97.0	646179.3
		Placebo	PRE	60	56	93.3	83.8	98.2	882.7	635.1	1226.9	<97.0	76630.7
			PII(M2)	59	55	93.2	83.5	98.1	829.3	589.8	1166.1	<97.0	108316.1
	AML	HZ/su	PRE	20	20	100	83.2	100	759.2	519.7	1109.1	241.1	3627.0
			PII(M2)	20	20	100	83.2	100	19597.6	9458.0	40607.5	1125.2	197660.5
		Placebo	PRE	16	16	100	79.4	100	1082.0	676.0	1732.0	170.1	5000.6
			PII(M2)	16	16	100	79.4	100	759.1	451.0	1277.5	132.1	5946.6
	Others	HZ/su	PRE	24	23	95.8	78.9	99.9	735.6	480.5	1126.1	<97.0	3566.4
			PII(M2)	23	23	100	85.2	100	21120.6	8305.6	53708.3	380.5	258669.5
		Placebo	PRE	25	25	100	86.3	100	1047.5	686.7	1597.9	190.4	6666.3
			PII(M2)	25	25	100	86.3	100	808.5	529.4	1234.7	114.0	4764.1

MM = Subjects with an underlying diagnosis of Multiple Myeloma; NHBCL = Subjects with an underlying diagnosis of Non-Hodgkin B-Cell Lymphoma; NHTCL = Subjects with an underlying diagnosis of Non-Hodgkin T-Cell Lymphoma; HL = Subjects with an underlying diagnosis of Hodgkin Lymphoma; AML = Subjects with an underlying diagnosis of Acute Myeloid Leukemia
Others = Subjects with all others diseases; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PII(M2) = Post-vaccination Dose II (Month 2)

The results of the TVC analyses, overall, were consistent with the results of the ATP analyses.

3. gE-specific CMI

Overall, in autologous HSCT recipients ≥18 YOA, gE-specific CMI responses were observed following two doses of HZ/su at one month post-dose 2 (Month 2). The highest immune responses were observed at one month post-dose 2; the observed gE-specific CMI responses were lower one year post-dose 2 (Month 13) but persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25). In the Placebo group, at all timepoints the observed median frequency of gE-specific CD4[2+] T-cells remained at pre-vaccination levels (Table 13).

Table 13. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells at Months 0, 1, 2, 13 and 25 (Adapted ATP cohort for cell-mediated immunogenicity)

Immune marker	Group	Timing	N	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	HZ/su	PI(M1)	41	365.97	765.79	0.0	3.7	8.2	355.9	3486.5
		PII(M2)	42	3087.26	6132.69	0.0	34.4	109.0	2716.4	24677.3
		PII(M13)	27	911.28	1936.68	0.0	13.1	43.6	977.8	7502.6
		PII(M25)	24	498.80	911.65	0.3	15.3	50.9	515.2	3126.4
	Placebo	PI(M1)	43	30.03	59.51	0.0	0.0	1.0	7.9	213.1
		PII(M2)	41	27.10	61.42	0.0	0.3	1.0	10.2	316.0
		PII(M13)	26	68.66	152.85	0.0	0.6	1.2	80.9	722.0
		PII(M25)	16	42.23	83.59	0.0	1.0	2.1	33.1	257.7

HZ/su = Herpes Zoster sub-unit vaccine group;Placebo = Placebo group; N = number of subjects with available results
SD = Standard Deviation; Q1,Q3 = First and third quartiles; Min/Max = Minimum/Maximum; PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13); PII(M25) = Post-vaccination Dose II (Month 25)

In the HZ/su group, the observed median (min - max) fold increase over pre-vaccination in the frequency of gE-specific CD4[2+] T-cells was 8.2 (0.0 – 3486.5), 109.0 (0.0 – 24677.3), 43.6 (0.0 – 7502.6) and 50.9 (0.3 – 3126.4) at Months 1, 2, 13 and 25.

In the HZ/su group, the VRR in the frequency of gE-specific CD4[2+] T-cells was 46.3% (95% CI: 30.7% - 62.6%), 92.9% (95% CI: 80.5% - 98.5%), 70.4% (95% CI: 49.8% - 86.2%) and 70.8% (95% CI: 48.9% - 87.4%) at Months 1, 2, 13 and 25. In the Placebo group, the VRR in the frequency of gE-specific CD4[2+] T-cells (point estimate) was not higher than 12.5% at any timepoint.

The results obtained in the 18-49 YOA and ≥50 YOA strata consistently showed in the HZ/su group gE-specific CMI responses above pre-vaccination levels at one month post-dose 2 (Month 2) that persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25) (Table 14).

Table 14. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells at Months 0, 1, 2, 13 and 25 by age strata (Adapted ATP cohort for cell-mediated immunogenicity)

Immune marker	Sub-group	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	18-49 YOA	HZ/su	PRE	16	4	149.82	207.50	1.0	9.7	77.9	213.9	816.3
			PI(M1)	15	5	2158.44	2752.61	129.5	483.2	1411.4	2180.0	10825.0
			PII(M2)	16	4	12754.89	9138.65	1.0	3591.1	12365.5	21624.6	26004.7
			PII(M13)	13	3	5500.69	4449.49	136.8	2133.7	4872.2	6709.3	13292.0
			PII(M25)	10	2	4979.02	4864.53	86.0	1969.9	3466.0	5087.5	16573.2
		Placebo	PRE	10	4	105.50	104.92	1.0	1.0	110.0	132.6	356.1
			PI(M1)	12	2	67.14	100.28	1.0	1.0	1.2	103.2	288.6
			PII(M2)	12	2	125.15	171.43	1.0	1.0	48.3	187.6	556.9
			PII(M13)	6	4	91.34	119.51	1.0	1.0	57.4	127.5	303.7
			PII(M25)	6	3	293.25	381.59	1.0	91.4	186.6	243.2	1050.8
	≥50 YOA	HZ/su	PRE	31	8	184.75	451.92	1.0	1.0	34.0	185.2	2469.7
			PI(M1)	34	5	1037.42	2421.66	1.0	127.8	382.3	1085.3	14121.1
			PII(M2)	35	4	10498.13	17757.65	1.0	1017.1	3294.2	11135.7	73143.3
			PII(M13)	19	7	2345.60	4051.31	1.0	453.8	1152.5	2463.4	17462.0
			PII(M25)	20	3	4218.91	7248.00	52.0	281.4	1519.6	3155.0	26020.4
		Placebo	PRE	37	4	107.15	164.75	1.0	1.0	43.8	193.5	874.9
			PI(M1)	38	3	98.42	141.34	1.0	1.0	31.6	155.2	597.0
			PII(M2)	36	5	108.64	120.50	1.0	1.0	84.8	171.0	408.7
			PII(M13)	23	2	147.57	204.90	1.0	1.0	80.9	173.2	722.0
			PII(M25)	12	2	141.01	194.78	1.0	1.0	65.3	244.0	642.5

18-49 YOA = 18-49 years old subjects; ⩾50 YOA = ⩾50 years old subjects; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects with available results; Nmiss = number of subjects with missing results SD = Standard Deviation; Q1,Q3 = First and third quartiles; Min/Max = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13) PII(M25) = Post-vaccination Dose II (Month 25)

The results obtained in autologous HSCT recipients ≥18 YOA by underlying diseases consistently showed in the HZ/su group gE-specific CMI responses above pre-vaccination levels at one month post-dose 2 (Month 2) that persisted up to two years post-dose 2 (Month 25) (Table 15).

Table 15. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells at Months 0, 1, 2, 13 and 25 by underlying diseases stratum (Adapted ATP cohort for cell-mediated immunogenicity)

Immune marker	Sub-group	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	Multiple myeloma	HZ/su	PRE	26	7	198.75	482.07	1.0	1.0	57.0	207.4	2469.7
			PI(M1)	28	5	1300.35	2673.38	1.0	92.0	470.4	1598.8	14121.1
			PII(M2)	29	4	11590.51	19400.56	1.0	1017.1	4110.1	9575.4	73143.3
			PII(M13)	16	8	2503.82	4270.49	1.0	476.4	1209.2	2788.5	17462.0
			PII(M25)	16	4	5151.11	7882.71	94.4	579.5	1691.0	3862.9	26020.4
		Placebo	PRE	28	4	109.11	115.29	1.0	1.0	81.7	195.1	356.1
			PI(M1)	28	4	102.71	131.50	1.0	1.0	44.8	166.0	439.4
			PII(M2)	27	5	144.07	139.95	1.0	15.0	118.3	195.7	556.9
			PII(M13)	15	6	148.64	196.76	1.0	1.0	80.9	229.3	682.1
			PII(M25)	10	3	171.58	200.84	1.0	1.0	111.8	243.2	642.5
	Other diagnoses	HZ/su	PRE	21	5	140.80	216.43	1.0	1.0	30.6	185.2	816.3
			PI(M1)	21	5	1487.57	2442.26	129.5	355.9	578.7	1411.4	10825.0
			PII(M2)	22	4	10699.46	8398.95	1.0	3017.3	9448.7	19334.4	26004.7
			PII(M13)	16	2	4750.89	4441.45	136.8	1172.9	3391.5	7106.0	13292.0
			PII(M25)	14	1	3696.47	4532.83	52.0	455.2	2965.2	3633.2	16573.2
		Placebo	PRE	19	4	103.38	199.59	1.0	1.0	39.0	116.2	874.9
			PI(M1)	22	1	75.90	135.03	1.0	1.0	16.0	87.2	597.0
			PII(M2)	21	2	72.53	114.94	1.0	1.0	8.3	94.8	371.3
			PII(M13)	14	0	122.32	188.73	1.0	1.0	75.4	127.5	722.0
			PII(M25)	8	2	216.98	351.71	1.0	1.0	97.0	244.0	1050.8

Multiple myeloma = Subjects with an underlying diagnosis of multiple myeloma; Other diagnoses = Subjects with all other diagnoses (including non-Hodgkin B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin T cell lymphoma, acute myeloid leukemia [AML], solid organ malignancies, etc.); HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects with available results; Nmiss = number of subjects with missing results; SD = Standard Deviation; Q1,Q3 = First and third quartiles Min/Max = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13); PII(M25) = Post-vaccination Dose II (Month 25)

The results of the TVC analyses, overall, were consistent with the results of the ATP analyses.

ZOSTER-028

Study design and population.

The focus of the ZOSTER-028 was to examine the immunological response to HZ/su, when subjects were immunocompromised through the use of chemotherapy. Enrolled subjects were adults who had been diagnosed with one or more solid tumours (defined as a solid malignancy, i.e., not a blood element malignancy) and would receive or were receiving a cytotoxic or IS chemotherapy (such that

investigational product could be administered no later than the start of the second cycle of chemotherapy). Subjects receiving only newer, more targeted therapies without a classical IC chemotherapy were not to be included. In addition, a chemotherapy course <28 days before first vaccination and chronic/planned administration of systemic glucocorticoids between 1 month prior to and 2 months post first vaccination were not allowed. The first vaccine dose was to be administered at least 8 days (up to 1 month) before the administration of a chemotherapy cycle (PreChemo group) or at the start of a chemotherapy cycle (OnChemo group).

Both humoral and cellular immune responses to the study vaccine were evaluated in subjects before vaccination (Month 0, Visit 1), one to two months post-dose 1 (Month 1, Visit 2, at the second dose administration and at the first day of a subsequent cycle of chemotherapy) and one month post-dose 2 (Month 2, Visit 3), within 4 to 13 months post-dose 1 (Month 6, visit 4, at the start of the last cycle of chemotherapy which coincided with the subject's lowest immune status) and approximately 12 months after the second dose of study vaccine/placebo (Month 13, Visit 5). The timing of this particular Visit 4 was variable depending on the subject's chemotherapy schedule and also on when they started vaccination in relation to their chemotherapeutic regimen. Dependent on the timing of Visit 4, it could coincide with Visit 5. The allowed interval between vaccinations for inclusion in the ATP cohort was defined as 30-84 days (Visit 1->Visit 2). The allowed interval between dose 2 and blood sample at Visit 3 was defined as 21-63 days. The allowed interval between dose 2 and blood sample at Visit 5 was defined as 335-425 days.
Humoral Immunogenicity was performed on all subjects of the PreChemo and OnChemo groups. The CMI sub-cohort comprised exclusively of subjects from the PreChemo Groups. This was a subgroup of the subjects in the study in selected countries at designated sites that had access to a PBMCs processing facility within the acceptable time window from sample collection to PBMC processing. CMI was not evaluated at visit 4.

The primary analysis of humoral and cellular immunogenicity were based on the ATP cohort for immunogenicity/persistence. Further analysis were conducted by PreChemo and OnChemo groups as well as by age strata (18-49 YOA, ≥50 YOA).

The immune ATP cohort analysis was based on the allowed intervals for and Visit 2->Visit 3.

Results

1. Immunogenicity study population

Out of the 117 and 115 subjects included in the TVC in the HZ/su group and Placebo group respectively, 87 (PreChemo, n=65; OnChemo, n=22) and 98 (PreChemo, n=78; OnChemo, n=20) subjects were included in the ATP cohort for Humoral immunogenicity in the HZ/su and Placebo group respectively. Sixty-eight (PreChemo, n=51; OnChemo, n=17) and 70 (PreChemo, n=56; OnChemo, n=14) subjects were included in the ATP cohort for Humoral persistence in the HZ/su and Placebo group respectively. Number of subjects excluded per reason was generally well balanced between groups with the exception of the number of subjects whom did not receive the second vaccine dose, i.e. 17 subjects in the HZ/su group and 5 subjects in the Placebo group. Immunogenicity data at month 2 was lacking for a slightly higher proportion of subjects in the HZ/su group compared to the placebo group.

Only subjects from the PreChemo group were included in the CMI sub-cohort. The TVC for the CMI immunogenicity included 39 and 37 subjects in the HZ/su group and Placebo group respectively. The ATP cohort for CMI immunogenicity included 27 and 31 subjects in the HZ/su and Placebo group respectively. Twenty subjects in the HZ/su group and 20 subjects in the Placebo group were included in the ATP cohort for CMI persistence. Consistently with the humoral immunogenicity cohort, 8 subjects in the HZ/su group,

did not receive the second dose and immunogenicity data at Month 2 were absent for 7 subjects in the HZ/su group and 3 subjects in the Placebo group.
Because of the small sample size of the PreChemo group tested for immunogenicity, results should be interpreted with caution.

The mean age was 55.5 and 57.0 years for the HZ/su and Placebo group respectively. More female than male subjects were included (65.5% and 61.2% female in the HZ/su and Placebo group, respectively). The most frequently reported solid tumor diagnoses in the ATP cohort for humoral immunogenicity were breast cancer (51.4%), colorectal cancer (21.1%), and other types of solid tumors (15.1%). The performance status (ECOG) of most subjects (83.0%) was fully active.

Gender distribution slightly differed for the TVC cohort CMI immunogenicity as well the proportion of several solid tumour organs. This difference in tumours distribution was also observed between PreChemo and OnChemo groups, between 18-49YOA and ≥50YOA groups, and for TVC.

Table 16. Summary of demographic characteristics (ATP cohort for CMI immunogenicity)

		HZ/su N = 27		Placebo N = 31		Total N = 58	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age[years] at vaccination dose:1	Mean	57.0	-	57.3	-	57.2	-
	SD	12.1	-	11.5	-	11.7	-
	Median	56.0	-	56.0	-	56.0	-
	Minimum	41.0	-	36.0	-	36.0	-
	Maximum	85.0	-	78.0	-	85.0	-
	Missing	0	-	0	-	0	-
Gender	Male	12	44.4	14	45.2	26	44.8
	Female	15	55.6	17	54.8	32	55.2
Ethnicity	American Hispanic or Latino	1	4.5	1	3.6	2	4.0
	Not American Hispanic or Latino	21	95.5	27	96.4	48	96.0
	Missing	5	-	3	-	8	-
Geographic Ancestry	African Heritage / African American	1	4.5	1	3.6	2	4.0
	American Indian or Alaskan Native	1	4.5	0	0.0	1	2.0
	White - Caucasian / European Heritage	20	90.9	27	96.4	47	94.0
	Missing	5	-	3	-	8	-
Solid Tumor diagnosis	Breast	10	37.0	15	48.4	25	43.1
	Colorectal	4	14.8	5	16.1	9	15.5
	Lung	2	7.4	4	12.9	6	10.3
	Melanoma	1	3.7	0	0.0	1	1.7
	Prostate	2	7.4	1	3.2	3	5.2
	Other^	8	29.6	6	19.4	14	24.1
Performance Status (ECOG)	Fully active*	21	77.8	22	71.0	43	74.1
	Restricted in physically strenuous activity**	6	22.2	8	25.8	14	24.1
	Ambulatory and capable of all selfcare***	0	0.0	1	3.2	1	1.7

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = Standard deviation; ECOG = Eastern Cooperative Oncology Group; ^Other includes gastric, endometrial, ovarian, head and neck, larynx, mouth, sinus, tonsil, liposarcoma mixoid, liver, oesophadeal, renal, sarcoma, stomach, testicular embryonic carcinoma, thyroid, tongue, cervix, urotelial, uterine leiomyrsarcoma
* = Fully active, able to carry on all pre-disease performance without restriction
** = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
*** = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.

From 30 days prior to Dose 1 up to 1 month post Dose 2 in the ATP cohort for Humoral immunogenicity, the most frequently administered subclasses of IS treatment (by >20% of subjects in the HZ/su group) included nitrogen and mustard analogues (47.1%) and other alkylating agents (40.2%), anthracyclines

(46.0%), platinium compound and pyrimidine analogues (both 39.1%), and antimitotic agents including antimicrotubule agents (26.4%).

2. Anti-gE specific humoral immune response

Confirmatory analyses

The primary and the first secondary confirmatory objectives were related to the PreChemo group and were met; The anti-gE Ab GM ratio (HZ/su PreChemo Group over Placebo PreChemo group) at Month 2 was 23.2 (95% CI: 17.9–30.0, p<0.0001) and the anti-gE Ab VRR (in the HZ/su PreChemo group) at Month 2 was 93.8% (95% CI: 85.0–98.3).

Since the third confirmatory secondary objective was not met (see point 3, gE-specific CMI), according to the hierarchical procedure applied, the following objectives were analysed descriptively.
The anti-gE humoral immune response at Month 2 in the HZ/su group compared to the Placebo group (all subjects), the observed adjusted GM ratio was 14.4 (95% CI: 10.7 – 19.5).
The VRR in anti-gE humoral immune response at Month 2 (post second vaccination) in the HZ/su group (all subjects) was 86.2 % (95% CI: 77.1– 92.7).

Descriptive analyses

Anti-gE humoral immune responses relative to pre-vaccination levels were observed in the HZ/su group at 1 month following the first and second dose and persisted up to 1 year post-dose 2, relative to the pre-vaccination level (**Table 17**).

Table 17. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, 6, and 13 (adapted ATP cohort for humoral immunogenicity)

				≥ 97 mIU/ml				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	HZ/su	PRE	87	86	98.9	93.8	100	1049.8	865.8	1273.0	<97.0	6659.6
		PI(M1)	85	85	100	95.8	100	24793.1	18747.8	32787.6	383.2	218252.5
		PII(M2)	87	87	100	95.8	100	18291.7	14432.1	23183.5	200.3	90761.1
		PII(M6)	42	42	100	91.6	100	7730.4	5358.4	11152.2	154.6	68989.4
		PII(M13)	68	68	100	94.7	100	4477.3	3482.4	5756.3	234.5	29519.1
	Placebo	PRE	94	93	98.9	94.2	100	1116.7	918.4	1358.0	<97.0	22349.0
		PI(M1)	97	96	99.0	94.4	100	1107.2	920.0	1332.6	<97.0	18838.0
		PII(M2)	98	97	99.0	94.4	100	1060.5	873.9	1287.1	<97.0	25756.1
		PII(M6)	43	43	100	91.8	100	1380.2	1066.3	1786.6	236.6	20172.3
		PII(M13)	70	70	100	94.9	100	1064.7	845.9	1340.1	135.8	20722.2

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M6) = Post-vaccination Dose II (Month 6); PII(M13) = Post-vaccination Dose II (Month 13)

VRRs in the HZ/su group at Month 1 and Month 2 were 85.9% (95% CI: 76.6 – 92.5) and 86.2% (95% CI: 77.1 – 92.7) respectively, and at Month 13, 51.5% (95% CI: 39.0 – 63.8). In the Placebo group, there were no subjects meeting the definition of responder at Months 1, 2 and 13.

Anti-gE humoral immune responses were observed in the HZ/su PreChemo and HZ/su OnChemo groups 1 month post first vaccination and 1 month post second vaccination. Persistence of humoral

immunogenicity at 1 year post second vaccination was also observed in HZ/su subjects and appeared to be similar for PreChemo and OnChemo groups despite the different administration schedules of each group (Table 18).

Table 18. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, 6, and 13 by PreChemo/OnChemo groups (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	PreChemo	HZ/su	PRE	65	64	98.5	91.7	100	1032.3	821.0	1298.0	<97.0	6295.3
			PI(M1)	64	64	100	94.4	100	34729.8	27485.9	43882.8	1168.9	218252.5
			PII(M2)	65	65	100	94.5	100	22974.3	19080.0	27663.5	3912.6	90761.1
			PII(M6)	32	32	100	89.1	100	8528.2	6150.1	11825.9	1747.9	68989.4
			PII(M13)	51	51	100	93.0	100	4563.0	3532.8	5893.7	718.0	29519.1
		Placebo	PRE	76	75	98.7	92.9	100	1185.4	959.3	1464.7	<97.0	22349.0
			PI(M1)	77	76	98.7	93.0	100	1157.9	946.3	1416.8	<97.0	18838.0
			PII(M2)	78	77	98.7	93.1	100	1120.9	903.9	1390.0	<97.0	25756.1
			PII(M6)	37	37	100	90.5	100	1325.9	989.6	1776.5	236.6	20172.3
			PII(M13)	56	56	100	93.6	100	1178.9	923.3	1505.1	201.5	20722.2
	OnChemo	HZ/su	PRE	22	22	100	84.6	100	1103.4	753.4	1616.0	204.9	6659.6
			PI(M1)	21	21	100	83.9	100	8876.6	4134.3	19058.6	383.2	99963.8
			PII(M2)	22	22	100	84.6	100	9328.0	4492.5	19368.2	200.3	81438.3
			PII(M6)	10	10	100	69.2	100	5645.4	1531.9	20805.3	154.6	53786.3
			PII(M13)	17	17	100	80.5	100	4229.5	2073.8	8626.0	234.5	23506.4
		Placebo	PRE	18	18	100	81.5	100	868.2	512.9	1469.7	119.4	4064.0
			PI(M1)	20	20	100	83.2	100	932.1	574.8	1511.5	113.4	4808.0
			PII(M2)	20	20	100	83.2	100	854.6	534.1	1367.2	110.4	3693.4
			PII(M6)	6	6	100	54.1	100	1768.2	1016.7	3075.1	1017.1	3719.5
			PII(M13)	14	14	100	76.8	100	708.5	376.9	1331.8	135.8	5216.4

PreChemo = first vaccination 8 days or more prior to the start of a chemotherapy cycle; OnChemo = first vaccination at the start of a chemotherapy cycle (+ or - 1 day); HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M6) = Post-vaccination Dose II (Month 6); PII(M13) = Post-vaccination Dose II (Month 13)

In line with these results, VRRs in the HZ/su PreChemo group at Month 1 and Month 2 were 93.8% (95% CI: 84.8 – 98.3) and 93.8% (95% CI: 85.0 – 98.3) respectively, and at Month 6 and Month 13, 75.0% (95% CI: 56.6 – 88.5) and 52.9% (95% CI: 38.5 – 67.1) respectively. VRRs in the HZ/su OnChemo group at Month 1 and Month 2 were 61.9% (95% CI:38.4 – 81.9) and 63.6% (95% CI: 40.7 – 82.8) respectively, and at Months 6 and Month 13, 70.0% (95% CI: 34.8 – 93.3) and 47.1% (95% CI: 23.0 – 72.2) respectively. In the Placebo PreChemo group, there were no subjects meeting the definition of responder at Months 1, 2 and 13. In the Placebo OnChemo group, there was 1 subject meeting the definition of responder but only at Month 6.

Comparable immune responses for both age strata were observed 1 month post first and 1 month post second vaccination up to 1 year post dose 2 (Table 19).

Table 19. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, 6, and 13 by age strata (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	18-49ys	HZ/su	PRE	27	27	100	87.2	100	992.1	722.8	1361.7	302.9	5936.7
			PI(M1)	27	27	100	87.2	100	24450.8	13910.2	42978.6	495.0	218252.5
			PII(M2)	27	27	100	87.2	100	15710.4	10327.8	23898.5	1003.8	69429.6
			PII(M6)	16	16	100	79.4	100	5591.3	3408.1	9173.0	599.2	38957.3
			PII(M13)	22	22	100	84.6	100	3328.5	2149.4	5154.5	494.5	26634.9
		Placebo	PRE	28	28	100	87.7	100	1067.1	801.4	1420.7	245.9	3801.1
			PI(M1)	28	28	100	87.7	100	1053.2	793.0	1398.8	242.5	4808.0
			PII(M2)	29	29	100	88.1	100	962.8	732.6	1265.2	230.8	3693.4
			PII(M6)	13	13	100	75.3	100	985.0	666.4	1456.0	321.5	2589.8
			PII(M13)	22	22	100	84.6	100	821.3	582.8	1157.3	182.8	2333.5
	≥ 50ys	HZ/su	PRE	60	59	98.3	91.1	100	1076.9	842.0	1377.3	<97.0	6659.6
			PI(M1)	58	58	100	93.8	100	24954.0	17993.7	34606.7	383.2	209816.0
			PII(M2)	60	60	100	94.0	100	19587.7	14604.7	26271.1	200.3	90761.1
			PII(M6)	26	26	100	86.8	100	9435.8	5623.5	15832.5	154.6	68989.4
			PII(M13)	46	46	100	92.3	100	5159.3	3785.6	7031.7	234.5	29519.1
		Placebo	PRE	66	65	98.5	91.8	100	1138.5	882.2	1469.4	<97.0	22349.0
			PI(M1)	69	68	98.6	92.2	100	1129.9	890.9	1433.1	<97.0	18838.0
			PII(M2)	69	68	98.6	92.2	100	1104.5	857.4	1423.0	<97.0	25756.1
			PII(M6)	30	30	100	88.4	100	1597.5	1150.7	2217.9	236.6	20172.3
			PII(M13)	48	48	100	92.6	100	1199.3	890.3	1615.5	135.8	20722.2

18-49ys = Subjects aged between 18 and 49 years; ⩾ 50ys = Subjects aged 50 years and older; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M6) = Post-vaccination Dose II (Month 6); PII(M13) = Post-vaccination Dose II (Month 13)

Regarding the 18-49 YOA stratum, VRRs in the HZ/su group both at Month 1 and Month 2 were 85.2% (95% CI: 66.3 – 95.8) and at Month 6 and Month 13, 68.8% (95% CI: 41.3 – 89.0) and 45.5% (95% CI: 24.4 – 67.8) respectively. Regarding the ≥ 50 YOA stratum, VRRs in the HZ/su group at Month 1 and Month 2 were 86.2% (95% CI: 74.6 – 93.9) and 86.7% (95% CI: 75.4 – 94.1) respectively, and at Month 6 and Month 13, 76.9% (95% CI: 56.4 – 91.0) and 54.3% (95% CI: 39.0 – 69.1) respectively. In the Placebo group for both age strata, there were no subjects meeting the definition of responder, except for 1 subject at Month 6 in the 18-49 YOA stratum.

Anti-gE analysed by age strata in PreChemo groups only were overall comparable.

Results of the analyses performed on the TVC were consistent with results of the analyses performed on the ATP cohort for Humoral immunogenicity and the ATP cohort for Humoral persistence.

3. gE-specific CMI

Confirmatory analyses

In contrast to the humoral results, the active phase results on CMI generated at first analysis and at end of study were not the same, secondary to changes in the lab CMI data release definitions allowing more CMI data release, even so there was no impact on study conclusions.

The second confirmatory secondary objective was related to the PreChemo group and was met; The anti-gE Ab GM ratio (HZ/su PreChemo Group over Placebo PreChemo group) at Month 2 was 13.67 (95% CI: 3.79–49.38, p=0.0002). Descriptive results obtained with the end of study analysis indicates that the observed GM ratio at Month 2 was 9.94 (95% CI: 3.63 – 27.19).

The third confirmatory secondary objective of the study was not met as the lower limit of the 95% CI of the VRR for gE-specific CD4[2+] T-cell frequencies in the HZ/su PreChemo group (at Month 2 (post second vaccination) was 33.5%. Therefore, the success criterion (at least 50%) was not demonstrated. The observed VRR was 57.9% (95% CI: 33.5 – 79.7). Descriptive results obtained with the end of study analysis indicated that the observed VRR at Month 2 was 50.0% (95% CI: 28.2 – 71.8).

Descriptive analyses

gE-specific CMI responses to HZ/su in the PreChemo group were above pre-vaccination levels 1 month after the first vaccination; stronger immune responses were observed 1 month after the second dose. Additionally, the persistence of gE-specific CMI at 1 year post-dose 2 in PreChemo HZ/su subjects was observed (Table 20).

Table 20. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells in PreChemo groups only (adapted ATP cohort for CMI immunogenicity)

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	HZ/su	PRE	25	2	178.47	187.11	1.0	49.7	127.3	192.4	662.4
		PI(M1)	25	2	521.79	656.39	1.0	139.7	391.9	603.7	3276.6
		PII(M2)	22	5	1187.06	1292.07	1.0	393.1	778.8	1098.2	4835.8
		PII(M13)	18	2	523.83	632.83	1.0	114.9	332.9	604.6	2416.0
	Placebo	PRE	27	4	179.31	359.33	1.0	27.5	104.8	151.5	1894.5
		PI(M1)	30	1	119.89	158.66	1.0	1.0	50.0	179.4	567.8
		PII(M2)	29	2	140.25	238.68	1.0	17.4	61.8	139.5	1234.1
		PII(M13)	19	0	125.78	169.65	1.0	1.0	51.2	288.6	497.1

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects with available results; Nmiss = number of subjects with missing results; SD = Standard Deviation; Q1,Q3 = First and third quartiles; Min/Max = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2) PII(M13) = Post-vaccination Dose II (Month 13)

The PreChemo 18-49YOA subgroups included 9 subjects which is too small for results interpretation.

Results of the analyses performed on the TVC were consistent with results of the analyses performed on the ATP cohort for CMI immunogenicity and the ATP cohort for CMI persistence.

Zoster-039

Study design and population are described in detail in Section 2.1.1 Clinical Efficacy.

Both humoral and cellular immune responses to the study vaccine were evaluated in all subjects (serology) or a sub-cohort (CMI) before vaccination (Month 0, Visit 1), one to 2 month post-dose 1 (Month 1, Visit 2), one month post-dose 2 (Month 2, Visit 3), and 12 (Month 13, Visit 4) months post-dose 2. There were always a flexibility on the time intervals between visits, i.e. 30-60 days Visit 1 -> Visit 2, 30-48 days Visit 2 -> Visit 3, 335-425 days Visit 2 -> Visit 4.

The assessment of correlation of HZ/su vaccine-induced humoral immune responses with protection against HZ was also included in the objectives of the study. Serology results of Visits 1 and 3 of subjects having experienced a HZ episode or be selected as a case control for this purpose (See efficacy section).

Subjects with NHBCL and CLL were excluded from the analyses for the primary humoral immunogenicity endpoint (anti-gE HI at Month 2), and subjects with NHBCL from those for the secondary humoral immunogenicity endpoint.

Further descriptive analysis was performed by treatment group and by age strata (n=2, 18-49 YOA, ≥50 YOA), underlying diseases (n= 3, NHBCL; CLL; Multiple Myeloma, Non-Hodgkin T-cell Lymphoma, Hodgkin Lymphoma and Other Hematologic Malignancies) and timing of vaccination in relation to the particular immunosuppressive cancer therapy cycle (n=2, vaccination during cancer therapy course and vaccination after the full cancer therapy course).

Results

1. Immunogenicity study population

Out of the 283 and 279 subjects included in the TVC in the HZ/su and Placebo groups, respectively, 217 and 198 subjects were included in this ATP cohort and 168 and 142 subjects were included in the ATP cohort for Humoral persistence.
Out of the 90 and 84 subjects of the CMI sub-cohort in the HZ/su and Placebo groups, respectively, 69 and 63 subjects were included in the ATP cohort for CMI and 54 and 46 subjects were included in the ATP cohort for CMI persistence.
Reasons for exclusions were comparable between groups.

Table 21 summaries the demographic characteristics for ATP cohort for humoral immunogenicity. The mean age of participants at first vaccination was 57.2 years. The gender distribution was 58.8% males and 41.2% females, and the majority of the subjects (71.3%) were White-Caucasian/of European heritage. The ECOG performance status of subjects in the ATP cohort for humoral immunogenicity was fully active for 65.7% of subjects and restricted in physically strenuous activity for 32.6% of subjects. In this cohort, reported hematologic malignancies included MM (22.7%), other hematological malignancies (21.0%), Hodgkin Lymphoma (18.8%), CLL (17.1%), NHBCL (15.9%) and NHTCL (4.6%). Of the subjects in the HZ/su group, 32.0% were vaccinated during IS cancer therapy, while 68·0% were vaccinated after the end of the cancer therapy.

Overall, these characteristics were similar to those of CMI immunogenicity, except for the proportion of subjects classified by haematological malignancies and by performance status ECOG (Table 22). The proportion of M/F also slightly differ. Demographic characteristics for ATP cohort for humoral immunogenicity are representative of those of the TVC.

Table 21: Summary of demographic characteristics (ATP cohort for humoral immunogenicity)

		HZ/su N = 217		Placebo N = 198		Total N = 415	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age [years] at vaccination dose:1	Mean	57.0	-	57.3	-	57.2	-
	SD	15.0	-	15.7	-	15.3	-
	Median	58.0	-	59.0	-	59.0	-
	Minimum	20.0	-	18.0	-	18.0	-
	Maximum	85.0	-	85.0	-	85.0	-
Gender	Male	127	58.5	117	59.1	244	58.8
	Female	90	41.5	81	40.9	171	41.2
Ethnicity	American Hispanic or Latino	8	3.8	13	6.8	21	5.3
	Not American Hispanic or Latino	201	96.2	178	93.2	379	94.8
	Missing	8	-	7	-	15	-
Geographic Ancestry	African Heritage / African American	1	0.5	1	0.5	2	0.5
	American Indian or Alaskan Native	0	0.0	1	0.5	1	0.3
	Asian - Central / South Asian Heritage	4	1.9	5	2.6	9	2.3
	Asian - East Asian Heritage	41	19.6	43	22.5	84	21.0
	Asian - South East Asian Heritage	4	1.9	0	0.0	4	1.0
	White - Arabic / North African Heritage	0	0.0	1	0.5	1	0.3
	White - Caucasian / European Heritage	154	73.7	131	68.6	285	71.3
	Other	5	2.4	9	4.7	14	3.5
	Missing	8	-	7	-	15	-
Haematological malignancy	Chronic lymphocytic leukaemia (CLL)	36	16.6	35	17.7	71	17.1
	Hodgkin lymphoma	39	18.0	39	19.7	78	18.8
	Multiple myeloma	52	24.0	42	21.2	94	22.7
	Non-Hodgkin B-cell lymphoma	33	15.2	33	16.7	66	15.9
	Non-Hodgkin T cell lymphoma	9	4.1	10	5.1	19	4.6
	Other Haematologic Malignancies	48	22.1	39	19.7	87	21.0
Performance Status ECOG	Fully active*	136	63.8	132	67.7	268	65.7
	Restricted in physically strenuous activity**	75	35.2	58	29.7	133	32.6
	Ambulatory and capable of all selfcare***	2	0.9	4	2.1	6	1.5
	Capable of only limited selfcare****	0	0.0	1	0.5	1	0.2
	Missing	4	-	3	-	7	-

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = Standard deviation; ECOG = Eastern Cooperative Oncology Group; * = Fully active, able to carry on all pre-disease performance without restriction ** = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work *** = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours **** = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

Table 22. Summary of demographic characteristics (ATP cohort for CMI)

		HZ/su N = 69		Placebo N = 63		Total N = 132	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age [years] at vaccination dose:1	Mean	59.4	-	60.3	-	59.8	-
	SD	14.7	-	14.8	-	14.7	-
	Median	61.0	-	64.0	-	62.0	-
	Minimum	21.0	-	24.0	-	21.0	-
	Maximum	85.0	-	85.0	-	85.0	-
Gender	Male	45	65.2	35	55.6	80	60.6
	Female	24	34.8	28	44.4	52	39.4
Ethnicity	American Hispanic or Latino	1	1.5	3	5.0	4	3.2
	Not American Hispanic or Latino	65	98.5	57	95.0	122	96.8
	Missing	3	-	3	-	6	-
Geographic Ancestry	Asian - Central / South Asian Heritage	0	0.0	1	1.7	1	0.8
	Asian - East Asian Heritage	18	27.3	15	25.0	33	26.2
	Asian - South East Asian Heritage	2	3.0	0	0.0	2	1.6
	White - Arabic / North African Heritage	0	0.0	1	1.7	1	0.8
	White - Caucasian / European Heritage	46	69.7	40	66.7	86	68.3
	Other	0	0.0	3	5.0	3	2.4
	Missing	3	-	3	-	6	-
Haematological malignancy	Chronic lymphocytic leukaemia (CLL)	12	17.4	14	22.2	26	19.7
	Hodgkin lymphoma	7	10.1	8	12.7	15	11.4
	Multiple myeloma	15	21.7	9	14.3	24	18.2
	Non-Hodgkin B-cell lymphoma	25	36.2	21	33.3	46	34.8
	Non-Hodgkin T cell lymphoma	1	1.4	3	4.8	4	3.0
	Other Haematologic Malignancies	9	13.0	8	12.7	17	12.9
Performance Status ECOG	Fully active*	38	55.9	44	72.1	82	63.6
	Restricted in physically strenuous activity**	29	42.6	14	23.0	43	33.3
	Ambulatory and capable of all selfcare***	1	1.5	2	3.3	3	2.3
	Capable of only limited selfcare****	0	0.0	1	1.6	1	0.8
	Missing	1	-	2	-	3	-

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = Standard deviation; ECOG = Eastern Cooperative Oncology Group; * = Fully active, able to carry on all pre-disease performance without restriction; ** = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; *** = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours **** = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

Demographic characteristics by age strata were different than for the overall ATP cohort for humoral immunogenicity. Due to the limited number of subjects by age strata, percentages of the different underlying diseases were different and not always balanced between age groups. Some imbalanced in gender distribution and in geographic ancestry between HZ/su and placebo groups were observed when analysed by haematological malignancies.

2. Anti-gE specific humoral immune response

Confirmatory analyses

The primary confirmatory objectives were assessed on the ATP cohort for humoral immunogenicity, excluding subjects with NHBCL and CLL, and were met; The anti-gE Ab VRR at Month 2 was 80.4% (95% CI: 73.1–86.5) and the anti-gE Ab adjusted GM ratio (vaccinees/placebo) at Month 2 was 29.75 (95% CI: 21.09–41.96).

The secondary confirmatory objectives were assessed on the ATP cohort for humoral immunogenicity, excluding subjects with NHBCL, and were met; The anti-gE Ab VRR at Month 2 was 69.0% (95% CI: 61.8–75.6) and the anti-gE Ab adjusted GM ratio at Month 2 was 9.02 (95% CI: 6.18–13.17).

Descriptive analyses

Descriptive analyses were performed on the adapted ATP cohort for humoral immunogenicity for all study subjects.
Overall, Anti-gE humoral immune responses were observed in the HZ/su group at 1 month following the first dose, with further increase after the second dose and persisted through 1 year post-dose 2 above pre-vaccination levels (Table 23).

Table 23. Seropositivity rates and geometric mean concentrations (GMCs) of anti-gE antibody at Month 0, 1, 2 and 13 (adapted ATP cohort for Humoral immunogenicity)

				≥ 97 mIU/ml				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	HZ/su	PRE	217	209	96.3	92.9	98.4	964.0	814.5	1140.8	<97.0	135141.5
		PI(M1)	215	212	98.6	96.0	99.7	4216.5	3328.6	5341.4	<97.0	159442.9
		PII(M2)	217	213	98.2	95.3	99.5	13445.6	10158.9	17795.6	<97.0	476261.9
		PII(M13)	167	166	99.4	96.7	100	5202.7	4074.8	6642.8	<97.0	139345.7
	Placebo	PRE	198	191	96.5	92.9	98.6	883.7	749.9	1041.4	<97.0	147865.4
		PI(M1)	196	188	95.9	92.1	98.2	824.2	699.4	971.3	<97.0	42583.3
		PII(M2)	198	189	95.5	91.5	97.9	832.0	701.1	987.3	<97.0	98937.7
		PII(M13)	142	136	95.8	91.0	98.4	895.4	734.5	1091.5	<97.0	15864.3

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M13) = Post-vaccination Dose II (Month 13)

The VRR in the HZ/su group was 44.2%, 65.4% and 52.1% at Months 1, 2 and 13, respectively. In the Placebo group, the VRR for anti-gE Ab concentrations was not higher than 3.6% at any timepoint.

Even if the stratified analyses, after HZ/su administration, anti-gE humoral immune responses showed a similar pattern as in the general population (i.e. a response was observed 1 month following the first dose, with further increase after the second dose and persisted through 1 year post-dose 2, above pre-vaccination levels), differences in Ab titers between strata were observed (Table 24, Table 25, and Table 26).

Within the HZ/su group, there is a trend towards a higher anti-gE humoral immune response in the 18–49 YOA than the ≥50 YOA age strata Table 24.

Table 24. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, and 13 by age strata (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	18-49 YOA	HZ/su	PRE	59	58	98.3	90.9	100	1122.6	846.1	1489.5	<97.0	50882.8
			PI(M1)	59	59	100	93.9	100	6086.0	3634.5	10191.1	154.9	124803.0
			PII(M2)	59	58	98.3	90.9	100	20914.0	12019.8	36389.7	<97.0	476261.9
			PII(M13)	46	46	100	92.3	100	7245.2	4556.1	11521.2	131.7	80754.9
		Placebo	PRE	55	52	94.5	84.9	98.9	863.1	651.4	1143.5	<97.0	4460.7
			PI(M1)	53	50	94.3	84.3	98.8	800.9	593.9	1079.9	<97.0	4782.2
			PII(M2)	55	52	94.5	84.9	98.9	824.7	614.1	1107.5	<97.0	5676.7
			PII(M13)	50	47	94.0	83.5	98.7	771.8	554.6	1073.9	<97.0	6590.0
	≥ 50 YOA	HZ/su	PRE	158	151	95.6	91.1	98.2	910.6	740.4	1120.0	<97.0	135141.5
			PI(M1)	156	153	98.1	94.5	99.6	3670.1	2825.1	4767.9	<97.0	159442.9
			PII(M2)	158	155	98.1	94.6	99.6	11400.8	8240.3	15773.5	<97.0	469032.8
			PII(M13)	121	120	99.2	95.5	100	4587.3	3438.3	6120.2	<97.0	139345.7
		Placebo	PRE	143	139	97.2	93.0	99.2	891.7	728.7	1091.2	<97.0	147865.4
			PI(M1)	143	138	96.5	92.0	98.9	833.0	683.4	1015.4	<97.0	42583.3
			PII(M2)	143	137	95.8	91.1	98.4	834.8	676.5	1030.1	<97.0	98937.7
			PII(M13)	92	89	96.7	90.8	99.3	970.7	755.6	1247.0	<97.0	15864.3

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M13) = Post-vaccination Dose II (Month 13)

Accordingly, VRRs in the HZ/su group within the 18–49 YOA and ≥50 YOA strata at Month 1 were 50.8% and 41.7%; at Month 2 were 72.9% and 62.7% and at Month 13 were 61.4% and 48.8%, respectively.

Within the HZ/su group, there is a trend towards a higher anti-gE humoral immune response in the MM and other diseases stratum than in the CLL or NHBCL strata (**Table 25**).

Table 25. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, and 13 by underlying diseases stratum (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	MM and other diseases	HZ/su	PRE	148	142	95.9	91.4	98.5	913.8	736.9	1133.2	<97.0	135141.5
			PI(M1)	147	146	99.3	96.3	100	6786.3	5080.7	9064.6	<97.0	159442.9
			PII(M2)	148	146	98.6	95.2	99.8	24450.7	17991.9	33228.1	<97.0	476261.9
			PII(M13)	113	112	99.1	95.2	100	7127.9	5361.2	9476.7	<97.0	139345.7
		Placebo	PRE	130	123	94.6	89.2	97.8	810.5	653.0	1006.1	<97.0	147865.4
			PI(M1)	129	121	93.8	88.1	97.3	743.3	599.6	921.5	<97.0	42583.3
			PII(M2)	130	121	93.1	87.3	96.8	737.0	587.3	924.8	<97.0	98937.7
			PII(M13)	92	86	93.5	86.3	97.6	858.7	656.2	1123.7	<97.0	15864.3
	CLL	HZ/su	PRE	36	34	94.4	81.3	99.3	928.6	614.0	1404.3	<97.0	7663.0
			PI(M1)	36	34	94.4	81.3	99.3	1134.7	734.6	1752.9	<97.0	11595.8
			PII(M2)	36	34	94.4	81.3	99.3	2620.7	1287.9	5332.9	<97.0	297192.5
			PII(M13)	25	25	100	86.3	100	2234.2	1210.5	4123.6	215.2	74522.3
		Placebo	PRE	35	35	100	90.0	100	1008.6	663.3	1533.7	150.2	19303.6
			PI(M1)	35	35	100	90.0	100	1013.5	669.7	1533.8	165.3	15633.2
			PII(M2)	35	35	100	90.0	100	1032.2	680.6	1565.5	152.4	18234.9
			PII(M13)	25	25	100	86.3	100	1119.8	707.9	1771.4	245.2	11369.4
	NHBCL	HZ/su	PRE	33	33	100	89.4	100	1275.8	908.5	1791.5	212.1	11001.8
			PI(M1)	32	32	100	89.1	100	2074.3	1433.4	3001.7	267.6	39966.3
			PII(M2)	33	33	100	89.4	100	5476.9	2985.7	10046.8	319.9	229368.6
			PII(M13)	29	29	100	88.1	100	3161.7	1703.9	5866.7	131.7	65862.9
		Placebo	PRE	33	33	100	89.4	100	1079.3	835.2	1394.8	203.4	4414.1
			PI(M1)	32	32	100	89.1	100	996.9	764.7	1299.6	198.4	4633.5
			PII(M2)	33	33	100	89.4	100	1067.3	820.7	1387.9	237.2	4831.9
			PII(M13)	25	25	100	86.3	100	835.2	593.8	1174.8	230.1	4087.7

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M13) = Post-vaccination Dose II (Month 13)

The VRRs in the HZ/su group within MM and other diseases, CLL and NHBCL strata at Month 1 were 59.9%, 5.6% and 15.6%; at Month 2 were 80.4%, 22.2% and 45.5% and at Month 13 were 66.7%, 20.0% and 24.1%, respectively.

Within the HZ/su group, there is a trend towards a higher anti-gE humoral immune response in subjects vaccinated after completion of immunosuppressive cancer therapy than in subjects vaccinated during the cancer therapy course (Table 26).

Table 26. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, and 13 by timing of vaccination in relation to the particular immunosuppressive cancer therapy cycle (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	During the cancer therapy	HZ/su	PRE	69	64	92.8	83.9	97.6	710.9	530.5	952.6	<97.0	20770.8
			PI(M1)	69	67	97.1	89.9	99.6	3167.6	2027.5	4948.6	<97.0	141277.7
			PII(M2)	69	66	95.7	87.8	99.1	5777.4	3342.5	9985.9	<97.0	252499.1
			PII(M13)	47	46	97.9	88.7	99.9	2639.7	1636.6	4257.7	<97.0	74522.3
		Placebo	PRE	64	62	96.9	89.2	99.6	935.8	666.4	1314.2	<97.0	147865.4
			PI(M1)	63	60	95.2	86.7	99.0	844.9	606.1	1178.0	<97.0	42583.3
			PII(M2)	64	61	95.3	86.9	99.0	850.1	620.6	1164.6	<97.0	24639.9
			PII(M13)	42	40	95.2	83.8	99.4	993.5	672.5	1467.7	<97.0	12171.2
	After the cancer therapy	HZ/su	PRE	148	145	98.0	94.2	99.6	1111.0	905.8	1362.6	<97.0	135141.5
			PI(M1)	146	145	99.3	96.2	100	4826.9	3654.7	6375.0	<97.0	159442.9
			PII(M2)	148	147	99.3	96.3	100	19934.7	14674.1	27081.2	<97.0	476261.9
			PII(M13)	120	120	100	97.0	100	6786.5	5162.2	8921.8	131.7	139345.7
		Placebo	PRE	134	129	96.3	91.5	98.8	859.8	715.5	1033.1	<97.0	24796.0
			PI(M1)	133	128	96.2	91.4	98.8	814.5	675.6	982.1	<97.0	22362.0
			PII(M2)	134	128	95.5	90.5	98.3	823.5	670.0	1012.1	<97.0	98937.7
			PII(M13)	100	96	96.0	90.1	98.9	857.1	679.2	1081.6	<97.0	15864.3

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M13) = Post-vaccination Dose II (Month 13)

The VRRs in the HZ/su group within the "during" and "after cancer therapy" strata at Month 1 were 39.1% and 46.6%; at Month 2 were 53.6% and 70.9% and at Month 13 were 42.6% and 55.9%, respectively.

Results of the analyses performed on the TVC were consistent with results of the analyses performed on the ATP cohort for Humoral immunogenicity and the ATP cohort for Humoral persistence.

3. gE-specific CMI

The gE-specific CMI responses were observed in the HZ/su group at 1 month following the first dose, with further increase 1 month after the second dose and persisted through 1year post-dose 2 above pre-vaccination levels (Table 27).

Table 27. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells at Month 0, 1, 2, and 13 (adapted ATP cohort for CMI immunogenicity)

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	HZ/su	PRE	52	17	226.78	659.84	1.0	1.0	77.5	191.4	4574.2
		PI(M1)	58	11	1261.67	2318.36	1.0	156.5	521.2	1215.2	13226.6
		PII(M2)	53	16	6083.98	10467.57	1.0	1766.2	3081.9	7413.6	71100.0
		PII(M13)	44	10	3626.87	7758.18	1.0	416.0	1006.7	3284.5	41312.7
	Placebo	PRE	49	14	147.30	191.91	1.0	1.0	101.2	193.1	835.9
		PI(M1)	51	12	196.74	332.52	1.0	1.0	114.6	257.7	2102.8
		PII(M2)	50	13	318.20	1000.90	1.0	1.0	99.1	268.3	6989.6
		PII(M13)	36	10	181.23	387.90	1.0	1.0	66.1	161.9	1710.6

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M13) = Post-vaccination Dose II (Month 13)

The VRR of the frequency of gE-specific CD4[2+] T-cells in the HZ/su group, at Months 1, 2 and 13 were 37.5%, 83.7% and 66.7%, respectively.

Descriptive analysis results performed on subjects with hematologic malignancies excluding subjects with NHBCL and CLL in the CMI sub-cohort were similar; At Month 2, the adjusted GM frequency of gE-specific CD4[2+] T-cells in the HZ/su group was 2740.4 (95% CI: 1787.6–4123.7) and the VRR was 73.7% (95% CI: 48.8% - 90.9%).

These results were confirmed by the descriptive statistics of the frequency of gE-specific CD4[2+] T-cells by underlying disease (Table 28).

Table 28. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells at Month 0, 1, 2, and 13 by underlying diseases stratum (adapted ATP cohort for CMI immunogenicity)

Immune marker	Sub-group	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	MM and other diseases	HZ/su	PRE	23	9	319.81	946.18	1.0	1.0	64.0	203.1	4574.2
			PI(M1)	28	4	1189.06	2095.71	1.0	254.2	506.6	1182.3	9115.6
			PII(M2)	25	7	4972.60	6177.81	1.0	1876.1	3109.2	6009.0	30597.1
			PII(M13)	18	5	4729.57	9586.67	1.0	409.2	1334.8	5558.4	41312.7
		Placebo	PRE	24	4	182.64	212.00	1.0	46.0	106.9	222.9	835.9
			PI(M1)	26	2	198.82	216.62	1.0	45.6	133.1	287.3	1003.3
			PII(M2)	24	4	236.77	342.89	1.0	1.0	131.2	292.7	1515.4
			PII(M13)	15	2	197.41	433.53	1.0	1.0	65.4	174.9	1710.6
	CLL	HZ/su	PRE	8	4	80.90	117.72	1.0	1.0	14.0	172.4	271.5
			PI(M1)	9	3	2528.80	4291.33	53.9	65.2	293.3	3305.7	13226.6
			PII(M2)	8	4	5769.89	5388.24	22.4	681.0	5714.0	9049.9	15247.0
			PII(M13)	5	3	3016.02	4644.40	1.0	1.0	176.3	4233.8	10668.1
		Placebo	PRE	10	4	105.07	95.02	1.0	1.0	120.9	193.7	216.9
			PI(M1)	8	6	73.43	103.93	1.0	1.0	25.4	144.7	244.2
			PII(M2)	9	5	158.20	272.08	1.0	1.0	1.0	191.9	832.3
			PII(M13)	8	3	90.57	94.82	1.0	1.0	86.8	136.3	275.3
	NHBCL	HZ/su	PRE	21	4	180.47	316.08	1.0	21.4	117.1	160.5	1478.8
			PI(M1)	21	4	815.42	1041.06	1.0	243.1	556.5	856.6	4854.0
			PII(M2)	20	5	7598.84	15391.17	476.3	1698.5	2642.4	8155.0	71100.0
			PII(M13)	21	2	2827.13	6716.79	1.0	490.8	957.9	2288.8	31720.2
		Placebo	PRE	15	6	118.92	205.82	1.0	1.0	49.9	144.8	797.7
			PI(M1)	17	4	251.57	506.63	1.0	1.0	104.4	277.6	2102.8
			PII(M2)	17	4	517.88	1671.92	1.0	1.0	94.8	199.6	6989.6
			PII(M13)	13	5	218.34	455.01	1.0	1.0	64.1	171.5	1685.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M13) = Post-vaccination Dose II (Month 13)

Similar CMI results were observed when analysed by age strata (Table 29).

Table 29. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells at Month 0, 1, 2, and 13 by age strata (adapted ATP cohort for CMI immunogenicity)

Immune marker	Sub-group	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	18-49 YOA	HZ/su	PRE	11	6	48.07	81.82	1.0	1.0	1.0	137.7	193.0
			PI(M1)	14	3	590.70	387.67	85.4	369.3	482.4	805.7	1517.7
			PII(M2)	14	3	4687.45	3452.09	476.3	1956.0	3816.0	7413.6	11808.3
			PII(M13)	13	1	2243.18	2000.11	386.9	441.2	1729.2	3280.6	6174.5
		Placebo	PRE	12	3	227.75	299.88	1.0	1.0	115.0	330.6	835.9
			PI(M1)	13	2	240.73	288.04	1.0	14.8	137.5	370.3	1003.3
			PII(M2)	13	2	219.96	409.68	1.0	1.0	58.1	171.4	1515.4
			PII(M13)	11	2	273.68	495.03	1.0	16.0	103.8	358.0	1710.6
	≥ 50 YOA	HZ/su	PRE	41	11	274.73	736.42	1.0	3.5	115.1	203.1	4574.2
			PI(M1)	44	8	1475.16	2624.14	1.0	151.9	536.9	1352.4	13226.6
			PII(M2)	39	13	6585.30	12036.80	1.0	1441.0	2877.9	7864.4	71100.0
			PII(M13)	31	9	4207.13	9137.49	1.0	340.4	996.0	3288.3	41312.7
		Placebo	PRE	37	11	121.21	137.02	1.0	1.0	94.6	189.3	670.6
			PI(M1)	38	10	181.68	348.71	1.0	1.0	110.9	236.5	2102.8
			PII(M2)	37	11	352.72	1141.45	1.0	1.0	103.5	268.3	6989.6
			PII(M13)	25	8	140.55	334.18	1.0	1.0	63.3	132.0	1685.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M13) = Post-vaccination Dose II (Month 13)

Similarly than for the humoral immune responses, results of the analyses performed on the TVC were consistent with results of the analyses performed on the ATP cohort for CMI and the ATP cohort for CMI persistence.

ZOSTER-041

Study design and population.

The study population was adults ≥ 18 YOA with renal transplant and on chronic immunosuppressive (IS) therapy for the prevention of allograft rejection for a minimum of 30 days prior to first vaccination.

The ABO compatible allogeneic renal transplant (allograft) was to be received not less than 4 months (120 days) and not more than 18 months (547 days) before the time of the first vaccination. Eligible subjects had transitioned to and were receiving stable (unchanging) chronic IS for the maintenance of the allograft (prevention of rejection) for a minimum of one month (30 days) prior to the first vaccination. The subjects had to be without any episode of allograft rejection over the previous three months (90 days) prior to the first vaccination and with stable renal function. Subjects had to have multiple dialysis options (peritoneal and/or more than one anatomical access site for haemodialysis) in the event that acute or chronic dialysis was needed. Subjects suffering from any recurring primary kidney disease or with more than one organ transplanted were excluded. Subjects with increased risk for chronic allograft dysfunction, histologic reports of chronic allograft injury, significant proteinuria, panel reactive antibody score unknown at the time of transplant, systemic autoimmune or pIMD, except those localized to kidney and those with diabetes mellitus with diabetic nephropathy, were also excluded. Subjects with confirmed or suspected human immunodeficiency virus (HIV), primary immunodeficiency disease, disseminated or untreated malignancy, or systemic infection were excluded as well. Subjects could not have been treated with anti-CD20 or other B-cell monoclonal antibody agents for prevention of allograft rejection within 9 months (274 days) of first study vaccination. Subjects who had previous HZ or varicella or vaccination

against HZ or varicella within the 12 months preceding the first dose of study vaccine/placebo were also excluded.

Humoral immune response to the study vaccine was evaluated in all subjects before vaccination (Month 0, Visit 1), one to 2 month post-dose 1 (Month 1, Visit 2), one month post-dose 2 (Month 2, Visit 3), and at 6 (Month 7, Visit 4) and 12 (Month 13, Visit 5) months post-dose 2. CMI was evaluated in a sub-cohort at Visit 1, 3, and 5. There were always a flexibility on the time intervals between visits, i.e. 30-60 days Visit 1 -> Visit 2, 30-48 days Visit 2 -> Visit 3, 152-212 days Visit 2 -> Visit 4, 335-425 days Visit 2 -> Visit 5.

The analyses of humoral and cellular immunogenicity and persistence were performed on all subjects or all subjects in the CMI sub-cohort within the ATP cohorts for humoral or for CMI immunogenicity (at Months 0, 1, and 2) and persistence (at Months 7 and 13), respectively. Further descriptive analysis was performed by treatment group and by age strata.

Results

1. Immunogenicity study population

The TVC included a total of 264 subjects; 132 in each of the study groups. The ATP cohort for Humoral immunogenicity included 121 subjects in the HZ/su and 119 subjects in the Placebo group. The ATP cohort for Humoral persistence at Month 7 included 110 subjects in the HZ/su and 115 subjects in the Placebo group, and, at Month 13, 111 subjects in each of study groups.

Of the 38 HZ/su and 40 placebo recipients in the TVC for CMI analysis, 36 subjects from each of the study groups remained in the CMI sub-cohort. 36 HZ/su and 33 placebo recipients remained in the sub-cohort for CMI persistence.

Reasons for exclusions were comparable between groups with the exception of higher proportion of non compliance with blood sampling schedule for the HZ/su group.

Demographic characteristics for ATP cohort for humoral immunogenicity are representative of those of the TVC (Table 30). The mean age was 52.5 years (51.9 years for the HZ/su and 53.1 years for the Placebo group). More male, than female, subjects were included in the ATP cohort for Humoral immunogenicity (71.1% of male subjects in the HZ/su and 70.6% in the Placebo group). Regarding the geographic ancestry, most of the subjects (69.2%) were of Caucasian/European ancestry.

Demographic characteristics of CMI immunogenicity slightly differ, including for proportion of F/M in the HZ/su group (19.4% and 80.6% respectively) and geographic ancestry (>90% in both groups). This was because the CMI sub-cohort was restricted to designated sites in selected countries that had access to PBMC processing facility (Table 31).

Table 30. Summary of demographic characteristics (ATP cohort for humoral immunogenicity)

		HZ/su N = 121		Placebo N = 119		Total N = 240	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	51.9	-	53.1	-	52.5	-
	SD	12.6	-	12.5	-	12.5	-
	Median	53.0	-	55.0	-	54.0	-
	Minimum	20	-	21	-	20	-
	Maximum	82	-	79	-	82	-
Gender	Female	35	28.9	35	29.4	70	29.2
	Male	86	71.1	84	70.6	170	70.8
Ethnicity	Hispanic or Latino	12	9.9	5	4.2	17	7.1
	Not Hispanic or Latino	109	90.1	114	95.8	223	92.9
Geographic Ancestry	African Heritage / African American	3	2.5	1	0.8	4	1.7
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	1	0.8	2	1.7	3	1.3
	Asian - East Asian Heritage	19	15.7	22	18.5	41	17.1
	Asian - Japanese Heritage	0	0.0	1	0.8	1	0.4
	Asian - South East Asian Heritage	8	6.6	3	2.5	11	4.6
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
	White - Arabic / North African Heritage	2	1.7	1	0.8	3	1.3
	White - Caucasian / European Heritage	80	66.1	86	72.3	166	69.2
	Other	8	6.6	3	2.5	11	4.6

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation

Table 31. Summary of demographic characteristics (ATP cohort for CMI immunogenicity)

		HZ/su N = 36		Placebo N = 36		Total N = 72	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	51.3	-	54.5	-	52.9	-
	SD	13.7	-	12.7	-	13.2	-
	Median	52.0	-	55.0	-	55.0	-
	Minimum	24	-	27	-	24	-
	Maximum	71	-	79	-	79	-
Gender	Female	7	19.4	12	33.3	19	26.4
	Male	29	80.6	24	66.7	53	73.6
Ethnicity	Hispanic or Latino	1	2.8	2	5.6	3	4.2
	Not Hispanic or Latino	35	97.2	34	94.4	69	95.8
Geographic Ancestry	African Heritage / African American	1	2.8	0	0.0	1	1.4
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	0	0.0	0	0.0	0	0.0
	Asian - East Asian Heritage	0	0.0	0	0.0	0	0.0
	Asian - Japanese Heritage	0	0.0	0	0.0	0	0.0
	Asian - South East Asian Heritage	0	0.0	0	0.0	0	0.0
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
	White - Arabic / North African Heritage	0	0.0	1	2.8	1	1.4
	White - Caucasian / European Heritage	35	97.2	34	94.4	69	95.8
	Other	0	0.0	1	2.8	1	1.4

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation

Demographic characteristics by age strata (18-49 YOA and ≥ 50 YOA) also slightly differ for F/M ratio (for stratum 18-49YOA, and strata CIS) and proportion of geographic ancestry compared with those of ATP cohort for humoral immunogenicity but were well balanced within each stratum.

Subjects were divided into 3 groups by type of maintenance IS therapy in use at Day 0 (i.e., mycophenolate compound [MC], calcineurin inhibitors/sirolimus [CIS], or corticosteroids [CS]): 92 and 91 subjects in the HZ/su and Placebo group, respectively received CIS+CS+MC; respectively 21 and 20 subjects received CIS+MC; and respectively 6 and 8 subjects received CIS+CS.
Demographic characteristics by type of IS therapy (CIS+MC+CS, CIS+MC, and CIS+CS) indicated some imbalanced for these characteristics within strata CIS+MC and CIS+CS.

2. Anti-gE specific humoral immune response

Confirmatory analyses

The primary confirmatory objective was assessed in all subjects in the ATP cohort for Humoral immunogenicity and was met; The anti-gE Ab VRR at Month 2 was 80.2% (95% CI: 71.9–86.9)

The secondary confirmatory objective was assessed on the ATP cohort for humoral immunogenicity and was met; The anti-gE Ab GM ratio at Month 2 was 14.0 (95% CI: 10.9 –17.99).

Descriptive analyses

Overall, Anti-gE humoral immune responses were observed in the HZ/su group at 1 month following the first dose, with further increase after the second dose and persisted through 1 year post-dose 2 above pre-vaccination levels (Table 32).

Table 32. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, 7, and 13 (adapted ATP cohort for humoral immunogenicity)

				≥ 97 mIU/ml				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	HZ/su	PRE	121	117	96.7	91.8	99.1	1354.4	1118.3	1640.4	<97.0	16059.9
		PI(M1)	121	119	98.3	94.2	99.8	9530.5	7111.3	12772.7	<97.0	323351.0
		PII(M2)	121	120	99.2	95.5	100	19163.8	15041.5	24416.0	<97.0	363305.3
		PII(M7)	110	109	99.1	95.0	100	13066.7	10291.5	16590.4	<97.0	327105.7
		PII(M13)	111	110	99.1	95.1	100	8545.1	6753.7	10811.5	<97.0	218175.7
	Placebo	PRE	119	117	98.3	94.1	99.8	1495.7	1202.3	1860.8	<97.0	25032.0
		PI(M1)	119	118	99.2	95.4	100	1501.9	1231.3	1832.0	<97.0	19176.5
		PII(M2)	119	117	98.3	94.1	99.8	1489.4	1215.8	1824.7	<97.0	19779.5
		PII(M7)	115	114	99.1	95.3	100	1533.7	1249.6	1882.3	<97.0	77604.2
		PII(M13)	111	109	98.2	93.6	99.8	1572.7	1269.6	1948.1	<97.0	42946.5

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M7) = Post-vaccination Dose II (Month 7); PII(M13) = Post-vaccination Dose II (Month 13)

The VRR in the HZ/su group was 63.6%, 80.2%, 75.5% and 66.7% at Months 1, 2, 7 and 13, respectively. In the Placebo group, the VRR for anti-gE Ab concentrations was not higher than 6.4% at any timepoint.

Although, after HZ/su administration, anti-gE humoral immune responses showed a similar pattern as in the general population (i.e. a response was observed 1 month following the first dose, with further increase after the second dose and persisted through 1 year post-dose 2, above pre-vaccination levels), differences in Ab titers between strata were observed, for both age strata (Table 33) and IS therapy (Table 34). Ab concentrations measured at any timepoint for the 18-49 YOA Placebo group were always slightly higher than for the >50YOA Placebo group. A trend for higher anti-gE Ab GMC were observed in patients under CIS+MC when compared to those under CIS+CS+MC.

Table 33. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, 7, and 13 by age strata (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	18-49ys	HZ/su	PRE	46	43	93.5	82.1	98.6	1570.3	1066.3	2312.6	<97.0	11286.4
			PI(M1)	46	44	95.7	85.2	99.5	17868.3	10233.1	31200.4	<97.0	323351.0
			PII(M2)	46	45	97.8	88.5	99.9	30000.5	19421.8	46341.2	<97.0	363305.3
			PII(M7)	41	40	97.6	87.1	99.9	19612.8	12458.6	30875.1	<97.0	327105.7
			PII(M13)	41	40	97.6	87.1	99.9	12051.5	7729.6	18789.8	<97.0	218175.7
		Placebo	PRE	41	41	100	91.4	100	2002.6	1423.3	2817.7	121.3	16326.7
			PI(M1)	41	41	100	91.4	100	2004.6	1462.6	2747.5	127.7	15115.2
			PII(M2)	41	41	100	91.4	100	1892.1	1383.5	2587.6	105.1	12911.9
			PII(M7)	39	39	100	91.0	100	2029.7	1437.9	2865.0	101.6	77604.2
			PII(M13)	40	40	100	91.2	100	2219.0	1582.1	3112.2	118.3	42946.5
	≥50ys	HZ/su	PRE	75	74	98.7	92.8	100	1236.9	1009.2	1516.1	<97.0	16059.9
			PI(M1)	75	75	100	95.2	100	6481.8	4779.7	8790.1	281.3	150939.4
			PII(M2)	75	75	100	95.2	100	14557.9	11054.9	19170.9	310.3	111089.5
			PII(M7)	69	69	100	94.8	100	10265.2	7903.5	13332.5	360.3	90437.2
			PII(M13)	70	70	100	94.9	100	6986.4	5360.4	9105.7	327.4	41157.6
		Placebo	PRE	78	76	97.4	91.0	99.7	1283.0	969.8	1697.4	<97.0	25032.0
			PI(M1)	78	77	98.7	93.1	100	1290.4	1002.9	1660.4	<97.0	19176.5
			PII(M2)	78	76	97.4	91.0	99.7	1313.3	1009.8	1708.2	<97.0	19779.5
			PII(M7)	76	75	98.7	92.9	100	1328.2	1030.4	1712.2	<97.0	20683.7
			PII(M13)	71	69	97.2	90.2	99.7	1295.4	988.4	1697.7	<97.0	23366.3

18-49ys = Subjects aged between 18 and 49 years; ≥50ys = Subjects aged 50 years and older; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum
PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2)
PII(M7) = Post-vaccination Dose II (Month 7); PII(M13) = Post-vaccination Dose II (Month 13)

Table 34. SPR and GMCs of anti-gE Ab at Month 0, 1, 2, 7, and 13 by immunosuppressive therapy (adapted ATP cohort for humoral immunogenicity)

					≥ 97 mIU/ml				GMC				
							95% CI			95% CI			
Antibody	Sub-group	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	CIS + CS+ MC	HZ/su	PRE	92	89	96.7	90.8	99.3	1394.7	1119.4	1737.9	<97.0	16059.9
			PI(M1)	92	90	97.8	92.4	99.7	8764.1	6173.9	12441.1	<97.0	323351.0
			PII(M2)	92	91	98.9	94.1	100	18164.8	13549.0	24353.2	<97.0	250074.3
			PII(M7)	84	83	98.8	93.5	100	12239.3	9265.3	16167.9	<97.0	112737.1
			PII(M13)	83	82	98.8	93.5	100	7739.9	5836.8	10263.5	<97.0	72354.3
		Placebo	PRE	91	90	98.9	94.0	100	1435.3	1116.6	1844.9	<97.0	25032.0
			PI(M1)	91	91	100	96.0	100	1439.9	1147.7	1806.6	117.8	19176.5
			PII(M2)	91	90	98.9	94.0	100	1442.2	1142.5	1820.5	<97.0	19779.5
			PII(M7)	86	86	100	95.8	100	1525.5	1201.9	1936.3	101.6	77604.2
			PII(M13)	86	85	98.8	93.7	100	1556.7	1215.2	1994.1	<97.0	42946.5
	CIS + MC	HZ/su	PRE	21	20	95.2	76.2	99.9	1144.5	732.9	1787.2	<97.0	5015.0
			PI(M1)	21	21	100	83.9	100	10594.3	5885.6	19070.1	1376.5	109251.0
			PII(M2)	21	21	100	83.9	100	23078.4	14901.9	35741.3	3543.7	111089.5
			PII(M7)	19	19	100	82.4	100	17470.6	11083.4	27538.6	2680.8	90437.2
			PII(M13)	20	20	100	83.2	100	10847.3	7053.7	16681.2	1334.8	41157.6
		Placebo	PRE	20	19	95.0	75.1	99.9	1708.4	935.0	3121.6	<97.0	10802.5
			PI(M1)	20	19	95.0	75.1	99.9	1750.5	1013.1	3024.8	<97.0	9669.1
			PII(M2)	20	19	95.0	75.1	99.9	1677.6	967.9	2907.4	<97.0	9129.6
			PII(M7)	21	20	95.2	76.2	99.9	1553.1	918.4	2626.4	<97.0	7967.4
			PII(M13)	18	17	94.4	72.7	99.9	1706.8	970.6	3001.2	<97.0	8081.4
	CIS + CS	HZ/su	PRE	6	6	100	54.1	100	2040.1	603.3	6898.9	370.6	9481.3
			PI(M1)	6	6	100	54.1	100	14961.1	2574.1	86956.3	1804.9	266533.0
			PII(M2)	6	6	100	54.1	100	20507.0	3907.4	107625.7	3299.3	363305.3
			PII(M7)	6	6	100	54.1	100	16558.2	2392.6	114590.2	1130.8	327105.7
			PII(M13)	6	6	100	54.1	100	15821.5	3131.5	79935.6	2050.7	218175.7
		Placebo	PRE	8	8	100	63.1	100	1715.5	708.5	4153.8	395.9	5389.7
			PI(M1)	8	8	100	63.1	100	1653.6	678.7	4028.6	308.1	4836.1
			PII(M2)	8	8	100	63.1	100	1596.0	641.3	3971.9	291.6	4545.1
			PII(M7)	8	8	100	63.1	100	1571.0	628.0	3929.9	390.4	5553.9
			PII(M13)	7	7	100	59.0	100	1444.6	533.3	3913.5	364.5	4911.3

CIS + CS+ MC = Subjects using calcineurin inhibitor or sirolimus, corticosteroids and mycophenolate compound as maintenance immunosuppressive therapy at visit 1; CIS + MC = Subjects using calcineurin inhibitor or sirolimus and mycophenolate compound (but not using corticosteroids) as maintenance immunosuppressive therapy at visit 1
CIS + CS = Subjects using calcineurin inhibitor or sirolimus and corticosteroids (but not using mycophenolate compound) as maintenance immunosuppressive therapy at visit 1; HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0)
PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M7) = Post-vaccination Dose II (Month 7); PII(M13) = Post-vaccination Dose II (Month 13)

Results of the VRR by age strata were consistent with GMC results

- For the 18-49 YOA stratum, VRR in the HZ/su group was 73.9%, 84.8%, 80.5% and 70.7% at Months 1, 2, 7 and 13, respectively. In the Placebo group, the VRR for anti-gE Ab concentrations was not higher than 7.7% at any timepoint.
- For the >50 YOA stratum, VRR in the HZ/su group was 57.3%, 77.3%, 72.5% and 64.3% at Months 1, 2, 7 and 13, respectively. In the Placebo group, the VRR for anti-gE Ab concentrations was not higher than 5.7% at any timepoint.

Post-hoc analysis confirmed the trend for higher induced-Ab responses with younger age (based on the GMCs and VRR results obtained for the 18-29 and 30-49 YOA strata).

Results of the VRR by IS therapy were consistent with GMC results
- For the CIS+CS+MC stratum, VRR in the HZ/su group was 58.7%, 77.2%, 72.6% and 62.7% at Months 1, 2, 7 and 13, respectively. In the Placebo group, the VRR for anti-gE Ab concentrations was not higher than 8.2% at any timepoint.
- For the CIS+MC stratum, VRR in the HZ/su group was 76.2%, 90.5%, 89.5% and 75.0% at Months 1, 2, 7 and 13, respectively. In the Placebo group, the VRR for anti-gE Ab concentrations was not higher than 5.0% at any timepoint.
Because of the low number of subjects included in the CIS+CS stratum, data were not evaluated.

Results of the analyses performed on the TVC were consistent with results of the analyses performed on the ATP cohort for Humoral immunogenicity and the ATP cohort for Humoral persistence.

3. gE-specific CMI
Confirmatory analysis

The third confirmatory, secondary objective was assessed in the CMI sub-cohort on the ATP cohort for CMI and was met; The VRR for gE-specific CD4[2+] T-cell frequencies in the HZ/su group at Month 2 was 71.4% (95% CI: 51.3–86.8).

The fourth confirmatory, secondary objective of the study was also met; the GM ratio (HZ/su group over Placebo group) in gE-specific CD4[2+] Tcell frequencies at Month 2 was 17.26 (95% CI: 5.92 – 50.36, P <0.0001).

Descriptive analyses

Descriptive analyses results were performed on adapted ATP cohort for CMI sub-cohort (Table 35). Specific CD4 T cells were detected after vaccination and decreased with time.

Table 35. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cell at Month 0, 2 and 13 (adapted ATP cohort for CMI immunogenicity)

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	HZ/su	PRE	31	5	110.90	182.09	1.0	1.0	21.2	105.0	716.3
		PII(M2)	32	4	2433.07	2102.29	1.0	569.4	2149.0	3695.1	9334.6
		PII(M13)	33	3	1320.92	1823.64	1.0	424.8	1066.3	1481.5	9230.7
	Placebo	PRE	30	6	165.75	242.92	1.0	1.0	59.7	205.9	978.7
		PII(M2)	31	5	156.98	274.81	1.0	1.0	75.5	199.3	1499.3
		PII(M13)	31	2	129.41	197.92	1.0	1.0	60.1	153.7	875.2

18-49ys = Subjects aged between 18 and 49 years; ⩾50ys = Subjects aged 50 years and older; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects with available results; Nmiss = number of subjects with missing results; SD = Standard Deviation; Q1,Q3 = First and third quartiles;Min/Max = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13)

The VRR of the frequency of gE-specific CD4[2+] T-cells in the HZ/su group, at Months 2 and 13 were 71.4% and 56.7%, respectively. In the Placebo group, no subject met the definition of responder at any timepoint.

CMI results by age strata showed a trend for lower CMI in the >50YOA stratum when compared to the younger stratum (Table 36).

Table 36. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cell at Month 0, 2 and 13 by age strata (adapted ATP cohort for CMI immunogenicity)

Immune marker	Sub-group	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	18-49ys	HZ/su	PRE	12	1	113.92	133.69	1.0	16.3	58.5	174.8	418.5
			PII(M2)	12	1	2617.08	1385.58	499.5	1504.9	2855.3	3695.1	4798.1
			PII(M13)	13	0	2181.56	2657.02	1.0	973.5	1247.2	1765.2	9230.7
		Placebo	PRE	12	0	267.49	236.41	1.0	59.7	253.2	423.0	684.2
			PII(M2)	10	2	129.47	98.29	1.0	43.1	144.3	199.3	268.4
			PII(M13)	11	0	204.90	188.49	1.0	33.4	153.7	367.3	574.1
	≥50ys	HZ/su	PRE	19	4	109.00	210.55	1.0	1.0	1.0	79.0	716.3
			PII(M2)	20	3	2322.67	2462.78	1.0	379.8	1908.8	3343.1	9334.6
			PII(M13)	20	3	761.51	553.31	1.4	214.9	849.9	1124.0	1841.0
		Placebo	PRE	18	6	97.92	228.74	1.0	1.0	20.8	87.9	978.7
			PII(M2)	21	3	170.08	329.21	1.0	1.0	61.4	189.5	1499.3
			PII(M13)	20	2	87.89	195.03	1.0	1.0	15.7	99.3	875.2

18-49ys = Subjects aged between 18 and 49 years; ≥50ys = Subjects aged 50 years and older; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects with available results; Nmiss = number of subjects with missing results; SD = Standard Deviation; Q1,Q3 = First and third quartiles;Min/Max = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PII(M2) = Post-vaccination Dose II (Month 2); PII(M13) = Post-vaccination Dose II (Month 13)

Similarly, than for the humoral immune responses, results of the analyses performed on the TVC were consistent with results of the analyses performed on the ATP cohort for CMI and the ATP cohort for CMI persistence.

Supportive studies

Shingrix has also been studied in two supportive phase I/II clinical studies (ZOSTER-001 and ZOSTER-015) in 135 adults ≥18 YOA with autologous HSCT (N=61) or Human Immunodeficiency Virus (HIV) infection (N=74). The data from these two studies were presented in the MAA. Both studies support the schedule selection in the immunocompromised (IC) clinical development plan (CDP) and the extension of indication. Relevant data are summarized below.

Zoster-001

ZOSTER-001 was a Phase I/IIa randomized, observer-blind, placebo-controlled, multicentre study that evaluated the safety and immunogenicity of HZ/su (gE/AS01B), in comparison to gE/AS01E (50 µg gE combined with half dose AS01B adjuvant) and to Placebo when administered IM as 2 doses or 3 doses.

Eligible subjects were patients ≥18 YOA who underwent autologous HCT within the past 50-70 days for treatment of Hodgkin lymphoma, non-Hodgkin lymphoma (T or B cell), myeloma or Acute Myeloid Leukemia (AML), and for who there are no plans for additional HCTs.

A total of 120 subjects were randomized into the following 4 groups:

- gE/AS01B 3-dose group: 3 doses of HZ/su at Months 0, 1, and 3 (30 subjects)
- gE/AS01E 3-dose group: 3 doses of gE/AS01E at Months 0, 1, and 3 (29 subjects)
- gE/AS01B 2-dose group: 1 dose of Placebo at Month 0 and 2 doses of HZ/su at Months 1 and 3 (31 subjects)
- Placebo group: 3 doses of Placebo at Months 0, 1, and 3 (30 subjects)

As part of the primary and secondary objectives, gE-specific humoral immune responses and CMI responses were evaluated at different time points. Both analyses were performed by treatment group and are summarized below (Table 37,Table 38 and Table 39).

Table 37. Seropositivity rates and geometric mean concentrations (GMCs) of anti-gE antibody at Months 0, 1, 2, 3, 4 and 15 (Total Vaccinated cohort excluding HZ cases)

				≥ 18 MIU/ML				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.GE AB.IGG	gEAS1B3	PRE	30	30	100	88.4	100	531.2	402.6	700.8	100.8	2031.2
		PI(M1)	30	30	100	88.4	100	1489.7	847.3	2619.0	64.0	36916.5
		PII(M2)	30	30	100	88.4	100	11963.0	4739.4	30196.6	167.1	394391.4
		PII(M3)	28	28	100	87.7	100	13412.9	4967.1	36219.7	141.9	450269.7
		PIII(M4)	29	29	100	88.1	100	29192.9	11004.7	77442.1	141.6	733821.4
		PIII(M15)	27	27	100	87.2	100	8052.7	3333.4	19453.7	156.1	254488.2
	gEAS1E3	PRE	26	25	96.2	80.4	99.9	528.9	286.6	975.9	<18.0	12917.6
		PI(M1)	26	25	96.2	80.4	99.9	1360.3	690.3	2680.4	<18.0	33046.2
		PII(M2)	26	26	100	86.8	100	14469.5	6478.0	32319.5	517.2	392981.1
		PII(M3)	25	25	100	86.3	100	17478.8	7312.5	41778.6	329.4	421271.3
		PIII(M4)	24	24	100	85.8	100	28990.6	10733.7	78300.8	260.8	456515.7
		PIII(M15)	22	22	100	84.6	100	9165.5	3796.0	22130.1	134.6	195308.8
	P_gE1B2	PRE	30	30	100	88.4	100	448.0	289.7	692.8	28.4	3151.2
		PI(M1)	30	30	100	88.4	100	376.1	239.7	590.1	24.6	3318.4
		PII(M2)	29	29	100	88.1	100	1047.8	564.8	1943.9	28.8	24089.9
		PII(M3)	28	28	100	87.7	100	972.6	520.6	1817.2	23.9	19146.1
		PIII(M4)	27	27	100	87.2	100	11064.6	4361.2	28071.8	283.7	392746.3
		PIII(M15)	23	23	100	85.2	100	2968.0	1184.7	7436.1	67.2	115866.5
	Placebo	PRE	28	28	100	87.7	100	661.8	464.9	942.2	197.0	5265.8
		PI(M1)	27	27	100	87.2	100	630.9	422.0	943.1	114.5	4728.5
		PII(M2)	26	26	100	86.8	100	525.2	341.6	807.4	85.1	4540.1
		PII(M3)	27	27	100	87.2	100	481.9	293.1	792.3	57.5	9580.3
		PIII(M4)	25	25	100	86.3	100	410.2	241.5	696.8	35.9	4312.6
		PIII(M15)	21	21	100	83.9	100	362.3	170.7	768.7	26.1	5988.9

gEAS1B3 = gE/AS01B 3 doses; gEAS1E3 = gE/AS01E 3 doses; P_gE1B2 = Placebo+ gE/AS01B 2 doses; Placebo = Placebo 3 doses; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range (anti-gE Ab concentration ≥ 18 mIU/mL)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Day 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M3) = Post-vaccination Dose II (Month 3); PIII(M4) = Post-vaccination Dose III (Month 4); PIII(M15) = Post-vaccination Dose III (Month 15)

Table 38. Descriptive statistics of the frequency gE-specific CD4(2+) T-cells at Months 0, 1, 2, 3 and 4 (Total Vaccinated Cohort)

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
ALL DOUBLES	gE/AS01$_B$3	PRE	27	3	116.53	180.53	1	1.0	63.9	165.9	709
		PI(M1)	30	0	856.69	1551.94	1	101.6	412.8	671.3	7591
		PII(M2)	29	1	8830.03	9745.11	691	2458.2	5025.4	9412.8	36999
		PII(M3)	28	2	7111.22	7755.09	462	1492.6	4243.9	10364.1	24253
		PIII(M4)	27	3	11963.56	11655.09	812	3632.1	7856.8	15436.4	43222
	gE/AS01$_E$3	PRE	27	2	145.97	217.01	1	1.0	55.4	245.0	900
		PI(M1)	29	0	1376.95	3358.49	1	104.9	299.8	986.3	16971
		PII(M2)	26	3	9128.95	12539.86	1	1572.7	2547.5	13228.0	47595
		PII(M3)	24	5	8415.89	12235.84	1	1004.8	3131.8	11450.4	46316
		PIII(M4)	25	4	8114.83	9957.55	28	1235.7	5165.0	9228.2	40406
	P_gE/AS01$_B$2	PRE	28	3	83.15	90.39	1	1.0	67.6	119.2	345
		PI(M1)	28	3	91.84	118.22	1	1.0	59.0	117.9	499
		PII(M2)	27	4	1528.60	3204.39	1	100.3	541.7	1005.4	12773
		PII(M3)	25	6	827.83	1508.97	1	37.2	364.8	595.9	7205
		PIII(M4)	22	9	6974.97	10437.53	109	286.7	1769.2	9970.4	35784
	placebo	PRE	27	3	97.48	148.32	1	1.0	38.8	95.8	636
		PI(M1)	26	4	133.85	204.90	1	1.1	61.8	146.7	891

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
		PII(M2)	26	4	124.53	160.24	1	9.2	65.9	190.9	638
		PII(M3)	25	5	158.13	180.84	1	13.5	92.8	259.6	610
		PIII(M4)	23	7	96.15	108.08	1	24.2	58.5	137.8	483

$gE/AS01_B3$ = $gE/AS01_B$ 3 doses; $gE/AS01_E3$ = $gE/AS01_E$ 3 doses; $P\_gE/AS01_B2$ = placebo for Dose 1 +$gE/AS01_B$ for Dose 2 and 3
placebo = placebo 3 doses; N = number of subjects with available results; Nmiss = number of subjects with missing results
SD = Standard Deviation; Q1,Q3 = First and third quartiles; Min/Max = Minimum/Maximum; PRE = Pre-vaccination (Day 0); PI(M1) = Post-vaccination Dose I (Month 1); PII(M2) = Post-vaccination Dose II (Month 2); PII(M3) = Post-vaccination Dose II (Month 3)
PIII(M4)= Post-vaccination Dose III (Month 4)

Table 39. Descriptive statistics of the frequency gE-specific CD4(2+) T-cells at Month 15 (Total Vaccinated cohort excluding HZ cases)

Immune marker	Group	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
ALL DOUBLES	gEAS1B3	26	4	6865.36	6557.75	772.6	2220.4	4617.1	9688.0	25175.7
	gEAS1E3	18	9	5900.24	7728.98	2.8	1946.4	3240.9	9559.5	32844.3
	P_gE1B2	18	13	3859.68	4771.08	1.0	505.5	2077.9	5109.7	19064.7
	Placebo	18	10	71.03	80.76	1.0	1.0	51.5	116.6	235.0

gEAS1B3 = $gE/AS01_B$ 3 doses; gEAS1E3 = $gE/AS01_E$ 3 doses; P_gE1B2 = Placebo+$gE/AS01_B$ 2 doses
Placebo = Placebo 3 doses; N = number of subjects with available results;Nmiss = number of subjects with missing results
SD = Standard Deviation; Q1,Q3 = First and third quartiles; Min/Max = Minimum/Maximum

Based on these results, a 2-dose schedule was selected for further evaluation of HZ/su in Phase II/III studies in IC populations.

Besides, the study groups in ZOSTER-001 that assessed a 3-dose and a 2-dose schedule of HZ/su were initiated at different time points after transplant, with the 3-dose schedule initiated 50-70 days after transplant and the 2-dose schedule initiated 1 month thereafter. Based on these results, an early initiation of vaccination, with the first dose given 50-70 days after autologous HSCT was chosen for ZOSTER-002.

Zoster-015

Zoster-015 was a Phase I/IIa randomized, observer-blind, placebo-controlled, multicenter, multi-country study evaluated the safety and immunogenicity of HZ/su when administered IM as 3 doses to HIV-infected adults ≥18 YOA.

Three cohorts of HIV-infected subjects were enrolled (n=123):

- ART High CD4 cohort (ARTHCD4, n=94): ART-treated subjects with a CD4 T cell count: ≥200 cells/mm^3.
- ART Low CD4 cohort (ARTLCD4, n=14): ART-treated subjects with a CD4 T cell count: 50-199 cells/mm^3.
- Non-ART High CD4 cohort (NARTHCD, n=15): ART-naïve HIV-infected subjects with a CD4 T cell count of ≥500 cells/mm^3.

Seventy-four of them were in the HZ/su group and 49 in the Placebo group. The ATP cohorts for immunogenicity consisted in 54 vaccinated (ARTHCD4 n=44, ARTLCD4 n=5, NARTCD n=5) and 37 placebo subjects (ARTHCD4 n=30, ARTLCD4 n=3, NARTCD n=4).

For the ART High CD4 and ART Low CD4 cohorts, subjects were to be stable on ART for at least 1 year, have a CD4 T-cell count ≥50 cells/mm3 at screening, and have an undetectable VL (i.e. < 40 copies/mL, based on the cut-off of the HIV VL test used) at screening.

At Visit 1, eligible subjects were allocated (3/2) to two parallel treatment groups (i.e., gE/AS01B and Placebo group, respectively). The gE/AS01B group received a dose of vaccine at Month 0, Month 2 and Month 6.

Specific humoral and cellular immune responses were evaluated one month post-final vaccination (Month 7) (primary objective) in addition to diverse timepoints up to 12 months post-final vaccination (secondary objectives).

Anti-gE Ab titers and frequencies of gE-specific CD4 T cells by time points are summarized in Table 40 and Table 41.

Table 40. SPR and GMCs of anti-gE Ab at Months 0, 1, 3, 6, 7, and 18 in all subjects (ATP cohort for persistence)

				≥ 18 mIU/ml				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
VZV.gE Ab.IgG	gEAS01B	PRE	49	49	100	92.7	100	1237.2	890.7	1718.4	142.5	19804.2
		PI(M1)	50	50	100	92.9	100	24555.2	18320.3	32912.0	2281.2	145765.8
		PI(M2)	49	49	100	92.7	100	17294.5	12838.0	23298.0	1688.1	135082.4
		PII(M3)	50	50	100	92.9	100	50648.7	40495.4	63347.7	4076.1	243583.5
		PII(M6)	50	50	100	92.9	100	34843.8	27358.4	44377.2	3127.4	228553.1
		PIII(M7)	50	50	100	92.9	100	65984.9	52287.0	83271.2	6545.4	343105.9
		PIII(M18)	49	49	100	92.7	100	25242.2	19618.9	32477.3	2154.9	240299.3
	Placebo	PRE	37	36	97.3	85.8	99.9	904.0	585.0	1397.0	<18.0	7690.7
		PI(M1)	36	36	100	90.3	100	1123.1	790.0	1596.7	29.9	7647.6
		PI(M2)	37	36	97.3	85.8	99.9	963.6	627.0	1480.9	<18.0	8016.9
		PII(M3)	37	36	97.3	85.8	99.9	1056.4	686.2	1626.1	<18.0	8183.2
		PII(M6)	37	36	97.3	85.8	99.9	1082.2	703.0	1666.0	<18.0	9187.3
		PIII(M7)	36	35	97.2	85.5	99.9	1086.9	694.0	1702.2	<18.0	9719.1
		PIII(M18)	37	36	97.3	85.8	99.9	918.0	588.0	1433.1	<18.0	11756.0

gEAS01B = 50 µg/AS01B - 3 doses; Placebo = Placebo - 3 doses; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration within the specified range (anti-gE Ab concentration ⩾ 18; mIU/mL); 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PI(M2) = Post-vaccination Dose I (Month 2); PII(M3) = Post-vaccination Dose II (Month 3); PII(M6) = Post-vaccination Dose II (Month 6); PIII(M7) = Post-vaccination Dose III (Month 7); PIII(M18) = Post-vaccination Dose III (Month 18)

Table 41. Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells at Months 0, 1, 2, 3, 6, 7, and 18 in all subjects (ATP cohort for persistence)

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4.polypositives CD40L+IL2+TNFa+IFNg	gEAS01B	PRE	32	18	225.05	255.97	1.0	17.0	112.8	386.1	1036.0
		PI(M1)	37	13	722.01	635.27	1.0	215.4	551.5	1001.2	2159.9
		PI(M2)	36	14	647.61	552.18	1.0	257.3	539.1	892.4	2642.2
		PII(M3)	40	10	3521.04	3007.50	306.0	1516.7	2667.7	4735.0	11672.1
		PII(M6)	27	23	2554.97	1964.71	349.1	1090.1	2028.1	3438.6	8677.8
		PIII(M7)	29	21	4775.12	5448.64	249.3	2066.8	2596.1	5298.6	26852.5
		PIII(M18)	49	1	1929.30	1603.50	1.0	770.0	1533.0	2643.1	6506.4
	Placebo	PRE	27	10	128.35	174.86	1.0	1.0	52.1	196.2	576.1
		PI(M1)	26	11	143.01	311.18	1.0	1.0	7.0	167.7	1514.7
		PI(M2)	26	11	163.92	223.43	1.0	1.0	58.1	297.2	692.6
		PII(M3)	28	9	177.49	251.89	1.0	1.0	42.0	297.5	905.5
		PII(M6)	21	16	206.37	344.92	1.0	1.0	146.0	229.8	1598.0
		PIII(M7)	20	17	220.09	367.29	1.0	10.7	122.6	270.4	1670.0
		PIII(M18)	35	2	139.50	219.57	1.0	1.0	71.8	156.9	1187.3

gEAS01B = 50 μ g/AS01B - 3 doses; Placebo = Placebo - 3 doses; GMC = geometric mean antibody concentration calculated on all subjects; N = number of subjects with available results; n/% = number/percentage of subjects with concentration within the specified range (anti-gE Ab concentration ⩾ 18; mIU/mL); 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination (Month 0); PI(M1) = Post-vaccination Dose I (Month 1); PI(M2) = Post-vaccination Dose I (Month 2); PII(M3) = Post-vaccination Dose II (Month 3); PII(M6) = Post-vaccination Dose II (Month 6); PIII(M7) = Post-vaccination Dose III (Month 7); PIII(M18) = Post-vaccination Dose III (Month 18)

2.3.4. Discussion on clinical pharmacology

1. Introduction

At the moment, Shingrix is indicated in adults aged above 50 years to prevent Herpes Zoster and PHN. Immuncompromised persons were addressed in the "warning section" of the SmPC. There was an unmet medical need for adults with immunosuppressed condition with increased risk of Herpes Zoster.

The MAH conducted 4 pivotal studies and 2 supportive studies in various immunocompromised (IC) adult populations. There is a large variety of IC population, and it was therefore not possible to study each population. The MAH selected the studied populations based on their high risk of VZV reactivation. The inclusion of these patient groups in the clinical trials deemed acceptable as representatives for immunocompromised subjects.

ZOSTER-001 (supportive) and ZOSTER-002 (pivotal) studies included autologous HCT recipients, study ZOSTER-015 (supportive) HIV-infected adults, study ZOSTER-028 (pivotal) adults with solid tumors and receiving chemotherapy, study ZOSTER-039 (pivotal) adults with hematologic malignancies who were vaccinated during a cancer therapy course or after the full cancer therapy course, and study ZOSTER-041 (pivotal) renal transplant recipients.

Patients were receiving various immunosuppressive (IS) or immunomodulating treatments to treat their underlying diseases, before, during or after the vaccination, that could interfere with the vaccine response. Depending of the underlying disease, the treatment (type and duration) and the timing of the vaccination, elicitation of gE-specific CD4 T cells and/or anti-gE Ab titers (as well as other immune cells not investigated) could be differently affected.

In study ZOSTER-002, only subjects who underwent autologous HCT within 50-70 days prior vaccination were eligible. This delay between transplant and vaccination was based on results of study ZOSTER-001. One month after the first vaccine dose, relatively similar anti-gE GMCs and frequencies of specific CD4 T cells were measured when vaccination occurred 50-70 days or 80-100 days after autologous HCT. Serology results were similar post-dose 2. An early vaccination post-transplant might be beneficial to this at risk population. The choice of this vaccination timing is endorsed.

In study ZOSTER-041, subjects needed to have received an ABO compatible allogeneic renal transplant 4 to 18 months prior to first vaccination, were receiving chronic IS therapy for the prevention of allograft rejection ≥1 month prior to first vaccination, were without an episode of allograft rejection ≤3 months prior to first vaccination, and had stable renal function and multiple dialysis options.

In study ZOSTER-015, subjects had to be HIV-1 infected with diagnosis ≥1 year prior to enrolment. Three sub-groups of subjects were to be enrolled in this study, (i) ART-treated subjects with a CD4 T cell count of ≥200 cells/mm^3, (ii) ART-treated subjects with a CD4 T cell count of 50-199 cells/mm^3, and (iii) ART-naïve HIV-infected subjects with a CD4 T cell count of ≥500 cells/mm^3. However, as indicated in the SmPC, the majority (76.42%) of the subjects were stable on antiretroviral therapy (for at least one year) with a CD4 T-cell count ≥200 /mm3. The immunogenicity findings are therefore applicable for these subjects only. '*Use of Shingrix in immunocompromised adults*' as missing information was removed from the updated RMP.

In all studies, subjects were excluded when vaccinated against HZ or varicella <1 year prior to first vaccination, planned to be vaccinated during the study with an HZ or varicella vaccine other than the study vaccine, if an HZ or varicella episode occurred <1 year prior to first vaccination, and if at risk of possible adverse reactions to the vaccine.

Except study ZOSTER-001, which was a small-scale early phase study, all other 5 studies were randomised observer-blind, placebo-controlled, multi-center studies, conducted in multiple countries. All the studies used the final selected HZ/su formulation, i.e. 50 µg gE adjuvanted with AS01B. In all 4 pivotal studies, HZ/su was administered according to a 2-dose flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose. This is different from the vaccination schedule used in previous studies supporting the initial MA, in which HZ/su was administered according to a fixed 0, 2-month schedule. The choice for a flexible schedule with an interval of 1-2 month between doses for IC individuals was driven by the results of study ZOSTER-001; anti-gE GMCs were comparable at one-month post-dose 2 when the two doses of HZ/su were administered at one or two months' time interval. These results were not confirmed by a larger study although ZOSTER-001 was a small size study. Stratified analyses according to the time interval between doses were not done in studies included in the present submission. However, not performing such analyses could be acceptable since there is no CoP and since an efficacy trial was conducted in IC population (study ZOSTER-002) and demonstrated VE using this flexible schedule. This flexible schedule allows for an easier integration of the vaccination into the medical interventions of IC patients. In addition, in the SmPC, the primary vaccination schedule remains unchanged, and the additional schedule is presented appropriately*: 'For subjects who are immunodeficient or immunosuppressed due to disease or therapy, and whom would benefit from a shorter vaccination schedule, the second dose can be given 1 to 2 months after the initial dose (see section 5.1).'*

The randomization algorithm used a minimization procedure accounting for age, gender, center, and relevant factors that were specific to each study, such as type of underlying disease, type of therapy, timing of vaccination in relation to timing of therapy. Subjects in the 5 studies were followed up for at least 12 months post last vaccination. Study design and methods are endorsed.

2. Immunogenicity

3.1. Objectives and endpoints, analyses

Confirmatory immunogenicity endpoints in the pivotal immunogenicity studies ZOSTER-028, ZOSTER-039 and ZOSTER-041 included both humoral (anti-gE Ab) and CMI (gE-specific CD4+ T-cells expressing ≥2 activation markers involved in immunity such as interferon gamma (IFN-γ), interleukin 2 (IL-2), tumor necrosis factor alpha (TNF-α), and cluster of differentiation marker 40 ligand (CD40L)) endpoints. The choice of both endpoints was endorsed by the CHMP, in spite of several limitations.

In ZOSTER-002, humoral immune responses to gE and cell-mediated immunity (CMI) responses were evaluated at different time points, as descriptive endpoints. Such analyses were also part of the endpoints of the studies supporting the initial MA.

Antibodies were shown to be involved in controlling both primary VZV infection and reactivation. Functional activities include antibody-dependent cell-mediated cytotoxicity (ADCC) and neutralization of cell-free virus (review in Laing 2018). Ab from varicella or HZ patients preferentially bind to gB and gE regions of VZV proteins, supporting the choice of the MAH to measure anti-gE specific Ab. However, the anti-gE ELISA assay does not measure the quality and functionality of the response. There is no characterization of the Ab in terms of sub-classes, affinity/avidity, and functionality which might be different in IC when compared to immunocompetent subjects. It is acknowledged that a good correlation of anti-VZV neutralizing Ab titers and anti-gE Ab titers was shown in samples from immunocompetent

subjects included in study ZOSTER-010 (submitted at the initial MAA). T and B cells of IC patients might however respond differently to the antigen according to their disease and/or immunosuppressive/immunomodulatory therapy, which would have an impact on the Ab generation (quality and magnitude).

The CMI endpoint is only a picture of the whole T cell immune response that may be induced by the vaccine. In addition to the induction of specific-Ab, innate immunity is activated and both CD4 and CD8 T cells are induced after VZV infection. Studies of systemic memory T cell responses in latently infected individuals reveal antigen-specific Th1 cells (expressing IFN-γ, IL-2, and TNF-α), cytotoxic T lymphocytes within both CD4 and CD8 subsets (review in Laing 2018). CD4 T cell reactivity to gE was observed in healthy virus carriers. It was also shown that VZV gE (an gB) is a major target of CD4 and CD8 T cells reconstituting during zoster after allogenic transplant (Kleemann, 2012), supporting the choice of the MAH to study the induction of gE-specific CD4 T cell after vaccination. These findings also suggest the potential clinical efficacy with the use of VZV glycoprotein subunit vaccines. Evidence of specific CD4[2+] T cells induction indicates a vaccine response after encountering VZV-antigens but the clinical relevance is not known. Comparison with the immune responses induced by the natural infection and additional characterization of the vaccine-induced responses, such as the characterization of the Th profile (Th17, Th2, Tfh, etc) or the memory profile (effector vs central memory), as well as the characterisation of antigens-specific CD8 T cells, might give a clearer descriptive view of immune responses overall and of the impact of the different diseases on VZV/gE responses. But it is acknowledged that the clinical relevance is not known.
Again, T (and B cells) of IC patients may respond differently to the vaccination (pre-existing memory cells but also naïve cells that would be primed by the vaccination) depending of the disease and/or the therapy of the patient. The quantity of circulating primed-cells and antigen-presenting cells might also be lower in immunocompromised subjects. Thus, the quantity and the quality of the response may be affected.

Immunogenicity endpoints were descriptive endpoints in study ZOSTER-002 and confirmatory immunogenicity endpoints in the pivotal immunogenicity studies ZOSTER-028, ZOSTER-039 and ZOSTER-041. In these last 3 studies a hierarchical procedure was applied to control for Type I error. The objectives were assessed sequentially in order of ascending rank until an objective was not met. At this point, the evaluation proceeded with descriptive analyses of the remaining objectives.

Success criteria, based on VRR and GM ratio, were defined to evaluate the magnitude of the humoral and cellular immune responses induced by the vaccine. These criteria were arbitrarily defined and relatively stringent (except for the CMI GM ratio for study ZOSTER-028). These criteria were considered acceptable by CHMP.

Humoral immunogenicity results were expressed in term of GMC, fold increase over pre-vaccination, seropositivity rate and vaccine response rate as for the pivotal studies supporting the MA which is appropriate. Whereas all different results expressions are informative, the GMC is considered as the best.

Cellular immunogenicity results were expressed in terms of frequency of CD4[2+] T cells, fold increase over pre-vaccination of gE-specific CD4[2+] T cells and VRR. In this case, the cut-off was considered to be 320 per 10^6 CD4 T cells. The rationale of the choice of this cut-off is not clear. The issue is however not pursued since this cut-off was used in all pivotal studies and was already applied in studies supporting the initial MA. The choice to express the CMI data in term of (at least) double-positive cell frequencies allow for better specificity compared to single-positive cells frequencies. However, the fact that the results were not expressed in number of circulating cells/ml of blood is a limitation for results interpretation. The number of circulating CD4 may be lower in IC than in immunocompetent subjects and may vary according to several factors, including underlying diseases and IS treatment (type and duration). CD4

number could also vary according to the time after transplant in HCT patients with an immune system under reconstitution.

For all pivotal studies, the primary immunogenicity analysis was based on the according to protocol (ATP) cohort for humoral immunogenicity or CMI, as appropriate and the primary persistence analysis was based on the ATP cohort for humoral or CMI persistence, as appropriate.
Analysis adjusting for relevant factors such as treatment, underlying disease or age were further performed.

3.2. Assays

Two assays were used in the pivotal trials, an ELISA to measure the concentration of Ab specific to gE and a flow cytometry assays to detect gE-specific CD4 T cells. Methods were overall endorsed. Validation and SOPs that were not yet submitted at the Initial MAA were submitted (except one) in the current application. A summary of the main changes was also provided.

Concentration of circulating Ab specific to gE was measured by ELISA by using the same protocol as for the pivotal studies supporting the initial MA.

Measurements of CMI responses were performed on thawed peripheral blood mononuclear cells (PBMCs) by intracellular cytokine staining (ICS). The gE ICS assay measures the frequency of gE-specific CD4+ T cells expressing the activation marker CD40L and three Th1 cytokines in vitro. Specific-CD8 T cells were not evidence by the current method. The validation of the assay was updated to ensure adequate measurement of low frequencies of gE-specific CD4 T cells. The protocol was also updated by integrating different changes that would improve the detection of specific T cell but also slightly affect the results. How the potential data analyses biases were minimized was not presented. However, because of the experience of the MAH and because results will not be strictly compared between studies, this is deemed acceptable. As mentioned above, an additional reason to not compare results between studies is that results were expressed in term of frequency and not in number of circulating cells/ml of blood.

The MAH provided further documentation to probe method validation for the Anti-gE ELISA analysis. Regarding gE ICS analysis, precision and linearity were further evaluated before using the assay on the pivotal study samples.
The PBMC viability evaluation upon thawing and after the ICS (at the time of PBMCs acquisition) was endorsed as well as the addition of an anti-human CD3 Ab for the PBMCs staining. Both staining (dead and CD3 cells) are a real added value to ensure the detection of the appropriate target cells.

3.3 Results

Vaccination
Based on the ZOSTER-001 study results, vaccine recipients were administered with the first dose 50-70 days post-transplant (see assessment ZOSTER-001, in section supportive studies). Although this is currently unusual to vaccinate as earlier after transplantation, this might be relevant since HCT recipients are at high risk of HZ.
The flexible 2-dose schedule is discussed in section clinical aspects, introduction. Although serology results might have been presented according to time interval between dose 1 and dose 2 to confirm results from study ZOSTER-001, such analysis are not deemed necessary in view of the efficacy results and the absence of CoP.

Demographic characteristics

Characteristics of the ATP cohort for humoral immunogenicity and the ATP cohort for CMI immunogenicity were generally comparable and representative of those of TVC. Age, gender and geographic ancestry were in general well balanced between groups. More subjects of the age stratum above 50 years of age were enrolled compared to the age stratum 18-49 years of age. Median age at first vaccination was in the same range for all studies (46.5-57.0 YOA). Most subjects were males, except for study ZOSTER-028. Most of the subjects were Caucasian. Some characteristics (gender and geographic ancestry) were imbalanced between groups in the ATP cohort for CMI immunogenicity (studies ZOSTER-028 and ZOSTER-041). This could be attributed to the fact that ATP cohort for CMI immunogenicity was a sub-group of the subjects selected in countries that had access to a PBMCs processing facility. The impact on the results is unknown.
Other characteristics were not always similar between ATP cohorts for humoral or CMI immunogenicity (such as proportion of haematological malignancies in ZOSTER-039 or of tumour in ZOSTER-028) or not always balanced between groups for the ATP cohort for CMI immunogenicity (such as proportion of tumour in ZOSTER-028). Many factors could influence the observed immunogenicity in addition to the gender and the underlying malignancy, such as the time interval between vaccination doses or between blood samples after-vaccination, the moment of the vaccination regarding the duration under IS or the number of chemotherapy cycles, etc. Because of these many variables, the impact of these differences in characteristics between ATP cohorts or between groups within an ATP cohort on the results is not known.

Baseline characteristics
Most of the subjects, both HZ/su vaccinated and placebo, were anti-gE seropositive at baseline (≥97 mIU/ml). This suggest that most of the subjects experienced a previous natural infection with VZV or a vaccination >1 year before HZ/su vaccination and that no (or very few) data for seronegative subjects were therefore generated. Results were not stratified according to the VZV infection or vaccination status. VZV-naive subjects are not at risk of HZ occurrence, questioning the impact of the HZ/su vaccination of VZV-naïve subjects in term of both safety and immunogenicity (see safety discussion). The MAH explained previously that NC data suggest that HZ/su is not expected to induce appropriate primary immune responses needed to protect VZV-naïve children against varicella and by extension to protect VZV-naïve individuals against varicella. Accordingly, the SmPC reflects that HZ/su is not indicated for prevention of primary varicella infection.
Very small numbers of subjects previously vaccinated against varicella were included in studies ZOSTER-028 (n=1), ZOSTER-039 (n=2) and ZOSTER-041 (n=3). History of previous vaccination was not collected in studies ZOSTER-001, ZOSTER-002 and ZOSTER-015. No specific analyses were therefore performed in this subset of subjects, and, consequently, it is not known if the vaccine response will be of the same magnitude and quality in subjects that did not experienced chickenpox because of vaccination against varicella in the infancy. At the moment, most of the subjects > 18YOA experienced varicella but this would change, at least in certain countries, in the coming years. In addition, these subjects are in general considered not at risk of reactivation. Literature indicates that HZ cases are nevertheless reported (Tseng 2011, Baxter 2013, Weinmann 2013, Civen 2016), although at a much lower incidence than in non-vaccinated children and adolescents. This incidence might increase with age and with IC conditions that subjects might experience. Based on study ZOSTER-048 results, no safety concern is expected in subjects previously vaccinated against varicella in the infancy. It is considered that the history of varicella vaccination will be taken into account in the official recommendations, and/or in the benefit/risk assessment made by the practitioner. The MAH is monitoring the epidemiology of VZV in Europe (Part II in the RMP). The MAH is also asked to discuss through the PSUR new data (vigilance, literature) on the medical need, immunogenicity/safety/efficacy of Shingrix in this particular subgroups of patients. See also efficacy and safety discussion.

Proportion of seropositive subjects with gE specific-CD4 T cells at baseline was not presented. Because the number of subjects for CMI analysis is limited, it is not expected that interpretable results would be available.

HZ/su-induced immunity

Overall, the vaccination with HZ/su induced a strong anti-gE Ab and a gE-specific T cell response in the IC recipients from all 4 pivotal studies and study ZOSTER-15 (based on confirmatory and descriptive analyses). VRRs and GMCs ratio results were consistent with the GMC results.

The confirmatory objectives of studies ZOSTER-028, ZOSTER-039 and ZOSTER-41 were met, except the secondary confirmatory objective in terms of VRR for gE-specific CD4 T cell frequencies at Month 2 that was not met.

Across IC population of studies ZOSTER-002, ZOSTER-039 and ZOSTER-041, post-vaccination anti-gE GMC peaked after 2 doses, then decreased but remained higher than the baseline level up to 1 or 2 years post dose 2 (depending of the studies). Range of values were comparable for ZOSTER-002 and ZOSTER-039 studies. Results of study ZOSTER-041 were higher than those observed in both other studies (and comparable to those of study ZOSTER-028 observed post-dose 2). In study ZOSTER-028, the anti-gE GMC peaked post-dose 1 and decreased thereafter. The absence of Ab titers enhancement by the second vaccine dose is surprising. This might be because the second dose was given at the first day of a subsequent chemotherapy cycle, blunting the immune response induced by the vaccine. Ab GMC remained higher than the baseline level 1 year post-vaccination. Range of values tended to be higher than those observed in study ZOSTER-002. The anti-gE Ab response, detected in all 4 pivotal studies, were however lower than those observed in the pivotal trial ZOSTER-006 conducted in immunocompetent adults (See SmPC, ZOSTER-006 study, median of anti-gE Ab level post-dose 2 was 53,375 mIU/ml with a median at baseline of 1283 mIU/ml).

Robust Ab response were already observed post-dose 2 in study ZOSTER-015. The response were in the same range than those observed in study ZOSTER-006. These subjects received a third of vaccine 6 month post first vaccination. Hence, the 1-year data cannot be compared with those of the pivotal studies.

Data were further analysed by age (all pivotal studies), underlying diseases (studies ZOSTER-002, ZOSTER-028, and ZOSTER-039), timing of vaccination in relation to the particular chemotherapy/IS cancer therapy cycle (studies ZOSTER-028 and ZOSTER-039), IS treatment (study ZOSTER-041) strata. No consistent trend was observed when comparing the vaccine-induced Ab results for the two age strata; Humoral responses were comparable between 18-49YOA and ≥50YOA groups in studies ZOSTER-002 and ZOSTER-028, whereas higher anti-gE GMC were observed in the younger group in studies ZOSTER-039 and ZOSTER-041.

In ZOSTER-002 and ZOSTER-039 studies, anti-gE Ab responses were higher for patients with multiple myeloma (MM) when compared to subjects with other underlying diseases, particularly NHBCL and CLL. This was already shown in study ZOSTER-001 (Stadtmauer, 2014) and anticipated for CLL patients. This lower vaccine-induced immune responses might be explained by the fact that NHBCL patients generally have undergone various chemotherapy treatments that could be highly lymphotoxic before the collection of PBMCs for the autologous stem cells transplantation. Conversely, the HCT is generally the first line treatment for MM, i.e. with no/few IS treatment before the PBMC collection or HZ/su vaccination. In study ZOTER-039, rituximab or a rituximab-containing regimen that deplete B cells were administered to the majority of the NHBCL and CLL patients within interval between 6 months prior to vaccination and 1 month post-dose 2. Immunosuppressive/immunomodulating therapy post-HCT is current practice after allo-transplant but also for other subgroups of patient. In addition, new therapies are currently used or may be developed, for which the impact on protective response might be important. Therapies such as Janus kinase (JAK) inhibitors and other treatments such as IL-2 inhibitors, IL-12/IL-23 inhibitor, leflunomide/teriflunomide, IL-17 inhibitor, abatacept and anti-integrin inhibitor have not been used in the

subjects who participated in pivotal IC studies.The consequences on the short and long-term protection is not known. This concern is addressed in the SmPC by stating that the studies were not designed to assess the impact of specific immunosuppressive treatments on vaccine efficacy. Not all types of immunosuppressive therapies were used in the populations studied.

In study ZOSTER-002, only 22.5% and 22.1% of the subjects received at least one IS treatment from HSCT up to 30 days after Dose 2 (mTVC). In study ZOSTER-039, higher anti-gE Ab responses from 1 month up to 1 year after the second vaccination dose were observed when the vaccine was administered after the cancer therapy when compared to an administration during the cancer therapy. In study ZOSTER-028, higher Ab GMCs were observed post-vaccination in the group of subjects vaccinated before the cancer therapy (PreChemo) when compared to the group of subjects vaccinated during the course of the therapy (OnChemo). Results of study ZOSTER-041 (slight differences in Ab GMCs according to the IS therapy) are in line with those of all three other pivotal studies, i.e. interference of IS therapy on the vaccine immunogenicity up to 1 year.
All these observations indicate that underlying diseases and/or associated IS/immunomodulatory/cytotoxic treatment(s), before, during and after the vaccination period interfere in a more or less important manner on the vaccine-induced immune responses in the short and the long term.
Analysis by relevant factors such as IS treatment, cycles or time after cancer therapy were not always performed in the different studies although all these factors might influence the vaccine-induced immune responses. The timing of vaccination post-transplantation and the duration under IS therapy might also modulate the short- and long-term immune responses. This is applicable for both humoral and CMI responses. However, because of the many factors that might influence the responses, the limited number of subjects included in the studies (and by strata), the limitation of the immunogenicity read-out, and the absence of CoP, such additional immunogenicity analyses might not be as informative. Data from ZOSTER-028 and ZOSTER-039 indicating that lower humoral immune responses were observed when Shingrix was administered during versus before or after IS cancer therapy is presented in the SmPC. A statement to draw the attention of the HCP on the fact that most patients were not under IS therapy is also included.

In the absence of CoP, it is not possible to translate anti-gE Ab titers in clinical protection and therefore to predict higher or lower vaccine efficacy in special populations based on vaccine-induced humoral response. In study ZOSTER-002, it appears, that although low humoral immune responses were observed, VE for NHBCL patients was roughly similar to the overall VE, which is somewhat reassuring but should not be taken as a demonstration of efficacy in NHBCL patients as 95% CI are very wide.

It may therefore be impossible to associate humoral immune responses or a threshold with protection; Circulating Ab titers might not be a good marker to evaluate the protective response for all immunosuppressive conditions or the Ab concentration needed for protection might be low. It is therefore not possible to predict protection in subgroups of the population for whom efficacy data are not available. In study ZOSTER-028, even if results should be interpreted with caution because of the variable timing of vaccinations and blood sampling, Ab GMCs were similar at 1 year post-vaccination for both PreChemo and OnChemo groups although higher Ab GMCs were observed early post-vaccination in the PreChemo group when compared to the OnChemo group. So, even if Ab responses are higher in the short-term post-vaccination, this does not guarantee a persistence of the immune responses of higher magnitude. The vaccine-induced response might be different depending on the time of vaccine administration respective to IS therapy, but still not optimal to induce an adequate immune memory. The underlying disease and/or the IS/immunomodulating/cytotoxic treatments might have impaired the induction of memory B cells and long-lived plasma cells that participate in the Ab production in the long term. The induction of

VZV-specific CD4 T cells, particularly T follicular helper cells, that are most probably involved in Ab persistence, might also be impaired. Persistence of specific Ab induced by the vaccination might therefore be different between IC and immunocompetent individuals. The clinical relevance of these observations is however not known. Results of long-term persistence data are described in the SmPC tables.

Taken together, whether and when a boost will be needed to ensure long term protection in (special populations of) IC population is not known. Several boosts might be needed. The need for a boost is also questioned for subjects that were vaccinated post-HCT several years ago and reaching 50 YOA. The question can also be extended to immunocompetent subjects since the duration of long-term protection is not known. The MAH acknowledges this concern since '*Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older'* and '*Long-term immunogenicity in adults 18 years of age and older'* are included as missing information in the RMP. Whereas a long term follow-up of VE on immunocompetent subjects is planned, the MAH does not plan to assess long-term vaccine efficacy of Shingrix in IC subjects as no conclusion on the long-term efficacy would be possible due to variability of the immune status that evolves over time depending on the clinical outcome (see efficacy discussion).

A follow-up of a sub-group included in the study ZOSTER-041 is planned to assess long-term immunogenicity as well as the safety and immunogenicity of 2 additional doses of Shingrix in IC subjects (study ZOSTER-073). Although this population were vaccinated during IS therapy, subjects mounted a higher anti-gE Ab responses than patients with haematological malignancies included in ZOSTER-002 and ZOSTER-039 studies. There is therefore a limitation for extrapolating the data that will be obtained in study ZOSTER-073 to different IC populations but, on the other hand, the immunogenicity results of study ZOSTER-073 might be informative for the IC populations where the patients are on similar chronic IS therapies. Safety and immunogenicity data of booster dose(s) were gathered in studies ZOSTER-049 and ZOSTER-060 conducted in older adults. Taken together, the safety data of the 3 studies in conjunction with the immunogenicity data that will be obtained in study ZOSTER-073 would support the decision of administering a booster dose in IC patients.

HZ/su-induced specific-CD4 T cells

CMI data were more limited than the Ab data. As mentioned earlier, the interpretation of these data is limited.
Confirmatory analyses and descriptive analysis demonstrate the capacity of two doses of vaccine to elicit a specific CD4 T cell response. The frequency of gE-specific CD4[2+] T cells was still present 1 year following vaccination, even if at a lower level. The clinical relevance of these findings are unknown. There were no consistent trend in the results across studies when analyses by strata (age and underlying diseases). Overall, CMI results were not associated with anti-gE Ab concentrations.

2.3.5. Conclusions on clinical pharmacology

HZ/su was shown to be immunogenic in all 5 populations of immunocompromised subjects that were evaluated. Anti-gE Ab response was high after 2 dose of HZ/su and Ab were still present, although at a lower level, up to 1 year. gE-specific CD4 T cells were detected after 2 doses of HZ/su.

Differences in the magnitude of the immune responses were observed depending on IC condition.
There are only limited data on the impact of specific therapies on the immune responses, but there is an indirect evidence that patients under anti-CD20 antibodies present much lower humoral responses. This indirect evidence is provided by the analyses by underlying disease showing that NHBCL and CLL patients present much lower humoral responses. Lower humoral immune responses were observed when Shingrix was administered during versus before or after IS cancer therapy. These data suggest that immune

responses might be affected by different factors such as the underlying disease and type of IS therapy, but also by the timing to vaccination (before, during, after), and/or interval between vaccination and the IS therapy. Short and long-term vaccine-induced immune responses might therefore be differently affected and be variable among the large and heterogeneous population of IC patients.

In the absence of a CoP, the clinical relevance of the immunogenicity results is not known. The findings regarding the variable immunogenicity with respect to the timing of vaccination would still need to be better reflected in the SmPC. The need for boost(s) (if and when) still needs to be determined.

2.4. Clinical efficacy

2.4.1. Main studies

Vaccine efficacy in the prevention of HZ was assessed in ZOSTER-002 and as a post-hoc analysis in ZOSTER-039.

ZOSTER-002

A phase III, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' herpes zoster gE/AS01B candidate vaccine when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients

ZOSTER-039

A Phase III, randomised, observer-blind, placebo-controlled, multicentre study to assess the safety and immunogenicity of GSK Biologicals' Herpes Zoster HZ/su candidate vaccine when administered intramuscularly on a two-dose schedule to adults aged 18 years and older with haematologic malignancies.

Methods

ZOSTER-002 and ZOSTER-039 were phase III, randomised, observer-blind, placebo-controlled, multicentre, multi-country (28 and 21 countries respectively) clinical trials to assess Shingrix when administered intramuscularly on a two-dose schedule respectively to adults recipients of autologous haematopoietic stem cell transplant (HCT) and to adults with hematologic malignancies. The second dose of study vaccine/placebo was administered 1-2 months after the first dose. Subjects were to be followed at least until approximately a year after the second dose.

ZOSTER-002 was primarily conducted to evaluate the efficacy of Shingrix in the prevention of HZ, while in ZOSTER-039, efficacy analyses were performed post-hoc.

In ZOSTER-002, the cut-off date for the final triggered analysis occurred when at least the pre-specified number of confirmed HZ cases in the primary cohort for efficacy required for final analyses were accrued and all subjects have completed the Month 13 Visit. At the time of the final analysis the study was unblinded. Once follow-up was completed for ongoing suspected HZ case for at least 90 days, the study ended.

Design of studies

ZOSTER-002 and ZOSTER-039 were Phase III, randomised, placebo-controlled, observer-blinded, multi-country study (respectively 28 and 21 countries) trials with two parallel groups.

Duration of the study:

For both studies, each subject was to be followed at least until approximately 12 months after the second dose of study vaccine/placebo.

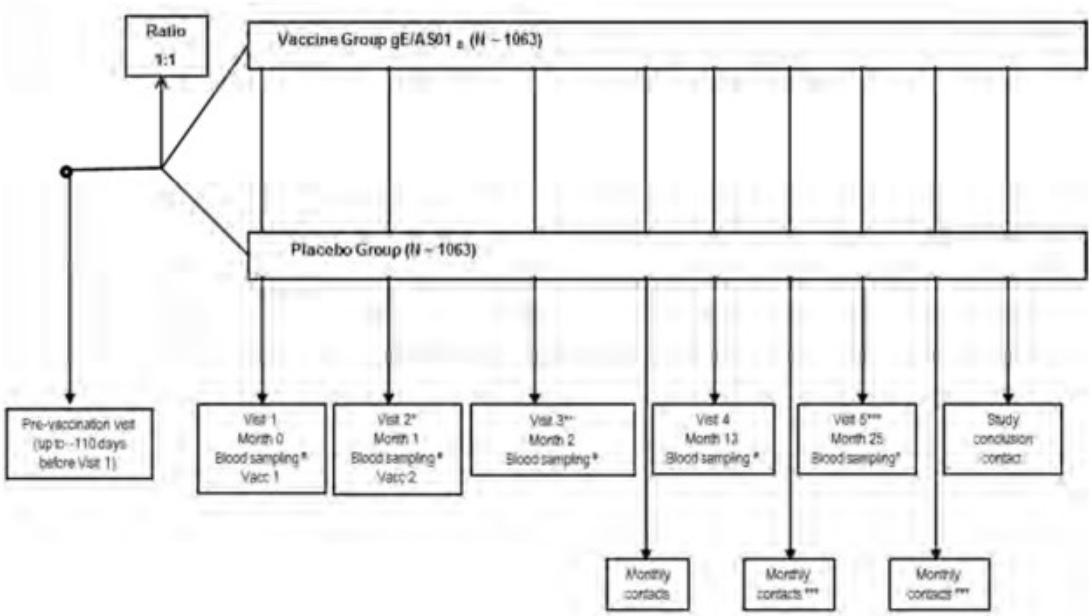
Final analysis and end of study:

ZOSTER-002:

The cut-off date for the final triggered analysis was planned when at least the pre-specified number of confirmed HZ cases in the primary cohort for efficacy required for final analyses have been accrued and all subjects have completed Visit 4 (Month 13). Study end was planned to take place when: (i) the conditions for final triggered analysis are met, and, (ii) follow-up was completed for each suspected HZ case that occurred up to the time that the study site was informed that the cut-off date for final analysis was established. Each suspected HZ case occurring up to the time that the study site was informed that the cut-off date for final triggered analysis was established, was followed for at least 90 days (unless the case is one without the characteristic HZ or VZV rash). At the time of the final analysis the study was unblinded.

ZOSTER-039:

Study end took place when all subjects had completed their Month 13/Visit 4 follow-up visit.



Blood samples will be collected from all subjects at Visit 1 and Visit 3, and additional blood samples will be collected from sub-cohorts of subjects at all study visits to assess immune responses. If criteria for study end are met before all subjects of the immunogenicity sub-cohorts reach Visit 5, then no blood sample for these subjects should be taken anymore at Visit 5.

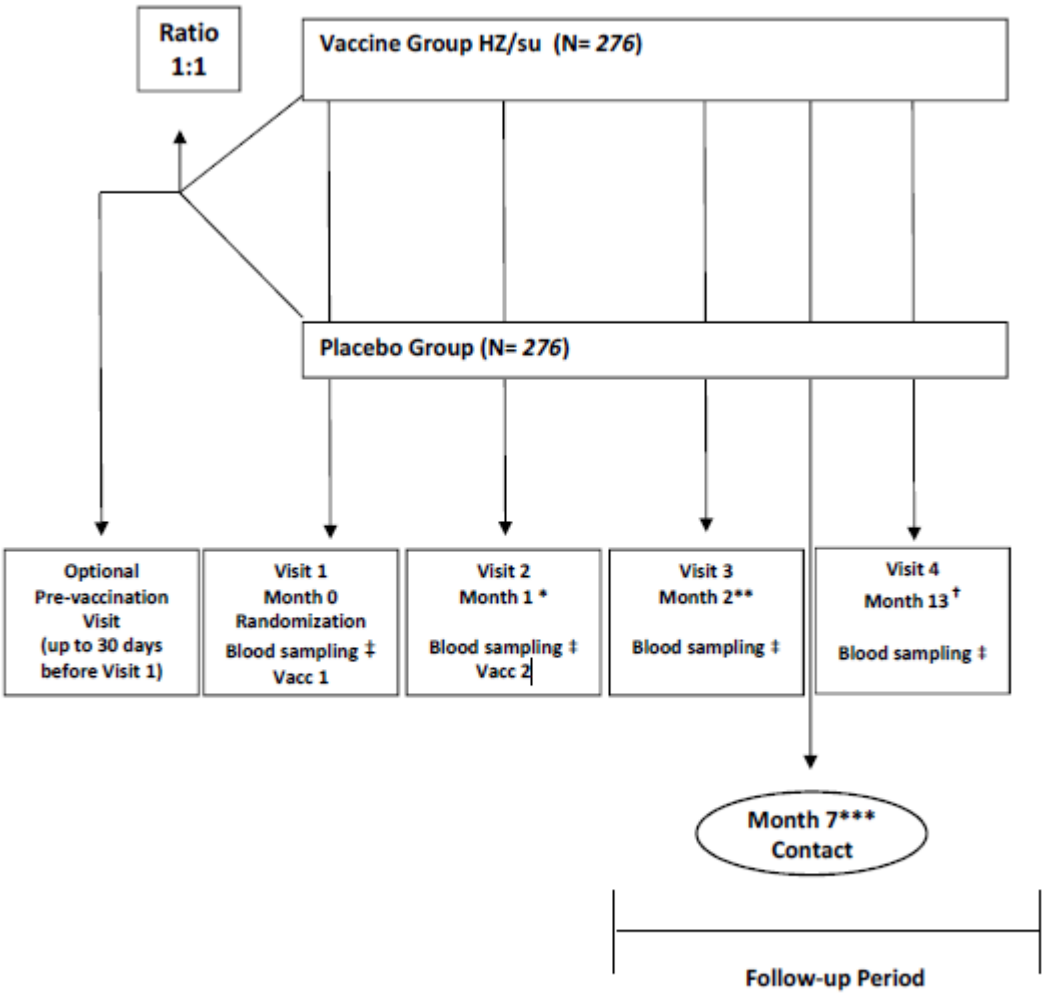
* The second dose of study vaccine/placebo will be administered 1 to 2 months after the first dose.

** Visit 3 occurs approximately one month after the second vaccination.

***Each subject will be followed at least until he/she completes Visit 4. If conditions for study end are met, all remaining monthly contacts after Visit 4, Visit 5, and monthly contacts after Visit 5 will not take place.

Note: When a subject is diagnosed as having suspected HZ, follow-up will occur as detailed in Section 5.4.2.

Figure 1: Study design ZOSTER-002 (From study protocol)



*The second dose of study vaccine/placebo was administered 1 to 2 months after the first dose.
**Month 2 (Visit 3) occurred 1 month after the second vaccination.
***Month 7 contact occurred 6 months after the second vaccination.
† Month 13 (Visit 4) occurred 12 months after the second vaccination.

Figure 2: Study design ZOSTER-039 (From study protocol)

Study participants

ZOSTER-002:

The main inclusion criteria for enrolment were:

- A male or female aged 18 years or older at the time of study entry.
- Has undergone or will undergo autologous HCT within 50-70 days prior to the first vaccination with the study vaccine/placebo, and there are no plans for additional HCTs (tandem autologous HCT recipients may participate following their final HCT);

The exclusion criteria were:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine/placebo, or planned use during the study period. However, the investigational use of a registered or non-registered product to treat the subject's underlying disease for which the HCT was undertaken, or a complication of the underlying disease, is allowed;

- Previous vaccination against HZ or varicella within the 12 months preceding the first dose of study vaccine/placebo;
- Planned administration during the study of a HZ vaccine (including an investigational or non-registered vaccine) other than the study vaccine;
- Occurrence of a varicella or HZ episode by clinical history within the 12 months preceding the first dose of study vaccine/placebo;
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine or study material and equipment;
- Prophylactic antiviral therapy with activity against VZV* expected to last more than 6 months after transplantation. *Prophylactic antiviral therapy with activity against VZV (e.g. Acyclovir, Valacyclovir, Famciclovir, Penciclovir, Brivudin, Ganciclovir, Valganciclovir) following HCT to be administered according to local standard of care based on the Investigator' s judgment (duration, choice of antiviral agent and dose of antiviral agent). Subjects for whom prophylactic antiviral therapy is expected to be given for 6 months or less following HCT may be enrolled;
- Administration and/or planned administration of a vaccine not foreseen by the study protocol between HCT and 30 days after the last dose of study vaccine/placebo. However, licensed non-replicating vaccines (e.g., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines and pneumococcal conjugate vaccines) may be administered up to 8 days prior to dose 1 and/or 2, and/or at least 14 days after any dose of study vaccine/placebo;
- HIV infection by clinical history;
- Pregnant or lactating female;
- Female planning to become pregnant or planning to discontinue contraceptive precautions (if of childbearing potential) before Month 13 (i.e., one year after the last dose of study vaccine/placebo).

ZOSTER-039:

The main inclusion criteria for enrolment were:
- A male or female, aged 18 years or older at the time of study entry.
- Subject who has been diagnosed with one or more haematologic malignancies prior to the first vaccination and who is receiving, is scheduled to receive or has just finished immunosuppressive cancer therapy to treat this condition.
- Cancer therapy may be chemotherapy and/or immunotherapy. If radiotherapy, it must be in combination with either chemotherapy or immunotherapy.
- No restrictions on date of diagnosis with respect to date of first study vaccination or on any cancer therapies subjects may have had prior to the first study vaccination.
- Life expectancy greater than or equal to 12 months, as assessed by the investigator.

The exclusion criteria were:
- Subject diagnosed with chronic lymphocytic leukaemia (CLL) who is receiving only oral cancer therapy (subject receiving intra-venous cancer therapy for CLL or intravenous cancer therapy in combination with oral therapy may be enrolled).
- Subject receiving radiotherapy alone as treatment for his/her haematologic malignancy.
- Planned haematopoietic stem cell transplant (HCT) during the study period. (If a HCT occurred prior to enrolment in the study, the subject may not receive study vaccine until at least 50 days after the transplant procedure.)
- HIV infection by clinical history.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine/placebo, or planned use during the study period. However, the investigational use of a registered product to treat the subject's underlying disease, is allowed.

- Previous vaccination against HZ or varicella within the 12 months preceding the first dose of study vaccine/placebo.
- Planned administration during the study of a HZ or varicella vaccine (including an investigational or non-registered vaccine) other than the study vaccine.
- Occurrence of a varicella or HZ episode by clinical history within the 12 months preceding the first dose of study vaccine/placebo.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Administration or planned administration of a live vaccine in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose of study vaccine.
- Administration or planned administration of a non-replicating vaccine (inactivated and subunit vaccines, including inactivated and subunit influenza vaccines and pneumococcal conjugate vaccines) within 8 days prior to or within 14 days after either dose of study vaccine.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions before Month 3 (i.e., 2 months after the last dose of study vaccine/placebo).

The timing of study vaccine administration was dependent upon the number of days in between immunosuppressive cancer treatments:

- If each cancer therapy treatment was separated by more than 20 days, the first vaccination had to be planned as late as possible during this time period while still allowing 10 days before the next foreseen treatment. For example, in a schedule with 30 days between treatments, study vaccination should ideally be given around days 17-20 after the previous treatment.
- If the cancer treatment cycle did not allow spacing the vaccination between each cancer treatment by at least 10 days, the first vaccination had to be scheduled from 10 days to 6 months after the full cancer therapy course.
- The second dose of study vaccine was to be given 1 to 2 months after the first dose. Study vaccination had again to be planned as late as possible during the time period in between cancer treatments while still allowing 10 days before the next foreseen cancer treatment.

Definition of cancer therapy and cancer therapy cycles:

1. Direct anti-cancer treatments (chemotherapy and/or immunotherapy; if radiotherapy it must be in combination with either chemotherapy or immunotherapy) that are immunosuppressive. Examples (not an exhaustive list): Chemotherapy: CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone), ICE (ifosfamide, carboplatin, etoposide), VAMP (e.g., vincristine, amethopterin, 6-mercaptopurine, prednisone) Immunotherapy: rituximab, lenalidomide

2. Immunosuppressive therapies administered as part of the anti-cancer treatment or to avoid/treat complications of the anti-cancer treatment. Examples (not an exhaustive list): Cyclosporine, tacrolimus, used mainly in case of allogenic hematopoietic stem cell transplantation; Steroids at high immunosuppressive doses equivalent to ≥20mg/day prednisone for more than 14 consecutive days.

Both (1) and (2) are the immunosuppressive cancer therapies which should be taken into account with respect to the timing of study vaccine administration.

Cancer therapy course: As used in the protocol, an entire series of cancer therapy cycles (repeated treatments) often lasting several months.

Cancer therapy cycle: Individual cancer therapy treatments typically scheduled every 1, 2, 3 or 4 weeks within the cancer therapy course.

Treatments

The vaccine (HZ/su or Placebo) was administered IM according to a flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose. The standard route was IM injection in the deltoid of the non-dominant arm.

All the studies used the final selected HZ/su formulation, i.e. 50 µg gE adjuvanted with AS01B.

Throughout this report, the GSK HZ vaccine is referred to as either Shingrix or HZ/su. Note that in ZOSTER-015, the vaccine has been referred to as gE/AS01B.

In ZOSTER-015, 3 vaccine doses were administered IM according to a 0, 2, 6-months schedule.

In all studies, the control group received placebo injections (lyophilized sucrose reconstituted with saline [NaCl] solution).

Study duration:

All subjects in the studies (except ZOSTER-001) were followed up for at least 12 months post last vaccination. In ZOSTER-002, the median follow-up for safety and efficacy was approximately 29 months and 21 months, respectively. In ZOSTER-028, ZOSTER-039 and ZOSTER-041, the study duration for each subject was 13 to 15 months. In ZOSTER-015, the study duration was approximately 18 months.
The vaccine (HZ/su or Placebo) was administered according to a flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose. The standard route was IM injection in the deltoid of the non-dominant arm.

Efficacy objectives and endpoints

Table 42: Efficacy objectives and endpoints

Level	Objectives	Endpoint
Primary	Evaluate VE in preventing HZ Criterion: Clinically meaningful overall HZ VE was demonstrated if the LL of the 95% CI was >0%	Incidence of confirmed HZ cases from Month 0 until study end
Secondary	Evaluate VE in reducing the total duration of severe "worst" HZ-associated pain over the entire pain reporting period in subjects with confirmed HZ	Duration of severe "worst" HZ-associated pain, i.e. HZ-associated pain rated as 3 or greater on the "worst pain" ZBPI question, following the onset of a confirmed HZ rash over the entire pain reporting period in subjects with confirmed HZ
	Evaluate VE in reducing confirmed HZ-associated complications	Incidence of confirmed HZ complications following the onset of HZ from Month 0 until study end
	Evaluate VE in preventing PHN	Incidence of PHN from Month 0 until study end
Tertiary	Evaluate VE in preventing HZ when all subjects reached 1-year post-HSCT	Incidence of confirmed HZ cases in subjects having 1-year post-HSCT
	Evaluate VE in preventing PHN in subjects with confirmed HZ	Incidence of PHN from Month 0 until study end in subjects with confirmed HZ
	Evaluate VE in reducing the severity of acute HZ-associated pain in subjects with confirmed HZ	Acute HZ severity as determined by the mean area under the curve (AUC) of the severity-by-duration of HZ-associated pain as measured by the ZBPI during a 4-week period following the onset of confirmed HZ in subjects with confirmed HZ
	Evaluate VE in improving QoL in subjects with confirmed HZ	Interference of HZ with QoL as measured by ZBPI, EQ-5D and SF-36 in subjects with confirmed HZ

Level	Objectives	Endpoint
	Evaluate VE in reducing HZ-related and overall mortality	Incidence of HZ-related and overall mortality from Month 0 until study end
	Evaluate VE in reducing HZ-related hospitalizations	Incidence of HZ-related hospitalizations from Month 0 until study end
	Evaluate VE in reducing the duration of pain medication in subjects with confirmed HZ	Duration of pain medication administered for HZ from Month o until study end in subjects with confirmed HZ
Post-hoc	Evaluate VE by region, actual duration of prophylactic antiviral therapy, and detailed underlying disease category	Incidence of confirmed HZ cases from Month 0 until study end
ZOSTER-039		
Secondary	Evaluate the incidence of confirmed HZ cases	Occurrence of confirmed HZ cases from Month 0 until study end
Post-hoc	Evaluate VE against HZ	Incidence of confirmed HZ cases from Month 0 until study end

Methods Used to Evaluate Efficacy

The below sections list the key elements of the efficacy assessments as performed for ZOSTER-002 and ZOSTER-039 (if applicable).

Suspected HZ case definition:

A suspected case of HZ was defined as: (1) a new rash characteristic of HZ (e.g., unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations), or a vesicular rash suggestive of VZV infection regardless of the distribution, and no alternative diagnosis; or (2) a clinical presentation (symptoms and/or signs) and specific laboratory findings* suggestive of VZV infection in the absence of characteristic HZ or VZV rash.

*Specific laboratory findings included VZV-positive PCR, culture, immuno-histochemical staining, or other test, performed in the course of a medical evaluation that strongly suggested VZV infection.

Evaluation of cases of suspected HZ with characteristic HZ or rash suggestive of VZV reactivation:

Subjects who experienced any symptom/sign suggestive of HZ or VZV reactivation were asked to visit the study site (preferably within 96 hours after the rash or pain began) for further evaluation. At Visit HZ-1 on Day HZ-0, the investigator performed a clinical examination. All clinically diagnosed suspected cases of HZ or VZV reactivation were documented by digital photography and rash lesion samples were collected to confirm the event by PCR.

In ZOSTER-002, subjects were additionally asked by the study staff/investigator to complete a Zoster Brief Pain Inventory (ZBPI) questionnaire to collect information on the severity and duration of the HZ-associated pain. The impact of the HZ episode on the subject's QoL was measured using the ZBPI, as well as the Euro-QoL 5 Dimension (EQ-5D) and Short form-36 (SF-36) questionnaires. After Visit HZ-1, 5 contacts and 1 additional HZ visit (Visit HZ-7 on Day HZ-91) were planned for follow-up of the HZ episode. Subjects with pain were followed until a 4-week pain-free period occurred or until at least Day HZ-91. For all subjects with ongoing HZ-associated pain at the cut-off date for final triggered analysis, follow-up continued until at least Visit HZ-7 (Day HZ-91). As soon as the HZ-associated pain ceased (defined as a 4-week pain-free period) and the HZ rash resolved, subsequent HZ follow-up visits or contacts were suspended, except for Visit HZ-7 if Day HZ-91 was foreseen to occur later than the cut-off date for final triggered analysis in order to capture all PHN cases if pain resumed after the 4-week pain-free period.

Evaluation of cases of suspected HZ without characteristic HZ or VZV rash:

In case of suspected HZ diagnosed according to criterion (2), i.e. without characteristic HZ or VZV rash, the HZ onset date was the date on which the signs/symptoms related to the clinical diagnosis of suspected HZ were first noted. The end date of the HZ episode was defined as the date on which the investigator or an attending physician considered the case as resolved.

Follow-up visits, contacts and study procedures, such as collection of rash lesion samples and taking of photographs of HZ rash, were not applicable. These cases were considered as serious adverse events (SAEs)/AEs and recorded as such, with the specification that the event was related to HZ.

In ZOSTER-002, these suspected HZ cases were evaluated if they occurred during the study period up to the cut-off date for final triggered analysis.

Confirmation of suspected HZ cases:

By PCR

Whenever possible, rash lesion samples were collected from subjects clinically diagnosed as having a suspected case of HZ based on criterion (1). A PCR algorithm was used to classify each suspected case of HZ as a confirmed HZ case or not. Three rash lesion samples were tested by PCR.

Cases of suspected HZ were not considered a confirmed case of HZ for the efficacy analysis if they potentially could constitute a primary VZV infection (varicella). For subjects born in 1980 or later, or before 1980 in a tropical region, and with no serological evidence of prior VZV infection available at the time of Visit 1 (baseline), a case of suspected HZ with a disseminated onset or a VZV infection without characteristic rash [criterion (2)] could represent a primary VZV infection. For those subjects, the following approach was taken: (i) With a VZV-positive PCR result, with a VZV inconclusive PCR result, or with no rash lesion samples available for PCR testing, the case was not considered a confirmed case of HZ if the subject was diagnosed with suspected HZ according to criterion (1) and presented with a disseminated rash from onset, and the subject was VZV seronegative at baseline (prevaccination at Visit 1) based on testing of pre-vaccination serum; (ii) Cases diagnosed in the absence of rash as suspected HZ according to criterion (2), and who were VZV seronegative at baseline (pre-vaccination at Visit 1) based on testing of pre-vaccination serum, were not considered a confirmed HZ case.

By the HZAC

The HZAC consisted of physicians with HZ expertise. HZAC members participating as investigator in the study did not evaluate cases from their own study site. HZAC members were blinded to treatment assignments. For every suspected case of HZ or VZV reactivation, each HZAC member was asked to make a clinical determination of whether the case was HZ based on review of the available clinical information and laboratory information from the study site. The HZAC classified cases as either 'HZ', 'not HZ' or 'not able to decide'.

However, the HZAC classification served as the final case confirmation only when the case could not be confirmed or excluded by PCR e.g., when all samples from a given subject were inadequate, or when no samples were available for a given subject, including when suspected HZ was based on criterion (2) without characteristic HZ or VZV rash. Therefore, when available, definitive PCR results determined the final HZ case assignment.

HZAC classification, as described above, would not have served as the final case determination for suspected cases of HZ who could potentially constitute a primary VZV infection (varicella). For these cases, baseline VZV serology was taken into account to determine whether the case was considered a confirmed case of HZ.

Evaluation of cases of suspected HZ without typical rash of HZ or of VZV:

In ZOSTER-002, cases of HZ without characteristic VZV or HZ rash were recorded as SAE and specified there as related to HZ. In ZOSTER-002, cases of HZ without characteristic VZV or HZ rash were recorded as SAEs/AEs, as appropriate, and specified there as related to HZ.

Assessment of HZ-associated complications:

In ZOSTER-002, PHN was defined by the presence of HZ-associated 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash. 'Worst' pain was defined as HZ-associated pain rated as 3 or greater on the 'worst' pain ZBPI question.

In ZOSTER-039, PHN was defined as clinically significant pain or painful abnormal sensations (e.g., allodynia or itch) that persisted 3 months or more after HZ rash onset. However, no ZBPI questionnaires were completed.

In both ZOSTER-002 and ZOSTER-039, any HZ complications, according to the definitions below, had to be recorded by the investigator. HZ complications were considered as AEs or SAEs. HZ complications associated with confirmed HZ are considered for analysis of the applicable secondary endpoint and include:

HZ vasculitis: Vasculopathy or vasculitis (based on clinical, laboratory or radiologic findings) that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by the VZV infection arising from the HZ episode.

Disseminated disease: Defined as ≥ 6 HZ lesions clearly outside the primary dermatome as per the investigator's judgment.

Ophthalmic disease: Defined as HZ affecting any eye structure as per the investigator's judgment.

Neurologic disease: Defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis, stroke, etc. that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by VZV infection arising from the HZ episode.

Visceral disease: Defined as an abnormality of one or more internal organs (e.g., hepatitis, pneumonitis, gastroenteritis, etc.) that is temporally associated with an episode of HZ and, in the opinion of the investigator, was caused directly by VZV infection arising from the HZ episode.

Evaluation of Severity and Duration of HZ-associated Pain and Quality of Life Assessment (ZOSTER-002):

Evaluation of severity and duration of HZ-associated pain using the ZBPI questionnaire

The ZBPI was used to quantify HZ pain and discomfort and measure selected Activities of Daily Living (ADL) and health.

Subjects with suspected HZ with characteristic HZ or VZV rash [by criterion (1)] were asked to complete the ZBPI questionnaire on Day HZ-0 (Visit HZ-1), daily from Day HZ-1 up to Day HZ-28, and weekly from Day HZ-29 onwards until HZ-associated pain ceased (defined as a 4-week pain-free period).

To assess the duration of HZ-associated pain, a 4-week pain-free period was used to confirm cessation of HZ-associated pain. If that pain-free period was not achieved or pain resumed after a 4-week pain-free period, and/or if pain did not cease, the time to event was censored at the last day of HZ-associated pain.

For all subjects with ongoing HZ-associated pain at the cut-off date for final triggered analysis, ZBPI data were collected until a 4-week pain-free period was documented OR until at least Day HZ-91.

Health-related Quality of Life assessment using the EQ-5D and SF-36 questionnaires

Both the EQ-5D questionnaire and SF-36 health survey questionnaire were completed by all subjects at Day 0 (Visit 1) to generate a baseline measurement, and at 1 month and 1 year post Dose 2. Subjects with suspected HZ with characteristic HZ or VZV rash [by criterion (1)] were asked to complete both questionnaires on a weekly basis during the period for which ZBPI questionnaires were completed (until Day HZ-28 at minimum).

Sample size

In ZOSTER-002, target enrolment was foreseen to be approximately 2126 eligible HCT recipients (1063 in the gE/AS01B group and 1063 in the placebo group). Enrolment was planned to be terminated when the target number of subjects had been reached.

In ZOSTER-039, target enrolment was approximately 552 eligible adults (276 per treatment group) diagnosed with haematologic malignancies.

Randomisation

In both studies, eligible subjects were randomised to the investigational vaccine gE/AS01B or placebo according to a 1:1 ratio (vaccine:placebo). The treatment allocation at the investigator site was performed using a central randomisation system on internet.

Blinding (masking)

The studies were conducted in an observer-blind manner because the HZ/su and Placebo vaccines differed in their preparation method and appearance. Therefore, HZ/su and Placebo were prepared and administered only by authorized medical personnel not involved in any of the clinical study evaluation assays. The blinding was maintained until study end. Of note for ZOSTER-015, the investigators and investigative staff could have become aware of treatment allocation (inadvertent unblinding) with respect to some data included in the Month 7 CSR.

Statistical methods

Study cohorts

Total Enrolled Cohort consisted of all subjects enrolled, that is all subjects who signed the ICF and were considered as eligible.

The Total Vaccinated Cohort (TVC) included all vaccinated subjects who received at least 1 dose of HZ/su or Placebo.

In ZOSTER-002, the modified Total Vaccinated Cohort (mTVC) excluded subjects in the TVC who did not receive the second vaccination, who received vaccine doses or replacement not on the same group (i.e., randomization failures) or who developed a confirmed case of HZ prior to 1 month post Dose 2. In addition, subjects with relapse of the original malignancy or disease for which the autologous HSCT was undertaken were censored from the mTVC analysis from the date they started the therapy to treat relapse.

The mTVC was the primary population for efficacy analyses.

The results of the complementary efficacy analysis based on the TVC and on the According-To-Protocol (ATP) cohort for efficacy were consistent with results obtained for the mTVC.

In ZOSTER-039, the incidence of confirmed HZ cases was assessed in the TVC. For the post-hoc analysis of VE against HZ and to align with VE calculations as performed in other ZOSTER efficacy studies, an mTVC was defined post-hoc using the same criteria, i.e., excluding subjects from the TVC who did not receive the second vaccination or who developed a confirmed case of HZ prior to 30 days post Dose 2.

The mTVC confirmed cases (ZOSTER-002) included subjects with at least one confirmed case of HZ and censored subjects as of the time a treatment for relapse of the underlying disease was initiated. The mTVC confirmed cases-HZ ZBPI Evaluable Subgroup included all subjects in the mTVC confirmed cases cohort who had a first ZBPI assessment within 14 days of rash onset. Both study cohorts were used to perform the QoL analyses in ZOSTER-002.

Statistical methodology for analysis of efficacy

In ZOSTER-002, all efficacy analyses were presented for the entire study population. Most efficacy analyses were also performed by age stratum (i.e., 18-49 YOA and ≥50 YOA), except for reduction of overall mortality and prevention of HZ during 1 year post-HSCT. The analysis of VE against HZ was additionally performed by region (Europe including South Africa, North America, South America and Austrasia), by duration of prophylactic antiviral therapy (PAT), and by detailed underlying disease category. Since the highest risk period for HZ reactivation is within the first year of autologous HSCT, an analysis was performed to evaluate VE in the prevention of HZ during the first year post-HSCT in ZOSTER-002.

In ZOSTER-039, VE against HZ for the entire study population was conducted as a post-hoc analysis.

All p-values reported were related to the null hypothesis test VE = 0 (or absence of effect of the vaccine). The confidence intervals (CIs) were produced with 5% α-level.

Reduction in HZ risk, primary inferential analysis (Poisson method)

The primary analysis method of VE was the Poisson method, which considered the exact inference on the relative risk (RR) conditionally to the total number of HZ cases observed and time at risk. Clinically meaningful overall efficacy of HZ/su against HZ was demonstrated if the lower limit (LL) of the 95% CI was >0%.

The Poisson method computes an exact CI around the rate ratio (ratio of the event rates in the HZ/su versus Placebo group) and takes into account the sum of the time at risk of the subjects within each group. The RR was defined as the ratio of the incidence rates of the HZ/su group over the Placebo group, and VE was defined as 1 minus the RR.

The time at risk was expressed in Person-Years and derived from the follow-up time (follow-up time in days/365.25). The follow-up time at risk period was expressed in days and, for mTVC, was considered as starting from the 30 days post Dose 2 date and ending on the date of the last visit/contact for subjects who did not have an event, on the last contact date for subjects who dropped out if not preceded by an event, or on the date of the event.

The number of Person-Years at risk was defined as the sum of the time at risk for all subjects at risk during, either up to the cut-off date for the analysis (4 November 2016), the censoring date (drop-out) or the occurrence of the first HZ case for a subject. In addition, subjects with relapse of the original malignancy or disease for which the autologous HCT was undertaken were censored from the mTVC analysis from the date they started the therapy to treat relapse.

For ZOSTER-039, VE against HZ was conducted as a post-hoc analysis in the way described above.

Analyses were performed to determine the effect of HZ/su on the reduction of the duration of pain, the overall reduction in the risk of HZ-associated complications (other than PHN), the reduction in overall PHN risk, the reduction in PHN incidence in subjects with confirmed HZ, the reduction of overall and HZ-

related mortality and HZ-related hospitalizations, and the reduction of duration of pain medication in subjects with confirmed HZ.

Statistical methodology for analysis of Quality of Life

In ZOSTER-002, an exploratory analysis of QoL was performed: p-values from statistical tests were not considered confirmatory.

Summary measures:

Summary measures of QoL scores were generated. In essence, a summary measure collapses the complete set of measurements of an individual into a single number. For evaluable cases of HZ, the worst score for each QoL scale during the HZ episode was calculated and compared between study groups. The Wilcoxon non-parametric test was used to compare study groups as the summary measures were not expected to be normally distributed.

Analysis of Quality of Life by ZBPI:

Time to resolution of clinically significant pain was analyzed for the mTVC confirmed cases - ZBPI Evaluable Subgroup. Clinically significant pain was defined as pain with a ZBPI score ≥3. An event was defined as having a 'worst' pain score <3 for a documented 4-week clinically significant pain-free period. Time-to-event curves were estimated using the Kaplan-Meier method. A logrank test was used to compare study groups.

As part of the area under the curve (AUC)-based analyses, the HZ severity-of-illness, severity-of-interference, burden-of-illness, and burden-of-interference scores were calculated using either the ZBPI 'worst' pain or average pain scores at 30, 90, or 182 days.

Analysis of Quality of Life by SF-36 and EQ-5D:

Analysis of repeated measures of QoL changes over time Data for HZ cases of the mTVC confirmed cases cohort were analyzed using descriptive statistics, repeated measures ANOVA, and a multivariate Rank Analysis for each study group at each assessment day, as described above for ZBPI. Both the mixed models and the multivariate Rank Analysis only included time points up to and including Week 10 post rash onset.
A model was fitted to estimate the HZ impact on SF-36 and EQ-5D utility scores in the Placebo group only stratified by age (i.e., 18-49 YOA and ≥50 YOA). The model included the baseline utility scores, i.e., the most recent pre-HZ assessment (at one of Months 0, 2, or 13) and the utility scores during the first 4 weeks of the HZ episode.

Results

ZOSTER-002:

- ***Studies' dates***

The first subject was enrolled in the study on 13 July 2012 and the last study visit/contact was on 1 February 2017.

The cut-off date for final efficacy analysis (also referred to as 'final triggered analysis' or 'final analysis') was 04 November 2016. All suspected HZ episodes with onset date up to and including 04 November 2016 were considered for efficacy analyses at the end of study.

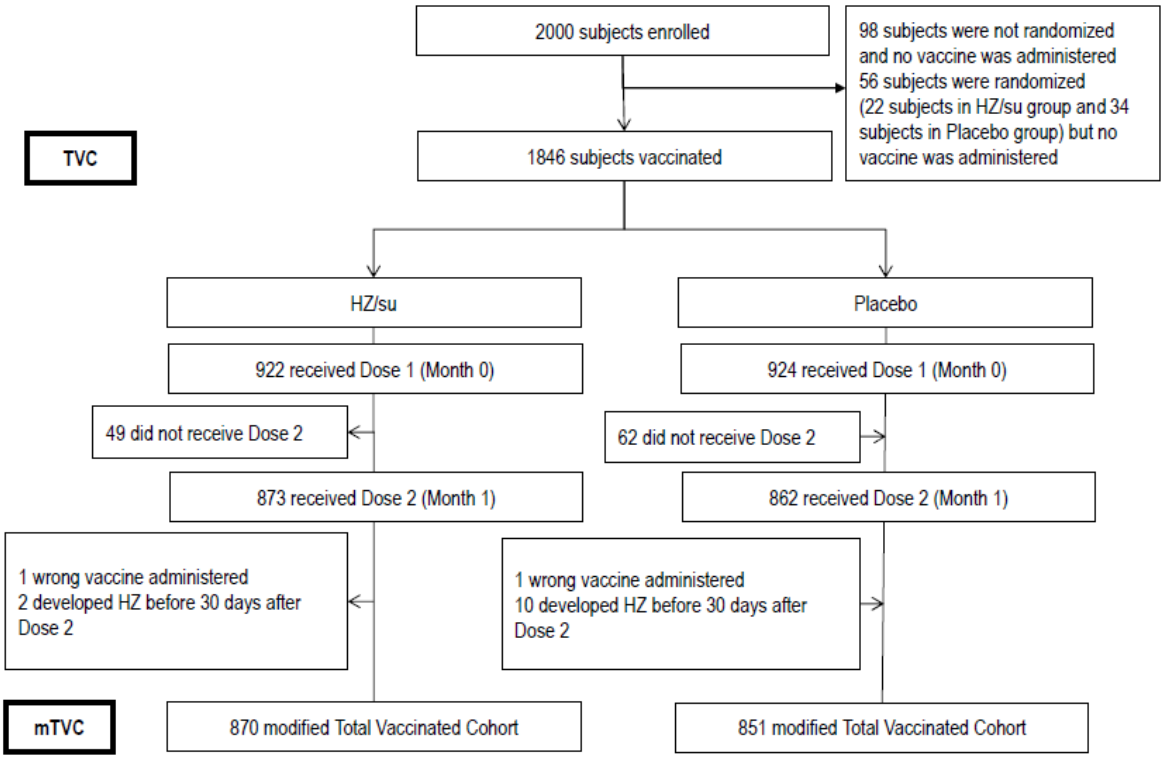
Database freeze (DBF) occurred on 05 September 2017.

Participant flow

Study cohorts:

There were 2000 subjects included in the Total Enrolled Cohort (subjects who signed the ICF and were considered as eligible). From the 2000 subjects included in the Total Enrolled Cohort, 154 subjects were not vaccinated and were not included in the TVC. These subjects were not vaccinated because they no longer met the eligibility criteria at the time of Visit 1. Out of these 154 subjects who were not vaccinated, 98 subjects were not randomized into a treatment group, 22 subjects were randomized into the HZ/su group, and 34 subjects were randomized into the Placebo group (Figure 3). Thus, a total of 1846 subjects were vaccinated and constituted the TVC; 922 subjects in the HZ/su group and 924 in the Placebo group.

Figure 3: Subject disposition: modified Total Vaccinated Cohort (Source: CSR Figure 3).



Subjects who did not reach the cut-off date for final analysis:

A total of 480 subjects included in the TVC (228 and 252 in the HZ/su group and Placebo group, respectively) did not reach the cut-off date for final analysis (04 November 2016) (Table 43).

Table 43: Number of subjects vaccinated, completed and withdrawn (Total Vaccinated Cohort)

	HZ/su		Placebo		Total	
	n	%	n	%	n	%
Number of subjects vaccinated	922	100	924	100	1846	100
Number of subjects completed	694	75.3	672	72.7	1366	74.0
Number of subjects withdrawn	228	24.7	252	27.3	480	26.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Vaccinated = number of subjects who were vaccinated in the study; Completed = number of subjects who completed until the cut-off date for final analysis (04NOV2019); Withdrawn = number of subjects who did not reach the cut-off date for final analysis (04NOV2019

Until Visit 4 (Month 13), in the TVC there were 244 withdrawals from the study (115 and 129 in the HZ/su group and Placebo group, respectively). The most common reason for withdrawal until Visit 4 was the occurrence of an SAE (in total 132 subjects, 65 in the HZ/su group and 67 in the Placebo group). There were 28 withdrawals from the study (14 in each group) due to a non-serious AE. There were 4 withdrawals due to the occurrence of a suspected HZ episode (1 in the HZ/su group and 3 in the Placebo group).

Between Visit 4 and Visit 5 (Month 25), in the TVC there were 135 withdrawals (65 in the HZ/su group and 70 in the Placebo group) withdrawn. The most common reason for withdrawal was an SAE (in total 73 subjects, 35 in the HZ/su group and 38 in the Placebo group). There were 12 withdrawals from the study (8 in the HZ/group and 4 in the Placebo group) due to a non-serious AE. There were 13 withdrawals due to other reasons (6 in the HZ/su group and 7 in the Placebo group). For 4 of these 13 subjects (2 in each group), the cut-off date for final analysis was reached before Visit 5 could take place.

Between Visit 5 and the cut-off date for final analysis, in the TVC there were 101 withdrawals (48 in the HZ/su group and 53 in the Placebo group). For the time frame between Visit 5 and the cut-off date for final analysis, the reason for withdrawal was not to be documented in the eCRF. Out of these 101 subjects, 49 subjects had fatal SAEs with an end date within this time frame (26 subjects in the HZ/su group and 23 subjects in the Placebo group).

Subjects who did not receive the second vaccination:

A total of 111 (6.0%) subjects out of 1846 included in the TVC did not receive the second vaccination; i.e., 49 (5.3%) out of 922 subjects in the HZ/su group and 62 (6.7%) out of 924 subjects in the Placebo group. The reasons, as reported in the eCRF, for subjects not having received the second dose were the following: At least one SAE and/or pIMD (6 subjects in each group); At least one non-serious AE (7 subjects in the HZ/su group and 5 subjects in the Placebo group); A suspected HZ episode (criterion 1) (8 subjects in the HZ/su group and 10 subjects in the Placebo group); Other reason (2 subjects in each group); The second vaccination visit (Visit 2) not performed (26 subjects in the HZ/su group and 39 subjects in the Placebo group).

mTVC and ATP:

There were 870 subjects of the HZ/su group and 851 subjects of the Placebo group included in the mTVC.

Additional criteria were applied to exclude subjects from the ATP cohort for efficacy. There were 682 subjects of the HZ/su group and 672 subjects of the Placebo group included in the ATP cohort of efficacy. The reasons for elimination from ATP were: (i) blinded study vaccine not administered according to the protocol (reconstitution of the vaccine not performed as per protocol, vaccine administered using a subcutaneous needle), (ii) vaccine administered despite a temperature deviation qualified by status QA GMP non-use, (iii) vaccine administered out of the expiration date, (iv) administration of vaccine(s) forbidden in the protocol, (v) randomisation code broken at the investigator site or at GSK safety department, (vi) protocol violation linked to the inclusion/exclusion criteria, (vii) administration of any medication forbidden by the protocol (excluding those used for disease progression or relapse), (viii) non-compliance with vaccination schedule (including wrong and unknown vaccination dates).

Table 44: Number of subjects enrolled into the study as well as the number excluded from modified Total Vaccinated Cohort and ATP cohort for efficacy with reasons for exclusion

	Total			HZ/su			Placebo			NOGRP		
Title	n	s	%	n	S	%	n	s	%	n	s	%
Total Enrolled cohort	2000			944			958			98		
Study vaccine dose not administered but subject number allocated (code 1030)	154	154		22	22		34	34		98	98	
Total Vaccinated Cohort	1846		100	922		100	924		100	0		-
Wrong replacement or study vaccine administered (code 1500)	2	2	0.1	1	1	0.1	1	1	0.1	0	0	-
Subjects who did not receive two doses (code 2500)	111	111	6.0	49	49	5.3	62	62	6.7	0	0	-
Subjects having an episode of HZ prior than 30 days after the dose 2 (code 3100)	12	12	0.7	2	2	0.2	10	10	1.1	0	0	-
modified Total Vaccinated Cohort	1721		93.2	870		94.4	851		92.1	0		-
Administration of vaccine(s) forbidden in the protocol (code 1040)	71	71	3.8	33	33	3.6	38	38	4.1	0	0	-
Randomisation code broken at the investigator site or at GSK safety department (code 1060)	11	11	0.6	4	4	0.4	7	7	0.8	0	0	-
Study vaccine dose not administered according to protocol (code 1070)	11	11	0.6	5	5	0.5	6	6	0.6	0	0	-
Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by status QA GMP non-use (code 1080)	1	1	0.1	0	0	0.0	1	1	0.1	0	0	-
Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration (code 1090)	1	1	0.1	0	0	0.0	1	1	0.1	0	0	-
Wrong replacement or study vaccine administered (code 1500)	2	2	0.1	1	1	0.1	1	1	0.1	0	0	-
Protocol violation linked to the inclusion/exclusion criteria (code 1600)	38	42	2.1	18	20	2.0	20	22	2.2	0	0	-
Administration of any medication forbidden by the protocol (excluding those used for disease progression or relapse) (code 2041)	27	30	1.5	17	17	1.8	10	13	1.1	0	0	-
Non-compliance with vaccination schedule (including wrong and unknown vaccination dates) (code 2080)	1	3	0.1	1	2	0.1	0	1	0.0	0	0	-
Subjects who did not receive two doses (code 2500)	96	111	5.2	43	49	4.7	53	62	5.7	0	0	-
Medication forbidden (prophylactic anti-viral treatment given for more than 6 consecutive months post-initial HCT at study entry) (code 3040)	194	230	10.5	99	117	10.7	95	113	10.3	0	0	-
Medication forbidden (prophylactic anti-viral treatment given for more than 186 days during the course of the study) (code 3041)	28	45	1.5	17	28	1.8	11	17	1.2	0	0	-
Subjects having an episode of HZ prior than 30 days after the dose 2 (code 3100)	11	12	0.6	2	2	0.2	9	10	1.0	0	0	-
ATP cohort for efficacy	1354		73.3	682		74.0	672		72.7	0		-

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; NOGRP = No assigned group; Note: subjects may have more that one elimination code assigned; n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number to the same corresponding cohort compared to the Total Vaccinated Cohort; s = number of subjects with the elimination code assigned; %= percentage of subjects (n) relative to the Total Vaccinated Cohort

Conduct of the study

There were no significant audit findings that impacted the validity of the data collected. Among the audit findings, 2 findings were found relevant. During the conduct of ZOSTER-002, the following incidents were identified by GSK after 2 for-cause CDQA site assessments:

- An internal audit was conducted by GSK at one United Kingdom (UK) site following the notification of a serious breach to the Medicines and Healthcare products Regulatory Agency. This site enrolled 5 out of the 1846 subjects included in the study. Findings from the internal audit included documentation deficiencies and other issues (including retrieval of diary cards, missed monthly contacts and out of window study visits). Based on the corrective and preventive actions implemented at this site, the study team considered that the GCP concerns were adequately addressed and data collected at the site were reliable and accurate and thus included in all analyses.

- At one site in New Zealand, an internal audit identified issues related to lack of evidence of Principal Investigator (PI) oversight at the site, documentation deficiencies, issues with temperature monitoring of vaccines and lack of monitoring oversight by the site. The site enrolled 3 out of the 1846 subjects included in the study. Despite the corrective actions put in place, significant weaknesses persisted, and it was decided to close the site after all subjects completed 1 year of follow-up after last dose as no other PI could be appointed to this site according to the institution. As all safety data had been correctly reported in the electronic Case Report Form (eCRF) and reviewed by medically trained site staff, the study team decided that the data could be used for all analyses.

Baseline data

Analysis of demographic characteristics overall:

The summary of demographic characteristics (age in years at first vaccination, gender, ethnicity and geographic ancestry) for the TVC and the mTVC is presented respectively in Table 45 and Table 46.

Regarding the TVC, mean age was 54.8 years and 55.1 years for the HZ/su and Placebo groups, respectively, and regarding the mTVC, mean age was 54.9 years and 55.1 years for the HZ/su and Placebo groups, respectively. More male than female subjects were included in each cohort in both the HZ/su group and the Placebo group in the TVC and mTVC. Regarding TVC and mTVC, percentages of subjects with geographical ancestry and ethnicity characteristics as specified, appeared to be similar in the HZ/su and Placebo groups.

Table 45: Summary of demographic characteristics (Total Vaccinated Cohort)

		HZ/su N = 922		Placebo N = 924		Total N = 1846	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	54.8	-	55.1	-	55.0	-
	SD	11.7	-	11.4	-	11.6	-
	Median	57.0	-	58.0	-	57.0	-
	Minimum	18	-	18	-	18	-
	Maximum	78	-	75	-	78	-
Gender	Female	342	37.1	346	37.4	688	37.3
	Male	580	62.9	578	62.6	1158	62.7
Ethnicity	American Hispanic or Latino	26	2.8	27	2.9	53	2.9
	Not American Hispanic or Latino	896	97.2	897	97.1	1793	97.1
Geographic Ancestry	African Heritage / African American	15	1.6	25	2.7	40	2.2
	American Indian or Alaskan Native	2	0.2	0	0.0	2	0.1
	Asian - Central/South Asian Heritage	6	0.7	5	0.5	11	0.6
	Asian - East Asian Heritage	83	9.0	91	9.8	174	9.4
	Asian - Japanese Heritage	43	4.7	38	4.1	81	4.4
	Asian - South East Asian Heritage	18	2.0	16	1.7	34	1.8
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
	White - Arabic / North African Heritage	9	1.0	12	1.3	21	1.1
	White - Caucasian / European Heritage	715	77.5	712	77.1	1427	77.3
	Other	31	3.4	25	2.7	56	3.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation

Table 46: Summary of demographic characteristics (modified Total Vaccinated Cohort)

		HZ/su N = 870		Placebo N = 851		Total N = 1721	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	54.9	-	55.1	-	55.0	-
	SD	11.5	-	11.3	-	11.4	-
	Median	57.0	-	58.0	-	57.0	-
	Minimum	18	-	18	-	18	-
	Maximum	77	-	75	-	77	-
Gender	Female	323	37.1	317	37.3	640	37.2
	Male	547	62.9	534	62.7	1081	62.8
Ethnicity	American Hispanic or Latino	24	2.8	25	2.9	49	2.8
	Not American Hispanic or Latino	846	97.2	826	97.1	1672	97.2
Geographic Ancestry	African Heritage / African American	15	1.7	23	2.7	38	2.2
	American Indian or Alaskan Native	2	0.2	0	0.0	2	0.1
	Asian - Central/South Asian Heritage	6	0.7	5	0.6	11	0.6
	Asian - East Asian Heritage	77	8.9	86	10.1	163	9.5
	Asian - Japanese Heritage	40	4.6	34	4.0	74	4.3
	Asian - South East Asian Heritage	15	1.7	14	1.6	29	1.7
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0
	White - Arabic / North African Heritage	8	0.9	11	1.3	19	1.1
	White - Caucasian / European Heritage	678	77.9	655	77.0	1333	77.5
	Other	29	3.3	23	2.7	52	3.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation

Analysis of demographic characteristics by age stratum and by underlying diseases:

For the mTVC, regarding the 18-49 YOA stratum, mean age was 38.5 years and 39.0 years for HZ/su and Placebo group, respectively; regarding the ≥50 YOA stratum, mean age was 60.2 years and 60.4 years for the HZ/su and Placebo group, respectively. For the mTVC, the percentage of female/male subjects in the HZ/su group was 40.4%/59.6% and 36.1%/63.9% for the 18-49 YOA and the ≥50 YOA strata, respectively; and in the Placebo group, 40.6%/59.4% and 36.2%/63.8% for the 18-49 YOA and the ≥50 YOA strata, respectively. For the mTVC, regarding the multiple myeloma stratum, mean age was 58.8 years and 58.6 years for HZ/su and Placebo group, respectively; regarding the other diagnoses stratum, mean age was 50.2 years and 50.8 years for the HZ/su and Placebo group, respectively. For the mTVC, the percentage of female/male subjects in the HZ/su group was 36.0%/64.0% and 38.4%/61.6% for the multiple myeloma and the other diagnoses strata, respectively; and in the Placebo group, 39.1%/60.9% and 35.0%/65.0% for the multiple myeloma and the other diagnoses strata, respectively.

Distribution of subjects by type of IS treatment:

Subjects of the pivotal studies were all on IS treatment for their underlying disease during the vaccination course or prior to vaccination. The distribution of subjects receiving IS treatment, classified by IS ingredient sub-class, is presented below. In ZOSTER-002, subjects received pre-and post-transplant IS regimen and/or post-transplant maintenance chemotherapy. From 30 days prior to HSCT up to 1 month post Dose 2 in the mTVC, the following ingredient subclasses of IS treatment were most frequently administered (by >20% of subjects in the HZ/su group): nitrogen and mustard analogues (96.3%), topoisomerase inhibitors (38.4%), pyrimidine analogues (33.1%) and nitrosoureas (32.0%). Results were in the same range for subjects in the HZ/su and Placebo groups. Post-transplant antineoplastic therapy with bortezomib was included as a separate minimization category because of the well-documented increased risk of HZ in persons treated with bortezomib.

Other clinical characteristics:

The median (Min.-Max.) duration of anti-VZV prophylaxis use after 1 month post Dose 2 excluding the subjects who never had Prophylaxis therapy during the same period was 57.0 days (1.0-1121.0) and 53.0 days (1.0-1442.0 (mTVC).

Numbers analysed

Of the 184 subjects with confirmed HZ episodes, 49 were in the HZ/su group and 135 in the Placebo group. Confirmed HZ episodes that occurred after start of treatment for relapse were not considered in this analysis. The overall incidence of HZ per 1000 person-years was 30.0 in the HZ/su group and 94.3 in the Placebo group.

Outcomes and estimation

a) modified Total Vaccinated Cohort analysis

HZ VE

HZ VE overall

HZ VE of 68.17% (95% CI: 55.56% - 77.53%; P<0.0001). The primary objective of the study was met since the LL of the 95% CI was above 0%.

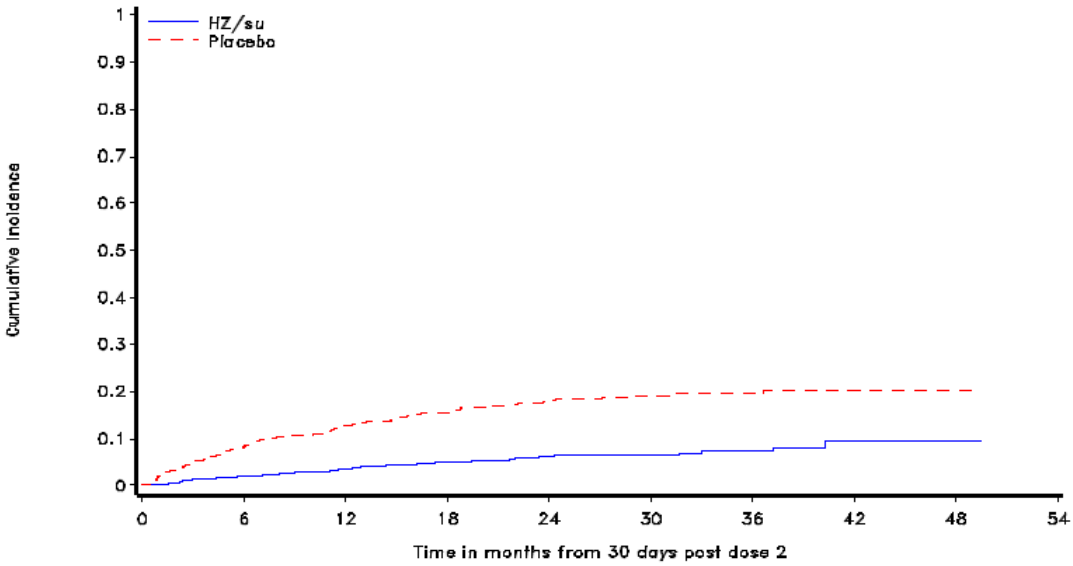
Table 47: Vaccine efficacy: First or only episode of HZ during the entire study period using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
OVERALL	870	49	1633.1	30.0	851	135	1431.9	94.3	68.17	55.56	77.53	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

For all subjects in the mTVC, the median follow-up time (from 30 days post-dose 2 until last contact documented in conclusion screens but limited until 04 November 2016) was approximately 21 months; with approximately 22 months in the HZ/su group and approximately 20 months in the Placebo group. Overall, the maximum follow-up time was 50 months after 30 days post-dose 2, with 49 months in the HZ/su group and 50 months in the Placebo group.

Figure 4: Cumulative incidence curve for HZ (modified Total Vaccinated Cohort)



Number at risk									
HZ/su	870	779	682	537	396	268	141	49	4
Placebo	851	704	604	464	337	209	112	40	6
Cumulative number of cases									
HZ/su	0	17	30	38	44	45	47	49	49
Placebo	0	69	100	117	130	133	134	135	135

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group

A sensitivity analysis was conducted on the mTVC including confirmed HZ episodes which occurred after the subject had started therapy to treat relapse. The HZ VE (first or only episode of HZ) during the entire study period including confirmed HZ episodes which occurred after the subject had started therapy to treat relapse was 67.34% (95% CI: 55.07% - 76.56%). Of the 199 subjects with confirmed HZ episodes, 54 were in the HZ/su group and 145 in the Placebo group. Compared to the analysis addressing the primary objective, there were 5 additional subjects with confirmed HZ episodes in the HZ/su group and 10 additional subjects with confirmed HZ episodes in the Placebo group; for these subjects confirmed HZ episodes were initiated after treatment for relapse.

Regarding the confirmed HZ episodes from subjects in the mTVC (including these confirmed HZ episodes that occurred after treatment for relapse), further details are provided:

- There were 3 subjects in the Placebo group and no subjects in the HZ/su group with more than one confirmed HZ episode (there were 2 confirmed HZ episodes for each of the 3 subjects in the Placebo group). One of these 3 subjects had a first HZ episode before treatment for relapse and another episode after treatment for relapse. The 2 other subjects had 2 HZ episodes before treatment for relapse.
- Of the suspected HZ episodes, in the HZ/su group 54 (73.0%) were confirmed HZ episodes, in the Placebo group 148 (77.9%) were confirmed HZ episodes.

There were a total of 202 confirmed HZ cases, of which 167 were confirmed by PCR and 35 were confirmed by HZAC. In the HZ/su group, of the 54 confirmed HZ cases, 45 were confirmed cases by PCR and 9 by HZAC. In the Placebo group, of the 148 confirmed HZ cases, 122 were confirmed cases by PCR and 26 by HZAC. The additional 35 cases determined by HZAC could not be classified by PCR (samples were inadequate or no samples were available). HZ episodes, confirmed by PCR or HZAC, and with a clinical presentation of disseminated rash at onset, could have constituted a primary VZV infection (varicella). In such cases, a per-protocol defined algorithm was applied. In the mTVC, for 3 subjects in

the HZ/su group, and 12 subjects in the Placebo group this algorithm was applied and all 15 cases were confirmed as HZ.

HZ VE by subgroup

Table 48: Vaccine efficacy: First or only episode of HZ during the entire study period by age strata using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
18-49 YOA	213	9	419.4	21.5	212	29	381.4	76.0	71.77	38.75	88.25	0.0006
≥50 YOA	657	40	1213.7	33.0	639	106	1050.5	100.9	67.34	52.60	77.89	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group;18-49 YOA = 18-49 years old subjects; ≥50 YOA = ≥ 50 years old subjects; N = total number of subjects in each group ; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

Table 49: Vaccine efficacy: First or only episode of HZ during the entire study period by underlying diseases stratum using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Multiple myeloma	472	22	907.2	24.2	465	69	786.7	87.7	72.35	54.76	83.71	<0.0001
Other diagnoses	398	27	725.8	37.2	386	66	645.2	102.3	63.63	42.29	77.66	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subject included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

Table 50: Vaccine efficacy : First or only episode of HZ during the entire study period by anticipated duration of post-transplant antiviral prophylaxis stratum using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Antiviral 0-3 months	503	31	925.5	33.5	476	75	787.4	95.2	64.84	45.89	77.64	<0.0001
Antiviral > 3-6 months	367	18	707.5	25.4	375	60	644.5	93.1	72.67	53.08	84.82	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Antiviral 0-3 months = Anticipated duration of post-transplant antiviral prophylaxis up to and including 3 months; Antiviral >3-6 months = Anticipated duration of post-transplant antiviral prophylaxis for more than 3 months and including 6 months ; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

Table 51: Vaccine efficacy : First or only episode of HZ during the entire study period by gender using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Female	323	16	614.3	26.0	317	61	524.6	116.3	77.60	60.66	87.95	<0.0001
Male	547	33	1018.8	32.4	534	74	907.3	81.6	60.28	39.37	74.48	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

HZ VE in subjects during 1-year post-HCT

Overall, limited to 1-year post-HCT, the median follow-up time was 7.6 months. In the HZ/su group, the median follow-up time was 7.7 months and in the Placebo group 7.6 months.

Table 52: Vaccine efficacy: First or only episode of HZ during 365 days post-Haematopoietic stem Cell Transplant (HCT) using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
OVERALL	870	21	516.2	40.7	851	82	480.6	170.6	76.15	61.11	85.98	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

Additional stratified analyses

No apparent differences were observed for VE against HZ across regions i.e., Europe, North America and Austrasia. Of note, VE was not calculated for South America because of the few subjects enrolled and the absence of confirmed HZ cases in this region.

Table 53: ZOSTER-002: Vaccine efficacy: First or only episode of HZ during the entire study period by region using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Europe	553	36	1045.8	34.4	519	80	911.4	87.8	60.78	41.19	74.30	<0.0001
North America	138	8	246.2	32.5	147	18	222.4	80.9	59.85	2.96	84.89	0.0417
South America	5	0	10.5	0.0	6	0	9.4	0.0	-	-	-	-
Austrasia	174	5	330.5	15.1	179	37	288.6	128.2	88.20	69.91	96.38	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Antiviral 0-3 months = Anticipated duration of post-transplant antiviral prophylaxis up to and including 3 months; Antiviral >3-6 months = Anticipated duration of post-transplant antiviral prophylaxis for more than 3 months and including 6 months ; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

Post-hoc analyses of VE against HZ were performed by actual duration of Prophylactic Antiviral Therapy.

Table 54: ZOSTER-002: Vaccine Efficacy: First or only episode of HZ during the entire study period by the use of Prophylactic Antiviral Therapy (PAT) duration during the entire study period using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
No PAT	454	27	852.6	31.7	426	80	693.2	115.4	72.56	57.08	82.95	<0.0001
1-60 days	226	10	408.1	24.5	262	40	449.4	89.0	72.48	43.99	87.73	<0.0001
>60 days	190	12	372.3	32.2	163	15	289.3	51.8	37.84	-42.26	73.43	0.2962

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Antiviral 0-3 months = Anticipated duration of post-transplant antiviral prophylaxis up to and including 3 months; Antiviral >3-6 months = Anticipated duration of post-transplant antiviral prophylaxis for more than 3 months and including 6 months ; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

Post-hoc analyses of VE against HZ was performed by detailed underlying disease category.

Table 55: Vaccine efficacy: First or only episode of HZ during the entire study period by detailed underlying disease category using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Multiple myeloma	472	22	907.2	24.2	465	69	786.7	87.7	72.35	54.76	83.71	<0.0001
NHBCL	237	19	438.5	43.3	244	45	410.6	109.6	60.46	31.02	78.16	0.0006
NHTCL	43	1	78.9	12.7	40	5	69.2	72.3	82.45	-56.81	99.63	0.1633
Hodg_L	74	5	136.9	36.5	60	7	110.2	63.5	42.50	-110.44	85.61	0.5028
AML	20	0	32.2	0.0	16	3	19.8	151.4	100.00	-48.86	100.00	0.1105
Other	24	2	39.4	50.8	26	6	35.4	169.4	70.00	-67.75	97.04	0.2253

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Multiple myeloma = subjects with an underlying diagnosis of multiple myeloma; NHBCL = subjects with an underlying diagnosis of non-hodgkin B-cell lymphoma; NHTCL= subjects with an underlying diagnosis of non-hodgkin T-cell lymphoma; Hodg_L = subjects with an underlying diagnosis of hodgkinl lymphoma; AML = subjects with an underlying diagnosis ofacute myeloid leukemia; Other = Subjects with an underlying diagnosis of any other diseases including Solid malignancies and Autoimmune diseases; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

Reduction of pain, PHN, HZ-associated complications, hospitalisation, and mortality

The reduction of duration of severe 'worst' HZ-associated pain in subjects with a confirmed HZ episode is presented below.

Table 56: Duration (days) of severe 'worst' HZ-associated pain over the entire pain reported period, in subjects with a confirmed HZ episode (modified Total Vaccinated Cohort)

		HZ/su	Placebo
Characteristics	**Parameters**	**Value**	**Value**
Duration of severe 'worst' HZ-associated pain	N	37	120
	Nmiss	12	15
	Mean	23.8	52.2
	SD	31.88	127.75
	Median	14.0	24.0
	Min	1.0	1.0
	Max	178.0	1025.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Duration = The last day with severe worst pain – The first day with severe worst pain + 1 (worst duration if more than 1 confirmed HZ episode); N = total number of subjects with at least one confirmed HZ episode with severe "worsts" HZ-associated pain; Nmiss = number of subjects with at least one confirmed HZ episode without sever "worst" HZ-associated pain; SD = standard deviation

Pain duration was reduced in vaccinated vs. Placebo confirmed HZ cases. At least one day of severe 'worst' HZ-associated pain (defined as ZBPI pain scores of 3 or more on the 'worst' pain ZBPI question) was reported in 76% and 89% of the subjects who had confirmed HZ in the HZ/su vs. Placebo group. The median (min - max) duration of severe 'worst' HZ-associated pain was 14.0 (1.0 - 178.0) days in the HZ/su group and 24.0 (1.0 -1025.0) days in the Placebo group.

In the mTVC at least one HZ complication was observed in 3 out of 870 subjects of the HZ/su group and 13 out of 851 subjects of the Placebo group (Table 57). Reported HZ complications were HZ meningoencephalitis (1 subject in the Placebo group) and HZ cutaneous disseminated (3 subjects in the HZ/su group and 12 subjects in the Placebo group). This analysis excluded HZ complications that were linked to a confirmed HZ case that occurred after the start of the treatment for relapse.

Table 57 presents results on PHN VE (first or only episode of PHN) using the Poisson method, of the 10 subjects with PHN episodes in the mTVC, 1 was in the HZ/su group and 9 were in the Placebo group. This table also presents the VE in reduction of PHN incidence in subjects with a confirmed HZ episode.

HZ-related mortality was not observed in the autologous HCT recipients ≥ 18 YOA. The reduction of overall and confirmed HZ episode related mortality and hospitalizations is presented in the tables below.

Table 57: Frequency of confirmed HZ episode related hospitalization during the entire study period in all subjects (modified Total Vaccinated Cohort)

	HZ/su			Placebo			Total		
Number of hospitalization	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
1	870	2	0.2	851	13	1.5	1721	15	0.9
2	870	0	0.0	851	0	0.0	1721	0	0.0
3 or more	870	0	0.0	851	0	0.0	1721	0	0.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects

Table 58: ZOSTER-002: Summary of vaccine efficacy against HZ and HZ-associated complications (first or only episode of HZ, mTVC)

VE objective in all subjects		HZ/su (N=870)		Placebo (N=851)			
		n	n/T (per 1000)	n	n/T (per 1000)	VE % (95% CI)	P-value
Prevention of HZ	during the entire study period	49	30.0	135	94.3	68.17 (55.56, 77.53)	<0.0001
	during 1 year post-HSCT	21	40.7	82	170.6	76.15 (61.11, 85.98)	<0.0001
Prevention of PHN during the entire study period		1	0.5	9	4.9	89.27 (22.54, 99.76)	0.0186
Reduction of confirmed HZ-associated complications (other than PHN) during the entire study period		3	1.6	13	7.1	77.76 (19.05, 95.93)	0.0175
Reduction of HZ-related hospitalizations during the entire study period		2	1.1	13	7.1	84.70 (32.15, 96.55)	0.0135
Reduction of overall mortality during the entire study period		106	54.8	106	56.4	2.92 (-27.08, 25.84)	0.8291
VE objective in confirmed HZ cases		**HZ/su (N=49)**		**Placebo (N=135)**			
		n	n/N'	n	n/N'	VE % (95% CI)	P-value
Prevention of PHN during the entire study period		1	2.04	9	6.67	69.39 (-77.38, 94.97)	0.2941
		n	T(day)	n	T(day)	VE % (95% CI)	P-value
Reduction of duration of pain medication during the entire study period		32*	1917.0	94*	15465.0	22.45 (-15.85, 48.09)	0.2144
Reduction of total duration of severe 'worst' HZ-associated pain over the entire pain-reporting period		37**	892.0	120**	6275.0	38.53 (11.05, 57.52)	0.0099

n = number of subjects having at least one event in each group; * number of subjects with a least one day of pain medication associated with HZ ** number of subjects with at least one day of severe "worst" HZ-associated pain; N = number of subjects with at least one confirmed HZ episode; n/T (per 1000) = Incidence rate of subjects reporting at least one event; N' = number of subjects with at least one confirmed HZ episode

Reduction in use and duration of HZ-associated pain medications in subjects with a confirmed HZ episode

VE in terms of pain medication associated with HZ, the distribution of pain medication associated with HZ and the duration of pain medication associated with HZ during the entire study period, in subjects with a confirmed HZ episode are presented below, as well as VE in terms of reduction of duration of pain medication associated with HZ.

Table 59: Vaccine efficacy: Pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode (modified Total Vaccinated Cohort)

					n/N			VE			
Type	Group	N	n+	n	%	LL	UL	%	LL	UL	p-value
OVERALL	HZ/su	49	65	32	65.31	50.36	78.33	6.21	-15.84	27.82	0.5937
	Placebo	135	262	94	69.63	61.13	77.24	-	-	-	-

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects with at least one confirmed HZ episode; n+ = number of events in each group (all confirmed HZ episodes considered); n = number of subjects reporting at least one event in each group (all confirmed HZ episodes considered); LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy using asymptotic standardized unconditional binomial test

Table 60: Distribution of pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode (modified Total Vaccinated Cohort)

	HZ/su			Placebo			Total		
Characteristics	N	n	%	N	n	%	N	n	%
At least one pain medication	49	32	65.3	135	94	69.6	184	126	68.5
1 pain medication only	49	19	38.8	135	34	25.2	184	53	28.8
2 pain medications only	49	8	16.3	135	23	17.0	184	31	16.8
3 pain medications or more	49	5	10.2	135	37	27.4	184	42	22.8

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = number of subjects with at least one confirmed HZ episode; n/% = number/percentage of subjects in the specified category (all confirmed HZ episodes considered)

Table 61: Duration of pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode (modified Total Vaccinated Cohort)

		HZ/su	Placebo
Characteristics	Parameters	Value	Value
Duration of pain medication associated with HZ	N	32	94
	Nmiss	17	41
	Mean	59.4	164.1
	SD	99.08	305.17
	Median	21.5	47.5
	Min	1.0	1.0
	Max	436.0	1642.0

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Duration = Sum (For each pain medication (last day of each pain medication – first day of each pain medication +1)) (worst duration if more than 1 confirmed HZ episode); N = number of subjects with at least one confirmed HZ episode with pain medication; Nmiss = number of subjects with at least one confirmed HZ episode without pain medication; SD = standard deviation

Table 62: Vaccine efficacy: Reduction of duration of pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode (modified Total Vaccinated Cohort

							VE			
	HZ/su			Placebo				95% CI		
Type	N	n	T(day)	N	n	T(day)	(%)	LL	UL	p-value
OVERALL	49	32	1917.0	135	94	15465.0	22.45	-15.85	48.09	0.2144

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Duration = Sum (For each pain medication (last day of each pain medication – first day of each pain medication +1)) (worst duration if more than 1 confirmed HZ episode); LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Cox regression model); P-value from Cox regression model

b) Total Vaccinated Cohort analysis

For all subjects in the TVC, the median follow-up time (from dose 1 until last contact documented in conclusion screens but limited until 04 November 2016) was approximately 26 months; with approximately 27 months in the HZ/su group and approximately 24 months in the Placebo group. Overall, the maximum follow-up time was approximately 52 months, with 51 months in the HZ/su group and 52 months in the Placebo group. Overall HZ VE results obtained for the TVC were consistent with results obtained for the mTVC.

Table 63: Vaccine efficacy: First or only episode of HZ during the entire study period using Poisson method (Total Vaccinated Cohort)

	HZ/su				Placebo				VE	95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
OVERALL	922	70	2017.5	34.7	924	172	1798.8	95.6	63.71	51.82	72.92	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of cases

c) ATP cohort for efficacy analysis

Overall, HZ VE results obtained for the ATP cohort for efficacy were consistent with results obtained for the mTVC.

Table 64: Vaccine efficacy: First or only episode of HZ during the entire study period using Poisson method (ATP cohort for efficacy)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
OVERALL	682	38	1259.7	30.2	672	112	1124.9	99.6	69.70	55.87	79.61	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group;; N = total number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode; T (year) = sum of follow/up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years; (n/T (per 1000) = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method); P-value = Two side Exact P-value conditional to number of case

d) QUALITY OF LIFE RESULTS 002

All the QoL analyses (of tertiary endpoints including by subgroup analyses) were exploratory. The study was not designed to draw confirmatory conclusions on these analyses as no control of type I error was done. A summary of the results of the QoL analyses is presented:

- Consistent differences were observed in favor of the HZ/su group compared to the Placebo group when measuring pain associated with the HZ episode using the ZBPI.
- The overall VE estimate for the ZBPI burden-of-illness score was 82.5% (95% CI: 73.6% - 91.4%). The overall VE estimate for the ZBPI burden-of-interference score was 82.8% (95% CI: 73.3% - 92.3%).
- The median time to resolution of clinically significant pain was 20 days in the HZ/su group and 31 days in the Placebo Group.
- Consistent differences were observed in favor of the HZ/su group compared to the Placebo group in the AUC scores for the ZBPI worst pain score, ZBPI average pain score, and ZBPI ADL score for all of the time periods, i.e., 30, 90 and 182 days suggesting that the severity of disease was reduced in the HZ/su group compared with the Placebo group.
- Some differences were observed between HZ/su and Placebo groups, in favor of HZ/su, when analyzing the SF-36 and EQ-5D scales, particularly at Week 1 of the HZ episode. No consistent differences in favour of either group were observed at other timepoints suggesting that the largest differences between HZ/su and Placebo groups in the impact on QoL were observed in the first week of the HZ episode.
- The estimated HZ Disutility Score by age group and timepoint assessed using the EQ-5D in the Placebo Group was estimated as -0.3328 (95% CI: -0.4383, -0.2274) and -0.2406 (95% CI: -0.3035,

-0.1778) on Day 0 in the age groups 18-49 YOA and ≥50 YOA, respectively, suggesting a major impact on QoL due to the HZ episode for non-vaccinated subjects.

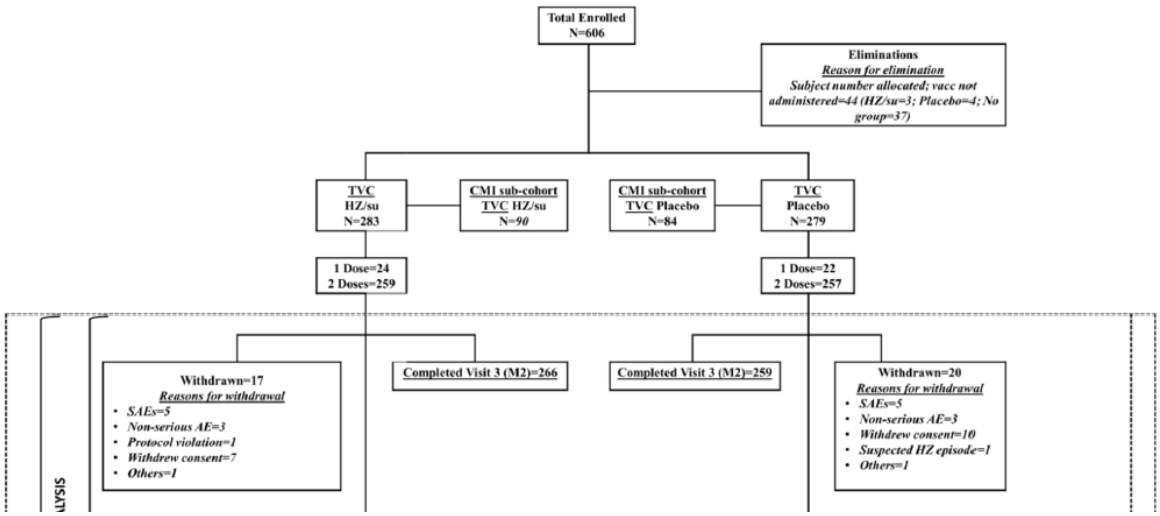
ZOSTER-039:

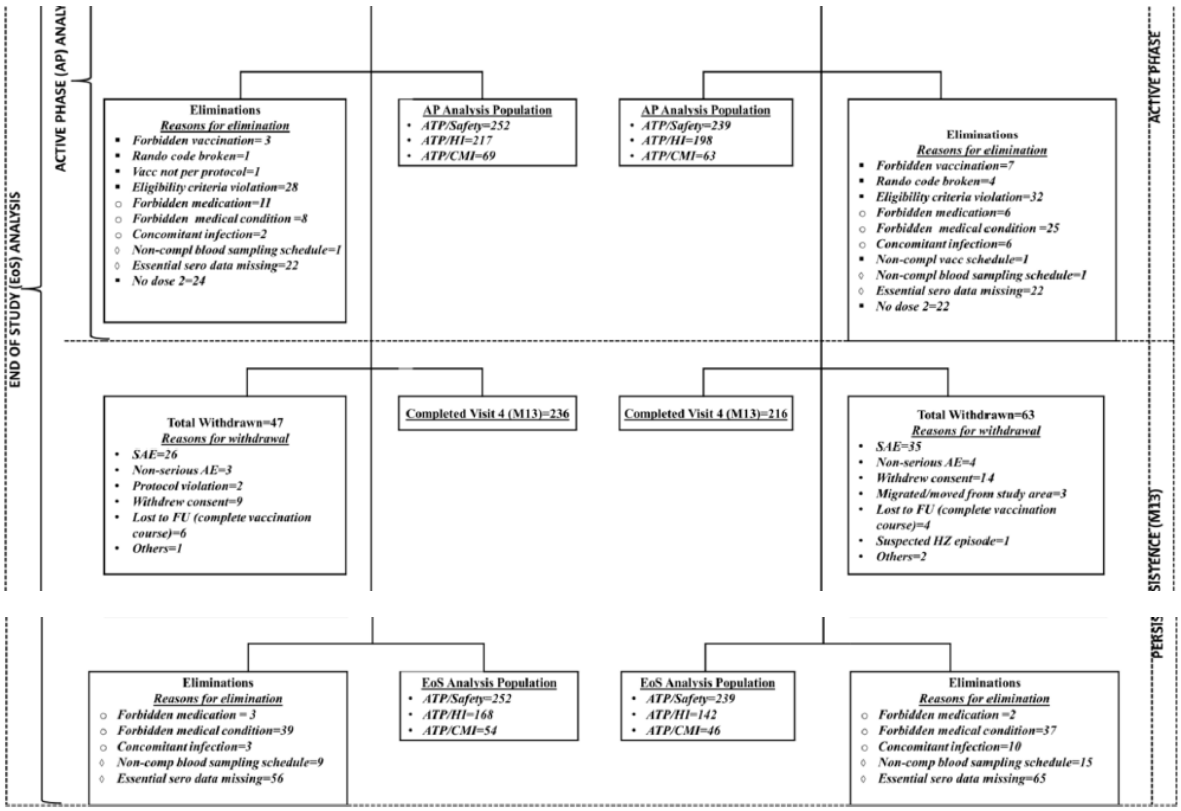
- ***Studies' dates***

The first subject was enrolled in the study on 01 March 2013. The last subject completed the active phase (Visit 3, Month 2) on 07 January 2016. The last study visit was on 06 January 2017.

Participant flow

Figure 5: Subject disposition





N = total number of subjects included in each group; TVC: Total vaccinated Cohort; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; CMI: Cell Mediated Immunogenicity; M: Month; SAE: Serious Adverse Event: AE: Adverse Event; AP: Active phase; ATP: According to Protocol cohort; HI: Humoral Immunogenicity; Rando: Randomization: Vacc: vaccination; Med cond: Medical condition; Non-comp: Non compliant; Sero: serology; FU: follow-up

Among the 606 subjects enrolled, 562 were vaccinated (283 in the HZ/su group and 279 in the Placebo group), 452 completed the study (236 in the HZ/su group and 216 in the Placebo group) and 110 were withdrawn (47 [16.6%] in the HZ/su group and 63 [22.6%] in the Placebo group).

Table 65: Number of subjects vaccinated, completed up to the study end and withdrawn with reason for withdrawal (Total Vaccinated Cohort)

	HZ/su		Placebo		Total	
	n	%	n	%	n	%
Number of subjects vaccinated	283	100	279	100	562	100
Number of subjects completed	236	83.4	216	77.4	452	80.4
Number of subjects withdrawn	47	16.6	63	22.6	110	19.6
Reasons for withdrawal:						
Serious Adverse Event	26	9.2	35	12.5	61	10.9
Non-Serious Adverse Event	3	1.1	4	1.4	7	1.2
Protocol violation	2	0.7	0	0.0	2	0.4
Consent withdrawal (not due to an adverse event)	9	3.2	14	5.0	23	4.1
Migrated/moved from study area	0	0.0	3	1.1	3	0.5
Lost to follow-up (subjects with incomplete vaccination course)	0	0.0	0	0.0	0	0.0
Lost to follow-up (subjects with complete vaccination course)	6	2.1	4	1.4	10	1.8
Suspected HZ Episode*	0	0.0	1	0.4	1	0.2
Sponsor study termination	0	0.0	0	0.0	0	0.0
Others	1	0.4	2	0.7	3	0.5

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; Vaccinated = number of subjects who were vaccinated in the study; Completed = number of subjects who completed last study visit; Withdrawn = number of subjects who did not come back for the last visit; *subject was withdrawn due to serious suspected HZ episode; % = (n/Number of subjects vaccinated) x 100

The number of subjects enrolled into the study as well as the number excluded from ATP cohort for safety analyses up to 30 days post-last vaccination with reasons for exclusion is presented below.

Out of the 283 and 279 subjects from the HZ/su and Placebo groups, respectively, included in the TVC, 252 and 239 were included in the ATP cohort for safety up to 30 days post-last vaccination. The following protocol deviations leading to elimination from this ATP cohort were: (i) administered concomitant vaccine(s) forbidden in the protocol up to 30 days post last vaccination, (ii) randomization code broken, (iii) vaccine administered not according to protocol, (iv) protocol violation linked to the inclusion/exclusion criteria including age.

Baseline data

The summary of demographic characteristics by timing of vaccination in relation to the cancer therapy cycle indicates that vaccination was done: During the cancer treatment for 102 vs. 106 subjects in the HZ/su and Placebo groups respectively; After the cancer treatment for 181 vs. 173 subjects in the HZ/su and Placebo groups respectively.

Findings are similar in the mTVC.

From 1 year prior to Dose 1 up to 1 month post Dose 2, the following subclasses of IS cancer therapy were most frequently administered (by >20% of subjects in the HZ/su group): nitrogen and mustard analogues (55.7%), anthracyclines (42.4%), antimitotic agents including antimicrotubule agents (34.4%), anti CD20 (28.6%), and pyrimidine analogues (22.9%). Results were in the same range for subjects in the HZ/su and Placebo groups.

Numbers analysed

The incidence rates of confirmed HZ cases from Month 0 until study end, performed on the TVC, are presented below, overall, and in stratified analyses.

Table 66: Incidence rate of confirmed HZ cases from Month 0 until study end (Total Vaccinated Cohort)

				Person-year rate		
					95% CI	
Group	N	n	T (year)	n/T (Per 1000)	LL	UL
HZ/su	283	6	296.39	20.24	9.09	45.06
Placebo	279	19	268.10	70.87	45.20	111.11

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects reporting at least one event in each group; T (years) = sum of follow-up period expressed in years; n/T = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits;

Table 67: Incidence rate of HZ confirmed cases from Month 0 until study end by age strata (Total Vaccinated Cohort)

					Person-year rate		
						95% CI	
Sub-group	Group	N	n	T (year)	n/T (Per 1000)	LL	UL
18-49 YOA	HZ/su	74	3	80.38	37.32	12.04	115.72
	Placebo	73	4	73.02	54.78	20.56	145.95
≥ 50 YOA	HZ/su	209	3	216.01	13.89	4.48	43.06
	Placebo	206	15	195.07	76.89	46.36	127.55

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects reporting at least one event in each group; T (years) = sum of follow-up period expressed in years; n/T = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits;

Table 68: Incidence rate of HZ confirmed cases from Month 0 until study end by underlying diseases stratum (Total Vaccinated Cohort)

					Person-year rate		
						95% CI	
Sub-group	Group	N	n	T (year)	n/T (Per 1000)	LL	UL
CLL	HZ/su	42	1	46.35	21.58	3.04	153.17
	Placebo	41	3	42.08	71.29	22.99	221.03
MM and other diseases	HZ/su	200	4	205.10	19.5	7.32	51.96
	Placebo	199	13	185.63	70.03	40.66	120.61
NHBCL	HZ/su	41	1	44.94	22.25	3.13	157.96
	Placebo	39	3	40.38	74.29	23.96	230.35

MM and other diseases = Multiple Myeloma, Non-Hodgkin T-cell Lymphoma, Hodgkin Lymphoma and other Haematologic Malignancies; CLL = Chronic Lymphocytic Leukaemia; NHBCL = Non-Hodgkin B-cell Lymphoma; HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects reporting at least one event in each group; T (years) = sum of follow-up period expressed in years; n/T = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits;

Table 69: Incidence rate of HZ confirmed cases from Month 0 until study end by timing of vaccination in relation to the particular immunosuppressive cancer therapy cycle (Total Vaccinated Cohort)

					Person-year rate		
						95% CI	
Sub-group	Group	N	n	T (year)	n/T (Per 1000)	LL	UL
After the cancer therapy	HZ/su	181	4	192.40	20.79	7.8	55.39
	Placebo	173	12	169.11	70.96	40.3	124.95
During the cancer therapy	HZ/su	102	2	103.99	19.23	4.81	76.9
	Placebo	106	7	98.99	70.72	33.71	148.34

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects reporting at least one event in each group; T (years) = sum of follow-up period expressed in years; n/T = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits;

Outcomes and estimation

Of the 16 subjects with confirmed HZ episodes (first or only confirmed HZ episode) in the mTVC, 2 were in the HZ/su group and 14 in the Placebo group after a median (min-max) follow-up time of 11.1 (0-15.6) months.

Table 70: Vaccine efficacy: First or only episode of HZ from 30 days after the second vaccination until study end using Poisson method (modified Total Vaccinated Cohort)

								VE			
HZ/su				Placebo					95% CI		
N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
259	2	236.1	8.5	256	14	211.6	66.2	87.20	44.25	98.59	0.0021

HZ/su = Herpes Zoster sub-unit vaccine group; Placebo = Placebo group; N = total number of subjects included in each group; n = number of subjects reporting at least one event in each group; T (years) = sum of follow-up period expressed in years; n/T = Incidence rate of subjects reporting at least one event; LL, UL = 95% Lower and Upper confidence limits;

Ancillary analyses

Correlate of protection analysis:

In the Cohort for correlate of protection (CCP), there were a total of 14 confirmed HZ cases, 2 confirmed HZ cases in the HZ/su group and 12 confirmed HZ cases in the Placebo group. The GMCs of anti-gE Ab at 1 month after receiving 2 doses of HZ/su in subjects who later developed confirmed HZ (HZ/su cases - 2 subjects) and in those who did not develop confirmed HZ (HZ/su Non-cases) in the 1 year follow-up were 184 and 12517.4, respectively. The fold increase in GMCs at 1 month after receiving 2 doses of HZ/su compared with baseline values was 1.59 times for confirmed HZ/su cases and 13.07 times for confirmed HZ/su Non-cases, respectively.

Occurrence of HZ and HZ-related complications, in the other studies:

In ZOSTER-028 and ZOSTER-041, the occurrence of suspected HZ and/or HZ complications constituted an AE or SAE, as appropriate. HZ complications, including but not limited to PHN (see above for ZOSTER-002), HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, and visceral disease,

were recorded by the investigator and considered as AEs or SAEs as appropriate. The reporting period for cases of HZ was from Month 0 to study end.

Suspected HZ was defined as onset of a rash characteristic of HZ (i.e., unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations), or a vesicular rash suggestive of VZV infection regardless of the dermatomal distribution, and without alternative diagnosis. Additionally, sometimes HZ cases do not present with the characteristic HZ or VZV rash, but have a clinical presentation and specific laboratory tests suggestive of VZV infection. These cases were also to be considered as occurrences of HZ.

In study ZOSTER-028, there were 1 and 2 suspected HZ episode in the HZ/su and placebo groups respectively. In study ZOSTER-041, there were 3 and 7 suspected HZ episode in the HZ/su and placebo groups respectively. None of the HZ cases were assessed by the investigator as causally related to vaccination and all cases recovered/resolved by the end of the study.

In study ZOSTER-028, no suspected HZ cases were reported as SAE.

In study ZOSTER-041, of the 7 placebo recipients who reported suspected HZ cases, 4 were reported as SAEs. All the subjects presenting with itching and pain. One developed a mild-grade 1, two a moderate-grade 2 and one a severe-grade 3 HZ. No complications were notified. No subjects in the HZ/su group reported HZ cases that were SAEs.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 71: Summary of Efficacy for trial ZOSTER-002

<table>
<tr><td colspan="4">Title: A phase III, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' herpes zoster gE/AS01B candidate vaccine when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients.</td></tr>
<tr><td>Study identifier</td><td colspan="3">115523 (ZOSTER-002)</td></tr>
<tr><td>Design</td><td colspan="3">phase III, randomized, observer-blind, placebo-controlled, multicenter trial</td></tr>
<tr><td></td><td colspan="2">Duration of main phase:

Duration of Run-in phase:
Duration of Extension phase:</td><td>Study initiation data: 13 July 2012
Study completion date: 01 February 2017
not applicable
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td>Treatments groups</td><td colspan="2">Vaccine group (HZ/su)</td><td>Subjects received 2 doses of HZ/su 1 to 2 months apart through IM injection, n=922 (TVC)</td></tr>
<tr><td></td><td colspan="2">Placebo group (NaCl)</td><td>Subjects received 2 doses of saline (150 mM NaCl) 1 to 2 months apart through IM injection, n=924 (TVC)</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>Efficacy in preventing HZ</td><td>Incidence of confirmed HZ cases from Month 0 until study end</td></tr>
<tr><td></td><td>Secondary endpoint</td><td>Efficacy in preventing PHN</td><td>Incidence of PHN from Month 0 until study end</td></tr>
</table>

	Secondary endpoint	Efficacy in reducing HZ-associated complications	Incidence of confirmed HZ complications following the onset of HZ from Month 0 to study end
	Secondary endpoint	Efficacy in reducing the total duration of severe 'worst' HZ-associated pain	Duration of severe 'worst' HZ-associated pain, i.e. HZ-associated pain rated as 3 or greater on the 'worst pain' ZBPI question, following the onset of a confirmed HZ rash over the entire pain reporting period in subjects with confirmed HZ
Notes	The tertiary and post-hoc objectives and endpoints are not included in this table, except the two most relevant endpoints for the B/R assessment; The efficacy in reducing the duration of pain medication in subjects with confirmed HZ and in reducing HZ-related hospitalisation are mentioned as notes at the end of the table.		
Database lock	05 September 2017		

Results and Analysis

Analysis description	**Primary Analysis, Efficacy in preventing HZ**		
Analysis population and time point description	mTVC, final analysis		
Descriptive statistics and estimate variability	Treatment group	Vaccine group	Placebo group
	Number of subject	870	851
	Number of subjects having at least one HZ confirmed case (n)	49	135
	Follow-up period in years (T)	1633.1	1431.9
	Incidence rate per 1000 person years (n/T)	30.0	94.3
Effect estimate per comparison	Primary endpoint	Comparison groups	Vaccine vs Placebo
		VE	68.17
		95% CI	55.56-77.53
		P-value	<0.0001
Analysis description	**Secondary analysis, Efficacy in preventing PHN**		
Analysis population and time point description	mTVC, final analysis		
Descriptive statistics and estimate variability	Treatment group	Vaccine group	Placebo group
	Number of subject	870	851
	Number of subjects having PHN (n)	1	9
	Follow-up period in years (T)	1897.9	1833.4
	Incidence rate per 1000 person years (n/T)	0.5	4.9
Effect estimate per comparison	Secondary endpoint	Comparison groups	Vaccine vs Placebo
		VE	89.27
		95% CI	22.54-99.76
		P-value	0.0186

Analysis description	**Secondary analysis, Efficacy in reducing HZ-associated complications**		
Analysis population and time point description	mTVC, final analysis		
Descriptive statistics and estimate variability	Treatment group	Vaccine group	Placebo group
	Number of subject	870	851
	Number of subjects having a reduction of confirmed HZ associated complications (other than PHN) during the entire study period (n)	3	13
	Follow-up period in years (T)	1893.9	1825.5
	Incidence rate per 1000 person years (n/T)	1.6	7.1
Effect estimate per comparison	Secondary endpoint	Comparison groups	Vaccine vs Placebo
		VE	77.76
		95% CI	19.05-95.93
		P-value	0.0175
Analysis description	**Secondary analysis, Efficacy in reducing the total duration of severe 'worst' HZ-associated pain**		
Analysis population and time point description	Confirmed HZ cases, final analysis		
Descriptive statistics and estimate variability	Treatment group	Vaccine group	Placebo group
	Number of subject	49	135
	Number of subjects having a reduction of total duration of severe 'worst' HZ-associated pain over the entire pain-reporting period (n)	37	120
	Median duration of severe 'worst' HZ-associated pain in days	14.0	24.0
	Min-Max duration of severe 'worst' HZ-associated pain in days	1.0-178.0	1.0-1025.0
Effect estimate per comparison	Secondary endpoint	Comparison groups	Vaccine vs Placebo
		VE	38.53
		95% CI	11.05-57.52
		P-value	0.0099
Notes	In addition to the reduction of severe 'worst' HZ-associated pain, less subjects in the vaccine groups used 3 or more pain medications compared to the placebo group (10.2% vs. 27.4%). The VE (95% CI) was 22.5 (-15.9-48.1). The duration of pain medication was shorter in the HZ/su group (median 21.5 days [min – max: 1.0 –436.0]) compared with the Placebo group (median 47.5 [min - max 1.0 – 1642.0]). The vaccine efficacy against first or only episode of confirmed HZ-related hospitalizations was 84.70% (95% CI: 32.15% - 96.55%) during the entire study period.		

Table 72: Summary of Efficacy for trial ZOSTER-039

Title: A Phase III, randomised, observer-blind, placebo-controlled, multicentre study to assess the safety and immunogenicity of GSK Biologicals' Herpes Zoster HZ/su candidate vaccine when administered intramuscularly on a two-dose schedule to adults aged 18 years and older with haematologic malignancies.			
Study identifier	116428 (ZOSTER-039)		
Design	phase III, randomized, observer-blind, placebo-controlled, multicenter trial		
	Duration of main phase:		Study initiation data: 01 March 2013 Study active phase completion date: 07 January 2016 Study completion date: 06 January 2017
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Vaccine group (HZ/su)		Subjects received 2 doses of HZ/su 1 to 2 months apart through IM injection, n=283 (TVC)
	Placebo group (NaCl)		Subjects received 2 doses of saline (150 mM NaCl) 1 to 2 months apart through IM injection, n=279 (TVC)
Endpoints and definitions	Secondary endpoint	Incidence of confirmed HZ cases	Occurrence of confirmed HZ cases from Month 0 until study end
	Post-hoc endpoint	Efficacy against HZ	Incidence of confirmed HZ cases from Month 0 until study end
Database lock	Active phase : 07 October 2016, End of study: 11 December 2017		
Results and Analysis			
Analysis description	**Secondary Analysis, Incidence of confirmed HZ cases** **Post-hoc Analysis, Efficacy in preventing HZ**		
Analysis population and time point description	mTVC, final analysis		
Descriptive statistics and estimate variability	Treatment group	Vaccine group	Placebo group
	Number of subject	259	256
	Number of subjects having at least one HZ confirmed case (n)	2	14
	Follow-up period in years (T)	236.1	211.6
	Incidence rate per 1000 person years (n/T)	8.5	66.2
Effect estimate per comparison	Post-hoc endpoint	Comparison groups	Vaccine vs Placebo
		VE	87.20
		95% CI	44.25-98.59
		P-value	0.0021

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Design:

ZOSTER-002 and ZOSTER-039 were phase III, randomised, observer-blind, placebo-controlled, multicentre, multi-country (28 and 21 countries respectively) trials to assess Shingrix when administered intramuscularly on a two-dose schedule respectively to adults recipients of autologous haematopoietic stem cell transplant (HCT) and to adults with hematologic malignancies. ZOSTER-002 was primarily conducted to evaluate the efficacy of Shingrix in the prevention of HZ, while in ZOSTER-039, HZ efficacy analyses were performed post-hoc.

Populations:

The ZOSTER-002 study population consisted in subjects aged 18 years or older who had undergone autologous HCT or for whom autologous HCT was planned, and with no plan for an additional HCTs. The first vaccination had to be done 50-70 days after HCT. HCT recipients are usually not vaccinated as early after transplant, as immunological responses continue to improve during the 1-2 years period following transplant. However, this time interval respective to HCT for the first vaccine dose is considered justified, based on the high short term risk of VZV reactivation and based on the immunogenicity results (see immunogenicity section).

The ZOSTER-039 study population consisted in subjects aged 18 years or older who had been diagnosed with an haematologic malignancy and who were receiving, were scheduled to receive, or had just finished immunosuppressive cancer therapy (defined as chemotherapy and/or immunotherapy). If each cancer therapy treatment cycle was separated by at least 20 days, the first vaccination had to be done as late as possible after a cycle while still allowing 10 days before the next foreseen cycle. If this was not possible, the first vaccination had to be scheduled from 10 days to 6 months after the full cancer therapy course. The same approach applied to the second dose.

In ZOSTER-002, subjects were excluded if prophylactic antiviral therapy with activity against VZV was expected to last more than 6 months after transplantation. In ZOSTER-039, subjects with a planned HCT during the study period were excluded. Those who had a HCT prior to enrolment could be included. In both studies, subjects were excluded if they were vaccinated against HZ or varicella within the 12 months preceding the first dose of study vaccine/placebo, or if they had presented a varicella or HZ episode by clinical history within the 12 months preceding the first dose of study vaccine/placebo.

Inclusion/exclusion criteria are appropriate. The MAH did not exclude all individuals who were administered a varicella vaccine in the past. The literature indicates that HZ cases are reported in individuals vaccinated against varicella, although at a much lower incidence than in non-vaccinated. See also immunogenicity and safety discussion.

Vaccination schedule:

The primary vaccination schedule for Shingrix consists of two doses separated by 2 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose (section 5.1 of SmPC). In the pivotal trials of this application, the MAH used a 2-dose schedule with an interval of 1-2 month between doses. The selection of this schedule allows for a flexible administration in IC individuals, who can be at short term risk of HZ.

Objective and endpoints:

The primary objective of ZOSTER-002 was to estimate VE in reducing the risk of developing HZ. The criterion used to demonstrate efficacy (lower limit of the 95% CI above 0%) is considered acceptable. The trial secondarily aimed at evaluating VE in the prevention of PHN, in reducing the incidence of HZ-associated complications, and in reducing the total duration of severe 'worst' HZ-associated pain. ZOSTER-002 also included an comprehensive set of relevant tertiary objectives, including the evaluation of VE in: (i) reducing the duration of severe HZ-associated pain, the severity of HZ-associated acute pain, and the duration of pain medication, in subjects with confirmed HZ; (ii) preventing HZ 1 year post-HSCT, (iii) improving QoL in subjects with confirmed HZ, (iv) reducing HZ-related hospitalizations and mortality, (v) preventing PHN in subjects with confirmed HZ.

Although HZ by itself is a mild disease, VZV reactivation can have serious complications such as PHN and HZ ophtalmicus (HZO), PHN being the most frequent. The neuropathic pain associated with PHN may be severe and persistent, particularly in IC patients, and is often very resistant to treatment. Preventing PHN, as well as other severe complications of VZV reactivation is regarded as much more clinically relevant than preventing HZ per se. Nevertheless, considering PHN as a secondary endpoint is acceptable, as the endpoint 'HZ' can be ascertained in a more robust manner (PCR assays). The secondary endpoint 'PHN' more clinically relevant but more prone to misclassification.

Overall, these objectives are endorsed as they allow for a comprehensive assessment of the effect of HZ/su with respect to HZ.

ZOSTER-039 was conducted to evaluate the safety and immunogenicity of HZ/su in patients 18 years of age and older diagnosed with haematologic malignancies. The description of the incidence of confirmed HZ cases was part of the secondary objectives. The analysis of VE was a post-hoc exploratory analysis.

In ZOSTER-002 and ZOSTER-039, a suspected case of HZ was defined as: (i) a new rash characteristic of HZ (unilateral and accompanied by pain, broadly defined), (ii) or a vesicular rash suggestive of VZV infection regardless of the distribution, and with no alternative diagnosis, (iii) or a clinical presentation and specific laboratory findings suggestive of VZV infection in the absence of characteristic HZ or VZV rash. The definition is thus broader than that used in ZOSTER-006/ZOSTER-022 trials (which was restricted to rash characteristic of HZ), and as such, takes account of the atypical clinical presentations of HZ in IC patients including zoster sine herpete (ZSH) and disseminated HZ. The additional components (ii) and (iii) of the definition of a suspected case are potentially more prone to misclassification, but clinically relevant in IC patients. VZV reactivation can produce chronic radicular pain as well as all the neurological disorders associated with HZ without rash (ZSH)[1].

In ZOSTER-002 and ZOSTER-039, for suspected cases with a typical HZ rash, the confirmation of HZ was done in a similar way as in ZOSTER-006 and ZOSTER-022. Subjects with symptoms suggestive of HZ were to be examined by investigators preferably within 96 hours. Clinically suspect cases were documented by digital photography and rash lesion samples were collected. HZ episodes were confirmed using PCR as the primary method of confirmation, or by the HZ Adjudication Committee (HZAC) if it was not possible to confirm by PCR. For suspected cases of HZ who could potentially constitute a primary VZV infection (varicella), baseline VZV serology was taken into account to determine whether the case was considered a confirmed case of HZ. In case of suspected HZ diagnosed without characteristic HZ or VZV rash, the HZAC classification had to serve as the final case confirmation. These cases were recorded as (S)AEs.

In ZOSTER-002, subjects with confirmed HZ were followed up for at least 90 days, and had to complete a Zoster Brief Pain Inventory (ZBPI) questionnaire to collect information on the severity and duration of the

[1] Gilden D, Cohrs RJ, Mahalingam R, and Nagel MA. Neurological Disease Produced by Varicella Zoster Virus Reactivation Without Rash. Curr Top Microbiol Immunol. 2010 ; 342: 243–253. (2) Gnann JW. Varicella-Zoster Virus: Atypical Presentations and Unusual Complications. The Journal of Infectious Diseases 2002;186(Suppl 1):S91–8. (3) Kennedy PG. Zoster sine herpete: it would be rash to ignore it. Neurology.2011 Feb 1;76(5):416-7.

HZ-associated pain. The Company also used the Euro-QoL 5 Dimension (EQ-5D) and Short form-36 (SF-36) questionnaires which are standardized non disease-specific instruments for describing and valuing health-related quality of life (HRQoL). These tools were also used in ZOSTER-006 and ZOSTER-022.

In ZOSTER-002, PHN was defined by the presence of HZ-associated 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash. 'Worst' pain was defined as HZ-associated pain rated as 3 or greater on the 'worst' pain ZBPI question. This definition is identical to the one used in the ZOSTER-006/ZOSTER-022 trials.

In contrast to ZOSTER-002, in ZOSTER-039, there were no planned follow-up visits for HZ cases, and no ZBPI questionnaires were completed. In this study, PHN was defined as clinically significant pain or painful abnormal sensations (e.g., allodynia or itch) that persisted 3 months or more after HZ rash onset.

Any other HZ-associated complications, according to a pre-defined protocol list, had to be recorded by the investigator. These complications included HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease including stroke, and visceral disease which in the opinion of the investigator, was caused directly by the VZV infection arising from the HZ episode. The definitions are similar as in the pivotal trials 006/022. HZ complications were considered as AEs or SAEs in ZOSTER-039, and only SAEs in ZOSTER-002. HZ complications associated with confirmed HZ were considered for analysis of the applicable secondary endpoint (ZOSTER-002).

Overall, efficacy endpoints are relevant and well defined. Study procedures to ascertain these endpoints are carefully designed and robust. Methods used to confirm HZ are similar in both studies, and similar to those used in the pivotal ZOSTER-006 and ZOSTER-022 trials, except for cases without a typical HZ rash. PHN was more appropriately defined in ZOSTER-002, based on a standardised tool to assess pain. HZ complications were collected in both studies based on a similar predefined list. In addition, in ZOSTER-002, the MAH undertook a comprehensive assessment of HZ-associated pain and impact on quality of life by using appropriate tools.

Randomisation:

Eligible subjects were randomised in a 1:1 ratio to either the gE/AS01B group or the placebo group. In ZOSTER-002, the randomisation algorithm used a minimisation procedure accounting for relevant factors, i.e. which predict the risk of HZ: (i) age (18-49 YOA and ≥50 YOA), (ii) underlying-disease (multiple myeloma vs. other diagnoses), (iii) post-transplant antineoplastic therapy (given the well-documented increased risk of HZ in persons treated with bortezomib, the included factor was bortezomib at the time of first vaccination, yes or vs no), (iv) anticipated duration of post-transplant antiviral prophylaxis (up to and including 3 months vs more than 3 months up to and including 6 months), (v) center, (vi) gender. In ZOSTER-039, enrolment was performed to ensure equal distribution of the population between the study groups across three underlying disease strata. In addition, within each underlying disease stratum, the randomisation algorithm used a minimisation procedure accounting for the timing of study vaccination in relation to the particular immunosuppressive cancer therapy cycle.

Only a limited number of characteristics could be included in the algorithm, and given the heterogeneity of the population, residual confounding is still possible. It is acknowledged that the inclusion of 'center' in the minimization procedure may attenuate the risk of potential imbalances, as all treatments were given according to local standard of care.

Statistical methods:

In ZOSTER-002, the modified Total Vaccinated Cohort (mTVC) was the primary population for efficacy analyses which excluded subjects in the TVC who were not administered with the second vaccination or who developed a confirmed HZ prior to 1 month after the second vaccination. Subjects with relapse of the original malignancy or disease for which the HCT was undertaken were censored from the mTVc analysis

as of the time they initiated the therapy to treat relapse. The primary analysis of VE was performed using the Poisson method. Clinically meaningful overall efficacy of HZ/su against HZ was demonstrated if the lower limit (LL) of the 95% CI was >0%, which is considered acceptable.

For ZOSTER-039, the incidence of confirmed HZ cases was evaluated as a secondary objective while VE was evaluated post hoc, in a mTVCdefined post-hoc using the same criteria as in ZOSTER-002, with similar statistical methods as in ZOSTER-002.

Cohort of analyses and statistical methods are endorsed. The approach is consistent with the VE analyses performed in the other efficacy studies (ZOSTER-006 and ZOSTER-022).

Efficacy data and additional analyses

ZOSTER-002:

A total of 1846 subjects were vaccinated and constituted the TVC (922 and 924 respectively in subjects in the HZ/su and Placebo groups). Of the subjects in the TVC, 24.7% and 27.3% withdrew before the cut-off date for final analysis respectively in the HZ/su and placebo groups. The main reasons for withdrawal (SAE, non-serious AE, protocol violation, consent withdrawal, moved from study area, lost to follow-up, suspected HZ episode) were balanced between groups.

Of the subjects in the TVC, 5.3% and 6.7% did not receive the second dose respectively in the HZ/su and Placebo groups and were excluded from the mTVC. For 2 subjects in the HZ/su group and 10 subjects in the Placebo group, an episode of confirmed HZ was reported within 30 days post-last vaccination; these subjects were also excluded from the mTVC. Two additional subjects (one in each group) were excluded because they received vaccine doses or replacement not on the same group. This resulted in 870 subjects of the HZ/su group and 851 subjects of the Placebo group included in the mTVC.

In the TVC and the mTVC, subjects had on average 55 YOA, and 63% were female. Groups were balanced with respect to demographic characteristics, including within each strata (18-49 YOA, ≥50 YOA). Most of the subjects were seropositive at baseline (anti-gE Ab titers ≥97 IU/ml), in both arms, suggesting that most of the subjects included in the study experienced a previous natural infection with VZV. The underlying diagnoses were evenly distributed across groups, the most represented diseases being multiple myeloma (54% vs. 55%) and non-Hodgkin B-cell lymphoma (27% vs. 29%). It was also observed that 52% vs. 50% of the subjects respectively in the HZ/su and Placebo groups did not receive Prophylactic Antiviral Therapy, 26% vs. 31% received up to 60 days of Prophylactic Antiviral Therapy, and 22% vs. 19% received >60 days of Prophylactic Antiviral Therapy. For subjects who received PAT the median duration of treatment was similar across groups.

Most (>99%) subjects received at least one IS treatment (during at least one 1 day) from 30 days prior to HSCT up to 30 days after Dose 2. However, only 22.5% and 22.1% of the subjects received at least one IS treatment from HSCT up to 30 days after Dose 2 (mTVC). The treatments received by >10% of subjects in the HZ/su group) were nitrogen and mustard analogues (96.3% vs. 97.2%), topoisomerase inhibitors (38.3% vs. 38.2%), pyrimidine analogues (33.1% vs. 32.7%), nitrosoureas (32.0% vs. 32.4%), anti-TNF non-monoclonal antibodies (14.7% vs 14.8%), other alkylating agents (11.0% vs. 11.3%). Data on therapies were recorded starting from 30 days prior to HSCT. Only 14% of the subjects received anti-CD20 monoclonal antibody within the interval between 30 days prior to HSCT up to blood sample 1 month post Dose 2 (not reported for the other diseases). It is however likely that most patients with NHBCL received rituximab in the period before transplant. The groups were balanced with respect to these treatments. However, these data are presented irrespective of duration and time interval to

vaccination, and thus say nothing about concomitant therapies, or about therapies given shortly before or after vaccination.

Of the suspected HZ episodes, 54 (73.0%) and 148 (77.9%) in the HZ/su and the Placebo group respectively were confirmed HZ episodes. Most of the 202 confirmed HZ episodes were confirmed by PCR (83% and 82% the HZ/su and Placebo groups). The other episodes were determined by HZAC only, as samples were inadequate or no samples were available for PCR. Three subjects in the Placebo group (none in the HZ/su group) had more than one confirmed HZ episode. There were 3 subjects in the HZ/su group, and 12 subjects in the Placebo group with a clinical presentation of disseminated rash at onset. A per-protocol defined algorithm was applied to determine whether the episode consisted in a primary VZV infection (varicella) or a VZV reactivation. Pre-existing immunity was taken into account. All the cases were confirmed as HZ.

The 'mTVC confirmed cases' included 49 and 135 subjects who presented at least one confirmed episode of HZ, respectively in the HZ/su and Placebo groups. The overall incidence of HZ per 1000 person-years was 30.0 in the HZ/su group and 94.3 in the Placebo group, over a median FU time of 21 months. The incidence of HZ in the ZOSTER-002 Placebo group was similar to that found in the ZOSTER-039 Placebo group (70.9 per 1000 person-years, see below), and 10-fold higher compared to the incidence of HZ in the ZOSTER-006 Placebo group (9.1 per 1000 person-years), which used a similar case-definition for HZ. As a reminder, immunocompromised patients and patients with HZ history were excluded from ZOSTER-006, in addition, patients with comorbidities affecting immunity were most probably underrepresented in this trial. Data from studies licensure trials and trials submitted in this application are in line with the literature. In a systematic review based on 11 European studies, the incidence rate of HZ increases sharply with age for individuals older than 50 years, and is estimated at around 7-8 per 1000[2,3]). According to the literature review presented by the MAH in the Clinical Overview, patients who undergo HSCT show the highest risk for HZ among the IC conditions with incidence rate 37 to 60 cases per 1000 person-year, especially during the first year following transplantation (cumulative incidence 8-28%).

In ZOSTER-002, overall HZ VE in autologous HCT adult patients was 68.17% (95% CI: 55.56% - 77.53%) over 21 months The primary objective of the study was met (LL of the 95% CI above 0%). As a reminder, in ZOSTER-006, VE against HZ in adults ≥50 YOA was 97.16% (95% CI: 93.72 to 98.97), over a median follow-up period of 3.1 years. Analysis of VE against HZ in ≥70 YOA using pooled ZOSTER-006 and ZOSTER-022 data (co-primary objective) was 91.30% (95% CI: 86.88 to 94.46).

There were 5 and 10 additional subjects with confirmed HZ episodes after treatment for relapse was initiated, respectively in the HZ/su and Placebo group, which were censored in the mTVC. A sensitivity analysis indicates that the VE was similar when including these cases (HZ VE 67.34% [95% CI: 55.07% - 76.56%]).

The HZ VE was 76.15% (95% CI: 61.11% - 85.98%) during 1 year post-HCT (that is the period of highest HZ's risk for HCT patients) (median follow-up time 7.6 months). Given the overall HZ VE of 68.17% (95% CI: 55.56% - 77.53% (median FU time of 231 months), this suggests that VE may decrease over time. The MAH does not plan to assess long-term vaccine efficacy of Shingrix in IC subjects enroled in studies ZOSTER-002, ZOSTER-028 and ZOSTER-039 as no conclusion on the long-term efficacy would be possible due to variability of the immune status that evolves over time depending on the clinical outcome. The number of patients enrolled in study ZOSTER-041 is too limited (approximatively 130 subjects/group) to estimate long-term efficacy. The absence of long-term efficacy follow-up in IC patients is therefore deemed acceptable, also considering that efficacy was demonstrated in subjects at high risk of HZ and during the period they were at their highest risk of HZ and that effectiveness may be evaluated

[2] Pinchinat S, Cebrián-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis. 2013 Apr 10;13:170.
[3] Ultsch et al. Herpes zoster in Germany: Quantifying the burden of disease. BMC Infectious Diseases 2011, 11:173.

in the EPI-ZOSTER-031 effectiveness study. The MAH considers that, in contrast, patients enrolled in study ZOSTER-041 have a relatively stable immune status. Long-term immunogenicity is being assessed in this population (see immuno discussion).

HZ VE was stable across age stratum (18-49 YOA vs. ≥50 YOA), and slightly higher in females compared to males. However, 95% CI largely overlapped. A difference was observed with respect to the different underlying malignancies. VE was higher in the subgroup of MM patients compared with all other diagnoses, i.e. 72.35% (95% CI: 54.76% -83.71%) versus 63.63% (95% CI: 42.29% - 77.66%). It should be noted that the observed efficacy difference is small and 95% CIs are overlapping. Overall, the stratified analyses do not point to an issue of lack of VE for specific underlying diseases, but estimates are imprecise. In contrast, vaccine-induced gE-specific Ab concentrations were not always comparable between these different sub-groups (see immunogenicity discussion). HZ VE was similar according to anticipated duration of post-transplant antiviral prophylaxis (≤3 months vs. >3 months to ≤6 months). For actual duration of post-transplant antiviral prophylaxis (i.e., none, ≤60 days, >60 days), VE was lower in those who received prophylaxis >60 days, but CI are very wide, and it is not clear whether this could reflect a true and meaningful difference. An evaluation of VE by region was also performed and results were consistent with the overall VE estimate. Definite conclusions on subgroups cannot be drawn given the small numbers, but no concern was raised. No subgroup analysis of patients under ongoing IS therapies, and no exploratory stratified analyses according to type of IS therapy was provided.

Pain duration was reduced in vaccinated vs. Placebo confirmed HZ cases (median [min.-max.] duration of severe 'worst' HZ-associated pain was 14.0 (1.0-178.0) days in the HZ/su group and 24.0 (1.0-1025.0) days in the Placebo group). In the HZ/su group less subjects with a confirmed HZ episode used 3 or more pain medications compared to the placebo group (10.2% vs. 27.4%). In addition, the duration of pain medication was shorter in the HZ/su group (median 21.5 days [min – max: 1.0 -436.0]) compared with the Placebo group (median 47.5 days [min - max 1.0 - 1642.0]).

Of the 10 subjects with PHN episode(s) in the mTVC of ZOSTER-002, 1 was in the HZ/su group and 9 in the Placebo group. The overall incidence of PHN per 1000 person-years was 0.5 in the HZ/su group and 4.9 in the Placebo group, i.e. 10-fold the incidence in immunocompetent adults ≥50 YOA as incidence of PHN in the Placebo group was 0.6 per 1000 person-years (ZOSTER-006).

The overall PHN VE of 89.27% (95% CI: 22.54% - 99.76%). As a reminder, in ZOSTER-006, VE against PHN was 100.00% (95% CI: 77.11-100.00) in the ≥50 YOA. In subjects with a confirmed HZ episode in the mTVC, PHN was reported in 1 out of 49 subjects of the HZ/su group and 9 out of 135 subjects of the Placebo group leading to a VE of 69.39% (95% CI: -77.38% - 94.97%) in reduction of PHN incidence in subjects with a confirmed HZ episode.

HZ complications were considered as AEs or SAEs, but only HZ complications associated with confirmed HZ were included for analysis of the applicable secondary endpoint. In case of suspected HZ diagnosed without characteristic HZ or VZV rash, the HZAC classification served as the final case confirmation. In ZOSTER-002, there was no confirmed HZ case without a typical rash, which may be surprising given the increasingly acknowledged entity ZSH and the importance of atypical presentation in IC patients. Reported HZ complications related to confirmed HZ (other than PHN) were HZ meningoencephalitis (1 subject in the Placebo group) and HZ cutaneous disseminated (3 subjects in the HZ/su group and 12 subjects in the Placebo group). In the mTVC, HZ/su efficacy was also demonstrated against HZ related complications, with an overall VE of 77.76% (95% CI: 19.05% - 95.93%). A high frequency of complications is commonly reported in IC patients. In the literature, the most frequently reported complications in IC patients are PHN and disseminated HZ (cutaneous or visceral involvement). However, there is limited data on actual incidence of HZ-related complications in IC populations. The MAH provided incidence data from a systematic literature review available for 34 studies, which also included ZOSTER-

002 and ZOSTER-039 studies [McKay, 2019] (Table 4). The frequency of HZ-related complications in the Placebo groups of ZOSTER-002 and ZOSTER-039 is in line with that reported in the literature.

Table 73: Proportion of subjects with HZ-related complications in ZOSTER-002 and ZOSTER-039 versus literature

HZ-related complication	HSCT		Hematologic malignancy	
	ZOSTER-002 (confirmed HZ cases in Placebo group; TVC)	McKay, 2019	ZOSTER-039 (confirmed HZ cases in Placebo group; TVC)	McKay, 2019
PHN (i.e. pain lasting >90 days after HZ)	10.5%	6% to 41%	15.8%	6% to 40%
Disseminated disease	11.9%	0% to 32%	-	-

Data Source: Table 1, Table 2, Table 3 and McKay, 20

There was no death related to HZ in this study, and overall mortality was similar in both groups. In the mTVC, HZ-related hospitalization was observed in 2 subjects of the HZ/su group and 13 subjects of the Placebo group. The VE against first or only episode of confirmed HZ-related hospitalizations was 84.70% (95% CI: 32.15% - 96.55%) during the entire study period.

ZOSTER-039:

In ZOSTER-039, 562 subjects constitute the TVC (283 in the HZ/su group and 279 in the Placebo group). Of the HZ/su group and the Placebo group, 16.6% and 22.6% subjects did not complete the trial. The attrition rate and the causes of attrition were balanced across groups. Respectively 259 and 256 subjects were included in the HZ/su and Placebo groups of the mTVC constituted for the post-hoc efficacy analysis.

Demographic characteristics were well balanced across groups. The mean age of participants at first vaccination was 57.3 years. The most represented underlying diseases were multiple myeloma (respectively 23.7% vs. 23.3% in the HZ/su and Placebo group), followed by Hodgkin lymphoma (17.3% vs. 16.8%), Chronic lymphocytic leukaemia (14.8% vs. 14.7%), Non-Hodgkin B-cell lymphoma (14.5% vs. 14.0%), Non-Hodgkin T cell lymphoma (4.6% vs. 5.7%), and other Haematologic Malignancies (25.1% vs. 25.7%). Physical performance status of the subjects (definition from the Eastern Cooperative Oncology Group) was also well balanced across groups. Most subjects were fully active (respectively 63.7% and 64.3% in the HZ/su and Placebo group). The vaccine was administered after the full cancer treatment course (from 10 days to 6 months post therapy) for respectively 64.0% and 62.0% of the subjects in the HZ/su and Placebo groups. For the other patients it was administered during the cancer treatment (with at least 10 days between cycles and each vaccination). The following subclasses of IS cancer therapy were the most frequently administered (i.e. by >20% of subjects in the HZ/su group), at least one day from 1 year prior to Dose 1 up to blood sample 1 month post Dose 2: nitrogen and mustard analogues, anthracyclines, antimitotic agents including antimicrotubule agents, and pyrimidine analogues. Immunotherapeutic agents specifically targeting B-cells (rituximab or a rituximab-containing regimen) were given to most subjects with NHBCL and CLL within the interval between 6 months prior to vaccination and 1-month post Dose 2. Only few subjects with other underlying diseases received such therapy.

Respectively 28 (9.9%) and 26 (9.3%) patients in the HZ/su group and the Placebo group had undergone *autologous* HSCT before vaccination. In addition, 19 (6.7%) and 21 (7.5%) patients in the HZ/su group and the Placebo group had undergone *allogeneic* HSCT before vaccination. No subgroup analysis of patients under ongoing IS therapies, and no exploratory stratified analyses according to type of IS therapy was provided.

Overall, the groups are balanced for the presented characteristics. Nevertheless, residual counfounding cannot be ruled out.

The incidence rate of confirmed HZ cases was 20.24 per 1000 person-years in the HZ/su group (6 cases out of 283 subjects) and 70.87 per 1000 person-years in the Placebo group (19 cases out of 279 subjects) (TVC). In a post-hoc analysis of ZOSTER-039, VE was 87.2% (95% CI: 44.25-98.59) over a median follow-up time of 11 months. This analysis is based on 2 and 14 subjects with confirmed HZ episodes in the mTVC, respectively in the HZ/su group and in the Placebo group.

Findings of this post hoc analysis in patients with hematologic tumours are consistent with the findings of ZOSTER-002. However, as discussed for ZOSTER-002, it is unclear whether efficacy can be extrapolated to all IC patients, in particular those who are under ongoing IS therapy or receive IS therapy after vaccination. In ZOSTER-039, HZ/su was administered after the full cancer treatment course (from 10 days to 6 months post therapy) for most patients (respectively 64.0% and 62.0% of the subjects in the HZ/su and Placebo groups), the remaining patients received HZ/su during the course of therapy. There was a marked difference in incidence rate in favour of HZ/su compared to placebo, whether the vaccine was administered during or after the immunosuppressive cancer therapy course. This a reassuring finding. However, definite conclusion are difficult to draw given the small number of cases. Additionally, differences in immunogenicity data were observed when the vaccine was administrated during or after the IS cancer therapy course. Vaccine immunogenicity also varied according to the underlying disease (which may be due to the type of therapy they receive). Moreover, VE might also varies according to other factors such as previous therapies (duration and cycles) that may affect the capacity of the cells to elicit an optimal immune responses.
In the HZ/su group (TVC), 3 subjects experienced HZ complications associated with a confirmed HZ episode (1 subject with disseminated HZ and PHN, and 2 other subjects with PHN). In the Placebo group (TVC), 4 subjects experienced HZ complications associated with a confirmed HZ episode (2 subjects had a severe HZ requiring hospitalisation all 4 subjects had one episode of PHN).

Factors that could influence protective immunity:

In general, it was considered useful for all studies to have a more in-depth insight in the nature of the study populations, in order to understand how far it is representative of other IC populations. The factors that could influence vaccine efficacy and immunogenicity are age, underlying disease, timing of vaccination in relation to transplantation and in relation to IS therapy, as well as the type and duration of IS therapy used by subjects before, during and after vaccination. The MAH was invited to provide any relevant data useful to understand the populations in that respect. The MAH provided limited additional data, and did not include new data for ZOSTER-002, as would have been expected.

The available data do not suggest that age importantly affects vaccine efficacy and immunogenicity in IC individuals. The data do not allow to conclude on the impact of underlying disease 'per se' on the immune responses and efficacy. There is an indirect evidence that patients under anti-CD20 antibodies present much lower humoral responses (see immunogenicity assessment). Lower humoral immune responses were observed when Shingrix was administered during versus before or after IS cancer therapy. The clinical relevance in terms of impact on efficacy, on the short and long term, is unknown. In both ZOSTER-002 and ZOSTER-039 (the studies which generated the efficacy data), subjects received IS therapies up to a few weeks before the vaccination course, but most subjects did not receive therapies during or shortly after the vaccination course. This also concurs to the conclusion that vaccine efficacy in subjects under concomitant IS therapy is not known. The SmPC reflects that studies were not designed to assess the impact of specific immunosuppressive treatments on vaccine efficacy. The SmPC also reflects that most vaccine recipients were not under IS therapy at the time of vaccination. *Correlate of protection:*

CoP assessment was performed in study ZOSTER-039. Given the very limited number of confirmed HZ cases included in the analysis (2 in the HZ/su group and 12 in the Placebo group), no conclusion can be drawn. Detailed on planned analyses were not presented.

An attempt to identify a CoP was already done with anti-gE Ab data of ZOSTER-006 and ZOSTER-022 studies at initial MAA. The methods and results were extensively discussed at that time and are summarized in the EPAR. Because of the many uncertainties and limitations that were remaining, it was concluded that the CoP is not sufficiently understood and validated to be considered as an established general CoP. It was however agreed that post-dose 2 anti-gE can be used as an immune marker for immunobridging in immunocompetent individuals ≥50 years of age and that in certain circumstances is possible based on anti-gE non-inferiority.

Based on the available efficacy and immunogenicity data, it appears that the exercise to identify a CoP for IC populations might be even more challenging. Because of the altered immune system that characterize IC subjects, and in contrast to immunocompetent subjects, circulating Ab titers might not be a good marker to evaluate the protective response in IC patients. The quality of the humoral immune response might be different than for immunocompetent people. This also applies to CMI.

2.4.3. Conclusions on the clinical efficacy

Shingrix administered according to a 2-dose schedule with an interval of 1-2 months between doses clearly demonstrated an efficacy in protecting adult autologous HCT patients against HZ, when vaccinated only 5-7 weeks after the transplant (68.17% [95% CI: 55.56% - 77.53%] over 21 months, ZOSTER-002). A similar level of efficacy was found in a post-hoc analysis performed in ZOSTER-039, which enrolled patients with haematological malignancies during or after the chemotherapy course (VE was 87.2% [95%CI: 44.25-98.59] over a median follow-up time of 11 months). Shingrix also reduced the incidence of PHN (VE of 89.27% [95% CI: 22.54% - 99.76%] in ZOSTER-002) and other HZ related complications, and the severity and duration of pain.

Both studies brought the proof that Shingrix is able to protect IC patients from HZ and to reduce the burden and severity related to HZ in them. Efficacy was lower compared to that found in immunocompetent individuals 50 YOA and over (97% for HZ).

There is no established CoP for Shingrix, and the level of efficacy can therefore not be derived from the immunogenicity data generated in the other IC populations (patients with solid malignancies vaccinated just before or during chemotherapy and patients who had undergone a solid organ transplant). Since VE was not evaluated in all immunosuppressed populations, different levels of VE in each population cannot be ruled out. Nonetheless, since immunogenicity, both humoral and cellular, was clearly demonstrated in all studied populations, an acceptable efficacy level (together with an absent of safety signals and an acceptable reactogenicity) can be assumed.

Altogether it is considered likely that Shingrix provides a benefit in IC adult patients. However, uncertainties remain as to the level of efficacy, particularly in patients under ongoing (certain types) of IS therapies. Uncertainties also remain about whether the efficacy is sustained over time.

2.5. Clinical safety

Introduction

- **Safety profile in the existing indication**

In the clinical studies included in the main and broader safety pooling analyses submitted for initial licensure, a total of 14,645 (ZOSTER-006 and ZOSTER-022 pivotal trials) and 15,493 (ZOSTER-006 and ZOSTER-022 pivotal trials and additional supportive studies) older adults ≥50 YOA have been vaccinated with at least one dose of HZ/su, respectively. Reactogenicity, both local and general was frequent, including for high grade events. In the overall population ≥50 YOA (ZOSTER-006), 79.1% of subjects experienced pain at the site of administration, and 6.7% experienced grade 3 pain. At least one solicited general symptom was reported for 66.1% of subjects, and at least one grade 3 solicited general symptom for 11.4% of subjects. The most frequently reported solicited general symptoms were myalgia (46.3% per subject) and fatigue (45.9% per subject). Fever (≥37.5°C) was reported in 21.5% of the subjects. In general, local and general symptoms lasted for a few days (median duration was 3 days for pain, days for myalgia and fatigue, 1 day for fever).

Within the ≥50 YOA immunocompetent population of ZOSTER-006, reactogenicity clearly increased with decreasing age. In the age categories 50-59 YOA, 60-69 YOA, and ≥70 YOA respectively, solicited local symptoms were reported by 89.6%, 84.6%, and 73.2% of subjects and solicited general symptoms were reported by 76.7%, 68.7%, 56.4% of subjects. Results for the subjects ≥70 YOA are in line in ZOSTER-006 and ZOSTER-022. Only limited safety data from the early development phase of HZ/su are available for immunocompetent subjects 18-49 YOA. The SCS submitted at MAA presents safety data from adults 18-30 YOA enrolled in EXPLO-CRD-004 and ZOSTER-023. Although on a small sample size (10 subjects per study), these data point to a higher reactogenicity in these 18-30 YOA individuals compared to ≥50 YOA individuals. Pain occurred in all subjects, and grade 3 pain respectively in 1/10 and 3/10 in EXPLO-CRD-004 and ZOSTER-023 respectively. Fatigue occurred in nearly all subjects (9/10 and 10/10 respectively), and grade 3 fatigue in 0/10 and 4/10 subjects respectively. Myalgia occurred in most subjects (7/10 and 10/10), and grade 3 myalgia in 0/10 and 3/10 subjects. Fever occurred in 3/10 and 7/10 subjects respectively.

Based on the data submitted at MAA, there was no identified risk. The following potential risks were listed: (i) Virus reactivation in immunocompetent individuals with a history of Herpes Zoster, (ii) Risk of potential Immune Mediated Disorders (pIMDs) following Shingrix vaccination. In addition, the Use of Shingrix in adults with pre-existing pIMD was considered as a missing information.

In pre-licensure clinical trials, which are not designed to assess rare outcomes, numerical differences between Shingrix and Placebo groups were noted for certain conditions, including: polymyalgia rheumatica (PMR), giant cell arteritis (GCA), Ischemic optic neuropathy (ION), Supraventricular tachycardia (SVT), and gout. After licensure, using an algorithm that preferentially maximizes sensitivity over specificity, the U.S. Vaccine Safety Datalink detected a statistical signal for Guillain-Barré syndrome (GBS) during active surveillance for Shingrix safety.

Two PASS are ongoing to evaluate the to evaluate the safety of Shingrix in adults ≥50 years of age in the United States: EPI-ZOSTER-030/032.

- **Summary of the methodology used**

This report describes the safety and reactogenicity results from the 6 clinical studies (4 pivotal studies [3 Phase III studies and 1 Phase II/III study] and 2 supportive Phase I/II studies) that support the HZ/su application in adults ≥18 YOA at increased risk of HZ. The methods used to evaluate safety and reactogenicity in the 6 studies were largely identical.

Safety endpoints:

In addition to Adverse Event (AE), Serious Adverse Event (SAE) and Medically Attended Adverse Event (MAE), the following safety endpoints were assessed: suspected herpes zoster and herpes zoster complications, potentially immune-mediated diseases (pIMD) and new onset autoimmune diseases

(NOAD), relapse cases (ZOSTER-002 and ZOSTER-001, recurrence of the underlying malignancy or disease for which the HSCT was undertaken), disease progression (ZOSTER-002), disease-related events (DRE, ZOSTER-039, included cases of relapse and occurrences of disease progression), biopsy-proven renal allograft rejections (ZOSTER-041), hematological and biochemical parameters measured at baseline and at pre-defined timepoints post vaccination (ZOSTER-001 and ZOSTER-015).

Standard definitions were used for Adverse Event (AE), Serious Adverse Event (SAE) and Medically Attended Adverse Event (MAE).

- *Suspected herpes zoster and herpes zoster complications*

The definition of suspected HZ, confirmed HZ, and complications of HZ used in ZOSTER-002 and ZOSTER-039 is described in the efficacy section of this report.

In ZOSTER-028, ZOSTER-039, and ZOSTER-041, the occurrence of suspected HZ and/or HZ complications constituted an AE or SAE, as appropriate.

In ZOSTER-039 and ZOSTER-002, the occurrence of HZ with characteristic VZV or HZ rash was recorded in HZ-specific electronic case report form (eCRF) screens.

In ZOSTER-002, cases of HZ without characteristic VZV or HZ rash were considered as an SAE and were specified on the SAE screen as related to HZ.

In ZOSTER-001 and ZOSTER-015, suspected cases of HZ were defined as a new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus, or other sensations) and no alternative diagnosis. Suspected HZ cases were collected throughout the study period and confirmed by polymerase chain reaction (PCR) or by a GSK expert. These cases were collected as endpoints for descriptive and exploratory evaluations.

In all studies, HZ complications, including but not limited to PHN (see above for ZOSTER-002), HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, and visceral disease, were recorded by the investigator and considered as AEs or SAEs as appropriate.

- *Adverse events of special interest, including potentially immune-mediated diseases and new onset autoimmune diseases*

In the pivotal studies, pIMDs were considered a subset of AEs that included autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. The method of collecting events of possible autoimmune etiology has evolved over time, from the former approach for the collection of NOADs and other immune-mediated inflammatory disorders (in ZOSTER-001 and ZOSTER-015 for this submission) to the current method of collecting pIMDs, which includes relevant events previously classified as NOADs and other immune-mediated inflammatory disorders. An 'immune-mediated' concept is used rather than 'autoimmune' as in some of these diseases, a true autoantibody-dependent pathophysiology has been argued/debated. The term 'potential' refers to the pathogenic etiology of the disease as 'potentially', representing an autoimmune or immune-mediated inflammatory process.

A pre-defined list is used across clinical development programs with vaccines using a combination of adjuvants or Adjuvant Systems. This list is regularly updated based on evolving scientific information on pIMDs and changes are applicable to new protocols developed after the update. As of 30 June 2017, after the completion of all studies included in this submission, GSK's pre-defined list of pIMDs was updated with the inclusion of 'gout' as a musculoskeletal disorder that could represent an immune-mediated inflammatory process of interest.

A list of corresponding terms for each of the diseases included in the most recent pre-defined list of pIMDs is linked to the MedDRA (i.e., using a customized query for pIMDs, GSKMQ_pIMD), to facilitate database encoding and to perform targeted searches for signal detection, safety monitoring, and analyses. This customized query is updated twice a year with each MedDRA versioning.

A disease-specific questionnaire for each disease in the pIMDs list is provided to investigators as general guidance and relevant information to obtain a clinical description in sufficient detail.

The investigator was asked to exercise his/her medical and scientific judgement in deciding whether diseases not included in the protocol-specified list had an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and to report those as pIMDs.

Assessment of intensity:

Pain at the injection site was scored as follows: grade 1: any pain neither interfering with nor preventing normal every day activities; grade 2: painful when limb is moved and interfered with everyday activities; grade 3: significant pain at rest that prevented normal every day activities.

The maximum intensity of local injection site redness/swelling (greatest surface diameter) was scored using GSK's standard grading scale based on the FDA guidelines for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials (FDA, 2007): 0 : <20 mm diameter; 1 : ≥20 mm to ≤50 mm diameter; 2 : >50 mm to ≤100 mm diameter; 3 : >100 mm diameter.

Temperature (measured by oral, axillary, or tympanic route) was scored as follows: 0 : <37.5° C; 1 : 37.5° C to 38.0° C ; 2 : 38.1° C to 39.0° C; 3 : >39.0° C (>39.5° C in ZOSTER-002). The preferred route for recording temperature was oral.

The intensity of solicited general symptoms (except fever) was scored as follows: grade 1: symptom that was easily tolerated; grade 2: symptom that interfered with normal activity; grade 3: symptom that prevented normal activity.

The investigator assessed the maximum intensity that occurred over the duration of the event for unsolicited AEs (including serious and non-serious AEs) recorded during the study. The assessment was based on the investigator's clinical judgment. The intensity was assigned to 1 of the following categories: Grade 1 (mild) was an AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with or preventing everyday activities; Grade 2 (moderate) was an AE which was sufficiently discomforting to interfere with normal everyday activities; Grade 3 (severe) was an AE which prevented normal everyday activities.

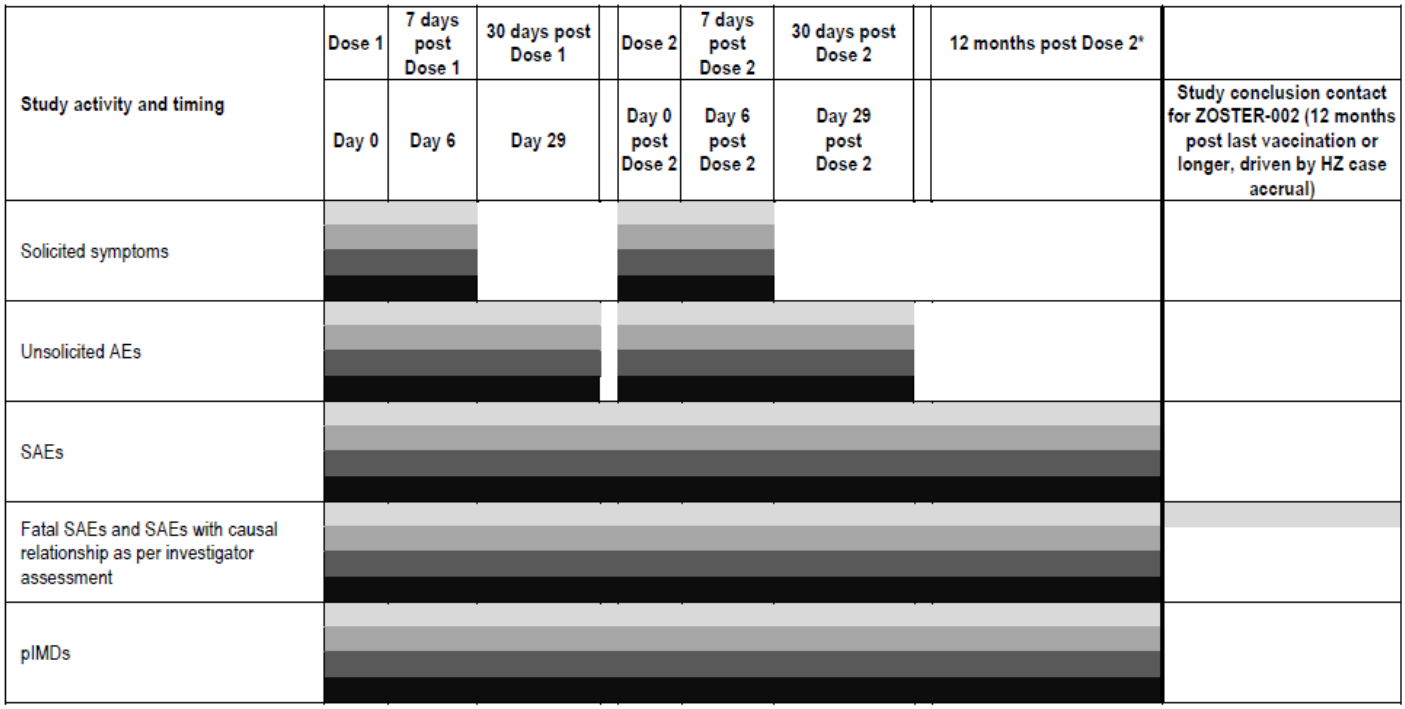
Assessment of causality

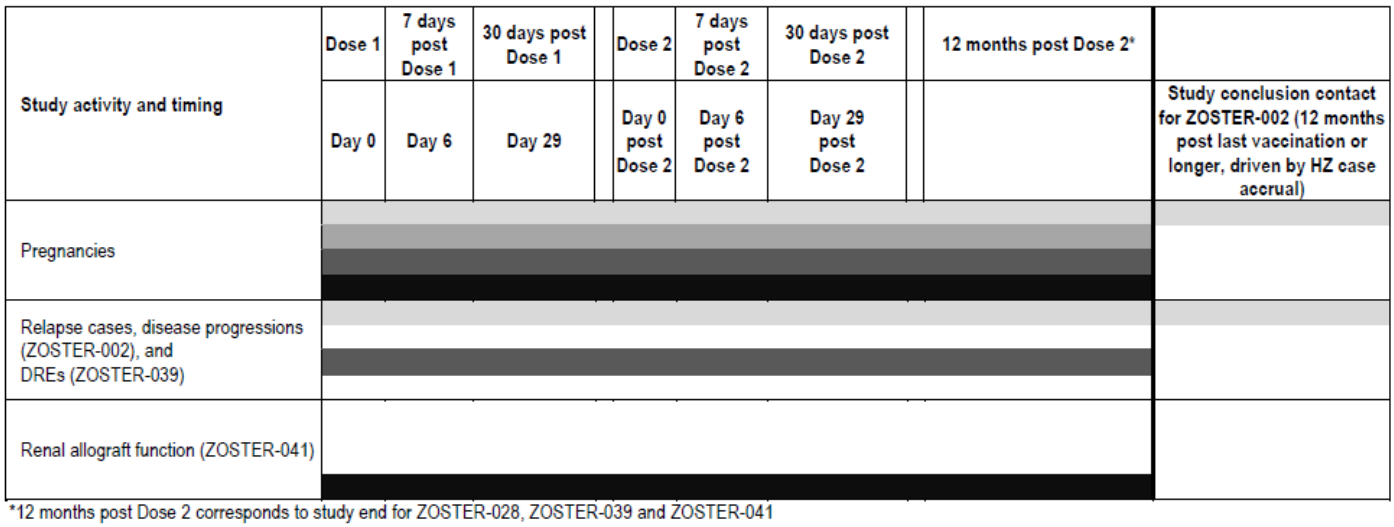
The investigator had to assess the relationship between the administered vaccine and the occurrence of each AE/SAE using clinical judgment, considering alternative plausible causes, and by consulting the Investigator Brochure to determine his/her assessment. All solicited local (injection site) reactions were considered causally related to vaccination.

Reporting periods:

The reporting periods For the safety endpoints, as defined per protocol are displayed in Table 74 for the pivotal studies and Table 75 for ZOSTER-001 and ZOSTER-015. In all studies except ZOSTER-002, the study duration lasted until 12 months post last vaccination. In ZOSTER-002, the study duration was longer, since follow-up was driven by HZ case accrual and ranged from a minimum of 12 months post last vaccination to 4 years at subject level (actual median safety follow-up time 29 months).

Table 74: Pivotal studies: Reporting periods per protocol for solicited symptoms, adverse events, serious adverse events, potentially immune-mediated diseases, pregnancies, relapse cases, disease progressions, disease-related events, and renal allograft function



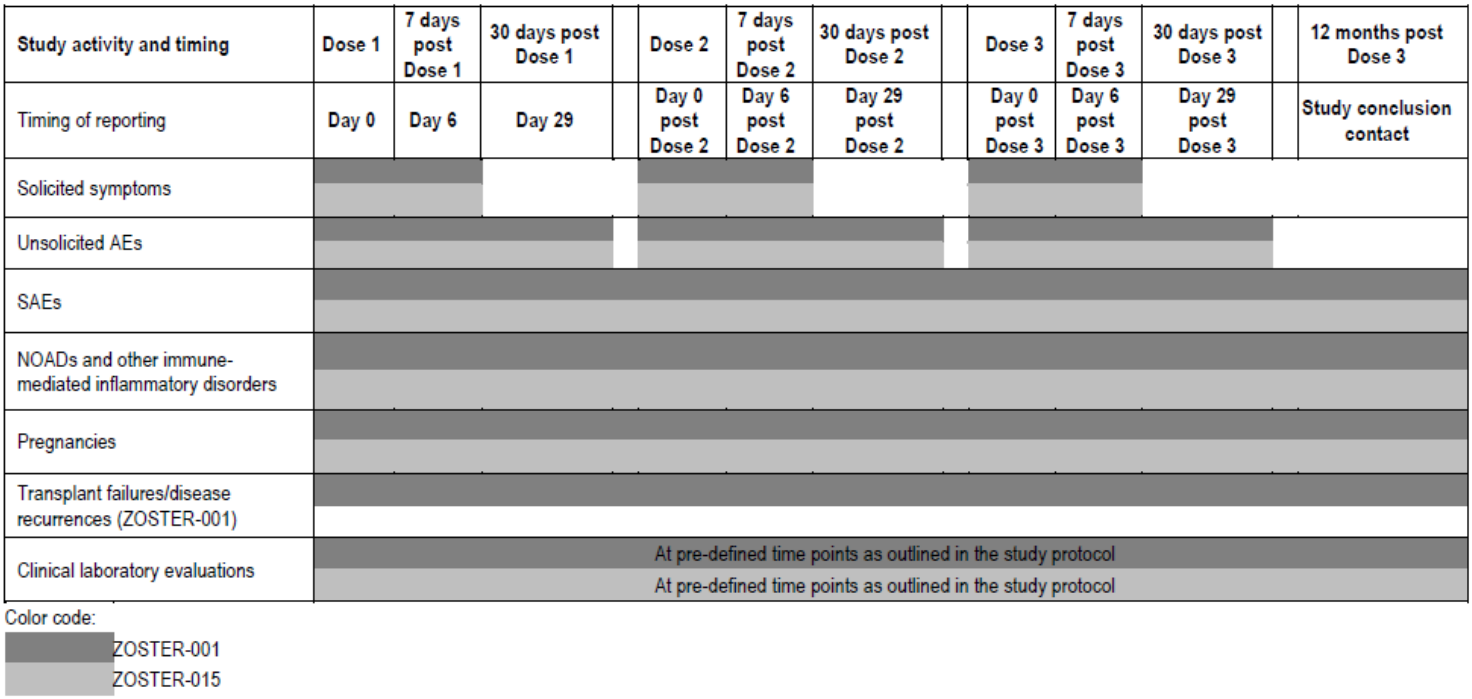


*12 months post Dose 2 corresponds to study end for ZOSTER-028, ZOSTER-039 and ZOSTER-041

Shading code:

- ZOSTER-002
- ZOSTER-028
- ZOSTER-039
- ZOSTER-041

Table 75: ZOSTER-001 and ZOSTER-015: Reporting periods for solicited symptoms, adverse events, serious adverse events, new onset of autoimmune diseases and other immune-mediated inflammatory disorders, pregnancies, transplant failures/disease recurrences, and clinical laboratory evaluations



Statistical methods:

In all studies, the primary analysis for safety was based on the Total Vaccinated Cohort (TVC), which included all subjects with at least 1 vaccine administration documented.

Descriptive analysis of the pre-defined safety endpoints was performed. overall and by age range (18-49 YOA and ≥50 YOA strata) for the 6 studies. In order to align the analysis time points between studies, an analysis cut-off of 365 days post last vaccination was chosen for ZOSTER-002.

Additionally, for each pivotal study separately, the percentage of subjects reporting the occurrence of other events of medical interest, classified by MedDRA Primary SOC and PT as AE (within the 30-day post-vaccination period) or SAE (within the 365-day post-vaccination period for all pivotal studies) was tabulated (post-hoc analysis after study completion). These events were selected based on the most frequently reported events observed in the IC clinical studies, medically relevant events for the specific population, or previous feedback from regulatory authorities during the initial file application (Table 76). This analysis was not pre-specified in the study protocols and was done in preparation for the current submission. The search strategy of the individual clinical study databases used standard customized MedDRA queries that contained a pre-defined list of PTs for each event of interest.

Table 76: Other events of medical interest presented in this Summary of Clinical Safety with rationale for presenting these specific events

Other medically relevant event	**Rationale for presenting these specific events**
Agranulocytosis and hematopoietic cytopenias	Relevant event in the IC population under study,especially subjects with HSCT, hematologic malignancies, and solid tumors
Anaphylactic reactions	AE of interest for vaccines in general
Hemorrhagic and ischemic cerebrovascular conditions	Specific concern from the Centers for Disease Control and Prevention (CDC) on the potential association of HZ with cerebrovascular accident [Sundström, 2015; Langan, 2014; Nagel, 2015]

Infective pneumonia	Most frequently reported events in IC studies taken up in this Summary of Clinical Safety
Upper respiratory tract infection	Most frequently reported events in IC studies taken up in this Summary of Clinical Safety
Serious ocular complications that may be due to vasculitis or inflammation.	Specific concern from US regulatory authorities (Center for Biologics Evaluation and Research [CBER]) in adults ≥50 YOA [AAO, 2018]

Patient exposure

In all 6 studies, a total of 1,587 subjects received at least 1 dose of HZ/su (443 subjects in the 18-49 YOA stratum and 1,144 in the ≥50 YOA stratum).

In the 4 pivotal studies, in which a 2-dose vaccination schedule was followed, the compliance with the 2-dose schedule was high, ranging from 85.5% to 95.5% in the HZ/su groups. By age stratum in all studies, the compliance was comparable between the 18-49 YOA and ≥50 YOA strata (Table 77).

Table 77: Pivotal studies: Summary of the number and percentage of subjects ≥18 YOA who received vaccine dose(s) by age strata (Total Vaccinated Cohort)

Total number of doses received	ZOSTER-002				ZOSTER-028				ZOSTER-039				ZOSTER-041			
	HZ/su				HZ/su				HZ/su				HZ/su			
	18-49 YOA N=230		≥50 YOA N=692		18-49 YOA N=31		≥50 YOA N=86		18-49 YOA N=74		≥50 YOA N=209		18-49 YOA N=48		≥50 YOA N=84	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	16	7.0	33	4.8	2	6.5	15	17.4	6	8.1	18	8.6	2	4.2	4	4.8
2	214	93.0	659	95.2	29	93.5	71	82.6	68	91.9	191	91.4	46	95.8	80	95.2
Any	230	100	692	100	31	100	86	100	74	100	209	100	48	100	84	100

Demographic and Other Characteristics of Study Population:

For subjects receiving HZ/su (gE/AS01B), the mean age at first vaccination ranged between 46.6 and 57.8 YOA across studies. In the HZ/su group of most studies, more male than female subjects were enrolled (range: 59.7%-93.2%), except for ZOSTER-028 (40.2% was male), and most subjects were of White - Caucasian/European heritage (range: 66.7%-96.8%). The demographic profile of subjects in the HZ/su and the Placebo group within each study was comparable with respect to mean age, gender, ethnicity, and geographic ancestry.

In all studies, the demographic characteristics were generally balanced between the 18-49 YOA and ≥50 YOA strata. However, in ZOSTER-028, the male:female balance was 9.7%:90.3% in the 18-49 YOA (while 51.2%:48.8% in the ≥50 YOA stratum). The higher proportion of females in the 18-49 YOA stratum relates to the incidence of the malignancies by gender (mainly breast cancer).

In ZOSTER-002, the reported underlying diseases included MM, NHBCL, Hodgkin lymphoma, NHTCL, AML, solid organ malignancies, and autoimmune diseases. MM was the most common disease in 53% of subjects. In the HZ/su group in ZOSTER-028, the most frequently reported solid tumor diagnoses were breast (45.3%) and colorectal (21.4%) tumors. The performance status (ECOG) of the majority of subjects (83.3%) was 'fully active'. In the HZ/su group in ZOSTER-039, the reported hematological malignancies included MM (23.7%), Hodgkin lymphoma (17.3%), CLL (14.8%), NHBCL (14.5%), NHTCL (4.6%), and other hematological malignancies (25.1%). The ECOG performance status was 'fully active' for 63.7% of subjects and 'restricted in physically strenuous activity' in 33.8% of subjects.

Adverse events

Below results are presented for the pivotal trials. When comparing incidences between study groups or age strata, the term 'within the same range' is used when the 95% CIs of the incidences overlap. Incidences were considered 'higher' or 'lower' in one group or the other based on non-overlapping 95% CIs.

- **Solicited symptoms overall**

In all pivotal studies, the overall incidence of solicited local symptoms (any grade) during the 7-day post-vaccination period was higher in the HZ/su group than in the Placebo group. In the HZ/su groups, the overall/subject incidence of solicited local symptoms was within the same range across the pivotal studies. In all pivotal studies, the overall/dose incidence of solicited general symptoms (any grade) during the 7-day post-vaccination period was higher in the HZ/su group than in the Placebo group. In ZOSTER-002 and ZOSTER-039, the overall/subject incidence was also higher in the HZ/su group than in the Placebo group, while it was within the same range in ZOSTER-028 and ZOSTER-041. In the HZ/su groups, the overall/subject incidence of solicited general symptoms was within the same range across the pivotal studies (Table 78).

Table 78: Pivotal studies: Incidence and nature of symptoms (solicited only) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
ZOSTER-002																
Dose 1	HZ/su	897	758	84.5	82.0	86.8	896	530	59.2	55.9	62.4	896	706	78.8	76.0	81.4
	Placebo	892	386	43.3	40.0	46.6	892	374	41.9	38.7	45.2	890	63	7.1	5.5	9.0
Dose 2	HZ/su	840	712	84.8	82.2	87.1	836	552	66.0	62.7	69.2	840	657	78.2	75.3	81.0
	Placebo	835	323	38.7	35.4	42.1	835	307	36.8	33.5	40.1	834	49	5.9	4.4	7.7
Overall/dose	HZ/su	1737	1470	84.6	82.8	86.3	1732	1082	62.5	60.1	64.8	1736	1363	78.5	76.5	80.4
	Placebo	1727	709	41.1	38.7	43.4	1727	681	39.4	37.1	41.8	1724	112	6.5	5.4	7.8
Overall/subject	HZ/su	902	809	89.7	87.5	91.6	901	678	75.2	72.3	78.0	901	773	85.8	83.3	88.0
	Placebo	894	476	53.2	49.9	56.6	894	455	50.9	47.6	54.2	892	93	10.4	8.5	12.6
ZOSTER-028																
Dose 1	HZ/su	112	104	92.9	86.4	96.9	112	80	71.4	62.1	79.6	112	88	78.6	69.8	85.8
	Placebo	110	53	48.2	38.6	57.9	110	52	47.3	37.7	57.0	110	3	2.7	0.6	7.8
Dose 2	HZ/su	98	75	76.5	66.9	84.5	97	67	69.1	58.9	78.1	98	56	57.1	46.7	67.1
	Placebo	105	60	57.1	47.1	66.8	104	60	57.7	47.6	67.3	105	5	4.8	1.6	10.8
Overall/dose	HZ/su	210	179	85.2	79.7	89.7	209	147	70.3	63.6	76.4	210	144	68.6	61.8	74.8
	Placebo	215	113	52.6	45.7	59.4	214	112	52.3	45.4	59.2	215	8	3.7	1.6	7.2
Overall/subject	HZ/su	112	107	95.5	89.9	98.5	112	91	81.3	72.8	88.0	112	94	83.9	75.8	90.2
	Placebo	110	73	66.4	56.7	75.1	110	73	66.4	56.7	75.1	110	7	6.4	2.6	12.7
ZOSTER-039																
Dose 1	HZ/su	278	226	81.3	76.2	85.7	278	162	58.3	52.2	64.1	278	210	75.5	70.0	80.5
	Placebo	271	105	38.7	32.9	44.8	271	99	36.5	30.8	42.6	271	27	10.0	6.7	14.2
Dose 2	HZ/su	256	212	82.8	77.6	87.2	255	171	67.1	60.9	72.8	255	183	71.8	65.8	77.2
	Placebo	248	107	43.1	36.9	49.6	247	95	38.5	32.4	44.8	248	34	13.7	9.7	18.6
Overall/dose	HZ/su	534	438	82.0	78.5	85.2	533	333	62.5	58.2	66.6	533	393	73.7	69.8	77.4
	Placebo	519	212	40.8	36.6	45.2	518	194	37.5	33.3	41.8	519	61	11.8	9.1	14.8
Overall/subject	HZ/su	278	251	90.3	86.2	93.5	278	206	74.1	68.5	79.1	278	233	83.8	78.9	87.9
	Placebo	274	142	51.8	45.7	57.9	274	134	48.9	42.8	55.0	274	48	17.5	13.2	22.5
ZOSTER-041																
Dose 1	HZ/su	131	117	89.3	82.7	94.0	131	71	54.2	45.3	62.9	131	108	82.4	74.8	88.5
	Placebo	132	62	47.0	38.2	55.8	132	59	44.7	36.0	53.6	132	8	6.1	2.7	11.6
Dose 2	HZ/su	125	102	81.6	73.7	88.0	125	70	56.0	46.8	64.9	125	94	75.2	66.7	82.5
	Placebo	128	52	40.6	32.0	49.7	128	50	39.1	30.6	48.1	128	7	5.5	2.2	10.9
Overall/dose	HZ/su	256	219	85.5	80.6	89.6	256	141	55.1	48.8	61.3	256	202	78.9	73.4	83.7
	Placebo	260	114	43.8	37.7	50.1	260	109	41.9	35.9	48.2	260	15	5.8	3.3	9.3
Overall/subject	HZ/su	131	121	92.4	86.4	96.3	131	90	68.7	60.0	76.5	131	115	87.8	80.9	92.9
	Placebo	132	75	56.8	47.9	65.4	132	73	55.3	46.4	64.0	132	12	9.1	4.8	15.3

Source: Module 5, ZOSTER-002 CSR Amendment 1, Table 40; ZOSTER-028 CSR Amendment 1, Table 35; ZOSTER-039 CSR Amendment 1, Table 33; ZOSTER-041 CSR Amendment 1, Table 8.3

In all pivotal studies, the overall incidence of grade 3 solicited local symptoms was higher in the HZ/su group than in the Placebo group. In the HZ/su groups, the overall/subject incidence of grade 3 solicited local symptoms was within the same range across the pivotal studies. In ZOSTER-002 and ZOSTER-039, the overall incidence of grade 3 solicited general symptoms was higher in the HZ/su group than in the respective Placebo groups, while in ZOSTER-028 and ZOSTER-041, the incidence in the HZ/su and Placebo group was within the same range. In the HZ/su groups, the overall/subject incidence of grade 3 solicited general symptoms was within the same range across the pivotal studies (Table 79).

Table 79: Pivotal studies: Incidence and nature of grade 3 symptoms (solicited only) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated Cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
ZOSTER-002																
Dose 1	HZ/su	897	96	10.7	8.8	12.9	896	52	5.8	4.4	7.5	896	66	7.4	5.7	9.3
	Placebo	892	30	3.4	2.3	4.8	892	28	3.1	2.1	4.5	890	3	0.3	0.1	1.0
Dose 2	HZ/su	840	138	16.4	14.0	19.1	836	90	10.8	8.7	13.1	840	88	10.5	8.5	12.7
	Placebo	835	33	4.0	2.7	5.5	835	33	4.0	2.7	5.5	834	0	0.0	0.0	0.4
Overall/dose	HZ/su	1737	234	13.5	11.9	15.2	1732	142	8.2	6.9	9.6	1736	154	8.9	7.6	10.3
	Placebo	1727	63	3.6	2.8	4.6	1727	61	3.5	2.7	4.5	1724	3	0.2	0.0	0.5
Overall/subject	HZ/su	902	190	21.1	18.4	23.9	901	119	13.2	11.1	15.6	901	128	14.2	12.0	16.7
	Placebo	894	56	6.3	4.8	8.1	894	54	6.0	4.6	7.8	892	3	0.3	0.1	1.0
ZOSTER-028																
Dose 1	HZ/su	112	20	17.9	11.3	26.2	112	15	13.4	7.7	21.1	112	10	8.9	4.4	15.8
	Placebo	110	11	10.0	5.1	17.2	110	11	10.0	5.1	17.2	110	0	0.0	0.0	3.3
Dose 2	HZ/su	98	17	17.3	10.4	26.3	97	16	16.5	9.7	25.4	98	4	4.1	1.1	10.1
	Placebo	105	10	9.5	4.7	16.8	104	10	9.6	4.7	17.0	105	0	0.0	0.0	3.5
Overall/dose	HZ/su	210	37	17.6	12.7	23.5	209	31	14.8	10.3	20.4	210	14	6.7	3.7	10.9
	Placebo	215	21	9.8	6.1	14.5	214	21	9.8	6.2	14.6	215	0	0.0	0.0	1.7
Overall/subject	HZ/su	112	28	25.0	17.3	34.1	112	25	22.3	15.0	31.2	112	13	11.6	6.3	19.0
	Placebo	110	17	15.5	9.3	23.6	110	17	15.5	9.3	23.6	110	0	0.0	0.0	3.3
ZOSTER-039																
Dose 1	HZ/su	278	30	10.8	7.4	15.0	278	20	7.2	4.4	10.9	278	18	6.5	3.9	10.0
	Placebo	271	10	3.7	1.8	6.7	271	10	3.7	1.8	6.7	271	0	0.0	0.0	1.4
Dose 2	HZ/su	256	47	18.4	13.8	23.7	255	34	13.3	9.4	18.1	255	27	10.6	7.1	15.0
	Placebo	248	12	4.8	2.5	8.3	247	12	4.9	2.5	8.3	248	0	0.0	0.0	1.5
Overall/dose	HZ/su	534	77	14.4	11.6	17.7	533	54	10.1	7.7	13.0	533	45	8.4	6.2	11.1
	Placebo	519	22	4.2	2.7	6.3	518	22	4.2	2.7	6.4	519	0	0.0	0.0	0.7
Overall/subject	HZ/su	278	61	21.9	17.2	27.3	278	43	15.5	11.4	20.3	278	37	13.3	9.5	17.9
	Placebo	274	17	6.2	3.7	9.7	274	17	6.2	3.7	9.7	274	0	0.0	0.0	1.3
ZOSTER-041																
Dose 1	HZ/su	131	13	9.9	5.4	16.4	131	7	5.3	2.2	10.7	131	10	7.6	3.7	13.6
	Placebo	132	5	3.8	1.2	8.6	132	5	3.8	1.2	8.6	132	0	0.0	0.0	2.8
Dose 2	HZ/su	125	16	12.8	7.5	20.0	125	12	9.6	5.1	16.2	125	10	8.0	3.9	14.2
	Placebo	128	8	6.3	2.7	11.9	128	8	6.3	2.7	11.9	128	0	0.0	0.0	2.8
Overall/dose	HZ/su	256	29	11.3	7.7	15.9	256	19	7.4	4.5	11.3	256	20	7.8	4.8	11.8
	Placebo	260	13	5.0	2.7	8.4	260	13	5.0	2.7	8.4	260	0	0.0	0.0	1.4
Overall/subject	HZ/su	131	20	15.3	9.6	22.6	131	13	9.9	5.4	16.4	131	14	10.7	6.0	17.3
	Placebo	132	11	8.3	4.2	14.4	132	11	8.3	4.2	14.4	132	0	0.0	0.0	2.8

Source: Module 5, ZOSTER-002 CSR Amendment 1, Table 41; ZOSTER-028 CSR Amendment 1, Table 36; ZOSTER-039 CSR Amendment 1, Table 34; ZOSTER-041 CSR Amendment 1, Table 8.4

Solicited local symptoms

For the pivotal studies, the overall incidence of each solicited local symptom is presented in Table 80.

- After receiving HZ/su, the most frequently reported solicited local symptom was pain (overall/subject range: 79.5%-87.0%; overall/dose range: 64.3%-78.1%), followed by redness (overall/subject range: 25.2%-41.4%; overall/dose range: 17.6%-30.4%), and swelling (overall/subject range: 11.5%-22.7%; overall/dose range: 8.2%-16.7%).

- The incidence of each solicited local symptom was lower in the Placebo group than in the HZ/su group in all pivotal studies.

- Pain was also the most frequently reported grade 3 solicited local symptom (overall/subject range: 9.8%-11.0%; overall/dose range: 5.7%-7.4%). In the Placebo groups, grade 3 pain was only reported in ZOSTER-002 (overall/subject: 0.3%; overall/dose: 0.2%).

Table 80: Pivotal studies: Overall incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort)

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su				Placebo				HZ/su				Placebo				HZ/su				Placebo				HZ/su				Placebo			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Symptom	Type	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Overall/dose																																	
		N=1736				N=1724				N=210				N=215				N=533				N=519				N=256				N=260			
Pain	All	1326	76.4	74.3	78.4	101	5.9	4.8	7.1	135	64.3	57.4	70.8	7	3.3	1.3	6.6	371	69.6	65.5	73.5	57	11.0	8.4	14.0	200	78.1	72.6	83.0	14	5.4	3.0	8.9
	Grade 3	122	7.0	5.9	8.3	3	0.2	0.0	0.5	12	5.7	3.0	9.8	0	0.0	0.0	1.7	36	6.8	4.8	9.2	0	0.0	0.0	0.7	19	7.4	4.5	11.3	0	0.0	0.0	1.4
Redness (mm)	All	418	24.1	22.1	26.2	9	0.5	0.2	1.0	53	25.2	19.5	31.7	0	0.0	0.0	1.7	162	30.4	26.5	34.5	6	1.2	0.4	2.5	45	17.6	13.1	22.8	2	0.8	0.1	2.8
	>100	31	1.8	1.2	2.5	0	0.0	0.0	0.2	2	1.0	0.1	3.4	0	0.0	0.0	1.7	12	2.3	1.2	3.9	0	0.0	0.0	0.7	1	0.4	0.0	2.2	0	0.0	0.0	1.4
Swelling (mm)	All	233	13.4	11.9	15.1	10	0.6	0.3	1.1	23	11.0	7.1	16.0	1	0.5	0.0	2.6	89	16.7	13.6	20.1	3	0.6	0.1	1.7	21	8.2	5.1	12.3	1	0.4	0.0	2.1
	>100	13	0.7	0.4	1.3	0	0.0	0.0	0.2	0	0.0	0.0	1.7	0	0.0	0.0	1.7	6	1.1	0.4	2.4	0	0.0	0.0	0.7	1	0.4	0.0	2.2	0	0.0	0.0	1.4
Overall/subject																																	
		N=901				N=892				N=112				N=110				N=278				N=274				N=131				N=132			
Pain	All	756	83.9	81.3	86.2	83	9.3	7.5	11.4	90	80.4	71.8	87.3	7	6.4	2.6	12.7	221	79.5	74.3	84.1	45	16.4	12.2	21.4	114	87.0	80.0	92.3	11	8.3	4.2	14.4
	Grade 3	99	11.0	9.0	13.2	3	0.3	0.1	1.0	11	9.8	5.0	16.9	0	0.0	0.0	3.3	29	10.4	7.1	14.6	0	0.0	0.0	1.3	13	9.9	5.4	16.4	0	0.0	0.0	2.8
Redness (mm)	All	301	33.4	30.3	36.6	9	1.0	0.5	1.9	40	35.7	26.9	45.3	0	0.0	0.0	3.3	115	41.4	35.5	47.4	5	1.8	0.6	4.2	33	25.2	18.0	33.5	2	1.5	0.2	5.4
	>100	28	3.1	2.1	4.5	0	0.0	0.0	0.4	2	1.8	0.2	6.3	0	0.0	0.0	3.3	12	4.3	2.3	7.4	0	0.0	0.0	1.3	1	0.8	0.0	4.2	0	0.0	0.0	2.8
Swelling (mm)	All	168	18.6	16.2	21.3	9	1.0	0.5	1.9	18	16.1	9.8	24.2	1	0.9	0.0	5.0	63	22.7	17.9	28.0	2	0.7	0.1	2.6	15	11.5	6.6	18.2	1	0.8	0.0	4.1
	>100	13	1.4	0.8	2.5	0	0.0	0.0	0.4	0	0.0	0.0	3.2	0	0.0	0.0	3.3	5	1.8	0.6	4.1	0	0.0	0.0	1.3	1	0.8	0.0	4.2	0	0.0	0.0	2.8

Source: Appendix Tables 10, 11, 12, and 13

Across the pivotal studies, in the HZ/su groups, the median duration of solicited local symptoms during the 7-day post-vaccination period was at most 3.0 days, except for redness and swelling in both ZOSTER-028 and ZOSTER-041 (4.0 days). In the Placebo group of all pivotal studies, the median duration of the majority of solicited local symptoms was at most 2.0 days.

Table 81: ZOSTER-002: Number of days with local symptoms during the solicited post-vaccination period (Total Vaccinated Cohort)

Solicited symptom	Dose	Group	N	n	Mean	Min	Q1	Median	Q3	Max
Pain	Dose 1	HZ/su	922	688	3.0	1.0	2.0	3.0	4.0	7.0
		Placebo	924	56	2.0	1.0	1.0	1.0	3.0	7.0
	Dose 2	HZ/su	873	638	3.2	1.0	2.0	3.0	4.0	7.0
		Placebo	862	45	2.0	1.0	1.0	1.0	2.0	7.0
	Overall/dose	HZ/su	1795	1326	3.1	1.0	2.0	3.0	4.0	7.0
		Placebo	1786	101	2.0	1.0	1.0	1.0	2.0	7.0
Redness	Dose 1	HZ/su	922	187	3.0	1.0	2.0	3.0	4.0	7.0
		Placebo	924	5	1.8	1.0	1.0	1.0	2.0	4.0
	Dose 2	HZ/su	873	231	3.5	1.0	2.0	3.0	5.0	7.0
		Placebo	862	4	1.5	1.0	1.0	1.0	2.0	3.0
	Overall/dose	HZ/su	1795	418	3.2	1.0	2.0	3.0	4.0	7.0
		Placebo	1786	9	1.7	1.0	1.0	1.0	2.0	4.0
Swelling	Dose 1	HZ/su	922	101	2.6	1.0	1.0	2.0	3.0	7.0
		Placebo	924	7	2.0	1.0	1.0	1.0	2.0	7.0
	Dose 2	HZ/su	873	132	3.1	1.0	2.0	3.0	4.0	7.0
		Placebo	862	3	1.3	1.0	1.0	1.0	2.0	2.0
	Overall/dose	HZ/su	1795	233	2.9	1.0	2.0	2.0	4.0	7.0
		Placebo	1786	10	1.8	1.0	1.0	1.0	2.0	7.0

The below tables present incidence of solicited local symptoms data within age stratum in the pivotal studies.

Table 82: ZOSTER-002: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by age strata (Total Vaccinated Cohort)

		18-49 YOA										≥50 YOA									
		HZ/su					Placebo					HZ/su					Placebo				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																					
Pain	All	223	181	81.2	75.4	86.1	217	17	7.8	4.6	12.2	673	507	75.3	71.9	78.5	673	39	5.8	4.2	7.8
	Grade 3	223	25	11.2	7.4	16.1	217	1	0.5	0.0	2.5	673	34	5.1	3.5	7.0	673	2	0.3	0.0	1.1
Redness (mm)	All	223	44	19.7	14.7	25.6	217	0	0.0	0.0	1.7	673	143	21.2	18.2	24.5	673	5	0.7	0.2	1.7
	>100	223	2	0.9	0.1	3.2	217	0	0.0	0.0	1.7	673	5	0.7	0.2	1.7	673	0	0.0	0.0	0.5
Swelling (mm)	All	223	31	13.9	9.6	19.1	217	0	0.0	0.0	1.7	673	70	10.4	8.2	13.0	673	7	1.0	0.4	2.1
	>100	223	0	0.0	0.0	1.6	217	0	0.0	0.0	1.7	673	1	0.1	0.0	0.8	673	0	0.0	0.0	0.5
Dose 2																					
Pain	All	205	168	82.0	76.0	87.0	207	13	6.3	3.4	10.5	635	470	74.0	70.4	77.4	627	32	5.1	3.5	7.1
	Grade 3	205	22	10.7	6.8	15.8	207	0	0.0	0.0	1.8	635	41	6.5	4.7	8.7	627	0	0.0	0.0	0.6
Redness (mm)	All	205	52	25.4	19.6	31.9	207	0	0.0	0.0	1.8	635	179	28.2	24.7	31.9	627	4	0.6	0.2	1.6
	>100	205	5	2.4	0.8	5.6	207	0	0.0	0.0	1.8	635	19	3.0	1.8	4.6	627	0	0.0	0.0	0.6
Swelling (mm)	All	205	34	16.6	11.8	22.4	207	0	0.0	0.0	1.8	635	98	15.4	12.7	18.5	627	3	0.5	0.1	1.4
	>100	205	4	2.0	0.5	4.9	207	0	0.0	0.0	1.8	635	8	1.3	0.5	2.5	627	0	0.0	0.0	0.6
Overall/dose																					
Pain	All	428	349	81.5	77.5	85.1	424	30	7.1	4.8	9.9	1308	977	74.7	72.2	77.0	1300	71	5.5	4.3	6.8
	Grade 3	428	47	11.0	8.2	14.3	424	1	0.2	0.0	1.3	1308	75	5.7	4.5	7.1	1300	2	0.2	0.0	0.6
Redness (mm)	All	428	96	22.4	18.6	26.7	424	0	0.0	0.0	0.9	1308	322	24.6	22.3	27.0	1300	9	0.7	0.3	1.3
	>100	428	7	1.6	0.7	3.3	424	0	0.0	0.0	0.9	1308	24	1.8	1.2	2.7	1300	0	0.0	0.0	0.3
Swelling (mm)	All	428	65	15.2	11.9	18.9	424	0	0.0	0.0	0.9	1308	168	12.8	11.1	14.8	1300	10	0.8	0.4	1.4
	>100	428	4	0.9	0.3	2.4	424	0	0.0	0.0	0.9	1308	9	0.7	0.3	1.3	1300	0	0.0	0.0	0.3
Overall/subject																					
Pain	All	224	196	87.5	82.4	91.5	219	24	11.0	7.1	15.9	677	560	82.7	79.7	85.5	673	59	8.8	6.7	11.2
	Grade 3	224	37	16.5	11.9	22.0	219	1	0.5	0.0	2.5	677	62	9.2	7.1	11.6	673	2	0.3	0.0	1.1
Redness (mm)	All	224	67	29.9	24.0	36.4	219	0	0.0	0.0	1.7	677	234	34.6	31.0	38.3	673	9	1.3	0.6	2.5
	>100	224	6	2.7	1.0	5.7	219	0	0.0	0.0	1.7	677	22	3.2	2.0	4.9	673	0	0.0	0.0	0.5
Swelling (mm)	All	224	46	20.5	15.4	26.4	219	0	0.0	0.0	1.7	677	122	18.0	15.2	21.1	673	9	1.3	0.6	2.5
	>100	224	4	1.8	0.5	4.5	219	0	0.0	0.0	1.7	677	9	1.3	0.6	2.5	673	0	0.0	0.0	0.5

Source: ZOSTER-002 CSR Amendment 1, Table 10.76

Table 83: ZOSTER-028: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by age strata (Total Vaccinated Cohort)

		18-49 YOA										≥ 50 YOA									
		HZ/su					Placebo					HZ/su					Placebo				
					95 % CI					95 % CI					95 % CI				95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																					
Pain	All	31	26	83.9	66.3	94.5	30	2	6.7	0.8	22.1	81	57	70.4	59.2	80.0	80	0	0.0	0.0	4.5
	Grade 3	31	4	12.9	3.6	29.8	30	0	0.0	0.0	11.6	81	4	4.9	1.4	12.2	80	0	0.0	0.0	4.5
Redness (mm)	All	31	11	35.5	19.2	54.6	30	0	0.0	0.0	11.6	81	22	27.2	17.9	38.2	80	0	0.0	0.0	4.5
	>100	31	0	0.0	0.0	11.2	30	0	0.0	0.0	11.6	81	2	2.5	0.3	8.6	80	0	0.0	0.0	4.5
Swelling (mm)	All	31	6	19.4	7.5	37.5	30	1	3.3	0.1	17.2	81	9	11.1	5.2	20.0	80	0	0.0	0.0	4.5
	>100	31	0	0.0	0.0	11.2	30	0	0.0	0.0	11.6	81	0	0.0	0.0	4.5	80	0	0.0	0.0	4.5
Dose 2																					
Pain	All	29	19	65.5	45.7	82.1	29	4	13.8	3.9	31.7	69	33	47.8	35.6	60.2	76	1	1.3	0.0	7.1
	Grade 3	29	1	3.4	0.1	17.8	29	0	0.0	0.0	11.9	69	3	4.3	0.9	12.2	76	0	0.0	0.0	4.7
Redness (mm)	All	29	8	27.6	12.7	47.2	29	0	0.0	0.0	11.9	69	12	17.4	9.3	28.4	76	0	0.0	0.0	4.7
	>100	29	0	0.0	0.0	11.9	29	0	0.0	0.0	11.9	69	0	0.0	0.0	5.2	76	0	0.0	0.0	4.7
Swelling (mm)	All	29	4	13.8	3.9	31.7	29	0	0.0	0.0	11.9	69	4	5.8	1.6	14.2	76	0	0.0	0.0	4.7
	>100	29	0	0.0	0.0	11.9	29	0	0.0	0.0	11.9	69	0	0.0	0.0	5.2	76	0	0.0	0.0	4.7
Overall/dose																					
Pain	All	60	45	75.0	62.1	85.3	59	6	10.2	3.8	20.8	150	90	60.0	51.7	67.9	156	1	0.6	0.0	3.5
	Grade 3	60	5	8.3	2.8	18.4	59	0	0.0	0.0	6.1	150	7	4.7	1.9	9.4	156	0	0.0	0.0	2.3
Redness (mm)	All	60	19	31.7	20.3	45.0	59	0	0.0	0.0	6.1	150	34	22.7	16.2	30.2	156	0	0.0	0.0	2.3
	>100	60	0	0.0	0.0	6.0	59	0	0.0	0.0	6.1	150	2	1.3	0.2	4.7	156	0	0.0	0.0	2.3
Swelling (mm)	All	60	10	16.7	8.3	28.5	59	1	1.7	0.0	9.1	150	13	8.7	4.7	14.4	156	0	0.0	0.0	2.3
	>100	60	0	0.0	0.0	6.0	59	0	0.0	0.0	6.1	150	0	0.0	0.0	2.4	156	0	0.0	0.0	2.3
Overall/subject																					
Pain	All	31	28	90.3	74.2	98.0	30	6	20.0	7.7	38.6	81	62	76.5	65.8	85.2	80	1	1.3	0.0	6.8
	Grade 3	31	4	12.9	3.6	29.8	30	0	0.0	0.0	11.6	81	7	8.6	3.5	17.0	80	0	0.0	0.0	4.5
Redness (mm)	All	31	14	45.2	27.3	64.0	30	0	0.0	0.0	11.6	81	26	32.1	22.2	43.4	80	0	0.0	0.0	4.5
	>100	31	0	0.0	0.0	11.2	30	0	0.0	0.0	11.6	81	2	2.5	0.3	8.6	80	0	0.0	0.0	4.5
Swelling (mm)	All	31	7	22.6	9.6	41.1	30	1	3.3	0.1	17.2	81	11	13.6	7.0	23.0	80	0	0.0	0.0	4.5
	>100	31	0	0.0	0.0	11.2	30	0	0.0	0.0	11.6	81	0	0.0	0.0	4.5	80	0	0.0	0.0	4.5

Source: ZOSTER-028 CSR Amendment 1, Table 8.181

Table 84: Appendix Table 20 ZOSTER-039: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by age strata (Total Vaccinated Cohort)

		18-49 YOA										≥ 50 YOA									
		HZ/su					Placebo					HZ/su					Placebo				
					95 % CI					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																					
Pain	All	74	65	87.8	78.2	94.3	70	9	12.9	6.1	23.0	204	134	65.7	58.7	72.2	201	17	8.5	5.0	13.2
	Grade 3	74	8	10.8	4.8	20.2	70	0	0.0	0.0	5.1	204	8	3.9	1.7	7.6	201	0	0.0	0.0	1.8
Redness (mm)	All	74	18	24.3	15.1	35.7	70	1	1.4	0.0	7.7	204	62	30.4	24.2	37.2	201	0	0.0	0.0	1.8
	>100	74	1	1.4	0.0	7.3	70	0	0.0	0.0	5.1	204	1	0.5	0.0	2.7	201	0	0.0	0.0	1.8
Swelling (mm)	All	74	14	18.9	10.7	29.7	70	0	0.0	0.0	5.1	204	33	16.2	11.4	22.0	201	2	1.0	0.1	3.5
	>100	74	0	0.0	0.0	4.9	70	0	0.0	0.0	5.1	204	1	0.5	0.0	2.7	201	0	0.0	0.0	1.8
Dose 2																					
Pain	All	68	50	73.5	61.4	83.5	66	8	12.1	5.4	22.5	187	122	65.2	57.9	72.0	182	23	12.6	8.2	18.4
	Grade 3	68	3	4.4	0.9	12.4	66	0	0.0	0.0	5.4	187	17	9.1	5.4	14.2	182	0	0.0	0.0	2.0
Redness (mm)	All	68	23	33.8	22.8	46.3	66	2	3.0	0.4	10.5	187	59	31.6	25.0	38.7	182	3	1.6	0.3	4.7
	>100	68	1	1.5	0.0	7.9	66	0	0.0	0.0	5.4	187	9	4.8	2.2	8.9	182	0	0.0	0.0	2.0
Swelling (mm)	All	68	15	22.1	12.9	33.8	66	0	0.0	0.0	5.4	187	27	14.4	9.7	20.3	182	1	0.5	0.0	3.0
	>100	68	1	1.5	0.0	7.9	66	0	0.0	0.0	5.4	187	4	2.1	0.6	5.4	182	0	0.0	0.0	2.0
Overall/dose																					
Pain	All	142	115	81.0	73.6	87.1	136	17	12.5	7.5	19.3	391	256	65.5	60.5	70.2	383	40	10.4	7.6	13.9
	Grade 3	142	11	7.7	3.9	13.4	136	0	0.0	0.0	2.7	391	25	6.4	4.2	9.3	383	0	0.0	0.0	1.0
Redness (mm)	All	142	41	28.9	21.6	37.1	136	3	2.2	0.5	6.3	391	121	30.9	26.4	35.8	383	3	0.8	0.2	2.3
	>100	142	2	1.4	0.2	5.0	136	0	0.0	0.0	2.7	391	10	2.6	1.2	4.7	383	0	0.0	0.0	1.0
Swelling (mm)	All	142	29	20.4	14.1	28.0	136	0	0.0	0.0	2.7	391	60	15.3	11.9	19.3	383	3	0.8	0.2	2.3
	>100	142	1	0.7	0.0	3.9	136	0	0.0	0.0	2.7	391	5	1.3	0.4	3.0	383	0	0.0	0.0	1.0
Overall/subject																					
Pain	All	74	67	90.5	81.5	96.1	71	13	18.3	10.1	29.3	204	154	75.5	69.0	81.2	203	32	15.8	11.0	21.5
	Grade 3	74	9	12.2	5.7	21.8	71	0	0.0	0.0	5.1	204	20	9.8	6.1	14.7	203	0	0.0	0.0	1.8
Redness (mm)	All	74	30	40.5	29.3	52.6	71	2	2.8	0.3	9.8	204	85	41.7	34.8	48.8	203	3	1.5	0.3	4.3
	>100	74	2	2.7	0.3	9.4	71	0	0.0	0.0	5.1	204	10	4.9	2.4	8.8	203	0	0.0	0.0	1.8
Swelling (mm)	All	74	20	27.0	17.4	38.6	71	0	0.0	0.0	5.1	204	43	21.1	15.7	27.3	203	2	1.0	0.1	3.5
	>100	74	1	1.4	0.0	7.3	71	0	0.0	0.0	5.1	204	4	2.0	0.5	4.9	203	0	0.0	0.0	1.8

Source: ZOSTER-039 CSR Amendment 1, Table 10.50

Table 85: Appendix Table 21 ZOSTER-041: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by age strata (Total Vaccinated Cohort)

		18-49 YOA										≥50 YOA									
		HZ/su					Placebo					HZ/su					Placebo				
					95 % CI					95 % CI					95 % CI				95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																					
Pain	All	48	42	87.5	74.8	95.3	49	3	6.1	1.3	16.9	83	65	78.3	67.9	86.6	83	5	6.0	2.0	13.5
	Grade 3	48	4	8.3	2.3	20.0	49	0	0.0	0.0	7.3	83	6	7.2	2.7	15.1	83	0	0.0	0.0	4.3
Redness (mm)	All	48	8	16.7	7.5	30.2	49	0	0.0	0.0	7.3	83	16	19.3	11.4	29.4	83	1	1.2	0.0	6.5
	>100	48	0	0.0	0.0	7.4	49	0	0.0	0.0	7.3	83	0	0.0	0.0	4.3	83	0	0.0	0.0	4.3
Swelling (mm)	All	48	3	6.3	1.3	17.2	49	0	0.0	0.0	7.3	83	7	8.4	3.5	16.6	83	1	1.2	0.0	6.5
	>100	48	0	0.0	0.0	7.4	49	0	0.0	0.0	7.3	83	0	0.0	0.0	4.3	83	0	0.0	0.0	4.3
Dose 2																					
Pain	All	46	35	76.1	61.2	87.4	47	3	6.4	1.3	17.5	79	58	73.4	62.3	82.7	81	3	3.7	0.8	10.4
	Grade 3	46	3	6.5	1.4	17.9	47	0	0.0	0.0	7.5	79	6	7.6	2.8	15.8	81	0	0.0	0.0	4.5
Redness (mm)	All	46	10	21.7	10.9	36.4	47	0	0.0	0.0	7.5	79	11	13.9	7.2	23.5	81	1	1.2	0.0	6.7
	>100	46	0	0.0	0.0	7.7	47	0	0.0	0.0	7.5	79	1	1.3	0.0	6.9	81	0	0.0	0.0	4.5
Swelling (mm)	All	46	4	8.7	2.4	20.8	47	0	0.0	0.0	7.5	79	7	8.9	3.6	17.4	81	0	0.0	0.0	4.5
	>100	46	0	0.0	0.0	7.7	47	0	0.0	0.0	7.5	79	1	1.3	0.0	6.9	81	0	0.0	0.0	4.5
Overall/dose																					
Pain	All	94	77	81.9	72.6	89.1	96	6	6.3	2.3	13.1	162	123	75.9	68.6	82.3	164	8	4.9	2.1	9.4
	Grade 3	94	7	7.4	3.0	14.7	96	0	0.0	0.0	3.8	162	12	7.4	3.9	12.6	164	0	0.0	0.0	2.2
Redness (mm)	All	94	18	19.1	11.8	28.6	96	0	0.0	0.0	3.8	162	27	16.7	11.3	23.3	164	2	1.2	0.1	4.3
	>100	94	0	0.0	0.0	3.8	96	0	0.0	0.0	3.8	162	1	0.6	0.0	3.4	164	0	0.0	0.0	2.2
Swelling (mm)	All	94	7	7.4	3.0	14.7	96	0	0.0	0.0	3.8	162	14	8.6	4.8	14.1	164	1	0.6	0.0	3.4
	>100	94	0	0.0	0.0	3.8	96	0	0.0	0.0	3.8	162	1	0.6	0.0	3.4	164	0	0.0	0.0	2.2
Overall/subject																					
Pain	All	48	44	91.7	80.0	97.7	49	5	10.2	3.4	22.2	83	70	84.3	74.7	91.4	83	6	7.2	2.7	15.1
	Grade 3	48	5	10.4	3.5	22.7	49	0	0.0	0.0	7.3	83	8	9.6	4.3	18.1	83	0	0.0	0.0	4.3
Redness (mm)	All	48	13	27.1	15.3	41.8	49	0	0.0	0.0	7.3	83	20	24.1	15.4	34.7	83	2	2.4	0.3	8.4
	>100	48	0	0.0	0.0	7.4	49	0	0.0	0.0	7.3	83	1	1.2	0.0	6.5	83	0	0.0	0.0	4.3
Swelling (mm)	All	48	5	10.4	3.5	22.7	49	0	0.0	0.0	7.3	83	10	12.0	5.9	21.0	83	1	1.2	0.0	6.5
	>100	48	0	0.0	0.0	7.4	49	0	0.0	0.0	7.3	83	1	1.2	0.0	6.5	83	0	0.0	0.0	4.3

Source: ZOSTER-041 CSR Amendment 1, Table 8.72

In both the 18-49 YOA and ≥50 YOA age strata in all pivotal studies, the median duration of the majority of solicited local symptoms was at most 3.0 days in the HZ/su groups and at most 2.0 days in the Placebo groups. In the HZ/su group of all pivotal studies, no apparent differences were observed between both age strata in the median duration of all solicited local symptoms.

Solicited general symptoms

For the pivotal studies, the overall incidence of each solicited general symptom is presented in Table 86.

- In all pivotal studies, after receiving HZ/su, the most frequently reported solicited general symptoms were fatigue (overall/subject range: 47.3%-69.6%; overall/dose range: 37.5%-54.1%) and myalgia (overall/subject range: 43.9%-53.7%; overall/dose range: 32.5%-41.2%). Fatigue and myalgia were reported more frequently in the HZ/su group than in the Placebo group in all pivotal studies, except for fatigue in ZOSTER-028 and ZOSTER-041 where the incidence was within the same range in the treatment groups.

- In ZOSTER-002 and ZOSTER-039, the incidence of each solicited general symptom was higher in the HZ/su group than in the Placebo group. In all pivotal studies, the incidence of myalgia and fever was higher in the HZ/su group than in the Placebo group.

- In all pivotal studies, after receiving HZ/su, the most frequently reported grade 3 solicited general symptoms were fatigue (overall/subject range: 3.1%-14.3%; overall/dose range: 2.7%-9.1%) and myalgia (overall/subject range: 6.2%-10.7%; overall/dose range: 3.7%-5.7%). In all pivotal studies, the incidence of grade 3 fatigue was within the same range in the HZ/su and Placebo groups, except for ZOSTER-002, where the incidence in the HZ/su group was higher. In ZOSTER-028 and ZOSTER-041, the incidence of grade 3 myalgia was within the same range in the HZ/su and Placebo groups, while in ZOSTER-002 and ZOSTER-039, the incidences in the HZ/su groups were higher than in the respective Placebo groups.

- In all pivotal studies, after receiving HZ/su, the most frequently reported solicited general symptoms assessed by the investigator as causally related to vaccination were also fatigue (overall/subject range: 11.5%-23.3%; overall/dose range: 6.3%-16.1%) and myalgia (overall/subject range: 16.0%-31.0%; overall/dose range: 9.8%-21.8%).

Across the pivotal studies, in the HZ/su groups, the median duration of solicited general symptoms during the 7-day post-vaccination period was at most 3.0 days, except for fatigue and gastrointestinal symptoms in ZOSTER-028 (both 4.0 days). In the Placebo group of all pivotal studies, the median duration was at most 5.0 days.

Table 86: Pivotal studies: Overall incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated Cohort)

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su				Placebo				HZ/su				Placebo				HZ/su				Placebo				HZ/su				Placebo			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Symptom	Type	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Overall/dose																																	
		N=1732				N=1727				N=209				N=214				N=533				N=518				N=256				N=260			
Fatigue	All	751	43.4	41.0	45.7	494	28.6	26.5	30.8	113	54.1	47.1	61.0	101	47.2	40.4	54.1	248	46.5	42.2	50.9	140	27.0	23.2	31.1	96	37.5	31.5	43.7	78	30.0	24.5	36.0
	G3	78	4.5	3.6	5.6	36	2.1	1.5	2.9	19	9.1	5.6	13.8	9	4.2	1.9	7.8	27	5.1	3.4	7.3	14	2.7	1.5	4.5	7	2.7	1.1	5.6	7	2.7	1.1	5.5
	R	277	16.0	14.3	17.8	96	5.6	4.5	6.7	21	10.0	6.3	14.9	18	8.4	5.1	13.0	86	16.1	13.1	19.5	24	4.6	3.0	6.8	16	6.3	3.6	10.0	6	2.3	0.9	5.0
	G3 R	41	2.4	1.7	3.2	7	0.4	0.2	0.8	3	1.4	0.3	4.1	1	0.5	0.0	2.6	8	1.5	0.7	2.9	1	0.2	0.0	1.1	0	0.0	0.0	1.4	0	0.0	0.0	1.4
Gastro-intestinal symptoms	All	292	16.9	15.1	18.7	232	13.4	11.9	15.1	73	34.9	28.5	41.8	60	28.0	22.1	34.6	101	18.9	15.7	22.5	40	7.7	5.6	10.4	31	12.1	8.4	16.7	30	11.5	7.9	16.1
	G3	19	1.1	0.7	1.7	19	1.1	0.7	1.7	7	3.3	1.4	6.8	8	3.7	1.6	7.2	10	1.9	0.9	3.4	4	0.8	0.2	2.0	1	0.4	0.0	2.2	1	0.4	0.0	2.1
	R	92	5.3	4.3	6.5	35	2.0	1.4	2.8	15	7.2	4.1	11.6	4	1.9	0.5	4.7	33	6.2	4.3	8.6	5	1.0	0.3	2.2	2	0.8	0.1	2.8	3	1.2	0.2	3.3
	G3 R	5	0.3	0.1	0.7	1	0.1	0.0	0.3	1	0.5	0.0	2.6	1	0.5	0.0	2.6	3	0.6	0.1	1.6	0	0.0	0.0	0.7	0	0.0	0.0	1.4	0	0.0	0.0	1.4
Headache	All	388	22.4	20.5	24.4	209	12.1	10.6	13.7	57	27.3	21.4	33.8	49	22.9	17.4	29.1	160	30.0	26.2	34.1	82	15.8	12.8	19.3	67	26.2	20.9	32.0	47	18.1	13.6	23.3
	G3	26	1.5	1.0	2.2	11	0.6	0.3	1.1	6	2.9	1.1	6.1	3	1.4	0.3	4.0	13	2.4	1.3	4.1	6	1.2	0.4	2.5	3	1.2	0.2	3.4	7	2.7	1.1	5.5
	R	146	8.4	7.2	9.8	52	3.0	2.3	3.9	17	8.1	4.8	12.7	6	2.8	1.0	6.0	71	13.3	10.6	16.5	19	3.7	2.2	5.7	14	5.5	3.0	9.0	4	1.5	0.4	3.9
	G3 R	15	0.9	0.5	1.4	1	0.1	0.0	0.3	2	1.0	0.1	3.4	0	0.0	0.0	1.7	3	0.6	0.1	1.6	1	0.2	0.0	1.1	1	0.4	0.0	2.2	0	0.0	0.0	1.4
Myalgia	All	714	41.2	38.9	43.6	323	18.7	16.9	20.6	82	39.2	32.6	46.2	40	18.7	13.7	24.6	173	32.5	28.5	36.6	60	11.6	9.0	14.7	90	35.2	29.3	41.3	42	16.2	11.9	21.2
	G3	64	3.7	2.9	4.7	20	1.2	0.7	1.8	12	5.7	3.0	9.8	4	1.9	0.5	4.7	25	4.7	3.1	6.8	5	1.0	0.3	2.2	12	4.7	2.4	8.0	4	1.5	0.4	3.9
	R	378	21.8	19.9	23.8	97	5.6	4.6	6.8	38	18.2	13.2	24.1	7	3.3	1.3	6.6	83	15.6	12.6	18.9	17	3.3	1.9	5.2	25	9.8	6.4	14.1	5	1.9	0.6	4.4
	G3 R	39	2.3	1.6	3.1	2	0.1	0.0	0.4	7	3.3	1.4	6.8	0	0.0	0.0	1.7	11	2.1	1.0	3.7	1	0.2	0.0	1.1	4	1.6	0.4	4.0	0	0.0	0.0	1.4
Shivering	All	301	17.4	15.6	19.2	132	7.6	6.4	9.0	47	22.5	17.0	28.8	30	14.0	9.7	19.4	87	16.3	13.3	19.7	23	4.4	2.8	6.6	33	12.9	9.0	17.6	22	8.5	5.4	12.5
	G3	35	2.0	1.4	2.8	7	0.4	0.2	0.8	8	3.8	1.7	7.4	3	1.4	0.3	4.0	11	2.1	1.0	3.7	0	0.0	0.0	0.7	4	1.6	0.4	4.0	3	1.2	0.2	3.3
	R	158	9.1	7.8	10.6	43	2.5	1.8	3.3	18	8.6	5.2	13.3	8	3.7	1.6	7.2	41	7.7	5.6	10.3	3	0.6	0.1	1.7	12	4.7	2.4	8.0	2	0.8	0.1	2.8
	G3 R	26	1.5	1.0	2.2	1	0.1	0.0	0.3	5	2.4	0.8	5.5	0	0.0	0.0	1.7	6	1.1	0.4	2.4	0	0.0	0.0	0.7	3	1.2	0.2	3.4	0	0.0	0.0	1.4
Fever/(*) (°C)	All	210	12.1	10.6	13.8	56	3.2	2.5	4.2	21	10.0	6.3	14.9	5	2.3	0.8	5.4	84	15.8	12.8	19.1	26	5.0	3.3	7.3	23	9.0	5.8	13.2	5	1.9	0.6	4.4
	G3	3	0.2	0.0	0.5	1	0.1	0.0	0.3	0	0.0	0.0	1.7	0	0.0	0.0	1.7	3	0.6	0.1	1.6	1	0.2	0.0	1.1	1	0.4	0.0	2.2	0	0.0	0.0	1.4
	R	113	6.5	5.4	7.8	15	0.9	0.5	1.4	15	7.2	4.1	11.6	1	0.5	0.0	2.6	46	8.6	6.4	11.3	6	1.2	0.4	2.5	9	3.5	1.6	6.6	0	0.0	0.0	1.4
	G3 R	3	0.2	0.0	0.5	0	0.0	0.0	0.2	0	0.0	0.0	1.7	0	0.0	0.0	1.7	2	0.4	0.0	1.3	0	0.0	0.0	0.7	1	0.4	0.0	2.2	0	0.0	0.0	1.4

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su				Placebo				HZ/su				Placebo				HZ/su				Placebo				HZ/su				Placebo			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Symptom	Type	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Overall/subject																																	
		N=901				N=894				N=112				N=110				N=278				N=274				N=131				N=132			
Fatigue	All	508	56.4	53.1	59.6	340	38.0	34.8	41.3	78	69.6	60.2	78.0	68	61.8	52.1	70.9	162	58.3	52.2	64.1	102	37.2	31.5	43.2	62	47.3	38.5	56.2	53	40.2	31.7	49.0
	G3	66	7.3	5.7	9.2	31	3.5	2.4	4.9	16	14.3	8.4	22.2	8	7.3	3.2	13.8	23	8.3	5.3	12.2	10	3.6	1.8	6.6	4	3.1	0.8	7.6	6	4.5	1.7	9.6
	R	210	23.3	20.6	26.2	79	8.8	7.1	10.9	19	17.0	10.5	25.2	14	12.7	7.1	20.4	63	22.7	17.9	28.0	22	8.0	5.1	11.9	15	11.5	6.6	18.2	4	3.0	0.8	7.6
	G3 R	35	3.9	2.7	5.4	7	0.8	0.3	1.6	3	2.7	0.6	7.6	1	0.9	0.0	5.0	8	2.9	1.3	5.6	1	0.4	0.0	2.0	0	0.0	0.0	2.8	0	0.0	0.0	2.8
Gastro-intestinal symptoms	All	238	26.4	23.6	29.4	183	20.5	17.9	23.3	51	45.5	36.1	55.2	49	44.5	35.1	54.3	76	27.3	22.2	33.0	29	10.6	7.2	14.8	24	18.3	12.1	26.0	24	18.2	12.0	25.8
	G3	18	2.0	1.2	3.1	17	1.9	1.1	3.0	6	5.4	2.0	11.3	7	6.4	2.6	12.7	9	3.2	1.5	6.1	3	1.1	0.2	3.2	1	0.8	0.0	4.2	1	0.8	0.0	4.1
	R	79	8.8	7.0	10.8	30	3.4	2.3	4.8	11	9.8	5.0	16.9	3	2.7	0.6	7.8	28	10.1	6.8	14.2	5	1.8	0.6	4.2	2	1.5	0.2	5.4	3	2.3	0.5	6.5
	G3 R	5	0.6	0.2	1.3	1	0.1	0.0	0.6	1	0.9	0.0	4.9	1	0.9	0.0	5.0	2	0.7	0.1	2.6	0	0.0	0.0	1.3	0	0.0	0.0	2.8	0	0.0	0.0	2.8
Headache	All	302	33.5	30.4	36.7	166	18.6	16.1	21.3	43	38.4	29.4	48.1	40	36.4	27.4	46.1	115	41.4	35.5	47.4	64	23.4	18.5	28.8	44	33.6	25.6	42.4	34	25.8	18.5	34.1
	G3	26	2.9	1.9	4.2	10	1.1	0.5	2.0	6	5.4	2.0	11.3	3	2.7	0.6	7.8	12	4.3	2.3	7.4	6	2.2	0.8	4.7	2	1.5	0.2	5.4	5	3.8	1.2	8.6
	R	123	13.7	11.5	16.1	46	5.1	3.8	6.8	16	14.3	8.4	22.2	6	5.5	2.0	11.5	52	18.7	14.3	23.8	16	5.8	3.4	9.3	12	9.2	4.8	15.5	4	3.0	0.8	7.6
	G3 R	15	1.7	0.9	2.7	1	0.1	0.0	0.6	2	1.8	0.2	6.3	0	0.0	0.0	3.3	2	0.7	0.1	2.6	1	0.4	0.0	2.0	1	0.8	0.0	4.2	0	0.0	0.0	2.8
Myalgia	All	484	53.7	50.4	57.0	234	26.2	23.3	29.2	60	53.6	43.9	63.0	31	28.2	20.0	37.6	122	43.9	38.0	49.9	48	17.5	13.2	22.5	65	49.6	40.8	58.5	31	23.5	16.5	31.6
	G3	56	6.2	4.7	8.0	19	2.1	1.3	3.3	12	10.7	5.7	18.0	4	3.6	1.0	9.0	22	7.9	5.0	11.7	5	1.8	0.6	4.2	9	6.9	3.2	12.6	3	2.3	0.5	6.5
	R	279	31.0	28.0	34.1	83	9.3	7.5	11.4	30	26.8	18.9	36.0	5	4.5	1.5	10.3	63	22.7	17.9	28.0	15	5.5	3.1	8.9	21	16.0	10.2	23.5	4	3.0	0.8	7.6
	G3 R	32	3.6	2.4	5.0	2	0.2	0.0	0.8	7	6.3	2.5	12.5	0	0.0	0.0	3.3	11	4.0	2.0	7.0	1	0.4	0.0	2.0	4	3.1	0.8	7.6	0	0.0	0.0	2.8
Shivering	All	237	26.3	23.5	29.3	115	12.9	10.7	15.2	39	34.8	26.1	44.4	25	22.7	15.3	31.7	69	24.8	19.9	30.3	18	6.6	3.9	10.2	29	22.1	15.4	30.2	16	12.1	7.1	18.9
	G3	35	3.9	2.7	5.4	7	0.8	0.3	1.6	6	5.4	2.0	11.3	3	2.7	0.6	7.8	11	4.0	2.0	7.0	0	0.0	0.0	1.3	4	3.1	0.8	7.6	2	1.5	0.2	5.4
	R	131	14.5	12.3	17.0	38	4.3	3.0	5.8	16	14.3	8.4	22.2	5	4.5	1.5	10.3	36	12.9	9.2	17.5	2	0.7	0.1	2.6	11	8.4	4.3	14.5	2	1.5	0.2	5.4
	G3 R	26	2.9	1.9	4.2	1	0.1	0.0	0.6	4	3.6	1.0	8.9	0	0.0	0.0	3.3	6	2.2	0.8	4.6	0	0.0	0.0	1.3	3	2.3	0.5	6.5	0	0.0	0.0	2.8
Fever/(*) (°C)	All	183	20.3	17.7	23.1	50	5.6	4.2	7.3	20	17.9	11.3	26.2	5	4.5	1.5	10.3	68	24.5	19.5	30.0	21	7.7	4.8	11.5	21	16.0	10.2	23.5	5	3.8	1.2	8.6
	G3	3	0.3	0.1	1.0	1	0.1	0.0	0.6	0	0.0	0.0	3.2	0	0.0	0.0	3.3	3	1.1	0.2	3.1	0	0.0	0.0	1.3	1	0.8	0.0	4.2	0	0.0	0.0	2.8
	R	101	11.2	9.2	13.5	15	1.7	0.9	2.8	14	12.5	7.0	20.1	1	0.9	0.0	5.0	36	12.9	9.2	17.5	4	1.5	0.4	3.7	9	6.9	3.2	12.6	0	0.0	0.0	2.8
	G3 R	3	0.3	0.1	1.0	0	0.0	0.0	0.4	0	0.0	0.0	3.2	0	0.0	0.0	3.3	2	0.7	0.1	2.6	0	0.0	0.0	1.3	1	0.8	0.0	4.2	0	0.0	0.0	2.8

Source: Appendix Tables 25, 26, 27, and 28

*Temperature is measured by oral, axillary, rectal (ZOSTER-041 and ZOSTER-002 only), or tympanic routes.

G3 = grade 3; R = related to vaccination as per investigator assessment.

In the HZ/su group of ZOSTER-028, ZOSTER-039, and ZOSTER-041, the incidence of the majority of solicited general symptoms (any grade, grade 3, related, and grade 3 related) was within the same range in the 18-49 YOA and ≥50 YOA strata.

In ZOSTER-039, myalgia (any grade) and related myalgia were reported with higher incidences in the 18-49 YOA stratum. In ZOSTER-002, grade 3 fatigue, headache (any grade), fever (any grade), and related fever were reported with higher incidences in the 18-49 YOA stratum.

In the Placebo group of all pivotal studies, the incidence of the majority of solicited general symptoms was within the same range in both age strata.

Table 87: ZOSTER-002: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by age strata (Total Vaccinated Cohort)

		18-49 YOA										≥50 YOA									
		HZ/su					Placebo					HZ/su					Placebo				
					95 % CI					95 % CI					95 % CI				95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																					
Fatigue	All	222	108	48.6	41.9	55.4	218	74	33.9	27.7	40.6	674	248	36.8	33.1	40.6	674	208	30.9	27.4	34.5
	Grade 3	222	13	5.9	3.2	9.8	218	3	1.4	0.3	4.0	674	17	2.5	1.5	4.0	674	13	1.9	1.0	3.3
	Related	222	43	19.4	14.4	25.2	218	14	6.4	3.6	10.5	674	81	12.0	9.7	14.7	674	41	6.1	4.4	8.2
	Grade 3 Related	222	9	4.1	1.9	7.6	218	1	0.5	0.0	2.5	674	7	1.0	0.4	2.1	674	3	0.4	0.1	1.3
Gastrointestinal symptoms	All	222	32	14.4	10.1	19.7	218	28	12.8	8.7	18.0	674	118	17.5	14.7	20.6	674	106	15.7	13.1	18.7
	Grade 3	222	2	0.9	0.1	3.2	218	0	0.0	0.0	1.7	674	4	0.6	0.2	1.5	674	7	1.0	0.4	2.1
	Related	222	7	3.2	1.3	6.4	218	7	3.2	1.3	6.5	674	34	5.0	3.5	7.0	674	15	2.2	1.3	3.6
	Grade 3 Related	222	0	0.0	0.0	1.6	218	0	0.0	0.0	1.7	674	1	0.1	0.0	0.8	674	0	0.0	0.0	0.5
Headache	All	222	52	23.4	18.0	29.6	218	37	17.0	12.2	22.6	674	104	15.4	12.8	18.4	674	84	12.5	10.1	15.2
	Grade 3	222	1	0.5	0.0	2.5	218	0	0.0	0.0	1.7	674	1	0.1	0.0	0.8	674	3	0.4	0.1	1.3
	Related	222	17	7.7	4.5	12.0	218	16	7.3	4.3	11.6	674	34	5.0	3.5	7.0	674	16	2.4	1.4	3.8
	Grade 3 Related	222	1	0.5	0.0	2.5	218	0	0.0	0.0	1.7	674	1	0.1	0.0	0.8	674	0	0.0	0.0	0.5
Myalgia	All	222	90	40.5	34.0	47.3	218	48	22.0	16.7	28.1	674	250	37.1	33.4	40.9	674	122	18.1	15.3	21.2
	Grade 3	222	8	3.6	1.6	7.0	218	4	1.8	0.5	4.6	674	14	2.1	1.1	3.5	674	7	1.0	0.4	2.1
	Related	222	45	20.3	15.2	26.2	218	15	6.9	3.9	11.1	674	125	18.5	15.7	21.7	674	35	5.2	3.6	7.1
	Grade 3 Related	222	4	1.8	0.5	4.5	218	0	0.0	0.0	1.7	674	10	1.5	0.7	2.7	674	1	0.1	0.0	0.8
Shivering	All	222	44	19.8	14.8	25.7	218	26	11.9	7.9	17.0	674	72	10.7	8.5	13.3	674	47	7.0	5.2	9.2
	Grade 3	222	3	1.4	0.3	3.9	218	0	0.0	0.0	1.7	674	3	0.4	0.1	1.3	674	6	0.9	0.3	1.9
	Related	222	24	10.8	7.1	15.7	218	10	4.6	2.2	8.3	674	32	4.7	3.3	6.6	674	17	2.5	1.5	4.0
	Grade 3 Related	222	3	1.4	0.3	3.9	218	0	0.0	0.0	1.7	674	1	0.1	0.0	0.8	674	1	0.1	0.0	0.8
Temperature/(*) (°C)	All	222	19	8.6	5.2	13.0	218	8	3.7	1.6	7.1	674	41	6.1	4.4	8.2	674	20	3.0	1.8	4.5
	>39.5	222	0	0.0	0.0	1.6	218	0	0.0	0.0	1.7	674	1	0.1	0.0	0.8	674	0	0.0	0.0	0.5
	Related	222	10	4.5	2.2	8.1	218	2	0.9	0.1	3.3	674	17	2.5	1.5	4.0	674	5	0.7	0.2	1.7
	>39.5 Related	222	0	0.0	0.0	1.6	218	0	0.0	0.0	1.7	674	1	0.1	0.0	0.8	674	0	0.0	0.0	0.5
Dose 2																					
Fatigue	All	203	104	51.2	44.1	58.3	207	52	25.1	19.4	31.6	633	291	46.0	42.0	49.9	628	160	25.5	22.1	29.1
	Grade 3	203	21	10.3	6.5	15.4	207	4	1.9	0.5	4.9	633	27	4.3	2.8	6.1	628	16	2.5	1.5	4.1
	Related	203	45	22.2	16.7	28.5	207	9	4.3	2.0	8.1	633	108	17.1	14.2	20.2	628	32	5.1	3.5	7.1
	Grade 3 Related	203	10	4.9	2.4	8.9	207	1	0.5	0.0	2.7	633	15	2.4	1.3	3.9	628	2	0.3	0.0	1.1

		18-49 YOA										≥50 YOA									
		HZ/su			95 % CI		Placebo			95 % CI		HZ/su			95 % CI		Placebo			95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Gastrointestinal symptoms	All	203	26	12.8	8.5	18.2	207	25	12.1	8.0	17.3	633	116	18.3	15.4	21.6	628	73	11.6	9.2	14.4
	Grade 3	203	2	1.0	0.1	3.5	207	2	1.0	0.1	3.4	633	11	1.7	0.9	3.1	628	10	1.6	0.8	2.9
	Related	203	6	3.0	1.1	6.3	207	4	1.9	0.5	4.9	633	45	7.1	5.2	9.4	628	9	1.4	0.7	2.7
	Grade 3 Related	203	1	0.5	0.0	2.7	207	0	0.0	0.0	1.8	633	3	0.5	0.1	1.4	628	1	0.2	0.0	0.9
Headache	All	203	77	37.9	31.2	45.0	207	36	17.4	12.5	23.3	633	155	24.5	21.2	28.0	628	52	8.3	6.2	10.7
	Grade 3	203	10	4.9	2.4	8.9	207	4	1.9	0.5	4.9	633	14	2.2	1.2	3.7	628	4	0.6	0.2	1.6
	Related	203	32	15.8	11.0	21.5	207	9	4.3	2.0	8.1	633	63	10.0	7.7	12.6	628	11	1.8	0.9	3.1
	Grade 3 Related	203	6	3.0	1.1	6.3	207	1	0.5	0.0	2.7	633	7	1.1	0.4	2.3	628	0	0.0	0.0	0.6
Myalgia	All	203	103	50.7	43.6	57.8	207	44	21.3	15.9	27.5	633	271	42.8	38.9	46.8	628	109	17.4	14.5	20.6
	Grade 3	203	16	7.9	4.6	12.5	207	4	1.9	0.5	4.9	633	26	4.1	2.7	6.0	628	5	0.8	0.3	1.8
	Related	203	52	25.6	19.8	32.2	207	13	6.3	3.4	10.5	633	156	24.6	21.3	28.2	628	34	5.4	3.8	7.5
	Grade 3 Related	203	8	3.9	1.7	7.6	207	1	0.5	0.0	2.7	633	17	2.7	1.6	4.3	628	0	0.0	0.0	0.6
Shivering	All	203	53	26.1	20.2	32.7	207	13	6.3	3.4	10.5	633	132	20.9	17.8	24.2	628	46	7.3	5.4	9.6
	Grade 3	203	13	6.4	3.5	10.7	207	0	0.0	0.0	1.8	633	16	2.5	1.5	4.1	628	1	0.2	0.0	0.9
	Related	203	28	13.8	9.4	19.3	207	6	2.9	1.1	6.2	633	74	11.7	9.3	14.5	628	10	1.6	0.8	2.9
	Grade 3 Related	203	11	5.4	2.7	9.5	207	0	0.0	0.0	1.8	633	11	1.7	0.9	3.1	628	0	0.0	0.0	0.6
Temperature/(*) (°C)	All	203	56	27.6	21.6	34.3	207	5	2.4	0.8	5.5	633	94	14.8	12.2	17.9	628	23	3.7	2.3	5.4
	>39.5	203	1	0.5	0.0	2.7	207	0	0.0	0.0	1.8	633	1	0.2	0.0	0.9	628	1	0.2	0.0	0.9
	Related	203	33	16.3	11.5	22.1	207	1	0.5	0.0	2.7	633	53	8.4	6.3	10.8	628	7	1.1	0.4	2.3
	>39.5 Related	203	1	0.5	0.0	2.7	207	0	0.0	0.0	1.8	633	1	0.2	0.0	0.9	628	0	0.0	0.0	0.6
Overall/dose																					
Fatigue	All	425	212	49.9	45.0	54.7	425	126	29.6	25.3	34.2	1307	539	41.2	38.6	44.0	1302	368	28.3	25.8	30.8
	Grade 3	425	34	8.0	5.6	11.0	425	7	1.6	0.7	3.4	1307	44	3.4	2.5	4.5	1302	29	2.2	1.5	3.2
	Related	425	88	20.7	17.0	24.9	425	23	5.4	3.5	8.0	1307	189	14.5	12.6	16.5	1302	73	5.6	4.4	7.0
	Grade 3 Related	425	19	4.5	2.7	6.9	425	2	0.5	0.1	1.7	1307	22	1.7	1.1	2.5	1302	5	0.4	0.1	0.9
Gastrointestinal symptoms	All	425	58	13.6	10.5	17.3	425	53	12.5	9.5	16.0	1307	234	17.9	15.9	20.1	1302	179	13.7	11.9	15.7
	Grade 3	425	4	0.9	0.3	2.4	425	2	0.5	0.1	1.7	1307	15	1.1	0.6	1.9	1302	17	1.3	0.8	2.1
	Related	425	13	3.1	1.6	5.2	425	11	2.6	1.3	4.6	1307	79	6.0	4.8	7.5	1302	24	1.8	1.2	2.7
	Grade 3 Related	425	1	0.2	0.0	1.3	425	0	0.0	0.0	0.9	1307	4	0.3	0.1	0.8	1302	1	0.1	0.0	0.4
Headache	All	425	129	30.4	26.0	35.0	425	73	17.2	13.7	21.1	1307	259	19.8	17.7	22.1	1302	136	10.4	8.8	12.2
	Grade 3	425	11	2.6	1.3	4.6	425	4	0.9	0.3	2.4	1307	15	1.1	0.6	1.9	1302	7	0.5	0.2	1.1
	Related	425	49	11.5	8.7	15.0	425	25	5.9	3.8	8.6	1307	97	7.4	6.1	9.0	1302	27	2.1	1.4	3.0
	Grade 3 Related	425	7	1.6	0.7	3.4	425	1	0.2	0.0	1.3	1307	8	0.6	0.3	1.2	1302	0	0.0	0.0	0.3

		18-49 YOA										≥50 YOA									
		HZ/su					Placebo					HZ/su					Placebo				
					95 % CI					95 % CI					95 % CI				95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Myalgia	All	425	193	45.4	40.6	50.3	425	92	21.6	17.8	25.9	1307	521	39.9	37.2	42.6	1302	231	17.7	15.7	19.9
	Grade 3	425	24	5.6	3.7	8.3	425	8	1.9	0.8	3.7	1307	40	3.1	2.2	4.1	1302	12	0.9	0.5	1.6
	Related	425	97	22.8	18.9	27.1	425	28	6.6	4.4	9.4	1307	281	21.5	19.3	23.8	1302	69	5.3	4.1	6.7
	Grade 3 Related	425	12	2.8	1.5	4.9	425	1	0.2	0.0	1.3	1307	27	2.1	1.4	3.0	1302	1	0.1	0.0	0.4
Shivering	All	425	97	22.8	18.9	27.1	425	39	9.2	6.6	12.3	1307	204	15.6	13.7	17.7	1302	93	7.1	5.8	8.7
	Grade 3	425	16	3.8	2.2	6.0	425	0	0.0	0.0	0.9	1307	19	1.5	0.9	2.3	1302	7	0.5	0.2	1.1
	Related	425	52	12.2	9.3	15.7	425	16	3.8	2.2	6.0	1307	106	8.1	6.7	9.7	1302	27	2.1	1.4	3.0
	Grade 3 Related	425	14	3.3	1.8	5.5	425	0	0.0	0.0	0.9	1307	12	0.9	0.5	1.6	1302	1	0.1	0.0	0.4
Temperature/(*) (°C)	All	425	75	17.6	14.1	21.6	425	13	3.1	1.6	5.2	1307	135	10.3	8.7	12.1	1302	43	3.3	2.4	4.4
	>39.5	425	1	0.2	0.0	1.3	425	0	0.0	0.0	0.9	1307	2	0.2	0.0	0.6	1302	1	0.1	0.0	0.4
	Related	425	43	10.1	7.4	13.4	425	3	0.7	0.1	2.0	1307	70	5.4	4.2	6.7	1302	12	0.9	0.5	1.6
	>39.5 Related	425	1	0.2	0.0	1.3	425	0	0.0	0.0	0.9	1307	2	0.2	0.0	0.6	1302	0	0.0	0.0	0.3
Overall/subject																					
Fatigue	All	223	143	64.1	57.5	70.4	220	87	39.5	33.0	46.3	678	365	53.8	50.0	57.6	674	253	37.5	33.9	41.3
	Grade 3	223	27	12.1	8.1	17.1	220	6	2.7	1.0	5.8	678	39	5.8	4.1	7.8	674	25	3.7	2.4	5.4
	Related	223	64	28.7	22.9	35.1	220	19	8.6	5.3	13.2	678	146	21.5	18.5	24.8	674	60	8.9	6.9	11.3
	Grade 3 Related	223	15	6.7	3.8	10.9	220	2	0.9	0.1	3.2	678	20	2.9	1.8	4.5	674	5	0.7	0.2	1.7
Gastrointestinal symptoms	All	223	47	21.1	15.9	27.0	220	40	18.2	13.3	23.9	678	191	28.2	24.8	31.7	674	143	21.2	18.2	24.5
	Grade 3	223	4	1.8	0.5	4.5	220	2	0.9	0.1	3.2	678	14	2.1	1.1	3.4	674	15	2.2	1.3	3.6
	Related	223	12	5.4	2.8	9.2	220	9	4.1	1.9	7.6	678	67	9.9	7.7	12.4	674	21	3.1	1.9	4.7
	Grade 3 Related	223	1	0.4	0.0	2.5	220	0	0.0	0.0	1.7	678	4	0.6	0.2	1.5	674	1	0.1	0.0	0.8
Headache	All	223	98	43.9	37.3	50.7	220	53	24.1	18.6	30.3	678	204	30.1	26.7	33.7	674	113	16.8	14.0	19.8
	Grade 3	223	11	4.9	2.5	8.7	220	4	1.8	0.5	4.6	678	15	2.2	1.2	3.6	674	6	0.9	0.3	1.9
	Related	223	40	17.9	13.1	23.6	220	21	9.5	6.0	14.2	678	83	12.2	9.9	14.9	674	25	3.7	2.4	5.4
	Grade 3 Related	223	7	3.1	1.3	6.4	220	1	0.5	0.0	2.5	678	8	1.2	0.5	2.3	674	0	0.0	0.0	0.5
Myalgia	All	223	129	57.8	51.1	64.4	220	61	27.7	21.9	34.1	678	355	52.4	48.5	56.2	674	173	25.7	22.4	29.1
	Grade 3	223	22	9.9	6.3	14.6	220	7	3.2	1.3	6.4	678	34	5.0	3.5	6.9	674	12	1.8	0.9	3.1
	Related	223	70	31.4	25.4	37.9	220	22	10.0	6.4	14.7	678	209	30.8	27.4	34.5	674	61	9.1	7.0	11.5
	Grade 3 Related	223	11	4.9	2.5	8.7	220	1	0.5	0.0	2.5	678	21	3.1	1.9	4.7	674	1	0.1	0.0	0.8
Shivering	All	223	70	31.4	25.4	37.9	220	35	15.9	11.3	21.4	678	167	24.6	21.4	28.1	674	80	11.9	9.5	14.6
	Grade 3	223	16	7.2	4.2	11.4	220	0	0.0	0.0	1.7	678	19	2.8	1.7	4.3	674	7	1.0	0.4	2.1
	Related	223	42	18.8	13.9	24.6	220	14	6.4	3.5	10.4	678	89	13.1	10.7	15.9	674	24	3.6	2.3	5.3
	Grade 3 Related	223	14	6.3	3.5	10.3	220	0	0.0	0.0	1.7	678	12	1.8	0.9	3.1	674	1	0.1	0.0	0.8

		18-49 YOA										≥50 YOA									
		HZ/su					Placebo					HZ/su					Placebo				
					95 % CI					95 % CI					95 % CI				95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Temperature/(*) (°C)	All	223	62	27.8	22.0	34.2	220	12	5.5	2.8	9.3	678	121	17.8	15.0	20.9	674	38	5.6	4.0	7.7
	>39.5	223	1	0.4	0.0	2.5	220	0	0.0	0.0	1.7	678	2	0.3	0.0	1.1	674	1	0.1	0.0	0.8
	Related	223	38	17.0	12.3	22.6	220	3	1.4	0.3	3.9	678	63	9.3	7.2	11.7	674	12	1.8	0.9	3.1
	>39.5 Related	223	1	0.4	0.0	2.5	220	0	0.0	0.0	1.7	678	2	0.3	0.0	1.1	674	0	0.0	0.0	0.5

Source: ZOSTER-002 CSR Amendment 1, Table 10.77

In the HZ/su group of all pivotal studies, no apparent differences were observed between both age strata in the median duration of all solicited general symptoms.

- **Analysis of adverse events by System Organ Class and Preferred Term**

All unsolicited (serious and non-serious) adverse events:

In each pivotal study, the percentage of subjects reporting the occurrence of at least 1 unsolicited AE within the 30-day post-vaccination period was within the same range in the HZ/su and Placebo group. In ZOSTER-028, the overall incidence of unsolicited AEs in both the HZ/su and the Placebo group was higher (85.5% in the HZ/su group and 89.6% in the Placebo group) than in the other studies (39.0% and 38.2% in ZOSTER-002, 47.3% and 45.9% in ZOSTER-039, and 38.6% and 33.3% in ZOSTER-041). The events were generally consistent with the underlying diseases, complications, and therapies of the study subjects, except for events associated with reactogenicity, which were mostly under the SOC of General disorders and administration site conditions.

In what follows, for each pivotal study a summarizing description of AEs is provided, which presents the PTs that were reported in ≥3.0% of subjects in any of the groups. As the overall incidence of AEs was higher in ZOSTER-028 than in the other studies, a higher cut-off (i.e., ≥13.0%) was chosen for this study. The source is an exhaustive table of PTs in Appendix Tables 40, 41, 42, and 43.

In ZOSTER-002, the most frequently reported SOCs in both groups were Infections and infestations, General disorders and administration site conditions, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, and Musculoskeletal and connective tissue disorders. By PT, events reported in ≥3.0% of subjects in any of the groups included upper respiratory tract infection (reported in 28 subjects [3.0%] in the HZ/su group and 30 [3.2%] in the Placebo group) and viral upper respiratory tract infection (23 [2.5%] and 30 [3.2%], respectively). By PT, none of the unsolicited AEs were reported with significantly higher incidence in any of the groups.

In ZOSTER-028, the most frequently reported SOCs in both groups were Gastrointestinal disorders, General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Blood and lymphatic system disorders, and Nervous system disorders. By PT, events reported in ≥13.0% of subjects in any of the groups included nausea (reported in 31 subjects [26.5%] in the HZ/su group and 28 [24.3%] in the Placebo group), asthenia (30 [25.6%] and 28 [24.3%], respectively), alopecia (21 [17.9%] and 23 [20.0%], respectively), constipation (16 [13.7%] and 12 [10.4%], respectively), and neutropenia (11 [9.4%] and 15 [13.0%], respectively. By PT, none of the unsolicited AEs were reported with significantly higher incidence in any of the groups.

In ZOSTER-039, the most frequently reported SOCs were Infections and infestations, Gastrointestinal disorders, General disorders and administration site conditions, Musculoskeletal and connective tissue disorders, and Respiratory, thoracic, and mediastinal disorders. The SOC of Neoplasms benign, malignant, and unspecified (including cysts and polyps), with an RR of 0.27 (95% CI: 0.09, 0.68; p-value: 0.0033) was reported with significantly higher incidence in the Placebo group than in the HZ/su group. By PT, events reported in ≥3.0% of subjects in any of the groups included nausea (reported in 11 subjects [3.9%] in the HZ/su group and 6 [2.2%] in the Placebo group), pyrexia (10 [3.5%] and 5 [1.8%], respectively), oropharyngeal pain (10 [3.5%] and 3 [1.1%], respectively), diarrhea (9 [3.2%] and 5 [1.8%], respectively), upper respiratory tract infection (9 [3.2%] and 1 [0.4%], respectively), cough (9 [3.2%] and 10 [3.6%], respectively), and nasopharyngitis (7 [2.5%] and 9 [3.2%], respectively). The PT of upper respiratory tract infection, with an RR of 8.87 (95% CI: 1.23, 388.9; p-value: 0.0228), was reported with significantly higher incidence in the HZ/su group than in the Placebo group and the PT of acute myeloid leukemia, with an RR of 0.12 (95% CI: 0.00, 0.92; p-value: 0.0371) was reported with significantly higher incidence in the Placebo group.

In ZOSTER-041, the most frequently reported SOCs were Infections and infestations, Gastrointestinal disorders, General disorders and administration site conditions, Musculoskeletal and connective tissue disorders, and Respiratory, thoracic, and mediastinal disorders. By PT, events reported in ≥3.0% of subjects in any of the groups included urinary tract infection (reported in 6 subjects [4.5%] in the HZ/su group and 3 [2.3%] in the Placebo group) and nasopharyngitis (3 [2.3%] and 5 [3.8%], respectively). By PT, none of the AEs were reported with significantly higher incidence in any of the groups.

By PT, the most frequently reported grade 3 unsolicited AEs (i.e., reported in ≥1.0% of subjects in any of the groups in any of the studies) were (Source: Appendix Tables 44, 45, 46, and 47).

- Neutropenia in ZOSTER-002 (10 subjects [1.1%] in the HZ/su group and 4 [0.4%] in the Placebo group), ZOSTER-028 (3 [2.6%] in both groups), and ZOSTER-039 (none in the HZ/su group and 3 [1.1%] in the Placebo group).

- Febrile neutropenia in ZOSTER-028 (4 [3.4%] and 2 [1.7%], respectively) and ZOSTER-039 (4 [1.4%] and 1 [0.4%], respectively).

- Acute kidney injury in ZOSTER-028 (none in the HZ/su group and 2 [1.7%] in the Placebo group);

- Acute myeloid leukemia in ZOSTER-039 (1 [0.4%] and 4 [1.4%], respectively).

In all pivotal studies, the percentage of subjects reporting the occurrence of at least 1 unsolicited AE with a medically attended visit was within the same range in the HZ/su and Placebo group (Source: Appendix Tables 48, 49, 50, and 51).

Incidences of unsolicited AEs by SOC and PT were within the same range in both age strata, except for the SOCs of Musculoskeletal and connective tissue disorders (18-49 YOA: 4 [1.7%] [95% CI: 0.5%, 4.4%]; ≥50 YOA: 45 [6.5%] [95% CI: 4.8%, 8.6%]) and Nervous system disorders (18-49 YOA: 1 [0.4%] [95% CI: 0.0%, 2.4%]; ≥50 YOA: 37 [5.3%] [95% CI: 3.8%, 7.3%]) in ZOSTER-002, which were reported more frequently in the ≥50 YOA stratum. Across the pivotal studies, in the Placebo groups, incidences between the age strata were within the same range, except for the PT of alopecia in ZOSTER-028 (18-49 YOA: 13 [43.3%] [95% CI: 25.5%, 62.6%]; ≥50 YOA: 10 [11.8%] [95% CI: 5.8%, 20.6%]). By SOC and PT, the incidence of grade 3 unsolicited AEs and MAEs was also within the same range in the HZ/su and Placebo group in all pivotal studies.

Unsolicited adverse events considered related to vaccination

Across the pivotal studies, the percentage of subjects reporting the occurrence of at least 1 unsolicited AE with causal relationship to vaccination as per investigator assessment within the 30-day post-vaccination period ranged between 3.4% and 8.5% in the HZ/su groups and between 1.8% and 7.8% in the Placebo groups. In each pivotal study, the incidence of related AEs was within the same range in both groups (Table 88). In both groups in all pivotal studies, related unsolicited AEs were mainly reported under the SOC of General disorders and administration site conditions (range in the HZ/su group: 1.5%-4.6%; range in the Placebo group: 0.6%-6.1%). By PT, each related unsolicited AE was reported in at most 1.0% of subjects per study group, except for injection site pruritus, reported in 2 subjects (1.7%) in the HZ/su group of ZOSTER-028 and 4 (1.4%) in the HZ/su group of ZOSTER-039 (while not reported in the Placebo groups of these studies), and asthenia and injection site pain reported in 2 (1.7%) in the HZ/su group of ZOSTER-028 (none in Placebo) (Source: Appendix Tables 64, 65, 66, and 67). In all pivotal studies, the incidence of grade 3 related unsolicited AEs was low and within the same range in the HZ/su and Placebo group. No grade 3 related AEs were reported in the Placebo group of ZOSTER-028, ZOSTER-039, and ZOSTER-041 (Source: Appendix Tables 68, 69, 70, and 71).

Table 88: Pivotal studies: Percentage of subjects reporting the occurrence of unsolicited (serious and non-serious) adverse events classified by MedDRA Primary System Organ Class with causal relationship to vaccination, within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

	ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
	HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
			95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	31	3.4	2.3	4.7	23	2.5	1.6	3.7	10	8.5	4.2	15.2	9	7.8	3.6	14.3	19	6.7	4.1	10.3	5	1.8	0.6	4.1	7	5.3	2.2	10.6	3	2.3	0.5	6.5
Blood and lymphatic system disorders (10005329)	5	0.5	0.2	1.3	3	0.3	0.1	0.9	0	0.0	0.0	3.1	1	0.9	0.0	4.7	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
Cardiac disorders (10007541)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	1	0.9	0.0	4.7	1	0.9	0.0	4.7	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
Gastrointestinal disorders (10017947)	1	0.1	0.0	0.6	5	0.5	0.2	1.3	1	0.9	0.0	4.7	0	0.0	0.0	3.2	2	0.7	0.1	2.5	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
General disorders and administration site conditions (10018065)	14	1.5	0.8	2.5	6	0.6	0.2	1.4	5	4.3	1.4	9.7	7	6.1	2.5	12.1	13	4.6	2.5	7.7	2	0.7	0.1	2.6	5	3.8	1.2	8.6	1	0.8	0.0	4.1
Infections and infestations (10021881)	1	0.1	0.0	0.6	3	0.3	0.1	0.9	2	1.7	0.2	6.0	0	0.0	0.0	3.2	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Investigations (10022891)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	0	0.0	0.0	3.1	1	0.9	0.0	4.7	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders (10028395)	2	0.2	0.0	0.8	1	0.1	0.0	0.6	1	0.9	0.0	4.7	1	0.9	0.0	4.7	5	1.8	0.6	4.1	0	0.0	0.0	1.3	2	1.5	0.2	5.4	0	0.0	0.0	2.8
Nervous system disorders (10029205)	0	0.0	0.0	0.4	3	0.3	0.1	0.9	1	0.9	0.0	4.7	1	0.9	0.0	4.7	1	0.4	0.0	2.0	3	1.1	0.2	3.1	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Respiratory, thoracic and mediastinal disorders (10038738)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders (10040785)	8	0.9	0.4	1.7	5	0.5	0.2	1.3	1	0.9	0.0	4.7	2	1.7	0.2	6.1	-	-	-	-	-	-	-	-	1	0.8	0.0	4.1	0	0.0	0.0	2.8
Vascular disorders (10047065)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Source: Appendix Tables 64, 65, 66, and 67

Serious adverse event/deaths/other significant events

- **Serious adverse events**

Serious adverse events from first vaccination up to 30 days post last vaccination:

Across the pivotal studies, the percentage of subjects reporting the occurrence of at least 1 SAE from first vaccination up to 30 days post last vaccination ranged between 4.5% and 13.7% in the HZ/su groups and between 3.8% and 12.2% in the Placebo groups. In each pivotal study, the incidence of SAEs was within the same range in both groups (Table 89).

Table 89: Pivotal studies: Percentage of subjects reporting the occurrence of serious adverse events classified by MedDRA Primary System Organ Class from first vaccination up to 30 days post last vaccination (Total Vaccinated Cohort)

	ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
	HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
			95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	68	7.4	5.8	9.3	66	7.1	5.6	9.0	16	13.7	8.0	21.3	14	12.2	6.8	19.6	17	6.0	3.5	9.4	29	10.4	7.1	14.6	6	4.5	1.7	9.6	5	3.8	1.2	8.6
Blood and lymphatic system disorders (10005329)	6	0.7	0.2	1.4	6	0.6	0.2	1.4	4	3.4	0.9	8.5	5	4.3	1.4	9.9	8	2.8	1.2	5.5	4	1.4	0.4	3.6	-	-	-	-	-	-	-	-
Cardiac disorders (10007541)	3	0.3	0.1	0.9	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
Ear and labyrinth disorders (10013993)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Eye disorders (10015919)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal disorders (10017947)	2	0.2	0.0	0.8	3	0.3	0.1	0.9	0	0.0	0.0	3.1	1	0.9	0.0	4.7	1	0.4	0.0	2.0	2	0.7	0.1	2.6	1	0.8	0.0	4.1	0	0.0	0.0	2.8
General disorders and administration site conditions (10018065)	3	0.3	0.1	0.9	1	0.1	0.0	0.6	1	0.9	0.0	4.7	1	0.9	0.0	4.7	0	0.0	0.0	1.3	3	1.1	0.2	3.1	-	-	-	-	-	-	-	-
Hepatobiliary disorders (10019805)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Immune system disorders (10021428)	-	-	-	-	-	-	-	-	0	0.0	0.0	3.1	1	0.9	0.0	4.7	1	0.4	0.0	2.0	3	1.1	0.2	3.1								
Infections and infestations (10021881)	22	2.4	1.5	3.6	24	2.6	1.7	3.8	7	6.0	2.4	11.9	5	4.3	1.4	9.9	9	3.2	1.5	6.0	8	2.9	1.2	5.6	5	3.8	1.2	8.6	1	0.8	0.0	4.1
Injury, poisoning and procedural complications (10022117)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	1	0.9	0.0	4.7	0	0.0	0.0	3.2	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
Investigations (10022891)	0	0.0	0.0	0.4	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Metabolism and nutrition disorders (10027433)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Musculoskeletal and connective tissue disorders (10028395)	1	0.1	0.0	0.6	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	24	2.6	1.7	3.8	28	3.0	2.0	4.4	1	0.9	0.0	4.7	1	0.9	0.0	4.7	2	0.7	0.1	2.5	9	3.2	1.5	6.0	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Nervous system disorders (10029205)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	2	1.7	0.2	6.0	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Renal and urinary disorders (10038359)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	0	0.0	0.0	3.1	2	1.7	0.2	6.1	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.2	0.0	0.8	4	0.4	0.1	1.1	1	0.9	0.0	4.7	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders (10040785)	1	0.1	0.0	0.6	2	0.2	0.0	0.8	0	0.0	0.0	3.1	2	1.7	0.2	6.1	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
Surgical and medical procedures (10042613)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
Vascular disorders (10047065)	1	0.1	0.0	0.6	0	0.0	0.0	0.4		1	0.9	0.0	4.7	0	0.0	0.0	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-

Source: Appendix Tables 80, 81, 82, and 83

For each pivotal study, a summarizing description is provided below, which presents the PTs that were reported in ≥1.0% of subjects in any of the groups (Source: Appendix Tables 80, 81, 82, and 83).

In ZOSTER-002, the most frequently reported SOCs in both groups were Neoplasms benign, malignant, and unspecified (including cysts and polyps) and Infections and infestations. By PT, events reported in ≥ 1.0% of subjects in any of the groups were pneumonia (reported in 12 subjects [1.3%] in the HZ/su group and 7 [0.8%] in the Placebo group) and plasma cell myeloma (6 [0.7%] and 9 [1.0%], respectively).

In ZOSTER-028, the most frequently reported SOCs in both groups were Infections and infestations and Blood and lymphatic system disorders. By PT, events reported in ≥1.0% of subjects in any of the groups were febrile neutropenia (reported in 4 subjects [3.4%] in the HZ/su group and 2 [1.7%] in the Placebo group), sepsis (2 [1.7%] and none, respectively), acute kidney injury (none and 2 [1.7%], respectively), and anemia (none and 2 [1.7%], respectively).

In ZOSTER-039, the most frequently reported SOCs in both groups were Infections and infestations and Blood and lymphatic system disorders. By PT, events reported in ≥1.0% of subjects in any of the groups were febrile neutropenia (reported in 7 subjects [2.5%] in the HZ/su group and 2 [0.7%] in the Placebo group), pneumonia (5 [1.8%] and none, respectively), acute myeloid leukemia (1 [0.4%] and 3 [1.1%], respectively), and plasma cell myeloma (1 [0.4%] and 3 [1.1%], respectively).

In ZOSTER-041, the most frequently reported SOC in both groups was Infections and infestations. By PT, pyelonephritis acute (reported in 2 subjects [1.5%] in the HZ/su group and 1 [0.8%] in the Placebo group) was the only event reported in ≥1.0% of subjects in any of the groups.

For the PTs pneumonia and febrile neutropenia (for which there was a numerical imbalance in absolute numbers heeling over to the HZ/su group in ZOSTER-002, ZOSTER-028, and ZOSTER-039), data are discussed below.

Across the pivotal studies, 4 SAEs were considered as causally related to vaccination by the investigator (all reported in ZOSTER-002): (i) -Neutropenia, reported in 1 subject (0.1%) in the HZ/su group; (ii) Constipation, HZ, and toxic skin eruption, each reported in 1 subject (0.1%) in the Placebo group.

Serious adverse events from first vaccination up to 12 months post last vaccination:

Across the pivotal studies, the percentage of subjects reporting the occurrence of at least 1 SAE from first vaccination up to 12 months post last vaccination ranged between 19.7% and 30.8% in the HZ/su groups and between 25.0% and 36.5% in the Placebo groups. In each pivotal study, the incidence of SAEs was within the same range in both groups (Source Table 19 SCS).

The most frequently reported SOCs in both groups in ZOSTER-002, ZOSTER-028, and ZOSTER-039 were Infections and infestations (range in the HZ/su group: 11.8%-14.1%; range in the Placebo group: 11.7%-13.0%) and Neoplasms benign, malignant, and unspecified (including cysts and polyps) (range of 6.0%-14.5% in the HZ/su group and 10.4%-11.8% in the Placebo group). In ZOSTER-041, Infections and infestations was the most frequently reported SOC in both groups (13.6% in the HZ/su group and 10.6% in the Placebo group).

The most frequently reported PTs (i.e., in ≥3.0% of subjects in any of the groups) were the following:

-In ZOSTER-002: plasma cell myeloma (59 [6.4%] in the HZ/su group and 41 [4.4%] in the Placebo group) and pneumonia (42 [4.6%] and 30 [3.2%], respectively).

-In ZOSTER-028: febrile neutropenia (5 [4.3%] and 2 [1.7%], respectively) and neutropenia (2 [1.7%] and 4 [3.5%], respectively).

-In ZOSTER-039: febrile neutropenia (14 [4.9%] and 11 [3.9%], respectively) and pneumonia (10 [3.5%] and 10 [3.6%], respectively).

-In ZOSTER-041: pyelonephritis acute (4 [3.0%] and 1 [0.8%], respectively), gastroenteritis (2 [1.5%] and 4 [3.0%], respectively), transplant rejection (2 [1.5%] and 4 [3.0]%, respectively), and HZ (none and 4 [3.0%], respectively).

An exploratory group comparison was performed to investigate the RR of developing SAEs within the 365-day post-vaccination period for both SOCs and PTs, in subjects that received HZ/su as compared to subjects receiving placebo. In ZOSTER-002, ZOSTER-028 and ZOSTER-041, none of the SAEs were reported with significantly higher incidence in any of the groups. In ZOSTER-039, the SOC of Gastrointestinal disorders was reported with significantly lower incidence in the HZ/su group compared to the Placebo group, with an RR of 0.20 (95% CI: 0.02, 0.93; p-value: 0.0363).

SAEs considered as causally related to vaccination by the investigator from first vaccination up to 12 months post last vaccination are presented in Table 90. In ZOSTER-028, no related SAEs were reported.

Table 90: Pivotal studies: Percentage of subjects reporting the occurrence of serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, from first vaccination up to 12 months post last vaccination (Total Vaccinated Cohort)

		ZOSTER-002*								ZOSTER-039								ZOSTER-041							
		HZ/su N = 922				Placebo N = 924				HZ/su N = 283				Placebo N = 279				HZ/su N = 132				Placebo N = 132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		3	0.3	0.1	0.9	4	0.4	0.1	1.1	1	0.4	0.0	2.0	1	0.4	0.0	2.0	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Blood and lymphatic system disorders (10005329)	At least one PT related to the corresponding SOC	2	0.2	0.0	0.8	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
	Febrile neutropenia (10016288)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
	Immune thrombocytopenic purpura (10074667)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Neutropenia (10029354)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiac disorders (10007541)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Atrial fibrillation (10003658)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal disorders (10017947)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Constipation (10010774)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
General disorders and administration site conditions (10018065)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
	Death neonatal (10011912)	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
	Mucosal inflammation (10028116)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Infections and infestations (10021881)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.4	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Herpes zoster (10019974)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Herpes zoster cutaneous disseminated (10074297)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Musculoskeletal and connective tissue disorders (10028395)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Arthralgia (10003239)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nervous system disorders (10029205)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Guillain-Barre syndrome (10018767)	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
	Burkitt's lymphoma (10006595)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	2.8	1	0.8	0.0	4.1
Skin and subcutaneous tissue disorders (10040785)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Cutaneous vasculitis (10011686)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Toxic skin eruption (10057970)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

- **Fatal serious adverse events**

Fatal serious adverse events from first vaccination up to 30 days post last vaccination:

Across the pivotal studies, the percentage of subjects with at least 1 fatal SAE from first vaccination up to 30 days post last vaccination ranged between 0.7% and 2.6% in the HZ/su groups and between 0.0%

and 3.2% in the Placebo groups. In each pivotal study, the incidence of fatal SAEs was within the same range in both groups (Table 91).

Table 91: Pivotal studies: Percentage of subjects reporting the occurrence of fatal serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term from first vaccination up to 30 days post last vaccination (Total Vaccinated Cohort)

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		20	2.2	1.3	3.3	19	2.1	1.2	3.2	3	2.6	0.5	7.3	2	1.7	0.2	6.1	2	0.7	0.1	2.5	9	3.2	1.5	6.0	1	0.8	0.0	4.1	0	0.0	0.0	2.8
Blood and lymphatic system disorders (10005329)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
	Thrombocytopenia (10043554)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
Cardiac disorders (10007541)	At least one PT related to the corresponding SOC	2	0.2	0.0	0.8	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Cardiac failure (10007554)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Cardiac failure congestive (10007559)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
Immune system disorders (10021428)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Anaphylactic shock (10002199)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
Infections and infestations (10021881)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.4	3	0.3	0.1	0.9	1	0.9	0.0	4.7	0	0.0	0.0	3.2	-	-	-	-	-	-	-	-	1	0.8	0.0	4.1	0	0.0	0.0	2.8
	Meningitis (10027199)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.8	0.0	4.1	0	0.0	0.0	2.8
	Pneumonia (10035664)	0	0.0	0.0	0.4	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Sepsis (10040047)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	1	0.9	0.0	4.7	0	0.0	0.0	3.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Investigations (10022891)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Transaminases increased (10054889)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	At least one PT related to the corresponding SOC	18	2.0	1.2	3.1	17	1.8	1.1	2.9	1	0.9	0.0	4.7	0	0.0	0.0	3.2	2	0.7	0.1	2.5	6	2.2	0.8	4.6	-	-	-	-	-	-	-	-
	Acute myeloid leukaemia (10000880)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	3	1.1	0.2	3.1	-	-	-	-	-	-	-	-
	Adenocarcinoma of colon (10001167)	-	-	-	-	-	-	-	-	1	0.9	0.0	4.7	0	0.0	0.0	3.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	B-cell lymphoma (10003899)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Central nervous system lymphoma (10007953)	2	0.2	0.0	0.8	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Diffuse large b-cell lymphoma (10012818)	2	0.2	0.0	0.8	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Hodgkin's disease (10020206)	2	0.2	0.0	0.8	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Lymphoma (10025310)	1	0.1	0.0	0.6	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Mantle cell lymphoma (10061275)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Metastases to meninges (10051696)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Myeloid leukaemia (10028549)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Non-Hodgkin's lymphoma (10029547)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Peripheral t-cell lymphoma unspecified (10034623)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Plasma cell leukaemia (10035222)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Plasma cell myeloma (10035226)	4	0.4	0.1	1.1	7	0.8	0.3	1.6	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	2	0.7	0.1	2.6	-	-	-	-	-	-	-	-

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Precursor t-lymphoblastic lymphoma/leukaemia (10036543)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	T-cell lymphoma (10042971)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nervous system disorders (10029205)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	1	0.9	0.0	4.7	0	0.0	0.0	3.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Hepatic encephalopathy (10019660)	-	-	-	-	-	-	-	-	1	0.9	0.0	4.7	0	0.0	0.0	3.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders (10038738)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	0	0.0	0.0	3.1	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Pleural effusion (10035598)	-	-	-	-	-	-	-	-	0	0.0	0.0	3.1	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders (10040785)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	0	0.0	0.0	3.1	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Skin haemorrhage (10064265)	-	-	-	-	-	-	-	-	0	0.0	0.0	3.1	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vascular disorders (10047065)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Embolism (10061169)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-

Source: Appendix Tables 108, 109, 110, and 111

The most frequently reported SOC in both groups was Neoplasms benign, malignant, and unspecified (including cysts and polyps). None of the reported deaths was considered causally related to vaccination as per investigator assessment.

Fatal serious adverse events from first vaccination up to 12 months post last vaccination:

Across the pivotal studies, the percentage of subjects with at least 1 fatal SAE from first vaccination up to 12 months post last vaccination ranged between 0.8% and 10.3% in the HZ/su groups and between 0.8% and 13.3% in the Placebo groups. In each pivotal study, the incidence of fatal SAEs was within the same range in both groups. In all pivotal studies except ZOSTER-041, the most frequently reported SOCs in both groups were Neoplasms benign, malignant, and unspecified (including cysts and polyps) and Infections and infestations. None of the deaths reported in subjects participating in the study was considered causally related to vaccination as per investigator assessment.

Of note, in ZOSTER-039, an event of neonatal death was reported as causally related to vaccination by the investigator. This event occurred in the offspring of a subject who was exposed to HZ/su 48 days prior to estimated pregnancy onset (pregnancy onset = last menstrual period + 14 days). The baby was born at 36 weeks of gestation and died 30 minutes after birth due to breathing difficulty. Obstetric ultrasounds during pregnancy showed normal fetal development. No additional details (Apgar score, length, and weight of the baby) are available and no autopsy was done. The mother was treated with chemotherapy (vinblastine, bleomycin, doxorubicin, dacarbazine) before pregnancy for her underlying malignancy. The investigator's initial assessment was that a possible cause of the neonatal death could be due to chemotherapy received for the underlying lymphoma. However, since the subject received the second dose of HZ/su just prior to her pregnancy onset, the investigator also assessed that a causal role of the vaccine for this SAE could not be excluded. The MAH considered that the causal association with the vaccine was unlikely and the event of early neonatal death was more likely related to perinatal causes such as respiratory distress syndrome due to perinatal asphyxia/hypoxia or infection rather than medications received before the pregnancy onset.

- **Other significant adverse events**

Adverse events leading to premature discontinuation of study vaccine and/or study:

In all pivotal studies, there were no apparent differences between the HZ/su and the Placebo group in the percentage of subjects who were withdrawn from the study or treatment up to 12 months post last vaccination (Table 92).

Table 92: Pivotal studies: Adverse events leading to premature discontinuation of study vaccine and/or study from first vaccination up to 12 months post last vaccination (Total Vaccinated Cohort)

	ZOSTER-002				ZOSTER-028				ZOSTER-039				ZOSTER-041			
	HZ/su N=922		Placebo N=924		HZ/su N=117		Placebo N=115		HZ/su N=283		Placebo N=279		HZ/su N=132		Placebo N=132	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Number of subjects withdrawn from study or treatment due to an (S)AE	85	9.2	86	9.3	15	12.8	12	10.4	30	10.6	41	14.7	4	3.0	2	1.5
Number of subjects withdrawn from study due to:																
An SAE	65	7.0	67	7.3	13	11.1	12	10.4	26	9.2	35	12.5	1	0.8	1	0.8
A fatal SAE	53	5.7	56	6.1	12	10.3	11	9.6	25	8.8	35	12.5	1	0.8	1	0.8
A non-serious AE	14	1.5	14	1.5	0	0.0	0	0.0	4	1.4	4	1.4	1	0.8	0	0.0
Number of subjects who did not receive the second vaccination due to an (S)AE but remained in the study	6	0.7	5	0.5	2	1.7	0	0.0	0	0.0	2	0.7	2	1.5	1	0.8

Source: Module 5, ZOSTER-002 CSR Amendment 1, Table 10.226; ZOSTER-028 CSR Amendment 1, Table 8.269; ZOSTER-039 CSR Amendment 1, Table 10.184, ZOSTER-041 CSR Amendment 1, Table 8.257

The following (S)AEs that led to premature discontinuation of treatment (i.e., subject did not receive the second vaccination but remained in the study) were considered causally related to vaccination by the investigator. In ZOSTER-002, 1 subject in the HZ/su group experienced a non-serious pIMD of psoriasis aggravated on Day 12 post-Dose 1. The event was recovered/resolved 142 days later. In ZOSTER-002, 1 subject in the Placebo group experienced a non-serious event of discoid eczema on Day 35 post-Dose 1. The outcome was not recovered/not resolved (status at the last follow-up before withdrawal). In ZOSTER-028, 1 subject in the HZ/su group experienced a non-serious event of tachycardia on the day of vaccination with Dose 1 (Day 0). The event was recovered/resolved the same day. In ZOSTER-041, 1 subject in the HZ/su group experienced a non-serious solicited symptom of fever on the day after the day of vaccination with Dose 1 (Day 1). The event was recovered/resolved 30 days later.

The following (S)AEs that led to premature discontinuation of the study were considered as causally related to vaccination by the investigator. In ZOSTER-002, 1 subject in the HZ/su group experienced a non-serious AE of myalgia (related as per investigator) on Day 21 post-Dose 1 and a non-serious AE of Hodgkin's lymphoma (unrelated as per investigator; relapse of underlying disease) on Day 56 post-Dose 1. This subject did not receive the second vaccination due to the AE of myalgia and was withdrawn from the study due to the AE of Hodgkin's lymphoma. The event of myalgia was recovered/resolved 36 days after onset, while the Hodgkin's lymphoma was not recovered/not resolved (status at the last follow-up before withdrawal). In ZOSTER-002, 1 subject in the HZ/su group was withdrawn from the study due to a non-serious event of neutropenia on Day 32 post-Dose 1, which was not recovered/not resolved (status at the last follow-up before withdrawal). In ZOSTER-002, 1 subject in the Placebo group was withdrawn from the study due to a serious event of generalized toxic skin exanthema on the day of vaccination with Dose 1 (Day 0), which was recovered/resolved 7 days later.

Potentially immune-mediated diseases:

Potentially immune-mediated diseases from first vaccination up to 30 days post last vaccination:

From first vaccination up to 30 days post last vaccination, pIMDs were reported by subjects participating in ZOSTER-002 and ZOSTER-039, as displayed in Table 93. In ZOSTER-002, 4 subjects (0.4%) in the HZ/su group and 2 (0.2%) in the Placebo group experienced a pIMD. In the HZ/su group, 3 of the 4

events were serious (PTs: autoimmune hemolytic anemia, interstitial lung disease, and psoriasis) and none of these 3 were considered related to vaccination as per investigator assessment. The other event (PT: psoriasis; pre-existing psoriasis reported as 'psoriasis aggravated') was not serious and considered related to vaccination as per investigator assessment. Both events in the Placebo group were not serious and not considered causally related to vaccination by the investigator. In ZOSTER-039, 1 subject (0.4%) in the HZ/su group reported an event of gout (note that gout was added to the pre-defined list of specific disorders after study completion). This event was not serious and not considered causally related to vaccination by the investigator.

Table 93: Pivotal studies: Percentage of subjects reporting the occurrence of potentially immune-mediated diseases classified by MedDRA Primary System Organ Class and Preferred Term from first vaccination up to 30 days post last vaccination (Total Vaccinated Cohort)

		ZOSTER-002								ZOSTER-039							
		HZ/su N=922				Placebo N=924				HZ/su N=283				Placebo N=279			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		4	0.4	0.1	1.1	2	0.2	0.0	0.8	1	0.4	0.0	2.0	0	0.0	0.0	1.3
Blood and lymphatic system disorders (10005329)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-
	Autoimmune haemolytic anaemia (10073785)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-
Metabolism and nutrition disorders (10027433)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3
	Gout (10018627)	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3
Musculoskeletal and connective tissue disorders (10028395)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-
	Spondylitis (10061371)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders (10038738)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-
	Interstitial lung disease (10022611)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders (10040785)	At least one PT related to the corresponding SOC	2	0.2	0.0	0.8	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-
	Psoriasis (10037153)	2	0.2	0.0	0.8	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-

Source: Appendix Table 124

Potentially immune-mediated diseases from first vaccination up to 12 months post last vaccination:

Across the pivotal studies, the percentage of subjects reporting the occurrence of at least 1 pIMD from first vaccination up to 12 months post last vaccination ranged between 0.0% and 3.0% in the HZ/su groups and between 0.7% and 1.5% in the Placebo groups (Table 94).

The most frequently reported PTs (i.e., reported in ≥2 subjects in any study group) were the following:

- Psoriasis, reported in 2 subjects (0.2%) in the HZ/su group and 1 (0.1%) in the Placebo group in ZOSTER-002;

- Gout, reported in 1 subject (0.4%) in the HZ/su group in ZOSTER-039 and 2 (1.5%) in the HZ/su group in ZOSTER-041;

- IgA nephropathy, reported in 1 subject (0.8%) in the HZ/su group and 2 (1.5%) in the Placebo group in ZOSTER-041;

- Interstitial lung disease, reported in 1 subject (0.1%) in the HZ/su group and 2 (0.2%) in the Placebo group in ZOSTER-002;

In ZOSTER-002, in both the HZ/su and the Placebo group, the majority of pIMDs were serious.

In ZOSTER-028, 1 subject (0.9%) in the Placebo group reported a serious event of autoimmune thyroiditis.

In ZOSTER-039, in the HZ/su group, 1 event (erythema nodosum) was serious. In the Placebo group, the event of Guillain-Barré syndrome was serious.

In ZOSTER-041, none of the events were serious.

Table 94: Pivotal studies: Percentage of subjects reporting the occurrence of potentially immune-mediated diseases classified by MedDRA Primary System Organ Class and Preferred Term up to 12 months post last vaccination (Total Vaccinated Cohort)

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		13	1.4	0.8	2.4	8	0.9	0.4	1.7	0	0.0	0.0	3.1	1	0.9	0.0	4.7	3	1.1	0.2	3.1	2	0.7	0.1	2.6	4	3.0	0.8	7.6	2	1.5	0.2	5.4
Blood and lymphatic system disorders (10005329)	At least one PT related to the corresponding SOC	3	0.3	0.1	0.9	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Autoimmune haemolytic anaemia (10073785)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Autoimmune pancytopenia (10069509)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
	Histiocytosis haematophagic (10048595)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Immune thrombocytopenic purpura (10074667)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Endocrine disorders (10014698)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	0	0.0	0.0	0.4	0	0.0	0.0	3.1	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Autoimmune thyroiditis (10049046)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	0	0.0	0.0	3.1	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Infections and infestations (10021881)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Myelitis (10028524)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Metabolism and nutrition disorders (10027433)	At least one PT related to the corresponding SOC	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	3	2.3	0.5	6.5	0	0.0	0.0	2.8
	Gout (10018627)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	2	1.5	0.2	5.4	0	0.0	0.0	2.8
	Type 1 diabetes mellitus (10067584)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.8	0.0	4.1	0	0.0	0.0	2.8

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Musculoskeletal and connective tissue disorders (10028395)	At least one PT related to the corresponding SOC	2	0.2	0.0	0.8	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Arthralgia (10003239)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Polymyalgia rheumatica (10036099)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Spondylitis (10061371)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Systemic scleroderma (10078638)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nervous system disorders (10029205)	At least one PT related to the corresponding SOC	2	0.2	0.0	0.8	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Facial paralysis (10016062)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Guillain-Barre syndrome (10018767)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Optic neuritis (10030942)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Renal and urinary disorders (10038359)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.8	0.0	4.1	2	1.5	0.2	5.4
	IgA nephropathy (10021263)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.8	0.0	4.1	2	1.5	0.2	5.4
Respiratory, thoracic and mediastinal disorders (10038738)	At least one PT related to the corresponding SOC	1	0.1	0.0	0.6	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Interstitial lung disease (10022611)	1	0.1	0.0	0.6	2	0.2	0.0	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders (10040785)	At least one PT related to the corresponding SOC	4	0.4	0.1	1.1	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
	Cutaneous vasculitis (10011686)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Erythema nodosum (10015226)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
	Hypersensitivity vasculitis (10020764)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Psoriasis (10037153)	2	0.2	0.0	0.8	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note that Type 1 diabetes mellitus was miscoded since it was not reported as a pIMD following vaccination. The patient underwent planned pancreatic transplant as treatment for pre-existing Type 1 diabetes mellitus.
Source: Appendix Table 127

The following events were considered causally related to vaccination by the investigator from first vaccination up to 12 months post last vaccination:

- In ZOSTER-002, in the HZ/su group, 1 event of arthralgia, 1 event of cutaneous vasculitis (both reported in the same subject and serious), 1 event of psoriasis (not serious), and 1 event of immune thrombocytopenic purpura (serious);

- In ZOSTER-039, in the Placebo group, 1 event of Guillain Barré syndrome (serious).

- **Pregnancies**

In ZOSTER-002, during the entire study period, a total of 14 pregnancy outcomes were reported in 11 subjects (7 in the HZ/su group and 4 in the Placebo group). For all pregnancies, there was exposure to HZ/su or placebo before estimated pregnancy onset. In the HZ/su group, 7 pregnancies reported in 6 subjects resulted in live infants with no apparent congenital anomaly and 1 pregnancy outcome in 1 other subject was an elective termination for socio-economic reasons. In the Placebo group, 4 pregnancies reported in 4 subjects resulted in live infants with no apparent congenital anomaly. One of these subjects also reported 2 events of spontaneous abortion with no apparent congenital anomaly. Pregnancy onset for 3 subjects was within 1 year after exposure to HZ/su (2 subjects) or placebo (1 subject).

In ZOSTER-039, during the entire study period, there were 2 pregnancy reports in 1 subject in the HZ/su group. The subject was exposed to the second dose of HZ/su prior to estimated onset of both the first and the second pregnancy. Both pregnancies resulted in live infants with no apparent congenital anomalies at birth. However, for the first pregnancy, the infant was born at 36 weeks of gestation and died 30 minutes after birth due to breathing difficulty.

In ZOSTER-041, during the entire study period, there was 1 pregnancy reported in 1 subject in the Placebo group, which resulted in spontaneous abortion with no apparent congenital anomaly. The subject was exposed to placebo prior to estimated pregnancy onset.

- **Relapse cases during the entire study period (ZOSTER-002)**

In ZOSTER-002, the percentage of subjects reporting a relapse of their underlying disease during the entire study period was within the same range in the HZ/su and the Placebo group (25.9% in the HZ/su group and 27.4% in the Placebo group).

By PT, the incidence of the relapses of underlying diseases were within the same range in the HZ/su and the Placebo group. The most frequently reported PT was plasma cell myeloma (reported in 133 subjects [14.4%] in the HZ/su group and 143 [15.5%] in the Placebo group). Events reported in ≥1.0% of subjects in any treatment group included lymphoma (19 [2.1%] in the HZ/su group and 20 [2.2%] in the Placebo group), B-cell lymphoma (18 [2.0%] and 20 [2.2%], respectively), diffuse large B-cell lymphoma (16 [1.7%] and 13 [1.4%]), Hodgkin's disease (12 [1.3%] and 9 [1.0%]), and non-Hodgkin's lymphoma (5 [0.5%] and 11 [1.2%], respectively).

- **Disease progression during the entire study period (ZOSTER-002)**

In ZOSTER-002, the percentage of subjects with progression of their underlying disease during the entire study period was within the same range in the HZ/su and the Placebo group (8.8% in the HZ/su group and 8.9% in the Placebo group).

The incidences of disease progressions were within the same range in the HZ/su and Placebo group. The most frequently reported PT was plasma cell myeloma (reported in 65 subjects [7.0%] in the HZ/su group and 64 [6.9%] in the Placebo group).

- **Disease-related events from first vaccination up to study end (ZOSTER-039)**

In ZOSTER-039, the percentage of subjects reporting at least 1 DRE (i.e., a relapse case or progression of the underlying disease) from first vaccination up to study end was within the same range in the HZ/su and Placebo group (15.9% in the HZ/su group and 20.8% in the Placebo group).

By PT, the incidence of the DREs were within the same range in the HZ/su and the Placebo group. Events reported in ≥1.0% of subjects in any treatment group included plasma cell myeloma (reported in 12 subjects [4.2%] in the HZ/su group and 20 [7.2%] in the Placebo group), acute myeloid leukemia (7 [2.5%] and 16 [5.7%], respectively), chronic lymphocytic leukemia (4 [1.4%] and 4 [1.4%], respectively), pneumonia (4 [1.4%] and none, respectively), Hodgkin's disease (3 [1.1%] and 1 [0.4%], respectively), and B-cell lymphoma (2 [0.7%] and 3 [1.1%], respectively).

- **Renal allograft function from first vaccination up to study end (ZOSTER-041)**

To assess allograft function during the study, clinically obtained serum creatinine measurements were recorded in ZOSTER-041. From first vaccination up to study end, 20 subjects (15.3%) in the HZ/su group and 26 (19.7%) in the Placebo group had ≥1.20-fold increase in serum creatinine levels compared to baseline (i.e., ≥20% increase; a 20% margin allowed for daily fluctuations to not be interpreted as pathology). There were 4 (3.1%), 3 (2.3%), and 2 (1.5%) subjects in the HZ/su group and 4 (3.0%), 2 (1.5%), and 1 (0.8%) in the Placebo group who had ≥1.50-, ≥1.75-, and ≥2-fold increases, respectively.

In the HZ/su group, 16 subjects (12.1%) had renal biopsies, of whom 4 (3.0%) were positive for allograft rejection (biopsy-proven rejection). In total, 3 of the 4 biopsy-proven rejections occurred in subjects with medium-high rejection risk as defined by their calculated panel-reactive antibody (cPRA) scores. In the Placebo group, 23 subjects (17.4%) had renal biopsies, of whom 7 (5.3%) were positive for allograft rejection. The 7 biopsy-proven rejections occurred in subjects with low rejection risk based on cPRA scores.

Of the subjects with biopsy-proven allograft rejection, 1 HZ/su recipient reported to the study site with acute symptoms of renal allograft dysfunction (i.e., for this subject, the diagnosis of the alloimmune response was clinically indicated), had a ≥2-fold increase in serum creatinine levels, and a biopsy-proven

rejection. For all other subjects, allograft biopsies were performed per study site's surveillance protocol (i.e., not clinically indicated).

- **Other events of medical interest reported as unsolicited adverse events within the 30-day post-vaccination period**

The percentage of subjects reporting the occurrence of additional events of medical interest as AE within the 30-day post-vaccination period is described in this section.

Agranulocytosis and hematopoietic cytopenias:

Across the pivotal studies, the percentage of subjects reporting the occurrence of at least 1 AE associated with agranulocytosis or hematopoietic cytopenia ranged between 0.8% and 17.9% in the HZ/su groups and between 0.0% and 16.5% in the Placebo groups. In each pivotal study, the incidence was within the same range in both groups. By PT, incidences were within the same range as well (Table 95).

Table 95: Pivotal studies: Percentage of subjects reporting the occurrence of unsolicited Agranulocytosis and Haematopoietic cytopenia events classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		42	4.6	3.3	6.1	36	3.9	2.7	5.4	21	17.9	11.5	26.1	19	16.5	10.3	24.6	16	5.7	3.3	9.0	13	4.7	2.5	7.8	1	0.8	0.0	4.1	0	0.0	0.0	2.8
Blood and lymphatic system disorders (10005329)	At least one PT related to the corresponding SOC	38	4.1	2.9	5.6	35	3.8	2.7	5.2	19	16.2	10.1	24.2	18	15.7	9.5	23.6	15	5.3	3.0	8.6	10	3.6	1.7	6.5	1	0.8	0.0	4.1	0	0.0	0.0	2.8
	Agranulocytosis (10001507)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Bone marrow failure (10065553)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Febrile neutropenia (10016288)	2	0.2	0.0	0.8	3	0.3	0.1	0.9	4	3.4	0.9	8.5	2	1.7	0.2	6.1	8	2.8	1.2	5.5	2	0.7	0.1	2.6	-	-	-	-	-	-	-	-
	Leukopenia (10024384)	4	0.4	0.1	1.1	0	0.0	0.0	0.4	1	0.9	0.0	4.7	0	0.0	0.0	3.2	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Lymphopenia (10025327)	3	0.3	0.1	0.9	1	0.1	0.0	0.6	1	0.9	0.0	4.7	0	0.0	0.0	3.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Neutropenia (10029354)	24	2.6	1.7	3.8	25	2.7	1.8	4.0	11	9.4	4.8	16.2	15	13.0	7.5	20.6	4	1.4	0.4	3.6	6	2.2	0.8	4.6	1	0.8	0.0	4.1	0	0.0	0.0	2.8
	Pancytopenia (10033661)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	2	0.7	0.1	2.5	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Thrombocytopenia (10043554)	6	0.7	0.2	1.4	4	0.4	0.1	1.1	5	4.3	1.4	9.7	3	2.6	0.5	7.4	2	0.7	0.1	2.5	2	0.7	0.1	2.6	-	-	-	-	-	-	-	-
Infections and infestations (10021881)	At least one PT related to the corresponding SOC	-	-	-	-	-	-	-	-	1	0.9	0.0	4.7	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Neutropenic sepsis (10049151)	-	-	-	-	-	-	-	-	1	0.9	0.0	4.7	1	0.9	0.0	4.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Investigations (10022891)	At least one PT related to the corresponding SOC	4	0.4	0.1	1.1	1	0.1	0.0	0.6	1	0.9	0.0	4.7	0	0.0	0.0	3.2	1	0.4	0.0	2.0	3	1.1	0.2	3.1	-	-	-	-	-	-	-	-
	Neutrophil count decreased (10029366)	4	0.4	0.1	1.1	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	2	0.7	0.1	2.6	-	-	-	-	-	-	-	-
	Platelet count decreased (10035528)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	1	0.9	0.0	4.7	0	0.0	0.0	3.2	1	0.4	0.0	2.0	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	White blood cell count decreased (10047942)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-

Source: ZOSTER-002 Additional Analysis; ZOSTER-028 Additional Analysis, ZOSTER-039 Additional Analysis; ZOSTER-041 Additional Analysis

Anaphylactic reactions:

In ZOSTER-039, 1 AE of anaphylactic shock was reported in 1 subject (0.4%) in the Placebo group. In all other pivotal studies, no events of anaphylactic reaction were reported.

Hemorrhagic and ischemic cerebrovascular conditions:

No AEs of hemorrhagic or ischemic cerebrovascular conditions were reported in any of the pivotal studies.

Infective pneumonia:

Across the pivotal studies, the percentage of subjects reporting the occurrence of at least 1 AE associated with infective pneumonia ranged between 0.0% and 2.6% in the HZ/su groups and between 0.0% and 1.4% in the Placebo groups. In each pivotal study, the incidence was within the same range in both groups. When considering the other reported PTs, incidences were within the same range in the HZ/su group and the Placebo group.

Table 96: Pivotal studies: Percentage of subjects reporting the occurrence of unsolicited Infective pneumonia events classified by MedDRA Primary System Organ Class and Preferred Term within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

		ZOSTER-002								ZOSTER-028								ZOSTER-039								ZOSTER-041							
		HZ/su N=922				Placebo N=924				HZ/su N=117				Placebo N=115				HZ/su N=283				Placebo N=279				HZ/su N=132				Placebo N=132			
				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI				95% CI			
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		17	1.8	1.1	2.9	10	1.1	0.5	2.0	3	2.6	0.5	7.3	0	0.0	0.0	3.2	4	1.4	0.4	3.6	4	1.4	0.4	3.6	-	-	-	-	-	-	-	-
Infections and infestations (10021881)	At least one PT related to the corresponding SOC	17	1.8	1.1	2.9	10	1.1	0.5	2.0	3	2.6	0.5	7.3	0	0.0	0.0	3.2	4	1.4	0.4	3.6	4	1.4	0.4	3.6	-	-	-	-	-	-	-	-
	Bronchopulmonary aspergillosis (10006473)	1	0.1	0.0	0.6	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	1	0.4	0.0	2.0	0	0.0	0.0	1.3	-	-	-	-	-	-	-	-
	Lung infection (10061229)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Pneumocystis jirovecii pneumonia (10073755)	2	0.2	0.0	0.8	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Pneumonia (10035664)	13	1.4	0.8	2.4	6	0.6	0.2	1.4	3	2.6	0.5	7.3	0	0.0	0.0	3.2	3	1.1	0.2	3.1	2	0.7	0.1	2.6	-	-	-	-	-	-	-	-
	Pneumonia bacterial (10060946)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0.0	0.0	1.3	1	0.4	0.0	2.0	-	-	-	-	-	-	-	-
	Pneumonia fungal (10061354)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Pneumonia pneumococcal (10035728)	0	0.0	0.0	0.4	1	0.1	0.0	0.6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Pneumonia pseudomonal (10035731)	1	0.1	0.0	0.6	0	0.0	0.0	0.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Source: ZOSTER-002 Additional Analysis; ZOSTER-028 Additional Analysis, ZOSTER-039 Additional Analysis; ZOSTER-041 Additional Analysis

Upper respiratory tract infection:

Across the pivotal studies, the percentage of subjects reporting the occurrence of at least 1 SAE associated with upper respiratory tract infection ranged between 0.7% and 1.7% in the HZ/su groups and between 0.0% and 0.9% in the Placebo groups. In each pivotal study, the incidence was within the same range in both groups. By PT, incidences were within the same range as well.

Serious ocular complications that may be due to vasculitis or inflammation:

No SAEs associated with ocular complications were reported in any of the pivotal studies.

Laboratory findings

In the pivotal studies, in the absence of a diagnosis, abnormal laboratory findings or other abnormal assessments that were judged by the investigator to be clinically significant were recorded as AE or SAE if they met the definition.

In ZOSTER-041, clinically obtained serum creatinine measures were recorded throughout the study to assess allograft function.

For ZOSTER-001 and ZOSTER-015, details on the biochemical and haematological values for the selected parameters with respect to normal ranges and the changes from baseline are tabulated.

In ZOSTER-001, at each time point in all 4 groups, subjects had analyte results generally within the normal range with the exception of red blood cell count, hemoglobin, and hematocrit for which the majority of subjects in all groups were below the reference range at most time points including pre-vaccination. This finding was considered most likely due to the disease state of the subjects.

In ZOSTER-015, over 70% of subjects in both the gE/AS01B and the Placebo group had values of hematological and biochemical parameters within the normal range at all time points.

No safety concerns arose from abnormal laboratory findings or other abnormal assessments in the 6 studies.

Post marketing experience

From the time of first approval of Shingrix in the US (13 October 2017) until 12 April 2019 (data lock point of the current Periodic Benefit Risk Evaluation Report (PBRER), dated 14 June 2019), it is estimated that 11 636 236 doses have been distributed worldwide. As vaccination with Shingrix could vary between 1 and 2 doses per subject depending on the compliance with the vaccination schedule, post-approval exposure to Shingrix is estimated to be between 5 818 118 and 11 636 236 subjects.

Safety information received since licensure has been regularly reviewed by the GSK Vaccines Clinical Safety and Pharmacovigilance Department. The spontaneous reports received since launch of Shingrix are generally consistent with what has been observed in the clinical trials and the information provided in the Reference Safety Information for Shingrix. Most AEs reported are adverse reactions that are anticipated and consistent with the reactogenicity profile of the vaccine. The data on important risks has remained unchanged since marketing authorisation was granted. Additionally, there have been no new data from studies in adults suggesting that efficacy is lower than that described in the submission dossiers. Since launch, no actions were taken for safety reasons concerning withdrawal, rejection or suspension of a Marketing Authorisation.

2.5.1. Discussion on clinical safety

Known safety profile:

In the clinical studies included in the main and broader safety pooling analyses submitted for initial licensure, a total of 14,645 (ZOSTER-006 and ZOSTER-022 pivotal trials) and 15,493 (ZOSTER-006 and ZOSTER-022 pivotal trials and additional supportive studies) older adults ≥50 YOA have been vaccinated with at least one dose of HZ/su, respectively. Based on the data submitted at MAA, there was no identified risk.

The following important potential risks were listed at MAA: (i) Risk of pIMDs following Shingrix vaccination; (ii) Virus reactivation in immunocompetent individuals with a history of Herpes Zoster. The latter concern is based on an observation from a small study (ZOSTER-33) performed in subjects with past history of Shingles which pointed to an unexpectedly high incidence of Shingles following HZ/su administration. ZOSTER-062 is conducted to meet this concern. Limited data from a post hoc analysis on the incidence of Herpes Zoster (HZ) and HZ-related adverse events in patients with a history of HZ versus no history of HZ in the pivotal IC studies do not raise concern.

Given the theoretical risk of exacerbating pre-existing pIMDs due to the inflammatory process induced by Shingrix, 'use in adults with pre-existing pIMD' has been considered as a missing information at licensure. The MAH recently submitted a Type-II variation to provide data (clinical studies, post-marketing data, observed/expected analysis and literature review) to support the MAH position that vaccination with Shingrix does not increase the risk of disease exacerbation in patients with pre-existing pIMDs (refer to EMEA/H/C/004336/II/0031).

In the pre-licensure clinical trials, which are not designed to assess rare outcomes, numerical differences between Shingrix and Placebo groups were noted for certain conditions, including: polymyalgia rheumatica (PMR), giant cell arteritis (GCA), Ischemic optic neuropathy (ION), Supraventricular tachycardia (SVT), and gout. After licensure, using an algorithm that preferentially maximizes sensitivity over specificity, the U.S. Vaccine Safety Datalink detected a statistical signal for Guillain-Barré syndrome (GBS) during active surveillance for Shingrix safety. Two PASS are ongoing to evaluate the safety of Shingrix in adults ≥50 years of age in the United States: EPI-ZOSTER-030/032.

From the time of first approval of Shingrix in the US (13 October 2017) until 12 April 2019 (data lock point of the current PBRER of the PBRER submitted on 17 June 2019), exposure to Shingrix is estimated to be between 5 818 118 and 11 636 236 subjects. The spontaneous reports received since launch of Shingrix are generally consistent with what has been observed in the clinical trials and the information provided in the Reference Safety Information for Shingrix. No safety signal was confirmed since MA.

Safety database in the proposed extension of indication:

In all 6 studies included in this application, a total of 1,587 subjects received at least 1 dose of HZ/su (443 subjects 18-49 YOA and 1,144 subjects ≥50 YOA). In the 4 pivotal studies, a total of 1,454 subjects received at least 1 dose of HZ/su (383 subjects 18-49 YOA and 1,071 ≥50 YOA). ZOSTER-002 makes the largest contribution (approximately 60%) to the safety database of the subjects exposed to HZ/su. (230 subjects 18-49 YOA and 692 ≥50 YOA), followed by ZOSTER-039 (230 subjects 18-49 YOA and 692 ≥50 YOA). In the 4 pivotal studies, the compliance with the 2-dose schedule ranged from 83% to 96% in the HZ/su groups, in both age stratum.

The mean age at first vaccination with HZ/su (gE/AS01B) ranged between 47 and 58 YOA across studies. In ZOSTER-002 and ZOSTER-039, multiple myeloma was the most common underlying diseases. In ZOSTER-028, the most frequently reported solid tumor diagnoses were breast and colorectal tumors. The demographic characteristics were generally balanced between the HZ/su and Placebo groups. Groups were also comparable with respect to reported underlying diagnoses.

The overall number of subjects in the safety database of IC patients is acceptable, considering the overall safety data already available for Shingrix. The number of IC subjects in the 18-49 YOA category (443 subjects) is limited but acceptable as: (i) there is no theoretical safety concern which is specific to this age category, (ii) this number is sufficient to assess whether reactogenicity is higher in the younger vs. oldest IC subjects. The safety data base however is limited (10 times lower than the database generated for immunocompetent individuals ≥50 YOA), and the population is extremely heterogeneous in terms of disease profile and treatment received. Important uncertainties thus remain with respect to the adverse events induced by vaccination in IC subjects.

The population targeted by the proposed indication is broader than the population included in the submitted 'IC' trials, among others subjects 18-49 YOA who are at-risk of HZ but not IC Only very limited data on these subjects are available from the early development of Shingrix. These data were generated in the exploratory phase I/II study EXPLO-CRD-004. This study evaluated the safety and immunogenicity of Shingrix in healthy subject 18-30 YOA (n=10) and 50-69 YOA (n=45). Solicited AE were very frequent in that study, and there was a trend for higher reactogenicity in the 18-30 YOA stratum when compared to the 50-69 YOA stratum for local and general solicited AEs. The available data are too limited to draw conclusions about reactogenicity in immunocompetent individuals 18-49 YOA, and about the magnitude of the age trend in immunocompetent individuals. It is however very likely that such age trend is present: (i) there is such trend in IC (see below), (ii) there is such trend amongst 'immunocompetent' adults ≥50 YOA, (iii) the literature suggest that incidence of solicited AEs seems lower with increasing age.

VZV circulates widely in Europe and above 95% of adults has antibodies against VZV. In most EU countries, the acquisition of antibodies to VZV takes place in the early childhood. The data from the pivotal trials are in line with this seroprevalence level. However, in some of the EU countries such as Germany and Italy, the circulation of the wild VZV is expected to diminish as a consequence of childhood varicella vaccination policies, which could potentially result in an increase in the proportion of (unvaccinated) adults who never had primary VZV infection. At this moment, the risk to inadvertently vaccinate a VZV-naïve individual is low and only a limited number of naïve subjects can be identified in the clinical studies implemented for Shingrix. The MAH performed a pooled analysis considering data from all 6 studies conducted in IC populations. Reactogenicity data from Shingrix vaccinated subjects who were seronegative at baseline (n=77) were compared to those from the overall group of vaccinees (n=1553). The seronegative group may include both true 'VZV-naïve' subjects and not necessary 'VZV-naïve' subjects (because of no detectable antibodies or loss of antibodies over time). The reactogenicity profile observed in baseline-seronegative subjects (local and systemic solicited AE, per dose and per subject) did not raise any concern. The MAH previously committed to include an update of the epidemiology of VZV in Europe in the section Part II module SI "Epidemiology of the indicator(s) and target population(s)" of the EU-RMP with recent published data.

Safety methods:

Safety endpoints, definitions, assessment methods (grading scale and causality assessments) and reporting periods are appropriate. Methods were consistent over the trials submitted in this application, and also consistent with those of the pivotal trials submitted at MAA. In addition to the predefined safety endpoints (AE, SAE, MAE, suspected herpes zoster and herpes zoster complications, pIMD, relapse cases, disease progression, biopsy-proven renal allograft rejections, hematological and biochemical parameters), other events of medical interest were tabulated post-hoc for the pivotal studies. These events were selected based on the most frequently reported events observed in the IC clinical studies, medically relevant events for the specific populations, or previous feedback from regulatory authorities. These events include: agranulocytosis and hematopoietic cytopenias, anaphylactic reactions, haemorrhagic and ischemic cerebrovascular conditions, infective pneumonia, upper respiratory tract infections, serious ocular complications that may be due to vasculitis or inflammation.

Reactogenicity:

Local reactogenicity in the 4 pivotal IC studies:

In ZOSTER-002, 85.8% of the subjects (vs. 10.4% in the Placebo group) had at least one solicited local symptom. Similar frequencies were found across the pivotal studies (83.8%-87.8% per subject). The frequency of grade 3 solicited local symptoms following HZ/su was 14.2% per subject in study ZOSTER-002, and similar across the 4 pivotal studies (10.7%-14.2% per subject). In the Placebo group, the frequency of grade 3 solicited local symptoms was <0.5% (per dose or subject). Pain occurred in 79.5%-87.0% of subjects (83.9% in ZOSTER-002). There was a high frequency of grade 3 pain (9.8%-11.0% of subjects, 11.0% in ZOSTER-002). Median duration of pain was 3.0 days across studies.

Systemic reactogenicity in the 4 pivotal IC studies:

The frequency of solicited general symptoms (at least one symptom) was 75.2% per subject (vs. 50.9% in the Placebo group) in study ZOSTER-002. A similar frequency of solicited general symptoms was found across studies in the HZ/su and in the Placebo groups (68.7%-81.3% per subject in the HZ/su group vs. 48.9%-66.4% in the Placebo group). The frequency was high in the control groups, reflecting the underlying population.

As expected, the discrepancies between groups was much more marked for grade 3 events than for events of any grade. The frequency of grade 3 solicited general symptoms following HZ/su was 13.2% per subject (vs. 6.0% in the Placebo group) in study ZOSTER-002. A similar frequency of grade 3 solicited general symptoms was found across the pivotal studies in the HZ/su group (9.9%-22.3% per subject).

Fatigue, headache, myalgia were the most frequently reported symptoms associated with HZ/su administration. The association of gastrointestinal symptoms with HZ/su administration is not clear. Shivering and fever were frequently reported as well, and strongly associated with HZ/su. There was an approximately three-fold to four-fold increase in the frequency of fever in the HZ/su vs. Placebo group. The frequency of fever (>37.5°) ranged from 9.0% to 15.8% (12.1% in ZOSTER-002) per dose in the HZ/su group (<5.0% in the Placebo groups, 3.2% in ZOSTER-002), depending on the studies.

Across the pivotal studies, in the HZ/su groups, the median duration of solicited general symptoms was at most 3.0 days. The maximal duration was 7 days.

Comparison to reactogenicity data at initial MAA:

Of the subjects ≥50 YOA (ZOSTER-006), 81.5% experienced at least one solicited local symptom (9.5% for grade 3), and 79.1% experienced pain at the site of administration (6.7% grade 3 pain). At least one solicited general symptom was reported for 66.1% of subjects, and at least one grade 3 solicited general symptom for 11.4% of subjects. The most frequently reported solicited general symptoms were myalgia and fatigue. Fever (≥37.5°C) was reported in 21.5% of the subjects. In general, local and general symptoms lasted for a few days (median duration was 3 days for pain, days for myalgia and fatigue, 1 day for fever).

In the 'IC' studies, the frequencies of both solicited local and general symptoms following HZ/su were in the same range in the adults ≥18 YOA enrolled in the 'IC' studies and in immunocompetent adults ≥50 YOA (ZOSTER-006). Available data are too limited to draw conclusions on the reactogenicity profile of 'immunocompetent' versus 'IC' individuals 18-49 YOA. When restricting the comparison to 'immunocompetent' and 'IC' populations ≥50 YOA, there was no substantial difference. However, there are limitations in comparing those populations in terms of systemic AEs, as the frequency of systemic events is high in the Placebo group of the IC studies. The frequency of systemic events attributable to HZ/su may be overestimated in the IC studies. Overall, it is considered likely that reactogenicity is higher in 'immunocompetent' compared with 'IC' population of similar age groups.

Age trend:

There was a general trend towards higher point estimates in the 18-49 YOA stratum compared to the ≥50 YOA stratum for the majority of the solicited local symptoms. In all pivotal studies, the frequency of (grade 3) pain was higher in the 18-49 years of age subjects, compared to the ≥50 years of age subjects (approximately 1.5-fold higher frequency of grade 3 pain). In contrast, there was no clear age trend in terms of frequency of general solicited symptoms, except for fever and shivering. In ZOSTER-002, a higher frequency (i.e., higher point estimates) of fever, shivering and grade 3 shivering was observed in the 18-49 YOA stratum (17.6%, 22.8%, 3.8% per dose and 27.8%, 31.4%, 7.2% per subject) compared to the ≥50 YOA stratum (10.3%, 15.6%, 1.5% per dose and 17.8%, 24.6%, 2.8% per subject) in HZ/su group in this study (while frequencies were similar across age categories in the Placebo Group). The 95% CI do not overlap for some of the comparisons such as for myalgia in the ZOSTER-039, and for grade 3 fatigue in the ZOSTER-002. There is a consistent trend across studies, but the comparison are not statistically meaningful in all studies, as the 95% CI overlap in many instances. The MAH performed a pooled analysis from all 6 studies conducted in IC populations. This analysis confirms what was observed in the individual studies. Pain at the injection site and most of the general AEs (fatigue, headache, myalgia, fever and shivering) were more frequent in the age stratum 18-49 YOA as compared to the age stratum ≥50 YOA.

In the data submitted at licensure, there is a clearly higher local and general reactogenicity observed with decreasing age within the ≥50 YOA population of the ZOSTER-006 trial (encompassing immunocompetent individuals, including patients with comorbidities). Only very limited data from the early development of HZ/su are available for immunocompetent subjects 18-49 YOA.

Safety findings in the submitted studies:

The analysis of unsolicited AEs classified by MedDRA Primary SOC points to a higher frequency of cardiac disorders in HZ/su over 30 days post-vaccination compared to Placebo vaccinees. Number are small, and 95% CI are in the same range. The MAH presented a pooled analysis of the cardiac disorders that did not identify any safety concern.

There were 2 cases of supraventricular tachycardia (SVT) assessed as not related to vaccination by the investigator. Nevertheless, SVT is included as event of interest in the post-authorization safety studies EPI-ZOSTER-030 and EPI-ZOSTER-032. In addition, 1 subject presented a SAE 'atrial fibrillation' considered as causally related to vaccination by the investigator.

This analysis of unsolicited AEs by SOC also pointed to imbalances for eye disorders and urinary/renal disorders over 30 days post-vaccination compared to Placebo vaccinees. An imbalance for the PT of upper respiratory tract infection was reported with significantly higher incidence in the HZ/su group than in the Placebo in ZOSTER-039. The MAH presented a pooled analysis of the disorders for which an imbalance was observed. The review of the post hoc pooled analysis did not identify any safety concern.

Across several studies, there was an approximately two-fold higher frequency of the AE 'febrile neutropenia', the grade 3 AE 'febrile neutropenia' and the SAE 'febrile neutropenia' over the period up to 30 days post second vaccination, in HZ/su vs. Placebo vaccinees. The MAH was requested to present additional data and discuss the biological plausibility. IC patients enrolled in studies ZOSTER-002, ZOSTER-028 and ZOSTER-039, diagnosed with malignancies and receiving chemotherapy, are at high risk of neutropenia and resultant infections. Febrile neutropenia is one of the most frequent and serious complications of cancer chemotherapy. In the pooled analysis combining safety data from the 6 IC studies, Shingrix administration was associated with an approximately two-fold increased risk of the (grade 3) AE and SAE 'febrile neutropenia' occurring up to 30 days post last vaccination. Numbers are limited and the 95% CI widely overlapping. The data per study indicate no imbalance in ZOSTER-002 (the

largest trial) for febrile neutropenia. There was also no imbalance for neutropenia, but there was an imbalance for grade 3 neutropenia. Imbalances for febrile neutropenia were seen in ZOSTER-039 and ZOSTER-028 only, which are the studies with the highest frequency of febrile neutropenia. In these studies, an imbalance was seen for febrile neutropenia, but not for neutropenia and neutropenic sepsis. Neutropenia often occurs between 7 and 12 days after receipt of chemotherapy [CDC]. In both studies, nearly all subjects who experienced febrile neutropenia as an unsolicited AE within 30 days post each vaccination received cancer chemotherapy within 15 days prior to its onset.

It was noted that transient Neutropenia is described as an AE after vaccination for several vaccines also in healthy adults in literature (Muturi-Kioi et al). Post-vaccination neutropenia is generally clinically benign and occurs typically in the first two weeks after vaccination. Four studies assessed neutrophil counts pre- and post-vaccination at specific time points according to protocol. In two studies (one in HIV-infected individuals, the other in adults ≥60 YOA), a higher frequency of neutrophils below the cut-off was observed at M2 post HZ/su vaccination vs. pre-vaccination. However, no AE 'neutropenia' or 'febrile neutropenia' were reported in these two studies. In addition, such transient fall in neutrophil counts was not consistently seen in the other two studies.

It was noted that over the period up to 30 days post second vaccination, the SAE 'pneumonia' was reported more frequently in the HZ/su vs. Placebo Group in ZOSTER-002 and ZOSTER-039 (no case in the other two studies). A pooled analysis was performed to combine safety data from the 6 IC studies. This pooled analysis confirmed a trend for more frequent pneumonia in the HZ/su vs. Placebo groups over the period up to 30 days post second vaccination. The data are limited and 95% CI are widely overlapping. There was no imbalance in the frequency of unsolicited AEs under the SOC Infections and infestations reported within the 30-day post each vaccination with Shingrix (16.3% in the Shingrix group and 15.2% in the placebo group).

Given the limitations of the data sources utilized in the 2 PASS studies EPI-ZOSTER-030 and EPI-ZOSTER-032, it is not warranted to include febrile neutropenia and serious infections as outcomes in these studies. The MAH will discuss cases of neutropenia (including febrile neutropenia and neutropenic sepsis) and of serious infections (including pneumonia) as events of special interest through the PSUR.

No increase in the occurrence of disease relapse cases, disease progression, biopsy-proven renal allograft rejections was observed in the HZ/su vs. Placebo groups in the pivotal studies.

From first vaccination up to 12 months post last vaccination, pIMDs were reported in 20 (21 events) and 13 subjects respectively in the HZ/su and Placebo groups of the four studies.

- In the HZ/su subjects, the following events occurred: autoimmune hemolytic anemia, Histiocytosis haematophagic, Immune thrombocytopenic purpura, Autoimmune pancytopenia, Autoimmune thyroiditis, Myelitis, Gout (n=3), Type 1 diabetes mellitus, Arthralgia, Polymyalgia rheumatic, Facial paralysis, Optic neuritis, IgA nephropathy, Interstitial lung disease, Cutaneous vasculitis, Erythema nodosum, Hypersensitivity vasculitis, Psoriasis and Psoriasis Aggravated).
- In the Placebo subjects, the following events occurred: autoimmune hemolytic anemia, Autoimmune thyroiditis, Myelitis, Type 1 diabetes mellitus, Spondylitis, Systemic scleroderma, Facial paralysis, Guillain-Barre syndrome, IgA nephropathy (n=2), Interstitial lung disease (n=2), Psoriasis.

Numerical imbalances between Shingrix and Placebo groups were noted in the pre-licensure trials for the pIMDS polymyalgia rheumatica [PMR], giant cell arteritis [GCA], Ischemic optic neuropathy [ION]. In the IC studies, one case of PMR and one case of optic neuritis were reported in HZ/su vaccinated subjects, and none in the Placebo subjects. The present data in IC subjects are thus consistent with imbalances. Two PASS are ongoing to evaluate the safety of Shingrix in adults ≥50 years of age in the United States: EPI-ZOSTER-030/032.

Numerical imbalances between Shingrix and Placebo groups were also noted in the pre-licensure trials for gout. Within the 30-day period following the last vaccination, there were 27 (0.18% [95% CI: 0.12-0.27]) and 8 (0.05% [95% CI: 0.02-0.11]) subjects in the RZV and Placebo groups, respectively, who reported an event of gout or gouty arthritis (relative risk [RR] 3.38 [95% CI: 1.49- 8.60]) (Source: PASS protocols, EPI-ZOSTER-030/032). Stimulation of inflammatory responses, in particular involving IL1, is a trigger of gout. It is considered plausible that vaccination with HZ/su triggers the clinical manifestations of gout in individuals with high uric acid. The MAH was invited to discuss the cases in the IC studies. Three non-serious cases of gout were reported in immunocompromised population (1 in study ZOSTER-039 and 2 in study ZOSTER-041), all in HZ/su group. In the pooling of the 6 IC studies, no other cases of gout were retrieved in the HZ/su group while two cases of gout were reported in the placebo group. Therefore there was no indication of an imbalance regarding gout in the IC population. In addition, time of occurrence of the 3 cases in the HZ/su group (31 days, 91 days, and 307 days post-vaccination) is not consistent with the hypotheses of clinical manifestations of gout triggered by reactogenicity in individuals with high uric acid (prevalent in patients under chemotherapies and patients with impaired renal function). Nevertheless, the MAH acknowledged that one of the cases of gout reported in PM could have been triggered following a possible dehydration due to severe reactogenicity after vaccination. The MAH intends to generate further data to investigate a possible putative association between Shingrix vaccination and increased risk of gout, if any, in studies EPI-ZOSTER-030 and EPIZOSTER-032.

There were more pIMDs under the SOC Blood and lymphatic system disorders in the HZ/su vs. Placebo Groups. The MAH was invited to discuss whether autoimmune haematological diseases could be related to vaccination, in the context of the signal related to febrile neutropenia. The pooled data from the IC studies showed no statistically and/or medically relevant differences between subjects vaccinated with Shingrix compared to subjects receiving placebo. The number of cases was very low and most cases could be attributed to the underlying disease. In addition, none of these events were co-reported with febrile neutropenia.

An imbalance was also seen for cutaneous vasculitis in the pivotal IC studies, with two cases in the HZ/su groups and none in the Placebo groups. Narrative were discussed, and it was concluded that the available data on cutaneous vasculitis did not highlight a safety concern. The MAH is continuously monitoring pIMDs, which includes immune mediated vasculitis, by enhanced pharmacovigilance activities.

Assessment of paediatric data on clinical safety

No data from the paediatric population were collected in the submitted trials. A PIP was submitted to the EMA on 12 March 2013. The Paediatric Committee (PDCO) granted a positive opinion on the PIP for the prevention of VZV reactivation in immunocompromised persons 1 to 17 years of age. The clinical trials ZOSTER-047 (a dose-confirmation study) and ZOSTER-040 (a safety/immunogenicity study with the selected dose) in IC persons 1-17 YOA were endorsed. The plan is fully deferred and will be initiated after establishment of the positive benefit/risk of HZ/su in IC adults. A waiver was granted for new-borns and infants from birth to less than 1 year of age. The EMA decision dated 29 July 2013 (reference P/0168/2013) confirmed the agreement of the PIP and the granting of the deferral and the waiver.

2.5.2. Conclusions on clinical safety

Shingrix induces high transient local and systemic reactogenicity in adults ≥18 YOA who are immunocompromised (IC) due to disease or therapy.

The study design does not allow a direct comparison between the reactogenicity of HZ/su in immunocompromised individuals and not immunocompromised individuals. Nonetheless, the reactogenicity profile observed in IC patients ≥18 YOA seems consistent with the data submitted at licensure for immunocompetent adults ≥50 YOA. This pattern reflects a short-term inflammatory

response induced by this adjuvanted vaccine. There is a clearly increasing reactogenicity with lowering age. There are only very limited data on reactogenicity in individuals 18-49 YOA who are not IC.

The safety database of IC patients is acceptable but limited. Moreover, the population of IC patients is extremely heterogeneous. Uncertainties thus remain with respect to the adverse events induced by vaccination in IC populations, and within subgroups of this population. In addition, the population targeted by the proposed indication is broader than the population included in the submitted 'IC' trials. Beside immunosuppressive diseases and treatments, many chronic diseases lead to an increased risk of HZ.

Overall, no new safety signal has been confirmed in the IC studies. In patients at high-risk of such conditions, the data point to non-statistically significant imbalances in febrile neutropenia and pneumonia over the period up to 30 days post second vaccination (approximately two-fold increased frequency in vaccinated vs. placebo). These events will be followed in the PSUR.

As in immunocompetent individuals, this adjuvanted vaccine with high reactogenicity could trigger pIMDs and exacerbations of pre-existing pIMDs in IC patients. The latter theoretical concern becomes even more important with this extension of indication as individuals with pre-existing pIMDs are part of the population 'at-risk' of HZ.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.2. is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination Virus reactivation in individuals with a history of Herpes Zoster
Missing information	Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older. Long-term immunogenicity in adults 18 years of age and older. Use of *Shingrix* in frail adults 50 years of age or older Use of *Shingrix* in adults with pre-existing pIMD Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
ZOSTER-049 Long-term follow-up (ZOE-FU) and assessment of 1-2 additional doses in adults 50 YOA or older Ongoing	To investigate long term efficacy, safety and immunogenicity, as well as to assess reactogenicity, safety and immunogenicity of one or two additional doses	Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older. Long-term immunogenicity in adults 18 years of age and older.	Interim report	31 May 2021
			Final report	31 Oct 2024
ZOSTER-060 Long term immunogenicity and assessment of re-vaccination with 2 additional doses in adults 60 years of age and older. Ongoing	To investigate persistence of immunogenicity, and safety, as well as to assess reactogenicity, safety and immunogenicity of two additional doses.	Long-term immunogenicity in adults 18 years of age and older.	Final report	31 Mar 2020
ZOSTER-064 a descriptive analysis of efficacy, safety and immunogenicity of *Shingrix* per frailty status in subjects of 50 years and above Ongoing	Observational study to assess frailty status and other prognostic factors for development of herpes zoster in an older adult population based on demographic characteristics and quality of life questionnaires completed by subjects during the ZOSTER-006 and ZOSTER-022 studies	Use of *Shingrix* in frail adults 50 years of age or older.	Final report	30 Sep 2020
EPI-ZOSTER-030 VS US DB Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults > 50 years of age in the U.S Planned	Non-interventional (observational) retrospective cohort study to evaluate the safety of *Shingrix* in older adults (≥ 50 YOA) in the US.	Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination.		
			Final report	31 Mar 2027
EPI-ZOSTER-032 VS US DB Targeted safety study (TSS) to evaluate the safety of *Shingrix* in adults > 50 years of age in the U.S Planned	Non-interventional (observational) targeted safety study to evaluate the safety of *Shingrix* in the Medicare population (65 YOA or older) in US	Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination.	Final report	30 Jun 2027
ZOSTER-069 An observer-blind, clinical study to assess the immunogenicity reactogenicity and safety of *Shingrix* in adults with pre-existing pIMD Planned	To evaluate safety, reactogenicity and immunogenicity of *Shingrix* in adults with pre-existing pIMD.	Use of *Shingrix* in adults with pre-existing pIMD.	Protocol submission	TBD
			Final report	30 Jun 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
ZOSTER-062 Immunogenicity and safety study of *Shingrix* on a two-dose schedule in adults ≥ 50 years of age with a prior episode of Herpes Zoster. Planned	To assess safety, immunogenicity and reactogenicity of *Shingrix* in subjects with a previous history of Herpes Zoster.	Virus reactivation in individuals with a history of Herpes Zoster	Final report	30 Jun 2022
ZOSTER-056 Cross-vaccination study of *Shingrix* in subjects who previously received placebo in ZOSTER-006 and ZOSTER-022 studies Ongoing	To evaluate safety in all subjects following administration of each dose of *Shingrix* (including subjects who experienced an episode of HZ before vaccination). To evaluate the incidence of suspected HZ episodes during the entire study period (including subjects who experienced an episode of HZ before vaccination)	Virus reactivation in individuals with a history of Herpes Zoster	Final report	31 Jul 2020
EPI-ZOSTER-031: Effectiveness of *Shingrix* in preventing HZ, PNH and other HZ-related complication Planned	To estimate the effectiveness of *Shingrix* in preventing HZ, PHN and HZO in US subjects aged 50 years and above, overall and by age groups. To estimate long-term vaccine effectiveness up to 10 years after vaccination with *Shingrix*.	Effectiveness of *Shingrix* in preventing HZ, PNH and other HZ-related complication	Final report	1 Aug 2033
ZOSTER-073 Long term immunogenicity study and assessment of revaccination with 2 additional doses in adult renal transplant participants from ZOSTER-041Planned	To evaluate long term immunogenicity and safety as well as reactogenicity, safety and immunogenicity of revaccination with two additional doses in adult renal transplant subjects from the study ZOSTER-041.	Long-term immunogenicity in adults 18 years of age and older.	Final study report	28 Feb 2026

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk: Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for: •Autoimmune thyroiditis •Gout •Guillain-Barré Syndrome •Idiopathic Thrombocytopenia •Inflammatory (non-infective) ocular disease •Inflammatory bowel diseases •Leukocytoclastic vasculitis •Multiple Sclerosis •Optic ischemic neuropathy (arteritic and non-arteritic) •Optic neuritis •Polymyalgia rheumatica •Psoriasis •Rheumatoid arthritis •Still's disease (adult onset) •Temporal arteritis **Additional pharmacovigilance activities:** EPI-ZOSTER-030 VS US DB EPI-ZOSTER-032 VS US DB
Important potential risk: Virus reactivation in individuals with a history of Herpes Zoster	**Routine risk minimisation measures:** Wording in SmPC sections 4.4 and 5.1	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZOSTER-062 ZOSTER-056
Missing information: Long-term efficacy and assessment of the need for additional doses in adults 18 years of age and older.	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZOSTER-049
Missing information: Long-term immunogenicity in adults 18 years of age and older.	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZOSTER-049 ZOSTER-060 ZOSTER-073
Missing information: Use of *Shingrix* in frail adults 50 years of age or older	**Routine risk minimisation measures**: wording in SmPC sections 4.4 and 5.1	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZOSTER-064
Missing information: Use of *Shingrix* in adults with pre-existing pIMD	No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** ZOSTER-069

Missing information: Effectiveness of *Shingrix* in preventing HZ, PHN and other HZ-related complications	No risk minimization measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None Additional pharmacovigilance activities: EPI-ZOSTER-031

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. In addition, the list of excipients has been updated in section 6 of the SmPC.

The Package Leaflet has been updated accordingly.

Annex II and IIIA have been updated to implement some editorial changes.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. The MAH provided a comparison (table PI) between the content of the previous user tested Package leaflet versus the proposed version. Therefore, the changes to the package leaflet are minimal and do not require a full or reduced user consultation with target patient groups. However, for further variations affecting the content of the Package leaflet any information on the consultation with target patient groups, reduced testing or concerning a justification for not carrying out a readability test shall be submitted in the module 1.3.4.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Shingrix (herpes zoster vaccine (recombinant, adjuvanted) is included in the additional monitoring list as new active substance and biological<include reason(s) since April 2018.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Currently, Shingrix is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN) in adults ≥50 YOA. The MAH proposes to amend the indication for Shingrix to include adults 18 years of age or older at increased risk of HZ to address the unmet medical need for HZ prevention in that population. The claimed indication is for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in (i) adults 50 years of age or older; (ii) adults 18 years of age or older at increased risk of HZ.

Herpes Zoster, commonly known as shingles, is caused by the reactivation of latent VZV and is thought to be associated with a decline in cell-mediated immunity (CMI) due to aging or to an immunosuppressive illness or treatment. HZ typically presents as an acute, painful, vesicular eruption distributed along a

single dermatome. The most common complication of HZ is PHN, which is often chronic and debilitating and difficult to treat effectively. Other less frequent HZ complications can also occur, including HZ ophthalmicus (HZO), neurological complications such as VZV encephalitis and meningitis, and disseminated HZ.

Epidemiological evidence confirms that the risk of HZ increases dramatically in adults ≥18 YOA who are immunocompromised (IC), placing them at a risk comparable to and in many instances far exceeding the risk seen in the general adult population ≥50 YOA. IC individuals are not only at increased risk for the development of HZ but also develop more severe HZ episodes, and more complications such as cutaneous dissemination, visceral involvement (including varicella pneumonitis and hepatitis), VZV retinitis and acute retinal necrosis, and meningoencephalitis. Chronic HZ may also occur in IC patients.

Beside immunosuppression, many chronic conditions such as diabetes, asthma, COPD, cardiovascular diseases, and renal diseases are associated with an increased risk of HZ. PHN also appears to be more severe and persistent in diabetic patients.

Patients who undergo hematopoietic cell transplant (HCT) show the highest risk for HZ among the immunocompromising conditions. Patients with malignancies are at risk for developing HZ, due to their underlying disease and immunosuppressive cancer therapy. Patients with autoimmune disease are also at increased risk of HZ reactivation. In addition to the risk autoimmune disease may independently pose, most of these conditions are managed with immunosuppressive therapies that impair T cell immunity.

Disease-induced immunosuppression has been proposed as a mechanism for increasing the risk of HZ in patients with other chronic diseases that directly affect CMI like HIV as well as those with less well-defined mechanism of immunosuppression like type II diabetes mellitus (**Table 97: Summary of the HZ incidence in various populations**Table 97).

Table 97: Summary of the HZ incidence in various populations

Population	HZ incidence
Overall population	
Overall	3 to 5 cases per 1000 PY
18-49 YOA	3.4 cases per 1000 PY
≥65 YOA	8.4 cases per 1000 PY
Patients ≥18 YOA who undergo HSCT	
Overall	37 to 60 cases per 1,000 PY
First year following autologous HSCT	8% to 28%
Other adults at risk	
Solid organ transplant recipients	8 to 20 cases per 1000 PY
Hematologic cancers, overall	29 to 31 cases per 1000 PY
Malignant lymphoma	Hazard ratios of 8.4 (6.7, 10.6)
Oesophageal cancer and brain tumors	Hazard ratios 4.0 (2.1, 7.8) and 3.7 (2.4, 5.7)
Auto-immune diseases, overall	3 to 38 cases per 1000 PY
systemic lupus erythematosus	6 to 37 per 1,000 PY
rheumatoid arthritis	8 to 16 per 1,000 PY
inflammatory bowel disease	4 to 11 cases per 1000 PY
psoriasis	5 to 9 cases per 1000 PY
HIV, prior to introduction of highly active ART	32 cases per 1000 PY
Diabetes mellitus	3 to 13 cases per 1000 PY

Asano-Mori 2008; Mao 2018; Sahoo 2017; Schröder 2017; Schuchter 1989; Offidani 2001; Barton 2001; Kamber 2015; Koc 2000; Steer 2000; Kroger 2011; Chen 2014; Habel 2013; Pergam 2011; Hata 2011; Chakravarty 2017; Winthrop 2014; Gilbert 2017; Gilbert 2019; Moanna 2013; Kwon 2016; Guinee 1985; Sorensen 2011; Sandherr 2006; Anaissie 1988; Hata 2002; Nucci 2009; Sorensen 2009; Chanan-Khan 2008; Kim 2008; Ohguchi 2009; Yi 2010; Rusthoven 1988; Wade 2006; Sandherr 2006; Mattiuzzi 2003; Borba 2010; Chen 2017; Hu 2016; Khan 2018; Smitten 2007; Veetil 2013; Yun 2016; Zisman 2016.

Other important risk factors described in the literature are co-morbidities such as renal diseases, COPD,

asthma, and cardiovascular diseases. Other non-medical factors such as a recent physical trauma, stress, sleep disturbance, depression, recent weight loss, family history of HZ, female gender and Afro-American ethnicity are also associated with an increased risk of HZ (Marin 2016, Kawai 2017, Marra 2020).

Results from a recent meta-analysis based on 88 studies, excluding studies that used immunosuppressive medications, are summarized below (Marra 2020) and confirm previous results observed in the meta-analysis performed by Kawai in 2017 (

Table 98).

Table 98. Summary the Relative Risk of HZ occurrence in subjects with co-morbidities and non-medical risk factors

Population	RR (95% CI)
Chronic renal disease	1.29 (1.10-1.51)
COPD	1.41 (1.28-1.55)
Cardiovascular conditions	1.34 (1.17-1.54)
Asthma	1.24 (1.16-1.31)
Depression	1.23 (1.11-1.36)
Physical trauma	2.01 (1.39-2.91)
Psychological stress	1.47 (1.03-2.10)
Family history	2.48 (1.70-3.60)
Sex (women)	1.19 (1.14-1.24)
Race (black)	0.69 (0.56-0.85)

3.1.2. Available therapies and unmet medical need

Antiviral treatment for HZ is available and has been shown to decrease the duration of HZ rash and the severity of pain associated with the rash. However, these benefits were most often demonstrated when patients are able to initiate antiviral therapy within 72 hours of onset of rash. Also, antiviral drugs were not conclusively shown to reduce the occurrence of PHN (meta-analyses of clinical trial data, Chen, 2004).

The duration of antiviral prophylaxis is not standardized for their use in HCT recipients and the effect depends on adherence to treatment. There is a high risk of HZ occurring once prophylaxis has stopped.

There is currently no licensed vaccine for the prevention of HZ in IC populations. Zostavax® (Merck & Co) is a live attenuated VZV vaccine, licensed in multiple countries to prevent HZ in persons ≥50 years of age.

The spectrum of subjects who are 'at increased risk of HZ', and may benefit from Shingrix, is broad and heterogeneous.

The unmet need is unquestionable for those with the highest burden of disease, i.e. patients who are immunodeficient or immunosuppressed due to disease or therapy (such as patients with malignancies, transplantation, autoimmune diseases, or patients with congenital immunodeficiencies). These patients are at increased risk of shingles and also experience more severe pain, and serious complications, as described above. Chronic herpes zoster may also occur in immunocompromised patients. Moreover, the live-attenuated VZV vaccine (Zostavax®,Merck & Co) is contraindicated in them due to concerns of possible vaccine-associated disseminated disease. Shingrix can also benefit those who might require IS treatment in the future.

There also is a clear unmet need in certain adult sub-populations with chronic medical conditions predisposing them to HZ (e.g., COPD, cardiovascular diseases, renal disease, rheumatoid arthritis,

asthma, type 2 diabetes mellitus), including patients taking low-dose immunosuppressive therapy (e.g., low dose of prednisone).

The unmet need might be less clear for other individuals with risk factors, such as stress, depression, or recent trauma, although they could also be considered at increased risk. Vaccination might be beneficial for some of them and this should be considered on a case-by-case basis.

3.1.3. Main clinical studies

The main evidence of efficacy in immunocompromised (IC) patients was generated in a phase III multicentre, randomized, observer-blind study comparing HZ/su (n=922) vs. saline placebo (n=924) in autologous HCT recipients ≥18 YOA vaccinated 50 to 70 days after transplant (ZOSTER-002).

VE was also assessed as post-hoc analysis in a second Phase III multicentre, randomized, observer-blind study comparing HZ/su (n=283) vs. saline placebo (n=279) in subjects ≥18 YOA with haematologic malignancies who were vaccinated during a cancer therapy course or after a full cancer therapy course (ZOSTER-039).

Vaccine immunogenicity was assessed in 3 Phase III and 1 Phase II/III randomised, observer-blind, placebo-controlled, multi-center studies. In addition to studies ZOSTER-002 and ZOSTER-039, study ZOSTER-028 and study ZOSTER-041 assessed both humoral and cellular immunity. ZOSTER-028 included adults with solid malignancies vaccinated during or 8-30 days prior to chemotherapy (n=117 and n=115 for HZ/su and placebo respectively). ZOSTER-041 included renal transplant recipients under ongoing IS therapy (n=132 for both for HZ/su and placebo).

These studies were multi-country studies conducted worldwide. In all 4 pivotal studies, HZ/su was administered according to a 2-dose flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose.

The MAH also undertook two supportive studies (in HIV infected individuals, and in patients who had HCT).

A total of 1,587 subjects received at least 1 dose of HZ/su (443 subjects 18-49 YOA and 1,144 subjects ≥50 YOA) in all 6 studies included in this application.

3.2. Favourable effects

Efficacy against HZ

In study ZOSTER-002, a total of 184 subjects reported a confirmed HZ episode, amongst which 49 were in the HZ/su group and 135 in the Placebo group. The overall incidence of HZ per 1000 person-years was 30.0 in the HZ/su group and 94.3 in the Placebo group, over a median follow-up time of 21 months. The overall HZ VE was 68.17% (95% CI: 55.56 - 73.57; p-value < 0.0001) over 21 months. The primary objective of study ZOSTER-002 regarding HZ VE was met as the LL of the 95% CI was above 0%.

A similar level of efficacy was found in the post-hoc analysis performed in study ZOSTER-039. The VE was 87.2% (95%CI: 44.25 - 98.59) over a median follow-up time of 11 months, based on 2 and 14 subjects with confirmed HZ episodes respectively in the HZ/su group and in the Placebo group.

Efficacy was lower compared to that found in immunocompetent individuals 50 YOA and over (97% for HZ).

Efficacy against HZ complications

In study ZOSTER-002, of the 10 subjects with PHN episode(s), 1 was in the HZ/su group and 9 in the Placebo group. The overall incidence of PHN per 1000 person-years was 0.5 in the HZ/su group and 4.9 in the Placebo group. The overall PHN VE was of 89.27% (95% CI: 22.54% - 99.76%).

Reported HZ complications related to confirmed HZ (other than PHN) were HZ meningoencephalitis (1 subject in the Placebo group) and HZ cutaneous disseminated (3 subjects in the HZ/su group and 12 subjects in the Placebo group). HZ/su efficacy was also demonstrated against HZ related complications, with an overall VE of 77.76% (95% CI: 19.05% - 95.93%).

Other aspects of efficacy of study ZOSTER-002

High VE was demonstrated when the vaccination occurs 50-70 days after transplant which is very early when compared with standard practice for vaccination of HCT transplant recipients. This indicates that HZ/su is efficacious when the immune responses are not yet reconstituted, and is beneficial to the patient since the first year following transplant is the period of highest HZ's risk.

The available data do not suggest that age importantly affects vaccine efficacy. VE in the two age strata (18-49 YOA and ⩾50 YOA) was 71.77% (95% CI: 38.75% - 88.25%) in the younger, versus 67.34% (95% CI: 52.60% - 77.89%) in the older age cohort, 95% CIS were overlapping. VE against PHN could be shown (89.27% [95% CI: 22.54% - 99.76%]), 10 subjects with PHN in the HZ/su group versus 9 in the placebo group.

VE was demonstrated by using a flexible 2-dose vaccination schedule, with the second dose being administered 1 to 2 months after the first. This offers a flexibility for the vaccination of IC subjects who may need protection as early as possible.

Pain duration was reduced in vaccinated vs. Placebo confirmed HZ cases. The median duration of severe 'worst' HZ-associated pain was 14.0 days (min.-max. 1.0-178.0) in the HZ/su group and 24.0 days (1.0-1025.0) in the Placebo group. In the HZ/su group less subjects with a confirmed HZ episode used 3 or more pain medications compared to the placebo group (10.2% vs. 27.4%). The duration of pain medication was shorter in the HZ/su group (median 21.5 days [min – max: 1.0 -436.0]) compared with the Placebo group (median 47.5 [min - max 1.0 - 1642.0]).

HZ-related hospitalization occurred in 2 subjects of the HZ/su group and 13 subjects of the Placebo group. The VE against first or only episode of confirmed HZ-related hospitalizations was 84.70% (95% CI: 32.15% - 96.55%).

Immunogenicity

The vaccine was shown to be immunogenic in all IC populations included in the 4 pivotal trials. Immunogenicity was also demonstrated in the supportive trial ZOSTER-015 that included HIV-infected adults.
Two intramuscular doses of the vaccine on a 2-dose flexible schedule elicited robust anti-gE ELISA titres and CMI responses to gE. GMCs of anti-gE Ab and frequencies of gE-specific CD4 [2+] T cells at 1 month post-Dose 2 decreased afterwards but remained higher than the baseline level at least up to 1 year post-Dose 2 (all pivotal trials), and up to 2 years post-Dose 2 (evaluated in ZOSTER-002).

The confirmatory primary and secondary objectives in terms of adjusted GMC ratio and VRR in anti-gE humoral immune responses were met in all IC studies with confirmatory objectives, except for study ZOSTER-002 for which objectives were descriptive. In solid tumor patients (ZOSTER-028), the confirmatory objective in terms of adjusted GM ratio for gE-specific CMI responses was met. In chronically immunosuppressed renal transplant recipients (ZOSTER-041), both confirmatory objectives in terms of adjusted GM ratio and VRR for gE-specific CMI responses were met.

3.3. Uncertainties and limitations about favourable effects

A correlate of protection (CoP) has not been established. Because of their altered immune system and in contrast to immunocompetent subjects, circulating Ab titers might not be a good marker to evaluate the protective response in IC patients. The quality of the humoral immune response might be different compared to immunocompetent people. This also applies to CMI. An additional limitation in interpreting CMI results is that they were expressed in percentages and the number of circulating CD4 T cells may vary according to several factors, including underlying diseases and IS treatment. The level of efficacy can therefore not be derived from the immunogenicity data generated in the patients with solid malignancies vaccinated just before or during chemotherapy, in patients who had undergone a solid organ transplant, and in HIV-infected individuals. The level of efficacy can also not be derived according to the timing of IS therapy respective to vaccination, and for the various types of IS therapies, of which several may greatly affect vaccine-induced responses.

In ZOSTER-002 and ZOSTER-039 (the studies which generated the efficacy data), most subjects did not receive IS therapies during or shortly after the vaccination course. The level of efficacy in patients under concomitant IS therapy is not known.

In ZOSTER-002 and ZOSTER-039 respectively, exploratory analyses did not suggest an important impact of underlying disease on VE. VE was also in the same range whether the vaccine was administered during or after the immunosuppressive cancer therapy course. However, the VE results observed in the sub-groups should be interpreted with caution because of very wide 95% CI.

The level of efficacy is unknown for patients presenting with other risk factors of HZ, such as patients with chronic conditions treated with corticoids. In the context of the MAA, the MAH undertook a post-hoc exploratory analysis of the pivotal trials (ZOSTER-006 and ZOSTER-022), which suggests that that HZ/su remains high in patients with common conditions that affect the risk of HZ and PHN, such as chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), depression, and diabetes. This is reassuring, but estimates are imprecise.

Differences in the magnitude of immune responses were observed depending on IC condition.

In studies ZOSTER-002 and ZOSTER-039, immune responses were lower in subjects with non-Hodgkin B-cell lymphoma and Chronic lymphocytic leukemia than in subjects with other malignancies. This is likely caused by B-cell depletion induced by the anti-CD20 monoclonal antibody rituximab, which is typically given to these patients before HCT. Beside this indirect evidence , there is no data according to type of therapy, with the exception of ZOSTER-041 which suggest no profound impact of the type of IS therapy used in renal transplant recipients. New therapies were since used or may be developed, for which the impact on immune response might be important.

Lower humoral immune responses were observed when Shingrix was administered during versus before or after IS cancer therapy.

Overall, these data suggest that immune responses might be affected by different factors such as the underlying disease and type of IS therapy, but also by the timing to vaccination (before, during, after), and/or interval between vaccination and the IS therapy. The consequences on the short and long-term protection are unknown.

Results of study ZOSTER-015 are mostly applicable for subjects stable on ART with CD4 $\geq$200 cells/mm3 only. It is not known if the study results can be extrapolated to subjects with CD4 <200 cells/mm3 or without stable ART.

Long term efficacy and persistence of immune responses as well as need and timing of additional doses is not established. The immunogenicity persistence results in IC-populations were lower compared to

healthy subjects above 50 years of age. Antibody titre decreases between the different IC-patient-groups were heterogeneous in the four pivotal trials one year after the second dose. A long-term follow-up of VE is ongoing in immunocompetent subjects from the pivotal trials submitted at MAA. As subjects of these studies were vaccinated while immunocompetent, it will not be possible to extrapolate these results to IC patients. There is no plan to follow VE in IC subjects. A follow-up of a sub-group included in the study ZOSTER-041 is planned to assess long-term immunogenicity and anamnestic response after revaccination.

The efficacy trial (ZOSTER-002) was performed with a flexible schedule, with the second vaccine dose being administered 1 to 2 months after the first dose, and a time of vaccination post-transplant of 50-70 days. Because of the lack of CoP, it is not known if efficacy would be different when vaccination is performed with a fixed schedule and/or at another time respective to HCT.

There is no immunogenicity data on co-administration with other vaccines in IC individuals of ≥18 YOA. In immunocompetent subjects, it was shown that Shingrix can be given concomitantly with unadjuvanted inactivated seasonal influenza vaccine, 23-valent pneumococcal polysaccharide vaccine (PPV23) or reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa). It is not expected that this would be different in IC subjects.

3.4. Unfavourable effects

Shingrix induces high transient local and systemic reactogenicity in adults ≥18 YOA who are immunocompromised (IC), reflecting a short-term inflammatory response induced by this adjuvanted vaccine.

There was a high frequency of pain (83.9%) and grade 3 pain (11.0%) following HZ/su administration in ZOSTER-002 (79.5%-87.0% and 9.8%-11.0% of subjects in the 4 pivotal trials). Pain lasted for a median duration of 3.0 days across studies.

In study ZOSTER-002, 75.2% of the subjects of the HZ/su group experienced solicited general symptoms, and 13.2% experienced grade 3 solicited general symptoms. The frequency was high in the control groups (50.9% and 6.0%) reflecting the underlying population. Similar frequencies were found across studies (68.7%-81.3% in the HZ/su group vs. 48.9%-66.4% in the Placebo group; 9.9%-22.3% in the HZ/su groups and 6.0%-15.5% in the Placebo groups). Myalgia, fever and shivering were strongly associated with HZ/su administration (two- to four-fold increased frequency compared to placebo subjects). Headache and fatigue were also increased with Shingrix. The frequency of fever (>37.5°C) ranged from 9.0% to 15.8% (12.1% in ZOSTER-002) per dose in the HZ/su group (<5.0% in the Placebo groups), depending on the studies. The median duration of solicited general symptoms was 3.0 days (maximal duration 7 days).

Overall, the reactogenicity profile observed in IC patients ≥18 YOA seems consistent with the data for immunocompetent adults ≥50 YOA (ZOSTER-006).

Reactogenicity is increasing with lowering age. Reactogenicity, both local and systemic, is higher in the 18-49 YOA vs. ≥50 YOA IC individuals. Such age trend was also observed within the ≥50 YOA immunocompetent population when comparing subjects 50-69 YOA with subjects ≥70 YOA.

Overall, no new safety signal has been confirmed. However, several safety findings that constitute potential new safety concerns need to be further documented in the PSURS.

3.5. Uncertainties and limitations about unfavourable effects

Reactogencity is not known in individuals 18-49 YOA who are not IC (but may be 'at-increased risk of HZ'). The available data are too limited to draw conclusions about reactogenicity in immunocompetent individuals 18-49 YOA, and about the magnitude of the age trend in immunocompetent individuals.

As in immunocompetent individuals, this adjuvanted vaccine could trigger exacerbations of pre-existing potential Immune-Mediated Disease (pIMDs) in IC patients. Therefore, vaccination should be considered on an individual basis in this population for which limited data are available. At initial MAA, the safety concern: 'Risk of pIMDs following Shingrix vaccination' was classified as important potential risk (theoretical risk considered for all vaccines containing adjuvant systems). The data showed no confirmed safety signal for a new pIMD onset at MAA, and in the pharmocovigilance setting. The same conclusion applies for the present studies in IC. Imbalances were observed, but available data are limited, considering the incidence of these diseases. This risk of pIMDs is followed by active surveillance and addressed by two PASS.

The important potential concern Virus reactivation in individuals with a history of Herpes Zoster is included in the safety concerns of the RMP based on an observation in a small study in subjects ≥50 YOA. A new study is ongoing in subjects ≥50 YOA to further evaluate this observation (ZOSTER-062).

In patients at high-risk of such conditions, the data point to non-statistically significant imbalances in febrile neutropenia and pneumonia over the period up to 30 days post second vaccination (approximately two fold increased frequency in vaccinated vs. placebo). These events will be followed in the PSUR.

There is no information on the use of Shingrix in VZV naïve individuals or individuals previously vaccinated against varicella. The SmPC reflects that Shingrix is not indicated for prevention of primary varicella infection. Vaccination of individuals previously vaccinated against varicella requires individual B/R assessment.

A total of 1,587 Immunocompromised subjects received at least 1 dose of HZ/su (443 subjects 18-49 YOA and 1,144 subjects ≥50 YOA). The safety database of IC patients is limited and the population of IC patients is extremely heterogeneous. Uncertainties thus remain with respect to the adverse events induced by vaccination in IC populations, and within subgroups of this population.

There is limited safety data in patients with chronic diseases even if a substantial number of adults ≥50 YOA with co-morbidities, the most frequently reported being COPD, type II diabetes mellitus, asthma, depression, respiratory disorders and renal disorders, were included in the pivotal studies ZOSTER-006 and ZOSTER-022 submitted in the initial MAA.

Subjects were followed up at least a year in the pivotal trials, and the median follow up period is 21 months in the largest trial (ZOSTER-002). Long term safety is not established in the IC population.

Safety and reactogenicity of booster dose(s) is not established in the IC population.

3.6. Effects Table

Table 99: Table 1. Effects Table for Shingrix for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), adults 18 years of age or older at increased risk of HZ

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
VE against	Based on	Number of	49 (30.0)	135 (94.3)	Primary	ZOSTER-

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
confirmed HZ	mTVC: Vaccine, n= 870 Placebo, n= 851 Autologous HCT recipients	subjects having at least one confirmed HZ episode (incidence per 1000)			endpoint; Strong evidence	002
		% (95% CI)	68.2 (55.6-77.5); p<0.0001 Over a median FU of 21 months			
VE against confirmed HZ	Based on mTVC: Vaccine, n= 259 Placebo, n= 256 Hematologic malignancies	Number of subjects having at least one confirmed HZ episode (incidence per 1000)	2 (8.5)	14 (66.2)	Post-hoc analysis	ZOSTER-039
		% (95% CI)	87.2 (44.3-98.6); p=0.0021 Over a median FU of 11 months			
VE against PHN	Based on mTVC: Vaccine, n= 870 Placebo, n= 851	Number of subjects with PHN (incidence per 1000)	1 (0.5)	9 (4.9)	Secondary endpoint	ZOSTER-002
		% (95% CI)	89.3 (22.5-99.8); p=0.0186 Over a median FU of 21 months			
VE against confirmed-HZ associated complications (other than PHN)	Based on mTVC: Vaccine, n= 870 Placebo, n= 851	Number of subjects with confirmed-HZ associated complications (incidence per 1000)	3 (1.6)	13 (7.1)	Secondary endpoint	ZOSTER-002
		% (95% CI)	77.8 (19.1-95.9); p=0.0175 Over a median FU of 21 months			
Reduction of the total duration of severe 'worst' HZ-associated pain	Based on subjects with a confirmed HZ episode: Vaccine, n= 49 Placebo, n= 135	Number of subjects with at least one day of severe 'worst' HZ-associated pain	37	120	Secondary endpoint	ZOSTER-002
		% (95% CI)	38.5 (11.1-57.5); p=0.0099			
		Median duration (min-max) in days	14.0 (1.0-178.0)	24.0 (1.0-1025.0)		
Reduction of duration of pain medication associated with confirmed HZ	Based on subjects with a confirmed HZ episode: Vaccine, n= 49 Placebo, n= 135	Number of subjects with a least one day of pain medication associated with HZ	32	94	Tertiary endpoint	ZOSTER-002
		% (95% CI)	22.5 (-15.9-48.1); p=0.2144			
		Median duration (min-max) in days	21.5 (1.0-436.0)	47.5 (1.0-1642.0)		
VE against confirmed HZ 1 year post-HCT	Based on: Vaccine, n= 870 Placebo, n= 851	Number of subjects having at least one confirmed HZ episode (incidence per 1000)	21 (40.7)	82 (170.6)	Tertiary endpoint	ZOSTER-002
		% (95% CI)	76.2 (61.1-86.0); p<0.0001			
VE against confirmed HZ-related hospitalization	Based on mTVC: Vaccine, n= 870 Placebo, n=	Number of subjects with confirmed-HZ associated hospitalisation	2 (1.1)	13 (7.1)	Tertiary endpoint	ZOSTER-002

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	851	(incidence per 1000)				
		% (95% CI)	84.7 (32.2-96.6); P=0.0135			
VE in preventing PHN in subjects with confirmed HZ	Based on subjects with a confirmed HZ episode: Vaccine, n= 49 Placebo, n= 135	Number of subjects with PHN (%)	1 (2.0)	9 (6.7)	Tertiary endpoint	ZOSTER-002
		% (95% CI)	69.4% (-77.4-95.0); p=0.2941			
Demonstration of humoral and cellular immunogenicity	Based on: Humoral: 560 vaccinees (5 studies) CMI: 199 vaccinees (5 studies)	Range of anti-gE Ab GMC (IU/ml) one month post-dose 2 Range of frequency CD4 [2+] CD4 T cells (%)one month post-dose 2	12,753-42,723 779-6,645	-	Both humoral and cellular immune responses remained higher than baseline level up to 1 year	ZOSTER-002, ZOSTER-028, ZOSTER-039, ZOSTER-041, ZOSTER-015
Unfavourable Effects						
Solicited local symptoms (mainly injection site pain)	Based on TVC: Vaccine, n= 1454 Placebo, n= 1450	Range of frequency (% subjects) Median duration (days)	83.8-87.8 (85.8 in ZOSTER-002) Grade 3: 10.7-14.2 (14.2 in ZOSTER-002) 3.0	6.4-17.5 (10.4 in ZOSTER-002) Grade 3: <0.5 (0.3 in ZOSTER-002)	Risk of local AE is increased vs. Placebo	Main pooled safety analysis (4 pivotal trials)
Solicited systemic symptoms (mainly myalgia, fever, shivering)		Range of frequency (% subjects)	68.7-81.3 (75.2 in ZOSTER-002) Grade 3: 9.9-22.3 (13.2 in ZOSTER-002)	48.9-66.4(50.9 in ZOSTER-002) Grade 3: 6.0-15.5 (6.0 in ZOSTER-002)	Risk of systemic AE is increased vs. Placebo. Risk of systemic AE high in the IC Placebo group due to underlying disease	Main pooled safety analysis (4 pivotal trials)

Abbreviations: VE: Vaccine Efficacy, HZ: Herpes Zoster, PHN: Post-herpetic neuralgia, CI: Confidence Interval, FU: Follow-up, GMC: Geometric Mean concentration; CMI: Cellular-Mediated Immunity

Notes: * number of subjects with at least one day of severe 'worst' HZ-associated pain. ** number of subjects with a least one day of pain medication associated with HZ

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Shingrix clearly demonstrated efficacy in protecting adult autologous HCT patients against HZ, when vaccinated only 50-70 days after the transplant (68.17% [95% CI: 55.56% - 77.53%] over 21 months). Shingrix also reduced the incidence of PHN (VE of 89.27% [95% CI: 22.54% - 99.76%]) and other HZ related complications, as well as the severity and duration of pain.

The immune responses tended to be different between the IC subpopulation studied between in the pivotal trials. Nonetheless, vaccine-induced humoral and cellular immune responses were demonstrated in the 5 studied IC populations, i.e. autologous HCT adult recipients, HIV infected adults, adults with solid tumors and receiving chemotherapy, adults with hematologic malignancies who were vaccinated during a cancer therapy course or after the full cancer therapy course, and renal transplant recipients. There is no established CoP for Shingrix, and the level of efficacy can therefore not be derived from the immunogenicity data generated in the other IC populations.

It is considered that these data proof the ability of Shingrix to protect IC patients, in whom the burden of HZ is high. The magnitude of the protective effect might be lower in subgroups of this population, and may vary according to disease and in patients under immunossupressive (IS) therapies, according to the type and timing of the therapy. The level of efficacy in patients under concomitant IS therapy is not known.

The duration of VE against HZ and PHN beyond 21 months is unknown in IC patients.

As in immunocompetent adults ≥50 YOA, Shingrix induces high transient local and systemic reactogenicity in IC adults. Fever and severe reactogenicity were not uncommon. These adverse reactions do not last more than a few days.

There is only very limited data from the early development of Shingrix for individuals 18-49 YOA who are not IC.

Based on the data submitted at MAA, there was no identified risk. Shingrix has been largely used since first approval and no safety signal was confirmed based on the routine pharmacovigilance system (since 13 October 2017, exposure to Shingrix is estimated to be between 5 818 118 and 11 636 236 subjects). No safety signal has been confirmed in the IC studies. However, febrile neutropenia and pneumonia need to be further monitored and discussed through the PSUR.As in immunocompetent individuals, this adjuvanted vaccine could trigger exacerbations of pre-existing pIMDs in IC patients. There is also a theoretical risk of triggering pIMDs, as for all vaccines containing adjuvant systems (important potential risk included in the RMP).

Given the limited safety database and the heterogeneity of the IC population, important uncertainties remain with respect to the adverse events induced by vaccination in IC populations, and within subgroups of this population.

3.7.2. Balance of benefits and risks

The efficacy data in patients with autologous HCT and/or hematologic malignancies, together with the evidence of robust immune responses in other IC populations, brought the proof that Shingrix is able to protect IC patients from HZ and PHN, as well as to reduce the burden and severity related to HZ in them. Altogether it is considered likely that Shingrix provides a benefit in adult patients with immunosuppressive conditions or therapies, in whom HZ may be particularly frequent and severe.

Uncertainties remain as to the level of efficacy according to the various diseases and according to the type and timing of the IS therapies. The main uncertainty is for patients under ongoing IS therapies. Uncertainties also remain about whether the efficacy is sustained over time.

The population targeted by the proposed indication is broader than the population included in the submitted IC trials. Beside immunosuppression, many conditions and individual characteristics lead to an increased risk of HZ. Both the very high efficacy demonstrated in immunocompetent subjects ≥50 YOA (including patients with comorbidities), and the evidence of efficacy in patients with hematologic malignancies, provide high reassurance about the benefit of Shingrix in the indication.

The reactogenicity profile of HZ/su in IC ≥18 YOA is similar to that in adult ≥50 YOA. There are very limited reactogenicity and safety data in individuals 18-49 YOA who are not IC.

Based on the data submitted at MAA, there was no identified risk. Since first approval in October 2017, it is estimated that 6-12 million persons have been exposed to Shingrix and no safety signal was confirmed based on routine pharmacovigilance. No safety concern related to the use of Shingrix was identified in the IC populations.

There is a theoretical risk of inducing pIMDs and to exacerbate pre-existing pIMDs, as with all vaccines containing adjuvant systems.

It is considered that the benefit largely outweighs the unfavourable effects linked mainly to reactogenicity.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Shingrix in the applied indication is positive. The extension of indication can be recommended for approval.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I II, IIIA and IIIB

Extension of Indication to include a new population for Shingrix: adults 18 years of age or older at increased risk of Herpes Zoster supported by the clinical studies ZOSTER-002 (MEA 001), ZOSTER-039 (MEA 002), ZOSTER-041 (MEA 003), ZOSTER-028 (MEA 004), ZOSTER-001 and ZOSTER-015.

As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated in order to delete a warning and to add new safety and efficacy information. The Package Leaflet is updated in accordance. The RMP version 2.2 has also been approved.

In addition, the list of excipients has been updated in section 6 of the SmPC.

Furthermore, the MAH took this opportunity to implement some editorial changes in Annex II and IIIA.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIA and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0222/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Shingrix-H-C-004336-II-0022'