Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart, Belgium

Primary Study vaccine	• GlaxoSmithKline Biologicals' Lyophilised formulation of the Herpes Zoster (HZ) vaccine (GSK 1437173A)
eTrack study number and Abbreviated Title	204926 (ZOSTER-060 EXT:003)
EudraCT number	2015-004400-30
Date of protocol	Final Version 1: 12 November 2015
Date of protocol amendment	Amendment 1 Final: 18 August 2017
Title	Long term immunogenicity and safety study of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine 1437173A and assessment of re-vaccination with 2 additional doses, in healthy subjects aged 60 years of age and older.
Detailed Title	A phase IIIB, open, long term extension study to evaluate the persistence of immune responses and the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine 1437173A, 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.
Co-ordinating authors (Amended 18 August 2017)	• PPD ***Scientific Writer*** • PPD (XPE Pharma & Science contractor for GSK Biologicals)
Contributing authors (Amended 18 August 2017)	• PPD ***Clinical Research and Development Lead*** • PPD Clinical Research and Development Lead • PPD ***Study Delivery Lead*** • PPD Study Delivery Lead • PPD Lead Statistician • PPD ***Project Statistician***

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Contributing authors (Amended 18 August 2017)	• PPD Project Statistician • PPD Study Manager • PPD Clinical Read-out Team Lead, Clinical Laboratories Science • PPD Study Manager, Clinical Laboratories Science • PPD Vaccine Supply Coordinator • PPD ***Clinical Safety representative*** • PPD Clinical Safety representative • PPD Project Data Manager • PPD Global Regulatory Affairs • PPD Global Patent • PPD Zoster Project Level Clinical Research and Development Lead, Belgian RDC • PPD Clinical ***and Epidemiology Project*** Lead ***for Zoster***, Belgian RDC

GSK Biologicals' Protocol DS v 14.1.1

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204926 (ZOSTER-060 EXT:003)
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Sponsor signatory (Amended 18 August 2017)	Lidia Oostvogels, Clinical ***and Epidemiology Project*** Lead ***for Zoster***, Belgian RDC
Signature	
Date	

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Protocol Amendment 1 Rationale

Amendment number: Amendment 1
Rationale/background for changes: • This protocol amendment was developed to clarify in Section 8.2.1 that: – All SAEs will be collected and recorded from the time of the first receipt of study vaccine at Visit 2 until the subject is discharged from the study or until the end of the study; – All AEs/SAEs leading to withdrawal from the study will be collected and recorded from Visit 1 up to the last study visit at the end of the study; and by aligning Table 4 and Table 15 with the text in Section 8.2.1. • Although no confirmed signals related to hypersensitivity reactions (including anaphylaxis) have been identified during the HZ/su clinical program, a mitigation strategy for the potential risk has been added to the Risk Assessment Section 1.3.1. • The list of the contributing authors was updated and minor typographic errors were corrected.

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational vaccine and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	204926 (ZOSTER-060 EXT:003)
EudraCT number	2015-004400-30
Date of protocol amendment	Amendment 1 Final: 18 August 2017
Detailed Title	A phase IIIB, open, long term extension study to evaluate the persistence of immune responses and the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine 1437173A, 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.
Investigator name	_____
Signature	_____
Date	_____
PPD **ame, function and title**	_____
Signature	_____
Date	_____

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.2.

GSK Biologicals Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.3.2.

SYNOPSIS

Detailed Title	A phase IIIB, open, long term extension study to evaluate the persistence of immune responses and the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine 1437173A, 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.
Indication	Prevention of Herpes Zoster (HZ) and related complications in adults aged 50 years and older and in immunocompromised (IC) adults aged 18 years and older.
Rationale for the study and study design	• Rationale for the study GlaxoSmithKline (GSK) Biologicals' candidate vaccine for the prevention of Herpes Zoster (HZ), HZ/su, a recombinant subunit (su) vaccine consisting of Varicella-Zoster virus (VZV) glycoprotein E (gE) as antigen and an adjuvant system (AS01), has been and is being evaluated in several studies in older adults and immunocompromised adults. In these studies it was shown to elicit strong cellular and humoral immune responses. Furthermore, the safety and reactogenicity profile of the candidate vaccine was acceptable. Based on phase II data from the antigen dose-ranging study, ZOSTER-003, and the adjuvant dose comparison study, ZOSTER-010, the formulation using gE antigen dose of 50 µg and the adjuvant system AS01B (HZ/su vaccine) was selected for the final vaccine and for use in all future studies. Henceforth, the final vaccine formulation will be referred to as HZ/su. The results of the previous studies in older adults demonstrated strong vaccine-induced immune responses following HZ/su administration at 0 and 2 months, supporting the selection of a 2-dose vaccine schedule. Two large pivotal Phase III trials (ZOSTER-006 enrolled subjects ≥ 50 YOA and ZOSTER-022 enrolled subjects ≥ 70 YOA) are ongoing to evaluate the vaccine efficacy (VE) and safety of HZ/su vaccine. These trials have enrolled more than 30,000 subjects who either received the HZ/su vaccine or placebo control vaccine on a 0, 2-month schedule. The final HZ/su vaccine efficacy results from the ZOSTER-006 Phase III trial demonstrated an overall vaccine efficacy against HZ of 97.2% [95% CI: 93.7-99.0], with no safety concerns raised. Results received up to date from the ZOSTER-022 Phase III trial and from a prespecified pooled analysis over both studies confirmed these findings.

In study ZOSTER-003, subjects were randomized into 5 groups and were administered different formulations including the candidate HZ/su vaccine. These subjects were then followed at Month 12 (ZOSTER-011), Month 24 (ZOSTER-012), and Month 36 (ZOSTER-013) for safety and immunogenicity of the different formulations. Study ZOSTER-024 followed all subjects who received 2 doses of the selected formulation (50µg gE/AS01B [HZ/su vaccine]) in study ZOSTER-003, at Months 48, 60 and 72. The results indicated that HZ/su-induced immune responses remained above baseline levels at Month 72. The current long-term follow-up (LTFU) study (ZOSTER-060) is planned to evaluate the persistence of immune response to the HZ vaccine as well as safety up to 10 years after the first dose of initial vaccination course. This study will also assess immune responses after re-vaccination with 2 additional doses of the HZ/su administered at ten years after the initial vaccination course from study ZOSTER-003. If the immune responses wane over time, the increase in immunogenicity following revaccination with 2 additional doses of HZ/su vaccine could support the concept of administering additional doses with the expectation that this may translate into preserving VE.

Even though an immunologic threshold of protection has not been identified, these data may provide information that will help us evaluate the potential of HZ/su to provide long-term protection against HZ.

- Rationale for the study design

In this LTFU study (ZOSTER-060), subjects who received 2 doses of HZ/su in the earlier ZOSTER-003 study will be followed up at Month 108/Year 9 and Month 120/Year 10 post first dose of vaccine for safety and immunogenicity.

In order to assess the effect of re-vaccination with 2 additional doses of HZ/su vaccine, all the subjects will receive 2 additional doses of the HZ/su vaccine, on a 0, 2-month schedule at ten years after the initial vaccination course in study ZOSTER-003.

In alignment with the previous persistence studies, this study has no control group.

Blood samples for the evaluation of persistence of humoral and cellular immunogenicity as well immunogenicity after re-vaccination will be taken from all subjects who participate in the study.

Objectives

Primary

- To evaluate persistence of humoral and cell mediated immune responses overall at Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003.

Secondary

For the persistence phase Months 108 and 120 post first dose of initial vaccination in study ZOSTER-003:

- To evaluate the persistence of humoral and cell mediated immune responses within each age cohort (60-69 YOA and ≥70 YOA at the time of the initial vaccination) at Months 108 and 120 post first dose of initial vaccination course.
- To evaluate the safety of the study vaccine from Months 108 to Months 120 post first dose of initial vaccination course.

For the re-vaccination phase:

- To evaluate humoral and cell mediated immune responses to a two dose re-vaccination course at one month after each dose (Months 121 and 123) and 12 months after last dose (Month 134) when administered 10 years after the initial vaccination course.
- To evaluate the reactogenicity and safety of the study vaccine after re-vaccination with two additional doses.

Study design

- Experimental design: Phase IIIB, open-label, multi-centric, single group.
- Duration of the study: The intended duration of the study per subject is approximately 26 months.
  - Epoch 001: Long-term follow-up starting at Visit 1 (Month 108, Year 9) and ending at Visit 6 (Month 134).
- Study group: Subjects vaccinated with 2 doses of HZ/su (group 50µg gE/AS01$_B$) in study ZOSTER-003 will be offered participation in this study.

Synopsis Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Epochs
		Epoch 001
50µg gE/AS01$_B$	~100	x

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups
HZ/su	VZV gE	50µg gE/AS01$_B$
	AS01B	

- Control: uncontrolled.
- Vaccination schedule: Visit 2 (Month 120) and Visit 4 (Month 122) in the re-vaccination phase.
- Treatment allocation: All subjects will receive HZ/su and will be assigned to the two age cohorts (60-69 years of age [YOA] and ≥ 70 YOA at the time of vaccination) as defined in the ZOSTER-003 study.
- Blinding: Open-label.

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	Open-label

- Sampling schedule: Blood samples for immunogenicity evaluation will be collected at the following study visits:
  - Visit 1 (Month 108/Year 9), Visit 2 (Month 120/Year 10), Visit 3 (Month 121/ one month after re-vaccination dose 1), Visit 5 (Month 123/ one month after re-vaccination dose 2) and Visit 6 (Month 134/ 12 months after re-vaccination dose 2).
- Type of study: extension of other protocols, i.e., ZOSTER-003.
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects Subjects who were vaccinated with 2 doses of HZ/su during study ZOSTER-003 will be offered enrolment into this LTFU study.

Endpoints

Primary

- Antigen-specific antibody (Ab) concentrations at Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003.
  - Anti-gE Ab concentrations as determined by ELISA at Months 108 and 120.
- Cell-Mediated Immunity (CMI) in terms of frequencies of antigen-specific CD4 T-cells at Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003.
  - Frequencies of CD4+ T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE as determined by Intracellular Cytokine Staining (ICS) at Months 108 and 120.

Secondary

For the follow-up of persistence phase Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003:

- Antigen-specific antibody (Ab) concentrations within each age cohort (60-69 YOA and ≥70 YOA at the time of initial vaccination) at persistence Months 108 and 120.
  - Anti-gE Ab concentrations as determined by ELISA at Months 108 and 120.
- Cell-Mediated Immunity (CMI) in terms of frequencies of antigen-specific CD4 T-cells within each age cohort (60-69 YOA and ≥70 YOA at the time of initial vaccination) at persistence Months 108 and 120 post first dose of initial vaccination course.
  - Frequencies of CD4+ T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE as determined by Intracellular Cytokine Staining (ICS) at Months 108 and 120.
- Serious Adverse events:
  - Occurrence of all serious adverse events (SAEs) related to study participation or to a concurrent GSK medication/vaccine (including HZ/su administered during the ZOSTER-003 study) between Months 108 and 120.

For the re-vaccination phase:

- Antigen-specific antibody (Ab) concentrations post re-vaccination.
  - Anti-gE antibody concentrations as determined by ELISA in all subjects at one month after each vaccine dose (Months 121 and 123) and 12 months after last dose (Month 134).
- Cell-Mediated Immunity (CMI) in terms of frequencies of antigen-specific CD4 T- cells at one month after each vaccine dose (Months 121 and 123) and 12 months after last dose (Month 134).
  - Frequencies of CD4+ T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE as determined by Intracellular Cytokine Staining (ICS) at Months 121, 123 and 134.
- Solicited local and general symptoms:
  - Occurrence and intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination in all subjects;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in all subjects;
- Unsolicited adverse events (AEs)
  - Occurrence, intensity and relationship to vaccination of unsolicited Aes during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects
- SAEs
  - Occurrence and relationship to vaccination of all SAEs from dose 1 of re-vaccination until study end.
  - Occurrence of any fatal SAEs from dose 1 of re-vaccination until study end.
- Potential immune-mediated diseases (pIMDs)
  - Occurrence and relationship to vaccination of any pIMDs from dose 1 of re-vaccination until study end in all subjects.

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LIST OF ABBREVIATIONS

Ab:	Antibody
AE:	Adverse Event
AIC:	Akaike's Information Criterion
$AS01_B$:	MPL, QS21 Stimulon®, liposome based Adjuvant System [50µg MPL and 50µg QS21]
ATP:	According-To-Protocol
CD40L:	CD40 Ligand
CDC:	Centers for Disease Control
CMI:	Cell-Mediated Immunity
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
FDA:	Food and Drug Administration, United States of America
GCP:	Good Clinical Practice
gE:	Glycoprotein E
GMC:	Geometric Mean Concentration
GSK:	GlaxoSmithKline
HZ:	Herpes Zoster
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IFN-γ:	Interferon gamma
IL-2:	Interleukin- 2
IMC:	Intercurent Medical Condition
IMP:	Investigational Medicinal Product

IRB:	Institutional Review Board
LSLV:	Last Subject Last Visit
LTFU:	Long-Term Follow-up
MedDRA:	Medical Dictionary for Regulatory Activities
mIU:	Milli International Unit
MPL:	3-O-desacyl-4'-Monophosphoryl Lipid A
PBMC:	Peripheral Blood Mononuclear Cells
PHN:	Postherpetic Neuralgia
pIMD:	Potential Immune-Mediated Disease
RDC:	Research and Development Centre
QS21: (Amended 18 August 2017)	*Quillaja saponaria Molina, fraction 21* (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA)
SAE:	Serious Adverse Event
SBIC:	Schwarz' Bayesian Information Criterion
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SPM:	Study Procedures Manual
su:	Subunit
TNF-α:	Tumor Necrosis Factor alpha
VZV:	Varicella-Zoster virus
YOA:	Years of Age

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all timepoints within that epoch allows to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.6.2 and 10.4 for details on criteria for evaluability).

Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Intercurrent Medical Condition:	It is defined as a condition with onset during the study period that has the capability of confounding the immune response to the study vaccine or its interpretation. Examples of IMCs include a confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., HIV infection, malignancy), occurrence of a suspected case of HZ during this study will be considered an intercurrent medical condition (IMC).
Investigational vaccine/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.

Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the synopsis), the names of the vaccines/products and/or medications will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
QS-21 **(Amended 18 August 2017)**	(*Quillaja saponaria* Molina, fraction 21) (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA).

1. INTRODUCTION

1.1. Background

Varicella-zoster Virus (VZV) causes two distinct diseases. Varicella (chickenpox) occurs shortly after primary VZV infection and is characterised by systemic illness and a widely disseminated rash. Herpes zoster (HZ), commonly called shingles, occurs when VZV reactivates from latency and typically manifests as a localised, dermatomal rash.

The typical HZ rash usually lasts 2 to 4 weeks and is typically accompanied by pain that is often described as burning, shooting, or stabbing. In some patients, even touching the affected area lightly may cause pain, a phenomenon known as allodynia. This HZ-associated pain may be severe, and pruritus, which can also be severe, may be as common as pain.

The most common complication of HZ is postherpetic neuralgia (PHN). PHN is defined as pain that persists after the resolution of the HZ rash. Affected patients typically report constant burning, throbbing, intermittent sharp or electric shock-like pain, or allodynia [Dworkin, 2007]. Other complications of HZ include ophthalmologic, neurological, cutaneous and visceral disease, which can result in severe disability. The most common ocular complications of HZ are keratitis and uveitis; other ophthalmologic complications include ptosis, episcleritis/scleritis, retinitis, secondary glaucoma and cataract [Schmader, 2008; Carter, 2008]. Neurologic complications associated with HZ include myelitis, motor neuropathy, ischaemic infarction of the brain and spinal cord, aneurysm, and subarachnoid and cerebral haemorrhage [Gilden, 2009; Schmader, 2008].

Age is the most common risk factor for developing HZ. The incidence of HZ is relatively constant at 2-3 cases per 1000 persons per year until age 40, and then increases progressively with age: at 50-59 years of age (YOA) the incidence is about 5 cases per 1000 persons per year, and it increases to 10 cases per 1000 persons per year in people ≥ 60 YOA [CDC, 2008; Oxman, 2005]. While most HZ incidence data come from the e United States (US) and Europe, available data indicate similar incidences of HZ in other parts of the world including Japan, Korea, Australia and Latin America [Araújo, 2007; Garcia Cenoz, 2008; Kang, 2008; Toyama, 2009].

Half of all HZ cases occur in patients over the age of 60, and individuals who reach 85 years old have a 50% chance of having HZ during their lifetime [Oxman, 2005]. Patients with impaired cell-mediated immunity (CMI) due to disease, drug treatment, medical interventions or advanced age are at increased risk for the development of HZ [Cohen, 2007]. Since the loss of VZV-specific T cell responses as a result of aging or immunosuppression leads to heightened susceptibility to HZ, vaccination is considered as a means to reduce the risk of HZ in older adults and immunocompromised persons [Oxman, 2005; Sperber, 1992].

GlaxoSmithKline (GSK) Biologicals' candidate vaccine for the prevention of HZ, HZ/su, a recombinant subunit (su) vaccine consisting of VZV glycoprotein E (gE) as antigen and an adjuvant system (AS01), has been and is being evaluated in several studies in older adults and immunocompromised adults. In these studies it was shown to elicit strong

cellular and humoral immune responses. Furthermore, the safety and reactogenicity profile of the candidate vaccine was acceptable. Based on phase II data from the antigen dose-ranging study, ZOSTER-003, and the adjuvant dose comparison study, ZOSTER-010, the formulation using gE antigen dose of 50 μg and the adjuvant system AS01B (HZ/su vaccine) was selected for the final vaccine and for use in all future studies. Henceforth, the final vaccine formulation will be referred to as HZ/su. The results of the previous studies in older adults demonstrated strong vaccine-induced immune responses following HZ/su administration at 0 and 2 months, supporting the selection of a 2-dose vaccine schedule.

Two large pivotal Phase III trials (ZOSTER-006 enrolled subjects ≥ 50 YOA and ZOSTER-022 enrolled subjects ≥ 70 YOA) are ongoing to evaluate the vaccine efficacy (VE) and safety of HZ/su vaccine. These trials have enrolled more than 30,000 subjects who either received the HZ/su vaccine or placebo control vaccine on a 0, 2-month schedule. The final HZ/su vaccine efficacy results from the ZOSTER-006 Phase III trial demonstrated an overall vaccine efficacy against HZ of 97.2% [95% CI: 93.7-99.0], with no safety concerns raised [Lal, 2015]. Results received up to date from the ZOSTER-022 Phase III trial and from a prespecified pooled analysis over both studies confirmed these findings.

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies of HZ/su vaccine.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

In study ZOSTER-003, subjects were randomized into 5 groups and were administered different formulations including the candidate HZ/su vaccine. These subjects were then followed at Month 12 (ZOSTER-011), Month 24 (ZOSTER-012), and Month 36 (ZOSTER-013) for safety and immunogenicity of the different formulations. Study ZOSTER-024 followed all subjects who received 2 doses of the selected formulation (50μg gE/AS01B [HZ/su vaccine]) in study ZOSTER-003, at Months 48, 60 and 72. The results indicated that HZ/su-induced immune responses remained above baseline levels at Month 72. The current long-term follow-up (LTFU) study (ZOSTER-060) is planned to evaluate the persistence of immune response to the HZ vaccine as well as safety up to 10 years after the first dose of initial vaccination course. This study will also assess immune responses after re-vaccination with 2 additional doses of the HZ/su administered at ten years after the initial vaccination course from study ZOSTER-003. If the immune responses wane over time, the increase in immunogenicity following revaccination with 2 additional doses of HZ/su vaccine could support the concept of administering additional doses with the expectation that this may translate into preserving VE.

Even though an immunologic threshold of protection has not been identified, these data may provide information that will help us to evaluate the potential of HZ/su to provide long-term protection against HZ.

1.2.2. Rationale for the study design

In this LTFU study (ZOSTER-060), subjects who received 2 doses of HZ/su in the earlier ZOSTER-003 study will be followed up at Month 108/Year 9 and Month 120/Year 10 post first dose of vaccine for safety and immunogenicity.

In order to assess the effect of re-vaccination with 2 additional doses of HZ/su vaccine, all the subjects will receive 2 additional doses of the HZ/su vaccine, on a 0, 2-month schedule at ten years after the initial vaccination course in study ZOSTER-003.

In alignment with the previous persistence studies, this study has no control group.

Blood samples for the evaluation of persistence of humoral and cellular immunogenicity as well immunogenicity after re-vaccination will be taken from all subjects who participate in the study.

1.3. Benefit : Risk Assessment

Please refer to the current Investigator Brochure for the summary of potential risks and benefits of HZ/su vaccine.

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment (Amended 18 August 2017)

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational HZ/su vaccine		
Risk of pIMD following the HZ/su vaccination.	No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.	Close monitoring of pIMDs as per study protocol. The potential risk of events of possible autoimmune aetiology to occur is mentioned in the ICF. In addition, the ICF advises subjects to contact the study doctor or the study staff immediately, should they get any symptoms that they feel maybe serious.
Hypersensitivity reactions (including anaphylaxis)	***No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.***	***Administration of the study vaccination is to be preceded by a review of the subjects' medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.*** ***As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.***
Study procedures (LTFU study)		
Risk of blood sampling	Blood sampling associated risk of syncope, dizziness, infection at the site after or during venipuncture	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health.

1.3.2. Benefit Assessment

Benefits include:

- Potential benefit of receiving the study vaccine that may provide a clinical benefit in reducing the risk of developing HZ.
- Medical evaluations/assessments associated with study procedures (e.g. physical examination).

1.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures to minimize risk to subjects participating in this study, the potential or recognized risks identified in association with the investigational HZ/su vaccine and the study procedures are offset by the potential benefits (prevention of HZ and related complications) that may be afforded to the subject(s).

2. OBJECTIVES

2.1. Primary objective

- To evaluate persistence of humoral and cell mediated immune responses overall at Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003.

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

For the persistence phase Months 108 and 120 post first dose of initial vaccination in study ZOSTER-003:

- To evaluate the persistence of humoral and cell mediated immune responses within each age cohort (60-69 YOA and ≥70 YOA at the time of the initial vaccination) at Months 108 and 120 post first dose of initial vaccination course.
- To evaluate the safety of the study vaccine from Months 108 to Months 120 post first dose of initial vaccination course.

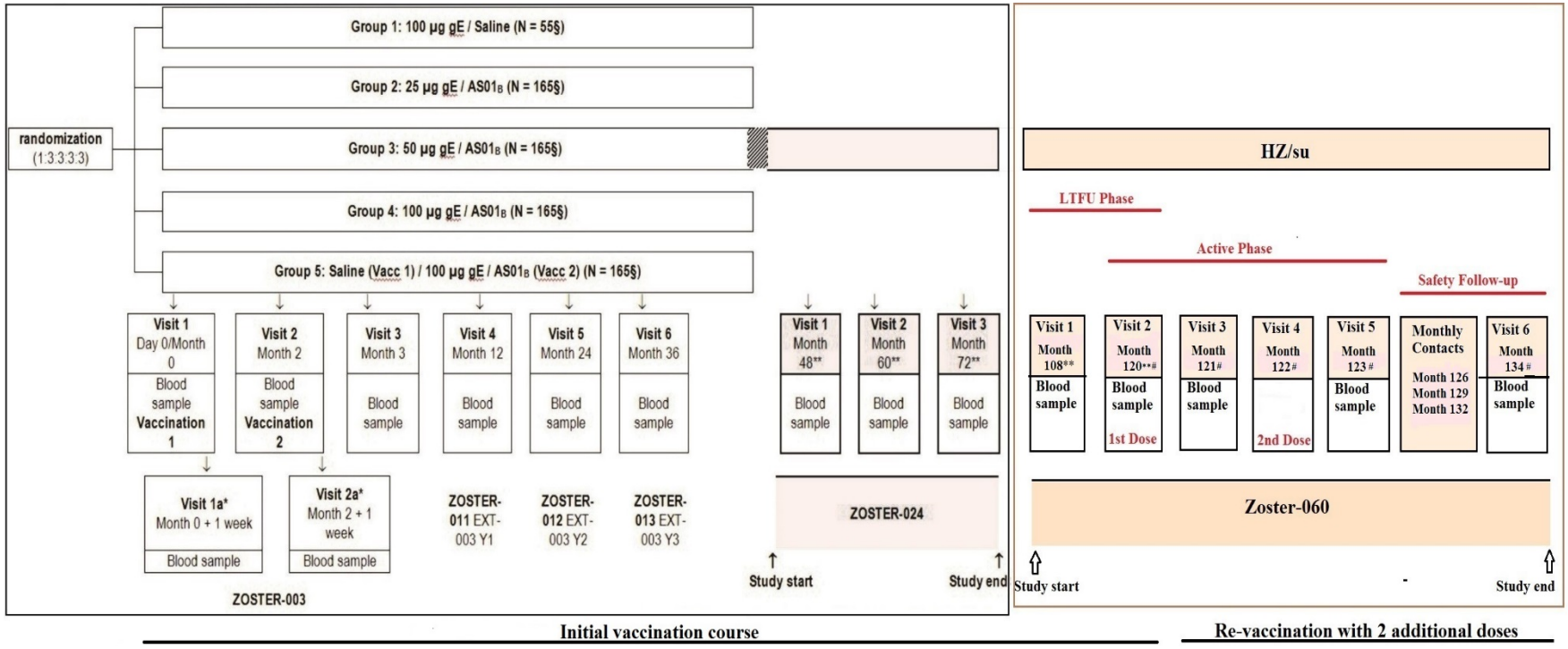
For the re-vaccination phase:

- To evaluate humoral and cell mediated immune responses to a two dose re-vaccination course at one month after each dose (Months 121 and 123) and 12 months after last dose (Month 134) when administered 10 years after the initial vaccination course.
- To evaluate the reactogenicity and safety of the study vaccine after re-vaccination with two additional doses.

Refer to Section 10.2 for the definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW

Figure 1 Study design overview



* Visits only performed by initial 104 subjects enrolled in Germany
** In ZOSTER-003, subjects received vaccination at Month 0 and Month 2. Months 48, 60, 72, 108 and 120 are respectively 48, 60, 72, 108 and 120 after first dose of vaccination.
# Months 120, 121, 122, 123 and 134 correspond to Month 0, 1, 2, 3 and 14 of the re-vaccination course.
§ N is the number of subjects that were planned to be enrolled in ZOSTER-003

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- Experimental design: Phase IIIB, open-label, multi-centric, single group.
- Duration of the study: The intended duration of the study per subject is approximately 26 months.
  - Epoch 001: Long-term follow-up starting at Visit 1 (Month 108, Year 9) and ending at Visit 6 (Month 134).
- Study group: Subjects vaccinated with 2 doses of HZ/su (group 50µg gE/AS01$_B$) in study ZOSTER-003 will be offered participation in this study.

Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Epochs
		Epoch 001
50µg gE/AS01$_B$	~100	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups
HZ/su	VZV gE	50µg gE/AS01$_B$
	AS01B	

- Control: Uncontrolled.
- Vaccination schedule: Visit 2 (Month 120) and Visit 4 (Month 122) in the re-vaccination phase.
- Treatment allocation: All subjects will receive HZ/su and will be assigned to the two age cohorts (60-69 years of age [YOA] and ≥ 70 YOA at the time of the initial vaccination) as defined in the ZOSTER-003 study.
- Blinding: Open-label.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	Open-label

- Sampling schedule: Blood samples for immunogenicity evaluation will be collected at the following study visits:
  - Visit 1 (Month 108/Year 9), Visit 2 (Month 120/Year 10), Visit 3 (Month 121/ one month after re-vaccination dose 1), Visit 5 (Month 123/ one month after re-vaccination dose 2) and Visit 6 (Month 134/ 12 months after re-vaccination dose 2).
- Type of study: extension of other protocols, i.e., ZOSTER-003.
- Data collection: Electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centres

Subjects who participated in study ZOSTER-003, in group 50 µg gE / $AS01_B$, and had complete vaccination vaccination course (2 doses of HZ/su) in study ZOSTER-003 will be offered enrolment into this LTFU study.

All subjects willing to participate in the ZOSTER-060 study will be enrolled and assigned to the two age cohorts (60-69 years of age [YOA] and ≥ 70 YOA at the time of the initial vaccination) as defined in the ZOSTER-003 study. Refer to Sections 4.1 and 4.3 for inclusion/exclusion criteria, respectively.

Overview of the recruitment plan

The study will include subjects in multiple centres in selected countries that previously participated in study ZOSTER-003.

At the time of initiation of the long-term follow-up study, the investigator will contact those subjects from his site who completed the study ZOSTER-003, were vaccinated with HZ/su and for whom he/she believes the subject can be eligible for and interested in participation in the ZOSTER-060 study. The reason for non-participation in the long-term follow-up study will be documented in the site's screening log.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits, ability to have scheduled contacts to allow evaluation during the study). Or subjects with a caregiver who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, vaccination visits, availability for follow-up contacts).
- Written informed consent obtained from the subject prior to performance of any study specific procedure.
- Previous participation in study ZOSTER-003, in group 50 µg gE / $AS01_B$, and who completed vaccination course (2 doses of HZ/su) in study ZOSTER-003.
- Subjects who can complete Visit 1 between 108 and 111 months after the first HZ/su dose of the previous vaccination course in study ZOSTER-003.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the first study visit (Day -29 to Day 0), or planned use during the study period.
- Use or anticipated use of immunosuppressants or immune-modifying drugs during the period starting six months prior to study start and during the whole study period. This includes chronic administration of corticosteroids (>14 consecutive days of prednisone at a dose of ≥20 mg/day [or equivalent]), long-acting immune-modifying agents (e.g., infliximab) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders).
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, human immunodeficiency virus [HIV] infection).
- Administration or planned administration of a live vaccine in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose of study vaccine, or, administration or planned administration of a non-replicating vaccine* within 8 days prior to or within 14 days after either dose of study vaccine.

  E.g., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines and pneumococcal conjugate vaccines.
- Previous vaccination against HZ since initial vaccination in ZOSTER-003.
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before study start, or planned administration during the study period.
- History of previous HZ.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent and subject informed assent, as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF and IAF, respecting the mandatory requirements of local regulations. The ICF and IAF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation of treatment

Subjects will keep the subject numbers that they were assigned in study ZOSTER-003.

5.2.1. Treatment allocation

The treatment allocation will be performed using SBIR. The treatment numbers will be allocated by dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding

This is an open-label study with only one treatment group.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.4.1. Data collection

After Visit 5, there will be 3 contacts between the subjects/subject's caregiver and the investigator and/or his delegate for the purpose of collecting information on any event of interest (see Table 4 and Section 5.6.8.1 for details). The contacts will take place using the most convenient method suited for the sites (e.g., telephone calls by site staff or designee, or visit by the study staff to the subject's home). A guidance document outlining the information that needs to be collected at each contact will be provided to each country, and will serve as a guidance to develop the local script. The logistic details on the set-up of the contacts will be documented by each site/country. At each contact, the subjects/subject's caregiver will respond to a standard set of questions in a language that is understandable to them. The investigator and/or his delegate will transcribe the relevant information or any event of interest in the appropriate section of the subject's eCRF, in English.

Diary cards to be completed by the subject/ subject's caregiver will be distributed and explained by the investigator or his/her delegate. Any supplied diary cards should be preferably completed by the subject themselves. In case of difficulty in self-completion of the diary cards, an aide (such as a family member or caregiver who is not involved in the study) may provide assistance with transcribing the subject's information in the diary cards.

The 7-day and 30-day diary cards will be dispensed on the day of vaccination to be completed by the subjects/ subjects' caregiver. The 7-day diary cards will be completed for solicited AEs (from Day 0 to Day 6 after each vaccination) and the 30-day diary cards will be completed for unsolicited AEs (from Day 0 to Day 29 after each vaccination) and any concomitant medication and vaccination taken from Day 0 to Day 29 after each vaccination (see Table 4 and Table 15).

When the completed diary cards are returned to the study staff, the study staff will ask the subject (at the time of return or at subsequent contact) if he/she received any assistance in completing diary cards. If the subject had assistance completing the diary card (e.g., by a caregiver), it should be noted in the eCRF.

5.5. Outline of study procedures

Table 4 List of study procedures

Epoch 001							
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Contacts**	**Visit 6**
Timepoints	**Year 9‡ Month 108 §**	**Year 10‡ Month 120 #**	**Month 121 #**	**Month 122 #**	**Month 123 #**	**Month 126 Month 129 Month 132**	**Month 134 #**
Sampling timepoints for Long-Term Follow-up Phase	**Post-Vacc**	**Post-Vacc**					
Sampling timepoints for Re-vaccination Phase		**Pre-Vacc1**	**Post-Vacc1**		**Post-Vacc2**		**Post-Vacc2**
Informed consent	●						
Check inclusion/exclusion criteria	●						
Collect demographic data	●						
Medical history	●	●					
History directed physical examination	O	O					
Check contraindications and warnings and precautions		●		●			
Pre-vaccination body temperature		●		●			
Vaccine administration		●		●			
Blood sampling for antibody determination ((5 ml)	●	● *	●		●		●
Blood sampling for CMI response ((20 ml)	●	● *	●		●		●
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●
Distribution of diary cards		O		O			
Return of diary cards			O		O		
Transcribing of solicited symptoms reported within 7 days post-vaccination			●		●		
Transcribing of non-serious adverse events reported within 30 days post-vaccination			●		●		
Recording of Intercurrent Medical Conditions (IMCs)	●	●	●	●	●	●	●
Recording of any SAEs ***after the first dose from the re-vaccination course at Visit 2*** **(Amended 18 August 2017)**		●	●	●	●	●	●
Recording of any AEs/SAEs leading to withdrawal from the study **(Amended 18 August 2017)**	●	●	●	●	●	●	●
Recording of SAEs related to investigational vaccine, study participation or to a concurrent GSK medication/vaccine †	●	●	●	●	●	●	●
Recording of any pIMDs		●	●	●	●	●	●
Recording of HZ cases **	●	●	●	●	●	●	●
Study Conclusion							●

Note: The double-line border following Month 108 and Month 123 indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Month 108/123.

Vacc: vaccination

● is used to indicate a study procedure that requires documentation in the individual eCRF

O is used to indicate a study procedure that does not require documentation in the individual eCRF

§ Subjects can complete Visit 1 between 108 and 111 months after the first HZ/su dose of the previous vaccination course in ZOSTER-003.

‡ Months 108 and 120 after first dose of initial vaccination course in study ZOSTER-003

Months 120, 121, 122, 123 and 134 correspond to Month 0, 1, 2, 3 and 14 of the re-vaccination course.
* Before vaccine administration.
** HZ cases will be collected in HZ specific screen in the eCRF.
† SAEs related to investigational vaccine include SAEs occurring between V1 and V2 considered as related to initial vaccination in ZOSTER-003 study and SAEs related to re-vaccination course occurring after administration of the 1st dose from re-vaccination course.

Table 5 Intervals between study visits

Interval	Length of interval	Maximum interval allowed[1]
Visit 1→Visit 2	12 months	365 - 401 days
Visit 2→Visit 3	1 months	28 - 48 days
Visit 2→Visit 4	2 months	49 - 83 days
Visit 4→Visit 5	1 months	28 - 48 days
Contacts between Visit 5 and Visit 6	3 months between each	75-105 days[2]
Visit 4→Visit 6	12 months	327 - 401 days

Whenever possible the investigator should arrange study visits within this interval.
[1] The investigator should endeavour to have the subjects come in for the visits within this interval. However subjects may not be excluded from the ATP cohort for analysis of immunogenicity if they make the study visit outside this interval.
[2] The phone contacts are to be as evenly spaced throughout time as possible. Phone contacts which are not at the intervals as specified in this table will not necessary result in elimination from the ATP cohort.

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed informed consent of the subject must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

Local laws and regulations (EC/RB recommendations and/or approvals) should be followed when a subject needs the assistance of a caregiver in completing study procedures.

The following are recommended and can be used as guidance in such cases:

- The need of a caregiver in completing study procedures will be confirmed during the informed consent process by the subject. In addition, the caregiver will also provide his/her agreement to be involved in the study and express willingness to act in a support role during the conduct of study specific procedures. The agreement of the caregiver to participate to the study will be included in the subject's ICF in a separate dedicated paragraph. The role of the caregiver will be fully explained in the ICF or annex where the subject and the caregiver will confirm their involvement in the study.

- The caregiver can stop assisting the subject in completing study procedures for any reason at any time, and he/she should be replaced by another caregiver, if still needed. The former caregiver must not be involved in the consent process and the appointment of a new caregiver. The new caregiver should confirm his/her willingness to assist the subject in completing study procedures by signing the annex part of the ICF together with the subject*.

  * Note that in this case, the subject would sign the annex part of the ICF to confirm his/her agreement with the new caregiver's assistance in completing study procedures. The signature would not be considered as a subject re-consent to study participation.

- At the start of the study, the subject/caregiver should be instructed to announce when the caregiver stops his/her involvement in the study (if possible, beforehand) and whether he/she will be replaced by another caregiver.

- The signature of the new caregiver can be obtained on study site. When the subject/caregiver are unable to visit the investigational site to sign the annex part of the ICF, other more convenient means are acceptable*, provided that they are in accordance with the protocol and local laws and regulations (local/regional/national EC/RB).

  *When explanation of the study procedures given to the new caregiver is done solely by telephone, proper documentation of the process (information provided, name of individual obtaining the annex of ICF, date annex obtained) should be included in the study records.

- If non-compliance with study procedures (as assessed by the investigator) results from changing the caregiver, the subject would be considered as a withdrawal.

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.1 and 4.3 before enrolment.

5.6.3. Collect demographic data

Record demographic data such as date of birth and gender in the subject's eCRF.

5.6.4. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in the subject prior to the study start and to the first study re-vaccination dose in the CRF/eCRF.

Below is a list of the type of medical conditions that should be collected as part of the medical history:

- Acute on-going medical conditions
- Chronic on-going medical conditions

- Serious medical conditions that happened in the past even if not currently on-going. The following criteria should be taken into account to assess a medical condition as serious:
  - A medical condition for which hospitalization was required;
  - A medical condition for which surgery was performed;
  - Life-threatening medical condition.

A condition that doesn't meet any of the criteria above but that the investigator considers to be serious or relevant, taking into account the population under study and the medical circumstances of subjects in that population.

Excluded from recording are: acute infections that have resolved (e.g., lobar pneumonia, influenza), medical events that have resolved (e.g., hip fracture with replacement, cataract treated with surgery). A predefined list of excluded categories and diseases will be available in the eCRF.

In addition, history of prior HZ episode must be recorded.

5.6.5. History directed physical examination

Visit 1: Perform a history directed physical examination. Collected information needs to be recorded in the source document.

Visit 2: Perform a history directed physical examination. If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled. Collected information needs to be recorded in the source document.

Medical information collected at both visits needs to be recorded in the source document. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.6. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 for more details.

5.6.7. Assess pre-vaccination body temperature

The axillary, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral. If the subject has fever (fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 5).

5.6.8. Training on self-reporting by subjects

Subjects/ subject's caregiver will be instructed at Visit 1 (and will be reminded at each visit or contact) to contact their study site immediately:

- should the subject manifest any signs or symptoms he/she perceive as serious;
- should the subject develop any symptoms suggestive of HZ. The subject/subject's caregiver must complete the HZ-specific diary card immediately upon development of these symptoms prior to visiting the study site for evaluation of the suspected HZ;
- if the subject has been diagnosed by an attending physician as having suspected HZ.

5.6.8.1. Reminder for follow-up contacts between Visit 5 and Visit 6

The subject/ subject's caregiver will be reminded that, after Visit 5, contacts between the subjects and the investigator and/or his delegate will take place in order to collect all relevant information on occurrence of a suspected episode of HZ, SAEs (Section 8.2), pIMDs, IMCs (Section 6.7) or the use of concomitant medications and/or vaccinations (Section 6.6.2), and that information will be recorded in the appropriate section of the subject's eCRF.

5.6.9. Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.9.1. Blood sampling for safety or immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.5 List of Study Procedures.

- A volume of about 5 mL of whole blood should be drawn from all subjects for each analysis of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at -20°C/-4°F (-80°C/-112°F is also acceptable) until shipment. Refer to the SPM for more details on sample storage conditions.
- A volume of about 20 mL of whole blood should be drawn from all subjects for analysis of cell-mediated immune (CMI) response at each pre-defined timepoint. The blood should be stored at the investigator's site at room temperature and it must not be centrifuged. Samples will be shipped at room temperature (15 to 25°C/68 to 77°F) to the designated laboratory for cell separation to be performed within 24 hours. Refer to the SPM for more details on sample storage conditions.

5.6.10. Study Vaccine administration

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.11. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.6.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.7.

5.6.12. Recording of AEs, SAEs and pIMDs

- Refer to Section 8.2 for procedures for the investigator to record AEs, SAEs and pIMDs. Refer to Section 8.3 for guidelines and how to report SAE and pIMD reports to GSK Biologicals.
- The subjects/subjects' caregiver will be instructed to contact the investigator immediately should they/the subjects manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to the subject/subject's caregiver. The subject/subject's caregiver will record body (oral) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 29 days occurring after vaccination.
- The subject/ subject's caregiver will be instructed to return the completed diary cards to the investigator at the next study visit. The study staff/investigator will collect and verify completed diary cards during discussion with the subject/ subject's caregiver on Visit 3 and Visit 5.
- Any unreturned diary cards will be sought from the subject/subject's caregiver through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

5.6.13. Study conclusion

At the study conclusion visit, the investigator will:

- collect a blood sample;
- collect and record SAEs, pIMDs, HZ cases, concomitant medications/vaccinations;
- review data collected to ensure accuracy and completeness;
- complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed, will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of cohorts to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

The biological samples collected in the study, the quantities needed, the units and the timepoints are described in Table 6.

Table 6 Biological samples

Sample type	Quantity (approximate volume)	Unit	Timepoint(s)
Blood (Humoral immunity)	5	mL	Visits 1, 2, 3, 5 and 6
Blood (Cell-mediated immunity)	20	mL	Visits 1, 2, 3, 5 and 6

mL = Millilitre

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis

Laboratory assays, which will be used in this study, are summarised in respectively in Table 7 (Humoral Immunity) and Table 8 (CMI).

Table 7 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory*
Serum	Varicella Zoster Virus.Glycoprotein E Ab.IgG	ELISA	NA	mIU/ml	**97**	GSK Biologicals**

*GSK Biologicals laboratory refers to the Clinical Laboratory in Rixensart, Belgium.
VZV = Varicella Zoster Virus; gE = Glycoprotein E; Ab = Antibody; IgG = Immunoglobulin class G; ELISA = Enzyme-linked Immunosorbent Assay; NA = Not applicable; ml = milliliter; mIU = milli international unit.

Table 8 Cell-Mediated Immunity (CMI)

System	Component	Challenge	Method	Unit	Laboratory*
PBMC	CD4.polypositives CD40L+IL-2+TNFα+IFNγ*	gE	ICS	Events	CEVAC+

IL-2 = Interleukin 2; TNFα = Tumor Necrosis Factor-alpha; IFNγ = Interferon-gamma; gE = Glycoprotein E; ICS = Intracellular cytokine staining.

* CD4.polypositives CD40L+IL2+TNFα+IFNγ = CD4+ T-cells expressing at least 2 activation markers (from among IFN-γ, IL-2, TNF-α and CD40L)

+ Centre for Vaccinology (CEVAC), Ghent University, Building A, 1st Floor, De Pintelaan, 185, 9000 Gent, Belgium

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint		No. subjects	Component
Type of contact and timepoint	Sampling timepoint		
Visit 1 (Month 108/Year 9)	Post-Initial Vacc	All	ICS gE
		All	Ab gE ELISA
Visit 2 (Month 120/Year 10)	Post-Initial Vacc	All	ICS gE
		All	Ab gE ELISA
Visit 3 (Month 121)	Month 1 Post-Re-Vacc 1	All	ICS gE
		All	Ab gE ELISA
Visit 5 (Month 123)	Month 1 Post-Re-Vacc 2	All	ICS gE
		All	Ab gE ELISA
Visit 6 (Month 134)	Month 12 Post-Re-Vacc 2	All	ICS gE
		All	Ab gE ELISA

ICS = Intracellular Cytokine Staining; gE = Glycoprotein E; Ab = Antibody; ELISA = Enzyme-linked Immunosorbent Assay.

5.7.5. Immunological correlates of protection

No generally accepted immunological correlate of protection against HZ has been demonstrated so far for the gE antigen used in the HZ/su candidate vaccine.

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

The candidate vaccine to be used has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccine is labelled and packed according to applicable regulatory requirements.

Table 10 Study vaccine

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered*	Number of doses
HZ/su	VZV gE	gE=50µg	Lyophilized pellet in a monodose vial	0.5 mL	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in a monodose vial		

*Refer to the SPM for the volume after reconstitution.
VZV = Varicella Zoster Virus, gE = recombinant purified Glycoprotein E; AS01B = Adjuvant System AS01B; MPL = 3-O-desacyl-4'-monophosphoryl lipid A; QS21 Stimulon® = Quillaja saponaria Molina, fraction 21 (purified saponin extract from the South American tree).

6.2. Storage and handling of study vaccine

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccine

After removal of the vaccine components from the temperature monitored refrigerator, the vaccine should be reconstituted and administered within 6 hours, and should be kept at room temperature (between 2°C/36°F and 30°C/86°F).

Vaccine will be administered as indicated in Table 11.

The reconstituted vaccine (0.5 mL) should be administered by IM injection into the deltoid muscle of the non-dominant arm using a standard aseptic technique.

Refere to the SPM for more details on vaccine reconstitution and administration.

Table 11 Dosage and administration

Type of contact and timepoint	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side[2]
Visit 2 (Month 120)	0.5 ml	50µg gE/AS01B	HZ/su	IM	Deltoid	Non-Dominant
Visit 4 (Month 122)						

[1]Intramuscular (IM)
[2] In rare situations when there is no other alternative, the injection may be given in the dominant arm.

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over supply), at least 5 % additional vaccine doses will be supplied to replace those that are unusable.

Additional doses of the study vaccine will be supplied if necessary.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to (further) administration of HZ/su. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4).

- Anaphylaxis following the administration of any previous dose of HZ/su.
- An SAE judged to be related to HZ/su by the investigator.
- Active HZ infection i.e. HZ lesions not completely crusted over at the moment of Visit 2 or an episode of HZ between Visit 2 (Month 120: re-vaccination dose1) and Visit 4 (Month 122: re-vaccination dose 2).

- Any confirmed or suspected immunosuppressive or immunodeficient condition, resulting from disease (e.g., malignancy, HIV infection) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders). However subjects who have received less than 15 days of immunosuppressants or other immune modifying drugs should not be contraindicated from receiving subsequent vaccinations. Corticosteroids, prednisone < 20 mg/day, or equivalent, as well as inhaled and topical steroids are allowed.
- Administration of a vaccine not foreseen by the study protocol within the period starting 30 days before the first dose of study vaccine, and ending 30 days after the last dose of study vaccine. However, licensed non-replicating vaccines (i.e. inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flus) may be administered up to 8 days prior to dose 1 and/or dose 2 and/or at least 14 days after any dose of study vaccine.
- Administration of vaccine against HZ or varicella (including an investigational or non-registered vaccine) other than the study vaccine.
- Participating or planned participation in another clinical study, from 30 days before Visit 2 up to 30 days post second dose, in which the subject is or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Other events that constitute contraindications to administration of HZ/su vaccine.
  - Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine(s)/product(s). Refer to Section 8.1.5.1 for the definition of pIMDs.

The following events constitute contraindications to administration of HZ/su at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.4).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines.

6.6. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator should question the subject and/or the subject's caregiver about any medications/products taken and vaccinations received by the subject.

6.6.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with the administration of each dose of study vaccine and ending 30 days (Days 0-29) after each dose of study vaccine must be recorded in the eCRF.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥37.5°C/99.5°F on oral, axillary or tympanic setting, or ≥38.0°C/100.4°F on rectal setting].
- Any vaccine not foreseen in the study protocol administered at any time during the period starting with the administration of each dose of study vaccine and ending 30 days (Days 0-29) after each dose of study vaccine must be recorded in the eCRF.
- Any investigational medication or vaccine administered throughout the study (i.e. from V1 through study conclusion) must be recorded in the eCRF.
- Concomitant medication, administered for the treatment of HZ or any related HZcomplications, from V1 until study conclusion, must be recorded in the eCRF.
- Any concomitant medications/products/vaccines listed in Section 6.6.2.
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE /pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

6.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis.

- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day for adult subjects), or equivalent. Inhaled, topical and intra-articular steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Immunoglobulins and/or any blood products administered during the study period.
- A vaccine against HZ or varicella (including an investigational or non-registered vaccine) other than the study vaccine during the study period.

6.7. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses

At each study visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (i.e. varicella or suspected HZ episode) or are confirmed to have an immunocompromising condition (e.g. HIV, cancer). HZ cases will be collected/reported in HZ specific screen in the eCRF.

Subjects who experience an episode of suspected HZ during the study will be eliminated from the ATP cohort for immunogenicity. These subjects will be analysed separately.

IMCs will be reported either as AE or SAEs (as appropriate) in the eCRF.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject/ subject's caregiver will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

The following local (injection-site) AEs will be solicited:

Table 12 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 13 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF. The preferred route for recording temperature in this study will be oral.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. imaging studies) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.1.5. Adverse events of specific interest

8.1.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 14.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 14 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)

Vasculitides	Blood disorders	Others
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

Liver disorders	Gastrointestinal disorders	Endocrine disorders
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis • Celiac disease • Autoimmune pancreatitis	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease • Polyglandular autoimmune syndrome • Autoimmune hypophysitis

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete, date and sign an electronic Expedited Adverse Events Report.

8.2. Detecting and recording adverse events and serious adverse events

8.2.1. Time period for detecting and recording adverse events and serious adverse events (Amended 18 August 2017)

All AEs starting 30 days following administration of each dose/the dose of study vaccine (Day 0 to Day 29) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

All SAEs will be collected and recorded from the time of the first receipt of study vaccine at Visit 2 until the subject is discharged from the study or until the end of the study (Table 15). See Section 8.3 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first study visit up to the last study visit at the end of the study.

SAEs related to initial vaccination course from study ZOSTER-003 will be collected and recorded from the time of the first study visit and will end at the time of the first receipt of dose one of re-vaccination course.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the

time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording of pIMDs will begin at Visit 2, the first receipt of study vaccine and will end 365 days following administration of the last dose of study vaccine. See section 8.3 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for AEs, SAEs, IMCs and pIMDs is given in Table 15.

Table 15 Reporting periods for collecting safety information

Event	Visit 1*	Visit 2				Visit 3	Visit 4			Visit 5	Contacts	Visit 6
Timepoint	Year 9	Year 10 Vacc 1	Post Vacc	Post Vacc		Post Vacc	Vacc 2	Post-Vacc	Post Vacc			
	Month 108	Month 120	6 days post V1	29 days post V1		Month 121	Month 122	6 days post V2	29 days post V2	Month 123	Month 126, 129 and 132	Month 134
Solicited local and general AEs												
Reporting of unsolicited AE												
Reporting of any SAEs ***after the first dose from the re-vaccination course at Visit 2*** **(Amended 18 August 2017)**												
Reporting of any AEs/SAEs leading to withdrawal from the study **(Amended 18 August 2017)**												
Reporting of all SAEs related to investigational vaccine, study participation or to a concurrent GSK medication/vaccine† **(Amended 18 August 2017)**												
Reporting of pIMDs												
Reporting of intercurrent medical conditions‡												

* i.e. consent obtained; Vacc 1- re-vaccination dose 1; Vacc 2- re-vaccination dose 2

† SAEs related to investigational vaccine include SAEs occurring between V1 and V2 considered as related to initial vaccination in ZOSTER-003 study and SAEs related to re-vaccination course occurring after administration of the 1st dose from re-vaccination course.

‡Including suspected cases of HZ

8.2.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 15. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.2.3. Evaluation of adverse events and serious adverse events

8.2.3.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject or the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

8.2.3.2. Assessment of adverse events

8.2.3.2.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described:

Table 16 Intensity scales for solicited symptoms in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/°F Temperature will be analysed in 0.5°C increments from ≥ 37.5°C Grade 3 fever is defined as > 39.0°C.
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Shivering	0	None
	1	Shivering that is easily tolerated
	2	Shivering that interferes with normal activity
	3	Shivering that prevents normal activity

*Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route. The preferred route for recording temperature in this study will be oral.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows using GSK Biologicals' standard grading scale based on the US Food and Drug Administration (FDA) guidelines for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials [FDA, 2007]:

0	:	< 20 mm diameter
1	:	≥ 20 mm to ≤ 50 mm diameter
2	:	> 50 mm to ≤ 100 mm diameter
3	:	> 100 mm diameter

The preferred route for recording temperature in this study is oral.

Grade 3 fever will be defined as temperature > 39.0°C (regardless the route used).

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.2.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccine and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the Expedited Adverse Events Report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines/products, it may not be possible to determine the causal relationship of general AEs to the individual vaccine administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccine.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational vaccine?

YES	:	There is a reasonable possibility that the vaccine contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

8.2.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.3. Reporting of serious adverse events and other events

8.3.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a SAE.

pIMDs that occur in the time period defined in Section 8.2 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 17 Timeframes for submitting serious adverse event and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	paper Expedited Adverse Events Report
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	paper Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD
‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD

8.3.2. Contact information for reporting serious adverse events and pIMDs

Study Contact for Reporting SAEs and pIMDs
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs and pIMDs
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD or PPD Email address: PPD

8.3.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.3.1. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow. As soon as the electronic reporting system is working again, the investigator (or designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.3.4. Reporting of pIMDs to GSK Biologicals

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD and whether it is serious or non serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the pIMD.

Refer to Section 8.3.3.1 for back-up system in case the electronic reporting system does not work.

8.3.5. Updating of SAE and pIMD information after removal of write access to the subject's eCRF

When additional SAE or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 17.

8.3.6. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.3.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.4. Follow-up of adverse events and serious adverse events

8.4.1. Follow-up of adverse events and serious adverse events

8.4.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 17).

All SAEs and pIMDs (serious or non-serious) documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

8.4.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, pIMDs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- with other non-serious AEs until 30 days after the last vaccination or they are lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF (refer to Section 6.6).

8.6. Subject card

Study subjects / subjects' caregiver must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject/ subject's caregiver. In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects / subjects' caregiver must be instructed to keep subject cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject himself/herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.4.1.2).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration page/screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject himself/herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

10. STATISTICAL METHODS

10.1. Primary endpoints

- Antigen-specific antibody (Ab) concentrations at Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003.
  - Anti-gE Ab concentrations as determined by ELISA at Months 108 and 120.
- Cell-Mediated Immunity (CMI) in terms of frequencies of antigen-specific CD4 T-cells at Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003.
  - Frequencies of CD4+ T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE as determined by Intracellular Cytokine Staining (ICS) at Months 108 and 120.

10.2. Secondary endpoints

For the follow-up of persistence phase Months 108 and 120 post first dose of initial vaccination course in study ZOSTER-003:

- Antigen-specific antibody (Ab) concentrations within each age cohort (60-69 YOA and ≥70 YOA at the time of initial vaccination) at persistence Months 108 and 120.
  - Anti-gE Ab concentrations as determined by ELISA at Months 108 and 120.

- Cell-Mediated Immunity (CMI) in terms of frequencies of antigen-specific CD4 T-cells within each age cohort (60-69 YOA and ≥70 YOA at the time of initial vaccination) at persistence Months 108 and 120 post first dose of initial vaccination course.
  - Frequencies of CD4+ T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE as determined by Intracellular Cytokine Staining (ICS) at Months 108 and 120.
- Serious Adverse events:
  - Occurrence of all serious adverse events (SAEs) related to study participation or to a concurrent GSK medication/vaccine (including HZ/su administered during the ZOSTER-003 study) between Months 108 and 120.

For the re-vaccination phase:

- Antigen-specific antibody (Ab) concentrations post re-vaccination.
  - Anti-gE antibody concentrations as determined by ELISA in all subjects at one month after each vaccine dose (Months 121 and 123) and 12 months after last dose (Month 134).
- Cell-Mediated Immunity (CMI) in terms of frequencies of antigen-specific CD4 T-cells at one month after each vaccine dose (Months 121 and 123) and 12 months after last dose (Month 134).
  - Frequencies of CD4+ T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE as determined by Intracellular Cytokine Staining (ICS) at Months 121, 123 and 134.
- Solicited local and general symptoms:
  - Occurrence and intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination in all subjects;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in all subjects;
- Unsolicited adverse events (AEs)
  - Occurrence, intensity and relationship to vaccination of unsolicited Aes during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects
- SAEs
  - Occurrence and relationship to vaccination of all SAEs from dose 1 of re-vaccination until study end.
  - Occurrence of any fatal SAEs from dose 1 of re-vaccination until study end.

- Potential immune-mediated diseases (pIMDs)
  - Occurrence and relationship to vaccination of any pIMDs from dose 1 of re-vaccination until study end in all subjects.

10.3. Determination of sample size

Subjects who participated in study ZOSTER-003, in group 50 µg gE / AS01B, and had complete vaccination course (2 doses of HZ/su) will be offered enrolment into this LTFU study.

10.4. Cohorts for Analyses

10.4.1. Total enrolled cohort

Total enrolled cohort will include all subjects enrolled in to the study.

10.4.2. ATP cohort for analysis of persistence (LTFU)

The According To Protocol (ATP) cohort for analysis of persistence will include all evaluable subjects i.e, those who were included in the ATP cohort for immunogenicity in the initial ZOSTER-003 study, or were excluded from this cohort solely because they had no blood samples taken or because of incompliance with blood sample schedule, and:

- Who did not receive a concomitant medication/ product leading to elimination from the ATP analysis for immunogenicity up to the considered time point of study ZOSTER-060 (see Section 6.6.2).
- Who did not present with an intercurrent medical condition leading to elimination from the ATP analysis for immunogenicity (including herpes zoster) up to the considered time point of study ZOSTER-060 (see Section 6.7).
- For whom persistence immunogenicity results are available at the considered time point.

10.4.3. Total Vaccinated cohort for re-vaccination phase

The Total Vaccinated Cohort (TVC) will include all subjects vaccinated with HZ/su in the ZOSTER-060 study.

The TVC for analysis of immunogenicity will include subjects vaccinated with HZ/su in the ZOSTER-060 study for whom immunogenicity data are available.

The TVC for analysis of safety will include all subjects with at least one HZ/su administration in the ZOSTER-060 study documented.

10.4.3.1. According-to-protocol (ATP) cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the TVC:

- Who meet all eligibility criteria.
- Who have received one or two doses of re-vaccination schedule up to the time point considered.
- For whom administration site of study vaccine is known/ and correct, as per protocol.
- Who have not received any vaccine forbidden in the protocol up to the timepoint considered.
- Who comply with the procedures and intervals defined in the protocol up to the timepoint considered.
- Who did not receive a medication/ product leading to exclusion from the ATP analysis (see Section 6.6.2) up to the timepoint considered.
- Who did not present with an intercurrent medical condition (including herpes zoster) leading to elimination from the ATP analysis (see Section 6.7) up to the timepoint considered.
- Who complied with the vaccination schedule up to the timepoint considered.
- Who complied with the blood sample schedule up to the timepoint considered.
- Who had immunogenicity results available up to the timepoint considered.

Subjects who experience an episode of suspected HZ up to the considered time point of study ZOSTER-060 will be eliminated from the ATP cohort for immunogenicity subsequent to that time point. These subjects will be analysed separately.

10.5. Derived and transformed data

10.5.1. Handling of missing data

- For the analysis of solicited symptoms, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the TVc will include only subjects/doses with documented safety data (i.e. symptom screen completed).
- For the analysis of unsolicited symptoms/SAEs/pIMDs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.
- For the analysis of immunogenicity, missing or non-evaluable measurements will not be replaced. Therefore, a subject will be excluded from an analysis timepoint if any measurements are missing or non-evaluable for that timepoint.

10.5.2. Humoral immune response

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 seropositivity rate is defined as the percentage of seropositive subjects.

The Vaccine Response Rate (VRR) for anti-gE is defined as the percentage of subjects who have at least:

- a 4-fold increase in the anti-gE Ab concentration as compared to the pre-vaccination anti-gE Ab concentration, for subjects who are seropositive at baseline, or,
- a 4-fold increase in the anti-gE Ab concentration as compared to the anti-gE Ab cut-off value for seropositivity, for subjects who are seronegative at baseline.

Note: Baseline is the pre-vaccination titre in the initial study ZOSTER-003.

The GMC calculations are performed by taking the anti-log of the mean of the log concentration transformations. Ab concentrations below the cut-off of the assay will be given an arbitrary value equal to half the cut-off for the purpose of GMC calculation.

The Mean Geometric Increase (MGI) is defined as the geometric mean of the within subject ratios of the post-vaccination titre to the Day 0 titre (pre-vaccination titre in the initial study).

10.5.3. CMI response

For the descriptive analyses, the frequency of CD4[2+] T-cells upon in vitro stimulation with the gE-antigen (induction condition) is calculated by dividing the number of activated CD4[2+] T-cells (numerator) over the total number of CD4 T-cells involved (denominator). The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate.

$$Freq\ {}^{CD4[2+]}_{Induction} = \frac{n^{2+}_{Induction}}{N^{CD4}_{Induction}}$$

$n^{2+}_{Induction}$ = number of CD4 T – cells secreting at least 2 activation markers after induction with the antigen

N^{CD4} = Total number of CD4 T – cells involved in the assay (induction)

The frequency of gE-specific CD4 T-cells for each individual subject is calculated as the difference between the frequency of CD4[2+] T-cells, upon in vitro stimulation with the gE antigen (induction condition) minus the frequency of CD4[2+] T-cells upon in vitro stimulation in medium only (background condition). The differences less or equal to one are imputed to one gE-specific CD4[2+] T-cell per 10^6 CD4+ T-cells. The same calculation will be performed for the frequency computation for any kind of cells and for each individual activation marker as appropriate.

$$Freq_{Specific}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} - \frac{n_{Background}^{2+}}{N_{Background}^{CD4}} \quad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} > 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$$Freq_{Specific}^{CD4[2+]} = 1 \quad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} \leq 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T-cells secreting at least 2 activation markers after induction with the gE-antigen

$n_{Background}^{2+}$ = number of CD4 T-cells secreting at least 2 activation markers in the medium conditions

N^{CD4} = Total number of CD4 T-cells involved in the assay (induction of background)

- The GM frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations.
- The CMI vaccine response to gE will be based on the gE-specific data as computed above. The lower limit of linearity (LLL) for the assay will be used as threshold for vaccine response assessment and the estimated value will be detailed in the Statistical Analysis Plan (SAP). The Vaccine Response (VR) is defined as the percentage of subjects who have:
  - at least a 2-fold increase as compared to the LLL, for subjects with pre-vaccination T-cell frequencies below the LLL;
  - at least a 2-fold increase as compared to pre-vaccination T-cell frequencies, for subjects with pre-vaccination above the LLL.

10.6. Analysis of demographics

The analysis of demography for the persistence phase at Month 108 and Month 120 post first dose of initial vaccination course will be performed on the Total enrolled cohort and the ATP cohort for persistence.

- Demographic characteristics (age at Month 108 and Month 120 persistence phase respectively, gender, geographic ancestry, race and ethnicity), cohort description and withdrawal status will be summarized overall.
- The mean age at Month 108 and Month 120 (plus range and standard deviation) of the enrolled subjects, as a whole, and stratified by age group will be calculated.
- The distribution of subjects enrolled among the study sites will be tabulated.
- Frequency tables will be generated for categorical variables such as gender.
- Mean, median and standard error will be provided for continuous data such as age.

The analysis of demography for the re-vaccination phase will be performed on the Total vaccinated cohort and ATP cohort for immunogenicity.

- Demographic characteristics (age at first re- vaccination dose, gender, geographic ancestry, race and ethnicity), cohort description and withdrawal status will be summarized overall.
- The mean age at first study re-vaccination dose (plus range and standard deviation) of the enrolled subjects, as a whole, and stratified by age group will be calculated.
- The distribution of subjects enrolled among the study sites will be tabulated.

- Frequency tables will be generated for categorical variables such as gender.
- Mean, median and standard error will be provided for continuous data such as age.

10.7. Analysis of immunogenicity

10.7.1. Assessment of follow-up of persistence phase Months 108 and 120 post first dose of initial vaccination course.

The analysis for the persistence phase at Month X (Month 108 and Month 120) post first dose of initial vaccination course will be performed on the ATP cohort for persistence at Month X – adapted for each time point. If, the percentage of subjects with serological results excluded from the ATP cohort for analysis of persistence is 5% or more, a second analysis based on the Total enrolled cohort will be performed to complement the ATP analysis.

All analyses will be performed overall and by age stratum if the number of subjects is sufficient in each stratum.

Humoral Immune response endpoint

For the humoral immune response, at each timepoint that a blood sample is available (at Months 0, 3, 12, 24, 36, 48, 60, 72, 108 and 120) post initial vaccination, the following parameters (with 95% CIs) will be tabulated overall, and by age group:

- Geometric mean concentrations (GMCs) of anti-gE Ab with 95% confidence interval (CIs).
- Humoral seropositivity rates with exact 95% confidence interval (CIs);
- Descriptive statistics of the fold over pre-vaccination in the initial study at months 3, 12, 24, 36, 48, 60, 72, 108 and 120 (Mean, Standard deviation, Min, Q1, Median, Q3, Max).
- The geometric mean of the ratio Post month x over pre-vaccination in the initial study with 95% CI.
- The distribution of antibody titres will be tabulated and also presented using reverse cumulative curves.

CMI endpoint

For CMI response, the following parameters (for gE specific CD4[2+] frequency and CD4[+2] T-cell following induction with gE) will be tabulated overall and by age group [60-69,>=70 YOA at time of initial vaccination in study ZOSTER-003] at Months 0, 3, 12, 24, 36, 48, 60, 72, 108 and 120 post first dose of initial vaccination:

Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of the following parameters will be tabulated:

- Descriptive statistics of the frequency of CD4+ T-cells secreting at least two activation markers (from among IFN-γ, IL-2, TNF-α, CD40L) for gE-specific stimulation.
- Descriptive statistics of the fold over pre-vaccination in the initial study at months 3, 12, 24, 36, 48, 60, 72, 108 and 120.

Exploratory analysis

A piece-wise linear mixed model and modified power law model for repeated measurements (all data available from month 0, 3, 12, 24, 36, 48, 60, 72, 108 and 120 post first dose of initial vaccination) will be used to model over time the frequency of CD4 T-cells producing at least 2 immunological activation markers following stimulation with gE [Ledent, 2009] and gE antibody concentrations. The covariates for the frequency of CD4 T-cells will include background CD4 frequency, log transformed prevaccination response and the log-transformed of the time elapsed (measured in months) following the initial vaccination. The covariates for the anti-gE will include log transformed prevaccination response. The model allows for random individual deviations from the overall mean response (random intercept) and, if necessary according to Schwarz' Bayesian Information Criterion (SBIC) and Akaike's Information Criterion (AIC) goodness-of-fit statistics , for a random individual deviation from the overall CD4-frequency decay over time (random coefficient [slope]).

10.7.2. Assessment of re-vaccination phase

The analysis of re-vaccination phase will be based on the ATP cohort for analysis of immunogenicity. If, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVc will be performed to complement the ATP analysis.

All analyses will be performed overall and by age stratum (60-69, ≥70 YOA at time of initial vaccination in study ZOSTER-003) if the number of subjects is sufficient in each stratum.

Humoral Immune response endpoint

For the humoral immune response, at each timepoint that a blood sample is available (at Months 120, 121 and 123) post-revaccination, the following parameters (with 95% CIs) will be tabulated overall, and by age group (60-69, ≥70 YOA at time of initial vaccination in study ZOSTER-003):

- Geometric mean concentrations (GMCs) of anti-gE Ab with 95% confidence interval (CIs);
- Humoral seropositivity rates with exact 95% confidence interval (CIs);
- Vaccine response rates [post re-vaccination over pre-vaccination in the initial study] with 95% confidence interval (CIs);

- The geometric mean of the ratio Post Month 1 (Month 121) and post Month 3 (Month 123) post re-vaccination (current study) over Visit Month 0 (Month 120), in the current study with 95% CI;
- The geometric mean of the ratio Post Month 1 (Month 121) and post Month 3 (Month 123) post re-vaccination (current study) over pre-vaccination in the initial study with 95% CI;
- The distribution of antibody titres will be tabulated and also presented using reverse cumulative curves.

CMI endpoint

For CMI response, the following parameters (for gE specific CD4[2+] frequency and CD4[+2] T-cell following induction with gE) will be tabulated overall and by age group (60-69, ≥70 YOA at time of initial vaccination in study ZOSTER-003) at Months M0 (Month 120), M1 (Month 121) and M3 (Month 123) post re-vaccination:

Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of the following parameters will be tabulated:

- Descriptive statistics of the frequency of CD4+ T-cells secreting at least two activation markers (from among IFN-γ, IL-2, TNF-α, CD40L) for gE-specific stimulation.

10.7.3. Assessment of persistence (Post re-vaccination)

Persistence data will be analyzed at Month 134 (i.e. 12 months after last dose of re-vaccination) timepoint after re-vaccination.

The analysis of antibody persistence (post re-vaccination) at Month 134 will be based on the ATP cohort for analysis of immunogenicity at month 134. If the percentage of subjects who come back for this follow-up with serological results excluded from the ATP cohort is higher than 5%, a second analysis based on the Total Vaccinated Cohort at Month 134 will be performed to complement the ATP analysis.

Humoral immune response endpoint:

For the humoral immune response, if a blood sample is available at Month 134, the following parameters (with 95% CIs) will be tabulated overall and by age group (60-69, ≥70 YOA at time of initial vaccination in study ZOSTER-003):

- GMC of anti-gE Ab with 95% CI;
- Humoral seropositivity rate with 95% CI;
- Vaccine response rates [Month 134 over pre-vaccination in the initial study] with 95% CI;
- The geometric mean of the ratio Month 134 over Visit Month 0 (Month 120), in the current study with 95% CI;

- The geometric mean of the ratio Month 134 over pre-vaccination in the initial study with 95% CI;
- The distribution of antibody titres will be tabulated and also presented using reverse cumulative curves.

CMI endpoint:

For CMI response, the following parameters (for gE specific CD4[2+] frequency and CD4[+2] T-cell following induction with gE) will be tabulated overall and by age group (60-69, ≥70 YOA at time of initial vaccination in study ZOSTER-003) at M134 (12 months after last dose of re-vaccination):

Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of the following parameters will be tabulated:

- Descriptive statistics of the frequency of CD4+ T-cells secreting at least two activation markers (from among IFN-γ, IL-2, TNF-α, CD40L) for gE-specific stimulation.

10.8. Analysis of safety

10.8.1. Persistence phase

Analyses in the follow-up of persistence phase will be performed on the Total enrolled cohort.

All safety analyses might be performed by age stratum (60-69 and ≥ 70 YOA at the time of initial vaccination course in study ZOSTER-003) when the size of the category is considered meaningful.

Proportion of subjects reporting at least one serious adverse events classified by MedDRA Primary System Organ Class and Preferred Term related to study participation or to a concurrent GSK medication/vaccine between Month 108 and Month 120 post first dose of initial vaccination will be tabulated, with exact 95% CI.

Proportion of subjects reporting at least one serious adverse events related to initial vaccination from study ZOSTER-003 classified by MedDRA Primary System Organ Class and Preferred Term between Month 108 and Month 120 post first dose of initial vaccination will be tabulated with exact 95% CI.

Proportion of subjects experiencing a suspected HZ episode between Month 108 and Month 120 post first dose of initial vaccination will be tabulated with exact 95% CI.

10.8.2. Re-vaccination phase

Analyses post the re-vaccination phase will be performed on the Total vaccinated cohort.

All safety analyses might be performed by age stratum (60-69 and ≥ 70 YOA at the time of initial vaccination as in ZOSTER-003 study) when the size of the category is considered meaningful.

- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AEs during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3;
- The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day follow-up period will be tabulated with exact 95% CI. For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination ;
- The percentage of subjects reporting temperature by half degree (°C) cumulative increments. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for any fever resulting in a medically attended visit ;
- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination will be tabulated with exact 95% CI;
- The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The proportion of AEs resulting in a medically attended visit will also be tabulated ;
- Total number/percentages of doses (per dose and overall) followed by AEs will be tabulated;
- Number of subjects with pIMDs will be tabulated;
- All SAEs will be tabulated;
- SAEs related to vaccine will be tabulated and described;
- SAEs related to study participation or to GSK concomitant medication/vaccine will be tabulated and described;
- Adverse events (AEs)/SAEs leading to withdrawal from the study will be tabulated;
- Intercurrent medical conditions will be tabulated.

10.9. Interpretation of analyses

Long term follow-up phase:

All the analyses will be descriptive with the aim to characterize the long-term immune profile.

Re-vaccination phase:

All the analyses will be descriptive with the aim to characterize the immune profile after 2 additional doses of HZ/su vaccine.

10.10. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.10.1. Sequence of analyses

The analysis will be performed in the following steps:

- Intermediate Month 108 analysis will be performed in order to explore the immunological response. No clinical report will be written at that time.
- Intermediate analysis after the active phase (one month after last dose of re-vaccination) will be performed. An intermediate clinical study report (CSR) will be written at this point of time. This report will also include the Month 108 analysis.
- A final analysis on immunogenicity and safety will be performed at the time of study end (Visit 6, Month 134), once all data are available and cleaned. An integrated clinical CSR will be written at this point of time.

10.10.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required. Because the analysis is purely descriptive, no adjustment on type I error is foreseen.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the eCRFwill serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor freezes completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit. At the time of publication, this protocol will be fully disclosed.

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before the initiation of the analysis/study.

Results are publicly registered within 8 months of the completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted within 18 months of the completion of the analysis. At the time of publication, this protocol will be fully disclosed.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

12.1. Requirements for Germany

EXPLANATORY STATEMENT CONCERNING GENDER DISTRIBUTION (ARTICLE 7, PARAGRAPH 2 (12) OF THE GERMAN GCP ORDER)

- There is no intention to conduct specific analyses investigating the relationship between the gender of the subjects and the efficacy, immunogenicity or safety of the GSK Biologicals' gE/AS01$_B$ vaccine.

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APPENDIX A LABORATORY ASSAYS

Specific Ab (anti-gE) measurements:

Anti-gE ELISA: Anti-gE Ab concentrations will be measured using an anti-gE ELISA. Diluted blood serum samples of study subjects will be added to microtitre wells pre-coated with gE antigen. Secondary peroxidase-conjugated anti-human Abs will be added, which bind to the primary human anti-gE Abs. After incubation of the microtitre wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE Ab concentrations are calculated from a standard curve. The assay cut-off is 97 mIU/mL.

Intracellular cytokine staining (ICS):

CMI responses will be performed by GSK Biologicals (or designated laboratory) on thawed Peripheral Blood Mononuclear Cells (PBMCs) by ICS. The assay will be performed on samples collected during the course of the study. This assay provides information on the frequency of CD4 T cells responding to culture medium or antigens (gE peptide pool) by secreting cytokine molecules involved in immunity such as IFN-γ, IL-2, TNF-α, and CD40L.

Briefly, PBMC collected from the subjects are stimulated for two hours using culture medium (for evaluation of the non-specific response), a pool of overlapping peptides covering the entire sequence of the vaccine antigen gE. Then, an intracellular block (brefeldin A) is added to inhibit cytokine secretion for a subsequent overnight incubation. Cells are then harvested, stained for surface markers (CD3, CD4 and CD8) and fixed. The fixed cells are then permeabilised and stained with anti-cytokine Abs, washed and analyzed by cytofluorometry.

The results of ICS assays are expressed as the frequency of specific CD4 T cells per million total CD4 T cells.

APPENDIX B CLINICAL LABORATORIES

Table 18 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium

GSK = GlaxoSmithKline

Table 19 Outsourced laboratories

Laboratory	Address
CEVAC - University of Ghent	De Pintelaan, 185 - B-9000 Ghent - Belgium

CEVAC = Centre for Vaccination

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccine Value & Health Science (VVHS) **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	204926 (ZOSTER-060 EXT:003)
EudraCT number	2015-004400-30
Amendment number:	Amendment 1
Amendment date:	18 August 2017
Co-ordinating author:	PPD Scientific Writer

Rationale/background for changes:

- This protocol amendment was developed to clarify in Section 8.2.1 that:
  - All SAEs will be collected and recorded from the time of the first receipt of study vaccine at Visit 2 until the subject is discharged from the study or until the end of the study;
  - All AEs/SAEs leading to withdrawal from the study will be collected and recorded from Visit 1 up to the last study visit at the end of the study;

  and by aligning Table 4 and Table 15 with the text in Section 8.2.1.
- Although no confirmed signals related to hypersensitivity reactions (including anaphylaxis) have been identified during the HZ/su clinical program, a mitigation strategy for the potential risk has been added to the Risk Assessment Section 1.3.1.
- The list of the contributing authors was updated and minor typographic errors were corrected.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Cover page:

Co-ordinating authors	• PPD ***Scientific Writer***
Contributing authors	• PPD ***Clinical Research and Development Lead***
	• PPD ***Study Delivery Lead***
	• PPD ***Project Statistician***

- PPD ***Clinical Safety representative***
- PPD ~~Zoster Portfolio level~~ Clinical ***and Epidemiology Project*** ~~Research and Development~~ Lead ***for Zoster***, Belgian RDC

Sponsor page:

Sponsor signatory	Lidia Oostvogels, ~~Zoster Portfolio level~~ Clinical ***and Epidemiology Project*** ~~Research and Development~~ Lead ***for Zoster***, Belgian RDC

LIST OF ABBREVIATIONS

QS21 ~~Stimulon®~~:	*Quillaja saponaria Molina, fraction 21~~)~~* (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA)

TRADEMARKS

Trademarks not owned by the GlaxoSmithKline group of companies	Generic descriptions
QS-21 ~~Stimulon®;~~	(*Quillaja saponaria* Molina, fraction 21) (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA).

Section 1.3.1 Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational HZ/su vaccine		
~~Theoretical risk of acquiring a vaccine induced autoimmune disease after vaccination~~***Risk of pIMD following the HZ/su vaccination.***	No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.	Close monitoring of pIMDs as per study protocol. The potential risk of events of possible autoimmune aetiology to occur is mentioned in the ICF. In addition, the ICF advises subjects to contact the study doctor or the study staff immediately, should they get any symptoms that they feel maybe serious.
Hypersensitivity reactions (including anaphylaxis.	***No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.***	***Administration of the study vaccination is to be preceded by a review of the subjects' medical history (especially with regard to previous vaccination and possible occurrence of undesirable events)***

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
		and a clinical examination. ***As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.***

Section 5.5 Outline of study procedures

Table 4 List of study procedures

	Epoch 001						
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Contacts**	**Visit 6**
Timepoints	**Year 9‡ Month 108 §**	**Year 10‡ Month 120 #**	**Month 121 #**	**Month 122 #**	**Month 123 #**	**Month 126 Month 129 Month 132**	**Month 134 #**
Sampling timepoints for Long-Term Follow-up Phase	**Post-Vacc**	**Post-Vacc**					
Sampling timepoints for Re-vaccination Phase		**Pre-Vacc1**	**Post-Vacc1**		**Post-Vacc2**		**Post-Vacc2**
Recording of any SAEs ***after the first dose from the re-vaccination course at Visit 2***		●	●	●	●	●	●
Recording of any AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●

Section 8.2.1 Time period for detecting and recording adverse events and serious adverse events

All AEs starting 30 days following administration of each dose/the dose of study vaccine (Day 0 to Day 29) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

~~The time period for collecting and recording SAEs will begin at the first study visit and will end at the end of the study for each subject.~~ ***SAEs that are related to the investigational vaccine administered during re-vaccination phase will be collected and recorded from the time of the first receipt of study vaccine at Visit 2 until the subject is discharged from the study or until the end of the study (Table 15).*** See Section 8.3 for instructions on reporting of SAEs.

~~SAEs related to initial vaccination course from study ZOSTER-003 will be collected and recorded from the time of the first study visit and will end at the time of the first receipt of dose one of re-vaccination course.~~

~~SAEs that are related to the investigational vaccine administered during re-vaccination phase will be collected and recorded from the time of the first receipt of study vaccine until the subject is discharged from the study.~~

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first study visit up to the last study visit at the end of the study.

SAEs related to initial vaccination course from study ZOSTER-003 will be collected and recorded from the time of the first study visit and will end at the time of the first receipt of dose one of re-vaccination course.

Table 15 Reporting periods for collecting safety information

Event	Visit 1*	Visit 2				Visit 3	Visit 4			Visit 5	Contacts	Visit 6
Timepoint	Year 9	Year 10 Vacc 1	Post Vacc	Post Vacc		Post Vacc	Vacc 2	Post-Vacc	Post Vacc			
	Month 108	Month 120	6 days post V1	29 days post V1		Month 121	Month 122	6 days post V2	29 days post V2	Month 123	Month 126, 129 and 132	Month 134
Reporting of any SAEs ***after the first dose from the re-vaccination course at Visit 2***												
Reporting of any AEs/SAEs leading to withdrawal from the study												
Reporting of all ~~serious adverse events (~~SAEs~~)~~ related to investigational vaccine, study participation or to a concurrent GSK medication/vaccine†												

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204926 (ZOSTER-060 EXT:003)
EudraCT number	2015-004400-30
Date of protocol amendment	Amendment 1 Final: 18 August 2017
Detailed Title	A phase IIIB, open, long term extension study to evaluate the persistence of immune responses and the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine 1437173A, 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.
Sponsor signatory (Amended 18 August 2017)	Lidia Oostvogels, Clinical ***and Epidemiology Project*** Lead ***for Zoster***, Belgian RDC
Signature	PPD
Date	30 Aug 2017

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