EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 January 2018
EMA/88588/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Shingrix

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

Procedure No. EMEA/H/C/004336/0000

Note

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

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List of abbreviations

Ab	Antibody
AE	Adverse Event
AS	Active Substance
$AS01_B$	Adjuvant System containing 50 µg MPL, 50 µg QS-21 and liposomes
BOI	Burden of Illness
CD4	Cluster of differentiation marker 4
CD8	Cluster of differentiation marker 8
CDP	Clinical Development Program
CFC	Cells Flow Cytometry
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovarian cells
CI	Confidence Interval
CLB	Concentrated Liposome Bulk
CMI	Cell Mediated Immunity
CPV	Continued Process Verification
CSR	Clinical Study Report
DOPC	Dioleoyl Phosphatidylcholine
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency, EU
EOS	End of Study
EPC	End-of-Production Cell bank
EU	European Union
FB	Final Bulk
FC	Final Container
FDA	Food and Drug Administration, US
FLU-D-QIV	GSK's unadjuvanted quadrivalent seasonal influenza vaccine
FP	Finished Product
GCP	Good Clinical Practice
gE	Glycoprotein E
GM	Geometric Mean
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
HCP	Host Cell Protein
HCT	Haematopoietic stem Cell Transplant
HI	Haemagglutinin Inhibition
HIV	Human Immunodeficiency Virus
HP	Hydrogen Peroxide
HZ	Herpes Zoster
HZO	HZ Ophthalmicus

HZ/su	The herpes zoster subunit candidate vaccine (50 µg gE/AS01$_B$), also called gE/AS01$_B$ candidate vaccine
IC	Immunocompromised
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon gamma
IM	Intramuscular
IgG	Immunoglobulin G
IL-2	Interleukin 2
L	Litre
LB	Liquid Bulk
LL	Lower Limit
LPS	Lipopolysaccharide
MCB	Master Cell Bank
MGI	Mean Geometric Increase
MPL	3-*O*-desacyl-4'-monophosporyl Lipid A
NOAEL	No-Observed Adverse Effect Level
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
Ph. Eur.	European Pharmacopoeia
PHN	Post-herpetic Neuralgia
PIP	Paediatric Investigation Plan
PM	In Process Monitoring
PP	Process Parameters
PPQ	Process Performance Qualification
PRNT	Plaque Reduction Neutralization Test
PS80	Polysorbate 80
QA	Quality Attributes
QC	Quality Control
QoL	Quality of Life
QS-21	*Quillaja saponaria* Molina fraction 21
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
RR	Relative Risk
SAE	Serious Adverse Event
SC	Subcutaneous
SCR	Seroconversion Rate
SmPC	Summary of Product Characteristics
SPR	Seroprotection Rate
TNF-α	Tumour Necrosis Factor alpha
TSE	Transmissible Spongiform Encephalopathy
TTC	threshold of toxicological concern
TVC	Total Vaccinated Cohort

UL	Upper Limit
VE	Vaccine Efficacy
VHP	Vaporised Hydrogen Peroxide
VRR	Vaccine Response Rate
VZV	Varicella Zoster Virus
YOA	Years Of Age
WFI	Water For Injection
ZBPI	Zoster Brief Pain Inventory

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant GSK Biologicals SA submitted on 25 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Shingrix, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The Applicant applied for the following indication:

Shingrix is indicated for prevention of herpes zoster (HZ) and HZ-related complications, such as post-herpetic neuralgia (PHN), in adults 50 years of age or older.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The Applicant indicated that Varicella Zoster Virus glycoprotein E antigen was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on Applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0168/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0168/2013 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 Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The Applicant requested the active substance Varicella Zoster Virus glycoprotein E antigen contained in the above medicinal product to be considered as a new active substance, as the Applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The Applicant received Scientific Advice from the CHMP on 24 April 2008, 24 September 2009, 21 January 2010, 19 January 2012, 20 September 2012, 20 March 2014, 1 April 2016 and 26 May 2016. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bart Van der Schueren Co-Rapporteur: Jan Mueller-Berghaus

- The application was received by the EMA on 25 November 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 23 March 2017.
- During the meeting on 24 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2017.
- The following GCP inspection were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
    - A GCP inspection at 3 sites: investigator sites in Brazil and in Taiwan and the sponsor in Belgium between 8 May 2017 and 12 May 2017, 7 March 2017 to 10 March 2017 and 15 May 2017 to 18 May 2017 respectively. The outcome of the inspection carried out was issued on 19 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant’s responses to the List of Questions to all CHMP members on 21 August 2017.
- During the PRAC meeting on 1 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the Applicant.
- The Applicant submitted the responses to the CHMP List of Outstanding Issues on 8 November 2017.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant’s responses to the List of Outstanding Issues to all CHMP members on 30 November 2017, 8 December 2017, 11 January 2018 and 19 January 2018.
- During the meeting on 22-25 January 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Shingrix on 25 January 2018.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Herpes zoster (HZ), commonly known as shingles, is caused by the reactivation of the varicella zoster virus (VZV). The clinical manifestation is a unilateral vesicular rash, characteristically restricted to a single dermatome, which is usually accompanied by radicular pain along that dermatome. Patients experience significant pain and discomfort that may last for weeks, months or even years in severe cases, diminishing the quality of life. Mortality rates associated with HZ ranged from 0.01 to 0.46 per 100,000 persons-years and the majority of deaths occurred in adults ≥ 60 years of age. When considering HZ coded as primary and secondary diagnosis, the mortality rate was estimated as 0.29 per 100,000 person-years in France and 0.6 per 100,000 person-years in Spain.

Disease incidence

More than 90% of adults have been infected with VZV and are, therefore, at risk of developing herpes zoster.

Studies using various designs and conducted in different populations in the US, Canada, South America, Europe, Asia and Australia showed that the incidence of HZ ranged between 3 and 5 per 1,000 person-years. The age-specific incidence of HZ is similar across countries, with a steep rise after 50 years of age. The incidence of HZ was about 6-8 per 1,000 person-years at 60 years of age and 8-12 per 1,000 person-years at 80 years of age. The incidence and severity of herpes zoster disease increase with age, with an exponential increase in incidence after the age of 50 years, which correlates with ageing-related decline in cell-mediated immunity. Among adults aged 22 years and over, approximately 70% of HZ cases occur after 50 years of age. Among adults who reach 85 years of age, it is estimated that approximately half will have suffered at least one episode of HZ.

A study of 27 countries in Europe showed HZ incidence varying by country from 2.0 to 4.6/1 000 person-years with no clearly observed geographic trend. Surveillance activities to monitor the incidence of herpes zoster and assess the impact of varicella and zoster vaccination are more frequently reported from those countries having introduced one or both of these vaccines into routine childhood and/or adult immunization schedules.

There is scarcity of literature on VZV and HZ incidence in low and middle income countries. Most estimates of HZ incidence have been made in developed countries with temperate climates. Where the burden of disease of VZV and HZ are compared, the burden of HZ is higher, mainly due to longer hospital stays. However, challenges with studying the herpes zoster health burden, especially in elderly populations, include appropriate attribution of herpes zoster as the primary cause of severe morbidity or mortality rather than a contributing cause or a coincidental finding. In developed countries, the lifetime risk of herpes zoster disease is approximately 30%.

2.1.2. Epidemiology and risk factors

Epidemiology of Varicella zoster virus (VZV)

Since a prerequisite for developing HZ is a past primary VZV infection, the epidemiology of varicella may also affect the epidemiology of HZ. There is some variation described in the epidemiology of VZV

infection between temperate and tropical climates. More than 90% of primary VZV infections in temperate climates occur before adolescence, in contrast to the tropics where a higher proportion of adults have not yet been infected with VZV. However, available data on varicella incidence and seroprevalence that is representative and population-based, suggest that it is uncommon not to acquire varicella by 40-50 years of age even in the tropical countries though exceptions exist, especially in island populations such as Sri Lanka.

Mathematical models that assume that external boosting plays an important role in maintaining VZV cell mediated immunity, and thereby delaying the onset of zoster in those who had primary VZV infection, predict that universal childhood varicella vaccination immunization programs will impact the incidence of herpes zoster, theoretically by reducing exposure to circulating wild virus and subsequent boosting.

Whilst an increase in herpes zoster incidence has been observed in the US and in other countries with childhood varicella vaccine programs, increasing trends have been noted in countries not using varicella vaccine universally in children. Additionally, in the US, the trend precedes the introduction of universal varicella vaccination and the rate of increase in herpes zoster did not change in the pre and post vaccine time periods suggesting that other factors are affecting the increase.

Studies continue to examine this issue and to explore what factors, including potentially vaccination, may be responsible for the increasing trend observed widely throughout the developed world.

Risk factors

Age is the most important risk factor for development of PHN, with most cases occurring in adults over 40 years of age and adults over 70 years having a four times increased risk of PHN than those younger than 60 years.

Besides increase in age, immunosuppression from any cause, including hematologic malignancies, HIV and immunosuppressive medications, is an important risk factor for herpes zoster, increasing the risk of HZ by at least 10-fold. An increased risk of HZ has been reported in infants whose mothers had had varicella in pregnancy. Prompt antiviral therapy, if available, is recommended for herpes zoster in healthy and immunocompromised patients.

Ethnicity is also a well described risk factor. Studies in both the US and UK reported that subjects from African ancestry and Hispanic ethnicity seem to be less susceptible (about one fourth to a half) to HZ than Caucasians. Other identified risk factors include stress or trauma, diabetes and female gender.

2.1.3. Aetiology and pathogenesis

The VZV remains dormant inside multiple dorsal root ganglia after the initial varicella infection with the virus. Subclinical reactivation can occur intermittently in immunocompromised and immunocompetent individuals with detection of VZV DNA in the blood with consequent boosting in immunity (endogenous boosting) or after exposure to varicella or HZ (exogenous boosting). Some studies have found that re-exposure to varicella-zoster virus or to children < 10 years is associated with a decreased risk of developing herpes zoster at a later stage in life, whereas other studies have not found this association. Clinical VZV reactivation (herpes zoster) occurs as result of a reduction in the level of T-cell immunity to VZV, described as the main mechanism of protection against herpes zoster, which is observed with increasing age.

Reactivation leads to ganglionitis with damaging of neurons and supporting cells followed by an intense inflammatory response. In 70-80% of herpes zoster cases, prodromal pain occurs, restricted to the affected dermatome. Vesicles appear for 3-4 days, followed by umbilication, ulceration and crusting of

the lesions. The rash is accompanied by pain which may be severe. The most common serious complication of herpes zoster is post-herpetic neuralgia (PHN), defined as pain that persists more than a defined period of time (90 days was used in the vaccine clinical trials), after onset of rash or after cutaneous healing. About 20% of patients with herpes zoster will develop PHN.

Other serious complications of herpes zoster include blindness secondary to ophthalmic zoster, bacterial superinfections of zoster skin lesions and disseminated infections, which occur more commonly in immunocompromised patients. Based on limited available data from 366 mothers, herpes zoster during pregnancy does not appear to increase the risk of intrauterine infection in the unborn.

2.1.4. Clinical presentation

Herpes zoster (HZ) is the reactivation of a viral infection caused by the same virus that causes chickenpox as primary infection (varicella-zoster virus, VZV). After the primary infection, the virus migrates to the central nervous system, where it establishes latency in sensory neurons of cranial and dorsal root ganglia. Following a variable period during which it remains latent, it can reactivate later in life to cause HZ.

HZ typically presents as an acute, painful, vesicular eruption distributed along a single dermatome. During the eruptive phase, acute local neurological pain occurs in up to 90% of immunocompetent individuals. The prodromal phase is typically 3-4 days in duration, but longer durations of ≥ 1 week are not uncommon. Fever, malaise and headache may be present. The rash typically heals in 2-4 weeks but may leave scaring and pigmentation changes. The median duration of acute pain is 2 weeks.

Post-herpetic Neuralgia (PHN) is the most common severe complication of HZ and can last for weeks, months or even years. PHN is a complex neuropathic pain condition which is a consequence of the nerve damage caused by the reactivation of VZV in the ganglia. The more conventional definition of PHN is dermatomal pain of clinically significant intensity, persisting at least 90 days after the appearance of the acute herpes zoster rash.

Other less frequent complications of HZ include HZ Ophthalmicus (e.g. keratitis, retinitis, glaucoma, optic neuritis), Ramsay Hunt Syndrome (HZ oticus), central nervous system complications (such as VZV encephalitis, meningitis, myelitis). Disseminated zoster (> 20 skin lesions outside a single dermatome), secondary bacterial infection with Staphylococcus aureus and, rarely, purpura and necrosis are also reported.

2.1.5. Management

Treatment of HZ

Oral antiviral therapy should be commenced as early as possible, within 72 hours of rash onset. Treatment is usually given for 7 days in the absence of complications of herpes zoster. 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.

Management of acute pain associated with herpes zoster is complex. A variety of approaches have been used with varying degrees of success, including acetaminophen, non-steroidal anti-inflammatory agents, tricyclic antidepressants, opiates, anticonvulsants, capsaicin, and topical anaesthetics. Conflicting evidence exists on the use of opioids.

Management of chronic pain associated with herpes zoster is challenging, too. A recent Cochrane review considered all randomized controlled trials (RCTs) of antiviral treatment given within 72 hours

after the onset of HZ for preventing PHN. The authors conclude that there is evidence that oral acyclovir does not significantly reduce the incidence of PHN, while there is insufficient evidence to determine the effect of other antiviral treatments. Treatment of PHN is aimed to control symptoms, as no disease-modifying therapy is currently available. Furthermore, the addition of systemic glucocorticoids to antiviral drugs during the acute phase of HZ does not reduce the incidence of PHN.

Systemic drugs are combined when pain is moderate or severe, despite the lack of robust evidence from RCTs showing a benefit of the combination compared to the single components. Among the systemic treatments, there is evidence to support the use of tricyclic antidepressants and the anti-epileptic drugs gabapentin and pregabalin. A recent Cochrane review has concluded that there is no convincing and unbiased evidence of a benefit of oxycodone in treating PHN.

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. Conflicting evidences exist on the use of potent opioids (such as oxycodone) and tramadol in treating PHN. 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.

Current prophylaxis of HZ

A live attenuated herpes zoster vaccine (Zostavax, Merck) was first licensed in 2006 and is currently licensed in over 60 countries including those in the EU, US, Canada and Australia. This VZV vaccine contains an OKA derived VZV strain that is given in a single dose and administered subcutaneously. It is licensed for use in immunocompetent individuals 50 years and over in Europe, Australia and the U.S. Recommendations for routine vaccine administration have been made in countries in Europe, US and Asia including Austria, Czech Republic, France and the UK.

Zostavax is contraindicated for people with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin, or any other component of the vaccine; with a history of primary or acquired immunodeficiency state, including leukemia, lymphoma, or other malignant neoplasm affecting the bone marrow or lymphatic system, or with acquired immunodeficiency syndrome or other clinical manifestation of infection with human immunodeficiency viruses; those receiving immunosuppressive therapy, including high-dose corticosteroids; or those who are or may be pregnant.

Unmet medical need

Shingrix was developed to address the medical need to prevent HZ and HZ-related complications such as post-herpetic neuralgia (PHN) in older adults (≥50 YOA) and to address the unmet medical need to prevent HZ and HZ complications in IC adults ≥18 YOA. The term HZ/su indicates the herpes zoster subunit candidate vaccine (50 µg gE/AS01 B) during clinical development, also called gE/$AS01_B$ candidate vaccine. Either of these names, but mostly HZ/su, is used in this report to indicate Shingrix.

About the product

HZ/su is a recombinant subunit vaccine (VZV gE), designed to induce strong cellular and humoral immune responses in individuals with pre-existing immunity against VZV and who are at increased risk of developing HZ due to age or immunodeficiency. To enhance both the magnitude and the duration of the protection, the gE antigen is combined with $AS01_B$. HZ/su was designed to be efficacious in persons at highest risk for HZ due to their weakened immune systems, in particular adults ≥70 YOA and IC adults. In addition, as HZ/su does not contain live virus, it is expected to be suitable for use in IC adults.

The HZ/su clinical development was designed to support the marketing authorization of HZ/su as a prophylactic vaccine for the prevention of HZ and HZ-related complications in persons at risk of HZ ≥ 50 YOA.

Type of Application and aspects on development

- Legal basis

  Article 8.3 of Directive 2001/83/EC - complete and independent application.

  Shingrix falls under the “mandatory scope” criterion (the Art. 3(1) of the (EC) No. 726/2004 Annex (1) Biotech medicinal product)

- Accelerated procedure

  N/A

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as a powder and suspension for suspension for injection containing 50 µg of glycoprotein E (gE) antigen (powder) adjuvanted with $AS01_B$ (suspension). Varicella Zoster Virus (VZV). gE is produced by recombinant DNA technology in Chinese Hamster Ovarian (CHO) cells. The $AS01_B$ adjuvant system is composed of 50 µg each of the immunoenhancers: plant extract Quillaja saponaria Molina, fraction 21 (QS-21™ and 3-O-desacyl-4’-monophosphoryl lipid A (MPL) from *Salmonella minnesota* (50 micrograms). These are combined with liposomes, which consist of the excipients dioleoyl phosphatidylcholine (DOPC) and cholesterol. These and all other excipients are listed below.

Other ingredients are:

Powder (gE antigen): sucrose; polysorbate 80; sodium dihydrogen phosphate dihydrate; dipotassium phosphate.

Suspension ($AS01_B$ adjuvant system): dioleoyl phosphatidylcholine; cholesterol; sodium chloride; disodium phosphate anhydrous; potassium dihydrogen phosphate; water for injections.

The monodose product (powder and suspension) is supplied in separate type I glass vials with butyl rubber stoppers.

2.2.2. Active substance

General information

VZV gE is the most abundant virion envelope glycoprotein and the predominant VZV glycoprotein expressed on the surface of VZV-infected cells. This protein plays a critical role in VZV infectivity as it is involved in virus entry and cell-to-cell spread of the virus. Structurally, VZV gE is a monomeric transmembrane glycoprotein of 623 amino acids (with a 30-amino acid cleavable signal sequence). This protein consists of a hydrophilic extracellular region (amino acids 1 to 544), a hydrophobic transmembrane domain (amino acids 545 to 561) and a C-terminal cytoplasmic tail (amino acids 562 to 623). The truncated version of the protein lacks the transmembrane anchor and carboxy-terminal domain and is therefore secreted into the culture supernatant when produced in CHO cells.

The product contains an active substance (AS) that has not previously been authorised in the EU and is therefore qualified as a new active substance.

Manufacture, process controls and characterisation

The name and address of the manufacturer involved in the manufacture and testing of the active Substance (AS) is GlaxoSmithKline Biologicals SA (Wavre Nord site): Parc de la Noire Epine, Avenue Fleming 20, 1300 Wavre (Belgium).

Description of manufacturing process and process controls

VZV gE antigen is produced in a bioreactor at production scale. First, a vial from the working cell bank (WCB) is thawed and cell culture is initiated. Cells are expanded at small scale before being transferred to the production bioreactor where the gE protein is secreted in the culture medium. At the end of the culture step, the harvested culture fluid is clarified by depth filtration. The clarified harvest is further processed by several purification steps, including different types of chromatography, ultrafiltration, nanofiltration, low pH treatment step for viral inactivation, a nanofiltration and filtration for bioburden control before freezing and storage. The filtered bulk antigen is filled into sterile containers and stored at -45°C. There is no reprocessing during AS manufacture.

One single cell culture provides one single harvest (intermediate) on which one single clarification is performed. From this, one single batch of gE bulk antigen is obtained by purification (gE Purified Bulk).

In-process monitoring (PM) tests and Quality Control (QC) tests are used throughout the AS manufacturing process and appropriate alert and/or action limits are established from historical data. The active substance manufacturing process is considered acceptable.

Control of materials

The CHO-K1 cell line used was derived from a parental CHO cell line. For the establishment of the pre-master cell bank: cells were transfected with the plasmid bearing the coding sequence of a truncated VZV gE antigen; a clone expressing high levels of gE was selected and further cultured in serum-free conditions.

The establishment of master and working cell banks (MCB and WCB, respectively) is described as is establishment of an end-of-production cell bank (EPC). Testing is in compliance with ICH 5A and 5D guidance and relevant Ph. Eur. monographs, confirming identity, freedom from adventitious agents and plasmid integrity. Genetic stability of the modified cells was tested by analysis of MCB, WCB and EPC. All raw materials and solutions used for cell culture and further steps have been described in detail. Evaluation of adventitious agents and TSE safety has been conducted extensively to confirm that no undue risk of contamination exists due to the materials applied for manufacture.

The composition of solutions and materials was provided. No human or animal-derived raw materials are used for the AS manufacturing process. Materials of human or animal-derived origin used in early steps of cell bank preparation have been adequately evaluated from a TSE and viral safety perspective (See adventitious agents section). All raw materials used in the AS manufacturing process are obtained with certificates of analysis from their respective suppliers and confirmatory identity and/or release testing are undertaken as necessary. Compendial raw materials are tested in accordance with the corresponding monograph.

Control of critical steps and intermediates

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical quality attributes (QA), process parameters (PP) and in-process tests. Clarification about actions taken if in-process tests

limits are exceeded were provided during the procedure. The company performs Quality Control (QC) release tests on the gE single harvest intermediate, on the AS and on the FP.

The gE Single Harvest step marks the end of the cell culture before purification, and is extensively tested for absence of adventitious agents. The gE Single Harvest intermediate is not stored; it is processed directly through the purification steps. Satisfactory quality control (QC) release testing results from gE single harvests used to prepare commercial and phase III clinical lots are provided. These also include testing for bioburden and adventitious viruses. The impact of storage or holding time steps applied during the AS manufacturing was approprietely assessed

Process validation

Five VZV gE Purified Bulk commercial scale/ process batches were produced at the commercial facility. Three of these (referred to as Process Performance Qualification PPQ) lots were used to demonstrate consistency and comparability to reference batches (phase III clinical batches and representative technical development batches).

The data includes an extensive technical package including process monitoring tests, process measurements, QC release and characterisation tests. All Critical Process Parameters (CPPs) were evaluated against the batch documentation targets and/or operating ranges to demonstrate consistency and control of the process. Process performance qualification (PPQ) performed by production of three full scale PPQ batches were tested and compared to reference batches (phase III clinical batches and technical development batches) in terms of manufacturing yield, gE protein recoveries and clearance profiles. These PPQ batches complied with the QC release acceptance criteria and also the extended characterization criteria including physico-chemical and immunological properties of gE. Validation also addressed clearance of host-cell proteins, endotoxin, DNA and bioburden. The ultrafiltration membrane and chromatography columns lifetime has been validated.

A Continued Process Verification (CPV) approach is used to provide assurance that the process remains in a state of control during routine commercial manufacturing. Process parameters, process performance attributes and product quality attributes are monitored, evaluated for trending, and reviewed for potential process improvements.

In general, the data presented demonstrate that the VZV gE manufacturing process is validated to meet process and product requirements.

Manufacturing process development

The AS manufacturing process has evolved during clinical and commercial development. As of 2014, the AS manufacturing process was transferred to the Company's commercial facilities and commercial gE Purified Bulk batches were produced.

The main changes introduced throughout development were scale-up, changes in antigen production to improve the yield, changes in the purification to improve antigen recovery, addition of a pH treatment step to ensure viral clearance robustness, optimization for the chromatography steps, increase of long-term stability of the active substance by storage of the gE Purified Bulks at -45°C, transfer of the manufacturing between different facilities which, for the last manufacturing development step involved transfer from the industrialisation facilities to the commercial facilities at Wavre-Nord.

Clinical batches applied in Phase III clinical trials have all been derived from full-scale processes that were quite close to the final commercial process. The data reported adequately confirm comparability of batches from different process stages.

A detailed description of the container closure system was provided. Container-closure integrity and sterility testing was performed. Leachables and extractables studies were conducted. The container closure system is adequately qualified.

Characterisation

The physico-chemical (including primary and secondary structure) and immunological properties of the AS were assessed using different analytical techniques. The gE antigen is a purified recombinant monomeric glycosylated protein; its molecular mass ranges between 67,000 and 68,000 Da, due to heterogeneity related to N-terminal clipping and a series of posttranslational modifications, such as O- and N-glycosylation, sialylation, sulphation and/or phosphorylation. This heterogeneity is inherent to the molecule and does not cause concern. Characterisation data are presented for the five gE purified bulk batches that were manufactured as part of the first commercial campaign (including the three PPQ lots). In addition, for each analytical method used, the data generated on the five batches are presented along with data from at least one clinical batch from previous clinical campaigns.

The characterisation data largely demonstrate that the production process used in the clinical phase III and first commercial campaigns results in batches which are consistent and comparable, and in which the antigen has retained its physico-chemical and immunological properties, as well as its purity profile, after transfer to the commercial facility.

The process- and product-related impurities present in the AS have been investigated:

- process-related impurities- including HCP, DNA.
- product-related impurities- including degradation impurities.

The concentration of these impurities was measured in the purified bulks of batches produced for the first commercial campaign. DNA clearance was assessed as part of process validation. Other process-related impurities and host cell proteins were also tested as part of characterisation of the gE purified bulk. Overall purity of the AS is very high and levels of process and product-related impurities are acceptable (very little protein degradation occurs during manufacture and during shelf life).

Specification

The AS specifications include appropriate tests for identity, physiochemical properties (pH, appearance, osmolality), antigen content, purity of gE antigen, relative abundance of gE primary sequence, impurities and protein content. The specifications are considered acceptable.

Analytical methods

For compendial analytical procedures, the company has made reference to Ph. Eur. monographs (pH, endotoxin). All in-house analytical procedures for the QC release of commercial gE purified bulks have been validated according to the relevant ICH guideline Q2 (R1).

Batch analysis

Batch analysis data (from commercial process and scale PPQ lots) of the active substance (VZV gE commercial Purified Bulk) were provided. QC release testing results for additional commercial batches of AS were also provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

A reference standard is used for the following tests: identity gE and antigenic activity gE. The reference standard is a gE Final Container development lot. There is no international standard available.

Stability

The company proposes a shelf-life of 60 months for gE Purified Bulks stored at - 45°C ± 10 °C.

Real time, real condition stability data on PPQ batches of active substance from the commercial manufacturing process stored in the intended container for 24 months and for up to 7 days under accelerated conditions at +37°C ± 2°C were provided. For ongoing studies, in accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Furthermore, stability data from one phase III Efficacy gE AS batch (- 45°C ± 10 °C for up to 74 months, +37°C ± 2°C for 7 days) and three phase III Consistency gE AS lots (- 45°C ± 10 °C for up to 72 months, +37°C ± 2°C for 7 days) were also provided.

These stability studies demonstrated that the tested stability-indicating parameters met the acceptance criteria for all gE Purified Bulk batches (Phase III Efficacy, Phase III Consistency and Commercial Consistency gE Purified Bulk batches).

Since the Phase III batches can be considered as representative of the commercial product (see AS Manufacturing process development section), the proposed shelf-life of 60 months for gE Purified Bulks stored at - 45°C ± 10 °C is acceptable.

2.2.3. Finished medicinal product- $AS01_B$ suspension (adjuvant system) vial

The finished product is presented as an adjuvant system vial and a powder vial (antigen).

Description of the product and Pharmaceutical development-$AS01_B$ suspension (adjuvant) vial

The primary packaging is a type I glass vial with butyl rubber stopper. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The $AS01_B$ adjuvant system is composed of two immunoenhancers, QS-21 (a triterpene glycoside purified from the bark of the tree *Quillaja saponaria* Molina) and MPL (3-Odesacyl- 4'-monophosphoryl lipid A), using liposomes as a vehicle. MPL is a purified, non-toxic endotoxin derivative prepared from the lipopolysaccharide of the R595 strain of *Salmonella minnesota* and is a compendial excipient. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol, buffered saline solution. DOPC and cholesterol are the key components of the liposomal bilayer membranes.

Aside from DOPC and QS-21, all excipients are compliant with Ph. Eur standards. It should be noted that QS-21 has not, thus far, been approved in an EU-approved medicinal product (novel excipient). Also DOPC and cholesterol are considered as novel excipients since they will be used for the first time in an EU-authorised product for intramuscular use. Stability data support the proposed shelf lives for QS-21 powder (60 months at -20°C), DOPC (36 months at -20°C) and cholesterol (36 months at -20°C). All these same excipients have nonetheless, been used for the company's malaria vaccine,

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Mosquirix, which was granted a positive CHMP opinion under Article 58 in June 2015. Appropriate information on these novel excipients in line with EU guidance and indeed, relevant information on all non-compendial excipients used to manufacture the adjuvant system has been provided.

With the exception of casamino acids, which are used during the production process of MPL, no materials from human or animal origin are used in the manufacture of the $AS01_B$ adjuvant system (see adventitious agents section for details).

Non-clinical and clinical studies demonstrated the need for an adjuvant to increase immunogenicity of the gE antigen. The $AS01_B$ adjuvant system, including both MPL and QS-21 immuno-enhancers, formulated in liposomes, was shown to be the most potent adjuvant system to induce gE-specific cellular and humoral responses in mice.

Important physicochemical and biological properties of the AS01B adjuvant system are adequately described in the dossier. The manufacturing process of AS01B adjuvant system has been developed through the implementation of a “Series” of manufacturing processes, which reflect changes applied to the manufacture of the intermediates, $AS01_B$ formulation or filling, from one “Series” to the next one (including site transfer and scale-up).

A lot history of the $AS01_B$ final container GMP lots used for clinical trials is provided. Consistency and comparability between clinical batches and commercial process has been demonstrated at the level of the concentrated liposome bulk (CLB) and the QS-21 liquid bulk (LB). For final bulk and the final container product, consistency and comparability has been demonstrated between pooled clinical/first commercial lots and final commercial process.

$AS01_B$ adjuvant system manufacturing involves mixing of intermediate bulk components to formulate $AS01_B$ final bulk (FB), which is subsequently filled into final containers. A satisfactory evaluation of extractables and leachables was performed on the container closure systems used for CLB, QS-21 LB and $AS01_B$.

$AS01_B$ adjuvant system is part of the AS01 family of adjuvant system that comprises other variants. The most closely related is the AS01E adjuvant system which contains half the amount of constituents of the AS01B adjuvant system and is part of GSK’s malaria vaccine Mosquirix (positive opinion via Article 58 procedure). The manufacturing process and specifications for the different adjuvant components, i.e. MPL, QS-21, DOPC and cholesterol, are identical between Mosquirix and Shingrix (only the amount of the components in the final adjuvant composition differs between the two vaccines).

Manufacture of the product and process controls-$AS01_B$ suspension (adjuvant) vial

The $AS01_B$ adjuvant system is produced at GlaxoSmithKline Biologicals SA (Wavre Nord site): Parc de la Noire Epine, Avenue Fleming 20, 1300 Wavre (Belgium) and QA conducted at GlaxoSmithKline Biologicals SA (Rixensart site): Rue de l’Institut 89, Rixensart (Belgium).

The manufacturing process of $AS01_B$ adjuvant system comprises the following steps:

1) Production of intermediate bulk components.

2) Formulation of $AS01_B$ Final Bulk (FB), which consists of mixing the intermediate bulk components and sterile filtration of the resulting formulated solution.

3) Filling step, in which the formulated FB is aseptically filled into 3 mL vials.

The control strategy is described and aims to ensure product quality and process performance. QC release specifications are established for CLB and QS-21 LB intermediates. Stability data are also presented to support storage of these two intermediates .

Sterile filtration and holding time of the final bulk in specified vessels between formulation and filling, has been adequately validated.

Process validation of $AS01_B$ adjuvant system manufacturing process was performed at the level of the two intermediates (CLB and QS-21 LB) as well as for the formulation and filling (including evaluation of sterile filtration) steps.

Product specification- $AS01_B$ suspension (adjuvant) vial

The $AS01_B$ FP specification includes appropriate tests for identity, physiochemical properties, content of adjuvant constituents, impurities (sterility). Note that a sterility test (Ph. Eur.) is also part of the $AS01_B$ final bulk release specification.

The potential impurities in $AS01_B$ adjuvant system and their control strategy have been presented. Possible impurities are controlled at release of $AS01_B$ or at release of the raw materials. The low levels of impurities that may be present in $AS01_B$ FC are clinically qualified and do not pose any safety concerns.

Analytical methods- $AS01_B$ suspension (adjuvant) vial

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis- $AS01_B$ suspension (adjuvant) vial

Batch analysis data for at least three batches each of phase III clinical batches and commercial PPQ batches were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials- $AS01_B$ suspension (adjuvant) vial

None of the QC release tests used for the testing of $AS01_B$ adjuvant system requires a final container lot for calibration and/or quantification. For the quantification of MPL, DOPC and Cholesterol, the company uses reference standards obtained from commercial suppliers. These standards are accompanied by certificates of analysis. For quantification of QS-21, an in-house produced reference standard is used. Qualification of new reference standards is described.

Stability of the product- $AS01_B$ suspension (adjuvant) vial

The Applicant proposes a shelf-life of 36 months at 2-8°C for $AS01_B$ adjuvant system filled in 3 mL glass vials. In addition to the 36 months shelf-life, the $AS01_B$ adjuvant system may sustain exposure to temperature excursion for up to 14 days at 25°C during the 36 months shelf-life.

Long term stability studies, accelerated stability studies (6 months at 37°C) and temperature cycling studies have been performed in containers representative of those used for commercial product. The temperature cycling stability studies have been designed to include real-time storage at 2-8°C and one period of storage for at 14 days at 25°C or 30 days at 30°C, with a return to real-time conditions. This storage for up to 14 days at 25°C during the 36 months shelf-life is a temperature excursion agreed for the company prior to marketing.

These long-term and temperature cycling stability studies included data up to 60 months on development lots and up to 24 months on lots of the commercial process. For ongoing studies, in accordance with EU GMP guidelines, the Applicant has agreed to report any confirmed out-of-specification result, or significant negative trend, to the Rapporteur and EMA.

The shelf-life proposed is acceptable.

2.2.4. Finished medicinal product- gE finished product

Description of the product and Pharmaceutical development-gE/AS01$_B$ reconstituted FP

The commercial presentation of gE (finished product) is a monodose vial. This finished product (FP) component is a powder containing 50 µg of glycoprotein E (gE) antigen (powder) containing the following excipients: sucrose; polysorbate 80; sodium dihydrogen phosphate dihydrate; dipotassium phosphate. All these excipients are compliant with Ph. Eur standards. No novel excipients or excipients from human or animal origin are used in the manufacture of gE powder.

The primary packaging of the powder is a type I glass vial with butyl rubber stopper. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Container closure integrity has also been investigated. In addition an extractables/leachables study has been performed to ensure safety of the container closure system.

Please see Finished medicinal product- AS01$_B$ adjuvant for details of the adjuvant suspension, used to reconstitute the gE powder, and the rationale for its inclusion in the finished product.

The composition of the reconstituted FP is shown in Table 1.

Table 1 Nominal composition of gE/AS01$_B$ Reconstituted Vaccine (vial)

Nominal composition of gE/AS01$_B$ Reconstituted Vaccine (vial)

Ingredients[1]	**Quantity (per 0.5 mL dose)**	**Function**	**Reference / Monograph standard**
Active substance			
gE	50 µg	Antigen	In house
Excipients			
3-O-desacyl-4'-monophosphoryl lipid A (MPL)	50 µg	Immuno-enhancer	*Ph. Eur.*
Purified Quillaja Saponin (QS-21)[2]	50 µg	Immuno-enhancer	In house
Water for injection (WFI)	*q.s. ad* 0.5 mL	Solvent	*Ph. Eur.* 0169, USP, JP

1. Other excipients include dioleoyl phosphatidylcholine (DOPC) (a liposome membrane constituent) ; cholesterol (a liposome membrane constituent and used for quenching of QS-21 haemolytic activity); sucrose (a stabiliser -cryoprotectant and lyoprotectant); polysorbate 80 (for protein solubilisation and recovery), sodium chloride (a tonicity agent); sodium dihydrogen phosphate dihydrate (a buffering agent); dipotassium phosphate (a buffering agent); disodium phosphate anhydrous (a buffering agent) potassium dihydrogen phosphate (a buffering agent). All of these excipients comply with Ph.Eur. In the absence of a respective Ph.Eur monograph for DOPC, an in-house specification applies.

2. Purified Quillaja Saponin is the full name of QS-21;

The compatibility between the AS01$_B$ adjuvant system and the lyophilised gE antigen for which it serves as solvent has been evaluated.

The formulation development of the finished product has been described and mainly involved a change from liquid to lyophilised formulation which required the addition of sucrose as a cryoprotectant and the subsequent addition of polysorbate 80 to prevent formation of protein aggregates.

The manufacturing of the gE finished product was initially performed by Henogen S.A. (Gosselies, Belgium), now referred to as Novasep for the initial Phase I/II studies. The process was scaled up and moved to the GSK industrial development facility for production of additional Phase I/II material. For the phase III trials the process was scaled up further. Finally, this process was moved to the GSK commercial facility. The lots used for pivotal clinical studies were prepared using AS manufactured according to full-scale processes that were close to the final commercial process. The company has justified, with appropriate data that changes introduced to establish the commercial AS process results in product that is comparable to that prepared using AS used for phase III studies (See AS development of the product section). Comparability between phase III FP and commercial FP was demonstrated.

Three FB, final container and reconstituted vaccine commercial PPQ lots were produced to demonstrate consistency among the PPQ lots and comparability to the phase III clinical efficacy and consistency lots listed. Consistency among the PPQ lots and comparability to reference lots were assessed through a technical package including QC release tests, process monitoring tests, process measurements and characterisation tests, as appropriate. Acceptance criteria and/or consistency/comparability ranges were defined for relevant quality and performance attributes. The comparability assessment of commercial lots vs. Phase III clinical materials has shown both materials have similar quality attributes, with one exception related to gE methionine oxidation levels.

The company has observed an increased level of gE methionine oxidation in the first commercial lots compared to clinical lots and investigation has concluded that this is due to the residual vaporised hydrogen peroxide (VHP) used in the commercial facility for surface decontamination of the isolators.

This issue has already been addressed in the context of an EMA scientific advice. As recommended by the CHMP, the Applicant has validated the methionine oxidation test and demonstrated that methionine oxidation raises no safety concerns. The impact on product quality has been investigated by the company: using several methods it was shown that secondary and tertiary structure of gE are not impacted by the higher levels of oxidation. The impact on immunogenicity and antigenicity has been assessed by *in vitro* and *in vivo* experiments in mice. The company has performed a safety evaluation to define methionine oxidation level which raises no toxicological concerns. The corrective plan for adjusting and controlling the methionine oxidation level is acceptable. After implementation of these CAPAs the level of methionine oxidation was shown to be decreased in comparison with the first commercial lots. The Applicant will further analyse methionine oxidation in a pre-defined number of commercial lots.

Manufacture of the product and process controls-gE FP

The gE powder vial is produced at GlaxoSmithKline Biologicals SA (Wavre Nord site): Parc de la Noire Epine, Avenue Fleming 20, 1300 Wavre (Belgium) and QA conducted at GlaxoSmithKline Biologicals SA (Rixensart site): Rue de I'Institut 89, Rixensart (Belgium)

The manufacturing process of the lyophilised gE (gE Lyo) Final Container (FC) is composed of the following steps:

1. Formulation of the Final Bulk-mixing of solutions of buffer, sucrose, and polysorbate 80 (PS80) with water for injection (WFI) and the appropriate amount of thawed gE antigen.

2. Filling/Freeze-drying- the formulated bulk is sterile filtered. The Final Bulk is aseptically filled into vials. Filled vials are then lyophilised, capped and visually inspected.

3. Labelling and Packaging.

A control strategy is in place with appropriate in-process monitoring. There is no intermediate produced between thawing of the frozen gE purified bulk and the final gE finished product. The formulation, aseptic filling and lyophilisation steps have been validated using three PPQ lots.

Product specification

The FP specification includes appropriate tests for identity, physiochemical properties (pH, appearance, osmolality), potency, impurities (endotoxin, sterility), protein and excipient content. Product is released on the basis of individual tests on adjuvant and gE antigen vials and product will be labelled with the shortest shelf life. The specifications are acceptable.

The finding of enhanced gE methionine oxidation levels in commercial lots compared to clinical lots has been intensely investigated. As recommended by the CHMP, the Applicant has validated the methionine oxidation test and demonstrated that methionine oxidation raises no safety concerns. The corrective plan for adjusting and controlling the methionine oxidation level is acceptable. Although these data are supportive of licensure, as proposed by the CHMP, the methionine oxidation will be further controlled for a given number of commercial lots. Based on the obtained results, it will then be decided whether further control (e.g. release testing) of the methionine oxidation level is required or whether testing can be omitted (see recommendations).

Residual hydrogen peroxide (HP) is a potential finished product manufacturing process-derived impurity. The HP content in the vials has been calculated to be clearly below the threshold of toxicological concern (TTC) value of 1.5 µg/day (dose), as specified in the EMA guideline on limits of genotoxic impurities. Aggregation of the gE in the active substance or in the finished product can cause product-related impurities. The aggregates concentration measured in both active substance and finished product was consistently present in the clinical development. Other AS manufacture-related impurities are discussed in the AS characterisation section.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data (PPQ batches at commercial scale and of the commercial formulation) of the Finished Product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

See AS section for information on the reference standard used.

Stability of the product

A shelf-life of 36 months at +2°C/+8°C is proposed for gE lyo final container lots. The finished product should be stored in the original package in order to protect from light.

See stability of the product- $AS01_B$ vial for details of the stability of the adjuvant. Stability studies were performed in line with ICH (resembling at least conditions as required by ICH, or more stringent

conditions (worst case, and thus acceptable)). An in-use stability statement, following reconstitution is also proposed in the SmPC (not longer than 6 hours at +2°C to +8°C).

Based on the real-time stability data for the Phase III efficacy (at least 3 lots-60 months), Phase III consistency (at least 3 lots-48 months) and commercial consistency PPQ lots (at least 3 lots-24 months) (in identical primary packaging as proposed for marketing), the proposed shelf-life of 36 months at +2°C/+8°C is acceptable for gE lyo final container lots. Appropriate stability-indicating tests were used. For ongoing studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA. The maximal holding time of the gE final bulk is also sufficiently justified by stability data obtained from phase III lots and commercial consistency lots.

The Phase III efficacy and Phase III consistency lot studies also included a temperature excursion of +25°C for 14 days or at +30°C for 30 days. The stability of the gE final container lots under stress conditions has also been investigated (i.e. exposure for up to 6 months at +37°C or for up to 193 days at +25°C). However, the storage conditions as proposed, and approved in the SmPC are +2-+8 °C for the duration of the shelf life.

Stability data were generated for gE final container lots and gE final container lots after reconstitution with $AS01_B$ (gE/$AS01_B$ reconstituted vaccine). Stability data of the reconstituted vaccine stored up to 24 hours after reconstitution at +30°C did not show impact to its physico-chemical properties. From a microbiological point of view, the product vaccine should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at +2°C to +8°C, as stated in the SmPC.

There is also a statement in the SmPC to store in the original package in order to protect from light.

Adventitious agents

The strategy used to ensure that the VZV gE active substance and the resulting Shingrix finished product are free of adventitious agents is in compliance with the relevant EU viral safety and TSE requirements and includes: control of raw materials; testing of the MCB and WCB, as well as end of production cells; in-process testing of harvest for adventitious agents and bacterial contamination and viral clearance validation studies.

Raw materials of human or animal origin were used for the first steps of cell bank system development (up to the pre-Master cell bank). A satisfactory evaluation of adventitious agents has been provided for these. The risk of TSE contamination is considered negligible due to the origin of the raw materials. The risk of other adventitious agent contamination is considered limited due to the process steps.

Animal/ human origin materials were not used directly for the manufacture of MCB/WCB but have been used in the manufacture of media components:

- MCB: bovine trypsin -TSE certificate provided, porcine-derived carboxypeptidase B, both used in a cell culture ingredient's manufacture.
- WCB: pepticase from bovine milk, beef peptone and beef extract- TSE certificates provided, porcine trypsin and L-threonine methyl ester (from porcine gelatin and avian feathers) all used in a cell-culture supplement's manufacture.

The TSE risk for these is considered negligible due to the origin of these materials and the TSE certificates, where applicable. The risk of other adventitious agent contamination is considered limited due to the process steps.

With the exception of casamino acids, which are used during the production process of MPL (AS01 adjuvant system), no materials from human or animal origin are used in the manufacturing process of AS or FP. This source of casamino acids is compliant with current EU TSE guidelines.

The AS manufacturing process contains various steps that were shown to contribute to virus removal/inactivation: chromatography steps, low pH and viral filtration. Virus removal/inactivation was properly validated in appropriate scale-down models using relevant model viruses.

The results confirm that the purification process has an adequate viral clearance capacity. In combination with the testing of starting materials and intermediates this viral clearance capacity reduces the risk of viral contamination to a very low and acceptable level.

2.2.5. Discussion on chemical, and pharmaceutical aspects

Shingrix consists of 50 µg of the recombinant subunit Varicella Zoster Virus (VZV) glycoprotein E (gE) antigen combined with GSK's proprietary adjuvant system $AS01_B$. The dossier was considered of high quality and no major issues were raised during the procedure.

Active substance

GSK performs manufacture and release testing of the VZV gE protein active substance (AS) at the Wavre site in Belgium. The manufacturing process consists of a conventional fermentation process whereby the VZV gE antigen is secreted by the CHO cells into the culture medium. The clarified harvest is further processed by several purification and virus inactivation and filtration steps to produce purified gE antigen. The filtered bulk antigen is then filled into sterile containers and stored at -45°C.

Raw materials are described and controlled. Production is done using a two-tiered cell bank system which has been properly tested and qualified. No human or animal-derived materials are used in the active substance manufacturing process. Comparability studies were performed showing that (phase III) clinical lots and PV/commercial lots are comparable.

The process and process controls are described in detail. Critical process parameters were identified. The AS manufacturing process has been adequately validated, including removal of process-related impurities, inactivation/removal of potential contaminating viruses, chromatography column lifetime studies and intermediate hold studies.

The quality of the AS is controlled by both in-process controls and release testing. Analytical methods were described in detail and were properly validated. Apart from the routine testing, the Applicant has also performed additional characterisation testing to verify primary, secondary structure and higher order structure, glycosylation pattern, molecular size, purity and biological function of the VZV gE AS. Process-related impurities including host cell protein and DNA) were very low and were shown to be efficiently cleared by the various process purification steps.

Acceptable justifications were provided for the specifications. The Applicant has also provided batch data for several AS lots. The stability studies demonstrated that all the tested parameters met the acceptance criteria for all gE Purified Bulk batches (Phase III Efficacy, Phase III Consistency and Commercial Consistency gE Purified Bulk batches). The proposed shelf-life and storage conditions of gE Purified Bulks is acceptable.

Finished product

gE/$AS01_B$ vaccine, also referred to as Herpes Zoster subunit (HZ/su) vaccine, is a preservative-free suspension for intramuscular injection intended for the prevention of Herpes Zoster (HZ) and HZ-

related complications. The vaccine consists of two components: the powder (or lyophilised preparation) containing the recombinant Varicella Zoster Virus (VZV) glycoprotein E (gE) and a liquid suspension consisting of the $AS01_B$ adjuvant system both supplied in monodose vials.

The pharmaceutical development of the vaccine and the process development were described in detail. Initially, the FP was manufactured in the GSK industrial development facility (Rixensart site, Belgium). For commercial production the FP manufacturing process was moved to the GSK commercial facility (Wavre site, Belgium). Suitable comparability studies were performed showing that (phase III) clinical FP lots and commercial FP lots are comparable.

GSK performs manufacture and release testing of the VZV gE lyo finished product and the $AS01_B$ adjuvant system at the Wavre site in Belgium.

AS01B adjuvant system

The manufacturing process of the $AS01_B$ adjuvant system was described. The different adjuvant compounds are added to the formulation tank and homogenized. After sterile filtration the adjuvant is filled in glass vials.

The process and process controls are described in detail. Critical process parameters were identified. The FP manufacturing process has largely been adequately validated. Quality of the FP is controlled by both in-process controls and release testing. Analytical methods were described in detail and were properly validated.

The novel excipients in the $AS01_B$ adjuvant system, more particularly QS21, cholesterol and dioleyl-phosphatidylcholine were described. Detailed information was provided on the manufacturing processes, product characterisations and product control.

Specifications are justified. The Applicant proposes a shelf-life of 36 months at +2-+8°C for $AS01_B$ adjuvant system filled in 3 mL glass vials. This is acceptable.

gE lyo FP and reconstituted FP

The manufacturing process of the lyophilised gE (gE Lyo) final container is composed of the following steps: formulation of the final bulk, sterile filtration, filling, freeze-drying, labelling and packaging. The process and process controls are described in detail. Critical process parameters were identified. The FP manufacturing process has, in general been adequately validated. Quality of the gE FP is controlled by both in-process controls and release testing. Analytical methods were described in detail and were properly validated.

In the first commercial batches an increased level of gE protein oxidation was observed in the FP. The root cause was the presence of hydrogen peroxide vapour residuals from sterilisation of the filling isolators). An investigation showed that this increased oxidation had no impact on the gE protein structure or potency. In addition, *in vitro* and *in vivo* experimental data also confirmed that the oxidation had no impact on the quality and potency of the FP. Nevertheless, after this observation, the company implemented measures to reduce hydrogen peroxide vapour in the filling isolators. More recent commercial batches show ‘normal’ oxidation levels which remain consistent (comparable to those of the clinical batches).

Specifications were justified. A shelf-life of 36 months at +2°C/+8°C is proposed for gE lyo final container lots. This is acceptable. An in-use stability statement, following reconstitution is also proposed in the SmPC (not longer than 6 hours at 2°C to 8°C). Product is released on the basis of individual tests on adjuvant and gE antigen vials and product will be labelled with the shortest shelf life.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.7. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends one point for investigation as described in the assessment above.

2.3. Non-clinical aspects

Nonclinical studies were performed with the gE/AS01$_B$ candidate vaccine formulation, the AS01 adjuvant system and its immunoenhancers QS-21 and MPL.

2.3.1. Introduction

The HZ/su candidate vaccine is a two-component vaccine consisting of the lyophilized gE antigen and the liquid AS01$_B$ adjuvant system, each presented in monodose glass vials. No preservative is included in either the gE formulation or the AS01$_B$ formulation. The final product for administration is prepared by reconstitution of the lyophilized gE cake with the liquid AS01$_B$.

A single human dose (HD) consists of 0.5 mL of gE/AS01$_B$. The vaccination schedule consists of two doses administered 2-6 months apart intramuscularly (IM). One dose of HZ/su contains 50 µg of gE, as active ingredient, adjuvanted with AS01$_B$ 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 [containing dioleoyl phosphatidylcholine (DOPC) and cholesterol].

QS-21 is a water soluble triterpene glycoside with amphiphilic character and known for its haemolytic activity. This activity can be eliminated nevertheless through formulation in liposomes in the presence of cholesterol as in AS01 (Garçon, 2011 and data from study TNO V20041). MPL is a detoxified form of lipid A derived from the lipopolysaccharide (LPS) isolated from bacterial cell walls of the Gram negative bacterium Salmonella minnesota R595. Even though detoxified, MPL retains the capacity of the natural LPS compound to act as an immunoenhancer.

Two different gE-based formulations were tested during clinical development: gE/AS01$_B$ and gE/AS01$_E$ (see table 2). The adjuvant selection was based on the comparison of the adjuvant system in preclinical models, in addition to the clinical experience gained by the Applicant with other candidate vaccines containing AS01.

Table 1. Adjuvant systems of the AS01 family and their components

Adjuvant system	Components (quantity per final human dose of 0.5 mL)*
AS01$_B$	MPL (50 µg); QS-21 (50 µg)
AS01$_E$	MPL (25 µg); QS-21 (25 µg)

*DOPC and Cholesterol are contained in both adjuvant systems in different amounts (AS01$_E$ contains half the amount vs. AS01$_B$)

The range of nonclinical pharmacology and toxicology studies undertaken with gE/AS01$_B$ vaccine formulation is in agreement with the relevant CHMP and WHO Guidelines. The main studies are:

- Primary pharmacodynamics studied in mice to evaluate cellular and humoral anti-gE antigen immune responses and to select the optimal formulations, specific primary pharmacodynamics in vitro (human or mouse cells) and in vivo (mice model) to investigate the adjuvanting effect of AS01$_B$ and its mode of action (these studies were previously included and evaluated in the context of the Mosquirix application), and other studies to support the gE/AS01$_B$ production
- GLP-compliant safety pharmacology studies with gE/AS01$_B$ in rats and AS01$_B$ in dogs
- Biodistribution of AS01$_B$ components in mice
- GLP-compliant toxicology studies include local tolerance and repeat-dose toxicity in rabbits, reproductive toxicity and male fertility study in rats.

Of note, as agreed following CHMP scientific advice, nonclinical toxicity studies with the QS-21 immunoenhancer were performed using a liposomal formulation of QS-21 (i.e. DQ; for detoxified QS-21), rather than solutions of QS-21, since DQ corresponds to the physical form of QS-21 in the gE/AS01$_B$ vaccine formulation. This liposomal formulation, via the specific inclusion of cholesterol, allowed the elimination of the intrinsic haemolytic activity of QS-21. Similarly, the nonclinical pharmacology studies with QS-21 were also performed using the DQ formulation.

2.3.2. Pharmacology

There is no appropriate animal model to study Varicella Zoster Virus (VZV) pathogenesis, latency or reactivation. Hence, no non-clinical data on protection against Herpes Zoster by vaccine candidates (challenge studies) were generated. It is considered acceptable that nonclinical pharmacology studies are limited to demonstration of immunogenicity. In addition, safety pharmacology studies were conducted with gE/AS01$_B$, AS01$_B$ and MPL.

An overview of the nonclinical pharmacology testing program for gE/AS01$_B$ and for the adjuvant system AS01 is given in tables 3 and 4 respectively.

Table 2. Non-clinical pharmacology studies for gE/AS01$_B$

Study number	Study type	Study objective	Study title	Formulation(s) evaluated[2]	Animal model
20060384	Primary pharmacodynamics[1]	Justification for inclusion of an adjuvant	Comparative immunogenicity of gE formulated with AS01B, AS01E, AS02A, AS03A, AS25A and AS50A in C57Bl6 mice	gE gE/AS01E gE/AS01B gE/AS50A gE/AS25A gE/AS02A gE/AS03A	C57Bl6 mice
20080194	Primary pharmacodynamics	Selection of the adjuvant	Comparative immunogenicity of gE formulated with AS01B, AS01E, AS02A, AS03A and AS04 in C57Bl6 mice	gE gE/AS01E gE/AS01B gE/AS02A gE/AS03A gE/AS04D	C57Bl6 mice
20140311	Primary pharmacodynamics	Selection of the adjuvant	Comparative immunogenicity of gE formulated with AS01B, AS01E, AS03A and AS04 in C57Bl6 mice	gE gE/AS01E gE/AS01B gE/AS03A gE/AS04C	C57Bl6 mice

Study number	Study type	Study objective	Study title	Formulation(s) evaluated[2]	Animal model
20110566	Primary pharmacodynamics	Comparison of SC vs IM route of administration	Comparison of the immunogenicity of gE/AS01B (HZ/su) vaccine candidate administered either subcutaneously or intramuscularly in Varilrix-primed C57Bl6 mice	gE/AS01B	C57Bl6 mice
20080765	Primary pharmacodynamics	Dose determination for the immunobridging studies	Vaccine dose range of VZV vaccine	1/5th, 1/10th, 1/20th, 1/50th, 1/250th of gE/AS01B	C57Bl6 mice
20070293	Primary pharmacodynamics	Immunobridging	Immunobridge of gE/AS01B vaccine produced at intermediate scale compared to small scale	gE/AS01B	C57Bl6 mice
20090790	Primary pharmacodynamics	Immunobridging	Immunobridge of gE/AS01B produced at final scale compared to intermediate scale	gE/AS01B	C57Bl6 mice
20130001	Primary pharmacodynamics	Immunobridging	Immunobridge of consistency compared to efficacy gE/AS01B vaccine	gE/AS01B	C57Bl6 mice
20150045	Primary pharmacodynamics	Immunobridging	Immunobridge clinical consistency lots compared to commercial consistency	gE/AS01B	C57Bl6 mice
20150311	Primary pharmacodynamics	Immunobridging	Evaluation of the potential impact of oxidation on gE immunogenicity in mice	gE/AS01B	C57Bl6 mice
HLS GVB 0006/062657	Safety pharmacology	Effects on cardiovascular and respiratory systems	VZV candidate vaccine (gE 100µg/AS01B) Cardiovascular and respiratory evaluation in the anaesthetised rat	gE/AS01B (full HD)	Wistar rats

1. Primary pharmacodynamics studies are immunogenicity studies. 2. Unless otherwise specified, 1/10th human doses were used for the Primary Pharmacodynamics studies. HD: human dose

Table 3. Nonclinical pharmacology studies of AS01 adjuvant system

Study type	Study number	Test System	Antigen	Read out
1. Contribution of MPL and QS-21 in AS01 effect on antibody and T cell response	20110060-20110061	C57Bl/6 mice	gE (Zoster recombinant antigen)	Serology (ELISA), ICS
2.Impact of spatio-temporal injection of $AS01_B$ and gE on innate and gE-specific adaptive immune responses in mice effect	20090807-20100654	C57Bl/6 mice	gE (Zoster recombinant antigen)	Serology (ELISA), ICS, CBA
3.Local distribution of $AS01_B$ at the injection site administered alone and in combination with the gE antigen	20110310	C57Bl/6 mice	gE (Zoster recombinant antigen, fluorescently labeled)	Immunostaining, confocal microscopy
4..Characterization of Local innate response induced by AS01	20110226	C57Bl/6 mice	gE (Zoster recombinant antigen, fluorescently labeled)	Flow cytometry
5.Contribution of MPL and QS-21 in AS01 effect on local innate response	20110202-20080761	C57Bl/6 mice	No antigen or ovalbumin or gE (Zoster recombinant antigen) model antigens	Flow cytometry
6. Evaluation of the impact of specific APCs induced *in vivo* by adjuvant systems of the AS01 family, on antigen-specific cellular response	20120490-20120517	Ex vivo assay[1]	Ovalbumin	Cell purification Flow cytometry
7. Role of IFNγ signaling in AS01 adjuvant effect	20080769-20080771-20090756	C57Bl/6 mice, IFNγ receptor-deficient mice	HBs or ovalbumin	Serology (ELISA), ICS Flow cytometry

ELISA: enzyme-linked immunosorbent assay; ICS: intracellular cytokine staining; HBs: hepatitis B surface antigen; gE: zoster recombinant antigen; 1. An *in vitro* model using primary cells collected *in vivo*

Primary pharmacodynamic studies

Primary pharmacodynamics studies address (1) immunogenicity of the candidate vaccine, (2) bioequivalence of manufacturing changes during development and (3) mode of action of the adjuvant system.

Several studies were conducted to explore immunogenicity of the candidate gE subunit vaccine, formulated with different adjuvant systems, including oil-in-water emulsions ± MPL ± QS-21 (AS02, AS03), MPL + Alum (AS04), and liposomes + ML + QS-21 at different quantities (AS01). Overall, these studies support the need for an adjuvant to induce strong humoral gE-specific immune responses, but differences between tested adjuvant systems are rather limited. The choice for $AS01_B$ is mainly based on its superior ability to induce cellular immune responses, measured as IFN-γ and/or IL-2 producing CD4 T Cells, compared to other adjuvant systems. The Applicant has not generated data on the functionality of the gE-antibodies in the non-clinical studies, but virus neutralization assays were performed on human sera.

In conclusion, the need and choice for the $AS01_B$ adjuvant system is supported by immunogenicity data. Efficacy (protection against Herpes Zoster) is only addressed clinically, as is the functionality of the induced gE-specific antibody response. No additional nonclinical primary pharmacology data were requested from the Applicant.

Several studies were performed to assess bioequivalence after changes in the manufacturing process. Altogether, these data demonstrate that gE antigen produced at different manufacturing scales (including final scale) and formulated with $AS01_B$ generate comparable immune response in terms of level of gE-specific antibodies and frequencies of gE-specific cytokine-producing CD4+ T cells (IFN-γ ± IL-2 producing T cells isolated from the spleen). The geometric mean ratios and the estimated 95% confidence intervals are within the [0.5-2] interval, and therefore the lots are considered bioequivalent. Likewise, the gE/$AS01_B$ lots produced for the clinical efficacy and clinical consistency campaigns and for the clinical consistency and commercial consistency campaigns elicit similar levels of gE-specific cellular and humoral responses in mice.

During the production of gE commercial lots, higher levels of gE methionine oxidation were observed compared to the clinical consistency lots, which was attributed to a transient exposure of gE final bulk to vaporized hydrogen peroxide (VHP) residues prior to the lyophilisation step. The Applicant demonstrated that artificial oxidation of gE, generate comparable immune responses compared to the reference lot in terms of level of gE-specific antibodies and frequencies of gE-specific cytokine-producing CD4+ T cells (IFN-γ ± IL-2 producing T cells isolated from the spleen). The geometric mean ratios and the estimated 95% confidence intervals are within the [0.5-2] interval, and therefore the lots are considered bioequivalent.

The mechanism of action of AS01 and individual components QS-21 and MPL was satisfactorily studied. The early response to AS01 has been investigated in a variety of nonclinical studies in order to better understand the mechanism behind antigen-specific adaptive responses promoted by AS01-containing vaccines. The AS01 adjuvant system differs from other licensed vaccine adjuvants in terms of ability to enhance antigen-specific T cell response in several model antigen systems (gE, CSP, HBs, OVA). Activation of the innate immune system by AS01 was transient and mediated via TLR4 signalling for MPL, while for QS-21 the signalling pathways are not fully elucidated but involve caspase I/ inflammasome activation. The maximum adjuvant effect of AS01 on adaptive response, especially T cell response, required spatio-temporal co-localization of AS01 with the antigen, consistent with an early and locally acting mechanism of the adjuvant. A combination of MPL and QS21 in AS01 induced a synergistic response, characterized by increased or sustained cytokine levels, associated with a more efficient induction of an adaptive response. For example, IL-6 or IFN-γ dependent cytokines are known to improve antibody and T cell responses respectively. MPL contributed to the early cytokine response in the muscle while QS-21 was more important for the early cytokine response in the draining lymph node (dLN), consistent with the biodistribution studies. The early IFN-γ secretion by NK within 6h after immunization results from a synergy between MPL and QS-21. The MPL and QS-21 combination favours a diversified population of activated antigen presenting cells, responsible for T cell priming, driven by the specific ability of MPL and QS-21 to activate DC and monocytes respectively. These data support addition of both immune enhancers in the liposome formulation.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed, in accordance with the Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/465/95) and Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004).

Safety pharmacology programme

Safety pharmacology studies are not usually required for adjuvants according to the Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004). However in line with the WHO guidelines on nonclinical evaluation of vaccines, the need for safety pharmacology studies for novel

vaccines, adjuvants and/or other components of the vaccine formulation should be assessed on a case by case basis. In this case, safety pharmacology studies in the context of the gE/$AS01_B$ vaccine development were deemed relevant only for the $AS01_B$ adjuvant as this is a novel adjuvant system.

Safety pharmacology studies were performed with the gE (100 µg)/$AS01_B$ vaccine formulation, $AS01_B$ and MPL. The study with the gE (100 µg)/$AS01_B$ vaccine formulation was performed in the anesthetized rat, studies with $AS01_B$ were performed in the anesthetized rat and in the dog, and the safety pharmacology study with MPL was performed in the dog.

An ICH S7-compliant safety pharmacology study in the conscious Beagle dog with the $AS01_B$ adjuvant did not raise any concern on cardiovascular and respiratory function when a full human dose was administered. In the anaesthetised rat, no acute cardiovascular and respiratory effects were observed after intravascular administration of gE/$AS01_B$ or $AS01_B$ at approximately 140-fold human dose on a body weight basis. Previous CHMP scientific advice pointed out that a justification for the choice of the rat should be provided as according to ICH S7B the rat is not considered being an appropriate species for investigation for the potential to prolong the QT interval (the ionic mechanisms of repolarization in adult rats and mice differ from larger species). This is no longer needed in view of the pivotal dog study. In addition, no adverse effects on cardiovascular or respiratory functions were observed after intravascular administration of MPL in anaesthetised dogs (140-fold human dose on a body weight basis). No additional studies are required.

In addition safety pharmacology studies with $AS01_B$ and MPL were already conducted for and included in the applications for other vaccines (Mosquirix, Cervarix and Fendrix).

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions studies do not apply to vaccines. Therefore, pharmacodynamic drug interactions studies were not conducted with the gE/$AS01_B$ candidate vaccine.

2.3.3. Pharmacokinetics

Pharmacokinetic studies are usually not required for vaccines based on current guidelines. However in some cases, distribution studies may be of value in understanding the mode of action of the adjuvant.

Given the limited frequency and dose of injection, pharmacokinetic (PK) or ADME (Absorption, Distribution, Metabolism and Excretion) studies are not considered relevant for adjuvants or adjuvant system. Biodistribution studies with immunoenhancers and adjuvant system have been conducted to aid understanding the mode of action of the immunoenhancers and adjuvant system, hence they should not be interpreted as PK or ADME studies.

To understand the mode of action of $AS01_B$, two mouse biodistribution studies were undertaken GSK-CH-01-09 with [^{14}C]QS-21 and [^{14}C]DOPC, and GSK-CH-01-015 with synthetic analogue of MPL (i.e. RC-529). The latter is a new study and the former was previously included and assessed in the Mosquirix application. They support its inclusion in the Applicant vaccine formulations.

Of note, additional biodistribution studies in rabbit (TSI MASON 2-R89 for ^{3}H-QS-21 in saline solution) and rat (Covance 1990/521, Covance 1990/522 for ^{14}C-MPL) were previously included in the Fendrix and other Applicant's vaccine formulations, and thus are not discussed in details in this report.

Taken together, the biodistribution studies with QS-21 and MPL administered in solution have shown that QS-21 and MPL are widely distributed throughout the body and are eliminated within several hours (48-168 h). However, the AS01-induced pro-inflammatory response at the injection site is transient and is fully resolved by day 7, which suggests that the retention of the MPL is either not due

to TLR4 ligand or alternatively a tolerance mechanism blunting the TLR4 response may also operate locally (van Maren, 2008).

2.3.4. Toxicology

Nonclinical toxicity studies were undertaken with the vaccine gE/AS01$_B$, the AS01$_B$ adjuvant system and its individual immune-enhancers QS-21 and MPL. Most studies were done in rat and rabbit, as both species demonstrated a good antibody response. The toxicity studies were usually performed by the IM route of administration since this is the proposed route of administration for clinical use. Toxicity studies were however also conducted by the SC route of administration to support a specific clinical trial.

Single dose toxicity

Single dose toxicity and local tolerance were evaluated in rabbits in two studies, with intramuscular and subcutaneous administration respectively. The observed slight inflammation at the injection sites is considered a direct consequence of an anticipated pharmacological action as it results from the stimulation of the immune system. DQ (QS-21) and MPL were considered to be well tolerated in supportive single dose toxicity studies with a sufficient safety margin over the anticipated human dose.

Repeat dose toxicity

Two repeat-dose toxicity studies were performed to evaluate local and systemic effects of gE/AS01$_B$ administration. Repeated IM injection of rabbits with the gE (100 µg)/AS01$_B$ vaccine formulation induced mild local effects at the injection site. Systemically, only a few haematology and clinical chemistry parameters related to the local inflammation were transiently affected by gE (100 µg)/AS01$_B$. Recovery of the mild local effects was ongoing in the gE (100 µg)/AS01$_B$ vaccine group at the end of the study period, four weeks after the last dose. In a second repeated dose study designed to compare IM and SC injection with the full human dose of the gE (50 µg)/AS01$_B$ candidate vaccine, the SC injections produced a lower incidence and severity of microscopically visible reactions at the injection site than did the IM injections. These SC data were included in this submission as supportive information. All gE/AS01$_B$ treated animals seroconverted as assessed by gE ELISA. Repeated dose toxicity has thus been evaluated in one relevant animal species (rabbits) and the studies have been conducted according to the relevant WHO and EMA guidelines, including recommendations on dose (full human dose), number of doses (exceeding proposed number in the clinic) and of route of administration (IM is proposed route of administration for licensure).

Repeated intramuscular administration of AS01$_B$ in rat and rabbit produced no signs of systemic toxicity but did produce a transient acute inflammatory response at the injection site. Systemically, only a few haematology and clinical chemistry parameters, and increased body temperature (in the rat only), all considered to be related to the local inflammation or the non-specific immune stimulation following AS01$_B$ injection, were transiently affected.

In the repeated dose toxicology studies in rats and rabbits, DQ induced some transient effects on haematology and clinical chemistry, and a higher mean body temperature in the high DQ dose group 24 hours after the first injection in the rabbits, which were considered to be part of the inflammatory and immunological processes following injection. Microscopically, some inflammatory response was observed at the injection sites, while complete recovery was observed after 28 days.

Repeat-dose toxicity studies in which MPL was administered once daily were performed for up to 8 days in rats and 14 days in Beagle dogs by the intravenous route, maximizing the systemic exposure. The no-observed adverse effect level (NOAEL) in beagle dogs was 6 µg/kg body weight/day and the 40 µg/kg body weight/day dose in rats was considered well-tolerated. Effects seen were generally dose-related (e.g. reversible decreased body weight gain and food consumption; few changes in haematology parameters; organ weight increase). The very few effects seen at the lowest dose of 40 µg/kg body weight/day in the rat were minor and consistent with an immunostimulatory action of MPL, such as increased white blood cell (WBC) count and spleen weight.

Therefore, single and repeated dose studies, including assessment of local tolerance, indicate that gE/AS01$_B$, or the constituents AS01$_B$, QS-21 (DQ) and MPL, are generally well tolerated by the animals at the proposed clinical levels, and the observed effects may be considered expected from the stimulation of the immune system.

Genotoxicity

The Applicant did not provide genotoxicity data for the final vaccine formulation gE/AS01$_B$, which is considered acceptable. In a rat micronucleus assay, AS01$_B$ showed no evidence of causing micronuclei. DQ and/or QS-21 were non-mutagenic in the Ames assay and mouse lymphoma assay. DQ did not show any indication of chromosomal damage and/or damage to the mitotic spindle apparatus of the bone marrow target cells of male rats. No genotoxic or mutagenic potential was associated with MPL, as demonstrated by in vitro mutagenicity (Ames) and clastogenicity (CHO cells) tests, and an in vivo rat micronucleus assay. Altogether these data support the lack of genotoxic potential of gE/AS01$_B$.

Carcinogenicity

Carcinogenicity studies were not performed. As carcinogenicity studies are not required for final vaccine formulations, adjuvants systems and/or immunoenhancers based on current guidelines, this was considered acceptable.

Reproduction Toxicity

gE/AS01$_B$ and AS01$_B$ reproductive toxicity was assessed in two studies both performed in rats, one covering pre-, peri- and post-natal development and one covering male fertility. In addition, for QS-21 (DQ) and MPL, embryofetal development was assessed in two species, rats and rabbit, and pre- and post-natal development was assessed in rats only. Apart from the MPL studies, it is the first time these studies are presented for assessment. Although for the target population in the proposed indication (> 50 years of age) reproductive toxicity is not a major concern, the adjuvant system is likely to be used for other vaccine formulations, justifying thorough assessment of these studies at this stage.

Treatment of male CD rats with 1/5th of a human dose of gE/AS01$_B$ or AS01$_B$ alone on three occasions prior to pairing (on Day -42, Day -28 and Day -14) did not affect male mating performance, fertility or early embryonic development. At termination, no treatment-related differences were detected in males in respect to reproductive organ weights, seminology parameters or macroscopic and microscopic appearance of the reproductive tissues.

Treatment of female CD rats with the candidate vaccine gE/AS01$_B$ or adjuvant AS01$_B$ at 40% of the full human dose per occasion, on 28 and 14 days before pairing and then on Days 3, 8, 11 and 15 of gestation and on Day 7 of lactation was well tolerated by the F0 females with effects restricted to slight, transient swelling at the injection site and did not adversely affect embryo-fetal or pre- and

post-natal survival, growth or development of the offspring up to Day 25 of age. Serological analysis data to support vaccine take in dams, foetuses and pups were provided at request of the CHMP and demonstrate vaccine exposure of dams during pregnancy and exposure of foetuses and offspring to anti-gE antibodies.

The potential effects of DQ on female fertility, reproductive performance and on embryofoetal and pre-/post-natal development were studied in rats and rabbits. DQ, at doses of 4, 20 and 40 µg of QS-21/occasion (corresponding to 16, 80 and 160 µg/kg of QS-21, assuming a 250 g female rat, respectively) did not adversely affect female fertility, embryofoetal or pre- and post-natal survival, growth or development of the offspring up to Day 25 of age. The NOAEL of DQ on female fertility, embryofoetal and pre and post-natal survival, growth and development is at least the highest dose level of DQ tested containing 40 µg of QS-21/occasion, corresponding to 160 µg/kg of QS-21 assuming a 250g female rat, therefore exceeding the human dose on µg/kg-basis.

The intramuscular administration of DQ adjuvant (200 µg/occasion) to New Zealand White 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. In addition, lower mean foetal weight was noted at this dose level. Defects of the aortic arch (retro or high arched) were observed in three foetuses from separate litters suggestive of a possible association with treatment at this dose.

Malformed kidneys were observed in 2 pups from females mated with the same male, and one pup from a female that mated with a different male, therefore excluding a cluster effect. Although historical control data and literature references indicate that kidney malformations do occur as a background finding in the rabbit, the incidence is very low and it is therefore considered highly speculative to conclude that 3 offspring from treated animals (high dose only) are affected by chance.

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 assessed. In the absence of adverse effects on maternal condition or embryofoetal and post-natal development in the intermediate dose group (100 µg/mL of QS-21), this is considered the NOAEL. PK data are not available. 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. It is therefore concluded that the adjuvant component QS-21 induced potentially 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.

Embryofoetal toxicity studies in the rabbit and the rat and a pre- and post-natal development study in the rat with subcutaneous administrations of MPL allowed determining a NOAEL of at least 100 µg/kg/day (maximum dose tested).

Toxicokinetic data

Toxicokinetic data were not generated since the determination of circulating levels of antigens is not required for vaccines. This is in line with the Guideline on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (WHO, 2013). The absence of toxicokinetic data is considered acceptable.

Local Tolerance

Please see “single dose toxicity” and “repeat dose toxicity” sections above.

Other toxicity studies

Not applicable.

2.3.5. Ecotoxicity / environmental risk assessment

Inactivated vaccines such as this one are exempted from requirement to conduct environmental risk assessment studies due to the nature of their constituents, and this is acceptable, in line with the CHMP Guideline on the environmental risk assessment of medicinal products for human use.

2.3.6. Discussion on non-clinical aspects

Nonclinical studies were performed with the gE/AS01$_B$ candidate vaccine formulation, the AS01 adjuvant system and its immunoenhancers QS-21 and MPL.

In absence of an appropriate animal model to study Varicella Zoster Virus pathogenesis, latency or reactivation, it is considered acceptable that nonclinical pharmacology studies are limited to demonstration of immunogenicity. Primary pharmacodynamics studies address (1) immunogenicity of the candidate vaccine, (2) bioequivalence of manufacturing changes during development and (3) mode of action of the adjuvant system. In addition, safety pharmacology studies were conducted with gE/AS01$_B$, AS01$_B$ and MPL. No concerns were identified and no additional studies are required.

Pharmacokinetic studies are normally not required for vaccines and this is considered acceptable also in this case. Several biodistribution studies on the adjuvant system were provided in an effort to help understand its mode of action. Genotoxicity data support the lack of genotoxic potential of AS01$_B$.

Non-clinical data reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity, local tolerance, and cardiovascular/respiratory safety pharmacology. Some concerns were raised regarding the reproductive toxicity, specifically after administration of QS-21. These were addressed for this product even though they are not relevant for the target population in the proposed indication (> 50 years of age). The final conclusion on the adjuvant component QS-21 is 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 raise any concern.

2.3.7. Conclusion on the non-clinical aspects

There are no concerns from a non-clinical point of view; this marketing authorisation application is approvable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The Applicant 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.

Six GCP inspections were performed at 3 study sites during the conduct of both pivotal studies ZOSTER-006 and ZOSTER-022. Deviations from GCP compliance were identified at one site; consequently the study site was closed and corrective actions taken to exclude those patients from all analyses. A sensitivity analysis was performed to detect safety signals at the impacted site. Sensitivity analyses for efficacy could not be performed, but it is considered that the overall efficacy results are not impacted.

Table 4. Overview of completed clinical studies included in the application

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects	
						ATP cohort for immuno	TVC
Pivotal studies							
ZOSTER-006	Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan Mexico, South Korea, Spain, Sweden, Taiwan, UK, US	Phase III, randomized, observer-blind, pivotal efficacy study in older adults ≥50 YOA. Follow-up (FU) driven by case accrual was at least 30 months after Dose 2 (actual median safety follow-up time 4.4 years). Primary objective: VE in the prevention of HZ in older adults ≥50 YOA Secondary objectives: VE by age group in terms of: • Prevention of HZ VE overall and by age group in terms of: • Prevention of overall PHN • Reduction in duration of severe 'worst' HZ pain in subjects with confirmed HZ • Reduction of HZ-related mortality and hospitalizations in subjects with confirmed HZ • Reduction in incidence of HZ-associated complications in subjects with confirmed HZ • Reduction in the use of pain medications in subject with confirmed HZ Safety and reactogenicity	Adults (≥ 50 YOA) stratified: 50-59 YOA, 60-69 YOA, 70 79 YOA and ≥80 YOA in a 8:5:3:1 ratio 2 doses: Months 0 and 2.	1) HZ/su 2) Placebo (saline)	Final scale	1,070 (humoral immuno M3)[a] 212 (CMI immuno M3)[a] 1,067 (humoral immuno M3)[a] 218 (CMI immuno M3)[a]	7,695 (EOS)[b] 7,344 (mTVC)[c] 7,710 (EOS)[b] 7,415 (mTVC)[c]

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects	
						ATP cohort for immuno	TVC
ZOSTER-022	Idem ZOSTER-006	Phase III, randomized, observer-blind, pivotal efficacy study in older adults ≥70 YOA. FU driven by case accrual was at least 30 months after Dose 2 (actual median safety follow-up time 4.2 years). Primary objective of ZOSTER-022: VE in the prevention of HZ in older adults ≥70 YOA. Secondary objectives of ZOSTER-022: VE in terms of: • Prevention of overall PHN • Reduction in duration of severe 'worst' HZ pain in subjects with confirmed HZ • Reduction of HZ-related mortality and hospitalizations in subjects with confirmed HZ • Reduction in incidence of HZ-associated complications in subjects with confirmed HZ • Reduction in the use of pain medications in subjects with confirmed HZ Safety and reactogenicity Co-primary objectives for pooled dataset of ZOSTER-006 and -022: • VE in the prevention of overall PHN in subjects ≥70 YOA • VE in the prevention of HZ in subjects ≥70 YOA Secondary objectives for pooled dataset of ZOSTER-006 and -022: VE in terms of: • Prevention of overall PHN in subjects ≥50 YOA • Prevention of PHN in subjects ≥50 YOA in subjects with confirmed HZ • Reduction in duration of severe 'worst' HZ pain in subjects ≥70 YOA in subjects with confirmed HZ Safety and reactogenicity in subjects ≥70 YOA	Adults (≥ 70 YOA) stratified: 70-79 YOA and ≥80 YOA in a 3:1 ratio 2 doses: Months 0 and 2	ZOSTER-022: 1) HZ/su 2) Placebo (saline) Pooled dataset of ZOSTER-006 and -022: 1) HZ/su 2) Placebo (saline)	FInal scale	387 (humoral immuno M3)[a] 412 (humoral immuno M3)[a] 1,457 (humoral immuno M3)[a] 1,479 (humoral immuno M3)[a]	6,950[b] 6,541 (mTVC)[d] 6,950[b] 6,622 (mTVC)[d] 14,645[b] 13,881 (mTVC)[e] 14,660[b] 14,035 (mTVC)[e]
ZOSTER-004	Canada, Germany, US	Phase III, randomized, open-label study, co-administration of HZ/su with quadrivalent seasonal influenza vaccine (FLU-D-QIV).	Adults (≥ 50 YOA)	1) Co-ad 2) Control	Final scale	386 395	413 415[f]

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects		
						ATP cohort for immuno		TVC
		Duration of FU: 12 months post last vaccination Co-primary objectives: • VRR to HZ/su (anti-gE Abs) in Co-Ad group at Month 3 • NI in terms of humoral immune response (GMC ratio for anti-gE Abs) in Co-Ad group at Month 3 vs. in Control group at Month 5 • NI in terms of HI antibody GMTs against the 4 influenza vaccine strains in Co-ad group vs. Control group at Day 21 post vaccination Secondary objectives: • NI in terms of HI SCR against the 4 influenza vaccine strains in Co-ad group vs. Control group at Day 21 post vaccination • GMTs, seroprotection rate, SCRs and Mean Geometric Increase in response to FLU-D-QIV • Safety and reactogenicity of both HZ/su and FLU-D-QIV	1) Co-Ad group: 2 doses HZ/su: Month 0 and 2 & 1 dose FLU-D-QIV: Month 0 2) Control group: 1 dose FLU-D-QIV: Month 0, and 2 doses HZ/su: Months 2 and 4					
ZOSTER-007[g]	Belgium, Canada, US	Phase III, randomized, double-blind, lot-to-lot consistency study. Duration of FU: 12 months post last vaccination Primary objective: Lot-to-lot consistency in terms of GMC ratio for anti-gE Abs at Month 3 between 3 HZ/su production lots Secondary objectives: • Lot-to-lot consistency of 3 manufacturing lots in terms of VRR to HZ/su (anti-gE Abs) at Month 3 • Characterize humoral immune responses (anti-gE) at Months 0 and 3 • Safety and reactogenicity	Adults (≥ 50 YOA) 2 doses: Months 0 and 2.	1) HZ/su Lot A 2) HZ/su Lot B 3) HZ/su Lot C	Final scale	210 210 202		218 217 216
ZOSTER-026	Estonia, US	Phase III, randomized, open-label, schedule comparison study. Duration of FU: 12 months post last vaccination Co-primary objectives: VRR to HZ/su (anti-gE Abs) at 1 month post Dose 2 in the 0,6-month and 0,12-month schedule groups If the 0,6-month schedule VRR objective is met: NI in	Adults (≥ 50 YOA) 1) Gr 0-2: HZ/su, 2 doses Month 0 and 2 2) Gr 0-6: HZ/su, 2 doses Month 0 and 6	1) Gr 0-2 2) Gr 0-6 3) Gr 0-12	Final scale	M3 118 M7 114 M13	M14[h] 117 M18[h] 115 M24[h]	119 119 116

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects		
						ATP cohort for immuno		TVC
		terms of GMC ratio for anti-gE Abs (0,2-month over 0,6-month group) at 1 month post Dose 2 If the 0,12-month schedule VRR objective is met: NI in terms of GMC ratio for anti-gE Abs (0,2-month over 0,12-month group) at 1 month post Dose 2 Secondary objectives: • Immunogenicity with respect to humoral immune response to gE at Day 0, 1 month post Dose 2 and one year post Dose 2 • Safety and reactogenicity	3) Gr 0-12: HZ/su, 2 doses Month 0 and 12			111	110	

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects			
						ATP cohort for immuno		TVC	
Supportive studies									
EXPLO CRD-004	Belgium	Phase I/II, exploratory, open-label, randomized study. Duration of FU: 10 months post last vaccination Co-primary objectives: • Safety and reactogenicity of HZ/su with or without *Varilrix* • Comparison of vaccine strategies to induce the optimum CD4+ and/or CD8+ T cell responses between vaccination groups at Month 3 Secondary objectives: • Safety as measured by haematology and biochemistry parameters • CMI responses elicited by various vaccine strategies • Humoral immune responses elicited by various vaccine strategies	Adults (18-30 YOA) 2 doses: Months 0 and 2 Adults (50-70 YOA) 2 doses: Months 0 and 2	1) gE/Y: HZ/su 2) gEVAR/Y: HZ/su + *Varilrix* 1) VAR/E: *Varilrix* 2) gE/E: HZ/su 3) gEVAR/E: HZ/su + *Varilrix*	Small scale	10 10 45 45 44		10 10 45 45 45	
ZOSTER-018, 019 (EXT:EXPLO CRD-004 M30 and M42)	Belgium	Phase I/II, open-label extension follow-up at Month 30 and Month 42 of subjects vaccinated with HZ/su in study EXPLO-CRD-004 - persistence study. Duration of FU: 28 and 40 months post last vaccination Primary objective: Descriptive assessment of persistence of the CMI responses to gE and VZV in HZ/su group at Months 30 and 42 Secondary objectives: • Persistence of humoral immune responses to gE and VZV in HZ/su group at Months 30 and 42 • Safety with respect to SAEs due to the study procedure during whole study (up to Month 30 and Month 42) • Clinically diagnosed HZ from Month 12 in the EXPLO-CRD-004 study till end of ZOSTER-019	Adults (18-30 YOA) Adults (50-70 YOA) No administration of HZ/su in this study	1) gE/Y: HZ/su 2) gE/E: HZ/su	No vaccination (extension studies)	M30 4 29	M42 3 20	M30 4 30	M42 3 20
ZOSTER-003	Czech Republic, Germany, Netherlands,	Phase II, single-blind, randomized, antigen dose-selection study. Duration of FU: 1 month post last vaccination Primary objectives:	Adults (≥ 60 YOA; Stratified: 60-69 YOA and ≥70 YOA in a 1:4 ratio)	1) gE251B: 25 µg gE/AS01$_B$ 2) gE501B: HZ/su 3) gE1001B: 100	Small scale	157 156		164 166	

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects	
						ATP cohort for immuno	TVC
	Sweden	Comparison of CD4+ T cell response to gE of gE/AS01$_B$ vaccines at Month 3 in subjects ≥70 YOA Secondary objectives: • Comparison of CD4+ T cell response to gE between gE1001B and gE100S groups at Month 3 in subjects ≥70 YOA • Comparison of humoral immune response to gE and VZV of gE/AS01$_B$ study vaccines at Month 3 in subjects ≥70 YOA • Immunogenicity after 1 and 2 doses of study vaccine formulations with respect to CMI and humoral immune responses in subjects 60-69 YOA and ≥70 YOA • Safety and reactogenicity (60-69 YOA and ≥70 YOA) • Clinically diagnosed HZ	2 doses: Months 0 and 2	μg gE/AS01$_B$ 4) gE100S: 100 μg gE/Saline 5) S gE1B: Saline, 1 dose, 100 μg gE/AS01$_B$, 1 dose		151 50 153	165 54 165

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects					
						ATP cohort for immuno			TVC		
ZOSTER-011, 012, 013 (EXT 003 Y1, Y2, Y3)	Czech Republic, Germany, Netherlands Sweden	A single-blind extension follow-up at Months 12, 24 and 36 of ZOSTER-003 - persistence study. Duration of follow-up: 10, 22 and 34 months post last vaccination Primary objectives: None Secondary objectives: • Persistence of CMI (gE specific CD4+ T cell response) and humoral immune responses (gE and VZV) at Months 12, 24 and 36 • Safety with respect to SAEs during whole study • Clinically diagnosed HZ up to Month 36	ZOSTER-003 population No administration of HZ/su in this study	1) gE251B: 25 µg gE/AS01$_B$ 2) gE501B: HZ/su 3) gE1001B: 100 µg gE/AS01$_B$ 4) gE100S: 100 µg gE/Saline 5) S gE1B: Saline, 1 dose, 100 µg gE/AS01$_B$, 1 dose	No vaccination (extension studies)	Months			Months		
						12	24	36	12	24	36
						146	126	117	156	150	147
						144	133	123	159	155	147
						147	135	127	159	154	150
						48	44	40	50	49	47
						145	133	128	161	157	154
ZOSTER-024	Czech Republic, Germany, Netherlands Sweden	Phase II, open-label, single group, extension follow-up at Months 48, 60 and 72 of HZ/su group of ZOSTER-003 - persistence study. Duration of FU: 70 months post last vaccination Primary objective: Evaluation of CMI (gE and VZV specific CD4+ T cells) and humoral immune responses (anti-gE and VZV Abs) in HZ/su group at Months 48, 60 and 72, overall and by age Secondary objectives: • Safety with respect to SAEs and pIMDs in each age range • Suspected cases of HZ episodes	ZOSTER-003 population No administration of HZ/su in this study	1) gE501B: HZ/su	No vaccination (extension studies)	Months			Months		
						48	60	72	48	60	72
						126	NA	NA	129	124	119

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects			
						ATP cohort for immuno		TVC	
ZOSTER-010	Czech Republic, Spain, US	Phase II, randomized, observer-blind, adjuvant dose-selection study. Duration of FU: 12 months post last vaccination Primary objective: Comparison of gE and VZV-specific CD4+ T cell mediated and humoral immune responses between HZ/su, gE/AS01$_E$ and gE/Saline groups at Month 3 in subjects ≥50 YOA Secondary objectives: • Comparison of gE and VZV mediated CMI (including overall CD8+ T cell) and humoral immune responses between HZ/su, gE/AS01$_E$, and gE/Saline groups at Month 3 by age (50-59 YOA, 60-69 YOA and ≥70 YOA) • Safety and reactogenicity • Suspected cases of HZ episodes	Adults (≥ 50 YOA) 2 doses: Months 0 and 2	1) gE/AS01$_B$: HZ/su 2) gE/AS01$_E$: 50 µg gE/AS01$_E$, 3) gE/Saline: 50 µg gE/Saline 4) Saline	Intermediate scale	140 138 71 37		150 149 73 38	
ZOSTER-023	Australia	Phase I, open-label, single country safety and immunogenicity study. Duration of FU: 6 months post last vaccination Primary objective: Safety and reactogenicity Secondary objective: Immunogenicity with respect to humoral immune response to gE and VZV	Ethnic Japanese Adults (18-30 YOA and 50-69 YOA) 2 doses: Months 0 and 2	1) 18-30 YOA: HZ/su 2) 50-69 YOA: HZ/su	Intermediate scale	10 8		10 10	
ZOSTER-032	Japan	Phase III, randomized, open-label study, SC vs. IM administration. Duration of FU: 12 months post last vaccination Co-primary objectives: • Descriptive assessment of VRR and GMC (anti-gE Abs) to HZ/su when administered SC vs. IM at Month 3 • Safety and reactogenicity up to Month 3 Secondary objectives: • Immunogenicity with respect to humoral immune responses (VRR and GMC) from Month 0 to Month 14 • Safety with respect to SAEs and pIMDs from Month 3 to Month 14	Adults (≥ 50 YOA) 2 doses: Months 0 and 2.	1) SC HZ/su 2) IM HZ/su	Final scale	M3 29 29	M14 30 28	M3 30 30	M14 30 30

Study ID	Study country(ies)	Study Design Objectives*	Population (age) Schedule of vaccination	Study groups	gE lots used°	Number of subjects	
						ATP cohort for immuno	TVC
ZOSTER-033	Canada, Russian Federation	Phase III, non-randomized, open-label study in adults with a previous episode of HZ. Duration of follow-up: 12 months post last vaccination Co-primary objectives: • VRR for anti-gE Abs at Month 3 • Safety and reactogenicity up to Month 3 Secondary objectives: • Immunogenicity with respect to anti-gE humoral responses by age (50-59 YOA, 60-69 YOA and ≥70 YOA) • Safety with respect to SAEs and pIMDs from 30 days post last vaccination until Month 14	Adults (≥ 50 YOA) 2 doses: Months 0 and 2.	1) HZ/su	Final scale	82	96

Ab = antibody; ATP = According to Protocol; CMI = Cell Mediated Immunity; EOS = end of study; FU = follow up; gE = glycoprotein E; GMC = Geometric Mean Concentration; GMT = Geometric Mean Titre; HI = Haemagglutinin Inhibition; HZ = Herpes Zoster; HZ/su = Herpes Zoster subunit candidate vaccine (50 µg gE/AS01$_B$); IM = intramuscular; M = Month; mTVC = modified TVC; NA = not applicable; NI = non-inferiority; PHN = post-herpetic neuralgia; pIMD = potential Immune-Mediated Disease; SAE = serious adverse event; SC = subcutaneous; SCR = Seroconversion Rate; TVC = Total Vaccinated Cohort; FLU-D-QIV = GSK's unadjuvanted quadrivalent seasonal influenza vaccine; UK = United Kingdom; US = United States; VE = Vaccine Efficacy; VRR = Vaccine Response Rate; vs. = versus; VZV = Varicella Zoster Virus, YOA = years of age

* The detailed objectives as specified in the protocol, the statistical analysis plan (SAP) and success criteria of study objectives are listed in the dossier; a summary is included in this report in section 2.4

[a] For ATP cohort of humoral or CMI immunogenicity at other timepoints than Month 3 (M3), refer to section 2.5.2 for ZOSTER-006 and ZOSTER-022

[b] TVC used for safety analysis

[c] mTVC used for final HZ efficacy analysis (Note: the mTVC for the EOS efficacy analysis included 7,340 subjects in the HZ/su group and 7,413 subjects in the Placebo group)

[d] mTVC used for efficacy analysis

The clinical development program of HZ/su consisted of the following studies (for details refer to the tabular overview):

Adults ≥ 50 YOA, Healthy (initial proposed indication)

	Study	Scope	Remark
Phase I	ExploCRD004	Exploratory safety and CMI	
	ZOSTER-018;019	FU ExploCRD004	
	ZOSTER-023	Adults of Japanese ethnic origin	
Phase II	ZOSTER-003	Antigen and adjuvant dose selection	
	ZOSTER011;12;13	FU ZOSTER-003; Y1,2,3	
	ZOSTER-024	FU ZOSTER-003; Y6	
	ZOSTR-060	FU ZOSTER-003	*ongoing*
	ZOSTER-010	Adjuvant dose selection	
Phase III	ZOSTER-006	Pivotal + pooled	
	ZOSTER-022	Pivotal + pooled	
	ZOSTER-049	FU 006/022; 6 years FU	*ongoing*
	ZOSTER-004	Coadmin Flu-D-QIV	
	ZOSTER-035	Coadmin Pneumovax23	*ongoing*[2]
	ZOSTER-042	Coadmin Boostrix	*ongoing*[2]
	ZOSTER-007	Lot to Lot consistency	
	ZOSTER-048	Previous Zostavax administration	*ongoing*
	ZOSTER-033	Adults with previous episode of HZ	
	ZOSTER-026	Schedule comparison	
	ZOSTER-032	SC vs IM	
	ZOSTER-056	Safety in 006/022 placebo recipients	*ongoing*

Adults ≥ 18 YOA, Immunocompromised (proposed extension of indication)

Phase I/IIa	ZOSTER-001	Autologous HCT recipients	
	ZOSTER-015	HIV-infected adults	
Phase II/III	ZOSTER-028	Solid Malignant Tumours chemotherapy	*ongoing*[2]
Phase III	ZOSTER-002	Autologous HCT recipients	*ongoing*
	ZOSTER-039	Hematologic malignancy patients	*ongoing*
	ZOSTER-041	renal transplant	*ongoing*

2.4.2. Pharmacokinetics

Biopharmaceutical studies are typically conducted for new drugs. For vaccines, biopharmaceutics concerns the bioavailability of the vaccine components after administration. In accordance with the EMA Guideline on Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005) and the EMA Guideline on adjuvants in vaccines for human use (EMEA/CHMP/VEG/134716/2004), pharmacokinetic studies including bioavailability and bioequivalence studies are usually not required for vaccines. Measurement of the plasma concentration of the vaccine over time is not feasible.

Pharmacokinetic studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients. The need for pharmacokinetic studies and their design was discussed during EMA scientific advice. $AS01_B$ adjuvant is not included in any EU licensed vaccine, but a similar version is included in Mosquirix (intended for use outside the EU). It has been characterised extensively in nonclinical pharmacology (PK and PD) studies. The absorption, distribution and elimination of AS01, QS-21 and MPL to investigate AS01, QS-21 and MPL-related material was investigated following IM administration of $AS01_B$ in mice, IM administration of QS-21 in the rabbit and IM and intravenous (IV) administration of MPL in rats. Part of the $AS01_B$, MPL and QS-21/DQ toxicity and safety pharmacology studies were included in the RTS,S (Mosquirix) application submitted to the

[2] These studies were concluded at the time of the CHMP opinion but the data will be submitted and assessed after authorisation

European Medicines Agency (EMA). In addition, the MPL toxicity and safety pharmacology studies were included in the Fendrix and Cervarix applications for marketing authorisation submitted to the EMA.

2.4.3. Pharmacodynamics

In relation to vaccines, pharmacodynamic studies are essentially comprised of the immunogenicity studies that characterise the immune response to the vaccine. Pharmacodynamic data, which comprised the humoral and cell mediated immune responses to the vaccine, were obtained from clinical studies.

Most of the studies were conducted in adults aged ≥ 50 years of age, who were nearly all seropositive at enrolment when tested, e.g. in study ZOSTER-006. Two studies were conducted in immunocompromised subjects, who enrolled adults ≥ 18 years of age (see section 2.5.4).

The company submitted a large data package of clinical trials, which consisted of 5 pivotal and 14 supportive studies. The route of administration and dosing of the glycoprotein gE as well as of the adjuvant $AS01_B$ were explored in 5 phase I/II studies in support of the clinical development of the Phase III trials of HZ/su, during which the immunogenicity and efficacy was investigated in two large, placebo controlled efficacy trials, which enrolled more than 16.000 subjects. Within a large lot-to-lot consistency study (more than 200 subjects/lot) the similar immune-responses between 3 lots were proven. A smaller study was conducted to determine the timeframe of the second dosing between 2 to 12 months after the first dosing. The 0, 6-month schedule was non-inferior in terms of gE-humoral responses compared to the 0, 2 month schedule. The 0, 12 month schedule compared to the 0, 2 month schedule did not meet the criteria of non-inferiority.

The results of individual studies are described in their respective sections; section 2.5.3 provides a summary of the main immunogenicity results of the pivotal trials (with focus on the pooled analysis) and section 2.5.6 presents a summary and discussion of the overall immunogenicity results with HZ/su.

Mechanism of action

HZ/su has been designed to induce antigen-specific cellular and humoral immune responses expected to translate into robust vaccine efficacy in individuals with pre-existing immunity against VZV. VZV gE was chosen as the subunit vaccine antigen because of both its prominence as a target for host immune responses and its functional significance during viral infection. A truncated version of the protein was selected that lacks the transmembrane anchor and carboxy-terminal domains, and is thereby secreted into the culture supernatant. In non-clinical studies, vaccination with gE induced anti-gE antibodies (Abs) and gE-specific cell-mediated immunity (CMI).

Non-clinical data further show that $AS01_B$ 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 in the draining lymph node, which in turn leads to the generation of gE-specific CD4+ T cells and antibodies. The adjuvant effect of $AS01_B$ is the result of interactions between MPL and QS-21 formulated in liposomes.

The immunogenicity profile of HZ/su vaccine was assessed through the measurement of humoral and cellular immune response.

Determination of optimal threshold for vaccine response

Since most subjects of the target population (adults ≥50 YOA) were previously infected with VZV, the majority of subjects enrolled in HZ/su studies were expected to be seropositive at pre-vaccination. Therefore, the fold-increase over pre-vaccination is a more relevant assessment to evaluate the immune response to the candidate HZ vaccine than only simply assessing the antibody concentrations. In most clinical studies with HZ/su, the immune response is evaluated in terms of vaccine response rate, i.e., the proportion of subjects with a vaccine response, defined as a pre-specified fold increase in Ab concentrations over pre-vaccination levels. Hence, the Applicant determined a definition for vaccine response. The determination of the optimal threshold for vaccine response is not reported here in full, but it was based on the Receiver Operation Characteristic (ROC) curve approach that discriminates a non-responder population (placebo recipients post-vaccination) from a responder population (recipients of the vaccine one month post-dose 2). This methodology was applied to the data from HZ/su Phase II clinical studies ZOSTER-003 and ZOSTER-010. ZOSTER-003 served as learning dataset and ZOSTER-010 as confirmatory dataset.

By using this approach, the following thresholds were selected: 1) 4-fold increase over pre-vaccination for humoral anti-gE ELISA responses; 2) 2-fold increase over pre-vaccination for gE-specific CD4[2+] T cell responses.

Laboratory Assays

Laboratory assays that were used in this exercise are summarized in Table 6 (see also following sections). Note that at the time of ZOSTER-003, the anti-gE Ab cut-off was defined at 109 EU/mL based on the Henogen gE ELISA. At the time of ZOSTER-010, the anti-gE Ab cut-off was defined at 18 mIU/mL, based on the currently used in-house gE ELISA. At present, the cut-off of this assay is set on 97 mIU/mL.

Table 5. Laboratory assays used for the establishment of vaccine response definition for HZ/su

Study	Assay type	Marker	Assay method	Assay unit	Assay cut-off	Laboratory
ZOSTER-003	ICS	CMI markers (IFN-γ, IL-2, TNF-α and CD40L)	Cells flow cytometry (CFC)	frequency of gE-specific T cells/10^6 T cells	NA	GSK Biologicals
	ELISA	anti-gE	ELISA	EU/mL	109	Henogen, Gosselies, Belgium
ZOSTER-010	ICS	CMI markers (IFN-γ, IL-2, TNF-α and CD40L)	CFC	frequency of gE-specific T cells/10^6 T cells	NA	GSK Biologicals
	ELISA	anti-gE	ELISA	mIU/mL	18	GSK Biologicals laboratory

The assay cut-off was changed in February 2014 following additional validation experiments from 18 mIU/mL to 97 mIU/mL. The higher assay cut-off was considered more precise based on additional assay validation utilizing VZV-naïve specimens from paediatric subjects.

Descriptive analysis of immune response parameters

Depending on the assays performed in each study for the humoral response, the following parameters were tabulated by treatment group, overall and by age cohort at the indicated time-points:

- Descriptive statistics of anti-gE Ab concentrations (mean, SD, min, first quartile [Q1], median, third quartile [Q3], max);
- Anti-gE and anti-VZV Ab GMCs with 95% CIs;
- Seropositivity rates for anti-gE and anti-VZV Abs (i.e. antibody concentrations ≥ assay cut-off value) with exact 95% CIs;
- Vaccine response rates (VRRs) for anti-gE and anti-VZV with 95% CIs. The vaccine response was defined as a post Dose 2 Ab concentration ≥4-fold the cut-off value for seropositivity for seronegative subjects at baseline or at least a 4-fold increase in post Dose 2 Ab concentration as compared to the pre-vaccination Ab concentration for seropositive subjects at baseline.
- MGI with exact 95% CI for anti-gE Ab concentrations (ZOSTER-006 and ZOSTER-022 only).
- Distribution of the fold increase from pre-vaccination, i.e., percentage of subjects with a more than X-fold (e.g., ≥2, ≥4, ≥6, ..., ≥40 -fold) increase in anti-gE and anti- VZV Ab concentrations tabulated per group with 95%CI.
- Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of the fold increase over pre-vaccination for anti-gE Ab concentrations.

Note that the analysis of the humoral immune response was also performed on pooled ZOSTER-006 and ZOSTER-022 in ≥70 YOA.

Depending on the assays performed in each study for CMI response (see Table 6), descriptive statistics of the following parameters were tabulated by treatment group, overall and by age cohort at the indicated time-points:

- Descriptive statistics of frequencies of gE and VZV-specific CD4 T cells, secreting at least 2 different immunological activation markers among IFN-γ, IL-2, TNF-α, and/or CD40L (hereafter referred to as CD4[2+]) upon in vitro stimulation with gE and VZV, respectively (N, mean, SD, min, Q1, median, Q3, max);
- VRRs for gE-specific and VZV-specific CD4[2+] T cells with 95% CIs. VRR for gE-specific/VZV-specific CD4[2+] T cells is defined as the percentage of subjects who had at least a 2-fold increase as compared to pre-vaccination CD4[2+] T cell frequencies (subjects with pre-vaccination CD4[2+] T cell frequencies above the assay cut-off), or as compared to the cut-off (subjects with pre-vaccination CD4[2+] T cell frequencies below the cut-off).
- Descriptive statistics of fold increase over pre-vaccination in the frequency of gE-specific and VZV-specific CD4[2+] T cells (N, mean, SD, min, Q1, median, Q3, max)
- Descriptive statistics of frequencies of gE and VZV-specific B cell memory response (N, mean, SD, min, Q1, median, Q3, max).

Cell-mediated immunity

The main assays used in the HZ/su clinical studies to evaluate CMI responses were:

- gE intracellular cytokine staining (ICS) assay: the Applicant has developed and validated an ICS assay to measure in vitro the frequency of gE-specific CD4+ T cells in peripheral blood mononuclear cells (PBMCs) isolated from whole blood samples of clinical study participants. The gE ICS assay allows measurement of CMI responses induced by HZ/su. The frequency of CD4+ T cells is determined through detection of at least 2 of the following immune markers: CD40 Ligand (CD40L), Interferon γ (IFN- γ), Tumour Necrosis Factor α (TNF- α), or Interleukin-2 (IL-2) upon stimulation with gE peptides. CMI responses were measured in

several clinical studies with HZ/su and the purpose varied depending on the phase in clinical development:

  - Phase I: CMI responses were evaluated to understand the immunogenicity of the vaccine;
  - Phase II: CMI (and humoral) responses were evaluated to establish the optimal vaccine formulation (both antigen and adjuvant doses), and whether one or 2 doses would be used;
  - Phase III: CMI data were collected in ZOSTER-006, where it was an exploratory objective to further characterize the immune response to the vaccine.

- VZV-ICS: In the early CDP (Phase I and II studies), and also in ZOSTER-006, an ICS assay measuring the vaccine- induced response by stimulating CD4+ T cells with VZV antigen was used to complement the gE ICS assay, and to provide additional characterization of the CMI response induced by HZ/su.

Since CMI responses are believed to be essential for protection against the development of HZ, strong and persistent CD4+ T cell responses as elicited by the adjuvanted HZ/su vaccine are believed to be key in the efficacy of HZ/su. Therefore, evaluation of CMI responses was the primary objective of several Phase I/II HZ/su clinical studies (EXPLO-CRD-004, ZOSTER-003 and their extension studies and ZOSTER-010).

In ZOSTER-006, gE-specific CD4[2+] T cell responses were assessed in the CMI component of the immunogenicity subset. One Month post Dose 2, high median frequencies of gE-specific CD4[2+] T cells were observed, which were 24.6-fold higher than those pre-vaccination. The gE-specific CD4[2+] T cell response was consistently high across age groups.

In all studies mentioned above, except ZOSTER-003, VZV-specific CD4+ T cell responses were also assessed. As was observed for gE-specific CD4[2+] T cells, high VZV-specific CD4[2+] T cell frequencies were elicited by HZ/su one month post Dose 2.

Memory B cell responses specific to gE and VZV were assessed one month post Dose 2 in ZOSTER-003 in a subset of subjects ≥70 YOA as an exploratory objective in a small sample size.

Humoral immunity

The main assay used in the HZ/su clinical studies to evaluate humoral immune was:

- Anti-gE enzyme-linked immunosorbent assay (ELISA): the Applicant has developed and validated an ELISA to determine the concentration of IgGs specific to gE in human serum samples. This assay allows quantitative measurement of the humoral immune response induced by HZ/su. Glycoprotein E is the only VZV-specific antigen in HZ/su. Therefore, assessment of gE-specific immunogenicity is the most direct way to confirm immune responses to HZ/su.

In addition, supportive assays were used in the HZ/su clinical studies to complement the results obtained with the main assays. The following supportive assays were used:

- Anti-VZV ELISA: the Applicant has validated a commercial anti-VZV ELISA kit (Enzygnost, Siemens) to determine the concentration of IgG specific to VZV antigens in human serum samples. The assay was used in the early CDP (Phase I and II studies) to obtain a general understanding of the immune responses against VZV elicited by the gE subunit HZ/su vaccine. Moreover, evaluation of the anti-VZV ELISA response elicited by HZ/su provides evidence that HZ/su is able to induce immune responses to VZV as was previously observed with the live attenuated VZV vaccine (Zostavax). The assay was also used to evaluate a correlation between

the anti-gE ELISA and the anti-VZV ELISA. This assay was still performed in the pivotal Phase III ZOSTER- 006/022 studies, but as the clinical development advanced (all later Phase III studies), the Applicant decided to use the anti-gE ELISA as the core assay and the anti-VZV ELISA became redundant.

- Anti-VZV neutralization assay: The correlation between antibody concentrations measured by the anti-gE ELISA and the VZV neutralizing antibody titres was explored on a subset of post-vaccination samples from ZOSTER-010 subjects. The anti-VZV Plaque Reduction Neutralization (PRN) was not performed in any further clinical studies with HZ/su.

In all HZ/su clinical studies included in this application, anti-gE Abs were measured by ELISA. In ZOSTER-006 and ZOSTER-022, anti-gE Abs were assessed in a subset of subjects. Very high levels of anti-gE Ab were reached in the HZ/su group at Month 3 (Median 53,375 mIU/mL) as compared to the baseline level (i.e. Median 1283 mIU/mL) in subjects ≥50 YOA (ZOSTER-006). Overall, HZ/su elicited higher anti-gE Ab responses one month post Dose 2 compared to placebo. Increases in anti-gE antibody concentrations with a VRR of 98.5% in ≥50 YOA and 96.6% in ≥70 YOA were observed. The humoral immune response was consistently high across age groups, although it modestly decreased with increasing age. For more details see section 2.5.3 on the pooled analysis across ZOSTER-006 and -022.

The cut-off values of anti-gE and anti-VZV ELISA assays were set up at 97 mIU/mL and 25 mIU/mL, respectively for the pivotal studies. It was clarified on which basis these values were set and adapted. In summary, cut-offs of both anti-gE and anti-VZV ELISAs were determined using representative clinical sample panels, allowing an accurate assessment of seroprevalence by both ELISAs. This was confirmed in retrospective analyses.

Immunogenicity data from the pooled analysis ZOSTER-006/-022 measured by the anti-VZV ELISA from Siemens became available during the procedure, but is not included in this report. A very good correlation was observed between the anti-gE ELISA and anti-VZV ELISA results across the entire range of antibody concentrations in post-vaccination samples from Phase II study ZOSTER-010 (r[Pearson]=0.92). Therefore, anti-VZV ELISA data do not add new information with regard to the immunogenicity of HZ/su.

During the procedure the Applicant was requested to discuss the baseline immunity results against Varicella Zoster Virus (VZV) by the anti-VZV IgG abs (in addition to the anti-gE abs data), in terms of sensitivity/specificity, risk of overestimating seroprevalence levels and comparability among assay. This is because most seroprevalence surveys use various VZV IgG assays. The data presented showed that the seroprevalence level (seropositivity at baseline) is consistently high (>99%) across studies (pooled ZOSTER-006/022 [adults ≥50 years], ZOSTER-003 [adults ≥60 years] and ZOSTER-010 [adults ≥50 years]), and for both assays (anti-VZV IgG ELISA and anti-gE ELISA). It is concluded that given the very high level of baseline immunity (pre-vaccination anti-gE and anti-VZV antibody levels well above the defined cut-offs), the risk to overestimate baseline seroprevalence in adults ≥ 50 years is very limited by using the Applicant's anti-gE ELISA.

Regarding the functionality of the generated anti-gE antibodies, the correlation between antibody concentrations measured by the anti-gE ELISA and the VZV neutralizing antibody titres measured by the anti-VZV Plaque Reduction Neutralization (PRN) was explored on a subset of post-vaccination samples from ZOSTER-010 subjects. This was needed to provide information on the functionality of the anti-gE Ab response elicited following vaccination, and to establish whether anti-gE Ab levels measured by ELISA are predictive of neutralization titres. Results showed a good correlation anti-VZV neutralizing antibody titres with both ELISA assays (anti-gE and anti-VZV ELISA). As a consequence, anti-VZV neutralization assay has not been performed in more recent ZOSTER studies, including ZOSTER-006,

as it would not provide substantial new insights into the immune response to vaccination nor would it change the conclusions of the study.

Primary and Secondary pharmacology

N/A

2.4.4. Discussion on clinical pharmacology

As evaluated in ZOSTER-010, post-vaccination anti-gE ELISA concentrations correlated with VZV neutralization titres. At Month 3, the Pearson correlation coefficient and the Spearman correlation coefficient were 0.7238 and 0.7412, respectively, indicating a good correlation between log anti-gE Ab concentrations and log anti-VZV neutralizing Ab titres. These data indicate that the anti-gE Ab concentrations measured by ELISA are predictive of neutralization responses and confirm that Abs induced by HZ/su are directed against the native and biologically active form of gE. Therefore the anti-VZV Plaque Reduction Neutralization (PRN) was not performed in any further clinical studies with HZ/su.

The results from exploratory immunogenicity objective for anti-VZV antibody responses (all time points) were considered during the procedure and do not alter the original study conclusions. A very good correlation was observed between the anti-gE ELISA and anti-VZV ELISA results across the entire range of antibody concentrations in post-vaccination samples e.g. in study ZOSTER-010, which indicate that antibodies elicited by HZ/su recognize the native gE present in the anti-VZV ELISA with a high specificity. Therefore the decision to use the anti-gE ELISA as the core assay is endorsed.

Regarding the relationship between cellular and humoral response only a moderately positive correlation has been demonstrated between humoral immune responses (based on GMCs for anti-gE Abs as measured by anti-gE ELISA) and CMI responses (based on gE-specific CD4[2+] T cell frequencies as measured by the gE ICS assay).

While anti-gE ELISA and VZV-ELISA titres reach a peak level already post dose 1 due to the relatively high titres pre-vaccination, VRR GMCs can be increased significantly after a second vaccine dose. This observation suggests that HZ/su vaccine induces multiple, yet undefined, immunological pathways.

Currently, no correlate of protection for HZ/su has been established. As specified in the ZOSTER-006 protocol, a correlate of protection analysis was performed on pooled ZOSTER-006 and ZOSTER-022 breakthrough HZ cases. See section 2.5.3 on the ZOSTER-006/-022 pooled analysis for details.

2.4.5. Conclusions on clinical pharmacology

The choice of assays for immunogenicity assessment and the results of the correlations across assays are endorsed. The candidate HZ/su vaccine elicits a strong humoral and cellular immune response and the data are robust. For more details please see section 2.5.3 on immunogenicity results across trials and section 2.5.6 on the discussion of the results.

2.5. Clinical efficacy

2.5.1. Dose response studies

Studies relevant for dosing recommendations are:

- ZOSTER-003: gE antigen dose selection study
- ZOSTER-010: adjuvant dose selection study

Studies relevant for posology recommendations are:

- ZOSTER-003 and EXPLO CRD-004: dose number selection studies
- ZOSTER-026: flexible dose schedule selection study
- ZOSTER-032: SC vs IM route of administration

Studies ZOSTER-003 and ZOSTER-010, in which different antigen and adjuvant system doses were tested, allowed to establish the final vaccine formulation with a glycoprotein dose (50 µg gE) and adjuvant dose $AS01_B$ in the older population. Two doses of HZ/su were required for optimal immune response, based on the observation that 2 doses provided higher gE-specific and VZV-specific CMI and humoral responses than one dose of HZ/su, which was investigated in the Phase II trials EXPLO CRD-004, ZOSTER-003 and ZOSTER-10. Data of the persistence follow-up studies of ZOSTER-003 indicated that the vaccine-induced immune response persisted at least around 72 months post Dose 1, following a 0, 2 dose schedule. See also section 2.5.3 on Persistence of immune responses (ZOSTER-024 study).

Non-inferiority in terms of gE ELISA antibody results of study ZOSTER-026 supports a two dose vaccination schedule with the doses being administered with an interval of 2 to 6 months. For details of study ZOSTER-026 see section 2.5.5.3.

In the small study ZOSTER-032 administration of HZ/su subcutaneous versus intramuscular was investigated. The results in terms of gE antibody titres were similar in both dose groups. However, subcutaneous route of administration was not chosen since it was linked to a higher incidence of local reactions (see warning in the SmPC).

2.5.2. Main studies

2.5.2.1. ZOSTER-006

Study title: A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of gE/$AS01_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.

ZOSTER-006 (ZOE-50) is a phase 3 efficacy trial performed in adults 50 years of age (YOA) or older in 18 countries in Europe, North America, Latin America, and Asia-Australia (268 Principal Investigators) in order to assess whether two doses of HZ/su reduce the risk of herpes zoster (HZ).

A total of 16,145 subjects were randomized 1:1 either to the HZ/su Group (N=8068) or to the Placebo Group (N=8077) among whom 14,759 were included in the mTVC for the final efficacy analysis (7344 in the HZ/su Group and 7415 in the Placebo Group).

The median follow-up period was 3.1 years (range: 0 to 3.7 years) in the mTVC at the time of the final efficacy analysis of HZ endpoint and 4.1 years (range: 0 to 4.5 years) at the time of the End of Study on HZ and Post-herpetic Neuralgia (PHN) analysis.

A pre-specified vaccine efficacy (VE) analysis was performed on pooled ZOSTER-006 and ZOSTER-022 efficacy data in ≥70 YOA at the time both studies were completed. The co-primary objectives of this analysis were to evaluate VE in the prevention of overall PHN and to consolidate the VE estimation in the prevention of HZ compared to placebo in subjects ≥70 YOA across both Phase III studies.

Persistence of protection against HZ is being evaluated in ZOSTER-049, which follows HZ/su recipients from ZOSTER-006 and ZOSTER-022 for a duration of at least 10 years after first vaccination. ZOSTER-049 data were not available at the time of the preparation of this application.

Methods

Study Participants

Subjects were enrolled in the following countries:

- Australasia: Australia, Hong Kong, Japan, S. Korea, Taiwan.
- Europe: Czech Republic, Estonia, Finland, France, Germany, Italy, Spain, Sweden, UK.
- Latin America: Brazil, Mexico.
- North America: Canada, US.

The enrolment target was about 7345 subjects for Europe. The allocation per region was provisional and could change depending on the enrolment.

Eligible subjects were male or female aged ≥ 50 YOA (ZOSTER-006) or ≥ 70 YOA (ZOSTER-022) at the time of first vaccination, who provided informed consent and had no prior history of HZ or previous vaccination against HZ or varicella.

Subjects were excluded if he/she had either of:

- history of allergic disease or reactions likely to be exacerbated by any component of vaccine
- acute disease and/or fever at enrolment
- any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy
- significant underlying illness. e.g. life-threatening disease likely to limit survival to < 4 years
- any other condition that, in the opinion of the investigator, could interfere with evaluations required by the study.

Overall inclusion and exclusion criteria in the present study are considered appropriate.

Treatments

In both studies, the gE/AS01$_B$ vaccine and placebo (NaCl solution) were administered in 0.5 mL volume, on a 0, 2-month schedule. The standard route was IM injection in the deltoid of the non-dominant arm.

Objectives

Primary objective

1. To evaluate VE in the prevention of HZ compared to placebo in adults ≥50 YOA, as measured by the reduction in HZ risk.

Secondary objectives

1. To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk;
2. To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;

3. To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
4. To evaluate VE in the reduction of overall and HZ-related mortality and hospitalizations compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
5. To evaluate VE in the reduction in incidence of HZ-associated complications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
6. To evaluate VE in the reduction in use of pain medications compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
7. To evaluate vaccine safety and reactogenicity.

Exploratory objectives

1. To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
2. To evaluate VE in improving Quality of Life (QoL) compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA, with confirmed HZ;
3. To evaluate VE in the mitigation of Burden-Of-Illness (BOI) caused by HZ compared to placebo in subjects ≥ 50 YOA and in subjects within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA;
4. To evaluate vaccine induced cell mediated and humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥ 50 YOA, and by age strata;
5. To evaluate anti-VZV neutralizing Ab titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥ 50 YOA, and by age strata.

Overall the objectives are endorsed.

Outcomes/endpoints

A. Efficacy Endpoints

The primary endpoint for efficacy evaluation was confirmed HZ cases during the study in the modified total vaccinated cohort (mTVC).

The secondary endpoints were:

1. Incidence of PHN calculated using the mTVC;
2. Duration of severe 'worst' HZ-associated pain following the onset of a confirmed HZ rash over the entire pain reporting period as measured by the ZBPI in subjects with confirmed HZ;
3. Incidence of overall and HZ-related mortality;
4. Incidence of HZ complications in subjects with confirmed HZ;
5. Incidence of overall and HZ-related hospitalizations;

6. Duration of pain medication administered for HZ;

7. Safety endpoints in a subset of subjects (refer to section 2.6).

Exploratory endpoints included: Acute HZ severity as determined by the mean Area Under 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; Interference of HZ with QoL as measured by ZBPI or EQ-5D or SF-36 in sbj with confirmed HZ; HZ BOI as determined by the mean AUC of the severity-by-duration HZ-associated pain during a 26 week period following the onset of the HZ rash in the mTVC; CMI in terms of frequencies of antigen-specific (gE and VZV) CD4 T cells at Months 0, 3, 14, 26 and 38; Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38. The latter included anti-gE and anti-VZV Ab concentrations as determined by ELISA (in a subset), and anti-VZV neutralizing Ab titres as determined by neutralization assay (in a subset).

Definitions

Each HZ case is ascertained by clinical criteria and laboratory results.

- A suspected case of HZ was defined as new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. Subjects clinically diagnosed as having a suspected case of HZ by the investigator were referred to as a case of 'suspected HZ'.
- A "confirmed case of HZ" was diagnosed by using standardized and validated real-time PCR assay targeting VZV ORF62 (lower detection limit of 10 VZV DNA copies per reaction), or by the HZ Adjudication Committee (HZAC) only in case that PCR confirmation is not possible (see further below).
- The HZ onset date was defined as the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted.
- The end date of a HZ episode was defined as the first time at which a subject had no rash (papules, vesicles, ulcers or crusts) present.
- Severe 'worst' pain was defined as HZ-associated pain rated as 3 or greater on the 'worst pain' ZBPI question.
- PHN was defined by the presence of HZ-associated severe 'worst' pain that was rated as 3 or greater on the Zoster Brief Pain Inventory (ZBPI) questionnaire, persisting or appearing more than 90 days after onset of the HZ rash. Alternative definitions of PHN, based on duration of pain of 30, 60, 120 and 180 days were also be used for reporting purposes.
- Cessation of pain was defined as a 28-day pain-free period, and was used to assess the duration of HZ-associated pain. If that pain-free period was not achieved, or if pain did not cease, the time-to-event was censored at the last day HZ-associated pain was recorded.
- Acute pain was defined as pain measured during the 4-week period following onset of confirmed HZ.

Ascertainment of suspected HZ cases

At Visit 1, all subjects had to be educated with regard to the signs and symptoms of HZ and then reminded at each visit. The subjects were also given a HZ specific diary card that they were instructed to complete as soon as they developed symptoms suggestive of HZ and prior to visiting the study site for evaluation of the 'suspected HZ'. The subjects were invited to visit the study site as soon as possible (within 48 hours if possible) for evaluation by the investigator of the 'suspected case of HZ'.

During that visit (first evaluation of the suspected case of HZ [Visit HZ-1 at Day HZ-0]), the investigator had to perform a clinical examination.

For 'clinically diagnosed suspected HZ cases', the following procedures had to take place at Visit HZ-1:

- The completed HZ-specific diary card returned by the subject had to be verified and relevant information regarding the HZ episode recorded in the eCRF (such as date of onset of pain and rash, date of clinical diagnosis of HZ, location and nature of HZ lesions, HZ-related complications if any);
- The rash had to be documented by digital photography and rash lesion samples (three replicate samples on the same day) had to be collected (if not possible, a further visit scheduled to collect samples);
- Concomitant medication, including medication for HZ treatment or any HZ-related complications were recorded;
- Instructions had to be provided to the subjects for completing the ZBPI, EQ-5D and SF-36 questionnaires.

After Visit HZ-1, visits or contacts had to take place for follow-up of the HZ episode every week up to Day HZ-28. Afterwards, a contact took place at Day HZ-56 and finally at Day HZ-91 (Visit HZ-7). Follow-up of HZ-associated pain persisting beyond Day HZ-91 (Visit HZ-7) or other complications had to be done at monthly contacts between the subjects and the investigator. At each visit or contact that occurred after Visit HZ-1, the study staff/investigator recorded relevant information regarding the suspected HZ case (including photographs and samples), concomitant medications and intercurrent medical conditions.

Confirmation of a suspected case of HZ

A suspected case of HZ could be confirmed in two ways:

- by PCR using standardised and validated assays and a hierarchical case definition algorithm, similar to the algorithm used by Merck in their Shingle Prevention Study (Zostavax efficacy study); a β-actin PCR was used as positive control to ensure the validity of the negative HZ PCR results. However if no conclusion was possible based on PCRs, then the classification by the HZAC (see below) was used to confirm or exclude the suspected HZ case;

  For PCR confirmation, three rash lesion samples from each suspected HZ case were tested, which were collected on the same day and of the highest priority lesion type available: 1) vesicle fluid; 2) crust; 3) crust swab; 4) papule swab.

- by the HZ Ascertainment Committee (HZAC), who classified all referred cases as either 'HZ' or 'not HZ'. The HZAC consisted of three to five physicians with HZ expertise that were blinded to treatment assignments. Each HZAC member made a clinical determination of every case based on review of the available clinical information. A suspected case of HZ was considered as 'HZ' if the HZAC members concurred unanimously; otherwise, it was classified as 'not HZ'. Following a protocol amendment the following possibility was added: 'Not able to decide'. Their classification served as the final diagnosis of referred cases, only when the case could not be confirmed or excluded by PCR.

Data collection related to pain and QoL

The Zoster Brief Pain Inventory (ZBPI) questionnaire was supplied to each suspected case of HZ during visit HZ-1 and was used to collect information on the severity and duration of HZ-associated pain and discomfort (incl. allodynia, pruritus or other sensations) during an HZ episode, on a 0-10 scale and for

worst, least, and average pain during the past 24 hours and at that moment. ZBPI question was also used to assess HZ interference with subject's QoL by measuring selected activity of daily life (ADL) on 7 functional status and ADL items: general activity, mood, walking ability, work, relations with others, sleep, enjoyment of life. EQ-5D and SF-36 questionnaires were also supplied for QoL parameter. ZBPI questions needed to be completed daily from Day HZ-1 up to Day HZ-28, then weekly from Day HZ-29 onwards until a 4-week pain-free period is documented. Evaluation of zoster pain persisting beyond Day HZ-91 was done at monthly contacts. The ZBPI was developed based on a validated and widely used pain severity measure, the Brief Pain Inventory (BPI). The ZBPI allows the estimation of pain severity as well as a severity-duration measure through the quantification of HZ-specific pain over time by using the area under the curve (AUC). This approach estimates the total burden of illness (BOI) imposed by HZ.

The impact of HZ on subject's QoL was also measured using the EQ-5D and SF-36 questionnaires, to be completed weekly during the entire period that the ZBPI questionnaires were completed and until HZ-associated pain ceased as defined above. Note that if pain reappeared in the same area after a 4-week pain-free period and was not accompanied by a new HZ rash, it was assigned to the previous HZ-episode and triggered again visits/contacts and questionnaires.

EQ-5D and SF-36 are standardized non disease-specific instruments for describing and valuing health-related quality of life (HRQoL). Such instruments are increasingly used for the evaluation of health care, in population health surveys, as well as in clinical trials. The EuroQoL-5 dimension (EQ-5D) and the Short Form-36 (SF-36) are the most widely used generic HRQoL questionnaires. The instruments are designed for self-completion by respondents and are available in many languages. Both are based on several dimensions of physical and mental health (including social functioning, mobility, physical functioning and pain). They yield a single summary score of overall HRQoL which can be used to calculate quality adjusted life years (QALYs).

Evaluation of severity of HZ-associated pain and HZ Burden-Of-Illness score

HZ Burden-Of-Illness (BOI) score and HZ severity score were derived from the data recorded in the ZBPI. Information on HZ-associated pain was derived from the ZBPI question: 'Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours', so called 'worst pain' in the protocol.

HZ Burden-Of-Illness (BOI) score: for each confirmed case of HZ, responses to the 'worst pain' question in the ZBPI were used to calculate a 'HZ severity-of-illness' score, defined as the area under the curve' (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of the case. A score of 0 was recorded for subjects in whom HZ did not develop during the study period.

HZ severity score: the methodology described for the HZ BOI score was applied to the 4 weeks during which a daily measure is taken and provide the HZ severity score.

Basically, the analysis of QoL and reduction of BOI was based on the Area Under the Curve (AUC) and carried out for durations of 30, 90 and 182 days, in the ZBPI evaluable subgroup (who had a first ZBPI evaluation visit within 14 days of the first date of rash) and/or the mTVC.

Analysis	Scales	AUC	Population
HZ severity of illness score	ZBPI Worst pain score ZBPI Average pain score	0-30, 0-90,0-182* 0-30, 0-90,0-182	HZ ZBPI evaluable subgroup, *Also for mTVC
HZ severity of interference score	ZBPI ADL	0-30, 0-90,0-182*	HZ ZBPI evaluable subgroup, *Also for mTVC
HZ burden-of-illness score	ZBPI worst pain	0-182	mTVC
HZ burden-of-Interference score	ZBPI ADL	0-182	mTVC

HZ complications

During the study, digital photographs of the rash were documented, use of medication was recorded, and subjects were monitored for zoster-related mortality and hospitalizations and HZ-related complications, such as HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, visceral disease, stroke, which were defined in the study protocol. The presence of HZ complications listed below was specifically documented in the eCRF, independently from the AE reporting. If a recorded complication was associated with a case of suspected HZ, and that case was finally not considered to be a confirmed case, the associated complication was not considered a complication of HZ.

- 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 outside the primary dermatome as per the investigator's judgment.
- Ophthalmic disease: Defined as HZ affecting any eye structure as per 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) 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.
- Stroke: A diagnosis of stroke requires that criteria 1, 2 and 3 are fulfilled or criteria 1 and 4 and in the opinion of the investigator is temporally associated with an episode of HZ. [Criterion 1: Rapid onset of localising neurological deficit and/or change in level of consciousness; Criterion 2: Localising neurological deficit or change in level of consciousness that lasts greater than 24 hours; Criterion 3: No other cerebral process, peripheral lesion, or other disorder is the cause of the localising neurological deficit or change in level of consciousness; Criterion 4: CT scan or MRI scan evidence of an acute thrombotic or haemorrhagic lesion.]

Additional information on data collection and study duration

After Visit 3 (Month 1 post vaccination 2), monthly contacts between the subjects and the investigator had to take place (except at months that coincide with the subject's scheduled visits) in order to collect information on any event of interest that may have occurred. The subject had to respond to a standard set of questions. Information on safety, the occurrence of HZ, and the follow-up of ongoing HZ cases was collected.

Yearly follow-up visits had to be performed at Month 14, Month 26, and Month 38 (Visit 6).

EQ-5D and SF-36 questionnaires had to be completed by all subjects at study entry, Visits 4 (M14), 5 (M26) and 6 (M38). Subjects with an ongoing suspected HZ episode had to follow a weekly schedule and did not need to additionally complete the questionnaires at these visits. The information from these questionnaires was transcribed into the eCRF only for subjects who had suspected HZ during the study.

Each subject had to be followed for at least 30 months after Dose 2. Subjects had to continue in the study at least until the cut-off date for end of study analysis regardless of their date of enrolment. The exact duration of the study for individual subjects could thus vary. The maximum total study duration

for each subject was expected to be approximately 4 to 5 years. Final HZ efficacy analysis could be triggered before study conclusion for several subjects.

B. Immunological endpoints

Blood samples had to be collected:

- From all subjects at Visit 1 (Month 0) and 3 (Month 3) to contribute to the correlate of protection assessment (should the subject experience a HZ episode or be selected as a control).
- From a subset of subjects at Visit 4 (Month 14), 5 (Month 26) and 6 (Month 38) to assess persistence of humoral immune response. In these subjects, the blood samples from Visit 1 and 3 were also assessed for humoral immune response.
- From a subset of subjects at Visit 1, 3, 4, 5 and 6 to assess cell mediated immunogenicity (CMI) response.

For subjects included in the Immunogenicity subset (humoral immunity), the following assays were planned for humoral immunity (Antibody determination) at specified time points:

- Varicella Zoster Virus Ab IgG (ELISA), i.e. anti-VZV Abs.
- gE Ab IgG (ELISA) i.e. anti-gE Abs.
- Varicella Zoster Virus Neutralizing Ab IgG (PRNT), i.e. anti-VZV neutralizing Ab assay on the serum blood samples from a subgroup of subjects of the Immunogenicity subset.

For a subgroup of subjects included in the CMI component of the Immunogenicity subset, the frequencies of gE- and VZV-specific CD4 T cells determined by intracellular cytokine staining (ICS) of IFN-gamma and/or IL-2 and/or TNFa and/or CD40L were measured. All assays were validated.

The cut-off values of anti-gE and anti-VZV ELISA assays were set up at 97 mIU/mL and 25 mIU/mL, respectively. A seronegative subject is a subject whose Ab concentration is below the cut-off value.
A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.
The VZV gE-specific humoral immune response to vaccine (vaccine response rate) for subjects who are seropositive at baseline is defined as a 4-fold increase in the anti-gE Ab concentration at the endpoint as compared to the pre-vaccination anti-gE antibody concentration. The VZV gE-specific humoral immune response to vaccine for subjects who are seronegative at baseline is defined as a 4-fold increase in the anti gE Ab concentration at the endpoint as compared to the anti-gE Ab cut-off value for seropositivity.
gE/VZV-specific CMI responses were expressed by gE/VZV-specific frequencies of CD4[2+] T cells, which were obtained by subtracting the response to stimulation with medium only.
For other immunological measurements refer to section 2.4.3.
Results obtained for the anti-gE and anti-VZV Ab ELISA assays were planned to be used for correlate of protection analysis. In study ZOSTER-006 attempts were made to correlate humoral immune responses at Month 3 with protection. Therefore, analysis of the humoral immune responses at pre-vaccination and Month 3 were performed on samples collected from vaccinated subjects who develop confirmed HZ and compared with the humoral immune responses at pre-vaccination and Month 3 from matched subjects that did not develop HZ.

Overall, trial's endpoints are relevant and well defined. Study procedures to ascertain these endpoints are carefully designed. The detection of HZ events and their virological confirmation (primary endpoint) rely on particularly well designed and reliable methods and procedures. In addition, the Applicant undertook a comprehensive assessment of HZ-associated pain and impact on quality of life by using relevant and validated tools. The use of a variety of methods reinforces the robustness of the data.

Sample size

Target enrolment was 15,980 eligible subjects (7,990 in the vaccine group and 7,990 in the placebo group). This sample size was selected in order to provide the required number of HZ cases within a follow-up time of about 3 years.

The following age-stratification ratio was applied: 8:5:3:1 (50-59, 60-69, 70-79 and ≥80 YOA) using a randomization ratio 1:1 for vaccine or placebo. The stratification ratios were selected in order to achieve similar numbers of HZ cases in the three main age strata (50-59 YOA, 60-69 YOA and ≥70 YOA). These numbers were finally not reached as the incidence did not increase with age as expected (table 7). Simulations were performed to estimate the sample size required as a consequence of unequal VE estimates by age strata. A drop-out rate of 5% per year and an incidence of 5% for non-compliance to vaccine schedule were taken into account for sample size calculations leading to a total sample size of 15,980 subjects. Apportionment of approximately 20-25% of the ≥70 YOA cohort to persons ≥80 YOA aimed to ensure that this particularly vulnerable population was adequately represented. The study was however not powered to demonstrate efficacy in any of the 2 sub-strata taken separately.

The cut-off date for final HZ efficacy analysis had to occur when at least 196 confirmed HZ cases were accrued in the modified Total Vaccinated cohort (mTVC) across all age strata (primary condition). It was estimated that 196 confirmed HZ cases and a two-sided type I error rate of 5% would provide ~97% power to demonstrate an overall HZ VE of at least 40% assuming a true HZ VE of 68%.

The end of study (EOS) analyses of the ZOSTER-006 and the ZOSTER-022 studies were planned after the accumulation at least 35 PHN cases in subjects ≥ 70 YOA in the pooled ZOSTER-006 and ZOSTER-022. All PHN cases should be accrued in the mTVC.

Table 6. Assumptions for incidences under placebo, and VE used for trial simulations

Age	HZ Incidence (% / Year)	HZ VE	PHN Incidence in HZ subjects (% /Year)	On top PHN VE in HZ subjects [2]	Overall PHN VE
Overall[1]	~0.7	~68%	~11%	NA	~71%
50-59	0.5	82%	5%	5%	83%
60-69	0.8	72%	9.5%	5%	73%
70-79	1.1	58%	17%	35%	73%
≥80	1.1	36%	28%	25%	52%
≥70 [1]	1.1	~53%	~19%	NA	~71%

[1] The overall HZ incidence and the incidence in the ≥ 70YOA age strata depends on the age-stratification considered
[2] VE against PHN in people with HZ, i.e., a comparison of VE between placebo recipients with HZ who got PHN versus vaccine recipients with HZ who got PHN.

The cut-off date for end of study analysis had to occur when at least 35 PHN cases in subjects ≥70 YOA were accrued in the mTVC when pooling the studies ZOSTER-006 and ZOSTER-022 (primary condition). This number of PHN cases would provide ~90% power to demonstrate PHN VE with Lower Limit (LL) above 0%.

With the confirmatory HZ VE analysis step, it was shown that HZ/su had a VE much higher than expected in preventing HZ. Moreover, HZ VE estimates were similar in the three main age strata. Given that subjects ≥70 YOA were randomized at the same sites and time in all countries to enrol into ZOSTER-006 and ZOSTER-022, it was reasonable to assume that HZ VE would be similar for the individuals enrolled in the ZOSTER-022 study. The Applicant thus re-estimated the statistical power of the ZOSTER-022 and of the pooled analysis. From these re-evaluations, it was concluded that the originally specified targeted numbers of HZ and PHN cases were higher than required to achieve an appropriate level of statistical power for the key HZ and PHN endpoints. Considering the statistical

power reached for the key endpoints and in order not to delay the time until subjects in the Placebo group could have been offered vaccination with HZ/su under a cross-vaccination protocol, on 16 April 2015 the Applicant decided to terminate ZOSTER-006 and ZOSTER-022 earlier than initially planned. The IDMC and consulted regulatory authorities had no objections against this plan.

Immunogenicity subset

The number of subjects to be included in each of the immunogenicity subsets was estimated at:

- 2538 subjects in the Immunogenicity subset (humoral immune response)
- 468 subjects in the CMI subset

The number of placebo subjects and vaccine subjects with blood sampled had to be equal in order to maintain the blind. However, only a fraction of the placebo samples were analysed as a reduced sample is sufficient to characterise the background gE or VZV-specific immunogenicity levels in the placebo group.

Randomisation

Studies ZOSTER-006 and ZOSTER-022 were conducted in parallel in the same centres. Prior to randomized treatment assignment, subjects ≥70 years of age were randomized to the two studies. Subjects between ≥50 and <70 were enrolled to study ZOSTER-006 only.

For each of the two studies, subjects were randomized in a 1:1 ratio to receive HZ/su or placebo. The randomization system used stratification (for region and age cohort within region) and minimization algorithms (for country within region and site within country) to determine the treatment to be used for the subject. Enrolment was stratified for age groups (8:5:3:1 for 50-59:60-69:70-79:≥80 in study ZOSTER-006; 3:1 for 70-79:≥80 in study ZOSTER-022). As soon as the target number of subjects in a specific stratification group had been reached, the recruitment was frozen for that age stratum. Additionally, random subsets of subjects were selected to be part of the 7-day diary card subset and immunogenicity subset (see below). A central randomization system on the internet was used to assign subjects.

Subset allocation

Subjects were randomly allocated to be part of the Immunogenicity subset. CMI analysis were performed in the randomly selected Immunogenicity subset of three countries (Czech Republic, Japan and United States) at designated sites that have access to a Peripheral Blood Mononuclear Cells (PBMC) processing facility within the acceptable time window from sample collection to PBMC processing. These countries had a target of approximately 156 subjects per country enrolled in the immunogenicity subset. Other countries had a target of approximately 138 subjects per country to be enrolled in the immunogenicity subset.

The randomisation methods used for treatment allocation are deemed appropriate. Stratification and minimization techniques were used to ensure balance between groups with respect to site and country.

Blinding (masking)

This trial was carried out in an observer-blinded way. No reconstitution is required for the NaCl solution (placebo), and the reconstituted gE/AS01$_B$ study vaccine differs in appearance from the NaCl solution placebo. To conduct the study in an observer-blind manner, the gE/AS01$_B$ vaccine and NaCl solution placebo doses had to be prepared and administered by study staff not involved in the clinical evaluation of the subjects. In this way, neither the subject nor the investigator (or other study personnel) responsible for the evaluation of any study endpoint would know which treatment was administered.

Immunological data, which could lead to the unblinding of the treatment groups, was not made available during the course of the trial to any investigator or any person involved in the clinical conduct of the study. The laboratory in charge of the laboratory testing was blinded to the treatment.

It was planned to maintain the whole team (Central, Local, Investigators) and subjects blinded up to end of study. Overall the blinding was considered appropriate.

Statistical methods

Analysis cohorts

Several analysis sets were used and were defined as follows:

In both studies there were 5 pre-specified analysis sets:

- the Total Vaccinated Cohort (TVC; all vaccinated subjects with at least one dose, excluding subjects from excluded sites); the TVC was used for sensitivity analyses;
- the modified Total Vaccinated Cohort (mTVC; TVC excluding patients having not received second dose or who developed a confirmed HZ case prior to 1 month after second dose or who wrongly received the vaccination); the mTVC was the primary population for efficacy analysis;
- and three According To Protocol cohorts (ATPc) for analysis of efficacy (supportive), safety and immunogenicity.

Of note, the TVC was analysed according to the vaccine actually administered and included only subjects for whom the efficacy endpoint was available.

All analyses were presented overall and by age stratum. In ZOSTER-006, the main age strata for reporting purposes were 50-59, 60-69 and ≥70 YOA. In addition, results were presented separately for 70-79 and ≥ 80 YOA subjects. Another set of analyses in subjects ≥ 60 YOA was also presented. In ZOSTER-022, the main age strata were 70-79 and ≥ 80 YOA.

In both studies, the number of subjects at risk, person-time, number of confirmed events (HZ), and incidence of confirmed HZ cases were tabulated overall and by age stratum separately for each treatment group. The results were presented over the whole study and by visit interval. Similar tables described the median time-to-event and hazard rate. Survival curves for each vaccine group were calculated non-parametrically, tabulated and presented graphically overall and by age stratum using the Kaplan-Meier method.

The two studies ZOSTER-006 and ZOSTER-022 were run in parallel. For each study, the primary hypothesis (see below) was tested separately on a 5% two-sided significance level. If both were successful, the studies were to be pooled. All further analyses in the gate-keeping strategy were based on pooled data only. Secondary endpoints for the single studies were thus supportive only and not part of the multiplicity control. Hochberg's step-up procedure was to be used to control the type I error within specified test families. This was only applicable for tests that were not part of the primary test sequence, i.e., the sequence of hypothesis to be tested in a confirmatory fashion, and hence this is of no further consequence.

The pre-planned null-hypotheses to be tested were

1. H_0: HZ VE ≤ 25% for all patients in mTVC (primary endpoint ZOSTER-006)
2. H_0: HZ VE ≤ 10% for all patients in mTVC (primary endpoint ZOSTER-022)

If 1 and 2 were rejected the following (null-) hypotheses were to be tested in the pooled data set (i.e., ZOSTER-006 and ZOSTER-022):

3. H_0: PHN VE ≤ 0% for all patients ≥ 70 years of age
4. H_0: PHN VE ≤ 0% for all patients
5. H_0: PHN VE ≤ 0% for all patients with confirmed HZ
6. H_0: $HR_{\text{time to ceassation of worst pain}} \geq 1$ for all patients ≥ 70 years of age

Sensitivity analysis in various age subgroups were conducted for most hypotheses and a re-estimate of HZ VE in subjects ≥ 70 years of age was conducted for the pooled data.

In both studies, two interim analyses for futility were pre-planned. The Applicant did not expect stopping for efficacy but reserved a small $\alpha = 0.0001$ for each interim analysis, which left a significance level of 0.0498 for the final analysis (similar to using a significance level of 5% 2-sided). Futility rules were to be described in the reporting and analysis plan (RAP). Missing data were not imputed for any analysis. Reasons for and timings of missing data were to be reviewed and discussed. Patterns for missing data were to be assessed.

The primary endpoint **(HZ vaccine efficacy)** was analysed using a Poisson model to compute the relative risk (RR) of HZ cases for vaccinated compared to unvaccinated subjects. The model was adjusted for the person-time in each vaccine group and stratified for age (only for overall VE) and regions. In ZOSTER-006 vaccine efficacy was analysed using the three main age strata as stratification levels. VE was then defined as 1 – RR. P-values were presented for a test against zero (i.e., no vaccine efficacy), while exact 95% confidence intervals were used to assess clinically meaningful superiority over placebo by comparison of the lower limit of the confidence interval to the pre-specified VE (25% in ZOSTER-006 and 10% in ZOSTER-022). As sensitivity analysis, a stratified Cox model was calculated to estimate vaccine efficacy.

Overall PHN vaccine efficacy was analysed analogously to HZ vaccine efficacy. The incidence of **PHN in subjects with an HZ episode**, overall and by sub-categories was compared with placebo using an asymptotic standardized unconditional binomial test. The analysis was stratified by age group and weights associated to each stratum were to be pre-specified (according to the study protocol). In the CSR, it is stated that weights associated to each stratum were the proportion of subjects by age stratum. Stratified analysis was not possible in case no events occurred in one age stratum. **Time-to-cessation of severe 'worst' pain** was analysed using a Cox model. It was based on patients with confirmed HZ only and (according to the protocol) included any subject reporting ZBPI pain scores of 3 or more at any time during the study. According to the CSR, patients without pain score above 3 were included as censored at time t = 1. Patients with severe "worst" pain (i.e., pain score >3) were considered as events with time to event being the inverse of duration of pain (1/t). This allows the computation of vaccine efficacy for the reduction of time to worst pain based on the derived hazard ratio.

Subgroup analyses by age group, by region and by time for all hypotheses were provided to assess consistency.

Due to GCP violations one Mexican study site was excluded from all analyses.

Planned analysis steps

It was predicted that study ZOSTER-006 would reach the conditions required for triggering final efficacy analysis of HZ primary endpoint about one year before those conditions being reached for study ZOSTER-022. The analyses of these studies were thus dissociated. The ZOSTER-006 study continued after the final HZ efficacy analysis until an adequate number of HZ cases accrued in ZOSTER-022 and an adequate number of PHN cases accrued in both ZOSTER-006 and ZOSTER-022. Both studies ended concurrently.

In study ZOSTER-006, the planned analysis steps were the following:

Step 1: Final HZ efficacy analysis (i.e. Final analysis of HZ primary endpoint)

The HZ incidence rate was determined with reference to the first confirmed HZ case observed in the patient, should several HZ cases occur in the same subject. The HZ-free period for a subject was calculated from HZ onset to time zero relative to the cohort considered:

- first vaccination for TVC and
- beyond the HZ-case exclusion period following the second injection for mTVC and ATP.

The number of Person-Years at risk over an interval of time is the sum of the confirmed HZ-free episodes over all subjects at risk during that interval, either up to the cut-off date for the analysis, the censoring date or the occurrence of the first HZ case for a subject.

Step 2: End of study analysis

The end of study analysis could not be performed before the final HZ efficacy analysis (step 1). At this step, all objectives of study were analysed. Objectives already analysed at step 1 were re-analysed. In addition, overall PHN VE in subjects ≥70 YOA, and other pre-specified endpoints were analysed in the pooled analyses of studies ZOSTER-006 and ZOSTER-022.

Different LL values of the 95% CI have been prospectively chosen for deciding whether or not a test was significant. In ZOSTER-006 the efficacy of HZ/su against overall HZ was demonstrated if the LL of the 95% CI of VE was above 25%. The efficacy in the age strata 50-59, 60-69 was demonstrated if the LL of the 95% CI of VE was above 10%. It is considered adequate that this LL value has been set at a lower level than the value chosen for the overall analysis.

The aim of ZOSTER-006 was to show an overall VE significantly larger than 25% (i.e. 95% CI >25%) but the study was powered to show a VE ≥ 40%. With an anticipated vaccine efficacy under the null hypothesis of 0.25, the power was above 99.9%.

Rationale for using mTVC for primary analysis

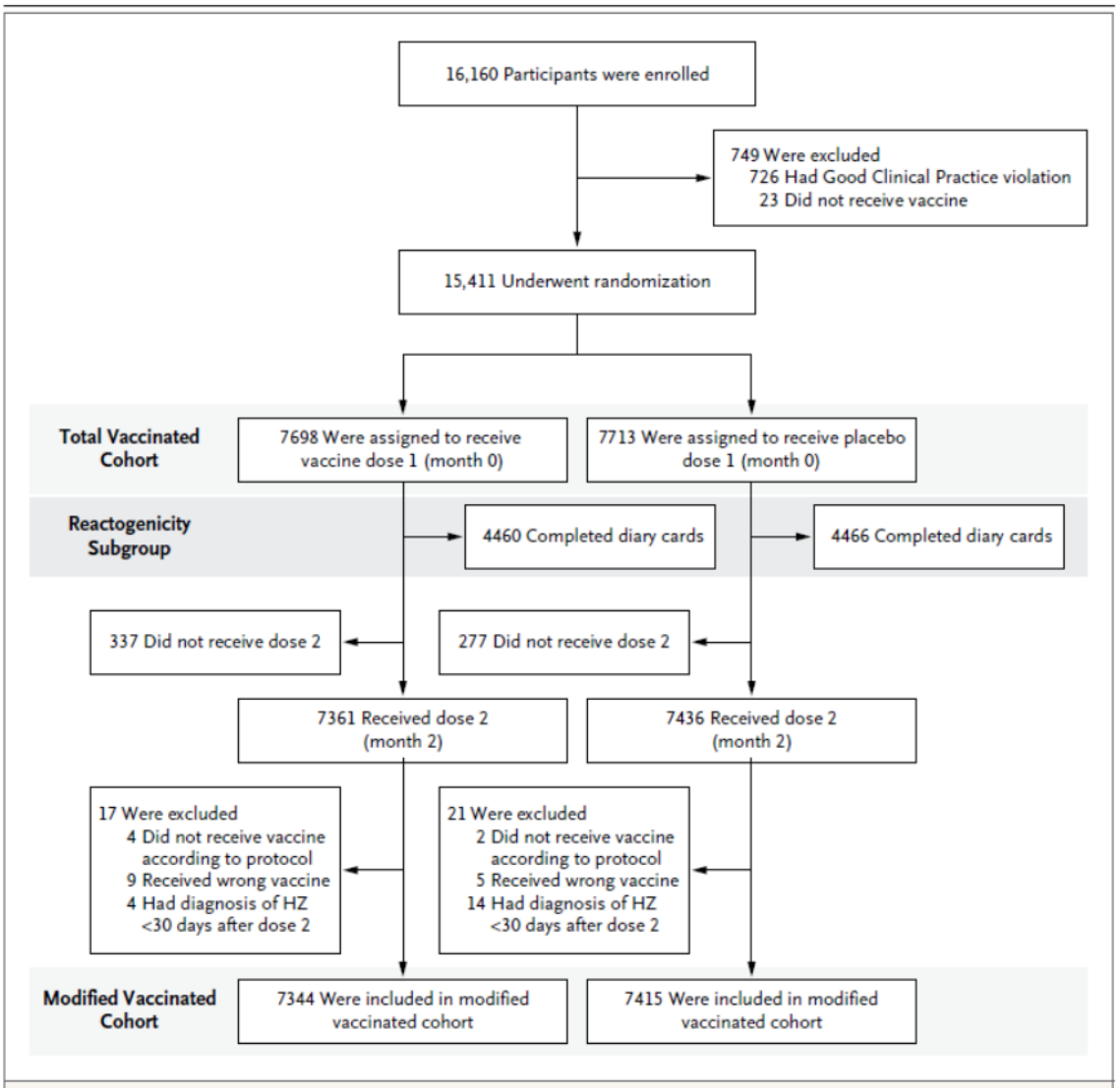
The mTVC was the primary population for efficacy analysis, which excludes subjects in the TVC for efficacy analysis who were not administered with the second vaccination or who develop a confirmed case of HZ prior to 1 month after the second vaccination.

Although the TVC (Intent-to-treat [ITT] population) analysis of efficacy is the one recommended according to ICH, the true assessment of the VE, according to the recommended schedule, can only be performed based on the mTVC, where subjects not completing the vaccination schedule due to an HZ episode or withdrawal will be excluded, as was done in an earlier HZ vaccine efficacy study [Oxman, 2005]. The analysis on the TVC is planned for sensitivity analyses and is expected to provide consistent results with the primary analyses. A delay of 1 month was selected prior to which any subject with confirmed HZ would be excluded from mTVC.

For those reasons, the Applicant believed that the VE estimate for registration purposes should be based on mTVC, provided there is no essential VE difference between the mTVC and TVC analyses. The proposal was to compare VE analyses on mTVC and TVC, and review the frequency for exclusion from mTVC. If the results were consistent between both cohorts then the VE estimate based on mTVC would be considered for registration purposes. The study methodology is acceptable.

Results

Participant flow



Of note, the flow is referring to the numbers of the Total Vaccinated Cohort as being the number of randomized subjects. In fact 16,145 were actually randomised, among whom 15,411 participants received at least one vaccination and constituted the TVC.

The notable deviations from protocol and GCP included:

- Mexico – one study site was found significant and systemic deviation from GCP guidelines, 2 other centers incorrectly applied the informed consent process, involving 671 and 9 subjects, respectively.
- US - one site was closed after the cut-off date (01 July 2014) decided for final HZ efficacy analysis. Thus data from 46 subjects were not endorsed by the principle investigator.

Up to final HZ efficacy analysis 1,431 subjects were withdrawn: 749 in vaccine group and 682 subjects in placebo group. The most common reason was consent withdrawal (not due to an adverse event) and SAE, with equal distributions between vaccinated and placebo groups.

In addition to the subjects excluded from the mTVC, 509 (6.6% of the TVC) and 549 subjects (7.1% of the TVC) were excluded from the ATP cohort for efficacy, respectively from the HZ/su and the Placebo group. The main reasons for exclusion from the ATP were, by order of frequency: administration of any medication forbidden by the protocol, randomisation code broken at the investigator site (for most of the subjects the unblinding was due to non-compliance with the observer-blind, non-compliance with vaccination schedule), administration of vaccine(s) forbidden in the protocol, vaccine temperature deviation, protocol violation linked to the inclusion/exclusion criteria including age.

Recruitment

The study was carried out by 268 Principal Investigators in 18 countries (Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, Mexico, Republic of Korea [South Korea], Spain, Sweden, Taiwan, United Kingdom and United States).

Overall, recruitment targets by region were reached although slightly lower recruitment than expected was observed in Latin America and Australasia.

Concerning the numbers of subjects by region for the mTVC at the EOS analysis step, the proportion of subjects from Latin America is much lower than expected, reflecting lower recruitment rate and the exclusion of subjects with protocol violation. Most study participants (approximately 50%) were enrolled in Europe, as planned by the Applicant in the study protocol.

Conduct of the study

The first subject was enrolled on 02 August 2010 and the study was completed on 27 July 2015 (last study visit/contact of the last subject). The cut-off dates (data lock) for the final HZ efficacy analysis and for the end of study (EOS) efficacy analysis were respectively 01 July 2014 and 21 April 2015.

Final HZ VE analysis was performed on blinded HZ data in adults ≥50 YOA when the prespecified number of HZ cases was reached. All suspected HZ episodes with onset before 1 July 2014, i.e. the data lock point for final HZ efficacy analysis, were included.

Overall, 74 and 335 subjects had at least one suspected episode of HZ respectively in the HZ/su and in the Placebo groups (mTVC - EOS). There were 84 and 340 episodes occurring in the subjects in the respective groups. Of the suspected episodes, 76% in the HZ/su group and 77% in the Placebo group had adequate samples and could be properly ascertained based on PCR. The rest of the subjects had inadequate samples (13% and 12%) or had no sample taken (11% and 11%).

The HZAC was not able to decide for large proportion of the episodes with no (adequate) sample (i.e. respectively, 10/20 and 22/79 in the HZ/su and the Placebo groups). Overall, this led to 88% and 94% of the suspected HZ events that could be ascertained (HZ confirmed or ruled out) either by PCR or by HZAC. The remaining suspected episodes could not be confirmed/ruled out. PCR and HZAC results were overall consistent for most of the episodes (amongst episodes with results available with both methods, respectively 55/60 and 207/232 had results which were in agreement in the HZ/su and the Placebo groups).

The Applicant described a major issue at a Mexican site (GCP violations) which lead to the elimination of data from all subjects at one site from all analyses. Issues at this site in addition to a few major protocol violations at other sites lead to the elimination of a substantial proportion (overall 5% of the randomised subjects eliminated from the TVC) of the randomised subjects from all analyses. Based on the available information, the Applicant's study oversight, management and decisions with regards compliance issues are deemed appropriate. The potential impact on study findings is likely to be limited given the randomisation methods and the fact that groups are balanced for exclusions.

With the exception of the issue described by the Applicant for the Mexican site (major protocol deviation), and given the information provided in the CSR, the study conduct raises no concern.

Baseline data

Overall and in mTVC, demographic characteristics were similar in 2 study groups ad within main age strata. The mean age at enrolment was 62.3 years, with a distribution of 47.3%, 29.1%, and 23.6% of participants at 50 - 59 YOA, 60 - 69 YOA, and ≥70 YOA, respectively. Most participants were female (61.2%) and white (71.8%), and were enrolled from Europe (51.6%). Results are similar for the TVC as well as in the EOS cohorts. The number of subjects in the age strata is consistent with the age stratification ratios (8:5:4). Age distribution was comparable across regions.

Women were overrepresented in the trial. Female gender has been described as a risk factor of HZ in the literature. However, study groups are well balanced with regards to baseline demographics, including within age strata, so that this is not expected to affect the validity of study findings.

Study groups were also well balanced with respect to pre-existing immunity to VZV. Nearly all subjects (99%) in the HZ/su and Placebo groups were seropositive for anti-gE antibodies pre-vaccination. Pre-vaccination GMCs of anti-gE Ab were comparable between groups. Pre-vaccination GMCs of anti-gE Ab were 1247.1 (95% CI: 1174.8 - 1323.8) mIU/mL, and 1311.9 (95% CI: 1234.8– 1393.9) mIU/mL, for the HZ/su group and Placebo group, respectively. Groups were well balanced at baseline with respect to CMI read-outs.

Groups are balanced for main comorbidities at baseline (medical history) such as diabetes.

Numbers analysed

For the Final analysis of HZ vaccine efficacy, from the 16,160 subjects enrolled, 8068 were randomized to the HZ/su group and 8077 to the Placebo group (15 subjects were not assigned to any group). From the 16,145 randomised subjects, 9 subjects were not vaccinated. Therefore, the number of subjects actually vaccinated is 16,136 (8061 in the HZ/su group and 8075 in the Placebo group).

From the 16,136 subjects actually vaccinated, 363 subjects from the HZ/su group and 362 subjects from the Placebo group were excluded from all statistical analyses. As such, the Total Vaccinated Cohort used for the Final analysis corresponds to 15,411 subjects (7698 in the HZ/su group and 7713 in the Placebo group). Of these 14,759 (95.8%) were included in the modified TVC (mTVC).

Table 7. Cohort of analysis for final HZ efficacy analysis step

	HZ/su Group	Placebo group
Total (randomised) cohort[1]	8068	8077
Total effective cohort (TEC)	7705	7715
Total Vaccinated Cohort (TVC)	7698	7713
Modified Total Vaccinated Cohort (mTVC)	7344	7415
Subjects excluded from TVC		
Subjects excluded from all analyses[2] (i.e. excluded from TEC)	363	362
Study vaccine dose not administered (i.e. excluded from TVC)	7	2
Subjects excluded from mTVC		
Subjects who did not receive two doses	337	277
Subjects having an episode of HZ prior than 30 days after dose 2	4	14
Study vaccine dose not administered according to protocol[3]	4	2
Wrong study vaccine administered[4]	9	5

[1]15 subjects were not assigned to any group.

[2]Major deviations from GCP compliance.

[3]Wrong or unknown site or route of administration (vaccine administered subcutaneously, into the thigh or buttock).

[4]Dose 2 administered was different from dose 1, and for one subject only the adjuvant component ($AS01_B$) was administered at dose 1.

The corresponding numbers for the End of Study (EOS) analysis are presented below:

Table 8. Cohort of analysis EOS

	HZ/su Group	Placebo group
Total (randomised) cohort[1]	8068	8078
Total effective cohort (TEC)[2]	7702	7713
Total Vaccinated Cohort (TVC)	7695	7710
Modified Total Vaccinated Cohort (mTVC)	7340	7413
According To Protocol (ATP) cohort for efficacy	6831	6864

Outcomes and estimation

Efficacy data is presented in the sections below by endpoint, i.e. 1) against HZ, PHN, 2) severe 'worst' pain, 3) confirmed HZ episode-related mortality and hospitalizations and HZ-related complications

(other than PHN), 4) use of pain medication, 5) PHN incidence in subjects with a confirmed HZ episode, 6) analysis of quality of life using the ZBPI questionnaire, 7) immunogenicity results.

1. Efficacy against HZ

The primary analysis of HZ VE occurred at step 1 (final HZ efficacy analysis step). Results regarding HZ VE by age stratum and overall (using the Poisson method) are presented for the mTVC. A descriptive analysis (re-estimation) of HZ VE was performed at EOS analysis. A supportive analysis was also performed on the TVC and the ATP cohort for efficacy.

All suspected HZ episodes with onset date up to and including the cut-off dates for step 1 and step 2 analysis were considered for the respective analysis.

Final HZ efficacy analysis overall and by age stratum (step 1)

Only very few confirmed HZ episodes occurred in the vaccinated subjects (6 in the HZ/su group in comparison with 210 in the Placebo group) (Table 10 below). No subject reported more than one confirmed HZ episode. Of the 216 confirmed HZ cases, the majority (89%) was PCR-confirmed and 11% were classified by the HZ Ascertainment Committee (HZAC).

The mean (SD) follow-up time was 3.1 (0.5) years. The median (min - max) follow-up time was 3.1 (0 - 3.7) years. The mean follow up time did not substantially differ between groups.

Overall VE against HZ was 97.16% (95%CI: 93.72%-98.97%) in subjects ≥50 YOA. The primary objective of study ZOSTER-006 regarding HZ VE in subjects ≥50 YOA was met as the lower limit of the 95% CI of the VE against HZ was largely above 25%. VE did not vary substantially with age.

Table 9. First or only episode of HZ during the entire study period by age strata and overall using Poisson method (mTVC - Final HZ efficacy analysis)

									VE			
	HZ/su				Placebo					95% CI		
Age strata	N	n	T(year)	n/T (per 1000)	N	N	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
50-59 YOA *	3492	3	11161.3	0.3	3525	87	11134.7	7.8	96.57	89.62	99.31	<0.0001
60-69 YOA *	2141	2	7007.9	0.3	2166	75	6952.7	10.8	97.36	90.14	99.69	<0.0001
≥ 70 YOA *	1711	1	5127.9	0.2	1724	48	5083.0	9.	97.93	87.91	99.95	<0.0001
≥ 60 YOA *	3852	3	12135.7	0.2	3890	123	12035.7	10.2	97.58	92.77	99.51	<0.0001
OVERALL **	7344	6	23297.0	0.3	7415	210	23170.5	9.1	97.16	93.72	98.97	<0.0001

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
50-59 YOA = 50-59 years old subjects
60-69 YOA = 60-69 years old subjects
≥ 70 YOA = ≥ 70 years old subjects
≥ 60 YOA = ≥ 60 years old subjects
N = number of subjects included in each group
n = number of subjects having at least one HZ confirmed case
T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) 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)
* : VE adjusted by region
** : VE adjusted by age strata and region
P-value=Two sided Exact P-value conditional to number of cases

End of study analysis overall and by age stratum (step 2)

Compared to the final HZ efficacy analysis step, HZ episodes were reported for 47 additional subjects. In total over the study, 9 occurred in the HZ/su group and 254 in the Placebo group. No subject had more than one confirmed HZ episode during the study period. The mean (SD) follow-up time was 3.9 (0.7) years. The median (min - max) follow-up time was 4.1 (0 - 4.5) years. Table 11 shows that findings are similar in the EOS analysis, with an overall VE against HZ of 96.50% (95%CI: 93.25%-98.46%) in subjects ≥50 YOA.

Table 10. First or only episode of HZ during the entire study period by age strata and overall using Poisson method (mTVC - EOS analysis)

									VE			
	HZ/su				Placebo					95% CI		
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
50-59YOA *	3491	4	13780.0	0.3	3523	103	13714.0	7.5	96.15	89.83	98.97	<0.0001
60-69YOA *	2140	3	8617.4	0.3	2166	90	8498.5	10.6	96.72	90.12	99.34	<0.0001
≥70YOA *	1709	2	6320.4	0.3	1724	61	6246.8	9.8	96.76	87.77	99.62	<0.0001
≥60YOA *	3849	5	14937.8	0.3	3890	151	14745.4	10.2	96.73	92.21	98.95	<0.0001
OVERALL **	7340	9	28717.8	0.3	7413	254	28459.4	8.9	96.50	93.25	98.46	<0.0001

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
50-59YOA = 50-59 years old subjects
60-69YOA = 60-69 years old subjects
≥70YOA = ≥70 years old subjects
≥60YOA = ≥60 years old subjects
N = 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) 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)
* : VE adjusted by region
** : VE adjusted by age strata and region
P-value=Two sided Exact P-value conditional to number of cases

HZ incidence rates

Overall, incidence rate of HZ was 9.1 per 1000 person-years in the placebo group and 0.3 person-years in the HZ/su group in the final HZ efficacy analysis (see table below together with the efficacy data against HZ). Similar results were obtained in the EOS analysis (0.3 vs. 8.9 per 1000 person-years overall). In the placebo group incidence rates of HZ tended to increase very slightly with age. In particular, the incidence rate tended to be slightly higher in subjects ≥60 YOA in comparison with those 50-59 YOA (10.2 vs. 7.8 per 1000 person-years).

Age (years)	HZ/su			Placebo			Vaccine efficacy (%) [95% CI]
	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 person years	Number of evaluable subjects	Number of HZ cases	Incidence rate per 1000 person years	
ZOSTER-006 (ZOE-50*)							
≥ 50	7,344	6	0.3	7,415	210	9.1	97.2 [93.7; 99.0]
50-59	3,492	3	0.3	3,525	87	7.8	96.6 [89.6; 99.4]
≥ 60	3,852	3	0.2	3,890	123	10.2	97.6 [92.7; 99.6]
60-69	2,141	2	0.3	2,166	75	10.8	97.4 [90.1; 99.7]

*Over a median follow-up period of 3.1 years

In the placebo group, there were trends for slightly higher incidence in females as compared to males (9.6 vs. 7.9 per 1000 person-years), and for variation across regions (from 7.1 in Europe to 12.3 in Australasia, 10.4 in Latin America and 9.6 in North America). However these variations are very small and no statistical tests were performed on the differences.

Sensitivity analyses

No substantial differences by gender or by region were observed for vaccine efficacy (VE) against HZ using the Poisson method.

HZ VE (first or only episode of HZ) during the entire study period by age stratum and overall determined using the Cox Regression method was similar to HZ VE determined in the primary analysis using the Poisson method.

HZ VE by time

VE by year following vaccine administration is presented in table 12. VE is maintained at high levels over 4 years. This is confirmed by cumulative VE estimations. The overall HZ VE was 98.38% (95% CI: 90.64% - 99.96%) up to Year 1, 96.16% (95% CI: 90.81% - 98.77%) up to Year 2, 97.49% (95% CI: 94.05% - 99.17%) up to Year 3, and 96.50% (95% CI: 93.25% - 98.46%) up to Year 4. Analyses show consistent findings across age strata.

Table 11. First or only episode of HZ during the entire study period by time using Poisson method (mTVC – EOS analysis).

									VE			
	HZ/su				Placebo					95% CI		
Time	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Year 1 *	7340	1	7279.8	0.1	7413	62	7312.1	8.5	98.38	90.64	99.96	<0.0001
Year 2 *	7190	4	7134.6	0.6	7192	68	7092.1	9.6	94.16	84.36	98.45	<0.0001
Year 3 *	7048	0	6972.6	0.0	6998	68	6891.0	9.9	100.00	94.52	100.00	<0.0001
Year 4 *	6859	4	7330.8	0.5	6741	56	7164.2	7.8	93.07	81.26	98.18	<0.0001

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
N = 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) 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)
* : VE adjusted by age strata and region

P-value=Two sided Exact P-value conditional to number of cases
Year 1 : From 30 days after second vaccination to 395 days after second vaccination
Year 2 : From >395 days after second vaccination to 760 days after second vaccination
Year 3 : From >760 days after second vaccination to 1125 days after second vaccination
Year 4 : From >1125 days after second vaccination until last contact date

VE in the TVC and ATP cohorts

Results in the TVC and ATP cohorts are consistent with the results in the mTVC. Overall VE are presented in Table 13 for the different cohorts.

Table 12. Overall vaccine efficacy: First or only episode of HZ during the entire study period according to cohort of analysis

	Final HZ efficacy analysis		EOS	
	VE	**95%CI**	**VE**	**95%CI**
mTVC	97.16%	(93.72%-98.97%)	96.50%	(93.25%-98.46%)
TVC	*	*	95.78%	(92.52%-97.85%)
ATP cohort for efficacy	*	*	96.60%	(93.18%-98.55%)

VE after one dose only

Overall HZ VE after one dose only was analysed in subjects above 50 years of age who developed HZ between dose 1 and dose 2. The overall HZ VE was 90.79% (95% CI: 62.07% - 98.96%) with a mean follow up of ~76 days. This finding is based on only 2 events in the HZ/su group and 20 events in the Placebo group. As stated by the Applicant, these results thus need to be interpreted with caution.

2. Efficacy against PHN

PHN efficacy analysis (EOS) overall and by age stratum

Cumulatively 18 cases of PHN were reported in the Placebo group, vs. none in the vaccinated group. Overall VE against PHN was 100.00% (95% CI: 77.11-100.00). Although the study was not powered for this, PHN VE was demonstrated, as the overall PHN VE was 100% with LL > 0 and p-value <0.0001.

VE did not appear to vary across age categories, but confidence intervals are very large within age strata. In the Placebo group, 8 cases occurred in the 50-59 YOA stratum and 10 cases in the ≥60 YOA group, of which 2 cases were in the 60-69 YOA stratum. Note that ZOSTER-006 was not powered for analysis of PHN VE by age strata, but as a result of the 100% VE against PHN reached in each age stratum, the LL of the 95% CI was also above 0% in the 50-59 YOA and ≥60 YOA strata. However, due to the low number of cases in the Placebo group in the 60-69 YOA stratum, PHN VE was not significant in this age stratum (LL of the 95% CI <0%). Efficacy against PHN by age category should be examined in the pooled analysis. The main analysis of PHN VE (primary objective in subjects ≥70 YOA) was performed on pooled data from ZOSTER-006 and ZOSTER-022 studies.

The incidence rate of subjects reporting at least one PHN episode per 1000 person-years was 0.0 in the HZ/su group and 0.6 in the Placebo group. PHN incidence increased with age (about twofold increased risk for individuals ≥70 YOA as compared to individuals <70 YOA).

Table 13. First or only episode of PHN during the entire study period by age strata and overall (≥50YOA) using Poisson method (mTVC - EOS analysis)

									VE			
	HZ/su				Placebo					95% CI		
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
50-59 YOA *	3491	0	13789.7	0.0	3523	8	13928.7	0.6	100.00	40.88	100.00	0.0081
60-69 YOA *	2140	0	8621.4	0.0	2166	2	8674.4	0.2	100.00	-442.83	100.00	0.5097
≥ 70YOA *	1709	0	6323.4	0.0	1724	8	6340.6	1.3	100.00	41.40	100.00	0.0078
≥ 60YOA *	3849	0	14944.8	0.0	3890	10	15015.0	0.7	100.00	55.25	100.00	0.0020
OVERALL **	7340	0	28734.6	0.0	7413	18	28943.7	0.6	100.00	77.11	100.00	<0.0001

HZ/su = Herpes Zoster subunit vaccine; Placebo = Placebo
50-59YOA = 50-59 years old subjects; 60-69YOA = 60-69 years old subjects;
≥60YOA = ≥60 years old subjects; ≥70YOA = ≥70 years old subjects
N = number of subjects included in each group; n = number of subjects having at least one PHN
T (year) = sum of follow-up period (censored at the first occurrence of PHN) 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)
*: VE adjusted by region
**: VE adjusted by age strata and region
P-value=Two sided Exact P-value conditional to number of cases

VE against PHN were not substantially different in the TVC cohort (100% CI: 80.72%-100.00%) and ATP cohort for efficacy (100% CI: 75.82%-100.00%).

3. Duration of severe 'worst' HZ-associated pain over the entire pain period

Findings with respect to the duration of severe 'worst' HZ associated pain over the entire pain reporting period (mTVC - EOS analysis) are described below.

The number of subjects who had at least one day of severe 'worst' HZ-associated pain was:

- In the HZ/su group, 7 of the 9 subjects with confirmed HZ episode.
- In the Placebo group, 221 of the 254 subjects with confirmed HZ episode.

Overall, the median (min - max) duration of severe 'worst' HZ-associated pain was:

- 11 days (3 - 78) days in the HZ/su group.
- 15 days (1 - 464) days in the Placebo group.

The overall VE in terms of reduction of duration of 'worst' HZ-associated pain was 26.87% (95% CI: -59.56% - 66.48%; p-value = 0.4318). Results were consistent in the TVC cohort. Although not statistically significant due to a low number of cases, these results show a trend in favour of the vaccine group.

4. Confirmed HZ episode-related mortality and hospitalizations, HZ-related complications (other than PHN)

Overall and in all age strata, no HZ-related mortality and no HZ-related hospitalization was reported (mTVC and TVC).

The number of subjects who reported HZ related complications (other than PHN) during the entire study period were as follows:

In the mTVC – EOS analysis:

- In the HZ/su group, 0 of the 9 subjects with confirmed HZ episode.
- In the Placebo group, 6 (2%) of the 254 subjects with confirmed HZ episode.

In the TVC – EOS analysis:

- In the HZ/su group, 0 of the 12 subjects with confirmed HZ episode.
- In the Placebo group, 8 (3%) of the 280 subjects with confirmed HZ episode.

The complications described in the Placebo group are as follows:

- HZ vasculitis (n=1)
- Ophthalmic disease (n=1)

- Neurologic disease (n=1)
- Disseminated disease (n=5)

Events fully recovered except one, the case of neurologic disease, which left sequelae. No conclusion can be drawn due to a low number of cases.

5. Use of pain medications

Overall, the use of HZ-associated pain medications was reported for 6 subjects in the HZ/su group out of 9 subjects with a confirmed HZ episode (67%), with a total of 13 occurrence of use. In the Placebo group, the use of HZ associated pain medication was reported for 190 subjects out of 254 subjects with a confirmed HZ episode (75%), with a total of 529 occurrence of use.

Overall, the median duration (min - max) of HZ-associated pain medication was 21.0 (8.0-63.0) days in the HZ/su group, and 22.0 (1.0-1266.0) days in the Placebo group. The median time to resolution of clinically-significant pain was 14.0 days in vaccine group and 17.0 days in placebo.

Results were consistent in the TVC. Although not statistically significant due to a low number of cases, these results show a trend in favour of the vaccine group.

6. PHN incidence in subjects with a confirmed HZ episode

Due to the high VE against HZ, resulting in a low number of HZ confirmed cases in the HZ/su group, it was not possible to conclude on VE in terms of reduction of PHN risk in subjects with confirmed HZ (p-value = 1.0). Overall, no PHN episode was reported in any of the subjects with a confirmed HZ episode in the HZ/su group (9 in the mTVC and 12 in the TVC cohorts). The overall risk of PHN in case of HZ episode was 7.1% in the Placebo group (18/254 in the mTVC). Results were similar in the TVC: 7.5% (21/280).

7. Analysis of quality of life using the ZBPI questionnaire

ZBPI score (mTVC HZ confirmed cases - HZ ZBPI evaluable subgroup)

For different parameters evaluated based on the ZBPI questionnaire, a trend towards higher QoL in the vaccine group compared to the Placebo group was observed in subjects with a confirmed HZ episode. Analyses were carried out in the mTVC HZ ZBPI evaluable subgroup who had a first ZBPI evaluation visit within 14 days of the first date of rash.

The mean (SD) 'ZBPI worst pain score' was: 5.5 (2.73) in the HZ/su vaccine group, and 6.7 (2.94) in the Placebo Group, with a p-value = 0.1133.

The mean (SD) 'ZBPI average pain score' observed over time was: 3.9 (1.89) in the HZ/su group, and 5.5 (2.74) in the Placebo group, with a p-value = 0.0486 (i.e. statistically significant difference), with lower scores in the HZ/su group.

The mean (SD) 'Activities of Daily Living' score was: 3.3 (2.98) in the HZ/su vaccine group, and 4.3 (3.13) in the Placebo Group, with a p-value = 0.3817.

Area under the curve analysis

The analysis of the AUC for worst pain score, AUC for average pain score, and AUC for ADL score showed no statistically significant difference between the HZ/su group and the Placebo group. However, all mean scores at all time points (30, 90 and 182 days) were lower in the HZ/su group than in the Placebo group.

BOI scores

The burden-of-illness (BOI) score incorporates the incidence of HZ with the severity and duration of acute and chronic HZ-related pain over a 6 month period following rash onset.

Overall, the mean (SD) AUC severity-of-illness score and mean AUC severity-of-interference score evaluated by ZBPI in the mTVC were significantly lower in the HZ/su group compared to the Placebo group overall and in all age strata, according to the Chop-lump test (p-value < 0.0001).

Over a 26-week period from zoster rash onset, the overall VE estimate against burden-of-illness score (BOI) caused by HZ was 98.4% (95% CI: 92.2%-100.0%) with consistent point estimates in all age strata.

The overall VE estimated against burden-of-interference measured on ADL score in the mTVC was 99.1% (95% CI: 86.2% - 100.0%) with consistent point estimates in all age strata.

Interference of HZ with QoL (EQ-5D and SF-36)

Over time, the mean (SD) 'SF-36 role physical' (RP) worst score (p-value = 0.0449) and the 'SF-36 bodily pain' (BP) worst score (p-value = 0.0338) were significantly different between the HZ/su group [RP = 69.44 (19.63), BP = 55.33 (16.85)] compared with the Placebo group [RP = 49.55 (31.45), BP = 39.97 (24.59)], suggesting higher (better) mean scores in the HZ/su group. No other statistically significant difference was observed between vaccine groups in the worst score for any other SF-36 scale scores. No statistically significant difference in the estimated EQ-5D utility score or EQ-5D VAS was observed between the HZ/su group and the Placebo group over time.

8. Humoral immunogenicity results

Humoral immune responses were analysed in the Immunogenicity subset (ATP cohort). Immune responses were assessed at Month 3 (one month post-dose 2) compared to Month 0 (pre-vaccination). Persistence of the immune responses was assessed at Months 14, 26 and 38 (one, two and three years post-dose 2). The anti-gE ELISA Ab results (all timepoints) are presented in the CSR. Data regarding the analysis of anti-VZV ELISA Ab have been submitted and evaluated during the procedure (see pharmacology section). Anti-VZV neutralizing Ab titres (at all timepoints) were not measured in this study, since the correlation between anti-VZV as well as anti-gE concentrations and anti-VZV neutralizing Ab titres has been explored in ZOSTER-010 showing a good correlation of anti-VZV neutralizing Ab titres with both ELISA assays (anti-gE and anti-VZV ELISA). As a consequence, anti-VZV neutralization assay has not been performed in more recent ZOSTER studies, including ZOSTER-006, as it would not provide substantial new insights into the immune response to vaccination nor would it change the conclusions of the study.

Very high levels of anti-gE Ab were reached in the HZ/su group at Month 3 (Median 53,375 mIU/mL) as compared to the baseline level (Median 1283 mIU/mL) and placebo level (Median 1292.2 mIU/mL). The majority of subjects (i.e. >98%) in the HZ/su and Placebo groups were seropositive for anti-gE antibodies pre-vaccination and all subsequent time-points (Months 0, 3, 14, 26 and 38). In the HZ/su group, post-vaccination GMCs of anti-gE Ab peaked at Month 3, than decreased one Year post-dose 2 but remained higher than the baseline level up to 3 years post dose 2 (see below table).

Table 14. Seropositivity rates and Geometric Mean Concentrations (GMCs) of anti-gE antibody at Month 0, 3, 14, 26 and 38 (Adapted ATP cohort for immunogenicity-Humoral)

				≥ 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(M0)	1069	1059	99.1	98.3	99.6	1247.1	1174.8	1323.8	<97.0	233132.9
		PII(M3)	1070	1070	100	99.7	100	52376.6	50264.1	54577.9	432.7	308834.6
		PII(M14)	1037	1037	100	99.6	100	17726.2	16910.7	18581.0	512.3	160387.0
		PII(M26)	1018	1018	100	99.6	100	13933.3	13290.4	14607.2	376.7	171049.4
		PII(M38)	967	967	100	99.6	100	11919.6	11345.6	12522.7	302.6	121520.7
	Placebo	PRE(M0)	1065	1057	99.2	98.5	99.7	1311.9	1234.8	1393.9	<97.0	230579.9
		PII(M3)	1067	1055	98.9	98.0	99.4	1213.3	1139.2	1292.3	<97.0	259629.7
		PII(M14)	1021	1013	99.2	98.5	99.7	1260.1	1183.6	1341.4	<97.0	30533.3
		PII(M26)	994	990	99.6	99.0	99.9	1336.3	1255.5	1422.4	<97.0	47396.8
		PII(M38)	946	939	99.3	98.5	99.7	1292.6	1209.5	1381.4	<97.0	74603.5

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
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(M0) = Pre-vaccination (Month 0)
PII(M3) = Post-vaccination Dose II (Month 3)
PII(M14) = Post-vaccination Dose II (Month 14)
PII(M26) = Post-vaccination Dose II (Month 26)
PII(M38) = Post-vaccination Dose II (Month 38)

The Mean Geometric Increase (MGI) of anti-gE Ab concentrations over pre-vaccination was 42.0 (95% CI: 39.3 - 44.8) at Months 3. GMCs of anti-gE Ab remained higher than at baseline up to Month 38 with MGI of 9.7 (95% CI: 9.1 - 10.4) at Month 38. In the Placebo group, GMCs remained at pre-vaccination levels at all time-points. The MGI over pre-vaccination was not higher than 1.0 at any time-point.

Anti-gE response to vaccine (Vaccine response rate [VRR]) was defined as follows: for subjects who were seropositive at baseline, a 4-fold increase in the anti-gE Ab concentration as compared to the pre-vaccination anti-gE Ab concentration; for subjects who were seronegative at baseline: a 4-fold increase in the anti-gE Ab concentration as compared to the anti-gE Ab cut-off value for seropositivity. In the HZ/su group, the VRRs for anti-gE Ab concentrations was 98.5% (95% CI: 97.6%-99.1%) and 80.9% (95% CI: 78.2%-83.3%) at Months 3 and 38, respectively.

Table 15. Vaccine response rates for anti-gE antibody ELISA concentrations at Month 3, 14, 26 and 38 (Adapted ATP cohort for immunogenicity-Humoral)

				Vaccine response			
						95% CI	
Test description	Group	Timing	N	n	%	LL	UL
VZV.gE Ab.IgG	HZ/su	PII(M3)	1069	1053	98.5	97.6	99.1
		PII(M14)	1017	910	89.5	87.4	91.3
		PII(M26)	998	832	83.4	80.9	85.6
		PII(M38)	952	770	80.9	78.2	83.3
	Placebo	PII(M3)	1065	14	1.3	0.7	2.2
		PII(M14)	1005	38	3.8	2.7	5.2
		PII(M26)	975	37	3.8	2.7	5.2
		PII(M38)	930	33	3.5	2.5	4.9

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
Vaccine response defined as :
For initially seronegative subjects, antibody concentration at post-vaccination ≥ 4 fold the cut-off for Anti-gE (4x97 mIU/ml)
For initially seropositive subjects, antibody concentration at post-vaccination ≥ 4 fold the pre-vaccination antibody concentration
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of responders
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PII(M3) = Post-vaccination Dose II (Month 3)
PII(M14) = Post-vaccination Dose II (Month 14)
PII(M26) = Post-vaccination Dose II (Month 26)
PII(M38) = Post-vaccination Dose II (Month 38)

GMCs of anti-gE antibody were similar across age categories. Based on MGIs, immunogenicity very slightly decreased with age. In the HZ/su group, the MGI over pre-vaccination was 48.4 (95% CI: 43.1 - 54.5), 42.9 (95% CI: 38.5 - 47.8) and 35.6 (95% CI: 31.6 - 40.0) at Month 3 respectively in the 50-59 YOA stratum, the 60-69 YOA stratum, and the ≥70 YOA stratum. Reverse cumulative curves indicate that anti-gE responses were very similar across age strata.

VRR at Month 3 were also consistent across age strata 99.2% (95%CI: 97.6%-99.8%) in the 50-59 YOA, 98.9% (95%CI: 97.2%-99.7%) in the 60-69 YOA and 97.5% (95%CI: 95.2-98.8) in the ≥70 YOA. However, VRR at Month 38 slightly decreased with age 87.3% (95%CI: 83.2-90.8) in the 50-59 YOA, 80.1% (95%CI: 75.3%-84.3%) in the 60-69 YOA and 75.2% (95%CI: 70.0%-79.9%) in the ≥70 YOA.

Anti-gE responses did not substantially vary across regions.

Inferential analysis on the log-transformed anti-gE Ab concentrations (Month 3) was performed by using a simple Analysis of Covariance (ANCOVA) model. The fixed-effect model included the treatment and age strata as fixed effect. The pre-vaccination log-transformed Ab concentrations (Month 0) were included as continuous covariate. Least-squares means and 95% CI were back-transformed to provide geometric means and ratios. Geometric means (GMs) of post-vaccination Ab concentrations were calculated for Month 3 conditionally to the means of the log-transformed concentrations at pre-vaccination calculated across the treatment groups. The difference of means between vaccine and placebo was calculated together with 95% CIs (2-sided) and back-transformed to the original units to provide GMCs and GM ratios. Results from this exploratory group comparison showed a higher adjusted GM anti-gE Ab concentration in the HZ/su group compared to the Placebo group: the adjusted GM ratio (HZ/su group/Placebo group) was 44.31 (95% CI: 41.68 – 47.09; p-value <0.0001).

9. CMI results (exploratory objective)

CD4+ T cells are believed to play a central role in preventing VZV reactivation and CD4+ T cells are deemed to decrease with age. gE-specific CMI overall (subjects ≥50 YOA) at Months 3, 14, 26 and 38 was assessed in a descriptive manner. The gE-specific CD4 showed a pattern similar to the anti-gE ab (peak one month post dose 2, persistence above baseline level 3 years post dose 2). CMI baseline levels and CMI responses were essentially similar across age strata, although there was a slight decrease in the CMI response rate with age.

CMI responses were evaluated in a fraction of the immunogenicity subset in ZOSTER-006, i.e. 430 subjects of which 212 were in the HZ/su group.

gE- and VZV-specific CD4[2+] T cell responses were evaluated up to Month 38 post Dose 1 in ZOSTER-006. One month post Dose-2, there was a 24.6-fold increase above pre-vaccination level in the median frequencies of gE/specific CD4[2+] T cells observed in ATP subjects ≥ 50 YOA. VZV-specific CD4[2+] T responses were also augmented, although to a lesser extent. No apparent age effect was observed for this analysis on very limited number of subjects.

Table 16. ZOSTER-006: gE-specific CD4[2+] T cell responses one month post-dose 2 elicited by HZ/su, overall and by age strata (in the CMI component of the subset of ATP cohort for immunogenicity at Month 3 – CMI)

Age group (years)	gE-specific CD4[2+] T cells		
	Number of evaluable subjects (N)	Frequency 1 month post Dose 2 vs. pre-vaccination Median (Q1, Q3)	Fold increase in frequency 1 month post Dose 2 vs. pre-vaccination Median (Q1, Q3)
≥50 YOA	164 149	1844.1 (1253.6 to 2932.3)	24.6 (9.9 to 744.2)
50-59 YOA	60 55	2210.9 (1528.8 to 3013.0)	23.0 (11.1 to 802.1)
60-69 YOA	52 51	2054.2 (1378.6 to 3722.5)	24.6 (8.2 to 362.6)
≥70 YOA	52 43	1494.6 (922.9 to 2067.1)	33.2 (10.0 to 1052.0)

Q1, Q3 = First and third quartiles

Elevated gE-specific CD4[2+] T cell responses in vaccinated subjects persisted up to Month 38 (3 years post-dose 2).

Table 17. Descriptive statistics of the frequency of gE-specific CD4[2+] T cells at Month 0, 3, 14, 26, and 38 (adapted ATP cohort for immunogenicity-CMI)

Immune marker	Group	Timing	N	Nmiss	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	HZ/su	PRE(M0)	174	38	149.53	219.81	1.0	1.0	89.8	202.4	1802.2
		PII(M3)	164	48	2336.50	1564.00	350.8	1253.6	1844.1	2932.3	8583.1
		PII(M14)	169	33	992.46	837.75	1.0	454.3	799.9	1277.3	6018.8
		PII(M26)	172	28	993.53	805.26	1.0	425.6	821.0	1277.5	5007.6
		PII(M38)	152	36	926.93	849.00	1.0	355.7	738.9	1206.5	5412.0
	Placebo	PRE(M0)	180	38	146.23	186.61	1.0	11.8	81.6	215.5	1310.6
		PII(M3)	176	42	130.44	160.89	1.0	1.0	91.0	170.6	1002.1
		PII(M14)	178	30	142.54	186.57	1.0	1.0	92.6	192.0	1104.6
		PII(M26)	169	32	151.83	222.21	1.0	15.3	103.8	195.5	2129.3
		PII(M38)	148	45	117.32	145.41	1.0	1.0	68.4	188.2	828.7

Table 18. Descriptive statistics of the fold-increase over pre-vaccination in the frequency of gE-specific CD4[2+] T cells at Month 3, 14, 26, and 38 (adapted ATP cohort for immunogenicity-CMI)

Immune marker	Group	Timing	N	Mean	SD	Min	Q1	Median	Q3	Max
CD4[2+]	HZ/su	PII(M3)	149	624.58	1203.42	1.2	9.9	24.6	744.2	6257.0
		PII(M14)	152	233.01	504.83	0.0	4.2	9.8	143.0	2576.0
		PII(M26)	151	205.53	447.06	0.0	3.7	8.4	85.6	2556.9
		PII(M38)	133	178.42	411.86	0.0	2.7	7.9	31.6	2028.6
	Placebo	PII(M3)	159	17.27	49.39	0.0	0.2	1.0	2.1	320.3
		PII(M14)	160	23.25	65.91	0.0	0.3	1.0	2.7	442.1
		PII(M26)	153	12.80	41.96	0.0	0.4	1.0	2.6	271.9
		PII(M38)	135	22.38	86.52	0.0	0.1	0.9	2.0	828.7

The table below compares the CMI response at Month 38 by age strata as reflected in the SmPC:

gE-specific CD4[2+] T cell response^			
Age group (years)	Month 38*		
	N	Median frequency (Q1; Q3)	Median fold increase of frequency vs. pre-vaccination (Q1; Q3)
ZOSTER-006			
≥ 50	152	738.9 (355.7; 1,206.5)	7.9 (2.7; 31.6)
≥ 70	46	480.2 (196.1; 972.4)	7.3 (1.7; 31.6)

ATP According-To-Protocol
^ gE-specific CD4[2+] T cell response = gE-specific CD4+ T cell activity, measured by intracellular cytokine staining (ICS) assay (CD4[2+] T cells = CD4+ T cells expressing at least 2 of 4 selected immune markers)
* Month 38 = 3 years post-dose 2
N Number of evaluable subjects at the specified time point
Q1; Q3 First and third quartiles

2.5.2.2. ZOSTER-022

Study title: A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical vaccination trial to assess the prophylactic efficacy, safety and immunogenicity of gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 70 years and older.

The study was conducted concurrently with ZOSTER-006 according to a similar study design and in the same countries and centres. Prior to treatment allocation, subjects 70-79 YOA and ≥80 YOA were randomized to either study ZOSTER-006 or ZOSTER-022. This procedure allowed the pooled analysis of two studies to be powered to demonstrate statistically significant PHN VE in subjects ≥ 70 YOA, and further to provide consolidated estimation of clinically meaningful HZ VE in this age group.

A total of 14,816 subjects were enrolled and randomized to HZ/su or placebo according to a 1:1 ratio (vaccine: placebo). Subjects were stratified by age (70-79 YOA and ≥80 YOA) in approximately a 3:1 ratio. The 70-79 YOA and ≥80 YOA strata were combined for the primary ≥70 YOA overall analyses and pooled with ZOSTER-006 data for the pooled analysis.

The anti-VZV ELISA data and the Correlate of protection analysis were conducted on ZOSTER-006 and ZOSTER-022 pooled data.

Methods

The study started and was conducted simultaneously at the same study sites as study ZOSTER-006, and applied a similar methodology (See ZOSTER-006).

It was predicted that study ZOSTER-006 would have reached the conditions required for triggering final analysis of HZ primary endpoint about one year before those conditions being reached for study ZOSTER-022. Therefore the Applicant decided, as originally planned in these circumstances, to dissociate the two studies in terms of timing of the analysis of each study. Moreover, a two step approach is allowed for the analysis of each study. Both studies were to end concurrently.

Objectives

The primary objective of ZOSTER-022 (same as ZOSTER-006) was to evaluate overall VE in reducing the risk of HZ, as compared with placebo, in adults ≥70 YOA.

Secondary objectives related to efficacy evaluation in ZOSTER-022: to assess VE against PHN and against HZ-related mortality and hospitalizations in subjects ≥70 YOA; VE in the ≥70 YOA subjects of a confirmed HZ episode, with respect to reducing total duration of severe "worst" HZ-associated pain over the entire pain reporting period, HZ-associated complications, and use of pain medications for HZ.

Exploratory objectives of ZOSTER-022 (same as the pooled analysis): to evaluate VE in mitigation of BOI caused by HZ compared to placebo in subjects ≥70 YOA; VE in ≥70 YOA subjects of a confirmed HZ episode, with respect to reducing severity of acute HZ-associated pain and improving QoL; to evaluate vaccine-induced humoral immune responses up to Month 38 post Dose 1 in a subset of subjects, and to assess correlation of the humoral immune responses at Month 3 with protection against HZ.

Endpoints

Primary, secondary and exploratory endpoints are the same as for study ZOSTER-006 except for the cell-mediated immunity (CMI) which was only evaluated for ZOSTER-006.

Sample size

The final HZ efficacy analysis of the ZOSTER-022 study was planned after the accumulation of at least 278 confirmed HZ cases across all age strata. This number of HZ cases would provide ~99% power to demonstrate HZ VE of at least 10% assuming a HZ VE of 53% with a two-sided type I error rate of 5%. With a follow up time of ~3 years and stratification ratio for age of 3:1 (70-79:≥80) and drop-out and non-compliance rates as for ZOSTER-006, this leads to a total sample size of 14,512 subjects.

The end of study (EOS) analyses of the ZOSTER-022 study (like the ZOSTER-006) was planned after the accumulation at least 35 PHN cases in subjects ≥ 70 YOA in the pooled ZOSTER-006 and ZOSTER-022. All PHN cases should be accrued in the mTVC (modified total vaccinated cohort).

Planning of ZOSTER-022 was in line with the success criterion, i.e. the goal to show a VE significantly larger than 10%.

For other aspect of the study refer to section 2.5.2.1 on ZOSTER-006 Methods.

Statistical methods

See ZOSTER-006.

Changes were introduced by protocol amendment 4 (dated 18 April 2014) for ZOSTER-022 and the pooled analyses. The two studies were dissociated for timing of analysis of each study and were to end concurrently. A 2-step approach was defined to allow for analysis of each study: step 1, the final HZ

efficacy analysis, and step 2, the EOS analysis. The conditions determining the cut-off dates of the 2 analysis steps were detailed.

In ZOSTER-022, PHN in subjects ≥70 YOA was demoted from co-primary endpoint to a descriptive secondary endpoint. The co-primary endpoint of PHN in subjects ≥70 YOA in pooled ZOSTER-006 and ZOSTER-022 was to be considered as the primary PHN analysis. The overall PHN in subjects ≥50 YOA (ZOSTER-006 and ZOSTER-022 pooled) originally planned became a secondary endpoint. The objectives and endpoints as well as gatekeeping strategy was updated accordingly. Pooled analyses of 2 studies were only to be conducted if the primary objective was demonstrated in both studies separately. The targeted total number of PHN cases required to trigger the pooled PHN analysis was reduced from previous 88 PHN cases to at least 35 PHN cases in subjects ≥70 YOA in the mTVC, while maintaining statistical robustness.

The cut-off of the anti-gE ELISA assay was changed from 18 to 97 mIU/mL due to background signal measured with samples from VZV naïve children.

Other changes

Subsequent to availability of the ZOSTER-006 final HZ VE results, ZOSTER-006 and ZOSTER-022 studies were terminated earlier than initially planned. The applicable cut-off date used for ZOSTER-022 (and ZOSTER-006) EOS efficacy analysis was 21 April 2015.

A suspected case of HZ, if falling into the categories “not HZ” and “no possible classification” based on the final HZAC assignment and the case could not be confirmed or excluded by PCR, would be considered as “not HZ” for analysis.

Testing of anti-VZV neutralizing Ab was not performed for ZOSTER-006 and ZOSTER-022 (see section 2.4.3).

Rationale for using mTVC for primary analysis

See ZOSTER-006.

Results

Study population

The mTVC was the primary population for the efficacy analysis, which excluded subjects in the TVC for analysis of efficacy who were not given the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination.

A total of 13,900 and 13,163 subjects were part of the TVC and mTVC, respectively. The mean age of participants at enrolment in the mTVC was 75.5 YOA (range: 62-96 YOA); 45.3% of the subjects were male and 54.7% female. The population was predominantly of White - Caucasian / European Heritage (77.0%) with 12.7% being of Asian – East Asian Heritage. The demographic characteristics of the TVC were similar to the mTVC.

The immunogenicity analyses were performed on a subset of subjects. A total of 799 subjects were part of the ATP cohort for immunogenicity. The mean age was 75.8 YOA (range: 70 to 92 YOA); 43.8% of the subjects were male and 56.2% female. The population was predominantly of White - Caucasian /European Heritage (69.0%) with 15.6% being of Asian - East Asian Heritage.

Individuals with certain comorbidities were included in the pivotal trials, which is acceptable for a general elderly population.

Table 19. Study population by age group- TVC, ZOSTER-022

	70-79YOA		≥80YOA	
Number of subjects	**HZ/su**	**Placebo**	**HZ/su**	**Placebo**
Planned, N	5442	5442	1814	1814
Randomized, N (Total Vaccinated Cohort)	5414	5420	1536	1530
Completed, n (%)	4647 (85.8)	4679 (86.3) *	1123 (73.1)	1082 (70.7)

Efficacy results

Primary objective: HZ Vaccine Efficacy (mTVC)

The HZ VE analysis was performed on cases with a DLP of 12 October 2015. The median follow-up period was 3.9 years (range: 0 to 4.5 years) and the mean (SD) follow-up period was 3.7 (0.8) years.

Overall, VE against HZ in adults ≥70 YOA was 89.79% (95% CI: 84.29% to 93.66%; p<0.0001), with 23 confirmed HZ cases in the HZ/su group and 223 in the Placebo group. Therefore, the primary objective of study ZOSTER-022 was met (LL of the 95% CI > 10%).

No age effect was observed when comparing the two age strata (HZ VE 90.02% [95% CI: 83.54% to 94.32%; p <0.0001] in the 70-79 YOA strata and HZ VE 89.08% [95% CI: 74.65% to 96.16%; p <0.0001] in the ≥80 YOA strata).

HZ VE during the 4th year remained high at 85.07 % (95 % CI: 64.47 – 94.83%; P<0.0001) in ≥70 YOA.

Secondary objectives: VE in the prevention of overall PHN (mTVC)

Although the study was not powered for this, PHN VE was demonstrated in adults ≥70 YOA [VE of 85.49% (95% CI: 58.52% to 96.30%; p <0.0001)], with 4 confirmed PHN episodes in the HZ/su group and 28 in the Placebo group. PHN VE was also demonstrated in the 70-79 YOA stratum (90.80% [95% CI: 62.57% - 98.95%]; p<0.0001). PHN VE could not be demonstrated in the ≥80 YOA stratum, which is likely due to the lower number of subjects reporting PHN episodes in the ≥80 YOA Placebo group.

Table 20. First or only episode of PHN during the entire study period by age stratum and overall using Poisson method (modified Total Vaccinated Cohort-ZOSTER-022)

									VE			
	HZ/su				Placebo					95% CI		
Age strata	**N**	**n**	**T (year)**	**n/T (per 1000)**	**N**	**n**	**T (year)**	**n/T (per 1000)**	**(%)**	**LL**	**UL**	**p-value**
70-79YOA *	5114	2	19371.4	0.1	5189	22	19571.1	1.1	90.80	62.57	98.95	<0.0001
>=80YOA *	1427	2	5065.5	0.4	1433	6	5030.3	1.2	65.76	-91.58	96.62	0.3072
OVERALL**	6541	4	24436.9	0.2	6622	28	24601.4	1.1	85.49	58.52	96.30	<0.0001

Other secondary objectives (mTVC)

Despite the low number of HZ confirmed cases in the HZ/su group, the secondary objective regarding overall VE in terms of reduction of **use of pain medication** associated with HZ in subjects ≥70 YOA was met. The overall VE in terms of reduction of use of pain medication associated with HZ during the entire study period was 39.60% (95% CI: 10.79; 64.75; p=0.0083) among participants who were ≥70 YOA, with 43.5% of subjects in the HZ/su group and 71.8% of subjects in the Placebo group having taken at least one pain medication for HZ. The vaccine significantly reduced the **duration of HZ-associated pain medication** with VE of 49.25% (95% CI: 2.92; 73.47). The median duration of pain medication use was 30 and 38 days in the vaccine and placebo groups respectively.

Other secondary objectives (VE in reducing the duration of severe 'worst' HZ-associated pain, reducing HZ-related mortality and hospitalizations and reducing the incidence of HZ-related complications [other than PHN]), were evaluated in subjects with confirmed HZ. Due to the high HZ VE, resulting in a low number of HZ confirmed cases in the HZ/su group, it was not possible due to lack of statistical power to conclude on objectives evaluating the VE in reducing the duration of severe 'worst' HZ-associated pain and the incidence of HZ-associated complications [other than PHN]. However, when considering the descriptive statistics of the median duration of severe worst HZ-associated pain in number of days, there was a trend for a shorter duration in the HZ/su group vs. Placebo group, i.e. 13.5 vs. 19.0 days in ≥70 YOA in ZOSTER-022.

It was not possible to conclude on the objective evaluating the VE in reducing HZ-related mortality and hospitalizations due to the low number of reported events. In this study, no subjects died due to HZ or HZ-related complications. In the HZ/su group, none of the subjects were hospitalized due to HZ, whereas in the Placebo group 5 subjects were hospitalized for HZ.

Pre-specified sensitivity analyses indicated that VE against HZ by region and by gender were generally consistent with the overall VE against HZ with VE estimates by region and by gender within the 95% CI of the overall VE.

QoL exploratory objectives

In subjects ≥70 YOA, the main average pain score and the mean worst pain score by ZBPI were not significantly lower in the HZ/su group compared to the Placebo group, i.e. 4.6 vs. 5.5 (p=0.1248) and 5.8 vs. 6.9 (p=0.0847), respectively. ZBPI severity of illness, burden of illness (BOI), severity of interference, and burden of interference mean area under the curve (AUC) scores in the mTVC were lower in the HZ/su group compared to the Placebo group, overall as well as by age strata.

Overall the different parameters evaluated for the QoL exploratory objectives trended towards a lower loss of QoL in subjects with confirmed HZ in the HZ/su group compared to the Placebo group.

Immunogenicity exploratory objectives

The results overall and in both age strata (70-79 YOA and ≥80 YOA) showed strong anti-gE Ab responses following 2 doses of HZ/su at 1 month post Dose 2 (Month 3 [32.8-fold above pre-vaccination levels]). After the peak immune response at 1 month post Dose 2, the observed anti-gE Ab responses were lower 1 year post Dose 2 (Month 14) but persisted well above pre-vaccination levels up to 3 years post Dose 2 (Month 38 [6.50- fold above pre-vaccination levels]).

The anti-gE Ab responses by age strata and by region were consistent with the overall analysis.

Ancillary analyses

n/a

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 21. Summary of Efficacy for trial ZOSTER-006

Title: A phase III, randomized, observer-blind, placebo-controlled, multicenter, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 50 years and older.			
Study identifier	110390 (ZOSTER-006)		
Design	phase III, randomized, observer-blind, placebo-controlled, multicenter trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Study initiation date: 02-August-2010 Study completion date: 27-July-2015 The maximum duration for each subject was expected to be ca. 4 to 5 years. not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Vaccine group (HZ/su)		Subjects received 2 doses of HZ/su about 60 days apart through IM injection. **N = 7695**
	Control group (NaCl)		Subjects received 2 doses of saline (150 mM NaCl) about 60 days apart through IM injection. **N = 7710**
Endpoints and definitions	Primary endpoint	Efficacy	Confirmed HZ cases in the modified Total Vaccinated Cohort (mTVC) in ≥ 50 YOA
	Secondary endpoint	Efficacy in ≥ 50 YOA and in the age ranges 50-59 YOA, 60-69 YOA and ≥ 70 YOA (unless otherwise indicated)	Confirmed HZ cases in age ranges 50-59 YOA, 60-69 YOA and ≥ 70 YOA
			Occurrence of overall PHN in the mTVC
			Duration of severe “worst” HZ-associated pain
			Incidence of overall* and HZ-related mortality
			Incidence of HZ complications
			Incidence of overall* and HZ-related hospitalizations
			Duration of pain medication administered for HZ
	Secondary endpoint	Safety	Solicited local and general symptoms in a subset of subjects
			Unsolicited AEs
			Serious Adverse Events (SAEs)
			Occurrence of pre-defined AEs (i.e. pIMDs)
			Occurrence of medically attended visits
	Exploratory endpoints	Quality of life (QoL)	Acute HZ severity
			Interference of HZ with QoL
			HZ BOI
	Exploratory endpoints	Immunogenicity	CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26, 38
			Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38**
			Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38***
*Evaluation of VE in the reduction of overall mortality and hospitalizations was not performed but descriptive safety tables and SAE listings were provided. **Data regarding anti-VZV ELISA Ab concentrations (all time points) are planned to be presented in a ZOSTER-006 annex report. *** The neutralizing Ab assay was not performed.			
Database lock	01-July-2014 (HZ VE) - 12 October 2015 (EOS)		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	≥ 50 YOA - mTVC - final HZ efficacy analysis (3.1 years FU) *Analysis population* **mTVC for analysis of efficacy** excluded subjects in the TVC for analysis of efficacy who were not administered with the second vaccination or who developed a confirmed case of HZ prior to 30 days after the second vaccination or for whom one of following criteria applied: (i) Site or route of study vaccine administration was wrong or unknown, study vaccine administration was not according to protocol for reason (other than site and route) specified by the investigator, and/or one of the administered doses was not compatible with the allocated treatment number; or (ii) Wrong replacement or wrong study vaccine administered. Although the TVC (Intent-to-treat [ITT] population) analysis of efficacy is the one recommended according to ICH, the true assessment of the VE, according to the recommended schedule, can only be performed based on the mTVC, where subjects not completing the vaccination schedule due to an HZ episode or withdrawal will be excluded. *Time point description* The cut-off date for ZOSTER-006 final HZ efficacy analysis (step 1) occurred on 01 July 2014 and was defined when the following conditions were met: - at least 196 confirmed HZ cases were accrued in the mTVC; - approximately 60 HZ cases in subjects 50-59 YOA and approximately 60 HZ cases in subjects 60-69 YOA were accrued in the mTVC; - approximately 75% of subjects in each stratum had completed at least 36 months follow-up after dose 2, and the remaining subjects had completed at least 30 months follow-up after dose 2. The mean (±SD) **follow-up time** was **3.1 (±0.5) years** for final HZ efficacy analysis. The median (min-max) follow-up time was 3.1 (0 - 3.7) years.

Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	7344	7415	
	number (n) of subjects having at least one HZ confirmed case	6	210	
	follow-up period T (year)	23297	23170.5	
	Incidence rate per 1000 person years (n/T)	0.3	9.1	

Effect estimate per comparison	Primary endpoint HZ VE ≥ 50 YOA	Comparison groups	Vaccine vs. placebo
		Vaccine efficacy	97.16 %
		95%CI	93.72 - 98.97
		P-value	<0.0001

Notes	The **primary objective** regarding HZ VE in subjects ≥ 50 YOA was met as the LL of the 95% CI of the VE against HZ was above 25%. The primary analysis method of the VE considered the exact inference on the relative risk stratified for age strata and regions conditionally to the total number of HZ cases observed and time at risk. All p-values reported were related to the null hypothesis test VE = 0 (The p-value for primary HZ VE endpoint was according to the statistical analysis plan to be related to the null hypothesis test VE≤25%). The primary analysis was supported by **sensitivity analyses** of the HZ VE in the 50-59 YOA and 60-69 YOA age strata, and confirmed by the EOS analysis.			
Analysis description	**Secondary objective** : HZ VE by age stratum			
Analysis population and time point description	50-59 YOA - mTVC - final HZ efficacy analysis (3.1 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	3492	3525	
	number (n) of subjects having at least one HZ confirmed case	3	87	
	follow-up period T (year)	11161.3	11134.7	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.3	7.8	
Effect estimate per comparison	Secondary endpoint HZ VE 50-59 YOA	Comparison groups	Vaccine vs. placebo	
		Vaccine efficacy	96.57 %	
		95%CI	89.62 - 99.31	
		P-value	<0.0001	
Notes	The **secondary objective** regarding HZ VE by age stratum was met for the 50-59 YOA as the LL of the 95% CI of HZ VE was above 10%.			
Analysis description	**Secondary objective**: HZ VE by age stratum			
Analysis population and time point description	60-69 YOA - mTVC - final HZ efficacy analysis (3.1 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	2141	2166	
	number (n) of subjects having at least one HZ confirmed case	3	75	
	follow-up period T (year)	7007.9	6952.7	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.3	10.8	

Effect estimate per comparison	Secondary endpoint HZ VE 60-69 YOA	Comparison groups	Vaccine vs. placebo	
		Vaccine efficacy	97.36%	
		95%CI	90.14 - 99.69	
		P-value	<0.0001	
Analysis description	**Secondary objective**: HZ VE by age stratum			
Analysis population and time point description	≥ 70 YOA - mTVC - final HZ efficacy analysis (3.1 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	1711	1724	
	number (n) of subjects having at least one HZ confirmed case	1	48	
	follow-up period T (year)	5127.9	5083.0	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.2	9.4	
Effect estimate per comparison	Secondary endpoint HZ VE ≥ 70 YOA	Comparison groups	Vaccine vs. placebo	
		Vaccine efficacy	97.93% 87.91 99.95	
		95%CI	87.91 - 99.95	
		P-value	<0.0001	
Analysis description	**Secondary objective**: Overall PHN VE			
Analysis population and time point description	≥ 50 YOA - mTVC - EOS analysis (4 years FU) *Time point description* The cut-off date for ZOSTER-006 End-of-protocol analysis was determined per protocol, when all conditions were also met for final HZ efficacy analysis in study ZOSTER-022. This was the case in study ZOSTER-022, as also approximately 75% of subjects in each stratum had completed at least 36 months follow-up after dose 2, and the remaining subjects had completed at least 30 months follow-up after dose 2. It is noted that, in accordance with the protocols of both studies, the EOS analysis (step 2) was not to be performed before the final HZ efficacy analysis (step 1). In study ZOSTER-022, the two-steps planned analyses occurred at once. Following the Applicant's decision to terminate the ZOSTER-006 and ZOSTER-022 studies earlier than initially anticipated, the cut-off date for EOS efficacy analysis (step 2) of the studies was 21 April 2015. The mean (±SD) **follow-up time** was **3.9 (±0.7) years** for EOS analysis. The median (min - max) follow-up time was 4.1 (0 – 4.5) years.			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	7340	7413	
	number (n) of subjects having first or only PHN episode	0	18	

	follow-up period T (year)	28734.6	28943.7	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.0	0.6	

Effect estimate per comparison	PHN VE ≥ 50 YOA	Comparison groups	Vaccine vs. placebo
		Vaccine efficacy	100%
		95%CI	77.11 - 100
		P-value	<0.0001
Analysis description	**Secondary objectives** Reduction of duration of severe “worst” HZ-associated pain Reduction of confirmed HZ episode-related mortality and hospitalizations Reduction of HZ-related complications (other than PHN) Reduction in use of pain medications Reduction of PHN incidence in subjects with a confirmed HZ episode		
Analysis population and time point description	EOS, mTVC, ≥ 50 YOA		
Notes	It was not possible to conclude on these objectives due to the high HZ VE, resulting in a low number of confirmed HZ cases in the HZ/su group. Overall and in all age strata, no HZ-related mortality and no HZ-related hospitalization was reported. VE in terms of reduction of HZ-related mortality or HZ-related hospitalization could not be calculated.		

Table 22. Summary of efficacy for trial ZOSTER-022

Title: A phase III, randomized, observer-blind, placebo-controlled, multicenter, clinical vaccination trial to assess the prophylactic efficacy, safety, and immunogenicity of gE/AS01$_B$ vaccine when administered intramuscularly on a 0, 2-month schedule in adults aged 70 years and older.			
Study identifier	113077 (ZOSTER-022)		
Design	phase III, randomized, observer-blind, placebo-controlled, multicenter trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Study initiation date: 02-August-2010 Study completion date: 27-July-2015 The maximum duration for each subject was expected to be ca. 4 to 5 years. not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Vaccine group (HZ/su)		Subjects received 2 doses of HZ/su about 60 days apart through IM injection. **N = 6541**
	Control group (NaCl)		Subjects received 2 doses of saline (150 mM NaCl) about 60 days apart through IM injection. **N = 6622**
Endpoints and definitions	Primary endpoint	Efficacy	Confirmed HZ cases in the modified Total Vaccinated Cohort (mTVC) in ≥ 70 YOA
	Secondary endpoint	Efficacy	Confirmed HZ cases in age ranges 70-79 YOA and ≥ 80 YOA
			Occurrence of overall PHN in the mTVC
			Duration of severe “worst” HZ-associated pain
			Incidence of overall* and HZ-related mortality
			Incidence of HZ complications

			Duration of pain medication administered for HZ
	Secondary endpoint	Safety	Solicited local and general symptoms in a subset of subjects
			Unsolicited AEs
			Serious Adverse Events (SAEs)
			Occurrence of pre-defined AEs (i.e. pIMDs)
			Occurrence of medically attended visits
	Exploratory endpoints	Quality of life (QoL)	Acute HZ severity
			Interference of HZ with QoL
			HZ BOI
	Exploratory endpoints	Immunogenicity	CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26, 38
			Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38**
			Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38***

*Evaluation of VE in the reduction of overall mortality and hospitalizations was not performed but descriptive safety tables and SAE listings were provided.
**Data regarding anti-VZV ELISA Ab concentrations (all time points) are planned to be presented in a ZOSTER-022 annex report.
*** The neutralizing Ab assay was not performed.

Database lock	12 October 2015 (EOS)

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	≥ 70 YOA - mTVC - EOS analysis (4 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	6541	6622	
	number (n) of subjects having at least one HZ confirmed case	23	223	
	follow-up period T (year)	24405.1	24167.8	
	Incidence rate per 1000 person years (n/T)	0.9	9.2	

Effect estimate per comparison	Primary endpoint HZ VE ≥ 70 YOA	Comparison groups	Vaccine vs. placebo
		Vaccine efficacy	89.79%
		95%CI	84.29 - 93.66
		P-value	<0.0001

Notes	The **primary objective** regarding HZ VE in subjects ≥ 70 YOA was met as the LL of the 95% CI of the VE against HZ was above 10%. The primary analysis was supported by **sensitivity analyses** of the HZ VE in the 70-79 YOA and ≥80 YOA age strata.
Analysis description	**Primary Analysis**: HZ VE by age stratum

Analysis population and time point description	70-79 YOA - mTVC - EOS analysis (4 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	5114	5189	
	number (n) of subjects having at least one HZ confirmed case	17	169	
	follow-up period T (year)	19346.5	19247.5	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.9	8.8	
Effect estimate per comparison	Secondary endpoint HZ VE 70-79 YOA	Comparison groups	Vaccine vs. placebo	
		Vaccine efficacy	90.02%	
		95%CI	83.54 - 94.32	
		P-value	<0.0001	
Analysis description	**Primary objective**: HZ VE by age stratum			
Analysis population and time point description	≥80 YOA - mTVC - EOS analysis (4 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	1427	1433	
	number (n) of subjects having at least one HZ confirmed case	6	54	
	follow-up period T (year)	5058.5	4920.3	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	1.2	11	
Effect estimate per comparison	Secondary endpoint HZ VE ≥80 YOA	Comparison groups	Vaccine vs. placebo	
		Vaccine efficacy	89.08%	
		95%CI	74.65 - 96.16	
		P-value	<0.0001	
Analysis description	**Secondary objective**: Overall PHE VE			
Analysis population and time point description	≥ 70 YOA - mTVC - EOS analysis (4 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	6541	6622	

	number (n) of subjects having at least one HZ confirmed case	4	28	
	follow-up period T (year)	24436.9	24601.4	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.2	1.1	
Effect estimate per comparison	Secondary endpoint PHN VE ≥ 70 YOA	Comparison groups	Vaccine vs. placebo	
		Vaccine efficacy	85.49%	
		95%CI	58.52 - 96.30	
		P-value	<0.0001	
Analysis description	**Secondary objective**: Overall PHN VE by age strata			
Analysis population and time point description	70-79 YOA - mTVC - EOS analysis (4 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	5114	5189	
	number (n) of subjects having first or only PHN episode	2	22	
	follow-up period T (year)	19371.4	19571.1	
	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.1	1.1	
Effect estimate per comparison	PHN VE 70-79 YOA	Comparison groups	Vaccine vs. placebo	
		Vaccine efficacy	90.80%	
		95%CI	62.57 - 98.95	
		P-value	<0.0001	
Analysis description	**Secondary objective**: Overall PHN VE by age strata			
Analysis population and time point description	≥ 80 YOA - mTVC - EOS analysis (4 years FU)			
Descriptive statistics and estimate variability	Treatment group	HZ/su vaccine group	Placebo group	
	Number of subjects	1427	1433	
	number (n) of subjects having first or only PHN episode	2	6	
	follow-up period T (year)	5065.5	5030.3	

	Incidence rate of subjects reporting at least one event (n/T) per 1000	0.4	1.2	

Effect estimate per comparison	PHN VE ≥ 80 YOA	Comparison groups	Vaccine vs. placebo
		Vaccine efficacy	65.76%
		95%CI	-91.58 - 96.62
		P-value	0.3072
Analysis description	**Secondary objectives** Reduction of duration of severe "worst" HZ-associated pain Reduction of confirmed HZ episode-related mortality and hospitalizations Reduction of HZ-related complications (other than PHN) Reduction of PHN incidence in subjects with a confirmed HZ episode		
Analysis population and time point description	EOS, mTVC, ≥ 70 YOA		
Notes	It was not possible to conclude on these objectives due to the high HZ VE, resulting in a low number of confirmed HZ cases in the HZ/su group. Although there was an indication of a trend towards VE against confirmed HZ episode related mortality or first episode of hospitalization in the overall population, it was not possible to conclude on this objective due to the low number of reported events.		
Analysis description	**Secondary objectives:** Reduction in use of pain medications		
Analysis population and time point description	EOS, mTVC, ≥ 70 YOA		
Effect estimate per comparison	Reduction in use of pain medications ≥ 80 YOA	Comparison groups	Vaccine vs. placebo
		Vaccine efficacy	39.60 %
		95%CI	10.79 - 64.75
		P-value	0.0083
Notes	This secondary objective regarding overall VE in terms of reduction in use of pain medication associated with HZ was met, also in the 70-79 YOA stratum (VE of 43.42% (95% CI: 10.77% -70.53%; P=0.0112)). It was not possible to conclude on VE in ≥ 80 YOA stratum due to the high HZ VE, resulting in a low number of confirmed HZ cases in the HZ/su group.		
Analysis description	**Secondary objectives:** Reduction in duration of pain medications		
Analysis population and time point description	EOS, mTVC, ≥ 70 YOA		
Effect estimate per comparison	Reduction in duration of pain medications ≥ 80 YOA	Comparison groups	Vaccine vs. placebo
		Vaccine efficacy	49.25%
		95%CI	2.92 - 73.47
		P-value	0.0404
Notes	This secondary objective regarding overall VE in terms of reduction in duration of pain medication associated with HZ was met, also in the 70-79 YOA stratum (VE of 58.94% (95% CI: 11.45% -80.96%; P=0.0232)). It was not possible to conclude on VE in ≥ 80 YOA stratum due to the high HZ VE, resulting in a low number of confirmed HZ cases in the HZ/su group.		

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

ZOSTER-006/022 pooled analysis

Pooled data analyses of ZOSTER-006 and ZOSTER-022 allowed for PHN to be selected as a primary endpoint in order to provide a direct assessment of the VE against PHN.

Methodology

The primary objective of ZOSTER-006 and ZOSTER-022 was to evaluate VE in the prevention of HZ compared to placebo in adults ≥50 YOA and ≥70 YOA respectively, as measured by the reduction in HZ risk. VE against PHN was evaluated in the individual ZOSTER-006 and ZOSTER-022 studies as a secondary objective. However, the analysis in these studies was not powered to demonstrate PHN VE.

A series of pooled analyses from the 2 studies were also pre-specified. PHN VE was assessed based on these pre-specified pooled analyses.

Pooling of ZOSTER-006 and -022 efficacy data was justified based on their similar study design and because the subjects ≥70 YOA were randomized between the 2 studies. The two studies started and were conducted simultaneously at the same study sites.

ZOSTER-022 was designed as a separate study from ZOSTER-006, to allow the evaluation of the VE against PHN by ensuring enrolment of a sufficiently large number of subjects ≥70 YOA. Including this large cohort of subjects ≥70 YOA in one study would have introduced an imbalance in the age group distribution in ZOSTER-006, that could have biased the overall estimate of efficacy against HZ in the ≥50 YOA cohort, under the assumption that efficacy would decrease with age. As the initial assumption on this candidate HZ vaccine was that the efficacy would likely decrease with age, the Applicant designed ZOSTER-006 specifically to provide an estimate of VE against HZ in the overall ≥50 YOA study population (primary objective) deemed to be more demographically representative of the older adult population.

It was predicted that ZOSTER-006 would reach the conditions for triggering final analysis of the HZ primary endpoint more than one year prior to those conditions being reached for ZOSTER-022. Therefore the Applicant decided to dissociate the analyses of the two studies.

Objectives

The co-primary objectives of the pooled analysis of ZOSTER-006 and ZOSTER-022 were:

1. To evaluate VE in the prevention of PHN and
2. To consolidate VE estimation in the prevention of HZ,

compared to placebo in subjects ≥70 YOA across both phase III studies.

The secondary objectives of the pooled analysis were:

1. To evaluate VE in the prevention of overall PHN compared to placebo in subjects ≥50 YOA;
2. To evaluate VE in the prevention of PHN compared to placebo in subjects ≥50 YOA with confirmed HZ;
3. To evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period compared to placebo in subjects ≥70 YOA, with confirmed HZ;
4. To evaluate vaccine safety and reactogenicity in subjects ≥70 YOA.

The exploratory objectives of the pooled analysis were:

1. To evaluate VE in reducing the severity of acute HZ-associated pain compared to placebo in subjects ≥70 YOA, with confirmed HZ;
2. To evaluate VE in improving QoL compared to placebo in subjects ≥70 YOA, with confirmed HZ;
3. To evaluate vaccine induced humoral immune responses and the persistence of each type of response after two injections of study vaccine in subjects ≥50 YOA and by age strata;
4. To evaluate anti-varicella-zoster virus (VZV) neutralizing antibody (Ab) titres in a subset of subjects at Month 0 (pre-vaccination), and at Months 3, 14, 26 and 38, in subjects ≥50 YOA and by age strata;
5. To assess correlation of the humoral immune responses at Month 3 with protection against HZ.

As a post-hoc analysis, the VE in the reduction in incidence of HZ-associated complications compared to placebo in all subjects ≥50 YOA and ≥70 YOA was also evaluated on the pooled data of ZOSTER-006 and ZOSTER-022.

Endpoints

Co-primary endpoints for pooled analysis were the occurrence of overall PHN and the occurrence of confirmed HZ during the entire study period in subjects ≥70 YOA.

Secondary endpoints for pooled analysis:

- Occurrence of PHN during the study in subjects ≥50 YOA
- Occurrence of PHN during the study in the ≥50 YOA subjects of a confirmed HZ episode
- Duration of severe 'worst' HZ-associated pain in the ≥70 YOA subjects of a confirmed HZ episode

In the pooled analysis, incidence of HZ complications was evaluated as a post-hoc analysis.

Exploratory endpoints for the pooled analysis (like in each individual study) were: acute HZ severity determined by mean Area Under Curve (AUC) score measured by ZBPI during a 4-week period after zoster rash onset, HZ interference with QoL in subjects of confirmed HZ, HZ BOI as determined by mean AUC score during a 26-week period after zoster rash onset in the mTVC.

In the pooled analysis, anti-gE and anti-VZV Ab concentrations at Months 0 and 3 in all subjects with confirmed HZ were compared to matched controls, to explore any correlation between antibody response and protection (refer to subsection on correlate of protection in this section).

Statistical power and analysis

The pooled analysis allowed for the estimation of overall PHN VE (subjects ≥50 YOA), PHN VE in subjects ≥70 YOA and a more robust estimation of HZ VE in subjects ≥70 YOA.

The pooled analysis of ZOSTER-006 and ZOSTER-022 provided the highest power to generate statistically significant results, and was powered to demonstrate statistically significant PHN VE in subjects ≥70 YOA. VE against PHN was demonstrated if the LL of the 95% CI was above 0%.

In addition, VE against PHN in subjects ≥50 YOA with confirmed HZ was performed on the pooled data from both studies as a secondary objective.

Table 23. Summary of statistical inferential evaluations of primary and secondary objectives for studies ZOSTER-006, ZOSTER-022 and the pooled analysis

Analysis	Endpoint	50-59 YOA	60-69 YOA	≥70 YOA	All age strata
ZOSTER-006	HZ VE	S	S	O	P
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
ZOSTER-022	HZ VE	-	-	P	-
	PHN VE	-	-	-	-
	PHN VE in HZ subjects	-	-	-	-
Pooled analysis	HZ VE	-	-	R	-
	PHN VE	-	-	***P***	***S***
	PHN VE in HZ subjects	-	-	-	S*

P: Primary objective, well powered
R: Re-estimation of VE for an objective already demonstrated previously in ZOSTER-006 or ZOSTER-022.
S: Secondary objective, appropriately powered
S*: Secondary objective, low power
O: Study not well powered under current assumptions although may lead to significance
- : Estimates not relevant or not considered for a statistical evaluation

The pooled analysis was also performed in the 70-79 YOA and ≥80 YOA strata.

Pooled analysis

The cut-off dates for end of study (EOS) analyses of the ZOSTER-006 and the ZOSTER-022 studies were planned after the accumulation at least 35 PHN cases in subjects ≥70 YOA in the pooled ZOSTER-006 and ZOSTER-022.

The pooled analysis (VE against PHN) could be undertaken only provided the primary objective of both studies (VE against HZ) were demonstrated (i.e. clinically meaningful overall HZ VE in subjects ≥50 YOA and in subjects ≥70 YOA was reached respectively in ZOSTER-006 and ZOSTER-022.

The primary analysis of efficacy was based on the modified TVC (mTVC) for efficacy (i.e. TVC for efficacy excluding subjects who did not receive the 2nd dose of HZ/su or who developed a confirmed case of HZ prior to 1 month after the 2nd dose).

An analysis on the TVC (Intent-to-treat [ITT] population) for efficacy was planned for sensitivity analyses according to ICH recommendation, in order to check for consistent results with the primary analyses. The TVC analysis started to count HZ cases from the first vaccination onwards.

Given the very high HZ VE observed in ZOSTER-006, the statistical power reached for the key HZ and PHN VE endpoints and because of the need to cross-vaccinate subjects in the Placebo group, the Applicant decided to terminate ZOSTER-006 and ZOSTER-022 earlier than initially planned. After review of the unblinded final HZ/su efficacy data and unblinded available safety data of ZOSTER-006, the IDMC stated that they did not have any objections to GSK's proposed plan for stopping both trials, ZOSTER-006 and ZOSTER-022, in terms of subjects' interest and data integrity.

Similarity of the VE across the strata analysed was to be assessed graphically. Similarity of the VE was also to be assessed by means of exact tests of homogeneity of the VE. However, these tests were only done for the pooled analysis due to the high similarity of VE across age strata. Consistent and high vaccine efficacies across strata justified the statement of homogeneity across strata.

In other situations, the impact of potential heterogeneity on the study conclusions was to be assessed using sensitivity analyses.

The objectives of the pooled analysis are endorsed. This analysis was well designed with strong rationale, and robust methods. The Applicant considered that the VE estimate for registration purposes should be based on mTVC, provided there was no essential VE difference between the mTVC and TVC analyses, which is endorsed.

Trials had a nearly identical study design. Beside age of the subjects, the only difference was that only subjects enrolled into ZOSTER-006 study were randomly allocated to be part of the CMI component as additional exploratory endpoint.

Results

The first subject enrolled in one of the 2 studies was on 02 August 2010. The last study visit/contact for the pooled analysis was 27 July 2015.

The cut-off date for EOS efficacy analysis was 21 April 2015 (i.e. all suspected HZ episodes with onset date up to and including 21 April 2015 were considered for efficacy analyses at the EOS analysis step). Database freeze for EOS analysis occurred on 12 October 2015.

At the time of the EOS HZ and PHN analysis, the median (min to max) follow-up periods (mTVC) were:

- ZOSTER-006: 4.1 (0 to 4.5) years.
- ZOSTER-022: 3.9 (0.4 to 4.5) years.
- Pooled for subjects ≥70 YOA: 4.0 (0 - 4.5) years.

Results of the pooled analysis are provided in the ZOSTER-022 EOS report. Correlate of protection (CoP) analysis conducted on ZOSTER-006 and ZOSTER-022 pooled were presented in a ZOSTER-022 annex report (see at the end of this section). Data regarding anti-VZV ELISA Ab concentrations (all time points) were presented in a ZOSTER-022 annex report (see section 2.4.3). The neutralizing Ab assay was not performed.

Study population

ZOSTER-006 enrolled subjects ≥50 YOA, of whom 15,405 were included in the EOS analysis (TVC). ZOSTER-022 enrolled subjects ≥70 YOA, of whom 13,900 subjects were included in the TVC.

Overall, for the pooled analysis:

- 29,305 were included in the pooled TVC (14,645 in the Hz/su Group and 14,660 in the Placebo Group).
- 27,916 were included in the pooled mTVC (13,881 in the HZ/su Group and 14,035 in the Placebo Group).

The number of subjects in the pooled mTVC by age category is presented in Table 25. 15,400 of the subjects (52.6%) from the pooled analysis (TVC) were enrolled in European sites.

Table 24. Number of subjects in the mTVC (subjects ≥50YOA -POOLED ZOSTER 006-022)

	HZ/su	**Placebo**
50-59 YOA	3491	3523
60-69 YOA	2140	2166
70-79 YOA	6468	6554
≥ 80 YOA	1782	1792
	13,881	14,035

Demographic characteristics and other baseline characteristics

Demographic characteristics at baseline were comparable across groups overall and within age strata. Women were overrepresented in both groups. In the ≥80 YOA strata, median age is 82 years in both group indicating that around 900 subjects in both groups were 82 YOA or above (i.e. <7%).

Efficacy analysis against HZ in subjects ≥70YOA (mTVC)

Efficacy against HZ overall and by age stratum

Only very few confirmed HZ episodes occurred in the vaccinated subjects (25 in the HZ/su group in comparison with 284 in the Placebo group). Overall VE against HZ was 91.30% (95%CI: 86.88%-94.46%) in subjects ≥70 YOA. The primary objective of the pooled analysis regarding HZ VE in subjects ≥70 YOA was met.

In the pooled analysis, VE was very high and consistent across age categories across and within studies using Poisson method.

In subjects ≥ 70 YOA, the overall incidence of HZ per 1000 person-years for the pooled ZOSTER-006/022 was 0.8 in the HZ/su group and 9.3 in the Placebo group. In the placebo group incidence rates of HZ tended to increase slightly with age.

Table 25. First or only episode of HZ during the entire study period by study and by age stratum and overall using Poisson method (mTVC Cohort, subjects ≥ 70YOA - POOLED ZOSTER 006-022)

		HZ/su				Placebo				VE	95% CI		
Study	Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Zoster 006	70-79YOA*	1354	2	5064.4	0.4	1365	47	5015.3	9.4	95.77	83.84	99.50	<0.0001
	≥80YOA*	355	0	1256.1	0.0	359	14	1231.5	11.4	100.00	70.60	100.00	0.0001
Zoster 022	70-79YOA*	5114	17	19346.5	0.9	5189	169	19247.5	8.8	90.02	83.54	94.32	<0.0001
	≥80YOA*	1427	6	5058.5	1.2	1433	54	4920.3	11.0	89.08	74.65	96.16	<0.0001
Pooled zoster 006-022	70-79YOA*	6468	19	24410.9	0.8	6554	216	24262.8	8.9	91.27	86.04	94.85	<0.0001
	≥80YOA*	1782	6	6314.6	1.0	1792	68	6151.9	11.1	91.37	80.22	96.94	<0.0001
	≥70YOA**	8250	25	30725.5	0.8	8346	284	30414.7	9.3	91.30	86.88	94.46	<0.0001

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
≥70YOA = ≥70 years old subjects
N = 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) 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)
*VE adjusted by region
**VE adjusted by age stratum and region
P-value=Two sided Exact P-value conditional to number of cases

Efficacy against HZ by time

VE by year following vaccine administration is presented in table 27. VE decreased slightly but was maintained at very high level over 4 years in individuals ≥ 70 YOA.

This is confirmed by cumulative VE estimations (post-hoc analysis). The overall HZ VE was 97.58% (95% CI: 90.97% - 99.71%; P<0.0001) up to Year 1; 94.71% (95% CI: 89.72% - 97.62%; P<0.0001) up to Year 2; 92.15% (95% CI: 87.31% - 95.43%; P<0.0001) up to Year 3 and 91.30% (95% CI: 86.88% - 94.46%; P<0.0001) up to Year 4. Analyses show consistent findings across age strata.

Table 26. First or only episode of HZ during the entire study period by time using Poisson method (modified Total Vaccinated Cohort, subjects ≥70YOA -POOLED ZOSTER 006-022)

									VE			
	HZ/su				Placebo					95% CI		
Time	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Year 1*	8250	2	8156.2	0.2	8346	83	8206.2	10.1	97.58	90.97	99.71	<0.0001
Year 2*	8039	7	7916.9	0.9	8024	87	7860.5	11.1	92.03	82.86	96.89	<0.0001
Year 3*	7736	9	7612.2	1.2	7661	58	7488.4	7.7	84.74	69.00	93.36	<0.0001
Year 4*	7426	7	7040.3	1.0	7267	56	6859.6	8.2	87.88	73.34	95.34	<0.0001

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
N = 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) 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)
*VE adjusted by age stratum and region
P-value=Two sided Exact P-value conditional to number of cases
Year 1: From 30 days after second vaccination to 395 days after second vaccination
Year 2: From >395 days after second vaccination to 760 days after second vaccination
Year 3: From >760 days after second vaccination to 1125 days after second vaccination
Year 4: From >1125 days after second vaccination until last contact date

Sensitivity analyses

No substantial differences were observed for VE against HZ using the Poisson method, by gender as well as by region.

Efficacy against PHN (mTVC)

Efficacy against PHN in ≥70YOA overall and by age stratum

A PHN episode was reported in 4 subjects in the HZ/su Group and 36 in the Placebo group. HZ/su significantly reduces the risk of PHN compared to placebo. Overall VE against PHN was 88.78% (95% CI: 68.70%-97.10%; P<0.0001). The co-primary confirmatory objective of the pooled ZOSTER-006/022 regarding PHN VE in subjects ≥70 YOA was met (Table 28). Incidence rates of subjects reporting at least one event of PHN per 1000 persons-years are presented in the same table.

PHN VE could not be demonstrated in the ≥80 YOA stratum, which is likely due to the lower number of subjects reporting PHN episodes.

VE against PHN were not substantially different in the TVC and ATP cohorts of analysis.

Table 27. First or only episode of PHN during the entire study period by study and by age stratum and overall using Poisson method (mTVC, subjects ≥ 70YOA - POOLED ZOSTER 006-022)

										VE			
		HZ/su				Placebo					95% CI		
Study	Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Zoster 006	70-79YOA*	1354	0	5067.3	0.0	1365	7	5089.3	1.4	100.00	30.52	100.00	0.0157
	≥80YOA*	355	0	1256.1	0.0	359	1	1251.3	0.8	100.00	-3864.04	100.00	1.0000
Zoster 022	70-79YOA*	5114	2	19371.4	0.1	5189	22	19571.1	1.1	90.80	62.56	98.95	<0.0001
	≥80YOA*	1427	2	5065.5	0.4	1433	6	5030.3	1.2	65.76	-91.58	96.62	0.3072
Pooled zoster 006-022	70-79YOA*	6468	2	24438.8	0.1	6554	29	24660.4	1.2	93.04	72.47	99.19	<0.0001
	≥80YOA*	1782	2	6321.5	0.3	1792	7	6281.6	1.1	71.16	-51.51	97.08	0.1844
	≥70YOA**	8250	4	30760.3	0.1	8346	36	30942.0	1.2	88.78	68.70	97.10	<0.0001

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
≥70YOA = ≥70 years old subjects
N = number of subjects included in each group
n = number of subjects having at least one PHN
T (year) = sum of follow-up period (censored at the first occurrence of PHN) 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)
*VE adjusted by region
**VE adjusted by age stratum and region
P-value=Two sided Exact P-value conditional to number of cases

Efficacy against PHN in ≥50 YOA and according to age

In subjects ≥50 YOA, a PHN episode was reported in 4 subjects in the HZ/su Group and 46 in the Placebo group. The overall PHN VE was 91.22% (95% CI: 75.95%-97.70%; P<0.0001). VE against PHN was very high in subjects 50-69 YOA, but with wide CI. VE against PHN was higher in subjects below 70 as compared to subjects ≥70 YOA. VE was higher in subjects 70-79 YOA as compared to subjects ≥80 YOA. VE tended to decrease with age (table 29). It has to be noted however, the number of cases is small within age categories, especially in the oldest, and CIs are wide.

Table 28. First or only episode of PHN during the entire study period by study and by age stratum and overall using Poisson method (mTVC, subjects ≥50YOA - POOLED ZOSTER 006-022)

										VE			
		HZ/su				Placebo					95% CI		
Study	Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	(%)	LL	UL	p-value
Zoster 006	50-59YOA*	3491	0	13789.7	0.0	3523	8	13928.7	0.6	100.00	40.88	100.00	0.0081
	60-69YOA*	2140	0	8621.4	0.0	2166	2	8674.4	0.2	100.00	-442.83	100.00	0.5097
	70-79YOA*	1354	0	5067.3	0.0	1365	7	5089.3	1.4	100.00	30.52	100.00	0.0157
	≥80YOA*	355	0	1256.1	0.0	359	1	1251.3	0.8	100.00	-3864.04	100.00	1.0000
Zoster 022	70-79YOA*	5114	2	19371.4	0.1	5189	22	19571.1	1.1	90.80	62.56	98.95	<0.0001
	≥80YOA*	1427	2	5065.5	0.4	1433	6	5030.3	1.2	65.76	-91.58	96.62	0.3072
Pooled zoster 006-022	50-59YOA*	3491	0	13789.7	0.0	3523	8	13928.7	0.6	100.00	40.88	100.00	0.0081
	60-69YOA*	2140	0	8621.4	0.0	2166	2	8674.4	0.2	100.00	-442.83	100.00	0.5097
	70-79YOA*	6468	2	24438.8	0.1	6554	29	24660.4	1.2	93.04	72.47	99.19	<0.0001
	≥80YOA*	1782	2	6321.5	0.3	1792	7	6281.6	1.1	71.16	-51.51	97.08	0.1844
	≥50YOA**	13881	4	53171.5	0.1	14035	46	53545.0	0.9	91.22	75.95	97.70	<0.0001

HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
50-59YOA = 50-59 years old subjects
60-69YOA = 60-69 years old subjects
70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
≥50YOA = ≥50 years old subjects
N = number of subjects included in each group
n = number of subjects having at least one PHN
T (year) = sum of follow-up period (censored at the first occurrence of PHN) 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)
* : VE adjusted by region
** : VE adjusted by age stratum and region
P-value=Two sided Exact P-value conditional to number of cases

PHN frequency in the Placebo group

The incidence rate of subjects reporting at least one PHN episode in the Placebo group tended to increase with age (from 0.6 in 50-59YOA to 1.1 in >80YOA). The overall risk of PHN in subjects who presented HZ was 9.6% (46/477), and also tended to increase with age.

Post-hoc analysis on vaccine efficacy against PHN (alternative definitions)

During the procedure the Applicant was requested to present the following results for the pooled analyses: Vaccine efficacy against PHN by time, and VE according to alternative definitions of PHN, based on duration of pain of 30, 60, 120 and 180 days (as indicated in ZOSTER-006 study protocol). These data were presented with the exception of VE in the prevention of PHN over time. VE in the prevention of PHN over time should be provided via the ZOSTER-049 trial.

The VE against PHN according to alternative PHN definitions (based on duration of pain of ≥30, ≥60, ≥120 and ≥180 days) were 93.25% (95% CI, 84.72% to 97.59%), 91.61% (95% CI, 77.08% to 97.80%), 95.41% (95% CI, 71.57% to 99.90%) and 100% (95% CI, 72% to 100%) in adults ≥70 YOA, respectively, in the pooled analysis. These VE results are in line with the point estimate of 85.49% (95% CI, 58.52% to 96.30%) in adults ≥70 YOA from ZOSTER-022 with PHN defined by pain duration ≥90 days.

The Applicant acknowledged that, according to the protocol, these VE endpoints were planned to be reported as secondary endpoints. However, only the generally accepted definition of PHN (i.e., ≥90 days) was used for VE analysis.

Reduction of duration of severe 'worst' HZ associated pain in subjects ≥ 70 YOA

In subjects with a confirmed HZ episode, the median (min - max) duration of severe 'worst' HZ-associated pain over the entire pain reported period was:

- 11.5 days (1.0 - 162.0 days) in the HZ/su group,
- 19.0 days (1.0 - 834.0 days) in the Placebo group.

The overall VE in terms of reduction of duration of severe 'worst' HZ-associated pain was 30.48% (95% CI: -10.52% - 56.27%). It was not possible to conclude on this objective due to the high HZ VE, resulting in a low number of confirmed HZ cases in the HZ/su group.

Reduction of PHN incidence in subjects ≥ 50 YOA with a confirmed HZ episode

In subjects with a confirmed HZ episode, PHN was reported in 4 out of 32 subjects of the HZ/su group and 46 out of 477 subjects of the Placebo group. The overall VE in terms of reduction of PHN incidence in subjects with a confirmed HZ episode was 0.29% (95% CI: -161.53% -65.57%). It was not possible to conclude on this objective due to the high HZ VE, resulting in a low number of confirmed HZ cases in the HZ/su group.

Numerically, 4/32 (12.50%) subjects with confirmed HZ in vaccine group developed PHN and 46/477 (9.64%) subjects in the placebo group, according to the pooled analysis. The concern of increasing PHN risk in these subgroups is theoretical but nevertheless the Applicant was asked during the procedure to re-calculate cases using "relax" PHN definition, i.e. zoster pain persisting or appearing more than 60 days or 30 days after rash onset, and to conduct additional analysis using re-calculated number of PHN cases.

For "relaxed" PHN 60 days: 5/32 (15.63%, 95%CI: 5.28, 32.79) subjects ≥ 50 YOA with confirmed HZ in vaccine group developed PHN whereas 64/477 (13.42%, 95%CI: 10.49, 16.81) subjects in placebo group.

For "relaxed" PHN 30 days: 8/32 (25.00%, 95%CI: 11.46, 43.40) subjects ≥ 50 YOA with confirmed HZ in vaccine group developed PHN whereas 126/477 (26.42%, 95%CI: 22.51, 30.61) subjects in placebo group.

With regard to 95%CI, similar patterns as those observed in primary analysis (i.e. PHN 90 days) are observed and therefore a valid statistical conclusion is still not possible.

The available data on efficacy of HZ/su in preventing PHN in subjects with confirmed HZ do not allow drawing a statistically relevant conclusion. However it is noted that with reduction of the number of days, the number of PHN cases increases in both groups, and the difference in the percentage of confirmed HZ cases developing PHN between two groups is reduced. In addition, the Applicant reported the observation that HZ and PHN episodes in vaccine group are generally milder in nature than those reported in placebo recipients.

Post-hoc analysis: efficacy against HZ-related complications (other than PHN)

Complications related to HZ were reported for 1 subject (1 complication) in the HZ/su Group and 16 subjects (17 complications) in the Placebo group (Pooled analysis, ≥50 YOA). The HZ related complications (other than PHN) reported during the entire study period were (mTVC) Ophthalmic disease (n=1) in the HZ/su Group and Ophthalmic disease (n=7), Disseminated disease (n=6),

Neurological disease (n=3) and HZ vasculitis (n=1) in the Placebo group. No cases of visceral disease or stroke were reported during these studies in either groups.

In the Placebo Group, the incidence of complications tended to increase with age. Most of the complications occurred in the subjects ≥70 YOA so that VE cannot be estimated in subjects 50-59 YOA and 60-69 YOA.

The overall VE against HZ related complications was:

- 93.71% (95% CI: 59.53% - 99.85%; P=0.0003) in subjects ≥ 50 YOA (1 vs. 16 cases, p-value: 0.0003)
- 91.62% (95% CI: 43.38% - 99.80%; P=0.0035) in subjects ≥ 70 YOA (1 vs. 12 cases, p-value: 0.0035).

Post-hoc analysis on vaccine efficacy against use and duration of pain medication

Use and duration of pain medication administered in subjects with confirmed HZ was not part of the objectives of the pooled analysis. During the procedure the Applicant was asked to perform a post hoc analysis on this parameter for subjects ≥70 YOA, using pooled data of ZOSTER-006 and ZOSTER-022 to improve the estimates obtained from ZOSTER-022.

Table 29. Vaccine efficacy: use of pain medication associated with HZ during the entire period by age strata and overall in subjects with a confirmed HZ episode (mTVC, subjects ≥ 70 YOA-pooled ZOSTER-006-022)

					n/N			VE			
Age strata	Group	N	n+	n	%	LL	UL	%	LL	UL	p-value
70-79YOA	HZ/su	19	16	8	42.11	20.25	66.50	42.07	11.28	68.36	0.0083
	Placebo	216	609	157	72.69	66.23	78.51	-	-	-	-
>=80YOA	HZ/su	6	18	3	50.00	11.81	88.19	29.17	-20.57	73.85	0.3671
	Placebo	68	170	48	70.59	58.29	81.02	-	-	-	-
OVERALL *	HZ/su	25	34	11	44.00	24.40	65.07	39.04	11.93	63.26	0.0055
	Placebo	284	779	205	72.18	66.58	77.31	-	-	-	-

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

* : VE adjusted by age strata

Table 30. Vaccine efficacy: reduction of duration of pain medication associated with HZ during the entire period by age strata and overall in subjects with a confirmed HZ episode (mTVC, subjects ≥ 70 YOA-pooled ZOSTER-006-022)

							VE			
	HZ/su			Placebo				95% CI		
Age strata	N	n	T(day)	N	n	T(day)	(%)	LL	UL	p-value
70-79YOA *	19	8	345.0	216	157	32126.0	58.21	14.69	79.52	0.0166
>=80YOA *	6	3	827.0	68	48	5584.0	3.03	-225.53	71.12	0.9602
OVERALL **	25	11	1172.0	284	205	37710.0	50.56	8.84	73.18	0.0240

N = number of subjects with at least one confirmed HZ episode
n = number of subjects with at least one day of pain medication associated with HZ
T (day) = sum of follow-up period (for subjects without pain medication T is 1, for subjects with pain medication T is the duration of pain medication) expressed in days
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)
* : VE adjusted by region
** : VE adjusted by age strata and region

P-value from Cox regression model

For both analyses, significant results obtained in study ZOSTER-022 are confirmed (Table 32). The median duration of pain medication use was 32.0 and 44.0 days in the HZ/su and placebo group, respectively.

Table 31. Summary of overall efficacy for use and duration of pain medication associated with HZ in ZOSTER-022 and in pooled ZOSTER-006/022 (mTVC, subjects ≥ 70 YOA-pooled ZOSTER-006-022)

	VE use of pain medication				VE duration of pain medication			
Study	**%**	**LL**	**UL**	**p-value**	**%**	**LL**	**UL**	**p-value**
Zoster-022	39.60	10.79	64.75	0.0083	49.25	2.92	73.47	0.0404
Pooled Zoster-006-022	39.04	11.93	63.26	0.0055	50.56	8.84	73.18	0.0240

LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy using asymptotic standardized unconditional binomial test

Post-hoc analysis on the incidence of severe and long-lasting zoster pain

In order to understand whether the vaccine can effectively reduce incidence of severe and long-lasting zoster pain, e.g. score of >600 by ZBPI, in the population of studied subjects, the Applicant was asked during the procedure to conduct such analysis.

The number of subjects with a ZBPI worst pain score Area Under the Curve (AUC) for days 0-182 >600 was calculated for both the ZOSTER-006 and ZOSTER-022 pooled data. In the ZOSTER-006 analysis, 0/8 subjects in the vaccine group and 7/241 in the placebo group had a ZBPI worst pain score AUC Days 0-182 >600.

Similarly, in the ZOSTER-022 pooled analysis 1/23 subjects in the vaccine group and 19/263 in the placebo group had a ZBPI worst pain score AUC Days 0-182 >600.

The analyses were performed on the Modified Total Vaccinated Cohort Confirmed Cases HZ ZBPI Evaluable Subgroup, which excludes any subject without a ZBPI questionnaire within 14 days following rash onset.

The point estimates would suggest that there is an attenuation of long term severity in breakthrough cases, however the confidence intervals are extremely wide due to the small sample size in breakthrough cases (i.e. due to very high vaccine efficacy). As such no definitive conclusion can be drawn from this analysis.

Exploratory objectives - Quality of Life results

After pooling, analysis of QoL parameters in the evaluable subgroup of mTVC HZ confirmed cases, who had a first ZBPI evaluation visit within 14 days of the first date of rash, revealed statistically significant reduction in the vaccine group compared to placebo group, in terms of worst ZBPI scores. In subjects ≥70 YOA (pooled data) with at least one confirmed HZ episode, HZ/su significantly reduced the maximum worst pain score vs. placebo over the entire HZ episode (mean = 5.7 vs. 7.0, P-value = 0.032) and the maximum average pain score (mean= 4.5 vs. 5.6, P-value = 0.043). There was no

statistically significantly difference in terms on worst ZBPI scores for Activities of Daily Living (ADL) (mean=3.9 vs. 4.6, P-value= 0.26).

There were no statistically significant differences between the HZ/su group and the Placebo group in the pooled analyses on AUC scores for ZBPI worst pain, ZBPI average pain and ZBPI ADL scores or on time to resolution of clinically significant pain, in HZ ZBPI evaluable subgroup of the mTVC HZ confirmed cases. However, all mean scores at all time points (30, 90 and 182 days) were generally lower in the HZ/su group than in the Placebo group.

The mean scores for severity of illness and severity of interference were statistically significantly lower in the HZ/su group compared to the Placebo group, overall and by age stratum (P<0.0001) according to Chang and Chop-lump tests. The overall VE estimate against burden of illness was 92.1% (95% CI: 90.4%-93.8%) in subjects ≥70 YOA (pooled analysis), with point estimates of 95.1% in the 70-79 YOA stratum and 82.2% in the ≥80 YOA stratum. The overall VE estimate against the burden of interference was 90.3% (95% CI: 88.5%-92.1%) with point estimates of 95.8% in the 70-79 YOA stratum and 73.8% in the ≥80 YOA stratum.

Only few statistically significant differences were observed between the study groups for the worst score over time in the SF-36 or EQ-5D scale, in favour of placebo, and the pattern was not consistently in favour of one of the groups.

Immunogenicity results – humoral (ZOSTER-006 and pooled ZOSTER-006/022)

In the 2 pivotal efficacy studies, humoral immune response evaluations were performed in a subset of subjects. A total of 2,137 and 799 subjects (of which 1,070 and 387 subjects were in the HZ/su group) were part of the ATP cohort for immunogenicity in ZOSTER-006 and ZOSTER-022, respectively.

For anti-gE antibody responses measured by ELISA at Month 3 post Dose 2, the median fold increase above pre-vaccination level was 41.9 in ATP subjects ≥50 YOA (ZOSTER-006) and 34.3 in ATP subjects ≥70 YOA (pooled analysis of ZOSTER-006 and ZOSTER-022).

Table 32. Anti-gE Abs responses to HZ/su one month post-dose 2, overall and by age strata in ZOSTER-006 and pooled 006-022 analysis (subset of ATP cohort of immunogenicity at Month 3 - humoral)

Studies and age groups	Anti-gE Abs			
	Number of evaluable subjects (N)	anti-gE Abs 1 month post Dose 2 GMC (95% CI)	VRR 1 month post Dose 2 % (95% CI)	Fold increase in anti-gE Abs 1 month post Dose 2 vs. pre-vaccination Median (Q1, Q3)
ZOSTER-006				
≥50 YOA	1070 1069	52376.6 (50264.1 to 54577.9)	98.5 (97.6 to 99.1)	41.9 (20.8 to 86.9)
50-59 YOA	356 355	53317.5 (49516.3 to 57410.4)	99.2 (97.6 to 99.8)	52.0 (25.5 to 98.1)
60-69 YOA	359/359	55806.0 (52460.9 to 59364.4)	98.9 (97.2 to 99.7)	41.0 (20.8 to 85.2)
Pooled ZOSTER-006 and ZOSTER-022				
≥ 70 YOA	742 741	49691.5 (47250.8 to 52258.2)	96.6 (95.1 to 97.8)	34.3 (16.7 to 68.5)
70-79 YOA	597 596	50046.8 (47317.5 to 52933.6)	96.6 (94.9 to 97.9)	35.8 (17.4 to 68.9)
≥ 80 YOA	145 145	48254.6 (42980.7 to 54175.7)	96.6 (92.1 to 98.9)	30.4 (14.2 to 65.7)

Q1 and Q3 represent the first and third quartiles.

Results from descriptive analyses regarding anti-gE humoral immunogenicity at Months 0, 3, 14, 26 and 38, by age stratum (≥70 YOA, 70-79 YOA and ≥80 YOA) performed on the ATP cohort for immunogenicity–Humoral are presented in the table below. The elevated humoral immune responses

assessed by GMCs and vaccine-response rates were still evident up to Month 38 post-vaccination in the pooled data, like was seen in ZOSTER-006 and ZOSTER-022 studies. Stratification by age stratum indicates no impact of age on humoral immunogenicity (Table 34).

Table 33. Seropositivity rates and Geometric Mean Concentrations (GMCs) of anti-gE antibody at Month 0, 3, 14, 26 and 38 by age group (ATP cohort for immunogenicity-Humoral, subjects ≥70YOA –POOLED ZOSTER 006-022)

					≥ 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	70-79YOA	HZ/su	PRE(M0)	596	592	99.3	98.3	99.8	1440.4	1325.9	1564.7	<97.0	233132.9
			PII(M3)	597	597	100	99.4	100	50046.8	47317.5	52933.6	863.2	308834.6
			PII(M14)	585	585	100	99.4	100	16077.4	15082.0	17138.5	727.0	160387.0
			PII(M26)	556	556	100	99.3	100	12775.6	12013.8	13585.8	494.4	98168.3
			PII(M38)	536	536	100	99.3	100	10485.8	9822.2	11194.2	374.5	107105.5
		Placebo	PRE(M0)	608	605	99.5	98.6	99.9	1442.5	1331.9	1562.2	<97.0	230579.9
			PII(M3)	608	604	99.3	98.3	99.8	1397.5	1288.9	1515.2	<97.0	259629.7
			PII(M14)	576	572	99.3	98.2	99.8	1281.1	1177.7	1393.4	<97.0	85917.5
			PII(M26)	544	542	99.6	98.7	100	1344.3	1238.2	1459.4	<97.0	29541.0
			PII(M38)	522	519	99.4	98.3	99.9	1286.8	1180.4	1402.8	<97.0	28881.1
	≥80YOA	HZ/su	PRE(M0)	145	144	99.3	96.2	100	1506.3	1273.7	1781.3	<97.0	26034.2
			PII(M3)	145	145	100	97.5	100	48254.6	42980.7	54175.7	2119.1	246399.1
			PII(M14)	134	134	100	97.3	100	15158.9	13163.4	17456.8	1125.0	79814.7
			PII(M26)	121	121	100	97.0	100	12897.8	11162.0	14903.5	1088.1	49613.3
			PII(M38)	112	112	100	96.8	100	10613.1	9153.2	12305.8	330.2	44617.5
		Placebo	PRE(M0)	160	159	99.4	96.6	100	1553.8	1317.1	1833.1	<97.0	21802.7
			PII(M3)	160	159	99.4	96.6	100	1462.1	1234.3	1732.0	<97.0	42407.0
			PII(M14)	151	149	98.7	95.3	99.8	1376.9	1141.5	1660.9	<97.0	41611.7
			PII(M26)	136	136	100	97.3	100	1582.9	1311.1	1911.1	104.9	26222.1
			PII(M38)	118	116	98.3	94.0	99.8	1460.1	1188.0	1794.6	<97.0	74603.5
	≥70YOA	HZ/su	PRE(M0)	741	736	99.3	98.4	99.8	1453.0	1349.2	1564.8	<97.0	233132.9
			PII(M3)	742	742	100	99.5	100	49691.5	47250.8	52258.2	863.2	308834.6
			PII(M14)	719	719	100	99.5	100	15902.1	15003.8	16854.2	727.0	160387.0
			PII(M26)	677	677	100	99.5	100	12797.4	12093.6	13542.1	494.4	98168.3
			PII(M38)	648	648	100	99.4	100	10507.7	9899.2	11153.6	330.2	107105.5
		Placebo	PRE(M0)	768	764	99.5	98.7	99.9	1465.0	1363.6	1574.0	<97.0	230579.9
			PII(M3)	768	763	99.3	98.5	99.8	1410.7	1311.4	1517.5	<97.0	259629.7
			PII(M14)	727	721	99.2	98.2	99.7	1300.4	1204.0	1404.5	<97.0	85917.5
			PII(M26)	680	678	99.7	98.9	100	1388.9	1287.6	1498.2	<97.0	29541.0
			PII(M38)	640	635	99.2	98.2	99.7	1317.1	1216.1	1426.6	<97.0	74603.5

70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
≥70YOA = ≥70 years old subjects
HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
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(M0) = Pre-vaccination (Month 0)
PII(M3) = Post-vaccination Dose II (Month 3)
PII(M14) = Post-vaccination Dose II (Month 14)
PII(M26) = Post-vaccination Dose II (Month 26)
PII(M38) = Post-vaccination Dose II (Month 38)

At month 38 post-vaccination, the median fold increase of concentrations vs. pre-vaccination (first and third quartiles) in subjects ≥50YOA (ZOSTER-006) was 9.3 (Q1:Q3=4.9; 19.5) and the GMCs (mIU/mL) were 11,919.6 (95% CI 11,345.6; 12,522.7). At Month 38, the post-vaccination, the median fold increase of concentrations vs. pre-vaccination (first and third quartiles) in subjects ≥70YOA

(pooled ZOSTER-006/ZOSTER-022) was 7.2 (Q1; Q3 = 3.5; 14.5) and the GMCs (mIU/mL) were 10,507.7 (95% CI 9.899.2; 11,153.6).

Vaccine response rates (VRR) with respect to anti-gE Abs and anti-gE Abs geometric means ratio for HZ/su over placebo in the HZ/su group were also very similar in the subjects 70-79 YOA and in those ≥80 YOA (Table 35 and Table 36).

Table 34. Vaccine response rates for anti-gE antibody ELISA concentrations at Months 3, 14, 26 and 38 by age group (ATP cohort for immunogenicity-Humoral, subjects ≥ 70YOA POOLED ZOSTER 006-022)

					Vaccine response			
							95% CI	
Test description	Sub-group	Group	Timing	N	n	%	LL	UL
VZV.gE Ab.IgG	70-79YOA	HZ/su	PII(M3)	596	576	96.6	94.9	97.9
			PII(M14)	570	471	82.6	79.3	85.7
			PII(M26)	544	410	75.4	71.5	78.9
			PII(M38)	526	370	70.3	66.2	74.2
		Placebo	PII(M3)	608	15	2.5	1.4	4.0
			PII(M14)	569	21	3.7	2.3	5.6
			PII(M26)	535	16	3.0	1.7	4.8
			PII(M38)	514	9	1.8	0.8	3.3
	≥80YOA	HZ/su	PII(M3)	145	140	96.6	92.1	98.9
			PII(M14)	133	108	81.2	73.5	87.5
			PII(M26)	119	86	72.3	63.3	80.1
			PII(M38)	111	79	71.2	61.8	79.4
		Placebo	PII(M3)	160	4	2.5	0.7	6.3
			PII(M14)	150	8	5.3	2.3	10.2
			PII(M26)	135	8	5.9	2.6	11.3
			PII(M38)	117	6	5.1	1.9	10.8
	≥70YOA	HZ/su	PII(M3)	741	716	96.6	95.1	97.8
			PII(M14)	703	579	82.4	79.3	85.1
			PII(M26)	663	496	74.8	71.3	78.1
			PII(M38)	637	449	70.5	66.8	74.0
		Placebo	PII(M3)	768	19	2.5	1.5	3.8
			PII(M14)	719	29	4.0	2.7	5.7
			PII(M26)	670	24	3.6	2.3	5.3
			PII(M38)	631	15	2.4	1.3	3.9

70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
≥70YOA = ≥70 years old subjects
HZ/su = Herpes Zoster subunit vaccine
Placebo = Placebo
Vaccine response defined as :
For initially seronegative subjects, antibody concentration at post-vaccination ≥ 4 fold the cut-off for Anti-gE (4x97 mIU/ml)
For initially seropositive subjects, antibody concentration at post-vaccination ≥ 4 fold the pre-vaccination antibody concentration
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of responders
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
PII(M3) = Post-vaccination Dose II (Month 3)
PII(M14) = Post-vaccination Dose II (Month 14)
PII(M26) = Post-vaccination Dose II (Month 26)
PII(M38) = Post-vaccination Dose II (Month 38)

Table 35. Adjusted geometric means and ratio for HZ/su over placebo of anti-gE antibody ELISA concentrations at Month 3 by age group (ATP cohort for immunogenicity-Humoral, subjects ≥70YOA –POOLED ZOSTER 006-022)

				Adjusted Geometric Mean			Adjusted Geometric Mean Ratio			
					95% CI			95% CI		
Timing	Sub-Group	Group	N	Value	LL	UL	Value	LL	UL	P-value for the ratio
PII(M3)	70-79YOA	HZ/su	596	50071.8	47215.6	53100.7	35.84	33.00	38.93	<.0001
		Placebo	608	1397.0	1318.1	1480.6	.	.	.	.
	≥80YOA	HZ/su	145	48673.2	43111.1	54952.9	33.55	28.38	39.67	<.0001
		Placebo	160	1450.7	1292.4	1628.4	.	.	.	.

70-79YOA = 70-79 years old subjects
≥80YOA = ≥80 years old subjects
HZ/su = Herpes Zoster subunit vaccine ; Placebo = Placebo
PII(M3)= Post-vaccination Dose II (Month 3)
N = number of subjects in a given category with available results
LL = Lower Limit, UL = Upper Limit and CI = Confidence Interval
Confidence Interval (CI) were back transformed to original units
The p-value is relative to the null hypothesis Ho: Vaccine / Placebo = 1

Persistence of immune responses

The results of the follow-up Phase II clinical studies ZOSTER-018, 019 (Extension of EXPLO-CRD-004; measurements at M30 and M42), ZOSTER-011, 012, 013 (Extension of 003- measurements at M12, M24, M36), and ZOSTER-024 (Extension of 003- measurements at M48, M60, M72) provided data on the persistence of the immunogenicity of the vaccine. Additionally, the immunogenicity of HZ/su was evaluated up until 3 years after vaccination in the Phase III clinical studies ZOSTER-006 and 022, as just discussed.

Immunogenicity data after 2 doses, measured 12, 24 and 36 months after the first dose in all ZOSTER-003 study groups were also generated in ZOSTER-011, ZOSTER-012 and ZOSTER-013, respectively, in the TVC for persistence. Data at all of these time-points on gE-specific and VZV-specific (only Month 36) CMI and humoral immune response to gE in the HZ/su group were re-analysed in the ATP cohort for immunogenicity in ZOSTER-024, a phase II, open-label, single group, follow-up clinical study in 119 adults ≥60 years. The primary objective of this study was to evaluate CMI and humoral immune responses to HZ/su in older adults (≥60 YOA at enrolment in ZOSTER-003), overall and within each age cohort (60-69 YOA and ≥70 YOA at enrolment in ZOSTER-003) at Months 48, 60 and 72.

The protocol for Study ZOSTER-024 described the usage of a mixed model for the frequency of CD4 T-cells producing at least 2 immunological activation markers with log-transformed background CD4 frequency, log-transformed pre-vaccination response and the log-transformed time elapsed (measured in months) following the last vaccination as covariates. A similar approach as to that described for the CMI endpoint was to be followed for Humoral Immune response. The covariates will include pre-vaccination response and time OR the log-transformed time elapsed following the last vaccination (measured in months) according to the goodness of fit statistics (AIC or SBIC). Three models were considered for persistence of immunogenicity: Piece-wise, Power-law and Fraser. Overall, the models applied to assess persistence of antibody titre were deemed acceptable.

Data from ZOSTER-024 indicate that the vaccine-induced immune response (humoral and CMI) persists up to approximately 6 years following a 0, 2-month schedule. The median anti-gE antibody concentration was greater than 7-fold above the baseline pre-vaccination median concentration. The median frequency of gE-specific CD4[2+] T cells was greater than 3.7-fold above baseline pre-vaccination median frequency.

To allow a better assessment of persistence of immune responses, clinically more relevant endpoints for persistence were considered, such as the percentage of responders as defined by the fraction of patients above the 95 percentile of baseline measures, or the fraction of patients with a k-fold increase to baseline. Modelling of the average population would not allow conclusions on the more extreme patients, which are generally more vulnerable. Therefore, during the procedure additional analyses were performed on the ZOSTER-024 data for the persistence of the immune response of HZ/su using the percentage of responders as defined by (i) the percentage of subjects above the 95th percentile of baseline measures, and (ii) the percentage of subjects with a k-fold increase from baseline.

The percentage of responders above the 95th percentile of baseline was 99.3% at Month 3, which then declined but was still 64.7% at 72 months post-vaccination. The cumulative percentage of subjects above a specific k-fold increase declined over time, but 70.6% of subjects still presented with at least a 4-fold increase in gE-specifc humoral immune response at 72 months post-vaccination.

The decline in the cell-mediated immune (CMI) response over time seemed more substantial than that observed for the anti-gE antibody humoral response. The percentage of responders above the 95th percentile of baseline declined over time but was still 27.3% at Month 72. The percentage of subjects above a specific k-fold increase declined over time, then reached a plateau. The percentage of subjects presenting with at least a 2-fold increase in gE-specific CMI response was still 62.7% at Month 72 post-vaccination.

Correlate of protection

Currently, no correlate of protection for HZ/su has been established. The identification of a CoP was a pre-specified endpoint of the phase III efficacy studies ZOSTER-006 and 022. The analysis was performed on pooled ZOSTER-006 and ZOSTER-022 breakthrough HZ cases and was provided with the responses to the D120 LoQ. Although it is generally assumed that the immune mechanism of protection against VZV reactivation is mainly cell-mediated, investigating a CoP for CMI poses significant challenges. Therefore the Applicant decided to explore a potential correlation between efficacy and the anti-gE antibody response 1 month post-vaccination using the Applicant's gE-ELISA assay, although as said it is unclear if this specific immune response is directly involved or not in protection against VZV reactivation. Of note, the anti-gE antibody response measured by ELISA one month after the second vaccine dose has been correlated with 1) the anti-VZV neutralizing response and 2) the gE-specific CD4+ T-cell response at the same time point.

The objectives of the CoP analyses in studies ZOSTER-006 and 022 were:

1. To evaluate if the anti-gE antibody concentrations, as determined by the gE-ELISA, at Month 3 (one month post-dose 2), and/or the anti-gE antibody fold increase from baseline, as determined by gE-ELISA at month 3 (one month post-dose 2), correlate with shingles protection (based on confirmed HZ cases);
2. To determine, if possible, a protective threshold.

The statistical method used to validate the correlate of protection (Prentice method), and the statistical method used to identify a threshold (Dunning regression) are not explained here. Additional methods have also been evaluated by the Applicant. The cohorts used for the analyses include all evaluable subjects from studies ZOSTER- 006 and 022 who received two doses of the vaccine, excluding:

- subjects who were excluded from all statistical analyses due to GCP issues (i.e. one study site in Mexico);
- subjects who received vaccine doses or replacement not according to their randomization group;

- subjects who developed a confirmed case of herpes zoster (HZ) prior to blood sampling at Month 3 (one month post dose 2).

A case-cohort subsample (i.e. Cohort for CoP) was taken and consisted of (i) an immunogenicity subset randomly selected from the whole study population, and (ii) all the subjects with a confirmed HZ case.

Overall the approaches (case-cohort design, non-mechanistic CoP, predictive paradigm, continuous approach) and methodological choices (Prentice and Qin frameworks) made by the Applicant are sound and well justified. It is also agreed that an immune marker not causally involved in the clinical protection could still constitute a good non-mechanistic CoP with respect to guiding regulatory decisions, the main condition being that it should reliably predict VE (validation based on statistical criteria).

The descriptive analysis of anti-gE antibody responses measured by gE-ELISA at Month 3 (i.e. one month after dose 2) and the reverse cumulative curve (RCC) of the gE ELISA concentration measure at the same time point by study and by clinical outcome (i.e. confirmed HZ cases or no cases) show a clear distinction between the placebo and vaccine recipients distribution, and a trend for lower titres in subjects with HZ cases, including in placebo recipients, which may be an indication that a decrease in natural anti-gE antibodies is associated with a greater risk of HZ.

The correlation was estimated at the individual level (between anti-gE ELISA and probability of protection) and at the population level (between regional anti-gE ELISA GMR and regional vaccine efficacy). Both analyses suggest that probability of protection (at the individual level) and efficacy (at the population level) might be predicted based on these immune measurements, and thus that anti-gE ELISA Ab might be a useful immune marker to guide regulatory decisions in individuals ≥50 years old.

However uncertainties and limitations remain.. Furthermore, the model linking anti-gE to probability of protection still needs to be further understood. The factors that could affect immunogenicity, efficacy, and the relationship between the CoP and VE were further explored, in particular age and pre-existing immunity level. Although the effect of age on both efficacy and immunogenicity is statistically significant, this effect is considered clinically negligible given the extremely high effect of the vaccine in this immunocompetent population. Concerning pre-existing immunity, given the very high efficacy level, a clinically relevant impact of the level of pre-existing immunity on VE is considered unlikely in the immunocompetent population studied. It is acknowledged that the Applicant plans to study the CoP in their IC efficacy trial.

At this stage, the CoP is not sufficiently understood and validated to be considered as an established general CoP. However post-dose 2 anti-gE can be used as an immune marker for immunobridging in immunocompetent individuals ≥50 years of age. The extent to which this immune marker can be extrapolated to other conditions or populations will have to be discussed on a case-by-case basis, as there could be a potential impact of CMI on protection which has not been considered.Notwithstanding, it is agreed that immunobridging in certain circumstances is possible based on anti-gE non-inferiority (see section2.5.6 and 3.3).

2.5.4. Clinical studies in special populations

Immunocompromised patients

HZ is more frequent and more severe in immunocompromised individuals. No vaccine is currently available for immunosuppressed individuals.

Two phase I/II clinical studies, ZOSTER-001 and ZOSTER-015, were conducted with HZ/su in subjects with autologous hematopoietic stem cell transplant or HIV infection, respectively. A total of 135 adults, of whom 73 were ≥50 years of age, received at least one dose of vaccine, which was shown to be immunogenic and well-tolerated.

Hematopoietic stem cell transplantation (HCT) recipients, whose T cell immunity is deeply impaired, have a high 30% risk of HZ during the first year following HCT. These patients are at increased risk for viremia and visceral dissemination during VZV reactivation and subsequent complications.

2.5.4.1. ZOSTER-001

Study title: A Phase I/IIa randomized, observer-blind, placebo-controlled, multicenter study to evaluate the safety and immunogenicity of gE/AS01$_B$ in comparison to gE combined with 1/2 dose AS01$_B$ adjuvant (gE/AS01$_E$) and to saline (placebo) when administered as 2 doses or 3 doses to autologous hematopoietic stem cell transplantation (HCT) recipients.

Methods

- **Objectives and inclusion criteria**

ZOSTER-001 was conducted at 10 centres in the United States in 2009-2011.

Co-Primary objectives were:

- To evaluate the safety and reactogenicity of the gE/AS01$_B$ and gE/AS01$_E$ study vaccines in adult autologous HCT recipients;
- To compare gE-specific humoral and cellular immune responses at Month 4 (one month post-final vaccination) between subjects who received three doses of gE/AS01$_B$ vaccine (Months 0, 1 and 3), subjects who received three doses of gE/AS01$_E$ vaccine (Months 0, 1 and 3), subjects who received two doses of gE/AS01$_B$ vaccine (Months 1 and 3) and subjects who received placebo.

Secondary objectives comprised the comparison of several additional humoral and cellular immunological assessments at different time points, and the description of the incidence, duration and severity of HZ and its complications during the entire study period in each of the four study groups.

Eligible subjects were patients 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 Leukaemia (AML), and for whom there are no plans for additional HCTs.

- **Study design**

A total of 120 eligible HCT recipients had to be randomised, according to a 1:1:1:1 ratio in four parallel groups:

1. gE/AS01$_B$ 3-dose (Months 0, 1 and 3); 30 subjects.
2. gE/AS01$_E$ 3-dose (Months 0, 1 and 3); 30 subjects.
3. gE/AS01$_B$ 2-dose (placebo at Month 0 and gE/AS01$_B$ at Months 1 and 3); 30 subjects.
4. The placebo group (placebo at Months 0, 1 and 3); 30 subjects.

Month 0 was defined as 50-70 days (approximately 2 months) post-HCT. The study lasted 15 months per subject, including follow-up for 12 months after the third vaccination to assess safety and persistence of immune response.

The randomization algorithm used a minimization procedure accounting for underlying-disease strata (Hodgkin lymphoma, non-Hodgkin T cell lymphoma or acute myeloid leukemia (AML); non-Hodgkin B-cell lymphoma; myeloma). Persons in Strata 1 typically do not receive post-HCT immunosuppressive therapy, while those in the other two strata do receive post-HCT immunosuppressive therapy. Strata 2 and 3 are separated because the nature of post-HCT immunosuppressive therapy differs significantly between those populations.

- **Treatment**

The dose of the VZV-gE antigen selected for use in this study was based on the results of a phase II dose ranging study (ZOSTER-003, individuals >60YOA) with or without $AS01_B$. Based on the data of this study, the 50 µg gE antigen dose with adjuvant was selected.

Vaccination started 2 months after HCT and this was based on existing data with an inactivated varicella vaccine (Varivax) and on the need to induce strong immunity as soon as possible after HCT.

Results

- **Study population**

A total of 120 subjects were enrolled and vaccinated. A total of 110 of the 120 (91.7%) vaccinated subjects completed the active phase of the study (up to Month 4). The most common reason for withdrawal was transplant failure/recurrence of underlying malignancy.

The four groups were comparable with respect to mean age and gender distribution, baseline seropositivity rates and geometric mean concentrations (GMCs) of anti-gE antibody, underlying disease leading to HCT, prior treatment, type of HCT and source of stem cells.

The most common concomitant medication in all four groups was HZ antiviral prophylaxis (received by 96%-100% of subjects overall). The proportion of subjects in each group who received any immunosuppressant was 27% ($gE/AS01_B$ 3-dose group), 28% ($gE/AS01_E$ 3-dose group), 19% ($gE/AS01_B$ 2-dose group) and 13% (3-dose placebo group).

- **Humoral responses through Month 4 of the study**

The first dose of both vaccines elicited at least a two-fold increase in GMC of anti-gE antibody.

One month after the second dose, the GMC increased 22- and 21-fold compared to baseline for both vaccines. At this time point, the anti-gE GMC following the first dose of $gE/AS01_B$ in the 2-dose Group was 2-fold higher compared to baseline.

At Month 4, the anti-gE GMC following the third dose of $gE/AS01_B$ and $gE/AS01_E$ was 55- and 42-fold higher, respectively, compared to baseline. At this time point the anti-gE GMC following the second dose of $gE/AS01_B$ in the 2-dose Group was 25-fold higher compared to baseline. GMCs of anti-gE ab were 13,413 mIU/mL (95%CI: 4967-36,220) at Month 3 (post-dose 2) and 29,193 mIU/mL (95%CI: 11,005-77,442) at Month 4 (post-dose 3) in the $gE/AS01_B$ three dose Group. Of note, GMCs of anti-gE ab levels in healthy subject were 52,377 mIU/mL (95%CI: 50,264-54,578) at Month 3 (post-dose 2) (ZOSTER-006).

The response rate 1 Month after the first dose was similar (about 30%) in the 2-dose schedule $gE/AS01_B$ (i.e. at Month 2) and in the 3-dose schedule $gE/AS01_B$ (i.e. at Month 1). At Month 4, vaccine response rates were similar across the 3 vaccinated Groups.

The superiority of three doses of $gE/AS01_B$ versus three doses of placebo was demonstrated, as well as the superiority of two doses of $gE/AS01_B$ versus three doses of placebo (with respect to the co-primary objective relative to anti-gE humoral immune response at Month 4). Geometric means fold increase of anti-gE antibody ELISA concentrations over placebo at Month 4 were:

- 74.41 (95%CI: 25.74-215.09) in the 3-dose gE/AS01$_B$ group.
- 42.20 (95%CI: 16.07 110.82) in the 2-dose gE/AS01$_B$ group.
- 52.11 (95%CI: 17.36 156.41) in the 3-dose gE/AS01$_E$ group.

The anti-gE humoral immune response in the gE/AS01$_B$ 3-dose group was not significantly higher compared to the gE/AS01$_E$ 3-dose vaccine at any post-vaccination time point as evidenced by a LL of the 95% CI < 1 for the fold increase in anti-gE GMC gE/AS01$_B$ over gE/AS01$_E$ for each comparison.

- **gE- and VZV-specific Cell mediated immune responses through M4 of the study**

The superiority of three doses of gE/AS01$_B$ versus three doses of placebo was demonstrated as well as the superiority of two doses of gE/AS01$_B$ versus three doses of placebo, with respect to cellular immune response to gE at Month 4. Geometric means fold increase (over placebo) in the frequency of CD4(2+) T-cells at Month 4 following induction with gE were:

- 32.31 (95%CI: 17.78-58.71) in the 3-dose gE/AS01$_B$ group.
- 9.51 (95%CI: 5.23-17.32) in the 2-dose gE/AS01$_B$ group.
- 16.49 (95%CI: 8.87-30.68) in the 3-dose gE/AS01$_E$ group.

- **Combined gE-specific humoral and cellular immune response multivariate assessment**

The superiority of three doses of gE/AS01$_B$ compared to two doses gE/AS01$_B$ was demonstrated at all time points.

- **Persistence of the immune response 12 months after the third vaccination**

At month 12, the anti-gE GMC point estimates had decreased by 3- to 4-fold in the three vaccine groups compared to Month 4.

Exploratory group comparisons at Month 15 suggested higher concentrations of anti-gE in gE/AS01$_B$ (2 and 3 doses) and gE/AS01$_E$ (3 doses) as compared to placebo (the lower limit of the 95% CI on the GM ratio [vaccine group/Placebo] was greater than 1).

Exploratory groups comparison at Month 15 suggested a higher frequency of CD4(2+) T-cells after induction with gE between gE/AS01$_B$ (2 and 3 doses) and gE/AS01$_E$ (3 doses) as compared to placebo (the lower limit of the 95% CI on the GMCs ratio [vaccine group/Placebo] was greater than 1).

This analysis did not support a difference in the frequency CD4(2+)T-cells after induction with gE between gE/AS01$_B$ 3-dose and gE/AS01$_E$ 3-dose group (the lower limit of the 95% CI on the GMCs ratio [gE/AS01$_B$ 3-dose group/gE/AS01$_E$ 3-dose group] was less than 1).

- **Occurrence of HZ**

Four cases of confirmed HZ (3 by PCR and 1 confirmed by the Applicant's expert) were reported during the course of the study up to Month 15 (i.e. 12 months post dose 3): two in the gE/AS01$_E$ 3-dose group and two in the placebo group.

- **Conclusion for study ZOSTER-001**

The 3-dose and 2-dose gE/AS01$_B$ regimens and the 3-dose gE/AS01$_E$ regimen elicited robust humoral and cellular immune responses superior to placebo in adult subjects who had undergone autologous HCT within 50 to 70 days prior to the first dose of vaccine.

Study ZOSTER-001 was well justified and methodologically adequate. The study was stratified for underlying disease responsible for the HCT. Data collected during the study allowed to show that groups are roughly comparable with respect to potential confounders such as the diagnosis leading to

the HCT, the treatment regimen prior to HCT, and antiviral prophylaxis. The proportion of subjects who received any immunosuppressant was higher in the gE/AS01$_B$ 3-dose group and the gE/AS01$_E$ 3-dose group in comparison to the two other groups (gE/AS01$_B$ 2-dose group and 3-dose placebo group). Despite this imbalance, immunogenicity levels were highest in the gE/AS01$_B$ 3-dose group and the gE/AS01$_E$ 3-dose group.

With all three schedules, the second dose elicited a 21-25 fold increase in GMC of anti-gE antibody. Following the third dose, anti-gE GMC was 55- and 42-fold higher, respectively in the gE/AS01$_B$ and gE/AS01$_E$ vaccines Groups, which is comparable to the responses induced in immunocompetent individuals. Responses in terms of CMI were also comparable. Results in terms of responses rates however were lower than in immunocompetent individuals, even with 3 doses.

Three doses of gE/AS01$_B$ administered at Months 0, 1 and 3 were significantly more immunogenic than 2 doses of gE/AS01$_B$ administered at Months 1 and 3.

The anti-gE humoral immune response in the gE/AS01$_B$ 3-dose group was not significantly higher compared to the gE/AS01$_E$ 3-dose vaccine at any post-vaccination time point. However, three doses of gE/AS01$_B$ tended to induced slightly better results with respect to several immunogenicity endpoints than three doses of gE/AS01$_E$.

Data showed that the candidate vaccines induced humoral and CMI immune responses that persisted until Month 15 (higher than placebo).

Thus HZ/su elicited a very robust immune response, although lower than in immunocompetent subjects, with the 3-dose schedule performing better than 2 doses. The clinical consequences of these findings are impossible to determine given the absence of correlate of protection. An efficacy study is currently ongoing in autologous HCT recipients ≥18 YOA (ZOSTER-002).

2.5.4.2. ZOSTER-015

Study title: A phase I/IIa randomized, observer-blind, placebo-controlled, multicentre study to evaluate the safety and immunogenicity of gE/AS01$_B$ in comparison to placebo when administered as 3 doses to adult HIV-infected subjects.

ZOSTER-015 was conducted in Germany, the United Kingdom (UK), and the United States (US).

Three cohorts of HIV-infected subjects were enrolled (n=123 of whom 28 ≥50YOA):

1. ART High CD4 cohort (n=74): ART-treated subjects with a CD4 T cell count: ≥200 cells/mm^3.
2. ART Low CD4 cohort (n=14): ART-treated subjects with a CD4 T cell count: 50-199 cells/mm^3.
3. Non-ART High CD4 cohort (n=15): ART-naïve HIV-infected subjects with a CD4 T cell count of ≥500 cells/mm^3.

Eligible subjects were randomised (3:2) to receive 3 doses of gE/AS01$_B$ or Placebo at Month 0, 2 and 6. A total of 123 eligible subjects were vaccinated (74 subjects in the 3-dose vaccine group and 47 subjects in the placebo group), and 116 subjects completed the study. The mean age of the study participants was 46.0 years (range: 23-74 years) in the ATP cohort for immunogenicity (N=91; primary analysis cohort for immunogenicity).

The primary objectives of the study were:

- To evaluate the safety and reactogenicity of the gE/AS01$_B$ study vaccine in HIV-infected subjects, by ART and CD4 count cohorts, and overall;

- To estimate the gE-specific humoral and cellular immune responses at Month 7 (one month post-final vaccination) in subjects who received three doses of gE/AS01$_B$ vaccine (Months 0, 2 and 6) in comparison to subjects who received placebo, in ART and non-ART cohorts presenting high CD4 counts at enrolment.

- **Results of cell-mediated immunogenicity**

In the gE/AS01$_B$ group, the observed median frequency of gE-specific CD4[2+] T cells (per 10^6 total CD4 T cells) at Month 7 was: 2546.4 for the ART High CD4 cohort, 12547.8 for the ART Low CD4 cohort, and 861.2 for the Non-ART High CD4 cohort. In the Placebo group, the observed Median frequency of gE-specific CD4[2+] T cells (per 10^6 total CD4 T cells) varied by cohort between 84.3 and 161.7 at month 7. Overall HZ/su induced robust gE-specific CMI vs. placebo whatever the cohort but no meaningful conclusions can be drawn on cohort-specific results due to the limited number of subjects.

The superiority of HZ/su compared to placebo in terms of the gE-specific CMI response one month after the third vaccination was demonstrated in subjects with high CD4 T cell count (ART+ and ART-naïve sbjs together), but could not be demonstrated in high CD4 T cell count ART-naïve subjects as too few subjects with valid results were included in this cohort.

- **Results of humoral immunogenicity**

Immunogenicity analysis was performed on the ATP cohort (primary analysis) and on the TVC. The analysis of immunogenicity by HIV status (ART High CD4, ART Low CD4, non-ART High CD4 cohorts) was performed on the ATP cohort for immunogenicity.

The superiority of gE/AS01$_B$ compared to placebo was demonstrated with respect to the gE specific humoral immune response at Month 7 (one month after the third vaccination) in subjects with high CD4 T cell count (≥200 cells/mm3 for subjects on ART and ≥500 cells/mm3 for ART-naïve subjects) at enrolment (LL of the 90% CI on the GM ratio [HZ/su group /Placebo group] was greater than 3) (Table 37).

Table 36. Geometric means and ratio of gE/AS01$_B$ over placebo in anti-gE antibody ELISA concentrations at Month 7 in subjects with high CD4 T-cell count at enrolment (ATP cohort for immunogenicity) in ZOSTER-015

		Geometric Mean			Geometric Mean Ratio			
			95 % CI			90 % CI		
Group	N	Value	LL	UL	Value	LL	UL	P-value for the ratio
gEAS01B	48	56305.23	38854.59	81593.42	46.22	33.63	63.53	<.0001
Placebo	33	1218.17	1080.80	1373.01	.	.	.	.

gEAS01B = 50µg/AS01B - 3 doses
Placebo = Placebo - 3 doses
N = number of subjects in a given category with available results
LL = Lower Limit, UL = Upper Limit and CI = Confidence Interval
Confidence Interval (CI) were backtransformed to original units
A vaccine group presents significantly higher humoral response as compared to placebo when the lower limit of the CI of the ratio of geometric means is greater than 3
The p-value is relative to the null hypothesis Ho: Vaccine / Placebo =< 1

The superiority of gE/AS01$_B$ compared to placebo was demonstrated in terms of the gEspecific humoral immune response one month after the third vaccination in the ART High CD4 and non-ART High CD4 cohorts (see table 38: LL of the 90% CI on the GM ratio [HZ/su /Placebo group] was greater than 1).

Table 37. Geometric means and ratio of gE/AS01$_B$ over placebo in anti-gE antibody ELISA concentrations at Month 7 in subjects with high CD4 T-cell count at enrolment by HIV status (ATP cohort for immunogenicity) in ZOSTER-015

			Geometric Mean			Geometric mean ratio			
				95 % CI			90 % CI		
Sub-Group	Group	N	Value	LL	UL	Value	LL	UL	P-value for the ratio
ARTHCD4	gEAS01B	43	66404.30	52325.85	84270.61	63.25	46.24	86.52	<.0001
	Placebo	29	1049.79	788.07	1398.45	.	.	.	.
NARTHCD	gEAS01B	5	25893.26	10649.57	62956.59	18.04	5.91	55.02	0.0010
	Placebo	4	1435.71	528.20	3902.45	.	.	.	.

- **Persistence of immune responses**

Data showed that gE-specific humoral and cell-mediated immune responses persisted in the gE/AS01$_B$ group at Month 18 (1 year post third vaccination) relative to pre-vaccination levels. GMC of anti-gE abs at Month 18 in all subjects in the ATP cohort for persistence were 25.242.2 mIU/mL (95% CI: 19,618.9; 32,477.3) vs. 1237.2 mIU/mLl (95% CI: 890.7 1718.4) pre-vaccination. Placebo GMCs in all subjects were 904 mIU/mL ((95% CI: 585.0 1397.0) pre-vaccination and 918 mIU/mL (95% CI: 588.0 1433.1) at Month 18. In the gE/AS01$_B$ group, the observed Median frequency of gE-specific CD4[2+] T-cells per 10^6 total CD4 T-cells (i.e. background subtracted) was 1533.0 at Month 18 and 112.8 at Month 0. In the Placebo group, the observed Median frequency of gE-specific CD4[2+] T-cells was 71.8 at Month 18 and 52.1 at Month 0.

- **Conclusion from study ZOSTER-015**

The 3-dose gE/AS01$_B$ regimen elicited robust humoral and cellular immune responses in HIV+ adult subjects, whatever the cohort (ART High CD4 cohort, ART Low CD4 cohort, Non-ART High CD4 cohort). Responses tended to be stronger in the 'ART High CD4' cohort. However, the number of subjects with low CD4 levels was low, and does not allow to firmly conclude for this group. Strong responses were observed after two doses. The third dose still induced an increase in anti-gE levels, but this increase was marginal for gE specific CD4[2+] T cells. gE-specific humoral and CMI responses persisted in the vaccine group at Month 18 (1 year post third vaccination) relative to pre-vaccination levels. Results also showed that HZ/su induced robust VZV-specific CMI and humoral responses in HIV infected subjects (not shown).

Overall, responses were of the same magnitude as those found in immunocompetent individuals in other studies.

2.5.5. Supportive studies

2.5.5.1. ZOSTER-007

Study Title: A phase III, randomized, double blind multicentre study, to evaluate consistency, immunogenicity, safety and reactogenicity of 3 lots of HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age.

- **Objectives and endpoints**

The primary objective of the trial was to demonstrate lot-to-lot consistency in terms of anti-gE humoral immunogenicity between three production lots of the HZ/su vaccine one month after the second dose (Month 3). The primary endpoint was anti-gE antibody concentration, as determined by ELISA, at Month 3. The criteria for consistency was defined as follows: one month after the second dose, the

two-sided 95%CI of the geometric mean concentration (GMC) ratio between all pairs of lots are to be within [0.67, 1.5].

The main secondary objective was to demonstrate the consistency of three manufacturing lots of HZ/su vaccine in terms of vaccine response rates one month after the second vaccine dose. For this objective the criteria for consistency was defined as follows: for each pair-wise comparison, the 2-sided 95%CI on the lot difference in vaccine response rate (VRR) to the HZ/su vaccine (in terms of the humoral anti-gE immune response) one month after the second vaccine dose are to be within the [-10%; +10%] margin. This secondary objective was assessed in a hierarchical manner.

- **Study design**

Generally healthy subjects ≥50 years of age were randomized (1:1:1) to the three groups (HZ/su Lot A, HZ/su Lot B, HZ/su Lot C). The randomisation algorithm used a minimisation procedure accounting for centre, age (50-59 YOA, 60-69 YOA and ≥ 70 YOA) and country. Each group had to comprise 217 subjects.

The subjects received one of three production lots of the HZ/su vaccine, each composed of unique randomized combinations of antigen and adjuvant lots, at 0 and 2 months.

The study was double-blind.

- **Study results**

A total of 651 enrolled subjects received at least 1 dose of vaccine (TVC) and 622 subjects (95.5% of the TVC) were included in the ATP cohort for immunogenicity. The main reason for exclusion from the ATP was 'no vaccine administration at Visit 2 Month 2'.

For the TVC, mean age was 64.5±9.0 years at the time of the first vaccination. There were 55.3% females overall. The demographic characteristics were similar for the ATP cohort for immunogenicity. The groups were similar with respect to age. The proportion of females was slightly higher in Lot B relative to the other lots.

The primary analysis was based on the ATP cohort for analysis of immunogenicity. A second complimentary analysis based on the TVC was performed since the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was more than 5% (14/216) in Lot C.

Anti-gE abs GMCs by ELISA adjusted for baseline concentration (adjusted GMC) were as follows (ATP cohort for immunogenicity):

- In HZ/su Lot A group: 59,263.5 mIU/mL (95%CI: 54,504.0-64,438.5).
- In HZ/su Lot B group: 61,033.6 mIU/mL (95%CI: 56,132.0-66,363.3).
- In HZ/su Lot C group: 62,053.6 mIU/mL (95%CI: 57,132.6-67,398.5).

The lot-to-lot consistency in terms of anti-gE humoral immunogenicity between the 3 manufacturing lots of the HZ/su vaccine one month post-dose 2 was demonstrated as all 95% CIs of the GMC ratios between all pairs of lots were within [0.67, 1.5], as shown below:

- Lot A over Lot B: 0.97 (95%CI: 0.86 1.09).
- Lot A over Lot C: 0.96 (95%CI: 0.85 1.08).
- Lot B over Lot C: 0.99 (95%CI: 0.88 1.10).

Vaccine response rate in terms of the anti-gE antibody ELISA concentrations at one month post-dose 2 were 95.7%, 97.6% and 97.5% respectively in Lot A group, Lot B group and Lot C group.

The secondary confirmatory objective for consistency of the 3 manufacturing lots of HZ/su vaccine in terms of VRR one month post-dose 2 was met as for each pair-wise comparison, the 2-sided 95% CIs on the lot difference in VRR to the HZ/su vaccine (in terms of the humoral anti-gE immune response) were within the [-10%; +10%] margin:

- Lot A minus Lot B: -1.90 (-5.86, 1.72),
- Lot A minus Lot C: -1.81 (-5.79, 1.92),
- Lot B minus Lot C: 0.09 (-3.30, 3.58).

The results were similar for the TVC cohort.

- **Conclusions for study ZOSTER-007**

Variability in production process of the final formulation of HZ/su does not pose specific issue. The lots used in the clinical trials are deemed representative of the commercial batches. The number of three lots examined in this Lot-to-Lot consistency study is thus considered as sufficient.

The criteria for concluding comparability between lots was pre-defined and based on anti-gE antibody (primary immunological endpoints throughout the development of HZ/su), which is endorsed. In this study, the consistency of the 3 manufacturing lots of HZ/su vaccine was demonstrated with respect to anti-gE GMC ratios and VRR. Differences between groups with respect to anti-gE were actually very small. Given the absence of correlate of protection the clinical relevance of the observed differences remains uncertain. However, the clinical impact of such differences is likely to be negligible.

Anti-gE antibody ELISA GMCs measured for the 3 lots were similar to those observed in study ZOSTER-006.

2.5.5.2. ZOSTER-004 [3]

Study title: A phase III, randomized, open-label, multicentre clinical trial to assess the immunogenicity and safety of HZ/su vaccine when co-administered with quadrivalent influenza vaccine FLU D-QIV versus separate administration of the two vaccines in adults aged 50 years and older.

The immunogenicity of FLU-D-QIV when co-administered with HZ/su was also assessed. The study was conducted in Canada, Germany and the United States.

A total of 828 adults ≥50 YOA were enrolled and randomized 1:1 to either receive i) one dose of HZ/su and one dose of FLU-D-QIV at Month 0, while a second dose of HZ/su was administered at Month 2 (Co-ad group) or ii) one dose of FLU-D-QIV at Month 0, while 2 doses of HZ/su were administered at Months 2 and 4 (Control group). The mean age was 63.4 YOA (range: 50 to 92 YOA).

The ATP cohort for immunogenicity included 781 subjects and the demographic characteristics were acceptable and similar to the TVC.

- **Study objectives**

Primary Objectives

- To evaluate the vaccine response rate (VRR) to the HZ/su (based on the humoral immune response) one month after the last vaccine dose in the HZ/su-FLU-D-QIV co-administration group.

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- To demonstrate non-inferiority in terms of humoral immune response of two doses of the HZ/su when FLU-D-QIV vaccine is co-administered with the first HZ/su dose, compared to two doses of HZ/su given alone, one month after the last vaccine dose.
- To demonstrate non-inferiority (in terms of HI antibody GMTs) of one dose of FLUD-QIV vaccine when co-administered with the first HZ/su dose compared to one dose of FLU-D-QIV vaccine given alone, for the four strains included in FLU-DQIV vaccine, at Day 21 post vaccination.

All co-primary objectives needed to be met. Therefore, no adjustment was needed for the type I error of each primary comparison.

Secondary Objectives

- To demonstrate non-inferiority (in terms of HI antibody SCRs) of one dose of FLUD-QIV vaccine when co-administered with the first HZ/su dose compared to one dose of FLU-D-QIV vaccine given alone, for the four strains included in FLU-DQIV vaccine, at Day 21 post vaccination.
- To assess the immunogenicity of FLU-D-QIV vaccine in terms of GMTs, SPR at Days 0 and 21 and SCR and Mean Geometric Increase (MGI) at Day 21. The assessment of SPR and SCR was based on US FDA criteria [The lower limit of the 95% confidence interval for SCR should be ≥40% in subjects aged 18-64 YOA or ≥30% in subjects ≥65 YOA; The lower limit of the 95% confidence interval for SPR should be ≥70% in subjects aged 18-64 YOA or ≥60% in subjects ≥65 YOA.]
- To evaluate the safety and reactogenicity following administration of HZ/su and FLU-D-QIV vaccines, up to one month post last vaccination, and during the whole follow-up period.

- **Immunogenicity results**

All co-primary objectives were met:

- The objective with respect to VRR was met as the LL of the 95% CI of the VRR for anti-gE Ab concentrations in the HZ/su-FLU D-QIV co-administration group was 93.3% which was greater than the pre-defined criteria of >60%.
- The non-inferiority of HZ/su co-administered with FLU-D-QIV compared to HZ/su administered alone with respect to GMCs for anti-gE antibodies was demonstrated as the UL of the 95% CI for the GMC ratio of the Control group over the HZ/su-FLU D-QIV co-administration group was 1.2 which was below the pre-defined criteria for non-inferiority of ≤1.5.
- The non-inferiority of FLU-D-QIV (all four strains) co-administered with HZ/su compared to FLU-D-QIV administered alone with respect to GMTs for anti-HI antibodies was demonstrated as the UL of the two-sided 95% CI for the GMT ratio of the Control group over the HZ/su-FLU D-QIV co-administration group was 1.2 which was below the pre-defined criteria for non-inferiority of ≤1.5.

The secondary objective of the non-inferiority of FLU-D-QIV (all four strains) coadministered with HZ/su compared to FLU-D-QIV administered alone with respect HI antibody SCRs was partially met since the UL of the two-sided 95% CI for the SCR difference of the Control group minus the HZ/su-FLU D-QIV co-administration group was above the pre-defined non-inferiority criterion of 10% for the strain B/Victoria (12.49%) but was below that criterion for strains A/H1N1 (7.35%), A/H3N2 (6.57%), B/Yamagata (4.31%).

The US FDA criteria for the HI antibodies SPR were met for all FLU D-QIV vaccine strains in both age groups and in both treatment groups, as the LL of the 95% CI for SPR was ≥ 70% in subjects aged 50-64 years of age and was ≥ 60% in subjects ≥65 years of age for all strains.

The US FDA criteria for the HI antibodies SCR were only reached in both age groups and in both treatment groups for the H1N1 strain, since the LL of the 95% CI for SCR was ≥ 40% in subjects aged 50-64 years of age and was ≥30% in subjects ≥65 years of age for that strain. In subjects 50-64 YOA, the US FDA criteria for SCR were also reached for the B/Victoria strain in the control group and for the B/Yamagata strain in the Co-ad group. In subjects ≥65 YOA, the US FDA criterion for SCR was not reached for any strains other than the H1N1 strain in any of the treatment groups.

2.5.5.3. ZOSTER-026

Study title: A phase III, randomised, open-label, multicentre, clinical trial to assess the safety and immunogenicity of HZ/su vaccine when administered intramuscularly according to a 0,2-month schedule, a 0,6-month schedule or a 0,12-month schedule in adults aged 50 years or older.

- **Co-Primary objectives**

1. To evaluate vaccine response rate (VRR) for anti-gE humoral immune responses at one month post-dose 2 in the 0,6-month and 0,12-month schedule groups.

Criterion to be used: The lower limit of the 97,5% confidence interval (CI) of the VRR for anti-gE enzyme-linked immunosorbent assay (ELISA) antibody concentrations at one month post-dose 2 in the 0,6-month or 0,12-month schedule groups is at least 60%.

If the objective above is met, the following objective will be evaluated:

2. To demonstrate the non-inferiority in terms of anti-gE humoral immune response one month post-dose 2 given according to a 0,6- or a 0,12-month schedule compared to a 0,2-month schedule.

Criterion for non-inferiority: The upper limit of the 97,5% CI for the anti-gE ELISA geometric mean concentration (GMC) ratio (0,2-month schedule over 0,6- or 0,12-month schedule) at one month post-dose 2 is below 1.5.

- **Study methods**

This was a phase III, open-label, randomised, multicentre study with three parallel groups conducted at sites in the US and Estonia in 2013-2015. Generally healthy male or female eligible subjects aged 50 years or older were randomised to group Gr0-2, Gr0-6 or Gr0-12 according to a 1:1:1 ratio. Subjects in each group were stratified by age with a minimum of 35 subjects in each stratum (50-59 YOA, 60-69 YOA and ≥ 70 YOA strata). Target enrolment was approximately 354 eligible subjects in order to have a sample size of 300 evaluable subjects (100 subjects per group).

The vaccination schedules were as follows: one dose of HZ/su vaccine at Visit Day 0 and one dose at Visit Month 2 or Month 6 or Month 12 in the respective groups Gr0-2, Gr0-6 or Gr0-12. The total duration of the study was approximately: 14, 18 and 24 months for groups Gr0-2, Gr0-6 and Gr0-12 respectively.

- **Study results**

A total of 354 subjects were randomised and vaccinated according to 3 groups (119 in Gr0-2, 119 in Gr0-6, 116 in Gr0-12). The mean age was 64.2 ±8.9 years at the time of the first vaccination, and age

was similar across groups. There were slightly more females in the Gr0-2 group (75.6%) as compared to the Gr0-6 group (64.7%) and the Gr0-12 (68.1%)

Of the 354 subjects in the TVC, 343 subjects were included in the ATP cohort for immunogenicity and 342 subjects were included in the ATP cohort for persistence. A primary analysis for safety/immunogenicity was done when all subjects had completed one month follow-up after the last vaccine dose for each group. An end of study analysis was done when all subjects had completed 12 months follow-up after the last vaccine dose for each group.

- **Confirmatory analyses**

The co-primary objectives to evaluate VRR for anti-gE humoral immune responses at one month post-dose 2 in the 0,6-month and 0,12-month schedule groups were met as shown in the Table below.

Table 38. Vaccine response rates for anti-gE antibody ELISA concentrations at one month post-dose 2 in Gr 0-6 and Gr 0-12 groups with 97.5 % CI (ATP cohort for immunogenicity)

		Vaccine response			
				97.5% CI	
Group	N	n	%	LL	UL
Gr 0-6	114	110	96.5	90.4	99.2
Gr 0-12	110	104	94.5	87.6	98.3

Gr 0-6 = One dose of HZ/su at Visit Day 0 and one dose at Visit Month 6
Gr 0-12 = One dose of HZ/su at Visit Day 0 and one dose at Visit Month 12
Vaccine response defined as:
For initially seronegative subjects, antibody concentrations at post-vaccination ≥ 4 fold the cut-off for Anti-gE (4x97 mIU/ml)
For initially seropositive subjects, antibody concentrations at post-vaccination ≥ 4 fold the pre-vaccination antibody concentration
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
97.5% CI = exact 97.5% confidence interval, LL = Lower Limit, UL = Upper Limit

The co-primary objective to demonstrate the non-inferiority in terms of anti-gE humoral immune response one month post-dose 2 given according to a 0,6-month schedule compared to a 0,2-month schedule was met as shown in Table 40, since the 97.5% CI upper limit of the antibody concentration ratio was below 1.5.

Table 39. Adjusted ratios of Gr 0-2 over Gr 0-6 anti-gE antibody ELISA concentrations GMCs at one month post-dose 2 (ATP cohort for immunogenicity)

Gr 0-2				Gr 0-6				Adjusted GMC ratio (Gr 0-2 / Gr 0-6)		
		97.5% CI*				97.5% CI*			97.5% CI	
N	Adjusted GMC	LL	UL	N	Adjusted GMC	LL	UL	Value	LL	UL
118	44352.6	39208.5	50171.5	114	38137.8	33642.5	43233.7	1.16	0.98	1.39

Gr 0-2 = One dose of HZ/su at Visit Day 0 and one dose at Visit Month 2
Gr 0-6 = One dose of HZ/su at Visit Day 0 and one dose at Visit Month 6
Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration and group age
N = Number of subjects with both pre- and post-vaccination results available
97.5% CI* = 97.5% confidence interval for the adjusted GMC (Ancova model: adjustment for baseline concentration and group age)- pooled variance/ LL = lower limit, UL = upper limit
97.5% CI = 97.5% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration and group age)- pooled variance/ LL = lower limit, UL = upper limit

The co-primary objective to demonstrate the non-inferiority in terms of anti-gE humoral immune response one month post-dose 2 for HZ/su given according to a 0,12-month schedule compared to a

0,2-month schedule was not met as the UL of the 97.5% CI for the anti-gE ELISA GMC ratio (Gr0-2 over Gr0-12) at one month post-dose 2 was 1.53 (not below 1.5) (Table 41).

Table 40. Adjusted ratios of Gr 0-2 over Gr 0-12 anti-gE antibody ELISA concentrations GMCs at one month post-dose 2 (ATP cohort for immunogenicity)

Gr 0-2				Gr 0-12				Adjusted GMC ratio (Gr 0-2 / Gr 0-12)		
		97.5% CI*				97.5% CI*			97.5% CI	
N	Adjusted GMC	LL	UL	N	Adjusted GMC	LL	UL	Value	LL	UL
118	44201.0	37183.6	52542.7	110	37019.9	30945.7	44286.3	1.19	0.93	1.53

Gr 0-2 = One dose of HZ/su at Visit Day 0 and one dose at Visit Month 2
Gr 0-12 = One dose of HZ/su at Visit Day 0 and one dose at Visit Month 12
Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration and group age
N = Number of subjects with both pre- and post-vaccination results available
97.5% CI* = 97.5% confidence interval for the adjusted GMC (Ancova model: adjustment for baseline concentration and group age)- pooled variance/ LL = lower limit, UL = upper limit
97.5% CI = 97.5% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for baseline concentration and group age)- pooled variance/ LL = lower limit, UL = upper limit

- **Estimation of vaccine efficacy based on the CoP Dunning model**

To further substantiate the clinical significance of the data from ZOSTER-026, the Applicant was asked during the procedure to predict the efficacy of the 0, 6-month (and 0, 2-month) schedule based on the anti-gE ELISA concentration one month post-dose 2 observed in ZOSTER-026 study using the Correlate of Protection Dunning model (refer to section 2.5.3 on the Correlate of protection). The results are presented here below:

Vaccine group	Predicted vaccine efficacy		
	Point estimate	95% CI	
		LL	UL
0,2-month	93.1	90.8	95.3
0,6-month	92.0	89.6	94.4

The efficacy estimates predicted by the model are very similar (point estimates respectively 93% and 92%), and also very close to the vaccine efficacy data of the ZOSTER-006 trial.

- **Conclusion for Study ZOSTER-026**

No efficacy data was generated for the 0, 6-month schedule. Non-inferiority in terms of anti-gE humoral immune response one month post-dose 2 was demonstrated for the 0,6-month schedule compared to a 0,2-month schedule (primary endpoints met), although GMCs were slightly lower for the 0,6-month schedule.

The primary objective was met if the lower limit (LL) of the protocol-defined confidence interval (CI) of the VRR for post Dose 2 anti-gE ELISA Ab concentrations was equal to or above a threshold of 60%. The optimal threshold (i.e., 4-fold increase of the anti-gE Ab concentrations) that discriminates a 'non-responder' population from a 'responder' population was defined using Receiver Operation Characteristic (ROC) curves. The ROC curve analysis was not intended to define the "adequate" vaccine-induced protective response, but the fold increase over pre-vaccination in humoral anti-gE ELISA responses that best balances the specificity and sensitivity in the ability to separate the vaccine responses post Dose 2 from placebo individual responses. The 60% criterion was selected as it was considered as an acceptable percentage of subjects who meet the definition of a vaccine responder. The rationale behind the criteria used to evaluate the primary objectives of ZOSTER-026 is endorsed.

No comparability data on CMI were generated for the 0, 6-month schedule vs 0, 2-month schedule. There is no clinically validated general correlate of protection for HZ/su. CMI responses are considered key in the prevention of VZV reactivation. The Applicant has opted for using anti-gE antibody ELISA concentrations GMCs for their co-primary endpoint, which is acknowledged. However, given the importance of CMI, the demonstration of the non-inferiority of the 0,6-month schedule compared to a 0,2-month schedule in terms of gE-specific CMI would have been reassuring.

The Applicant justified how a change of timing of the second doses could affect the CMI responses, based on theoretical considerations and on limited experience with this vaccine and with other AS01 vaccines. This evidence suggests that a gE-specific CD4 T cell memory response is already established after 1 dose of HZ/su. After a high level of proliferation, the antigen-specific CD4 T cells differentiate into memory cells that could persist for at least 10 months after a single administration of 100 µg gE/AS01$_B$. Thus, the recall response to the second dose of HZ/zu can be established at 6 months after the first dose. Whether the recall responses will be in the same range as established for a 0, 2 month schedule cannot be concluded at the moment. The Applicant thus provided some data suggesting that the CMI recall responses could be elicited upon a second dose of HZ/su given at either Month 2 or 6.

Although the data presented are limited, they are consistent with the concept that increasing the interval between vaccine doses generally does not impair the immune responses to live and inactivated vaccines. The justification provided by the Applicant is considered as credible and relevant.

The Applicant was asked to substantiate the clinical significance of the data from the ZOSTER-026 based on their CoP Dunning model (predicted efficacy of the 0,6 schedule based on the anti-gE ELISA concentration one month post-dose 2 observed in ZOSTER-026 study). In addition, the Applicant has estimated the predicted efficacy of the 0, 2-month schedule, based on the anti-gE data generated in the ZOSTER-026 study. Both predicted efficacy estimated by the model are very similar (point estimates and 95% CI respectively 93.1% (90.8%-95.3%) and 92.0% (89.6%-94.4%)), and also very close to the vaccine efficacy data of the ZOSTER-006 trial.

Overall, the inclusion of the 0,6 month schedule in the SmPC is considered acceptable based on the available data. However, due to the limitations of these data, the SmPC should refer to the 0,2 month schedule as preferable. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose.

2.5.5.4. ZOSTER-033

This phase III, non-randomized, open-label, multi-center clinical trial assessed the immunogenicity and safety of HZ/su when administered intramuscularly on a 0 and 2 Month schedule to adults ≥50 YOA with a prior episode of HZ (physician-documented). This study was conducted 2013/2014 in Canada and the Russian Federation. The target enrolment was approximately 96 eligible subjects to provide 84 subjects evaluable for immunogenicity. Subjects were stratified by age: 50- 59 YOA; 60-69 YOA and ≥70 YOA. The Applicant used historical controls in ZOSTER-033, but no formal analysis was performed with historical controls.

In ZOSTER-033, the immunogenicity of HZ/su in subjects with previous HZ was determined based on the humoral vaccine response rate (VRR) in terms of anti-gE ELISA Abs as the primary objective. The VRR was defined the percentage of subjects who have at least a 4-fold increase in post Dose 2 Ab concentration over pre-vaccination for seropositive subjects at baseline (or above the cut-off value for seropositivity for seronegative subjects at baseline).

The primary objective in ZOSTER-033 was met if the lower limit (LL) of the protocol-defined confidence interval (CI) of the VRR for post Dose 2 anti-gE ELISA Ab concentrations was equal to or above a

threshold of 60%. The optimal threshold (i.e., 4-fold increase of the anti-gE Ab concentrations) that discriminates a 'non-responder' population from a 'responder' population was defined using Receiver Operation Characteristic (ROC) curves. The ROC curve analysis was not intended to define the "adequate" vaccine-induced protective response, but the fold increase over pre-vaccination in humoral anti-gE ELISA responses that best balances the specificity and sensitivity in the ability to separate the vaccine responses post Dose 2 from placebo individual responses. The 60% criterion was selected as it was considered as an acceptable percentage of subjects who meet the definition of a vaccine responder. The justification for the criteria used to evaluate the immunogenicity primary objective of the study was accepted.

In this study, it was shown that the humoral immune response obtained at Month 3 after 2 doses of HZ/su administered 2 months apart in adults aged ≥50 years with a prior history of HZ is consistent with that seen in studies conducted with HZ/su in older adults without a documented history of HZ (VRR and anti-gE antibody concentration). The anti-gE GMC at 1 month after the last vaccine dose was 47,758.7 mIU/mL (95% CI: 42,258.8; 53,974.4) and the median fold increase of anti-gE concentrations from pre-vaccination was 25.6 (Q1: 10.2; Q3: 43.8). The vaccine response rate (anti-gE antibodies) at 1 month post-vaccination was 90.2% (95% CI: 81.7; 95.7).

Pre-vaccination GMCs were higher in subjects who had within the last 4 years an episode of HZ compared to subjects with HZ-episodes 5 to 10 years ago. The VRRs 14.5 were to be lowest in participants with more recent HZ episodes (within 4 years prior to vaccination) compared to 35.8 (5 to 9 years) and 38.9 (more than 10 years). However no apparent differences were noticed in anti-gE antibody concentrations after 2 doses of HZ/su in subjects with history of HZ.

During this study, 9 suspected HZ cases were reported in 6 participants until Month 14 (6.3%) which was higher than the recurrence rate reported in the literature (up to 6.2% over a 7.3 year follow-up period) especially in the context of the 97.2% efficacy shown in a phase III clinical trial in adults aged 50 years and older. As the study was not designed to formally evaluate HZ recurrence (uncontrolled study with a limited sample size and no laboratory confirmation of the cases), conclusions regarding this specific aspect of the study have to be considered with caution. Further investigation is needed (see section 2.5.6).

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

- **Study design and conduct**

The pivotal studies ZOSTER-006 and ZOSTER-022 were randomised placebo controlled safety and efficacy trials of nearly identical study design. Beside the age of the subjects, the only other difference was that only subjects enrolled into ZOSTER-006 study were randomly allocated to be part of the CMI investigations as exploratory endpoint. Studies were adequately designed. The use of a saline placebo was justified as an active comparator was not yet commercially available at the time of the studies. The randomisation, stratification and minimization techniques used to ensure balance between groups with respect to age, site and country are deemed appropriate. A few study sites in Mexico had significant GCP violation or incorrectly applied the informed consent process, accounting to 4.21% (680/16,160) of the totally enrolled subjects in ZOSTER-006 and 5.84% (865/14,816) in ZOSTER-022. In total, 4.75% of the enrolled in ZOSTER-006 and 6.50% in ZOSTER-022 were excluded from TVC analyses; this is unlikely to have affected results.

Apart from immunosuppressive conditions, common comorbidities were not excluded from the trials. The collection of baseline medical conditions relied on the medical history performed at baseline by the Investigator, i.e. standardised definitions and scores of co-morbidities should be considered in future studies. The analysis of the medical history data suggests that groups are balanced for common conditions, including a range of diseases such as chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), depression, and diabetes that affect the risk of HZ and PHN. This indicates that efficacy estimates in the pivotal trials are unlikely to be biased by imbalance in the pre-existing medical conditions.

- **Target population**

The target population for HZ/su (adults 50 YOA and older) is known to have many comorbid conditions, of which the most frequent ones as reported in the literature are cardiovascular diseases, cancer, pulmonary disease (including chronic obstructive pulmonary disease), hypertension and diabetes. Although certain comorbidities were included in the trials (in total approximately 13,000 subjects with underlying medical conditions from the 2 studies), and exclusion criteria were not very restrictive, it was considered that specific subpopulations may be underrepresented in the trials, e.g. frail elderly including those with multiple comorbidities, and that overall the population studied may have been healthier than the general population that is the target of vaccination. In addition the baseline status should have been more thoroughly characterised (e.g. accounting for frailty). The potential impact on the external validity of the study findings was discussed in the course of the procedure, including the need to conduct further studies post-authorisation. Based on a number of observations, it was concluded that the impact on the study findings is not a concern and relevant uncertainties in specific subgroups can be followed up post-authorisation (for details refer to the section on subpopulations of interest in this chapter). Overall the target population was adequately selected to support an age-based indication, i.e. adults 50 years of age and above.

- **Study endpoints**

Clinical efficacy was assessed in ZOSTER-006 and ZOSTER-022 using the same methodology in both studies over a follow-up period of 3-4 years. The primary endpoint in both studies was the detection of HZ events and their virological confirmation, which is relevant. Study procedures to ascertain these endpoints are carefully designed.

A suspected case of HZ was defined as new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. Subjects clinically diagnosed as having a suspected case of HZ by the investigator were referred to as a case of 'suspected HZ'. The HZ onset date was defined as the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted. The end date of a HZ episode was defined as the first time at which a subject had no rash (papules, vesicles, ulcers or crusts) present. Severe 'worst' pain was defined as HZ-associated pain rated as 3 or greater on the 'worst pain' ZBPI question.

Secondary endpoints in both studies included the detection of PHN, HZ-related complications (other than PHN), mortality and hospitalizations, and use of pain medication. However, the analysis in these studies was not powered to demonstrate PHN VE, since, in view of the assumptions taken for VE, the sample size in each study should have been much larger. Therefore, PHN VE was assessed based on the pre-specified pooled analyses as a co-primary endpoint, i.e. HZ and PHN VE in subjects ≥70 YOA. Studies were not adequately powered to demonstrate VE against PHN in subjects with a confirmed case of HZ.

PHN was defined as the presence of HZ-associated severe 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash. Alternative definitions of PHN, based on duration of pain of

30, 60, 120 and 180 days were also used for reporting purposes. Overall, it is unlikely that persisting pain has been missed as subjects with suspected HZ had to complete the ZBPI questionnaire until they had no HZ-associated pain for 4 consecutive weeks. There is no international standard regarding the exact definition of PHN, and variations in PHN case definitions influence the estimates of PHN incidence, as described by the Applicant. It is agreed that the pivotal studies used a more specific case definition compared to those described in a recent systematic review of PHN: most studies defined PHN as a (neuropathic) pain persisting beyond 3-4 months after the onset of the herpetic rash, i.e. no "worst" pain nor score cut-off was used as criteria.

The protocol procedures are particularly well designed to assess the pain over the acute phase (the 4 initial weeks); in particular the Zoster Brief Pain Inventory (ZBPI) is considered appropriate to assess HZ pain. After Day 28 post HZ onset, the ZBPI was completed weekly by the subjects (in contrast with daily completion during the initial 4-week period). Information on HZ-associated pain is derived from the ZBPI 'worst pain' question for the ascertainment of BOI and PHN. It is acknowledged that HZ BOI (which is determined by the mean AUC of the severity-by-duration HZ associated pain during a 26 week period following the onset of the HZ rash) is valid despite fluctuations in daily ZBPI worst pain scores over time. Overall reliability of weekly pain assessment based on ZBPI past the initial 4-week period is endorsed.

After Visit 3 (Month 1 post vaccination 2), monthly contacts between the subjects and the investigator had to take place (except at months that coincide with the subject's scheduled visits) in order to collect information on any event of interest that may have occurred. Appropriate instructions were provided to the investigator and delegate to ensure accurate collection of long term data and to appropriately capture the relevant data up to study end.

Overall, the presentation of exploratory endpoints related to pain severity, duration, and quality of life did not seem to be fully consistent with endpoints previously defined in the study protocol (ex. burden-of-interference). The Applicant acknowledged that the protocol description of the quality of life (QoL) analysis was vague and has therefore clarified and detailed all QoL-related analysis in the corresponding statistical analysis plan (SAP) QoL, which was internally approved prior to unblinding and conduct of analysis.

- **Early termination of pivotal studies**

Since the VE against HZ at final analysis of ZOSTER-006 was substantially higher than anticipated, and assuming that the VE in ≥70 YOA in ZOSTER-022 (randomized at the same sites and time in all participating countries) would be similar to that obtained at final analysis in ZOSTER-006, the Applicant proposed stopping both studies ZOSTER-006 and ZOSTER-022 earlier than initially planned. Subjects in the Placebo group could then be offered HZ/su under the cross-vaccination protocol (ZOSTER-056) at the earliest possible time point. This decision was made to minimise the risk of the placebo recipients developing HZ and its complications, such as PHN. At the data lock point, the pre-specified number of HZ and PHN cases was reached in both studies, and the scientific integrity of the studies was not impacted by the early termination. This was also the conclusion of the IDMC that reviewed the unblinded final HZ/su efficacy data and unblinded available safety data of ZOSTER-006 before trial termination.

- **Statistical aspects**

All analysis in ZOSTER-006 and ZOSTER-022 were conducted according to the as-treated principle, although analyses according to the intention-to-treat principle are requested for all primary and key secondary hypotheses as this is the primary analysis set as requested by the "Guideline on Clinical Evaluation of new Vaccines" (EMEA/CHMP/VWP/164653/2005). This is however acceptable as overall it is agreed that the ITT analyses are in line with the TVC analyses. Only very few randomization errors

occurred. Concerns related to the multiple testing strategy and to the description and strategy of the interim analysis were clarified during the assessment and are believed not to have impacted the interpretation of the study results, also in light of the size of the treatment effect.

- **Conclusions on study design**

Overall, ZOSTER-006, ZOSTER-022, and their pre-specified pooled analyses thus addressed the most relevant clinical questions and overall the objectives and endpoints are endorsed. Methods, conduct, analysis and reporting of results from the main studies are considered appropriate. The study design is in accordance with legal requirements, available guidelines and scientific advice previously given.

Efficacy data and additional analyses

- **Efficacy against Herpes Zoster (HZ)**

In two phase III, placebo-controlled, observer-blind efficacy studies (ZOSTER-006 in 15,405 randomised adults ≥ 50 years and ZOSTER-022 in 13,900 randomised adults ≥70 years), strikingly high efficacy levels were obtained with HZ/Su.

In subjects ≥50 YOA at the final efficacy analysis, the overall VE against HZ was 97.2 [95% CI: 93.7-99.0]) in the modified Total Vaccinated Cohort (mTVC), i.e. excluding adults who did not receive the second dose of vaccine or who had a confirmed diagnosis of HZ within one month after the second dose, over a mean follow-up period of 3.1 years. This resulted in only few breakthrough cases in the HZ/su group (6 vs. 210 cases in placebo). VE was very consistent across age categories, gender, regions as well as cohorts of analysis and statistical models. VE against HZ was slightly higher <70 YOA as compared to ≥70 YOA. More detailed analyses across age categories (such as VE against PHN by age, VE again HZ over time by age, VE above 80 YOA) were assessed in the pooled analysis.

Very high VE against HZ in the ≥70 YOA was confirmed in ZOSTER-022 [89.79% (95% CI: 84.29% to 93.66%; p<0.0001)] and re-estimated in the pooled analysis at 91.30% (95% CI: 86.88%-94.46%) in the mTVC. This was based on 25 cases of HZ vs. 284 cases in placebo in the pooled analysis ≥70 YOA. Vaccine efficacy against HZ was very similar by age, i.e. 91.27% in the 70-79 YOA and 91.37% in the ≥80 YOA in pooled analysis. The co-primary objective of the pooled analysis regarding HZ and PHN VE in subjects ≥70 YOA was met (see below for results on PHN endpoint).

Breakthrough cases were very few so the assessment of their clinical and immunological profile even at baseline did not show specific common denominator or other aspects that could explain their occurrence.

A sensitivity analysis VE against HZ over time was performed at ZOSTER-006 EOS in ≥50 YOA and on pooled ZOSTER-006 and ZOSTER-022 data in ≥70 YOA. VE against HZ persisted for at least 4 years in both age strata, with estimated efficacy at Year 4 of 93.07% (95% CI: 81.2; 98.2) for subjects ≥50 YOA and 87.88% (95% CI: 73.3; 95.4) for those ≥70 YOA, in the mTVC. Of note, a longer follow-up of vaccine efficacy up to 10 years is ongoing in vaccinated subjects of the ZOSTER-006 and ZOSTER-022 studies, as well as a cross-vaccination study of the placebo groups. The need and timing of booster dose(s) will also be assessed in these studies.

- **Efficacy against Post-Herpetic Neuralgia (PHN)**

Two doses of HZ/su vaccine given on a 0, 2 month schedule produced high protective efficacy against post-herpetic neuralgia as a consequence of HZ prevention: 100% efficacy (95% CI 77.1; 100] in individuals >50 YOA (ZOSTER-006, no cases of PHN in the vaccine group) as well as by age strata (50-59 and 60-69 YOA). In the co-primary analysis of the pooled data from ZOSTER-006 and ZOSTER-022, the overall VE against PHN occurrence in those ≥70 YOA was 88.78% (95% CI 68.7; 97.1) in the

mTVC (4 cases of PHN occurred in the vaccine group). In the individual studies PHN VE was evaluated as a secondary objective and they were not powered for this analysis. However, if the success criteria for demonstrating PHN VE in the pooled analysis were to be applied for these age strata, they would be met for PHN VE in ≥50 YOA and ≥70 YOA.

In the pooled analysis, VE against PHN was demonstrated also in the 70-79 YOA (93.04% [95% CI 72.4; 99.2]; LL of the 95% CI well above 0%. For those ≥80 YOA, firm conclusion could not be drawn (VE 71.2% with 95% CI <0; 97.1) likely due to the lower number of subjects reporting PHN episodes, but PHN cases were numerically lower in the vaccine group compared to placebo group (2 vs. 7).

VE against HZ remained high in both studies up to the end of the study (median follow-up time of 4.1 years in ZOSTER-006 and 3.9 years in ZOSTER-022). More data on the persistence of protection against PHN is expected to be generated in long term follow up efficacy studies.

VE against PHN was estimated also in overall subjects with a confirmed case of HZ ≥50 YOA. This analysis was included as a secondary objective in the ZOSTER-006/ZOSTER-022 pooled analysis, however it could not be demonstrated in the mTVC cohort (VE 0.29%, p=0.5417). This is reflected in the SmPC. Similar results were obtained in TVC and ATP cohorts. Of note, due to the high efficacy of HZ/su in preventing HZ, which is the precondition for developing PHN, an unfeasible high sample size would have been required to show on top efficacy against PHN, in addition to the PHN efficacy that is the direct consequence of prevention of HZ. Therefore, the analysis of PHN prevention in subjects with confirmed HZ was not adequately powered. The actual reported PHN cases among confirmed HZ cases were 4/32 (12.50%) in the vaccine group and 46/477 (9.64%) in the placebo group, in the mTVC. The amount of cases is so low that a conclusion based on these numbers is not possible.

- **Efficacy against HZ-related complications other than PHN**

A relevant post-hoc analysis suggests that VE against HZ-related **complications** other than PHN is of the same magnitude as the VE against HZ and PHN. In the pooled analysis of ZOSTER-006 and ZOSTER-022, the vaccine significantly reduced HZ-related complications (other than PHN) by 93.7% (95% CI: 59.5; 99.9) and 91.6% (95% CI: 43.3; 99.8) in adults ≥ 50 years (1 vs. 16 cases) and adults ≥ 70 years (1 vs. 12 cases), respectively. The complications observed in the placebo group were confined to HZ vasculitis, disseminated disease, neurological disease and ophthalmic disease, and their incidence tended to increase with age. No cases of visceral disease or stroke associated with HZ reported during the study in either group. The complication reported in the vaccine group was ophthalmic disease.

However, this analysis was of limited power. In addition, these complications are very heterogeneous, with various underlying mechanisms and aetio-pathogenesis. More robust data could be needed over a larger range of complications and over the long term. To this end, the Applicant is currently conducting a feasibility assessment in relevant large healthcare databases already identified to ensure the robustness, reliability and interpretability of a post-authorisation effectiveness study.

Overall, incidence of HZ, PHN and HZ ophthalmicus in the studies were at the lower range of what is described in the literature. This could be linked to the relatively healthy and immunocompetent profile of the subjects, however the pivotal studies also used more stringent/specific case definitions compared to those described in recent literature. Based on a number of elements evaluated during the procedure (e.g. relevance and validation of ZBPI tool to measure pain even in an intermittent way), underreporting is considered unlikely. Two post-authorisation studies will evaluate long term efficacy and immunogenicity of the vaccine in subjects vaccinated in earlier studies, and may provide further information on efficacy against PHN or other complications.

Zoster sine herpete (ZSH) is, albeit uncommon, an increasingly described HZ-related complication; however no standard diagnosis tool is available and virological confirmation can be challenging. Given

the protocol definition of HZ, ZSH was not collected either as a HZ-complication or as an adverse event, so no cases of ZSH have been reported in the trials. This is not considered a major problem since there is no reason to believe that the vaccine will not be efficacious against variants of HZ onset, such as ZSH. However the definition of HZ in IC clinical studies and other future studies will include atypical HZ cases comprising ZSH, so more information may be gathered.

- **Other secondary endpoints**

No firm conclusion can be drawn on VE in reducing HZ-related **mortality and hospitalization**, due to a low number of breakthrough cases accrued. There were no cases of HZ-related mortality and no HZ-related hospitalization in subjects >50 YOA (ZOSTER-006 and ZOSTER-022), except for 5 subjects that were hospitalised for HZ in the placebo group of ZOSTER-022.

Similarly, no statistically significant VE in reducing **total duration of severe "worst" zoster pain** was shown in individual studies or in the pooled analysis. However, there was a trend for a shorter duration in the vaccine group vs. the placebo group in all analyses, i.e. 11.0 vs. 15.0 days in ≥ 50 YOA in ZOSTER-006 (reduction of 27%), 13.5 vs. 19.0 days in ≥ 70 YOA in ZOSTER-022, and 11.5 vs. 19.0 in ≥ 70 YOA in the pooled analysis (reduction of 30.5%).

An impact of HZ/su on use of pain medication associated with HZ was demonstrated, although the association is of a lower magnitude compared to other endpoints, which is not unexpected given the lower specificity of this endpoint. In ZOSTER-022, HZ/su significantly reduced the **use and the duration of HZ-associated pain medication** by 39.60% and 49.25%, respectively, in the mTVC confirmed HZ cases (secondary objective met). However, no statistically significant difference was observed in ZOSTER-006. A *post hoc* pooled analysis for the ≥70 YOA was conducted to provide a more accurate estimate (reduced use and duration of HZ-related pain medication by 39% (95% CI: 11.9; 63.3) and 50.6% (95% CI: 8.8; 73.2), respectively). The median duration of pain medication use was 32.0 and 44.0 days in the vaccine and placebo group, respectively.

- **Exploratory endpoints**

No statistically significant difference was seen between vaccine and placebo groups for worst pain score measured by ZBPI questionnaires in subjects with at least one confirmed HZ episode in individual studies; however in subjects ≥70 years (pooled data), the vaccine significantly reduced the maximum worst pain score versus placebo over the entire HZ episode (mean = 5.7 vs. 7.0, P-value = 0.032). In addition, the vaccine significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 3.9 vs. 5.5, P-value = 0.049 in subjects ≥50 years (ZOSTER-006), and mean = 4.5 vs. 5.6, P-value = 0.043, in subjects ≥ 70 years (ZOSTER-006 and -022 pooled).
No statistically significant differences were seen for the ZBPI AUC analysis for worst pain score, average pain score and activities of daily living (ADL) score. However, there was a trend towards less severe zoster pain and higher QoL in vaccinated subjects compared to placebo.
A post-hoc analysis was performed to assess whether vaccination with HZ/su can significantly reduce the incidence of severe and long-lasting zoster pain, e.g. with score of >600 by ZBPI, in the studied subjects. The point estimates would suggest an attenuation of long term severity in breakthrough cases, but, as cases are too few, CI are wide so no definitive conclusion can be drawn (see section 2.5.3).
The burden-of-illness (BOI) score incorporates the incidence of HZ with the severity and duration of acute and chronic HZ-related pain over a 6 month period following rash onset. The mean AUC scores for severity-of-illness and severity-of-interference evaluated by ZBPI in the mTVC were significantly lower in the vaccine group compared to placebo group, overall and in all age strata. The estimated overall VE against BOI was 98.4% (95% CI: 92.2; 100) in the mTVC ≥ 50 YOA (ZOSTER-006), and 92.1% (95% CI: 90.4; 93.8) in mTVC ≥ 70 YOA (pooled analysis of ZOSTER-006 and ZOSTER-022). Similar results were seen for VE against burden of interference measured on activities of daily living

(ADL) score (99.1%). These relevant data address total pain associated with HZ, and are reflected in SmPC.

Overall, many analysis related to pain scores (pain severity, severity by duration) and interference with QoL did not show statistically significant differences between groups because of the small number of breakthrough cases in the HZ/su group. Most scores tended to be lower in the HZ/su group than in the Placebo group. Notably, there was a statistically significant and favourable impact of HZ/su on BOI scores. Overall, these data suggest lower severity of pain and burden of illness and a lower loss of QoL in the HZ/su group in subjects with confirmed episode of HZ, and are considered clinically relevant for inclusion in the SmPC.

Immunogenicity data

The clinical development program demonstrated strong and persistent cellular and humoral immune response induced by HZ/su. Evaluation of CMI responses was the primary objective of several Phase I/II HZ/su trials, since CMI responses are known to be essential for protection against reactivation of VZV and development of HZ. Generally the median frequencies of gE-specific CD4 T-cells one month post Dose 2 were consistently high across studies and investigated age strata. The humoral immune responses in terms of anti-gE Ab VRRs, GMCs and fold increase over pre-vaccination anti-gE Ab concentrations measured by anti-gE ELISA 1 month post Dose 2 are consistently high in all presented studies, although mostly more than 99 % of subjects were seropositive at baseline.

Humoral immune responses to HZ/su were evaluated up until 3 years post-dose 2 (Month 38) in the Phase III clinical studies ZOSTER-006 and 022, whilst cellular immune responses were measured only in ZOSTER-006.

In ZOSTER-006, a total of 2,137 subjects ≥50 YOA (13.9% of TVC, of which 1,070 were in the vaccine group) were included in the ATP cohort for immunogenicity-Humoral at Month 3 (1 month after Dose 2). At Month 3, a median fold increase of 41.9 (Q1;Q3 = 20.8; 86.9) in anti-gE ELISA titres was observed vs. pre-vaccination titres. The elevated responses persisted up to Month 38 post Dose-1 (median fold increase of abs concentrations: 9.3 [Q1;Q3 = 4.9; 19.5] vs. pre-vaccination). At Month 3, anti-gE GMCs responses were 52,376.6 (95% CI 50,264.1; 54,577.9) as compared to the baseline level (1247.1 mIU/mL [95% CI: 1174.8 - 1323.8]) and to placebo (baseline: 1311.9 (95% CI: 1234.8– 1393.9) mIU/mL; similar results at all time points). At month 3 a median fold increase vs. pre-vaccination of 24.6 (Q1;Q3 = 9.9; 74.2) in gE-specific CD4[2+] T cell frequency was observed in subjects ≥50 YOA, whilst in subjects ≥70 YOA was 33.2 (Q1;Q3 = 10.0; 1052.0).

After peak titres at Month 3, the observed anti-gE antibody responses declined, but GMCs remained to be 11,919.6 (95% CI 11,345.6; 12,522.7) at Month 38 post Dose-1. The vaccine response rate (VRR) was calculated by the percentage of subjects whose post-dose 2 anti-gE titres had at least a 4-fold increase over the assay cut-off value for seropositivity (for subjects seronegative at baseline), or whose post-dose 2 anti-gE titres had at least a 4-fold increase above the pre-vaccination titre (for subjects seropositive at baseline). In the vaccine group, VRRs were 98.5% (95% CI 97.6; 99.1) at Month 3 and 80.9% (95% CI: 78.2%-83.3%) at Month 38.

In the pooled analysis, a total of 2.936 subjects (of which 2,137 from ZOSTER-006 and 799 from ZOSTER-022, of which 387 were in the vaccine group for the latter study) were included in the ATP cohort for immunogenicity to evaluate induced humoral responses and persistence in subjects ≥ 50 YOA and by age strata. In subjects ≥ 70 YOA, 99.3% of subjects were seropositive at pre-vaccination (i.e. with abs concentration above the assay cut-off value, ≥97mIU/mL). At Month 3, all subjects were seropositive for anti-gE antibody, presenting high GMCs of 49,691.5 (95% CI: 47,250.8 to 52,258.2 mIU/mL) vs. 1410.7 in placebo, a median fold increase of abs titres vs. pre-vaccination of 34.3 (Q1;

Q3 = 16.7; 68.5), and a VRR of 96.6% (95% CI: 95.1% to 97.8%) vs. VRR of 2.5% (95% CI 1.4; 4.0) in the placebo group.

At Month 38, all subjects ≥70 YOA in the pooled analysis remained seropositive for anti-gE antibody in the vaccine group, with high GMCs of 10,507.7 (95% CI: 9,899.2 to 11,153.6 mIU/mL), a median fold increase of 7.2 (Q1; Q3: 3.5; 14.5) vs. pre-vaccination, and a VRR of 70.5% (95% CI: 66.8% to 74.0%) vs. 2.4% in the placebo group. The results obtained in 70-79 YOA and ≥80 YOA strata were consistent with overall analysis in the ≥70 YOA, with a trend toward decreasing response with increasing age.

The analysis of persistence of humoral responses showed that anti-gE antibody concentrations as well as anti-gE specific CD4 T cells decline over the years but remain almost stable from year 4 to year 6, with immune responses persisting above pre-vaccination levels for at least up to Month 72 post-vaccination (i.e. 6 years). At month 72 in ZOSTER-024 (phase II follow up study of ZOSTER-003), the median anti-gE antibody concentration was greater than 7-fold above the baseline pre-vaccination median concentration. The median frequency of gE-specific CD4[2+] T cells was greater than 3.7-fold above baseline pre-vaccination median frequency.

The potential for exhaustion of the immune system due to the high immune responses induced by HZ/su and consequent implications for protection against other pathogens in a population that is already experiencing immunosenescence due to age were discussed during the procedure. Based on the clinical data observed in the coadministration study and in the IC studies as well as the non-clinical data, this phenomenon is considered unlikely both in the healthy and the IC populations.

- **Additional dosing schedule (0,6 months)**

In a phase III, open-label clinical study (ZOSTER-026), 238 adults ≥50 years of age were equally randomised to receive 2 doses of HZ/su 2 or 6 months apart. No efficacy data was generated for the 0,6 months schedule. The 0,6 months schedule was shown to be non-inferior to the 0,2 months schedule in terms of anti-gE humoral immune response one month post-dose 2 (primary endpoints met). The anti-gE GMC at 1 month post-dose 2 was 38,153.7 mIU/mL (95% CI: 34,205.8; 42,557.3) and the median fold increase of anti-gE concentrations from pre-vaccination was 36.8 (Q1: 17.6; Q3: 68.4). Anti-gE GMCs were slightly higher for the 0,2-month schedule (44376.3 mIU/mL (95% CI: 39697.0; 49607.2)). The demonstration of non-inferiority of the 0,12-month schedule was nearly missed.

This immunobridging strategy was sufficiently justified given that the new dosing schedule involves similar mechanisms of protection as compared to the pivotal trials. Based on the immunogenicity data, the use of the 0,6-months schedule is considered acceptable, although with a preference for the 0,2-months schedule, due to the limitations mentioned. The SmPC reflects that, if flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose.

- **Coadministration with other vaccines**

In a phase III, controlled, open-label clinical study (ZOSTER-004), 828 adults ≥ 50 years of age were randomized to receive 2 doses of HZ/su 2 months apart administered either concomitantly at the first dose (N=413) or non-concomitantly (N=415) with an unadjuvanted seasonal influenza vaccine. Following co-administration of HZ/su with the unadjuvanted influenza vaccine, the anti-gE GMC at 1 month after the last vaccine dose was 52,860.0 mIU/mL (95% CI: 48,386.3; 57,748.8) and the median fold increase of anti-gE concentrations from pre-vaccination was 42.9 (Q1: 17.2; Q3: 90.9). The VRR following coadministration of the 2 vaccines was 95.8% (95% CI: 93.3; 97.6). The antibody responses to both vaccines were similar, whether administered concomitantly or non-concomitantly.

Based on the results from study ZOSTER-004, HZ/su can be given concomitantly with unadjuvanted inactivated influenza vaccine. No data are currently available regarding concomitant use with other vaccines. More studies are ongoing to investigate co-administration with Pneumovax 23 (Pneumococcal polysaccharide conjugate vaccine), Prevenar 13 and with Boostrix (Diphtheria, tetanus and pertussis vaccine).

- **Correlate of protection analysis**

The investigation to identify a CoP was considered scientifically robust and it indicates that anti-gE ELISA Abs may correlate with protection, however many uncertainties remain which prevents to conclude on a validated CoP for the time being. Therefore the level of immune response that provides protection against HZ is unknown. The SmPC reflects that an immunological correlate of protection has not been established. The Applicant is encouraged to continue the CoP development with their approach.

Nevertheless, it is agreed that post-dose 2 anti-gE can be used as immune marker for immunobridging in certain circumstances based on demonstration of anti-gE antibodies non-inferiority. However, this needs to be assessed on a case-by-case basis, especially considering that the CMI component is deemed crucial for protection based on current knowledge.

Subpopulations of interest

- **Individuals with comorbidities and frailty**

The studies were not designed to demonstrate efficacy and safety in subgroups of frail individuals, including those with multiple comorbidities. Given the target age, certain comorbidities were included in the trials and exclusion criteria were not very restrictive but frail patients and those with comorbidities are likely to be underrepresented in the pivotal studies, also based on the requirements of trial design (e.g. patients affected by psoriasis or chronic pain syndrome or physically impaired may not have been included). The finding that incidence of HZ does not increase as expected with age provides an additional indirect indication that patients enrolled in ZOSTER-006 and ZOSTER-022 are likely to be substantially healthier than the population actually targeted by the vaccine (especially the oldest age categories), which may limit the external validity of the efficacy/safety results.

Post-hoc exploratory analysis suggests that VE against HZ is not significantly affected by frequent baseline conditions such as chronic obstructive pulmonary disease, diabetes, depression and chronic kidney disease, as compared to the overall efficacy in the pivotal studies. In addition a robust immune response was found in immunocompromised individuals, and all these elements are reassuring with respect to external validity of the HZ efficacy findings. Routine pharmacovigilance is therefore considered sufficient for post-marketing safety monitoring of HZ/su.

As the level of efficacy of HZ/su is extremely high in the pivotal trials and consistent according to age and common comorbidities as mentioned, there is no reason to believe that VE would be drastically lower in frail subjects. Nevertheless use of the vaccine in frail patients is included as missing information in the RMP and the limited data is reflected in the SmPC. Two studies (ZOSTER-063 and -064) are planned in subjects >50 YOA and it is expected that they will provide useful confirmatory information in frail subjects, although they will not assess efficacy according to frailty (see also section 2.7). ZOSTER-063 will allow for the evaluation of reactogenicity according to frailty level. Both studies are included in the RMP as a measure to address missing information.

Post-authorisation effectiveness studies are not expected to lead to any findings that would question the benefit-risk balance of the product, but would provide additional perspective on estimates of vaccine efficacy against HZ-related complications (taking into account the limitations of conducted

clinical studies in this respect) and also may allow for the assessment of vaccine benefits among relevant patient subgroups that are otherwise difficult to study in randomized controlled trials such as the frail population or specific co-morbidities groups. The Applicant is currently conducting a feasibility assessment for a post-authorisation effectiveness study included in the RMP in the context of missing information.

No data are available on efficacy and safety of HZ/su in patients from less prevalent subgroups such as patients with pre-existing autoimmune diseases (AIDs) or potentially immune mediated diseases (pIMDs) with or without immunosuppressive treatment, for which there is a significant medical need due to the high incidence of HZ. This is considered as missing information in the RMP and will be followed up post-authorisation in a dedicated immunogenicity and safety study (ZOSTER-069, currently under feasibility assessment; see also safety section 2.6).

- **Individuals with a history of HZ or previous varicella/zoster vaccination**

These individuals were excluded from the pivotal trials. This is appropriate in order not to bias the results by including patients presenting specific immunological profiles. The Applicant has undertaken specific trials targeting these subjects (ZOSTER-033 on subjects with a history of HZ, and ZOSTER-048 on subjects previously vaccinated with Zostavax- the latter not included in this submission).

In ZOSTER-033, the immune responses induced in adults ≥ 50 years of age with a history of HZ did not differ from the HZ/su induced immune responses seen in the other presented studies. Over a one-year follow-up period 9 reports of suspected HZ were reported in 6 individuals, which might point towards a higher recurrence rate than generally reported in observational studies in unvaccinated individuals with a history of HZ. In view of the methodological limitations of ZOSTER-033 (limited sample size (n=96), non-controlled, no CMI assessment and no laboratory confirmation of HZ cases) no firm conclusions could be made, and any hypothesis of HZ/su being ineffective or even triggering the recurrence of HZ in these patients is speculative and based on limited observations made with other herpes viruses (CMV in particular). For this reason, the risk is only a potential risk that would benefit from further investigation (see also safety and RMP sections 2.6.5, 2.6.9 and 2.7). This is reflected in the SmPC and in the RMP. Additional evidence regarding use of HZ/su in subjects with a history of HZ will be generated in a new study, ZOSTER-062, and in study ZOSTER-056, which is an ongoing Phase IIIb, open-label, cross-vaccination study evaluating the safety of HZ/su. In this study, subjects who received placebo in the two pivotal studies were offered cross-vaccination with HZ/su candidate and followed-up for 12 months post last vaccination, enrolling ~200 subjects with previous HZ. A subgroup analysis of the subjects with a history of HZ will be performed.

The vaccine is proposed for the prevention of zoster, and therefore acts as a booster of pre-existing immunity against the natural varicella infection. Currently, it is estimated that the large majority of the target population (>95% in Europe) have had a varicella infection and is therefore seropositive. However, seroprevalence levels vary by region based on epidemiology of infection and varicella vaccination policies. At present, the probability to vaccinate a VZV-seronegative subject in the EU is very low, and this probability is not expected to increase over the short term. In this context, and based on the absence of theoretical concern, inadvertent vaccination of seronegative subjects is deemed as acceptable. In addition, varicella vaccinated individuals could still develop varicella due to vaccine failure or vaccine virus becoming latent. The rationale to vaccinate these individuals with HZ/su is therefore endorsed. This uncertainty will be followed up post-authorisation via routine pharmacovigilance in PSURs. A study investigated the use of HZ/su in individuals previously vaccinated with Zostavax (ZOSTER-048). Data have become available only at the end of this procedure therefore it will be assessed after authorisation.

- **Immunocompromised individuals**

The Applicant is conducting a dedicated clinical development plan in immunocompromised adults targeting several well-defined sentinel populations. Two completed studies were submitted in this application for assessment (ZOSTER-015 in HIV+ patients, and ZOSTER-001 in HCT recipients for a total of 135 adults of whom 73 were ≥50 YOA) and four clinical trials are ongoing (solid tumour, Autologous HCT recipients, Hematologic malignancy, renal transplant) and will be evaluated in future applications.

In ZOSTER-015, the 3-dose HZ/su regimen elicited robust humoral and cellular immune responses in HIV+ adult subjects, whatever the cohort (ART High CD4 cohort, ART Low CD4 cohort, Non-ART High CD4 cohort). Strong responses were also observed after two doses. The third dose still induced an increase in anti-gE levels, but this increase was marginal for gE specific CD4[2+] T cells. Overall, responses were of the same magnitude as those found in immunocompetent individuals in other studies.

In ZOSTER-001, the 3-dose and 2-dose gE/AS01$_B$ regimens and the 3-dose gE/AS01$_E$ regimen (half dose adjuvant) elicited robust humoral and cellular immune responses superior to placebo in adult subjects who had undergone autologous HCT within 50 to 70 days prior to the first dose of vaccine. HCT recipients responded well to HZ/su immunization in terms of CMI, which has been shown also for other vaccines, and the Applicant concluded that the most plausible rationale is that the AS01 adjuvant may support the expansion of gE-specific memory CD4+ T cells present in the transplant by providing them with a competitive advantage during T cell compartment reconstitution. The vaccine overall elicited a very robust immune response although lower than in immunocompetent subjects even after 3 doses, with the 3-dose schedule superior to the 2-dose schedule.

The immunogenicity results of ZOSTER-001 and ZOSTER-015 are reflected in the SmPC section 5.1 to inform prescribers. The timing between administration of chemotherapy and/or immunosuppressive drugs and/or immunomodulators and vaccination is likely to be important for the response to HZ/su, but this will be further discussed once the development is concluded and more data will be available.

The need for specific follow-up measures in IC subjects 50 YOA and older, who are not excluded from the initial indication, was considered. Altogether, the potential use of HZ/su in ≥50 YOA IC adults does not raise concern based on the available data and therefore specific post-marketing follow-up measures in this population, beyond the planned routine pharmacovigilance for safety monitoring and the ongoing studies, are not deemed necessary.

2.5.7. Conclusions on clinical efficacy

The candidate HZ/su demonstrated very high efficacy against HZ and PHN in adults ≥ 50 YOA which was consistent across age strata, gender, regions as well as cohorts of analysis and statistical models. Following 2 intramuscular administrations separated by 2 months, the vaccine provided protective efficacy of 97.16% in subjects ≥50 YOA in ZOSTER-006. VE against zoster in the ≥70 YOA was confirmed in ZOSTER-022 and the pooled analysis (89.79% and 91.30%, respectively). High VE against HZ was maintained for at least 4 years (93.07% for subjects ≥50 YOA and 87.88% for the ≥70 YOA at year 4). The duration of VE of HZ/su beyond 4 years will be further evaluated post-licensure.

The ability of the vaccine to reduce PHN incidence as a consequence of HZ prevention, overall and by age strata, was evident, including in the older age groups. In powered analysis on pooled ZOSTER-006 and ZOSTER-022, VE against PHN was estimated as 88.78% for the ≥70 YOA and 93.04% for the 70-79 YOA stratum. A statistically significant PHN VE could not be demonstrated in the ≥80 YOA stratum (71.2%, 95% CI <0; 97.1), likely due to the lower number of subjects reporting PHN episodes. VE

against PHN tended to decrease slightly with age and with time but was maintained at very high level over 4 years. No demonstrative VE was seen with respect to reducing PHN occurrence in breakthrough cases due to lack of study power. Therefore the benefit of the vaccine in the prevention of PHN can be attributed to its effect on the prevention of HZ. However the data related to pain and BOI obtained from secondary and exploratory endpoints suggest that HZ/su ameliorates the acute disease in breakthrough cases.

Efficacy against HZ-related complications other than PHN is less clearly demonstrated due to lack of power. No cases of visceral disease or stroke associated with HZ were reported during the pivotal studies. Whether the vaccine can be effective in preventing these HZ complications remains open question. This information is reflected in the SmPC.

An immunological correlate of protection has not been established; therefore the SmPC reflects that the level of immune response that provides protection against HZ is unknown. However post-dose 2 anti-gE antibodies can be considered as immune marker for immunobridging on a case by case basis. The vaccine generated strong and persistent antigen-specific CD4 T-cell responses, which were consistently high across studies and investigated age strata. The results on humoral responses on anti-gE ELISA in terms of anti-gE Ab VRRs, GMCs and fold increase over pre-vaccination anti-gE Ab concentrations elicited 1 month post Dose 2 are consistently high in all presented studies; they peak 1 month after dose 2 and then decline but remain always higher than pre-vaccination titres (of at least 9 fold) up until 3 years after vaccination in the pivotal studies. Persistence of humoral responses was further analysed in other studies; anti-gE antibody concentrations as well as frequencies of anti-gE specific CD4 T cells decline over the years but remain almost stable from year 4 to year 6 after vaccination.

The need and timing of additional doses has not been established. However, the follow-up studies ZOSTER-049 and ZOSTER-060 will evaluate long-term vaccine efficacy and persistence of immune responses up to 10 yearsafter initial vaccination and further boostability of the immune response at 5 and 10 years post-vaccination respectively.

Clinical efficacy in subjects with previous history of HZ has not been evaluated. Subjects with previous history of HZ were excluded from the pivotal studies. The vaccine was shown to be immunogenic in one small study. This study had many limitations so more data from ongoing or planned studies (see below) are needed to clarify the uncertainty raised by the study (potential higher risk of HZ).

Potential ‘inadvertent’ administration of the vaccine to VZV naïve individuals (hence use as a priming vaccine) in terms of safety, efficacy and immunogenicity will be followed up by routine pharmacovigilance. One study investigating HZ/su vaccination of subjects who have previously received Zostavax was only recently completed and data will be assessed post-authorisation (ZOSTER-048).

HZ/su can be given concomitantly with unadjuvanted inactivated seasonal influenza vaccine, and more co-administration data are currently being generated (see below).

Although data are limited (a total of 135 individuals either HIV+ or HCT patients), the vaccine was shown to be immunogenic in an immunocompromised adult population. Given the consistently high HZ VE in older adults, including the oldest age group who generally have a weaker immune response, it is expected that HZ/su will also prevent HZ in adults with weakened immune responses due to disease or medication. No definite conclusion regarding HZ/su efficacy in IC adults can however be drawn before the results from the 4 ongoing studies are available.

The CHMP considers the following measures necessary to address missing information related to efficacy/immunogenicity:

- Long term efficacy and immunogenicity and need for one or more additional doses in individuals >50YOA: ZOSTER-049 (LTFU study of ZOSTER-006 and -022) and ZOSTER-060 (LTFU of ZOSTER-003);
- Use of HZ/su in frail adults 50 YOA or older: ZOSTER-063 and ZOSTER-64;
- Use of HZ/su in immunocompromised adults: ZOSTER-002, -028, -039, -041;
- Use of HZ/su in individuals with a history of zoster: ZOSTER-062 and ZOSTER-056 (cross-vaccination study of the placebo groups in the pivotal studies);
- Use of HZ/su in adults with pre-existing pIMDs: ZOSTER-069 (feasibility assessment ongoing)
- Effectiveness of HZ/su in preventing HZ, PHN and HZ-related complications in subjects 50YOA and older and long term effectiveness (feasibility assessment ongoing): EPI-ZOSTER-031.

The CHMP recommends to submit the following data as soon as available:

- ZOSTER-035 (Coadministration with Pneumovax23);
- ZOSTER-042 (Coadministration with Boostrix);
- ZOSTER-059 (coadministration with PCV13)
- ZOSTER-048 (vaccination of subjects who have previously received Zostavax).

2.6. Clinical safety

Summary of the methodology used

The "main" safety pooling analysis, which comprises the safety data from the 2 pivotal ZOSTER-006 and ZOSTER-022 studies, was performed on all safety endpoints. These 2 studies have a similar study design and were performed simultaneously. This analysis includes a comparative analysis performed on safety data of the HZ/su group vs. the Placebo group (saline) in order to assess the relative risk (RR) of safety events.

The broader safety pooling analysis comprises a descriptive analysis performed on all safety data (except reactogenicity endpoints) of the HZ/su group only (no Placebo group as comparison) of all studies included in this application with a safety follow-up period of at least one year post Dose 2 of HZ/su. This analysis was designed for the purpose of additional safety signal detection and evaluation.

The following safety endpoints were analysed in the pooled safety analyses:

- Solicited general/local symptoms during each 7-day post-vaccination period and overall, with further analysis of grade 3 solicited symptoms and solicited general symptoms with relationship to vaccination (in the 7-day diary card subset of ZOSTER-006 and ZOSTER-022 in the main safety pooling analysis only).

  Note: It was considered that the reactogenicity endpoints were sufficiently characterized in the main safety pooling analysis, since the majority of HZ/su recipients with reactogenicity assessment (85.4%) are included in this safety pooling.

- Unsolicited AEs during the 30-day post-vaccination period according to MedDRA[4], with further analysis of grade 3 unsolicited AEs and unsolicited AEs with relationship to vaccination or with a medically attended visit.

[4] Medical Dictionary for Regulatory Activities

- SAEs during the 30-day post-vaccination period, with further analysis of fatal SAEs and SAEs with causal relationship to vaccination.
- SAEs during the one year post last vaccination period, with further analysis of fatal SAEs and SAEs with causal relationship to vaccination.
- SAEs during the whole post-vaccination follow-up period, with further analysis of fatal SAEs and SAEs with causal relationship to vaccination.
- pIMDs during the 30-day post-vaccination period.
- pIMDs during the one year post last vaccination period.
- pIMDs during the whole post-vaccination follow-up period, with further analysis of pIMDs with causal relationship to vaccination.

All solicited symptoms and unsolicited AEs were rated for intensity and the intensity was assigned to one of the following categories: grade 1 (mild, easily tolerated); grade 2 (moderate, interferes with normal everyday activities) and grade 3 (severe, prevents normal everyday activities).

In addition, clinical laboratory evaluations were analysed in Phase I/II trials (EXPLOCRD- 004, ZOSTER-003 and ZOSTER-010 in older adults ≥50 YOA, and ZOSTER-001 and ZOSTER-015 in IC adults).

'Suspected cases of HZ' (whether or not clinically diagnosed by the investigator) was a safety endpoint in trials in the early CDP of HZ/su; 'confirmed cases of HZ' (by PCR or by a GSK expert) was a safety endpoint in trials in IC adults (ZOSTER-001 and ZOSTER-015). In all other studies, suspected cases of HZ were collected as part of the endpoints for safety analyses and followed the standard AE or SAE reporting process as applicable and as described in each individual study protocol.

In a subset of subjects (7-day diary card subset) in ZOSTER-006 and ZOSTER-022, solicited local and general symptoms were recorded on a diary card for 7 days (Days 0-6) after each vaccination, while all other AEs occurring during the 30-day (Days 0-29) post-vaccination period were recorded as unsolicited AEs on the 30-day diary card. Subjects who did not belong to the 7-day diary card subset recorded all AEs occurring during the 30-day post-vaccination period as unsolicited AEs using the 30-day diary card. This also pertained to AEs associated with PTs covering the local and general symptoms recorded as solicited by subjects who were part of the 7-day diary card subset.

- In ZOSTER-006, the 7-day diary card subset included 8,921 subjects, i.e., 2,667 subjects from the 50-59 YOA stratum, 2,666 subjects from the 60-69 YOA stratum and all 3,588 subjects from the ≥70 YOA stratum. Of note, 1 subject <50 YOA was allocated to the 50-59 YOA stratum (Placebo group).
- In ZOSTER-022, the 7-day diary card subset included 1,025 subjects, i.e., 574 subjects from the 70-79 YOA stratum and 451 subjects from the ≥80 YOA stratum.

In addition, potential immune-mediated diseases (pIMDs) were collected during the 30-day post-vaccination period and up to one year post-vaccination (all studies included in the safety pooling, except ZOSTER-003) and beyond one year post-vaccination in studies with longer follow-up time (ZOSTER-006, ZOSTER-022 and ZOSTER-024). pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest, which may or may not have an autoimmune aetiology. The Applicant performed this assessment since there is a hypothetical concern regarding exacerbation or triggering of pIMDs linked to the immune-enhancing effects of the adjuvant (HZ/su contains the $AS01_B$).

2.6.1. Patient exposure

In the 19 pivotal and supportive studies submitted for licensure, a total of 17,204 individuals received at least one IM dose of the final formulation of HZ/su. This includes 30 subjects younger than 50 years of age and 133 immunocompromised individuals. In the target population, i.e. adults 50 years of age and older, overall 17,041 individuals received at least one IM dose of the commercial formulation of HZ/su. 14,645 adults 50 years and older were included in the main safety pooling analysis, which comprises individuals who received HZ/su in the pivotal studies ZOSTER-006 and ZOSTER-022. Of them, 5887 were 50 to 69 years of age, and 8758 ≥70 years of age. In studies included in the broader safety pooling analysis, a total of 15,493 older adults ≥50 YOA have been vaccinated with at least 1 dose of HZ/su. 6,415 were 50-69 YOA and 9,078 were ≥70 YOA. A total of 30,234 doses were administered in all clinical studies included in the broader safety pooling analysis.

The compliance with the 2-dose schedule was 95.1% for HZ/su recipients in all studies included in the broader safety pooling analysis. The 11 studies included in the safety pooling analyses are completed and have a safety follow up of at least 1 year post Dose 2.

Although the procedure to request approval of HZ/su vaccination in immunocompromised adults will be part of a subsequent application, two completed studies (ZOSTER-001 and ZOSTER-015) conducted in IC adults were included in the submission. 74 HIV infected individual received 3 doses of HZ/su and 30 and 31 autologous HCT recipients received 2 and 3 doses of HZ/su, respectively.

The demographic profile of subjects included in the TVC of the main safety pooling analysis was comparable between the HZ/su and the placebo group in respect to age, sex, ethnicity, and geographic ancestry. Overall, the mean age at first vaccination in the main safety pooling analysis was 68.6 years, slightly more females than males were enrolled (58.2% versus 41.8%), and the majority of participants were White/Caucasians (73.7%). Demographic characteristics did not significantly change in the broader safety analysis and the subset with 7-day diary card.

Table 41. Clinical Studies with HZ/su Included in the 2 Pooled Analyses of Safety data

Study	Age category	Number of Subjects included in the pooled analysis		Main pooling (comparative analyses)	Broader pooling (descriptive analyses)
		HZ/su	Placebo		
ZOSTER-006	≥50 YOA	7,695	7,710	X	X
ZOSTER-022	≥70 YOA	6,950	6,950	X	X
ZOSTER-003* HZ/su group	≥60 YOA	166	-		X
ZOSTER-004 HZ/su staggered group	≥50 YOA	406°	-		X
ZOSTER-010 HZ/su group	≥50 YOA	150	-		X
ZOSTER-032 HZ/su IM group	≥50 YOA	30	-		X
ZOSTER-033 HZ/su all	≥50 YOA	96	-		X
Total		15,493	14,660	14,645 HZ/su recipients	15,493 HZ/su recipients

* ZOSTER-003 safety evaluation comprises also the follow-up studies ZOSTER-011, -012, -013 and -024, with safety follow-up data up to 10, 22, 34, and 70 months post last vaccination, respectively.
° Although 415 subjects were part of the Total Vaccinated Cohort and received FLU-D-QIV at Dose 1 (see Table 2), only 406 of them received at least 1 dose of HZ/su at the subsequent doses.

In general, the demographic characteristics of the total exposed database were similar to the TVC. More female subjects than male subjects were included (58% vs 58.3% for vaccinated and control respectively). Median age was 68.6 for both groups. The proportion of White Caucasian was above 73% in both groups. (73.7% and 73.6%, respectively), whereas 14.0% and 13.9% were from East

Asian heritage, 4.2% and 4.2% were Japanese, and 1.5% and 1.3% were African or African American, respectively.

2.6.2. Adverse events

Solicited AEs - Reactogenicity

Reactogenicity was analysed in the TVC with 7-day diary card from the main safety pooling analysis. In the HZ/su group, the most frequently reported solicited local symptom was pain at the injection site (68.1% overall/dose and 78.0% overall/subject) and the most frequent solicited general symptoms were myalgia, fatigue and headache (32.9%, 32.2% and 26.3% overall/dose and 44.7%, 44.5% and 37.7% overall/subject, respectively). In the Placebo group the most frequently reported solicited local symptom was pain (6.9% overall/dose and 10.9% overall/subject) and the most frequently reported solicited general symptoms were fatigue, headache and myalgia (10.5%, 9.6% and 7.3% overall/dose and 16.5%, 15.5% and 11.7% overall/subject, respectively). The majority of solicited symptoms were mild to moderate in intensity. Most of the solicited general symptoms were considered related to vaccination by the investigator.

In the HZ/su group, there was no difference between doses in incidence of solicited local symptoms, whereas there was a small increase in incidence of solicited general symptoms from Dose 1 to Dose 2, especially for grade 3 solicited general symptoms. The solicited symptoms typically lasted few days, i.e., median duration overall/dose in the HZ/su group was 3 days for solicited local symptoms, at most 2 days for solicited general symptoms, and at most 2 days and 1 day for grade 3 solicited local and general symptoms, respectively. The incidence of solicited symptoms was lower in the ≥70 YOA group compared to the 50-69 YOA group, especially for solicited general symptoms (42.5% versus 59.3% of HZ/su doses, respectively). Meanwhile, in the HZ/su cohort, the incidence of overall grade 3 symptoms (solicited and unsolicited, general and local) was higher after Dose 2 (13.8%) compared to after Dose 1 (11.7%) in the 50-69 YOA and (8.0%) compared to post-Dose 1 (6.4%) in the >70 YOA. Grade 3 (severe) was defined as an Adverse Event which prevented normal, everyday activities.

Table 42. 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 with 7-day diary card)

		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
Dose 1	HZ/su	4866	3803	78.2	77.0	79.3	4847	2459	50.7	49.3	52.1	4861	3578	73.6	72.3	74.8
	Placebo	4869	1273	26.1	24.9	27.4	4865	1079	22.2	21.0	23.4	4865	413	8.5	7.7	9.3
Dose 2	HZ/su	4704	3530	75.0	73.8	76.3	4697	2461	52.4	51.0	53.8	4699	3260	69.4	68.0	70.7
	Placebo	4717	921	19.5	18.4	20.7	4711	776	16.5	15.4	17.6	4715	295	6.3	5.6	7.0
Overall/dose	HZ/su	9570	7333	76.6	75.8	77.5	9544	4920	51.6	50.5	52.6	9560	6838	71.5	70.6	72.4
	Placebo	9586	2194	22.9	22.0	23.7	9576	1855	19.4	18.6	20.2	9580	708	7.4	6.9	7.9
Overall/subject	HZ/su	4886	4130	84.5	83.5	85.5	4876	3159	64.8	63.4	66.1	4884	3944	80.8	79.6	81.9
	Placebo	4881	1646	33.7	32.4	35.1	4881	1419	29.1	27.8	30.4	4880	572	11.7	10.8	12.7

Table 43. Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall by age strata (Total Vaccinated Cohort with 7-day diary card)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Sub-group	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	50-69Y	HZ/su	2671	313	11.7	10.5	13.0	2671	205	7.7	6.7	8.8	2671	180	6.7	5.8	7.8
		Placebo	2662	59	2.2	1.7	2.8	2662	57	2.1	1.6	2.8	2662	6	0.2	0.1	0.5
	≥70Y	HZ/su	2298	146	6.4	5.4	7.4	2298	76	3.3	2.6	4.1	2298	89	3.9	3.1	4.7
		Placebo	2315	36	1.6	1.1	2.1	2315	35	1.5	1.1	2.1	2315	2	0.1	0.0	0.3
Dose 2	50-69Y	HZ/su	2560	354	13.8	12.5	15.2	2560	273	10.7	9.5	11.9	2560	169	6.6	5.7	7.6
		Placebo	2572	49	1.9	1.4	2.5	2572	45	1.7	1.3	2.3	2572	7	0.3	0.1	0.6
	≥70Y	HZ/su	2186	175	8.0	6.9	9.2	2186	109	5.0	4.1	6.0	2186	101	4.6	3.8	5.6
		Placebo	2201	31	1.4	1.0	2.0	2201	29	1.3	0.9	1.9	2201	3	0.1	0.0	0.4
Overall/dose	50-69Y	HZ/su	5231	667	12.8	11.9	13.7	5231	478	9.1	8.4	10.0	5231	349	6.7	6.0	7.4
		Placebo	5234	108	2.1	1.7	2.5	5234	102	1.9	1.6	2.4	5234	13	0.2	0.1	0.4
	≥70Y	HZ/su	4484	321	7.2	6.4	8.0	4484	185	4.1	3.6	4.7	4484	190	4.2	3.7	4.9
		Placebo	4516	67	1.5	1.2	1.9	4516	64	1.4	1.1	1.8	4516	5	0.1	0.0	0.3
Overall/subject	50-69Y	HZ/su	2671	544	20.4	18.9	21.9	2671	405	15.2	13.8	16.6	2671	298	11.2	10.0	12.4
		Placebo	2662	97	3.6	3.0	4.4	2662	91	3.4	2.8	4.2	2662	13	0.5	0.3	0.8
	≥70Y	HZ/su	2298	278	12.1	10.8	13.5	2298	168	7.3	6.3	8.5	2298	162	7.0	6.0	8.2
		Placebo	2315	62	2.7	2.1	3.4	2315	59	2.5	1.9	3.3	2315	5	0.2	0.1	0.5

Note: this analysis is conducted on the pooled data from studies ZOSTER-006 and -022 (1 subject below 50 YOA in ZOSTER-006 is allocated to 50-69YOA age strata)

Solicited local symptoms

Table 44. 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 with 7-day diary card)

		50-69Y										≥70Y									
		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	2615	2081	79.6	78.0	81.1	2610	250	9.6	8.5	10.8	2246	1336	59.5	57.4	61.5	2255	128	5.7	4.8	6.7
	Grade 3	2615	129	4.9	4.1	5.8	2610	6	0.2	0.1	0.5	2246	42	1.9	1.4	2.5	2255	1	0.0	0.0	0.2
Redness (mm)	All	2615	762	29.1	27.4	30.9	2610	26	1.0	0.7	1.5	2246	606	27.0	25.2	28.9	2255	17	0.8	0.4	1.2
	>100	2615	48	1.8	1.4	2.4	2610	0	0.0	0.0	0.1	2246	43	1.9	1.4	2.6	2255	0	0.0	0.0	0.2
Swelling (mm)	All	2615	540	20.7	19.1	22.3	2610	16	0.6	0.4	1.0	2246	355	15.8	14.3	17.4	2255	17	0.8	0.4	1.2
	>100	2615	13	0.5	0.3	0.8	2610	0	0.0	0.0	0.1	2246	17	0.8	0.4	1.2	2255	0	0.0	0.0	0.2
Dose 2																					
Pain	All	2539	1848	72.8	71.0	74.5	2546	174	6.8	5.9	7.9	2160	1241	57.5	55.3	59.6	2169	107	4.9	4.1	5.9
	Grade 3	2539	137	5.4	4.5	6.3	2546	7	0.3	0.1	0.6	2160	60	2.8	2.1	3.6	2169	3	0.1	0.0	0.4
Redness (mm)	All	2539	706	27.8	26.1	29.6	2546	13	0.5	0.3	0.9	2160	582	26.9	25.1	28.9	2169	14	0.6	0.4	1.1
	>100	2539	32	1.3	0.9	1.8	2546	0	0.0	0.0	0.1	2160	39	1.8	1.3	2.5	2169	0	0.0	0.0	0.2
Swelling (mm)	All	2539	486	19.1	17.6	20.7	2546	7	0.3	0.1	0.6	2160	344	15.9	14.4	17.5	2169	10	0.5	0.2	0.8
	>100	2539	10	0.4	0.2	0.7	2546	0	0.0	0.0	0.1	2160	15	0.7	0.4	1.1	2169	0	0.0	0.0	0.2
Overall/dose																					
Pain	All	5154	3929	76.2	75.0	77.4	5156	424	8.2	7.5	9.0	4406	2577	58.5	57.0	59.9	4424	235	5.3	4.7	6.0
	Grade 3	5154	266	5.2	4.6	5.8	5156	13	0.3	0.1	0.4	4406	102	2.3	1.9	2.8	4424	4	0.1	0.0	0.2
Redness (mm)	All	5154	1468	28.5	27.3	29.7	5156	39	0.8	0.5	1.0	4406	1188	27.0	25.7	28.3	4424	31	0.7	0.5	1.0
	>100	5154	80	1.6	1.2	1.9	5156	0	0.0	0.0	0.1	4406	82	1.9	1.5	2.3	4424	0	0.0	0.0	0.1
Swelling (mm)	All	5154	1026	19.9	18.8	21.0	5156	23	0.4	0.3	0.7	4406	699	15.9	14.8	17.0	4424	27	0.6	0.4	0.9
	>100	5154	23	0.4	0.3	0.7	5156	0	0.0	0.0	0.1	4406	32	0.7	0.5	1.0	4424	0	0.0	0.0	0.1
Overall/subject																					
Pain	All	2626	2248	85.6	84.2	86.9	2617	334	12.8	11.5	14.1	2258	1562	69.2	67.2	71.1	2263	199	8.8	7.7	10.0
	Grade 3	2626	225	8.6	7.5	9.7	2617	13	0.5	0.3	0.8	2258	90	4.0	3.2	4.9	2263	4	0.2	0.0	0.5
Redness (mm)	All	2626	1012	38.5	36.7	40.4	2617	37	1.4	1.0	1.9	2258	851	37.7	35.7	39.7	2263	27	1.2	0.8	1.7
	>100	2626	71	2.7	2.1	3.4	2617	0	0.0	0.0	0.1	2258	70	3.1	2.4	3.9	2263	0	0.0	0.0	0.2
Swelling (mm)	All	2626	748	28.5	26.8	30.3	2617	23	0.9	0.6	1.3	2258	519	23.0	21.3	24.8	2263	25	1.1	0.7	1.6
	>100	2626	21	0.8	0.5	1.2	2617	0	0.0	0.0	0.1	2258	30	1.3	0.9	1.9	2263	0	0.0	0.0	0.2

Solicited general symptoms

Table 45. Incidence of solicited general symptoms reported during the 7-day post-vaccination period overall by age strata (Total Vaccinated Cohort with 7-day diary card)

		50-69Y										≥70Y									
		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
Overall/subject																					
Fatigue	All	2624	1347	51.3	49.4	53.3	2617	479	18.3	16.8	19.8	2252	825	36.6	34.6	38.7	2264	326	14.4	13.0	15.9
	Grade 3	2624	178	6.8	5.9	7.8	2617	33	1.3	0.9	1.8	2252	79	3.5	2.8	4.4	2264	17	0.8	0.4	1.2
	Related	2624	1196	45.6	43.7	47.5	2617	355	13.6	12.3	14.9	2252	699	31.0	29.1	33.0	2264	220	9.7	8.5	11.0
	Grade 3 Related	2624	151	5.8	4.9	6.7	2617	24	0.9	0.6	1.4	2252	67	3.0	2.3	3.8	2264	14	0.6	0.3	1.0
Gastrointestinal symptoms	All	2624	538	20.5	19.0	22.1	2617	254	9.7	8.6	10.9	2252	304	13.5	12.1	15.0	2264	172	7.6	6.5	8.8
	Grade 3	2624	40	1.5	1.1	2.1	2617	17	0.6	0.4	1.0	2252	26	1.2	0.8	1.7	2264	10	0.4	0.2	0.8
	Related	2624	426	16.2	14.8	17.7	2617	137	5.2	4.4	6.2	2252	210	9.3	8.2	10.6	2264	91	4.0	3.2	4.9
	Grade 3 Related	2624	32	1.2	0.8	1.7	2617	8	0.3	0.1	0.6	2252	16	0.7	0.4	1.2	2264	4	0.2	0.0	0.5
Headache	All	2624	1185	45.2	43.2	47.1	2617	487	18.6	17.1	20.2	2252	653	29.0	27.1	30.9	2264	268	11.8	10.5	13.2
	Grade 3	2624	128	4.9	4.1	5.8	2617	24	0.9	0.6	1.4	2252	34	1.5	1.0	2.1	2264	10	0.4	0.2	0.8
	Related	2624	1041	39.7	37.8	41.6	2617	326	12.5	11.2	13.8	2252	547	24.3	22.5	26.1	2264	185	8.2	7.1	9.4
	Grade 3 Related	2624	115	4.4	3.6	5.2	2617	15	0.6	0.3	0.9	2252	28	1.2	0.8	1.8	2264	6	0.3	0.1	0.6
Myalgia	All	2624	1390	53.0	51.0	54.9	2617	345	13.2	11.9	14.5	2252	790	35.1	33.1	37.1	2264	225	9.9	8.7	11.2
	Grade 3	2624	186	7.1	6.1	8.1	2617	23	0.9	0.6	1.3	2252	62	2.8	2.1	3.5	2264	10	0.4	0.2	0.8
	Related	2624	1260	48.0	46.1	50.0	2617	264	10.1	9.0	11.3	2252	689	30.6	28.7	32.5	2264	157	6.9	5.9	8.1
	Grade 3 Related	2624	165	6.3	5.4	7.3	2617	17	0.6	0.4	1.0	2252	53	2.4	1.8	3.1	2264	5	0.2	0.1	0.5
Shivering	All	2624	868	33.1	31.3	34.9	2617	171	6.5	5.6	7.5	2252	439	19.5	17.9	21.2	2264	110	4.9	4.0	5.8
	Grade 3	2624	149	5.7	4.8	6.6	2617	7	0.3	0.1	0.6	2252	49	2.2	1.6	2.9	2264	6	0.3	0.1	0.6
	Related	2624	768	29.3	27.5	31.1	2617	118	4.5	3.7	5.4	2252	380	16.9	15.3	18.5	2264	75	3.3	2.6	4.1
	Grade 3 Related	2624	137	5.2	4.4	6.1	2617	6	0.2	0.1	0.5	2252	44	2.0	1.4	2.6	2264	4	0.2	0.0	0.5
Temperature/(*) (°C)	All	2624	679	25.9	24.2	27.6	2617	84	3.2	2.6	4.0	2252	323	14.3	12.9	15.9	2264	61	2.7	2.1	3.4
	[37.5 - 38.1[	2624	457	17.4	16.0	18.9	2617	63	2.4	1.9	3.1	2252	244	10.8	9.6	12.2	2264	48	2.1	1.6	2.8
	[38.1 - 39.1[	2624	208	7.9	6.9	9.0	2617	13	0.5	0.3	0.8	2252	68	3.0	2.4	3.8	2264	8	0.4	0.2	0.7
	>39.0	2624	11	0.4	0.2	0.7	2617	5	0.2	0.1	0.4	2252	3	0.1	0.0	0.4	2264	3	0.1	0.0	0.4
	Related	2624	607	23.1	21.5	24.8	2617	54	2.1	1.6	2.7	2252	265	11.8	10.5	13.2	2264	30	1.3	0.9	1.9
	>39.0 Related	2624	10	0.4	0.2	0.7	2617	2	0.1	0.0	0.3	2252	3	0.1	0.0	0.4	2264	0	0.0	0.0	0.2

Unsolicited AEs

When considering the TVC from the main safety pooling analysis, unsolicited AEs within the 30-day post-vaccination period were significantly more frequently reported in the HZ/su group compared to the Placebo group, i.e. after 10,624 of HZ/su doses (37.2%) by 7,393 subjects (50.5%), and after 5,579 placebo doses (19.4%) by 4,689 subjects (32.0%; RR = 1.58 [95% CI: 1.52-1.64], unadjusted p < 0.00001). Note that this imbalance is mainly due to the fact that the subjects who were not included in the 7-day diary card subset have reported expected local and general symptoms as unsolicited AEs. Indeed, the majority of unsolicited AEs which were significantly more frequently reported in the HZ/su group compared to the Placebo group (unadjusted p-value <0.05) fell under the System Organ Class (SOC) of 'General disorders and administration site conditions', and were associated with PTs covering the local and general symptoms recorded as solicited on the 7-day diary card by subjects who were part of the TVC with 7-day diary card, i.e. local injection site symptoms (including pain, redness and swelling) and general symptoms (including fever, headache, fatigue, chills [PT covering the solicited general symptom of shivering], myalgia and nausea). Among the other significantly more frequently reported unsolicited AEs by subject in the HZ/su group compared to Placebo group, 4 additional unsolicited AEs were reported with an incidence ≥1.0% in HZ/su recipients, and at least twice as often in the HZ/su group compared to the Placebo group. These are:

- Injection site pruritus (2.2% in the HZ/su group vs. 0.2% in the Placebo group; RR = 9.07 [95% CI: 6.38-13.25])
- Malaise (1.7.% vs. 0.3% of subjects, respectively; RR = 5.91 [95% CI: 4.27-8.37])
- Pain (1.4% vs. 0.2% of subjects, respectively; RR = 6.01 [95% CI: 4.16-8.91]),
- Injection site warmth (1.0% vs. <0.1% of subjects, respectively; RR = 29.83 [95% CI: 12.50-93.22]).

In the TVC of the broader safety pooling analysis, unsolicited AEs within the 30-day post-vaccination period were reported following 10,915 HZ/su doses (36.1%) by 7,642 subjects (49.3%).

When considering the TVC with 7-day diary card from the main safety pooling analysis, no imbalances have been observed between HZ/su and Placebo groups, i.e. unsolicited AEs within the 30-day post-vaccination period were reported following 1,720 HZ/su doses (17.7%) and following 1,570 placebo doses (16.1%). Overall per subject, unsolicited AEs were reported by 1,451 subjects (29.2%) in the HZ/su group and 1,371 subjects (27.5%) in the Placebo group. The most frequently reported unsolicited AEs following at least 1.0% of HZ/su doses were nasopharyngitis (1.6% of HZ/su and placebo doses by 2.9% and 3.0% of subjects in the HZ/su and Placebo groups, respectively) and upper respiratory tract infection (1.0% and 0.6% of doses by 1.9% and 1.1% of subjects, respectively). However, none of these AEs had a frequency of more than 2-fold higher in the HZ/su group than in the Placebo group, and are therefore not included in the section 4.8 of the SmPC. By age stratum, the incidence of unsolicited AEs was similar in subjects 50-69 YOA and subjects ≥70 YOA.

In the TVC from the main safety pooling, unsolicited AEs considered related as per investigator assessment and within the 30-day post-vaccination period were reported after 7,489 HZ/su doses (26.2%) by 5,052 subjects (34.5%), and after 1,085 placebo doses (3.8%) by 968 subjects (6.6%). By PT, apart from the related unsolicited AEs also reported as local and general symptoms in the TVC with 7-day diary card, the most frequently reported related unsolicited AEs in the HZ/su group (≥1.0% of subjects) were injection site pruritus, following 1.3% of doses by 2.1% of subjects, malaise, following 0.9% of doses by 1.6% of subjects, pain, following 0.7% of doses by 1.2% of subjects, and injection site warmth, following 0.6% of doses by 1.0% of subjects.

All adverse reactions proposed for inclusion in the section 4.8 'Undesirable effects' of the SmPC are presented in table 47.

Table 46. Adverse reactions included in the proposed SmPC of HZ/su

System Organ Class	Frequency	Adverse reactions	Incidence % (95% CI)
Blood and lymphatic system disorders	Uncommon (≥1/1,000 to <1/100)	lymphadenopathy	0.1 (0.0-0.1) overall/dose
Nervous system disorders	Very common (≥1/10)	headache	26.3 (25.4-27.2) overall/dose
Gastrointestinal disorders	Very common (≥1/10)	gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain)	10.7 (10.1-11.3) overall/dose
Musculoskeletal and connective tissue disorders	Very common (≥1/10)	myalgia	32.9 (31.9-33.8) overall/dose
	Uncommon (≥1/1,000 to <1/100)	arthralgia	0.9 (0.8-1.0) overall/dose
General disorders and administration site conditions	Very common (≥1/10)	pain at injection site redness at injection site swelling at injection site fatigue chills fever	68.1 (67.1-69.0) overall/dose 27.8 (26.9-28.7) overall/dose 18.0 (17.3-18.8) overall/dose 32.2 (31.3-33.2) overall/dose 17.6 (16.8-18.3) overall dose 12.8 (12.1-13.5) overall/dose
	Common (≥1/100 to <1/10)	injection site pruritus malaise	1.3 (1.2-1.4) overall/dose 1.0 (0.9-1.1) overall/dose

Overall, the majority of the imbalances between HZ/su and placebo recipients that were observed in terms of unsolicited AEs were related to PTs referring to solicited symptoms, with a few additional unsolicited AEs (chills, injection site pruritus and malaise) identified in the HZ/su group.

2.6.3. Serious adverse events and deaths

Deaths

In the main safety pooling analysis, 634 subjects (4.3%) in the HZ/su group and 680 subjects (4.6%) in the Placebo group died during the entire study period.

Table 47. Main safety pooling analysis: Percentage of subjects reporting the occurrence of serious adverse events with fatal outcome classified by MedDRA Primary System Organ Class during the whole postvaccination follow-up period overall and by age stratum (sorted by incidence in the HZ/su group) (Total Vaccinated Cohort)

	HZ/su						Placebo					
	Overall N=14645		50-69Y N=5887		**≥70Y** N=8758		Overall N=14660		50-69Y N=5887		**≥70Y** N=8773	
Primary System Organ Class (SOC)	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
At least one symptom	634	4.3	95	1.6	539	6.2	680	4.6	100	1.7	580	6.6
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	182	1.2	32	0.5	150	1.7	177	1.2	25	0.4	152	1.7
Cardiac disorders (10007541)	174	1.2	22	0.4	152	1.7	193	1.3	25	0.4	168	1.9
Infections and infestations (10021881)	103	0.7	10	0.2	93	1.1	107	0.7	11	0.2	96	1.1
General disorders and administration site conditions (10018065)	72	0.5	14	0.2	58	0.7	78	0.5	15	0.3	63	0.7
Respiratory, thoracic and mediastinal disorders (10038738)	60	0.4	6	0.1	54	0.6	65	0.4	11	0.2	54	0.6
Nervous system disorders (10029205)	57	0.4	4	0.1	53	0.6	68	0.5	7	0.1	61	0.7
Injury, poisoning and procedural complications (10022117)	26	0.2	7	0.1	19	0.2	25	0.2	7	0.1	18	0.2
Vascular disorders (10047065)	26	0.2	1	0.0	25	0.3	30	0.2	7	0.1	23	0.3
Renal and urinary disorders (10038359)	23	0.2	3	0.1	20	0.2	21	0.1	5	0.1	16	0.2
Gastrointestinal disorders (10017947)	21	0.1	1	0.0	20	0.2	21	0.1	8	0.1	13	0.1
Hepatobiliary disorders (10019805)	14	0.1	2	0.0	12	0.1	9	0.1	1	0.0	8	0.1
Metabolism and nutrition disorders (10027433)	6	0.0	0	0.0	6	0.1	9	0.1	1	0.0	8	0.1
Psychiatric disorders (10037175)	5	0.0	4	0.1	1	0.0	6	0.0	1	0.0	5	0.1
Congenital, familial and genetic disorders (10010331)	3	0.0	1	0.0	2	0.0	1	0.0	1	0.0	0	0.0
Blood and lymphatic system disorders (10005329)	2	0.0	1	0.0	1	0.0	5	0.0	1	0.0	4	0.0
Musculoskeletal and connective tissue disorders (10028395)	1	0.0	1	0.0	0	0.0	2	0.0	0	0.0	2	0.0
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0	0.0	0	0.0	3	0.0	0	0.0	3	0.0

50-69Y = subjects 50-69 YOA; ≥70Y = subjects ≥70 YOA
HZ/su = Herpes Zoster subunit vaccine
Placebo = NaCl solution
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
* Incidences of 0.0% either indicate that no cases were reported (n=0) or that the incidence is <0.05% (n≥1)
Note: this analysis is conducted on the pooled data from studies ZOSTER-006 and -022

In the broader safety pooling analysis, 9 additional subjects in the HZ/su group died during the whole post-vaccination follow-up period (643 subjects [4.2%]). The majority of fatal SAEs had a time to onset of longer than 1 year post last vaccination. In the main pooling, 17 subjects (0.1%) in the HZ/su group and 21 subjects (0.1%) in the Placebo group died from the first administered dose up to 30 days post last vaccination, while 153 subjects (1.0%) in the HZ/su group and 168 subjects (1.1%) in the Placebo group reported fatal SAEs up to 1 year post last vaccination. Based on the main safety pooling analysis, the most common fatal SAEs in the HZ/su group by PT (≥0.2% of HZ/su recipients) and placebo group (≥0.1% of placebo recipients) were cardiac failure (0.3% in the HZ/su group and 0.4% in the Placebo group), pneumonia and myocardial infection (0.3% and 0.3%, respectively), cardiac arrest (0.2% and 0.2%, respectively), death (not otherwise specified; 0.2% and 0.3%, respectively) and lung neoplasm malignant (0.2% and 0.1%, respectively). When considering these specific PTs in the broader safety pooling analysis, 1 additional PT of myocardial infarction and 3 additional PTs of 'death' (not otherwise specified) were reported as fatal SAE.

The majority of fatal SAEs during the entire study period occurred in subjects ≥70 YOA (6.2% and 6.6% of subjects in the HZ/su and Placebo groups, respectively, in the main safety pooling, and 6.0% in the HZ/su group in the broader safety pooling), while the incidence in subjects 50-69 YOA was 1.6% and 1.7% in the HZ/su and Placebo groups, respectively, in the main safety pooling, and 1.5% in the HZ/su group in the broader safety pooling. By age range in the 50-59 YOA, 60-69 YOA, 70 79 YOA and ≥80 YOA strata, the percentage of subjects reporting fatal SAEs during the whole post-vaccination follow-up period increased with age in both groups, as expected.

One fatal SAE was considered by the investigator to be vaccine related: a subject with a history of stable immune thrombocytopenic purpura developed AML 75 days following the first dose of HZ/su in study ZOSTER-022. The subject was being treated with azacitidine. 97 days following dose 1 of HZ/su the subject was hospitalised with febrile neutropenia; their condition deteriorated under therapy with filgrastim and Piperacillin/Tazobactam and the subject died the day after hospital admission. The investigator considered that it cannot be ruled out that HZ/su might have been the cause of AML and the associated neutropenic sepsis. The CHMP considers a relationship between vaccination and AML highly unlikely as the neutropenic sepsis and subsequent events are considered most likely side effects of the ongoing acazitidine therapy.

Serious adverse events

Overall, no imbalances between the HZ/su and Placebo groups have been observed in terms of SAEs reported over the entire study period, i.e. 12.8% (95% CI: 12.3-13.4) of HZ/su recipients and 13.3% (95% CI: 12.7-13.8) of subjects in the Placebo group (RR = 0.97 [95% CI: 0.91-1.03], unadjusted p-value = 0.31578).

Table 48. Main safety pooling analysis: Percentage of subjects reporting the occurrence of serious adverse events classified by MedDRA Primary System Organ Class during the whole post-vaccination follow-up period (sorted by incidence in the HZ/su group) (Total Vaccinated Cohort)

System Organ Class	HZ/su N=14645		Placebo N=14660	
	n	%*	n	%*
At least one symptom	1880	12.8	1945	13.3
Cardiac disorders	511	3.5	559	3.8
Infections and infestations	455	3.1	477	3.3
Neoplasms benign, malignant and unspecified	405	2.8	392	2.7
Injury, poisoning and procedural complications	263	1.8	253	1.7
Nervous system disorders	245	1.7	275	1.9
Gastrointestinal disorders	186	1.3	225	1.5
Respiratory, thoracic and mediastinal disorders	148	1.0	176	1.2
General disorders and administration site conditions	137	0.9	141	1.0
Vascular disorders	125	0.9	169	1.2
Musculoskeletal and connective tissue disorders	112	0.8	115	0.8
Renal and urinary disorders	88	0.6	97	0.7
Hepatobiliary disorders	76	0.5	84	0.6
Metabolism and nutrition disorders	68	0.5	75	0.5
Psychiatric disorders	36	0.2	38	0.3
Blood and lymphatic system disorders	35	0.2	41	0.3
Reproductive system and breast disorders	27	0.2	26	0.2
Eye disorders	22	0.2	34	0.2
Skin and subcutaneous tissue disorders	18	0.1	21	0.1
Ear and labyrinth disorders	10	0.1	15	0.1
Endocrine disorders	6	0.0	8	0.1
Immune system disorders	6	0.0	7	0.0
Congenital, familial and genetic disorders	5	0.0	4	0.0
Investigations	4	0.0	7	0.0
Surgical and medical procedures	1	0.0	2	0.0

Source: m5.3.5.3 Integrated Summary of Safety, Table 54
HZ/su = Herpes Zoster subunit vaccine
Placebo = NaCl solution
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
* Incidences of 0.0% either indicate that no cases were reported (n=0) or that the incidence is <0.05% (n≥1)
Note: this analysis is conducted on the pooled data from studies ZOSTER-006 and -022

No medically relevant clusters of events (in terms of incidence and nature of SAEs) were observed in the HZ/su group compared to the Placebo group. In the main safety pooling analysis, SAEs were reported by 1,880 subjects (12.8%) in the HZ/su group and by 1,945 subjects (13.3%) in the Placebo group during the entire study period. From the first administered dose up to 30 days post last vaccination, SAEs were reported by 342 subjects (2.3%) receiving HZ/su and 327 subjects (2.2%) receiving placebo. In the broader safety pooling analysis (HZ/su group only), 100 additional HZ/su recipients reported SAEs during the entire study period. From the first administered dose up to 30 days post last vaccination, SAEs were reported by 366 subjects (2.4%) in the broader safety pooling analysis.

SAEs reported in the HZ/su group by PT (≥0.3% of HZ/su recipients) during the entire study period were pneumonia (0.8% in the HZ/su group and 0.7% in the Placebo group), cardiac failure (0.5% and 0.6%, respectively), myocardial infarction (0.5% each), atrial fibrillation (0.4% each), cerebrovascular accident (0.4% and 0.3%, respectively), coronary artery disease and cardiac failure congestive (0.3% each in both groups), and urinary tract infection (0.3% and 0.2%, respectively). The most frequently reported SAEs were similar in the broader safety pooling analysis.

In the main safety pooling analysis, SAEs considered related to vaccination by the investigator were reported by 15 subjects (0.1%) in the HZ/su group and by 13 subjects (0.1%) in the Placebo group

during the entire study period. In the HZ/su group, all related SAEs were reported by at most 1 subject. From the first administered dose up to 30 days post last vaccination, related SAEs were reported by 8 subjects (0.1%) in both the HZ/su and Placebo group. In the broader safety pooling analysis, no additional related SAE was reported in the HZ/su group.

During the entire study period, SAEs were reported with a higher incidence in subjects ≥70 YOA (16.5% and 17.3% in the HZ/su and Placebo groups, respectively, in the main safety pooling, and 16.6% in the HZ/su group in the broader safety pooling) compared to subjects 50-69 YOA (7.4% and 7.2% in the HZ/su and Placebo groups, respectively, in the main safety pooling, and 7.3% in the HZ/su group in the broader safety pooling). Considering the related SAEs in the HZ/su group, 12 of them were reported in ≥70 YOA, and 3 of them in 50-69 YOA. In the Placebo group, the incidence of related SAEs was similar between the ≥70 YOA (8 subjects) and 50-69 YOA (7 subjects) strata. By age range in the 50-59 YOA, 60-69 YOA, 70 79 YOA and ≥80 YOA strata, the percentage of subjects reporting SAEs during the whole post-vaccination follow-up period increased with age in both groups.

SAEs of special interest

Potential Immune-Mediated Disease (pIMDs)

Potential immune mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest, which may or may not have an autoimmune aetiology. For all vaccines containing adjuvant systems, including $AS01_B$, pIMDs are considered events of interest based on their possible effects on the regulation of the immune system and the potential (yet theoretical) risk that they may induce unwanted immune processes in susceptible individuals.

No medically relevant differences have been observed between the HZ/su and Placebo groups in terms of incidence and nature of pIMDs reported over the entire study period. In the main safety pooling analysis during the whole post-vaccination follow-up period, pIMDs were reported by 179 subjects (1.2%) in the HZ/su group and by 202 subjects (1.4%) in the Placebo group. By PT, the most frequently reported pIMDs (≥10 subjects) in both groups were polymyalgia rheumatica (32 subjects in the HZ/su group and 29 subjects in the Placebo group), rheumatoid arthritis (20 and 26 subjects, respectively), psoriasis (15 and 18 subjects, respectively) and autoimmune thyroiditis (13 and 10 subjects, respectively). In the broader safety pooling analysis, 5 additional subjects in the HZ/su group reported pIMDs during the entire study period (i.e. a total of 184 subjects [1.2%]).

In the main safety pooling analysis, pIMDs considered to be vaccine related by the investigator were reported in 16 subjects (0.1%) in the HZ/su group and 18 subjects (0.1%) in the Placebo group during the entire study period. By PT, most of the related pIMDs were reported by at most 1 subject in the HZ/su group, except for rheumatoid arthritis (2 subjects) and psoriasis (2 subjects). In the broader safety pooling analysis, no additional related pIMD was reported in the HZ/su group. The following pIMDs were additionally recorded in the broader safety analysis: 1 additional polymyalgia rheumatic, 1 additional psoriasis, 2 additional cases of trigeminal nerve paresis, one additional Crohn`s disease, 2 additional colitis ulcerative, and 8 additional IVth nerve paralysis.

The percentage of subjects reporting pIMDs by age stratum was comparable in the 50-69 YOA and ≥70 YOA strata (0.2% in each vaccine group).

Hypersensitivity (including anaphylaxis)

As for other vaccines, hypersensitivity reactions, including anaphylaxis to one or several components of the vaccine are considered AEs of special interest. Anaphylaxis following immunization is a serious but rare occurrence, i.e. estimates are in the range of 1-10 per 1 million doses distributed depending

on the vaccine studied. During the clinical development of HZ/su, subjects with known hypersensitivity to one or several components of the vaccine were excluded from enrolment.

Overall, no case of HZ/su-related anaphylaxis was identified in the main or broader safety pooling analysis. Several unsolicited AEs (by PT) indicative of hypersensitivity reaction and considered to be vaccine related by the investigator were recorded in the HZ/su vaccine group in the main safety pooling analysis. This includes, anaphylactic reaction (1 subject), hypersensitivity (3 subjects), rash generalized (4 subjects), rash macular (2 subjects), rash pruritic (3 subjects), urticarial (4 subjects), flushing (8 subjects in the vaccine and no subjects in the placebo group), and hot flush (6 subjects).

A statement on hypersensitivity is included in the "4.3 Contraindications" section of the SmPC.

2.6.4. Laboratory findings

Biochemical and hematological evaluations were conducted at baseline and at pre-defined time points in older adults in studies EXPLO-CRD-004, ZOSTER-003, ZOSTER-010 and ZOSTER-023, as well in immunocompromised adults in the phase I/IIa studies ZOSTER-001 and ZOSTER-015. The hematological laboratory parameters evaluated were hemoglobin concentration, white blood cell counts, differential white blood cells (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelets in all studies; red blood cell counts and hematocrit in all studies except for ZOSTER-015; and mean corpuscular volume in ZOSTER-010. Biochemical laboratory parameters tested included serum creatinine, aspartate aminotransferase and alanine aminotransferase in all studies; lactate dehydrogenase (LDH), calcium, fibrinogen, prothrombin time, partial thromboplastin time (PTT) and total protein levels in ZOSTER-001 and ZOSTER-015; and sodium, potassium, bicarbonate, glucose, alkaline phosphatase, bilirubin (direct and total) and albumin in ZOSTER-015. The great majority of subjects in all studies had laboratory values within normal ranges for all evaluated parameters at all time points. No clinical relevant changes pre- and post-vaccination were observed. The proportion of subjects with variations in laboratory values before and after vaccination was balanced between the vaccine groups in the different studies that evaluated laboratory parameters. Based on these data, no clinically significant alteration of hematologic or biochemical laboratory parameters has been observed following vaccination with HZ/su.

2.6.5. Safety in special populations

Pregnancy

There are no data on the use of HZ/su in pregnant women. Animal studies performed with HZ/su administered to female rats do not indicate any harmful effects with respect to pregnancy. The effect on breast-fed infants of administration of HZ/su to their mothers has not been studied. Only one pregnancy was recorded in all submitted studies. This subject was enroled in ZOSTER-023, a Phase I, open label, single-group study to evaluate the safety, reactogenicity and immunogenicity of HZ/su in 20 healthy adults of Japanese ethnic origin, stratified by age in a 1:1 ratio: 18-30 YOA and 50-69 YOA. Ten subjects were of child-bearing age. The pregnancy occurred in a 29-year old female, about 4 months after she received the second dose of HZ/su. About 12 months after the last vaccination, the woman gave birth to a healthy live female infant after 39 weeks of gestation.

Subjects with previous history of HZ (ZOSTER-033)

In ZOSTER-033, the evaluation of the safety and reactogenicity following administration of HZ/su from the first vaccination up to 30 days post last vaccination in all study subjects ≥50 YOA with a previous episode of HZ (by descriptive statistics) was a co-primary objective.

In all 96 subjects ≥50 YOA with a physician-documented history of HZ who were vaccinated in this study, the HZ/su vaccine was well tolerated and no safety concerns were identified. No vaccine-related SAEs, fatal SAEs or pIMDs were reported up to study end (12 months post vaccination). The safety and reactogenicity of the vaccine is not influenced by previous HZ episode, and although no control group was included in this study the safety profile was generally similar to that seen in other clinical studies in a population with no history of HZ. There were 9 episodes of suspected HZ reported in 6 (6.3%) subjects during this study, which was higher than the recurrence rate reported in the literature (up to 6.2% over a 7.3 year follow-up period). Considering laboratory confirmation of cases was not required per protocol, combined with the fact that some suspected cases were based on self-reporting by the subjects (some of them without medical diagnosis), an over-reporting of HZ is suspected, especially in the context of the high HZ VE shown in adults ≥50 YOA. Indeed, study participants were trained to recognize and report symptoms of HZ during the initial visit, which may have contributed to an increased awareness of HZ signs. Note that none of these suspected HZ cases were considered related to vaccination by the investigator. Furthermore, in Phase III clinical trials, between 24.8% and 40.2% of self-reported cases were confirmed as false positives after more rigorous testing. In addition, when epidemiological data suggest that the incidence does not differ between regions, the reported cases all occurred in the same country (Canada). As the study was not designed to formally evaluate HZ recurrence (uncontrolled study with a limited sample size and no HZ confirmatory testing), conclusions regarding this specific aspect of the study have to be considered with caution. See section 2.6.9 for more details. See also sections 2.5.5.4 and 2.5.6 for study details and discussion around efficacy aspects.

Safety of HZ/su when administered subcutaneously

ZOSTER-032 was a Phase III, open-label, uncontrolled study to evaluate the safety and immunogenicity of HZ/su when administered SC as compared to IM according to a 0, 2-month schedule. A total of 60 Japanese adults 50 years and older were vaccinated, 30 subjects each in the IM and SC vaccine group. The immune response after SC and IM injection of HZ/su in that very limited number of subjects appeared to be comparable. Efficacy was not evaluated following SC vaccination. The safety profile was comparable for the two routes of administration. Reactogenicity including severe reactions following SC was higher than following IM administration of HZ/su. This observation is known from other vaccines.

The incidence of solicited symptoms (local and general) overall per subject was only slightly higher in the SC compared with the IM vaccine group (100% of subjects versus 93.3%, respectively). Local reactogenicity was higher in the SC vaccine group compared with the IM vaccine group. Apart from injection site pain that was reported in a comparable proportion of subjects in the SC and the IM vaccine group (93.3% versus 90.0%) all other solicited local reactions were far more frequently reported in the SC compared with the IM vaccine group. Injection site redness and swelling were overall reported by 86.7% versus 31.3%, and 80.0% versus 22.7% of subjects, respectively. Injection site pruritus was reported by 70% of subjects in the SC and 33.3% in the IM vaccine group, respectively. Severe redness was reported by 56.7% in the SC vaccine group versus 0.8% in the IM group, severe injection site swelling by 33.3% versus 0.8% of subjects, and severe injection site pain by 6.7% versus 0.0%. Systemic reactogenicity was also higher in the SC vaccine group, but less than local reactogenicity. The most frequent symptom in both groups was fatigue reported by 70% versus 53.3% of subjects, followed by headache (56.7% versus 43.3%). The fever incidence was comparable in both groups (20.0% versus 23.3%, respectively). Severe solicited systemic symptoms were low in both groups and occurred not in a higher incidence in the SC vaccine compared with the IM vaccine group (overall per subject 3.3% versus 10.0%, respectively).

The incidence of unsolicited AEs was comparable in both groups (30.0% in the SC and 20.0% in the IM vaccine group). Unsolicited AEs considered to be vaccine related were reported by 3.3%, each.

No subjects died during the study. Three subjects, 2 in the SC HZ/su group and 1 in the IM HZ/su group, experienced non-fatal SAEs during the study. None of these SAEs were considered related to vaccination by the investigator.

Immunocompromised subjects (ZOSTER-001, ZOSTER-015)

In both ZOSTER-001 and ZOSTER-015, the evaluation of the safety and reactogenicity of the investigational HZ vaccine formulations used in these studies in subjects ≥18 YOA with a selected IC condition (autologous HCT and HIV infection, respectively) was a co-primary objective.

More than half of the subjects participating in ZOSTER-001 and ZOSTER-015 (N=73; 54%) were ≥50 YOA.

Safety in adult autologous hematopoietic stem cell recipients≥ 18 years of age

ZOSTER-001 was a Phase I/IIa, randomized, observer-blind, placebo-controlled study to evaluate the safety and immunogenicity of 3 and 2 IM injections of the final formulation of HZ/su (50 µg gE/$AS01_B$) in comparison to 3 IM injections of gE combined with 1/2 dose (i.e. 25µg) $AS01_B$ adjuvant (50 µg gE/$AS01_E$) and to 3 doses of Placebo administered to autologous HCT recipients ≥18 years of age. The TVC included 120 subjects equally randomised into the 4 parallel groups in a 1:1:1:1 ratio. The incidence of symptoms was comparable in the three vaccine groups and lower in the 3-dose placebo group. During the 7-day post-vaccination period overall, 93.1% to 96.7% of gE/AS01 vaccine recipients experienced at least one solicited or unsolicited symptom compared to 66.7% in the 3-dose placebo control group. The incidence of local symptoms was 82.8% to 90% in gE/AS01 vaccine recipients versus 23.3% in the 3-dose placebo group, and was 86.2% to 93.1% versus 63.3% for general symptoms, respectively. The reactogenicity and safety profile of HZ/su administered to a limited number of HCT recipients according to a 3 and 2 dose schedule did not reveal any safety concern.

Safety in adult HIV subjects

ZOSTER-015 was an observer-blind, placebo-controlled study with 2 treatment groups randomized to receive 3 doses of HZ/su or placebo at 0, 2, 6 months. A total of 123 subjects were vaccinated (74 in the gE/$AS01_B$ group and 49 in the placebo group). Local reactogenicity overall per subject was notably higher in the vaccine compared with the placebo group. 97.3% versus 12.2% of subjects reported unsolicited and solicited local symptoms. The majority of local solicited symptoms were mild or moderate. Grade 3 injection site symptoms occurred in 16.4% (injection site pain) to 1.4% (injection site swelling) of subjects. General solicited symptoms occurred in overall 75.3% (fatigue) to 50.7% of subjects (shivering) in the vaccine cohort. Fever was reported by 30.1% of gE/$AS01_B$ recipients, respectively. The majority of solicited general symptoms were mild or moderate. Severe solicited general symptoms were reported by 12.3% (shivering) to 1.4% (gastrointestinal symptoms). No grade 3 fever was reported. In summary, the safety and reactogenicity profile of HZ/su administered to the 74 HIV infected subjects did not raise any safety concern.

Conclusion

Several Phase III studies in IC adults are ongoing, and so far, the IDMCs overseeing 3 (ZOSTER-002, ZOSTER-039 and ZOSTER-041) of these 4 ongoing studies have not raised any safety concern. Therefore, it can be concluded that HZ/su was well tolerated when administered to IC adults ≥50 YOA with autologous HCT or HIV infection, although based on a very limited number of adults ≥18 YOA with a selection of IC conditions. The procedure to request approval of HZ/su vaccination in immunocompromised adults 18 years and older will be the subject of a subsequent application.

2.6.6. Safety related to drug-drug interactions and other interactions

In study ZOSTER-004 the safety and reactogenicity of HZ/su administered concomitantly or sequentially with the Applicant's D-QIV influenza vaccine was evaluated in subjects≥50 years of age. A total of 828 subjects were vaccinated either concomitantly with D-QIV or sequentially. Of note, solicited local and general symptoms occurred within the same range in the co-ad and the control group and the incidence was comparable overall per subject. Unsolicited AEs, pIMDs, SAEs and deaths occurred in a comparable proportion of subjects in both groups. None of the pIMDs, the SAEs and the deaths was considered being vaccine related. In summary the co-administration of HZ/su with D-QIV did not impact the reactogenicity or safety profile of HZ/su or D-QIV. The study did not reveal any safety concern.

There is no data on co-administration with Prevenar 13, Hepatitis B adjuvanted vaccine or other Influenza adjuvanted vaccine. Two additional co-administration studies are currently ongoing with Pneumovax and Boostrix.

2.6.7. Discontinuation due to adverse events

Of the 15,405 and 13,900 subjects included in the TVC at ZOSTER-006 End Of Study and in ZOSTER-022, 1,824 and 2,369 subjects were withdrawn, respectively. The most common reason for discontinuation was consent withdrawal in ZOSTER-006 (N=722), and withdrawal due to an SAE in ZOSTER-022 (N=943). A total of 462 subjects of ZOSTER-006 were withdrawn due to an SAE.

No apparent imbalance was observed between HZ/su and Placebo groups in either study regarding subjects withdrawn due to any reason.

Of the 15,411 subjects included in the TVC at ZOSTER-006 final analysis, 1,431 subjects were withdrawn. The most common reason for discontinuation was consent withdrawal (N = 607). A total of 370 subjects were withdrawn due to an SAE. No apparent imbalance was observed between HZ/su and Placebo groups in either study regarding subjects withdrawn due to any reason.

During the whole post-vaccination follow-up period, 77 subjects receiving HZ/su (0.5%) and 33 subjects receiving placebo (0.2%) were withdrawn from the study due to a non-serious AE, while 683 subjects receiving HZ/su (4.7%) and 722 subjects receiving placebo (4.9%) were withdrawn due to an SAE. In the broader safety pooling analysis, 3 additional subjects receiving HZ/su were withdrawn due to a non-serious AE and 1 additional subject due to an SAE.

In the main safety pooling analysis up to 1 month post Dose 2 (Month 3), 62 subjects receiving HZ/su (0.4%) and 17 subjects receiving placebo (0.1%) were withdrawn from the study due to a non-serious AE. In addition, 54 subjects receiving HZ/su (0.4%) and 48 subjects receiving placebo (0.3%) were withdrawn due to an SAE.

2.6.8. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The general safety profile of HZ/su is considered acceptable.

The safety data base is large and adequately represents the target population. A total of 17,041 individuals≥ 50 years of age received at least one IM dose of the commercial formulation of HZ/su.

14,645 adults 50 years and older were included in the main safety pooling analysis, that comprises individuals who received at least one dose of HZ/su in the pivotal studies ZOSTER-006 and ZOSTER-022. Of them, 5887 were 50 to 69 years of age, and 8758 ≥70 years of age. A total of 15,493 older adults≥ 50 YOA have been included into the broader safety pooling analysis, comprising additional studies conducted with different designs. Of them 6,415 were 50-69 years of age and 9,078 were ≥70 years of age. Solicited local and general AEs were collected in a subset of 4969 subjects. The incidence of solicited (local and general) symptoms is based on the TVC with 7-day diary card, and the incidence of unsolicited AEs is based on the TVC. The frequencies of the adverse reactions reported in the SmPC are based on the main safety pooling analysis.

Solicited AEs were more frequently reported by subjects in the vaccine group compared with the placebo group. Relative risks are statistically significant and above 1 for overall solicited AEs. Among HZ/su recipients, 80.8% (71.5% overall/dose) had at least one local symptom, and 64.8% (51.6% overall/dose) had at least one general symptom within the 7-day post-vaccination period vs. 11.7% (7.4% overall/dose) and 29.1% (19.4% overall/dose) of subjects in the Placebo group, respectively. The most frequently reported solicited local AE in the HZ/su and the placebo group was injection site pain, reported respectively by 70.3% overall/subject (68.1% overall/dose) and by 10.9% overall/subject (6.9% overall/dose). More than 40% of subjects in the HZ/su group reported solicited systemic AEs. The most frequently reported overall per subject in the 2 groups were myalgia (44.7% versus 11.7% overall/subject), fatigue (44.5% versus 16.5% overall/subject) and headache (37.7% versus 15.5% overall/subject). Fever was reported by 20.5% of subjects in the HZ/su group, but grade 3 fever (i.e. temperature > 39°C) occurred in only 0.3% of HZ/su recipients in that group. Grade 3 (severe) was defined as an Adverse Event which prevented normal, everyday activities. The great majority (>90%) of solicited AEs was graded as mild or moderate and resolved usually within the first 3 days. Severe solicited local AEs occurred overall per subject in not more than 6.4% (injection site pain) and severe systemic AEs in not more than 5.1% (myalgia). Severe AEs lasted at most 2 days (solicited local AEs) and 1 day (solicited general AEs).

Reactogenicity was higher in the younger age stratum (50-69 years of age) compared with the older one (≥70 years of age), especially for solicited general adverse reactions. The lower reactogenicity in older subjects is known from other vaccines. Incidence and severity of solicited local symptoms did not tend to increase by dose in the pivotal studies. Solicited general AEs were reported in a slightly higher proportion of subjects following dose 2, especially grade 3 solicited general symptoms. The observed reactogenicity is not unexpected for an adjuvanted vaccine and the results do not reveal any concern. The safety profile of HZ/su was acceptable within the follow-up period in all studies and all populations included into the studies. The drop-out rate due to (S)AEs was low and balanced between the HZ/su and Placebo groups.

Apart from expected local and general reactions that were recorded as unsolicited AEs in the SOC of general disorders and administration site conditions (e.g. injection site reactions, malaise, fatigue, chills), nervous system disorders (headache and dizziness), and musculoskeletal tissue disorders (myalgia, arthralgia), unsolicited AEs recorded in the HZ/su group did not show any specific pattern or cluster. Arthralgia is considered a common expected adverse reaction following vaccination. There is a biological plausibility for the occurrence of lymph node pain, lymphadenitis, and lymphadenopathy; hence it was included in the SmPC as uncommon ADR.

An imbalance was observed in the occurrence of Gout and Gouty arthritis between the vaccinated and the placebo groups with a relative risk above 3. This statistical association was discussed by the Applicant and no cause-effect relationship could be demonstrated. However as a biological plausibility cannot be ruled out, the Applicant will follow up on this specific unsolicited event (gout) by active and enhanced surveillance.

There are no specific concerns with regards to hypersensitivity reactions including anaphylaxis.

Incidence and nature of serious adverse events (SAEs, related and unrelated) was balanced between the HZ/su and the placebo group with no medically relevant clusters of SAEs reported in the HZ/su group compared to the Placebo group. SAEs considered to be HZ/su related by the investigator did not occur in more than one subject. The most frequently reported SAEs when classified by SOC were cardiac disorders, followed by infections and infestations (mainly of the respiratory tract) and neoplasms (benign, malignant and unspecified). The majority of SAEs HZ/su vaccine appeared to be associated with the target/studied population's risk factors (e.g. advanced age). The Incidence Rate is in line with epidemiological studies in a similar population. Same is true for fatal cases. One fatal SAE was considered being vaccine related by the investigator, but it is the view of the CHMP/PRAC that a relationship between vaccination and AML is highly unlikely based on the nature of the event (no biological plausibility). The neutropenic sepsis is considered most likely a side effect of the concomitant acazitidine therapy.

The distribution of SAEs at day 30, 1y and 4y post 1st dose for some PTs were not well-balanced. In the vaccinated cohort (especially after 1 year of 1st dose), some individual Medra-PTs showed an increased RR for SAEs and were attributed to Basal cell carcinoma, Pneumoniae and Lung Neoplasm. Also, the distribution of fatal outcomes at day 30, 1y and 4y post-vaccination for same specific PTs (except basal carcinoma) were not balanced between the 2 cohorts. The potential implications of this imbalance in terms of safety of the vaccine were further discussed during evaluation. The clinical and non-clinical data available for AS01- and other adjuvanted vaccines collectively indicate that the occurrence of a sustained dysregulation of the innate immune response that could accelerate/facilitate the development of infections or cancer induced by AS01 in combination with gE is unlikely. The fact that the innate immune responses triggered by AS01 to enhance gE specific response are transient and return to baseline by day 7 is additionally reassuring. It was concluded that from a scientific/medical point of view biological plausibility of the events discussed above and a potential correlation with vaccination appears unlikely, and other factors may directly intervene in the cause-effect relationship.

The Applicant discussed the concomitant prophylactic use of paracetamol around the time of vaccination to relieve vaccine solicited events (reactogenicity) such as pain. In the absence of robust data on the potential impact of antipyretics/analgesics on HZ/su immunogenicity and reactogenicity and based on the inconclusive literature data available from other vaccines in adult populations, a definitive recommendation cannot be given.

The inclusion and exclusion criteria of clinical studies with HZ/su allowed recruitment of an overall older adult population, including subjects with co-morbidities. However no formal assessment of frailty status was foreseen or performed at enrolment in any of the studies that have been completed to date. The clinical impact of the very common AEs (especially of grade 3) on the frail population is currently unknown and needs to be assessed. Therefore 'Use of HZ/su in frail adults 50 years of age or older' is included as missing information in the RMP. The post-marketing commitments to address safety of HZ/su in the frail population are reflected in the next section.

Adjuvanted vaccines are considered as a potential trigger for onset of autoimmune disease. The theoretical risk of acquiring an autoimmune disease derives from the immunological mechanism of action, i.e. in particular the immune enhancing effect of the adjuvants. In the trials conducted during the clinical development of HZ/su subjects were followed up at least for 6 months and up to 1 year after the last vaccine dose in order to detect autoimmune disease onset related to vaccination. The incidence and nature of pIMDs was balanced in the two vaccine groups. In the pooled analysis of safety there were 179 pIMDs reported after HZ/su administration (1.2%) compared to 202 cases (1.4%) reported in control group. 16 out of the 179 pIMDs in the vaccine group versus 18 in the placebo group were considered as related to the vaccine. Most frequently reported PTs in both groups are polymyalgia

rheumatica, rheumatoid arthritis, psoriasis and autoimmune thyroiditis. The reviewed safety data do not reveal a safety signal with respect to the potential risk of developing autoimmune disease following HZ/su vaccination, including the oldest age categories (>70 YOA) and populations undergoing immunosuppressive treatment (ZOSTER-001) or immunocompromised (ZOSTER-015). However the power of pre-licensure clinical trials to detect very rare events such as new onset of autoimmune disease is limited due to the sample size, since incidence rates of different AD vary roughly from 1 to 20/100,000 per year. AS01 is a new generation of adjuvant inducing a strong innate immune response. The experience with this novel adjuvant is still limited and the working mechanisms are not fully understood. Although the issues of occurrence of pIMDs as a result of vaccination and potential exacerbation of existing/underlying pIMDs (see below) are shared with other adjuvanted vaccines, an elderly population might have in principle a higher risk linked to general systemic inflammation or immune-dysregulation that they may experience as a results of ageing. For those reasons, the theoretical risk of developing a pIMD after HZ/su vaccination is considered as a potential safety concern in the RMP for post-authorisation follow-up via surveillance and safety study.

In subjects with pre-existing IMDs, clinical exacerbation triggered by $AS01_B$-adjuvanted vaccine was not identified but cannot be ruled out either, since a significant proportion of patients with pre-existing pIMDs and/or treated with steroids or immune-modulators would have been excluded from the pivotal studies based on the exclusion criteria as the studies were not designed for investigating those risks. Only a small number of relevant events were identified after vaccination. No specific mechanism explaining a new onset or exacerbation of a pre-existing IMD after HZ/su exposure was found. Nevertheless this will be included as missing information and will be followed up by routine and enhanced surveillance (targeted follow up questionnaires). ZOSTER-069 has been proposed as a new study to address this safety concern, currently under feasibility assessment (the study protocol will be further discussed post-authorisation).

ZOSTER-033 showed an overall acceptable reactogenicity/safety after vaccination of subjects with previous HZ, but a higher number of HZ cases than the recurrence rate generally reported in observational studies was observed. As the study was not designed to formally evaluate HZ recurrence (uncontrolled study with a limited sample size and no HZ cases confirmatory testing), it is not possible to conclude on the risk of triggering VZV reactivation in immunocompetent individuals with a history of HZ, which is thus added as an important potential risk in the RMP. Further data from well-designed studies are needed to make sure that HZ/su can be given safely to subject with history of HZ (studies ZOSTER-062 and ZOSTER-056, refer to sections 2.5.6 and 2.7).

The limited available data about transplanted (haematologic) as well as HIV+ patients are reassuring showing no safety signals including for an increase incidence of pIMDs. Based on the available data the vaccine is well tolerated. More studies among patients suffering for malignancy and other IC patients including those <50 YOA are ongoing and will be assessed in the post-authorisation phase.

The co-administration of HZ/su with D-QIV did not impact the reactogenicity or safety profile of HZ/su or D-QIV. The study did not reveal any safety concern. There are no data on co-administration with other vaccines.

Maladministration of HZ/su via SC route may lead to an increase in transient local reactions.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The general safety profile of HZ/su is acceptable. The main pooled safety analysis is based on data from more than 14,000 subjects from different geographic regions who received the HZ/su vaccine in the 2 phase III pivotal clinical trials. The most frequently reported adverse reaction were pain at the injection site (68.1% overall/dose), myalgia (32.9% overall/dose), fatigue (32.2% overall/dose), headache (26.3% overall/dose), fever (12.5% overall/dose) and gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain (10.7% overall/dose). The majority of these reactions were of mild to moderate severity and were not long-lasting (median duration of 2 to 3 days). Reactogenicity did not tend to increase by dose. Reactogenicity of HZ/su was slightly lower in the older age group (i.e. ≥70 years of age) compared with the younger one (50 to 69 years of age). The observed reactogenicity is not unexpected for an adjuvanted vaccine and the results do not raise any concern. Unsolicited AEs and SAEs did not indicate any cluster or specific pattern.

SAEs, including fatal cases, were overall equally distributed between HZ/su group and placebo with a frequency of ~13% for all SAEs and 0.1% for related SAEs (as per investigator assessment) in each group. The majority of SAEs, including fatal cases, occurred in ≥70 YOA and with time to onset longer than one year after last vaccination, and mostly appeared to be associated with the target/studied population's risk factors (e.g. advanced age). On basis of the overall results with a mean follow-up period of more than 3 years post-vaccination, no important identified risk has been found and no safety concern is raised from SAEs data.

pIMDs were equally distributed between HZ/su group and placebo, with a frequency of ~1% for all pIMDs and 0.1% for related pIMDs (as per investigator assessment) in each group. The incidence of pIMDs was balanced between age groups, and about half of the pIMDs occurred with time to onset longer than one year after last vaccination. The (theoretical) risk of acquiring a pIMD following HZ/su vaccination is included as important potential risk in the RMP. Routine and enhanced surveillance will follow up the risk post-authorisation; in addition a targeted safety study is planned (see below). Moreover possible exacerbation of pre-existing IMD after HZ/su vaccination needs further investigations in the post-marketing phase; hence it has been included as missing information in the RMP and will be followed up via routine and enhanced surveillance. In addition an immunogenicity and safety trial in adults with pre-existing pIMDs is planned (ZOSTER-069, currently under feasibility assessment).

Furthermore a certain number of uncertainties persist. Safety data on a very limited number of immunocompromised subjects with HIV or haematopoietic stem cell transplant are available. The use of HZ/su in subjects with other confirmed or suspected immunosuppressive or immunodeficient conditions is under investigation. As a consequence, the administration of HZ/su to immunocompromised subjects should be based on careful consideration of potential benefits and risks. There are very limited safety data to support use of HZ/su in subjects with a history of previous HZ. The risk of VZV reactivation following vaccination is included as potential risk in the RMP and more studies are planned. There are limited safety data subjects with underlying medical conditions including conditions associated with a higher risk of HZ. Also, there are limited safety data to support use of HZ/su in frail elderly subjects and in patients with immune mediated diseases. Vaccination should be considered on an individual basis. The use of the vaccine in all these subpopulations is included as missing information in the RMP and will be followed up via dedicated studies.

Co-administration of unadjuvanted inactivated seasonal influenza vaccine did not impact the safety profile of HZ/su, but there is no data available on coadministration with other vaccines. The Applicant is recommended to submit for assessment the results of the ongoing/planned coadministration studies as soon as available (coadministration study with Pneumovax23 (ZOSTER-035), PVN13 (ZOSTER-059) and Boostrix (ZOSTER-042)).

There is no safety data to support interchangeability of HZ/su with other HZ vaccines. A study ongoing at the time of this application investigated HZ/su vaccination of subjects who have previously received Zostavax (ZOSTER-048; data have recently become available and will be assessed post-authorisation).

The CHMP considers the following measures necessary to address safety concerns (missing information and important potential risks, see also section 2.7):

- Safety concern (important potential risk): risk of potential Immune Mediated Disorders: EPI-ZOSTER-030 VS (targeted safety study);
- Safety concern (important potential risk): VZV reactivation in immunocompetent individuals with a history of herpes zoster: ZOSTER-062 and ZOSTER-056;
- Safety concern (missing information): Use of HZ/su in frail adults 50 YOA and older: studies ZOSTER-063 and ZOSTER-64;
- Safety concern (missing information): Use of HZ/su in immunocompromised adults: studies ZOSTER- ZOSTER-002, ZOSTER-028, ZOSTER-039 and ZOSTER-041;
- Safety concern (missing information): Use of HZ/su in adults with pre-existing pIMDs: study ZOSTER-069;
- Safety Concern (missing information): Long term follow up studies ZOSTER-049 and ZOSTER-060 will provide more information on long term safety up to 10 years post-primary vaccination and on safety and reactogenicity after booster dose(s).

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Risk of potential Immune Mediated Disorders (pIMDs) following *Shingrix* vaccination • Virus reactivation in immunocompetent individuals with a history of Herpes Zoster
Missing information	• Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older. • Long-term immunogenicity in adults 50 years of age and older. • Use of *Shingrix* in frail adults 50 years of age or older • Use of *Shingrix* in immunocompromised adults • Use of *Shingrix* in adults with pre-existing pIMD • Effectiveness of *Shingrix* in preventing HZ, PHN and HZ-related complications

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
ZOSTER-049: A phase IIIb, open-label, multi-country, multi-centre, long-term follow-up study (ZOE-LTFU) of studies 110390 and 113077 (ZOSTER-006/022) to assess the prophylactic efficacy, safety, and immunogenicity persistence of *Shingrix* and assessment of 1 or 2 additional doses on a 0 or 0, 2-month schedule in two subgroups of adults 50 years of age and older (Category 3)	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 50 years of age and older. Long-term immunogenicity in adults 50 years of age and older.	Started	Interim report: 31 May 2021. Final Clinical Study Report (CSR): 31 Oct 2024.
ZOSTER-060: A phase IIIb, open, long term extension study to evaluate the persistence of immune responses and the safety of *Shingrix* at Months 108 and 120 post-vaccination and the assessment of re-vaccination with two additional doses administered at 10 years after the initial vaccination in study ZOSTER-003 in healthy subjects aged 60 years of age and older. (Category 3)	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 50 years of age and older.	Started	Interim report: 30 Apr 2019 Final CSR: 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 based on encoding of quality of life questionnaires completed by subjects during studies ZOSTER-006 and ZOSTER-022 and demographic characteristics (Category 3)	Observational study to assess frailty status and other prognostic factors for development of herpes zoster in an older adultpopulation 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.	Planned	Final CSR: 30 Sep 2020
ZOSTER-063: Study to evaluate the impact of reactogenicity on Quality of Life (QoL), after administration of *Shingrix* in adults ≥ 50 years of age (Category 3)	To assess the imact of reactogenicity of *Shingrix* on Quality of Life.	Use of *Shingrix* in frail adults 50 years of age or older.	Started	Final CSR: 31 Dec 2019
EPI-ZOSTER-030 VS: Target Safety Study (Category 3)	Non-interventional (observational) prospective 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.	Planned	Final CSR: 30 Mar 2025)

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
ZOSTER-002: A phase III, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of *Shingrix* when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients (Category 3)	To evaluate the vaccine efficacy in prevention of HZ, immunogenicity and safety of *Shingrix* in autologous HCT recipients 18 YOA or older (ZOSTER-002).	Use of *Shingrix* in immunocompromised adults.	Started	Final CSR: 31 Mar 2019
ZOSTER-039: A Phase III, randomised, observer-blind, placebo-controlled, multicentre study to assess the safety and immunogenicity of *Shingrix* when administered intramuscularly on a two-dose schedule to adults aged 18 years and older with haematologic malignancies (Category 3)	To evaluate safety, reactogenicity and immunogenicity following administration of *Shingrix* in subjects with haematological malignancies aged 18 YOA or older.	Use of *Shingrix* in immunocompromised adults.	Started	Final CSR: 31 Mar 2019
ZOSTER-041: A Phase III, randomised, observer-blind, placebo-controlled, multicentre clinical study to assess the immunogenicity and safety of *Shingrix* when administered intramuscularly on a 0 and 1 to 2-months schedule to adults ≥18 YOA with renal transplant (Category 3)	To evaluate safety, reactogenicity and immunogenicity of *Shingrix* in subjects with renal transplant aged 18 YOA or older.	Use of *Shingrix* in immunocompromised adults.	Started	Final CSR: 31 Mar 2019
ZOSTER-028: A Phase II/III randomised, observer-blind, placebo-controlled, multicenter, clinical trial to assess the immunogenicity and safety of *Shingrix* when administered intramuscularly on a 0 and 1 to 2 months schedule to adults ≥18 YOA with solid tumours receiving chemotherapy (Category 3)	To evaluate safety, reactogenicity and immunogenicity of *Shingrix* in subjects aged 18 YOA or older with solid tumors receiving chemotherapy.	Use of *Shingrix* in immunocompromised adults.	Started	Final CSR: 31 Mar 2019
ZOSTER-069: A Phase III, randomised, observer-blind, placebo-controlled, multicentre clinical study to assess the immunogenicity, reactogenicity and safety of *Shingrix* when administered intramuscularly on a 0- and 1- to 2-months schedule to adults with pre-existing pIMD (Category 3)	To evaluate safety, reactogenicity and immunogenicity of *Shingrix* in adults with pre-existing pIMD.	Use of *Shingrix* in adults with pre-existing pIMD.	Planned	Final CSR: 30 Jun 2025
ZOSTER-062 A phase III, randomized, observer-blind, placebo	To assess safety, immunogenicity and reactogenicity of	Virus reactivation in immunocompetent individuals with a	Planned	Final CSR: 30 Jun 2022

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
controlled, multicentre clinical trial to assess the safety, reactogenicity and immunogenicity of *Shingrix* when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of Herpes Zoster. (Category 3)	*Shingrix* in subjects with a previous history of Herpes Zoster.	history of Herpes Zoster		
ZOSTER-056: Cross-vaccination studyof *Shingrix* in subjects who previously received placebo in ZOSTER-006 and ZOSTER-022 studies (Category 3)	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 immunocompetent individuals with a history of Herpes Zoster	Started	Final CSR: 31 Jul 2020
EPI-ZOSTER-031: An observational (non-interventional) retrospective cohort study to evaluate vaccine effectiveness in subjects aged 50 years and above in the US (Category 3)	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 the vaccine effectiveness on the long term up to 10 years after vaccination with *Shingrix.*	Effectiveness of *Shingrix* in preventing HZ, PNH and HZ-related complication	Planned	Feasibility assessment report: 31 Jul 2018 Final CSR: 1 Aug 2033

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks		
Risk of potential Immune Mediated Disorders (pIMDs) following Shingrix vaccination	None	None
Virus reactivation in immunocompetent individuals with a history of Herpes Zoster	Yes, wording in SmPC sections 4.4 and 5.1	None
Missing information		
Long-term efficacy and assessment of the need for additional doses in adults 50 years of age and older	None	None
Long-term immunogenicity in adults 50 years of age and older	None	None
Use of Shingrix in frail adults 50 years of age or older	Yes, wording in SmPC sections 4.4 and 5.1	None
Use of Shingrix in immunocompromised adults	None	None
Use of Shingrix in adults with pre-existing pIMD	None	None
Effectiveness of Shingrix in preventing HZ, PHN and HZ-related complications	None	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The Applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 13.10.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The Applicant declared that Varicella Zoster virus glycoprotein E has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers Varicella Zoster virus glycoprotein E to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

During the procedure the CHMP contested the inclusion of HZ complications in the indication since complications of a disease are prevented as a consequence of the disease prevention, and as such there is no need to specifically include 'prevention of complications' in the indication.

However in the case of PHN, intended as a complication of zoster disease (i.e. shingles), the CHMP agreed to explicitly list PHN in the indication of Shingrix, because of the peculiarity of vaccines for shingles and the strict link to PHN as the most common and disruptive complication of zoster, which drives the clinical use of vaccines authorised against zoster and is therefore one of the main objectives for such prophylactic intervention. The CHMP considered the expected impact of the wording of the indication on the appropriate use of this vaccine and to avoid misinterpretations.

This decision was taken by majority. Some CHMP members were not in agreement with the majority view and their divergent positions are annexed to the Opinion.

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. 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 it contains a new active substance, which on 1st January 2011 was not contained in any medicinal product authorised in the EU.

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

Shingrix indication is for prevention of HZ and PHN in adults ≥50 YOA.

The aim of a HZ prophylaxis is to provide a larger benefit in terms of protection in subjects from 50 YOA onwards, especially in adults ≥ 70 YOA than offered by the currently available options. A reduction of the burden of HZ in adults ≥50 YOA (including ≥70 YOA) is expected, thus maintaining QoL. This is considered a better approach to management of this disease (rather than treatment of HZ and PHN) and to bring benefit from a health-economic perspective as well.

3.1.2. Available therapies and unmet medical need

The currently authorized HZ vaccine (Zostavax, Merck) demonstrated efficacy against HZ, but has some important limitations. Efficacy in preventing HZ in ≥60 YOA is moderate (51.3%), it is further reduced in ≥70 YOA (37.6%), the non-immunocompromised population at highest risk for both HZ and PHN, and it decreases over time. Since it is a live attenuated vaccine, it is contra-indicated in adults with immunosuppression or immunodeficiency due to the risk of vaccine-associated rash or disseminated disease.

In countries where no HZ vaccine is marketed, no other preventive options are available. Antiviral treatment for HZ is available, but in order to be effective it should be given early after HZ onset. Although timely initiation (within 72 hours) of antiviral treatment has been shown to reduce the severity as well as the associated pain of an HZ episode, no curative therapy is currently available for the treatment of PHN once it occurred. Therefore, the HZ/su vaccine is being developed to better address the medical need to prevent HZ and HZ-related complications such as post-herpetic neuralgia (PHN) in older adults (≥50 YOA) and to address the unmet medical need to prevent HZ and HZ complications in IC adults ≥18 YOA (future development).

The candidate vaccine has high efficacy and can be used in a broader target population than the currently available HZ vaccines.

3.1.3. Main clinical studies

The main evidence of efficacy submitted was generated in the two phase III multicentre, randomized, observer-blind studies comparing HZ/su (n=14,645) vs. saline placebo (n=14,660) in adults ≥50 YOA.

3.2. Favourable effects

Efficacy against HZ in adults ≥ 50 YOA (all ages from study ZOSTER-006)

A total of 216 subjects reported a confirmed HZ episode, amongst which 6 were in the HZ/su group and 210 in the Placebo group. No subject reported more than one confirmed HZ episode. The mean (SD) follow-up time was 3.1 (0.5) years. The median (min - max) follow-up time was 3.1 (0 - 3.7) years. The overall incidence rate of HZ per 1000 person-years was 0.3 in the HZ/su group and 9.1 in the Placebo group.

The overall HZ VE was 97.16% (95% CI: 93.72% - 98.97%; p-value < 0.0001) among participants who were ≥ 50 YOA. The primary objective of study ZOSTER-006 regarding HZ VE in subjects ≥50 YOA was met as the LL of the 95% CI of the VE against HZ was above 25%.

HZ VE was consistent across age strata:

- 50-59 YOA: 96.57% (95% CI: 89.62% - 99.31%; p-value < 0.0001)
- 60-69 YOA: 97.36% (95% CI: 90.14% - 99.69%; p-value < 0.0001)
- ≥70 YOA: 97.93% (95% CI: 87.91% - 99.95%; p-value < 0.0001)

The secondary objective regarding HZ VE by age stratum was met for the 50-59 YOA and 60-69 YOA strata as the LL of the 95% CI of HZ VE was above 10%. Although the study was not powered for this, significant VE against HZ was demonstrated in subjects ≥70 YOA as the LL of the 95% CI for HZ VE was far above 10% for that age stratum.

Efficacy against HZ in adults ≥70 YOA (pooled analysis)

A total of 309 subjects reported a confirmed HZ episode, of which 25 were in the HZ/su group and 284 in the Placebo group. No subject reported more than one confirmed HZ episode. The median (min - max) follow-up time was 4.0 (0 – 4.5) years. The overall efficacy against HZ ≥70 YOA was 91.3% (95% CI: 86.8% - 94.5%; P<0.0001).

HZ VE was consistent across age strata:

- 70-79 YOA: 91.3% (95% CI: 86.0% - 94.9%; P< 0.0001)
- ≥ 80 YOA: 91.4% (95% CI: 80.2 % - 97.0%; P< 0.0001)

The overall incidence rate of HZ per 1000 person-years was 0.8 in the HZ/su group and 9.3 in the Placebo group for the pooled analysis ≥70 YOA.

Efficacy against PHN in adults ≥50 YOA (all ages from study ZOSTER-006)

Overall, VE against PHN was 100% (95% CI: 77.1; 100), and therefore demonstrated in adults ≥50 YOA with no PHN cases in the HZ/su group vs. 18 in the Placebo group.

The PHN VE observed for the two age strata was:

- 50-59 YOA: 100% (95% CI: 40.8; 100), with no PHN cases in the HZ/su group and 8 in the Placebo group. Note that analysis was not powered for PHN VE by age strata, but as a result of the high VE against PHN reached in this age stratum the LL of the 95% CI was above 0.
- 60-69 YOA: 100% (95% CI: <0; 100), with no PHN cases in the HZ/su group and 2 in the Placebo group. The LL of the 95% CI was <0 (not statistically significant) due to the low number of PHN cases observed in this age stratum.

The overall incidence rate of PHN per 1000 persons-years was 0.0 in the HZ/su group and 0.6 in the Placebo group.

Efficacy against PHN in adults ≥ 70 YOA (pooled analysis)

Overall, VE against PHN was 88.78% (95% CI: 68.70 to 97.10), and therefore demonstrated in adults ≥70 YOA with 4 PHN cases in the HZ/su group vs. 36 in the Placebo group.

The PHN VE observed for both age strata was:

- 70-79 YOA: 93.04% (95% CI: 72.47 to 99.19), with 2 PHN cases in the HZ/su group and 29 in the Placebo group. Note that pooled analysis was not powered for PHN VE by age strata, but as a result of the high VE against PHN reached in this age stratum, the LL of the 95% CI was also above 0%.
- ≥80 YOA: 71.16% (95% CI: -51.51 to 97.08). However, the LL of the 95% CI was <0% due to the low number of PHN cases observed in this age stratum, i.e. 2 PHN cases in the HZ/su group and 7 in the Placebo group.

Results on VE against PHN in ≥70 YOA in the pooled analysis are consistent with ZOSTER-022, overall and by age stratum, and ZOSTER-006 EOS analysis. In the pooled analysis ≥70 YOA the overall incidence rate of PHN per 1000 persons-years was 0.1 in the HZ/su group and 1.2 in the Placebo group.

Other aspects of efficacy

In post-hoc analysis on pooled data, the vaccine significantly reduced the incidence of HZ associated vasculitis, disseminated disease, neurological disease and ophthalmic disease, with overall VE of

93.71% in the ≥50 YOA and 91.62% in the ≥70 YOA. No cases of visceral disease or stroke associated with HZ reported during the study.

The vaccine significantly reduced the use and the duration of HZ-associated pain medication by 39% (95% CI: 11.9; 63.3) and 50.6% (95% CI: 8.8; 73.2), respectively, in subjects ≥70 YOA (pooled data). The median duration of pain medication use was 32.0 and 44.0 days in the vaccine and placebo group, respectively.

In subjects ≥70 years (pooled data), the vaccine significantly reduced the maximum worst pain score using ZBPI versus placebo over the entire HZ episode (mean = 5.7 vs. 7.0, P-value = 0.032). In addition, the vaccine significantly reduced the maximum average pain score versus placebo over the entire HZ episode (mean = 3.9 vs. 5.5, P-value = 0.049 and mean = 4.5 vs. 5.6, P-value = 0.043, in subjects ≥50 years (ZOSTER-006) and ≥70 years (ZOSTER-006 and -022 pooled), respectively).

The AUC scores for severity-of-illness and severity-of-interference evaluated using ZBPI were significantly lower, overall and by age strata, in the vaccine group compared to placebo group. The estimated VE in pooled analysis in mitigating the BOI was 92.1% in ≥70 YOA, 95.1% in 70-79 YOA and 82.2% in ≥80 YOA. Similarly high efficacy in mitigating burden-of-interference was observed, overall and by age strata.

Overall, the data obtained for the exploratory endpoints suggest lower severity of pain and burden of illness and a lower loss of QoL in the HZ/su group.

In vaccinated subjects, 2 intramuscular doses of the vaccine on a 0, 2-month schedule elicited strong anti-gE ELISA titres (up to 42 median fold increase vs. pre-vaccination) and CMI responses to gE (up to 33 median fold increase vs. pre-vaccination) and VZV antigens, with elevated levels of induced immune response for up to 3 years post Dose 1 (more than 9 fold increase in anti-gE ELISA titres over pre-vaccination). The median anti-gE antibody concentration and the frequency of anti-gE specific CD4 T cells decline over the years but remain almost stable from year 4 to year 6 after vaccination (greater than 7 and 3.7-fold above baseline pre-vaccination, respectively). Immune responses to the 0,6-month schedule were non-inferior to immune responses to the 0,2-months schedule, for which efficacy was demonstrated.

The vaccine was shown to be immunogenic in a limited number of IC adults (135 HCT and HIV+ patients).

3.3. Uncertainties and limitations about favourable effects

Frail patients including those with multiple comorbidities seem to be under-represented in the pivotal trials, especially in the oldest age categories. Frailty has not been taken into account at enrolment and was not monitored during the study period. Information concerning vaccine efficacy in frail patients is limited; however two studies are planned in frail subjects >50 YOA.

Efficacy against HZ complications was based on a post-hoc analysis of limited power. No cases of visceral disease, stroke associated with HZ or ZSH were reported during the pivotal study. Whether the vaccine can be effective in preventing these zoster complications remains open question. The Applicant is currently investigating the feasibility of an effectiveness study with respect to the evaluation of the impact of the vaccine on HZ-related complications.

No demonstrative efficacy was seen against PHN occurrence in breakthrough cases due to insufficient power of the trials due to the high efficacy of the vaccine against HZ. However, given the overall body of data on VE agains PHN in overall population, VE against PHN in HZ-breakthrough cases is considered as supportive but not essential for the granting of the indication, also in view of the methodological

complications that would render this approach unfeasible in terms of attaining statistical significance. More data on these aspects can be generated from the planned effectiveness study and the long term efficacy studies.

Long term efficacy and persistence of immune responses as well as need and timing of additional doses is not established. However, two long-term follow-up efficacy and immunogenicity studies will evaluate these aspects.

Efficacy data in immunocompromised is limited at this stage to HIV+ and HCT patients but the vaccine was shown to be immunogenic. The clinical development is still ongoing including individuals down to 18YOA and 4 more studies are planned in different conditions.

Individuals with a history of HZ, excluded from the pivotal clinical trials, were investigated in one small non-controlled study. The vaccine was shown to be immunogenic but the number of HZ cases was higher than expected, although the study has many limitations so no conclusion can be drawn. More data is expected from 2 ongoing/planned studies (see also section 3.5).

There were no efficacy data against HZ generated for the 0, 6-month schedule, and no CMI data. Overall, the inclusion of the 0,6 month schedule in the SmPC is considered acceptable based on the available humoral immunogenicity data. However, due to the limitations of these data, the 0,2 month schedule is preferable. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 2 and 6 months after the first dose.

A correlate of protection has not been established. However, post-dose 2 anti-gE antibodies can be used for immunobridging, as it was done in immunocompetent individuals ≥50 years of age and for coadministration studies, based on the evidence that robust immune response are generated following vaccination.

There is no information on use of Shingrix in VZV naïve individuals or individuals previously vaccinated against varicella. This will be followed up by routine pharmacovigilance. One study investigated HZ/su vaccination of subjects who have previously received Zostavax but data have only recently become available and will be assessed post-authorisation. There are no safety, immunogenicity or efficacy data to support replacing a dose of Shingrix with a dose of another HZ vaccine, so this is not recommended.

Immunogenicity data on coadministration with other vaccines is limited to the quadrivalent unadjuvanted inactivated influenza vaccine; three more studies are ongoing to investigate coadministration with polysaccharide pneumococcal vaccine, PCV13 and DTaP vaccine.

3.4. Unfavourable effects

Nature and incidence of recorded local and general AEs are in line with what can be expected from an adjuvanted vaccine. Based on a main safety pooled analysis on 14,645 adults ≥50 YOA who have received at least one dose of Shingrix, the most frequently reported adverse reactions after vaccination were pain at the injection site (68.1% overall/dose; 3.8% grade 3/dose), myalgia (32.9% overall/dose; 2.9% grade 3/dose), fatigue (32.2% overall/dose; 3.0% grade 3/dose) and headache (26.3% overall/dose; 1.9% grade 3/dose). Other very common adverse reactions were injections site redness/swelling, chills, fever and gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain). More than 90% of these reactions were of mild to moderate severity and were not long-lasting (median duration of 2 to 3 days). Severe (grade 3) reactions lasted 1-2 days. Data showed a higher reactogenicity within the youngest age strata as compared to those >70 YOA, especially for solicited grade 3 (severe) general symptoms. The overall reactogenicity did not tend to increase by dose.

Overall, there was neither imbalance nor medically relevant clusters of serious adverse events in the HZ/su group compared to the Placebo group. No safety signal has been detected. Co-administration of Shingrix with unadjuvanted inactivated seasonal influenza vaccine did not impact the safety profile of Shingrix (see below). Maladministration via SC route may lead to an increase in transient local reactions. Shingrix has shown a clinically acceptable safety profile when administered to a limited number of immunocompromised adults (see below).

Overall, based on a large safety database from controlled clinical trials (15,493 individuals in the broader safety pooling) with an average follow up time of about 3 years, Shingrix showed an acceptable safety profile and good tolerability in adults ≥50 years of age.

3.5. Uncertainties and limitations about unfavourable effects

Pending further investigation (four more trials are ongoing including individuals down to 18YOA), only limited safety data are available in immunocompromised subjects with HIV or haematopoietic stem cell transplant. Although the vaccines showed an acceptable safety profile in HIV+ and HCT patients, due to the limitation of the data the administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks.

There is limited safety data to support the use of Shingrix in individuals with a history of HZ and the study has methodological limitations, so the theoretical risk of VZV reactivation in immunocompetent individuals with a history of HZ is included in the RMP as important potential risk. One specific study is planned (ZOSTER-062 - placebo controlled study) and another one will provide additional information (ZOSTER-056).

There are limited safety data to support the use of Shingrix in individuals with frailty or with multiple underlying medical conditions, including conditions associated with a higher risk of HZ. The uncertainty is mostly linked to aspects of frailty such as immunosenescence, immune dysregulation and inflammation. Two studies are planned to investigate safety and reactogenicity by frailty status.

The data in patients with immune mediated diseases show no safety signal for a new pIMD onset after vaccination or for exacerbation of a pre-existing pIMD, but it is considered limited, also considering the incidence of these diseases. Thus the risk of pIMDs is reflected as safety concern (important potential risk) in the RMP, and it will be followed by routine pharmacovigilance and by a study. Another study is planned in individual with existing pIMDs with or without immunosuppressive treatment.

Vaccination should be considered on an individual basis in population for which limited data are available.

There are no safety data to support interchangeability of Shingrix with other HZ vaccines, so this is not recommended. Safety data on the use of Shingrix in subjects who have previously received Zostavax have only recently become available (to be assessed post-authorisation).

Three studies are ongoing/planned to investigate safety of coadministration of Shingrix with other vaccines (Pneumovax23, Boostrix and Prevenar13). Until this data become available coadministration is not recommended.

Safety and reactogenicity of booster dose(s) and long term safety are not established and will be investigated post-authorisation in 2 long term follow up studies up to 10 years post-primary vaccination.

3.6. Effects Table

Table 49. Effects Table for Shingrix for the prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older

Effect	Unit	Vaccine	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects					
VE against HZ*[1] **50-59YOA**	% (95% CI) over a median FU of 3.1 years	96.57 (89.62-99.31) HZ cases: 3	- HZ cases: 87	Secondary endpoint, appropriately powered	ZOSTER-006
VE against HZ **60-69YOA**	% (95% CI) over a median FU of 3.1 years	97.36 (90.14-99.69) HZ cases: 2	- HZ: cases 75	Secondary endpoint, appropriately powered	ZOSTER-006
VE against HZ **≥70YOA**	% (95% CI) over a median FU of 4 years	91.30 (86.88-94.46) HZ cases: 25	- HZ cases: 284	Re-estimation of VE (P<0.0001) Similar results across age strata 70-79 and >80 YOA	Pooled analysis*[2]
VE against PHN*[1] **50-59YOA**	% (95% CI) over a median FU of 4.1 years	100.00 (40.88-100.0) PHN cases: 0	- PHN cases: 8	Secondary objective not powered	ZOSTER-006
VE against PHN **60-69YOA**	% (95% CI) over a median FU of 4.1 years	100.00 (<0-100.00) PHN cases: 0	- PHN cases: 2	Secondary objective not powered	ZOSTER-006
VE against PHN **≥70YOA**	% (95% CI) over a median FU of 4 years	88.78 (68.70-97.10) PHN cases: 4	- PHN cases: 36	Primary objective, well powered. Similar results in 70-79YOA, VE lower >80YOA.	Pooled analysis*[2]
Unfavourable effects					
Injection site pain*[3]	Overall incidence rate (%) per vaccine dose	68.1% overall/dose 3.8% severe/dose	6.9% overall/dose	The risk for local & systemic solicited AEs is significantly increased vs. placebo	Main pooled safety analysis*[2]

Effect	Unit	Vaccine	Placebo	Uncertainties/ Strength of evidence	References
Solicited systemic ADRs (myalgia, fatigue, headache)*[3]	As above	~26-33% overall/dose 2-3% severe/dose	~7-10% overall/dose	Fever was reported by 12.8% overall/dose	As above

Abbreviations: VE (Vaccine Efficacy); HZ (Herpes Zoster); PHN (Post-herpetic neuralgia); YOA (years of age); CI (confidence interval); FU (follow-up); ADR (adverse drug reaction); AE (Adverse event)

***Notes**: *[1]: VE was calculated as 1-RR (RR is the relative risk of HZ or PHN cases for vaccinated vs. unvaccinated subjects); *[2]: the term 'pooled analysis' refers to the pooled efficacy and safety data from the 2 pivotal studies ZOSTER-006 and ZOSTER-022; *[3]: only the most frequently reported solicited local and general ADRs are reflected in the table. Refer to the SmPC for a full safety profile.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Shingrix has shown high efficacy against HZ and PHN in adults ≥50 YOA and consistently in all age strata with only slight decrease with age and time until around 4 years post-vaccination. Due to this high efficacy, the evidence in support of VE against other HZ-related complications and against PHN in breakthrough cases is limited or absent. The duration of VE against HZ and PHN beyond 4 years and the need for a booster dose in case of waning efficacy is unknown. These aspects should be further evaluated post-licensure via long term efficacy follow-up and effectiveness studies.

The true magnitude of the protective effect could potentially be smaller in real life than that estimated in the pivotal trials due to identified uncertainties regarding the study populations in terms of comorbidities, frailty and underlying auto-immune disorders.

The use of Shingrix in subjects immunocompromised (IC) is possible although at the moment there is limited efficacy and safety data available to support a specific recommendation for use, pending ongoing studies.

Severe reactogenicity was not uncommon. Even if reactogenicity in terms of headache, fatigue, fever might have debilitating effects in particular in frail elderly, or individuals suffering from underlying comorbidities, most adverse reactions are temporary and could be managed by standard medical care.

The submitted data did not reveal a higher incidence of pIMDs in the vaccine group compared with the placebo group. However, the power of pre-licensure clinical trials to detect very rare events such as new onset of autoimmune disease is limited due to the sample size, since incidence rates of different autoimmune diseases vary roughly from 1 to 20/100,000 per year. The (theoretical) risk of acquiring a vaccine induced pIMDs following HZ/su vaccination will be followed up post-licensure.

Only limited data from a study with methodological limitations are available for subjects with previous history of HZ, based on which it is not possible to conclude on the potential risk of HZ recurrence, pending ongoing studies.

3.7.2. Balance of benefits and risks

The main aim of HZ/su is to prevent HZ infection and HZ-related complications in the population ≥50 years of age having an increased risk of developing HZ due to immunosenescence. Clear evidence for high vaccine efficacy against HZ, overall by treatment group and by age strata, is given. As a consequence of HZ prevention, a highly reduced PHN incidence was demonstrated overall and by age strata including in the older age groups. Shingrix can be used in immunocompromised individuals.

Based on the available safety data in over 15,000 HZ/su vaccine recipients, it can be concluded that there is no major safety concern related to the use of Shingrix in the target population (adults ≥50 YOA). There is no important identified risk and there are two important potential risks included in the RMP: pIMDs (theoretical risk considered for all vaccines containing adjuvant systems) and use in subjects with a history of HZ (potential reactivation of VZV). The reactogenicity and safety profile of HZ/su is considered acceptable in the target population.

It is therefore considered that the high vaccine efficacy largely outweighs the unfavourable effects linked mainly to reactogenicity as no important risks were otherwise identified.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Shingrix is positive.

The divergent positions are appended to the opinion.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Shingrix is favourable in the following indication:

“Shingrix is indicated for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN), in adults 50 years of age or older (see section 5.1).

The use of Shingrix should be in accordance with official recommendations.”

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

Not applicable.

Obligation to conduct post-authorisation measures

Not applicable

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

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Varicella Zoster virus glycoprotein E is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

APPENDIX 1

DIVERGENT POSITION

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Shingrix.

The reasons for divergent opinion were as follows:

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the final wording of the indication for use of Shingrix, granted for prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN) in adults 50 years of age or older.

The reason for the divergent opinion relates to the inclusion of prevention of post-herpetic neuralgia in the indication statement. This is for the following reasons:

It is not agreed that PHN is an integral part of shingles. It is a sequela of clinically apparent shingles that affects a proportion of patients. It is intuitive that a medicinal product that is highly efficacious in preventing a disease will also prevent the complications and sequelae of that disease. It is not usual for the indication statements of vaccines to refer to the complications of an infectious disease, the occurrence of which will obviously be reduced by preventing the disease in the first place.

Consequently, an indication statement specifically for prevention of PHN logically refers to breakthrough cases of HZ that occur despite vaccination. Granting of such an indication is not supported by evidence. Shingrix is a highly efficacious vaccine against shingles. Thus, with very few breakthrough cases, the data available cannot support a conclusion that the vaccine prevents PHN in breakthrough cases. It is acknowledged that the data do suggest that it ameliorates the acute disease in breakthrough cases. This is not unexpected since licensed vaccines against primary HZ infection are well known to reduce the number of lesions and shorten the course of the disease in breakthrough cases. This fact alone is not evidence for prevention of PHN.

The fact that another authorised vaccine for HZ includes prevention of PHN in the wording of its indication is not considered an argument to do the same for Shingrix. As mentioned, this needs to be seen in context of the individual efficacy profiles and in the case of a relatively ineffective vaccine, enough breakthrough cases observed to support a conclusion that vaccination reduced the incidence of PHN in the breakthrough cases.

London, 25 January 2018

CHMP Members expressing a divergent position:

Greg Markey	25 January 2018	Signature: …….
Johann Lodewijk Hillege	25 January 2018	Signature: …….
Robert Hemmings	25 January 2018	Signature: …….