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

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' Lyophilized formulation of the Herpes Zoster subunit (HZ/su) vaccine (GSK 1437173A)
eTrack study number and Abbreviated Title	204486 (ZOSTER-056)
Investigational New Drug (IND) number	BB-IND-13857
EudraCT number	2015-000965-30
Date of protocol	Final Version 1: 09 November 2015
Date of protocol amendment	Amendment 1 Final: 17 December 2015 Amendment 2 Final: 11 January 2017 Amendment 3 Final: 30 May 2017
Title	Cross-vaccination study of GSK Biologicals' Lyophilized formulation of the Herpes Zoster subunit (HZ/su) vaccine (GSK 1437173A) in subjects who previously received placebo in ZOSTER-006 and ZOSTER-022 studies.
Detailed Title	A Phase IIIB, non-randomized, open-label, multi-country, multi-centric cross-vaccination study to evaluate the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine when administered intramuscularly on a two-dose schedule to subjects who previously received placebo in ZOSTER-006 and ZOSTER-022 studies.
Co-ordinating authors	PPD Scientific Writer; PPD, Scientific Writer (XPE Pharma and Science for GSK Biologicals)
Contributing authors	• PPD, Clinical Research and Development Lead • PPD, Project Statistician • PPD, Study Delivery Lead • PPD, Vice President, Vaccine Development Lead • PPD, Vaccine Supply Coordinator

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Contributing authors	• PPD, Clinical Safety representative • PPD, Oversight Data Manager • PPD and PPD (USA), Global Regulatory Affairs • PPD, Global Patent • PPD, Lead Statistician • PPD, Clinical and Epidemiology Project Lead for Zoster, Belgian RDC

GSK Biologicals' Protocol DS v 14.1.1

Protocol Amendment 3 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204486 (ZOSTER-056)
IND number	BB-IND-13857
EudraCT number	2015-000965-30
Date of protocol amendment	Amendment 3 Final: 30 May 2017
Detailed Title	A Phase IIIB, non-randomized, open-label, multi-country, multi-centric cross-vaccination study to evaluate the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine when administered intramuscularly on a two-dose schedule to subjects who previously received placebo in ZOSTER-006 and ZOSTER-022 studies.
Sponsor signatory	Lidia Oostvogels, Clinical and Epidemiology Project Lead for Zoster, Belgian RDC
Signature	_____
Date	_____

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Protocol Amendment 3 Rationale

Amendment number: Amendment 3
Rationale/background for changes: • This country specific protocol amendment was developed in order to remove the Voice of the Patient (VoP) initiative text from Section 12.3 since this initiative was not adopted in Japan. • This is a country specific administrative change for the US since the back-up study contact telephone number for reporting SAEs, pregnancies and pIMDs in the US was removed from Section 8.4.2. This US telephone number, which was originally provided to the US sites as a courtesy, became inactivated over the course of the study and the US Fax number is retained as the back-up study contact number for reporting SAEs, pregnancies and pIMDs.

Protocol Amendment 3 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	204486 (ZOSTER-056)
IND number	BB-IND-13857
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Investigator name	_____
Signature	_____
Date	_____
Leiter der klinischen Prüfung name, function and title	_____
Signature	_____
Date	_____

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GSK Japan study representative/Joint Vaccine Co representative name, 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 8.4.2.

SYNOPSIS

Detailed Title

A Phase IIIB, non-randomized, open-label, multi-country, multi-centric cross-vaccination study to evaluate the safety of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine when administered intramuscularly on a two-dose schedule to subjects who previously received placebo in ZOSTER-006 and ZOSTER-022 studies.

Indication

Prevention of Herpes Zoster (HZ) and related complications in adults aged 50 years and older and in immunocompromised 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 HZ, a recombinant subunit (su) vaccine consisting of Varicella-zoster Virus (VZV) glycoprotein E (gE) as antigen and an adjuvant system (AS01), has been evaluated in previous studies in healthy 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, a gE antigen dose of 50 µg and the adjuvant system $AS01_B$ were selected for the final vaccine formulation. Henceforth, the final vaccine formulation will be referred to as HZ/su.

Two large pivotal Phase III trials (ZOSTER-006 enrolling subjects ≥ 50 Years Of Age [YOA], and ZOSTER-022 enrolling subjects ≥ 70 YOA,) are being conducted to evaluate the Vaccine Efficacy (VE) and safety of GSK Biologicals' HZ/su vaccine. These trials 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 VE results from the ZOSTER-006 Phase III trial demonstrated the HZ/su vaccine to be highly efficacious in the prevention of HZ with no safety concerns raised in this population of subjects ≥ 50 YOA. Results received up to date from the ZOSTER-022 Phase III trial and from a prespecified pooled analysis over both studies confirmed these findings.

According to the ZOSTER-006/ZOSTER-022 protocol and Informed Consent form (ICF), once these studies are concluded and HZ/su vaccine proved to be efficacious and safe, the control vaccine group would be offered the HZ/su vaccine in a cross-vaccination setting.

Potentially eligible subjects who previously received placebo in ZOSTER-006/ZOSTER-022 will now be offered cross-vaccination.

In a previously completed study (ZOSTER-033) conducted in older adults (≥ 50 YOA) with a history of previous HZ, the immunogenicity profile and the safety profile of HZ/su did not appear to be different from what has been observed in other studies in older adults with no previous history of HZ. Clinical efficacy against recurrent HZ, was not evaluated in this population. However based on the very high efficacy observed in the phase III clinical efficacy studies in individuals without previous HZ (ZOE-50 and ZOE-70) who received the HZ/su vaccine, anticipated benefits against recurrence of HZ may be expected.

- Rationale for the study design

Since the HZ/su vaccine has not yet been licensed and marketed, this study is being conducted to enable potentially eligible subjects who previously received placebo in ZOSTER-006 or ZOSTER-022 to receive the HZ/su vaccine.

Study ZOSTER-056 is an open-label, multi-centric and single arm study to cross-vaccinate and collect safety data from subjects ≥ 50 YOA who previously received placebo.

Objective

Primary

- To evaluate the safety, in terms of unsolicited Adverse Events (AEs), Serious Adverse Events (SAE) and potential Immune Mediated Disease (pIMD) in all subjects, following administration of each dose of the HZ/su vaccine.

Secondary

- To evaluate the incidence of suspected HZ episodes (self-reported or medically diagnosed) during the entire study period.

Study design

- Experimental design: Phase IIIB open-label, non-randomised, multi-centric , multi-country cross-vaccination study, with a single group.
- Duration of the study: Approximately 14 months. Each subject will be followed for safety for approximately 12 months after the second vaccine dose.
  - Epoch 001: Primary starting at Visit 1 (Month 0) and ending at final phone contact (Month 14, i.e. 12 months post dose 2).

- Study groups:

Synopsis Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min - Max)	Epochs
			Epoch 001
HZ/su Group	~ 14,550	> 50 YOA	x

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Product name	Study Group
		HZ/su Group
HZ/su	VZV gE	x
	AS01B	

- Control: uncontrolled.
- Vaccination schedule: 0, 2 months.
- Treatment allocation: non-randomised.
- Blinding: open-label.

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule: no sampling.
- Type of study: self-contained.
- Data collection: electronic Case Report Form (eCRF).

Number of subjects Target enrolment will be approximately 14,550 potentially eligible subjects (all in one vaccine group).

Endpoints **Primary**

- Occurrence of unsolicited 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.
- Occurrence of SAEs.
  - Occurrence and relationship to vaccination of all SAEs from Month 0 until study end (Month 14, i.e. 12 months post dose 2).
- Occurrence of AEs of special interest.
  - Occurrence of any pIMDs from Month 0 until study end (Month 14, i.e. 12 months post dose 2).

Secondary

- Occurrence of suspected HZ cases.
  - Occurrence of suspected HZ cases from Month 0 to study end.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF APPENDICES

PAGE

LIST OF ABBREVIATIONS (Amended 30 May 2017)

AE:	Adverse Event
ANCA:	Anti-Neutrophil Cytoplasmic Antibody
ANSM:	Agence Nationale de Sécurité du Médicament
$AS01_B$:	MPL, QS21, liposome based Adjuvant System (50 µg MPL and 50 µg QS21)
ATP:	According-To-Protocol
CDC:	Centres for Disease Control
CNIL:	Commission Nationale de l'Informatique et des Libertés
CRA:	Clinical Research Assistant
eCRF:	electronic Case Report Form
CTR:	Clinical Trials Register
eTDF:	Electronic Temperature excursion Decision Form
EDD:	Estimated Date of Delivery
EGA:	Estimated Gestational Age
EMA:	European Medicines Agency
GCP:	Good Clinical Practice
gE:	Glycoprotein E
GSK:	GlaxoSmithKline
HIV:	Human Immunodeficiency Virus
HZ:	Herpes Zoster
IAF:	Informed Assent Form
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
(I)EC:	(Independent) Ethics Committee

IM:	Intramuscular/Intramuscularly
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
(I)RB:	(Institutional) Review Board
LAR:	Legally Acceptable Representative
LMP:	Last Menstrual Period
MACDP:	Metropolitan Atlanta Congenital Defects Program
MedDRA:	Medical Dictionary for Regulatory Activities
PHN:	Postherpetic Neuralgia
PID:	Personal Identification Number
PT:	Preferred Terms
pIMD:	Potential Immune-Mediated Disease
QS-21:	Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
RDC:	Research and Development Centre
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SPM:	Study Procedures Manual
su:	Subunit
TVC:	Total Vaccinated Cohort
US:	United States
VE:	Vaccine Efficacy
VZV:	Varicella-zoster Virus
YOA:	Years of Age

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

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.
Caregiver	Someone who lives in the close surroundings of a subject having a continuous caring role or may be someone having substantial periods of contact with a subject and is engaged in his/her daily health care (e.g. a relative of the subject, a nurse who helps with daily activities in case of residence in a nursing home). In a context of a clinical study, a caregiver could include an individual appointed to oversee and support the subject's compliance with protocol specified procedures.
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.
Investigational vaccine **(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.

Legally acceptable representative **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
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.

Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
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 during the clinical study.

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 descriptions
Varivax® (Merck & Co)	Varicella vaccine consisting of live attenuated varicella-zoster virus (Oka strain)
Zostavax® (Merck & Co)	Herpes zoster vaccine consisting of high-titre live attenuated Varicella-zoster virus (Oka strain)

1. INTRODUCTION

1.1. Background

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

The typical Herpes Zoster (HZ) rash usually lasts 2 to 4 weeks and is usually 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. Older age is a clear risk factor for PHN. Other risk factors may include a severe HZ rash and a painful HZ prodrome. PHN tends to improve over a period of months. About 70-80% of cases resolve within 1 year, however, in some persons PHN persists for many years [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]. The risk for PHN is also highest in older people with HZ, occurring in 18-50% of those aged 70 years and older [Oxman, 2005; Scott, 2006]. Patients with impaired cell-mediated d immunity 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, a recombinant subunit (su) vaccine consisting of VZV glycoprotein E (gE) as antigen and an adjuvant system (AS01), has been evaluated in previous studies in healthy 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, a gE antigen dose of 50 µg and the adjuvant system $AS01_B$ were selected for the final vaccine formulation. Henceforth, the final vaccine formulation will be referred to as HZ/su.

Two large pivotal Phase III trials (ZOSTER-006 enrolling subjects ≥ 50 YOA, and ZOSTER-022 enrolling subjects ≥ 70 YOA,) are being conducted to evaluate the Vaccine Efficacy (VE) and safety of GSK Biologicals' HZ/su vaccine. These trials 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 VE results from the ZOSTER-006 Phase III trial demonstrated the HZ/su vaccine to be highly efficacious in the prevention of HZ subjects ≥ 50 YOA, 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.

In a previously completed study (ZOSTER-033) conducted in older adults (≥ 50 YOA) with a history of previous HZ, the immunogenicity profile and the safety profile of HZ/su did not appear to be different from what has been observed in other studies in older adults with no previous history of HZ. Clinical efficacy against recurrent HZ, was not evaluated in this population. However based on the very high efficacy observed in the phase III clinical efficacy studies in individuals without previous HZ (ZOE-50 and ZOE-70) who received the HZ/su vaccine, anticipated benefits against recurrence of HZ may be expected.

Please refer to the current Investigator Brochure (IB) 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

According to the ZOSTER-006/ZOSTER-022 protocol and Informed Consent Form (ICF), once these studies are concluded and HZ/su vaccine proven to be efficacious and safe, the control vaccine group would be offered the HZ/su vaccine in a cross-vaccination setting. Potentially eligible subjects who previously received placebo in ZOSTER-006/ZOSTER-022 will now be offered cross-vaccination.

1.2.2. Rationale for the study design

Since the HZ/su vaccine has not yet been licensed and marketed, this study is being conducted to enable potentially eligible subjects who previously received placebo in ZOSTER-006 or ZOSTER-022 to receive the HZ/su vaccine.

Study ZOSTER-056 is an open-label, multi-centric and single arm study to cross-vaccinate and collect safety data from subjects ≥ 50 YOA who previously received placebo.

1.3. Benefit : Risk Assessment

Please refer to the current IB 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

Important Potential Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational study vaccine Hz/su		
Theoretical risk of acquiring a vaccine induced autoimmune disease after 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 potential Immune-Mediated Diseases (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 may be serious.

1.3.2. Benefit Assessment

Benefits include:

- Benefit of receiving HZ/su vaccine during the study that may have clinical utility.
- 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 study procedures are offset by the potential benefits (prevention of HZ and related complications) that may be afforded to the subject(s).

2. OBJECTIVE

2.1. Primary objective

- To evaluate the safety, in terms of unsolicited Adverse Events (AEs), Serious Adverse Events (SAEs) and pIMD in all subjects, following administration of each dose of the HZ/su vaccine.

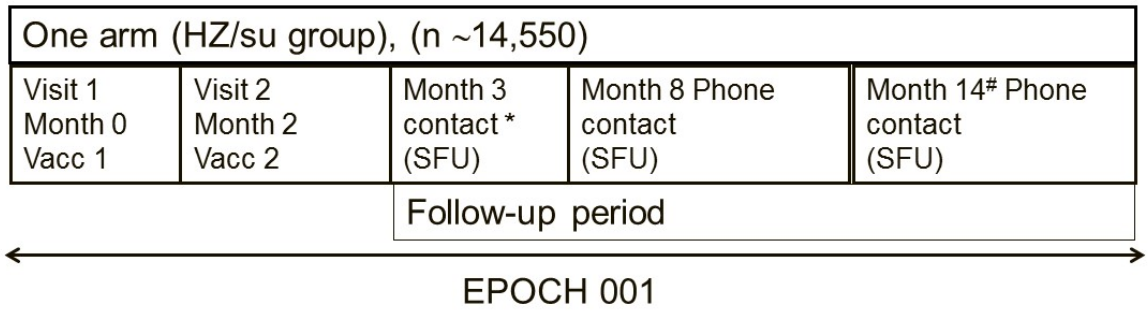
Refer to Section 10.1 for the definition of the primary endpoint(s).

2.2. Secondary objective

- To evaluate the incidence of suspected HZ episodes (self-reported or medically diagnosed) during the entire study period.

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

3. STUDY DESIGN OVERVIEW



*Could be a visit or a phone contact. Operational details will be defined in the Study Procedure Manual (SPM)
i.e. 12 months post dose 2
n: number of subjects
Vacc: vaccination
SFU: Safety follow-up

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, non-randomised, multi-centric , multi-country cross-vaccination study, with a single group.

- Duration of the study: Approximately 14 months. Each subject will be followed for safety approximately 12 months after the second vaccine dose
  - Epoch 001: Primary starting at Visit 1 (Month 0) and ending at final phone contact (Month 14, i.e. 12 months post dose 2)
- Study groups:

Table 1 Study groups and epochs foreseen in the study

Study Groups	Number of subjects	Age (Min – Max)	Epochs
			Epoch 001
HZ/su Group	max 14,550	> 50 YOA	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups
HZ/su	VZV gE	HZ/su Group
	$AS01_B$	

- Control: uncontrolled.
- Vaccination schedule: 0, 2 months.
- Treatment allocation: non-randomised.
- Blinding: open-label.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule: no sampling.
- Type of study: self-contained.
- Data collection: electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centres

Approximately 14,550 potentially eligible subjects who received placebo in the ZOSTER-006/ZOSTER-022 studies will be contacted and invited to participate in this cross-vaccination study with GSK Biologicals' HZ/su vaccine. Refer to Section 4.2 and Section 4.3 for eligibility criteria.

Overview of the recruitment plan

Potentially eligible subjects who participated and received placebo in ZOSTER-006/ZOSTER-022 studies will be contacted and considered for entry in ZOSTER-056 study. The rationale for not enrolling any of these subjects will be recorded 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, vaccination visits, follow-up contacts). Or subjects' Legally Acceptable Representative(s) [LAR(s)]/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/LAR(s) of the subject prior to performing any study specific procedure. If the subject is not capable of giving consent, his/her assent to participate should be obtained to the extent possible.
- Subject who previously participated in ZOSTER-006 or ZOSTER-022 studies and received at least one dose of placebo.
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the glossary of terms for the definition of menarche and menopause.

- Female subjects of childbearing potential may be enrolled in the study, if the subject:
  - has practiced adequate contraception for 30 days prior to vaccination, and
  - has a negative pregnancy test on the day of vaccination and
  - has agreed to continue adequate contraception during the entire treatment period* and for 2 months after completion of the vaccination series.

  *treatment period refers to vaccination days and the interval between them.

Please refer to the glossary of terms for the definition of adequate contraception.

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 dose of study vaccine (Day -29 to Day 0), or planned use up to 30 days post Dose 2.
- Previous vaccination against VZV or HZ.
- Planned administration of VZV or HZ vaccination during the study (including an investigational or non-registered vaccine), with the exception of the study vaccine.
- Planned administration/administration of a vaccine/product not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of vaccine administration, with the exception of 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). These vaccines 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.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine dose and up to 30 days post Dose 2. For corticosteroids, this will mean prednisone ≥ 20 mg/day or equivalent. Inhaled, topical and intra-articular corticosteroids are allowed.
- Administration of long-acting immune-modifying drugs (e.g. infliximab, rituximab) within six months prior to the first vaccine dose up to 30 days post Dose 2.
- Concurrently participating in another clinical study, at the time of enrolment or planned participation up to the 30 days post second dose, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, Human Immunodeficiency Virus [HIV] infection) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmugne disorders).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Active HZ infection at the time of enrolment (i.e. HZ lesions not completely crusted over).
- Pregnant or lactating female.

- Any condition which, in the opinion of the investigator, prevents the subject from participating in the study.
- Any condition which in the judgment of the investigator would make intramuscular injection unsafe.

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 International Conference on Harmonisation (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/subject's (LAR[s]) 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 and/or each subject's LAR(s) and subject informed assent, as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model 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.

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, those subjects who can only be enrolled in the study with the consent of the subject's LAR, should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written

Informed Assent Form (IAF). It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by his/her legal representative.

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

5.2.1. Subject identification

Subjects who have consented to participate in the study will be assigned a subject identification number linked to those used in ZOSTER-006/ZOSTER-022.

5.2.2. Randomisation of treatment

Even though there will be no randomisation of treatment, randomisation system on internet (SBIR) will be used for treatment number allocation and for enrolment tracking purposes.

5.2.2.1. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.1.1. Study group and treatment number allocation

There is only one study group, and the target to be enrolled is approximately 14,550 potentially eligible subjects.

After obtaining the signed/thumb printed and dated ICF (and IAF if applicable and possible) from the subject/subject's LAR and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will provide the treatment number to be used for the first dose.

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

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

5.2.2.1.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number to be used for the second 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 a single treatment group, no blinding will be applied.

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 2, there will be 3 contacts between the subject/subject's LAR/caregiver and the investigator and/or his delegate for the purpose of collecting information on any event of interest (see Table 4 and Section 5.6.16 for details). Month 3 contact will either be a site visit or a phone contact depending on the needs of the subject. Logistical details pertaining to Month 3 contact will be included in the SPM. Months 8 and 14 will be phone contacts. The phone contacts will take place using the most convenient method suited for the sites (e.g., telephone calls by site staff or designee, and/or by call centre). 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 LAR/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.

30-day diary cards will be completed by all subjects/subject's LAR/caregiver for unsolicited AEs (from Day 0 to Day 29 after each vaccination), including episodes of suspected HZ (self-reported or medically diagnosed) and any concomitant medication and vaccination taken from Day 0 to Day 29 after each vaccination.

Episodes of suspected HZ occurring from Day 0 to Day 29 after each vaccination should be collected in the diary cards (by subject/LAR/caregiver) and in the HZ section of the eCRF (if considered an AE by the investigator and/or his delegate) or in the SAE and HZ section of the eCRF (if considered an SAE by the investigator and/or his delegate). Episodes of suspected HZ occurring outside of this period should be reported in the HZ section (if a Non-Serious AE) or in the SAE and HZ section of the eCRF (if an SAE). If the investigators become aware of an HZ episode between study visits, they should report it at that time in the eCRF, as per above.

The diary cards to be completed will be distributed and explained by the investigator or his/her delegate. Any supplied diary cards should be completed by the subject/subject's LAR/caregiver.

5.5. Outline of study procedures

Table 4 List of study procedures

Epoch	*Primary*				
Type of contact	**visit**	**visit**	**contact [1]**	**phone contact**	**phone contact**
Timepoint identification	**Visit 1**	**Visit 2**	**Visit 3/Month 3 Phone contact**	**Month 8 Phone contact**	**Month 14* Phone contact**
Time value	**Month 0**	**Month 2**	**Month 3**	**Month 8**	**Month 14***
Sampling timepoints	**Vacc 1**	**Vacc 2**	**Post-Vacc 2**	**SFU**	**SFU**
Informed consent (and assent if applicable)	●				
Check inclusion/exclusion criteria	●				
Collect demographic data [2]	●				
Medical history	●				
History directed physical examination	O	O			
Pregnancy test if applicable [3]	●	●			
Check contraindications and warnings and precautions	O	O			
Pre-vaccination body temperature	●	●			
Treatment number allocation	O				
Treatment number allocation for subsequent dose		O			
Recording of administered treatment number	●	●			
Vaccine administration	●	●			
Distribution of diary cards for the recording unsolicited AEs and concomitant medications/vaccinations by the subject/LAR/caregiver [4]	O	O			
Training of subjects/LAR/caregiver on completion of diary cards	O	O			
Training on self-reporting by subjects/LAR/caregiver [5]	O	O	O	O	
Training on signs/symptoms of typical HZ	O	O	O	O	O
Reminder for follow-up contact		O	O	O	
Return of diary cards		O	O[6]		
Reception of diary cards [7]		O	O		
Diary card transcription by study staff/investigator		●	●		
Record any concomitant medications/vaccinations	●	●	●	●	●
Recording of unsolicited AEs within 30 days post-vaccination	●	●	●		
Recording of suspected HZ episodes	●	●	●	●	●
Recording of SAEs, pregnancies, pIMDs and AEs leading to withdrawal	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●
Study Conclusion					●

Vacc: vaccination; SFU: safety follow-up

● 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

* i.e. 12 months post dose 2

[1] At Month 3 contact, the subject will either come to the study site or be contacted by phone. Operational details will be defined in the SPM.
[2] Subjects will be assigned the same PID numbers as those used in ZOSTER-006/ZOSTER-022
[3] Only applicable for females of childbearing potential. A urine pregnancy test is sufficient. A serum pregnancy test instead of a urine pregnancy test should only be considered if required by country, local or ethics committee regulations.
[4] One diary card for unsolicited AEs up to 30 days post vaccination
[5] Subject will be instructed to contact their study site immediately if he/she manifests any symptoms he/she perceives as serious and, in case of pregnancy for women of childbearing potential
[6] Subjects will be asked to mail the diary cards 30 days after Visit 2 if their Month 3 contact will be by phone or to bring along their diary card if their Month 3 contact will be a site visit. Operational details will be defined in the SPM
[7] It is the responsibility of the site to follow up until the diary cards are received

Table 5 Intervals between study visits

Interval	Optimal length of interval 1	Allowed interval
Visit 1→Visit 2	60 days (2 months)	49 days - 83 days
Visit 2 → Visit 3/Month 3 Phone contact	30 days (1 month)	30 - 48 days
Visit 2 → Month 8 Phone contact	180 days (6 months)	180 - 240 days
Visit 2 → Month 14* Phone contact	365 days (12 months)	335 –395 days

[1] Whenever possible the investigator should arrange study visits within this interval
*i.e. 12 months post dose 2

5.6. Detailed description of study procedures

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. A signed informed assent should preferably be obtained from subjects who are not capable of consenting and for whom a LAR would sign the ICF (as assessed by the investigator). Refer to Table 6 and 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 should be confirmed during informed consent process by the subject or his/her LAR. In addition, the caregiver should also provide his/her agreement for the role that he/she is playing in the study, (helping the subject to comply with study procedures). The role of the caregiver should be fully explained to him/her and the caregiver should confirm his/her agreement by signing the dedicated part of the ICF. In case the LAR takes the supplementary role to act as a caregiver, the LAR will sign as well the part dedicated for caregiver (Table 6). If required by local regulations, the witness signature is also obtained, confirming the fact that the study procedures were explained appropriately to the caregiver.

- 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. Any change of the caregiver should be documented in the eCRF. 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/subject's LAR(s)* (Table 6).
  * Note that in this case, the subject/subject's LAR(s) 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/subject's LAR re-consent to study participation.
- At the start of the study, the subject/subject's LAR(s)/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/subject's LAR/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.

Table 6 Guidelines on the consent process

Who signs what / Situation	Consent (to study participation)	Assent (to study participation)	ICF Caregiver statement (to help with study procedures)	Annex part of the ICF in case the caregiver changes during the study period (to be helped with study procedures)	Annex part of the ICF in case the caregiver changes during the study period (to help with study procedures)
Subject able to consent and to comply with study procedures	Subject	-	-	-	-
Subject unable to consent but able to comply with study procedures	LAR	Subject	-	-	-
Subject able to consent and unable to comply with study procedures alone	Subject	-	Caregiver	-	-
Subject unable to consent and unable to comply with study procedures alone	LAR	Subject	Caregiver	-	-
Subject with caregiver changed during the study period	-	-	-	Subject or LAR	New Caregiver

5.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. Collect demographic data

Record demographic data such as year of birth, gender in the subject's eCRF.

5.6.4. Medical history

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

Clinically relevant prior medical history is defined as: chronic disease or medical conditions requiring continued or chronic treatment (e.g. diabetes, psoriasis), any previous malignant cancer, acute disease resolved with sequelae (e.g. hemiplegia due to cerebrovascular accident), pIMD (see Table 9).

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 categories and diseases will be available in the eCRF.

In addition, history of prior HZ episodes must be recorded (from HZ collected during the ZOSTER-006/ZOSTER-022 studies until the first visit in the study ZOSTER-056).

5.6.5. History directed physical examination

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 eCRF.

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. Pregnancy test

Female subjects of childbearing potential are to have a urine or serum pregnancy test prior to any study vaccine administration. The study vaccines may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

A urine pregnancy test is sufficient. A serum pregnancy test instead of a urine pregnancy test should only be considered if required by country, local or ethics committee regulations.

5.6.7. 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 Section 6.5 for more details.

5.6.8. Assess pre-vaccination body temperature

The axillary, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccines 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).

5.6.9. Treatment number allocation

At each vaccination visit, the subject will be assigned a treatment number which must be recorded in the eCRF.

If there is a need for a site to use a replacement vaccine, then that treatment number needs to be transcribed into the eCRF (see Section 6.4).

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. Training on self-reporting by subjects

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

- should the subject manifest any signs or symptoms he/she perceive as serious;
- should the subject become pregnant (for women of childbearing potential)

5.6.12. Training and reporting signs/symptoms of typical HZ

Subjects/subject's LAR/caregiver will be instructed at Visit 1 and Visit 2 to:

- recognize the signs and symptoms of typical HZ
- to record in the diary card information related to suspected HZ (Day 0 to Day 29 post-vaccination).

At each subsequent visit and contact until study end at Month 14, subjects will be reminded of the signs and symptoms of typical HZ and will be questioned about occurrence of a suspected HZ episode from previous study visit or contact.

5.6.13. Check and record concomitant medication/vaccination

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

5.6.14. Recording of AEs, SAEs, pregnancies and pIMDs

- Refer to Section 8.3 for procedures for the investigator to record AEs, SAEs, pregnancies and pIMDs. Refer to Section 8.4 for guidelines and how to report SAE, pregnancy and pIMD reports to GSK Biologicals.
- The subjects/subjects'LAR(s)/caregiver will be instructed to contact the investigator immediately should 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 LAR(s)/caregiver. The subjects/subject's LAR/caregiver will be trained on how to complete the diary cards The subject/subject's LAR(s)/caregiver will record any unsolicited AEs (i.e. occurring on the day of vaccination and during the next 29 days after vaccination).
- All subjects/subject's LARs/caregivers will be instructed to return the completed diary card to the investigator at the next study visit. Collect and verify completed diary cards during discussion with the subject/subject's LAR(s)/caregiver on Visit 2 and Visit 3/Month 3 phone contact.
- Any unreturned diary cards will be sought from the subject/subject's LAR(s)/caregiver through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

5.6.15. Recording of suspected HZ episodes

5.6.15.1. Suspected HZ

A suspected case of HZ is defined as a new rash characteristic of HZ (e.g., unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations).

A diagnosis of suspected HZ will be based upon investigator or the attending physician judgment. The occurrence of suspected HZ will be reported as an AE/SAE, as appropriate. The reporting period for cases of suspected HZ will be from Day 0 to study end.

5.6.15.2. Study procedures in case of suspected HZ

The subject card will include a request to the attending physician to provide information about the clinical diagnosis of a case of suspected HZ, when contacted by the investigator or delegate. When a clinical diagnosis of suspected HZ has been made by an attending physician, the subject should ensure the study site is informed about the case.

When the investigator or delegate becomes aware that a clinical diagnosis of suspected HZ has been made by an attending physician, he/she will contact the attending physician. The investigator or delegate will obtain the relevant information from the attending physician and this information will be recorded in the HZ section or SAE and HZ section of eCRF, as applicable.

When the suspected HZ cases is self-reported, the investigator or his delegate will collect all information regarding the suspected HZ episode and this will be recorded in the HZ section or SAE and HZ section of eCRF, as applicable.

Note: Non-serious episodes of suspected HZ do not require immediate reporting to the site. The investigator/study staff will question the subject at each scheduled visit and contact regarding the onset of signs and symptoms of the suspected HZ.

5.6.16. Reminder for follow-up contact

The subject/subject's LAR/caregiver will be reminded that, after Visit 2, three contacts between the subjects/subject's LAR/caregiver and the investigator and/or his delegate will take place in order to collect all relevant information on any event of interest that may have occurred (including SAEs, pIMDs, suspected HZ [Section 8.3], the use of concomitant medications and/or vaccinations [Section 6.6] or pregnancy [Section 8.3]), and that information will be recorded in the appropriate section of the subject's eCRF.

5.6.17. Study conclusion

At the study conclusion contact, the following procedures will take place:

- Recording of all suspected HZ episodes and SAEs (including related to study participation, or to a concurrent GSK medication/vaccine).
- Recording of pIMDs.
- Recording of pregnancies.
- Checking and recording specific concomitant medication/vaccination.
- Reviewing of the data collected to ensure accuracy and completeness and completing the Study Conclusion screen in the eCRF by the investigator.

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

The candidate vaccine/product 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 7 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; $AS01_B$: Adjuvant System $AS01_B$; MPL: 3-O-desacyl-4'-monophosphoryl lipid A; QS21: *Quillaja saponaria* Molina, fraction 21 (purified saponin extract from the South American tree)

6.2. Storage and handling of study vaccine

The study vaccine 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). Refer to the SPM for details on vaccine reconstitution.

Vaccine will be administered as indicated in Table 8.

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.

Table 8 Dosage and administration

Type of contact and timepoint	Volume to be administered	Study group	Treatment name	Route [1]	Site	Side[2]
Visit 1 (Month 0) Visit 2 (Month 2)	0.5 ml	HZ/su Group	HZ/su	IM	Deltoid	Non-dominant

[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-randomisation when applicable), 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 8.5).

- Anaphylaxis following the administration of vaccine Dose 1.

- Pregnancy (see Section 8.2.1).
- An SAE judged to be vaccine-related by the investigator.
- An episode of suspected HZ at Visit 1 (Month 0, Vaccination 1) and/or Visit 2 (Month 2, Vaccination 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. Also, for corticosteroids, prednisone < 20 mg/day, or equivalent, is allowed. Inhaled and topical steroids are allowed.
- 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, exposes 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. Refer to Section 8.1.4.1 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 8.5).

- 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.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.

6.6. Concomitant medications/products and concomitant vaccinations

At each study visit/contact the investigator should question the subject and/or the subject's LAR(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 medications/products, except vitamins and dietary supplements, administered during 30 days following each study vaccine dose.
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ending 30 days following the second dose of study vaccine.
- 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 According-To-Protocol (ATP) analyses

Not applicable.

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 AE or SAE as provided in this protocol.

Each subject/subject's LAR(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).

All 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 clinical 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.

  Refer to Section 5.6.4 for the definition of pre-existing clinical conditions.

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. 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.

8.1.4. Adverse events of specific interest

8.1.4.1. 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 9.

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 9 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. Events or outcomes not qualifying as adverse events or serious adverse events

8.2.1. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.4.1 and 8.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the European Medicines Agency (EMA) Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.

- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [Centers for Disease Control Metropolitan Atlanta Congenital Defects Program CDC MACDP, 2007] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported to GSK Biologicals as described in Section 8.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

8.3. Detecting and recording adverse events, serious adverse events and pregnancies

8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs starting 30 days following administration of each 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 receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine for each subject. See Section 8.4 for instructions on reporting of SAEs.

The occurrence of suspected HZ will constitute an AE or SAE, as appropriate (and shall be reported in the HZ section of the eCRF [if an AE] or in the SAE and HZ section of the eCRF [if an SAE]). During the study, the time period for collecting and recording of suspected HZ will range from first receipt of study vaccine to study end. When a suspected HZ episode has been reported, specific clinical information about the case, following the first vaccination visit (Month 0) until study end (Month 14), will be entered into the eCRF. Please refer to the SPM for information about recording the details of suspected HZ cases.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine.

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 pregnancies will begin at the first receipt of study vaccine and will end 12 Months following administration of the last dose of study vaccine. See Section 8.4 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end 12 Months following administration of the last dose of study vaccine. See Section 8.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 10 (see also reporting methods below).

Table 10 Reporting periods for collecting safety information

Study activity	Pre-Vacc 1*	Visit 1 (Vacc 1)			Visit 2 (Vacc 2)		Visit 3/Month 3 phone contact (Post-vacc 2)		Month 8 phone contact SFU	Month 14# phone contact SFU
Time of reporting		**Day 0/Month 0**	**Day 29 post Dose 1**		**Day 0/Month 2**	**Day 29 post Dose 2**	**Month 3**		**Month 8**	**Month 14#**
Reporting of unsolicited AEs[1]										
Reporting of suspected HZ [2]										
Reporting of AEs/SAEs leading to withdrawal from the study										
Reporting of all SAEs[2]										
Reporting of SAEs related to study participation or GSK concomitant medication/ vaccine										
Reporting of pregnancies										
Reporting of pIMDs										

AE: Adverse Event; SAE: Serious Adverse Event; pIMD: potential Immune-Mediated Disease; Vacc: Vaccination; M: Month

* i.e. consent obtained;

i.e. 12 months post dose 2

[1] Unsolicited AEs will be recorded in 30 day diary card

[2] At pre-vaccination, suspected HZ episodes will be collected as medical history (see section 5.6.4.). Post vaccination, suspected HZ will be recorded in the diary card as an AE/SAE within the Day 0 –Day 29 period and will also be reported during the Month 3, 8 and 14 contacts.

Type	Unsolicited adverse events/ SAEs, SAEs related to study participation or to GSK concomitant medication/vaccine; AEs/SAEs leading to withdrawal from the study.
Method of 'unsolicited' follow-up including suspected HZ	Diary cards
Method for reporting SAEs, SAEs related to study participation or to GSK concomitant medication/vaccine, Serious suspected HZ cases *and pIMDs,*	Electronic Expedited Adverse Events Report.
Suspected HZ cases (non-serious or serious)	HZ (if an AE)/HZ and SAE (if an SAE) screen of the eCRF
AEs/SAEs leading to withdrawal from the study	AEs/SAE screen of the eCRF

8.3.2. 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 10. 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.

8.3.3. Evaluation of adverse events and serious adverse events

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

As a consistent method of collecting AEs, the subject or the subject's LAR(s) 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.

8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

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. Such an AE would, for example prevent attendance at work and would necessitate the administration of corrective therapy.

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.

8.3.3.2.2. 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 and/or summary of product characteristics 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/product administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

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).

8.3.3.3. 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).

8.4. Reporting of serious adverse events, pregnancies, and other events

8.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 11, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 11, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 11, once the investigator determines that the event meets the protocol definition of a pIMD.

Note: the procedure described in this section will also apply to suspected HZ episodes qualifying as SAEs.

Table 11 Timeframes for submitting serious adverse event, pregnancy 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*	electronic Expedited Adverse Events Report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	electronic 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

8.4.2. Contact information for reporting serious adverse events, pregnancies and pIMDs

Study Contact for Reporting SAEs, pIMDs and pregnancies
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, pIMDs and pregnancies
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD or PPD Email address: PPD US sites only: Fax: PPD **(Amended 30 May 2017)** Canadian sites only: Fax: PPD

8.4.3. 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.

8.4.3.1. 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.

8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the Estimated Gestational Age (EGA) of a pregnancy is dated from the first day of the Last Menstrual Period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the Estimated Date of Delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.4.5. 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 8.4.3.1 for back-up system in case the electronic reporting system does not work.

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

When additional SAE, pregnancy, 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 11.

8.4.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. 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.

8.5. Follow-up of adverse events, serious adverse events, and pregnancies

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

8.5.1.1. 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 11).

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.

8.5.1.2. 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 an electronic Expedited Adverse Events Report and/or pregnancy 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.

8.5.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

8.6. 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).

8.7. Subject card

Study subjects/subjects' LAR(s)/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 LAR(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' LAR(s)/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 is available for the concluding contact 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 was not available for the concluding contact 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, by the subject's LAR(s), 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/the subject's LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's LAR(s), 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 8.5.1.2).

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 screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject himself/herself by the subject's LAR(s), 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

- Occurrence of unsolicited 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.
- Occurrence of SAEs.
  - Occurrence and relationship to vaccination of all SAEs from Month 0 until study end (Month 14, i.e. 12 months post dose 2).
- Occurrence of AEs of special interest.
  - Occurrence of any pIMDs from Month 0 until study end (Month 14, i.e. 12 months post dose 2).

10.2. Secondary endpoints

- Occurrence of suspected HZ cases.
  - Occurrence of suspected HZ cases from Month 0 to study end.

10.3. Determination of sample size

No sample size is calculated for this study. Potentially eligible subjects who received placebo in the ZOSTER-006/ZOSTER-022 studies will be invited to participate in this cross-vaccination study. An estimate of the maximum number to be potentially enrolled can be calculated by considering for both studies the currently placebo vaccinated subjects that are still alive. This gives a maximum number of approximately 14,550.

10.4. Cohorts for Analyses

This study will collect only safety data. The statistical analysis of the safety endpoints will be based on the Total Vaccinated Cohort (TVC); hence no elimination criteria or ATP cohorts are defined for the purpose of statistical analysis.

10.4.1. Total vaccinated cohort

The Total vaccinated cohort will include all subjects with at least one HZ/su vaccine administration documented for whom data are available:

- A safety analysis based on the Total vaccinated cohort will include all vaccinated subjects.

10.5. Derived and transformed data

- Safety
  - For the analysis of unsolicited AEs, SAEs and pIMDs, missing or non-evaluable measurements will not be replaced. Subjects who missed reporting of unsolicited AEs (including SAEs/pIMDs) will be treated as subjects who did not report an event. In case of significant non-compliance of study procedures for reporting events, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.

10.6. Analysis of demographics

Demographic characteristics (age at first study vaccination in years, gender), withdrawal status will be summarised using descriptive statistics:

- Frequency tables will be generated for categorical variable such as centre.
- Mean, median, standard deviation will be provided for continuous data such as age.

10.7. Analysis of safety

The primary analysis for safety will be based on the TVC.

All analysis may be performed by age group at inclusion in the ZOSTER-006/022 (50-59, 60-69 and ≥70 YOA).

When appropriate, tabulations will be presented overall and by time of occurrence related to last vaccination (e.g. using windows such as Days 0-29 and more than 30 days post-vaccination.

The results for the analysis of safety will be tabulated as follows:

- The proportion of subjects with at least one report of an unsolicited AE during the 30-day (Days 0–29) follow-up period after each vaccination classified according to the MedDRA System Organ Class and Preferred Terms 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.
- SAEs and withdrawal due to AE(s) will be described in detail.
- Number of subjects with pIMDs will be tabulated.

10.8. Analysis of suspected HZ incidence

Descriptive statistics

The number of suspected HZ cases will be tabulated.

10.9. Interpretation of analyses

Not applicable, all analyses will be descriptive.

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

All analyses will be conducted on cleaned data. There will be an analysis at the end of the study and a study report will also be written.

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.

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 a 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 eCRF will 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

All countries will comply with AE and SAE reporting as described in Section 8.4 of the protocol. Additionally, countries and sites will follow all applicable local regulations and guidelines for AE and SAE reporting as required by their respective healthcare authorities and ethics committees.

12.1. Requirements for France

This section includes all the requirements of the French law (n^0 2004-806 of 09 August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol.

Concerning the « STUDY POPULATION »

- In line with the local regulatory requirements, the following text about «PAYMENT TO SUBJECTS » is added:

  Subjects will be paid for the inconvenience of participating in the study. The amount of payment is stated in the ICF. Subjects not completing the study for whatever reason could be paid at the discretion of the Investigator, generally on a pro rata basis.

- In line with the local regulatory requirements, the following text about **« NATIONAL FILE »** is added:

All subjects who will be paid, will be recorded into the "national File" by the investigator. They could be identified and monitored under the « Fichier national ».

The following details will be described:

- Reference of the study
- Surname and first name,
- Date and place of birth
- Sex
- Dates of beginning and termination of the study,
- Exclusion period,
- The total amount of allowance.
- In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS » is added:

  A subject will be eligible for inclusion in this study if he/she is either affiliated to or beneficiary of a social security category.

  It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"

- The expected number of patients to be recruited in France is declared to the French regulatory authority.

Concerning the "STUDY CONDUCT CONSIDERATIONS"

- In section "Regulatory and Ethical Considerations, Including the Informed Consent Process"

Concerning the process for informing the patient or his/her legally authorized representative, the following text is added:

- French Patient ICF is a document which summarizes the main features of the study and allows collection of the patient's written consent in triplicate. It also contains a reference to the authorisation of ANSM and the approval from the French Ethic committee and the maintenance of confidentiality of the returned consent form by GSK France.

Concerning the process for obtaining subject informed consent:

- When **biomedical research is carried out on an adult in the care of a "tutelle" guardian**, consent is given by their legal representative and, if the committee mentioned in article L. 1123-1 considers that the research in question, because of the gravity of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, by the family council if it has been instated, or by the judge of "tutelle" guardians.
- When biomedical research is carried out on an adult in the care of a "curatelle" guardian, consent is given by the subject assisted by his guardian.

  However, if the adult in the care of a "curatelle" guardian is invited to participate in research which the committee mentioned in article L. 1123-1 considers, because of the gravity of the restraints or the specificity of the medical acts involved, to entail a serious risk of affecting their private life or the integrity of their body, the matter is submitted to the judge of guardians who decides whether the adult is capable of giving his consent. In the case of incapacity, the judge will decide whether or not to authorise the biomedical research.
- When biomedical research, which complies with the conditions laid down in article L. 1121-8, is considered for **an adult incapable** of expressing his consent and not under a legal protection order, consent is given by a person of confidence as defined in article L. 1111-6 and, failing this, by a person who maintains close and stable links with the subject. However, if the committee mentioned in article L. 1123-1 considers that the research in question, because of the gravity of the restraints or the specificity of the medical acts involved, entails a serious risk of affecting their private life or the integrity of their body, consent is given by the judge of guardians.

Concerning the management of the Patient ICFs, the following text is added:

- The first copy of the Patient ICF is kept by the investigator. The second copy is kept by the Director of the Medical Direction of GSK France and the last copy is given to the patient or his/her legally authorized representative.
- The second copy of all the consent forms will be collected by the investigator at the end of the trial under the Clinical Research Assistant's (CRA's) control, and placed in a sealed envelope bearing only:
  - the study number,
  - the identification of the Centre : name of the principal investigator and number of centre),

- the number of informed consents,
- the date,
- and the principal investigator's signing.

Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.

In section concerning the " NOTIFICATION TO THE HOSPITAL DIRECTOR " the following text is added (if applicable)

- In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

In section concerning the " INFORMATION TO THE HOSPITAL PHARMACIST " the following text is added (if applicable)

- In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

In section " DATA MANAGEMENT " the following text is added

- " Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK Laboratory (Clinical Operations Department)."

Concerning Monitoring visits

- The Health Institution and the Investigator agree to receive on a regular basis a CRA of GSK or of a service provider designated by GSK. The Health Institution and the Investigator agree to be available for any phone call and to systematically answer to all correspondence regarding the Study from GSK or from a service provider designated by GSK. In addition, the Health Institution and the Investigator agree that the CRA or the service provider designated by GSK have direct access to all the data concerning the Study (test results, medical record, etc …). This consultation of the information by GSK is required to validate the data registered in the eCRF, in

particular by comparing them directly to the source data. In accordance with the legal and regulatory requirements, the strictest confidentiality will be respected.

Concerning Data entry into the eCRF

The Health Institution and the Investigator agree to meet deadlines, terms and conditions of the Study's eCRF use here below :

The Health Institution and the Investigator undertake:

1. That the Investigator and the staff of the investigator centre make themselves available to attend the training concerning the computer system dedicated to the eCRF of the Study provided by GSK or by a company designated by GSK.
2. That the Investigator and the staff of the investigator centre use the IT Equipment loaned and/or the access codes only for the purpose of which they are intended and for which they have been entrusted to them, namely for the Study achievement, to the exclusion of any other use.
3. That the Investigator and the staff of the investigator centre use the IT Equipment loaned according to the specifications and manufacturer's recommendations which will have been provided by GSK.
4. To keep the IT Equipment and/or access codes in a safe and secure place and to only authorize the use of this IT Equipment by investigator centre staff designated by the principal investigator to enter the data of the Study.
5. That the Investigator and the staff of the investigator centre enter the data of the eCRF related to a patient visit in the 3 days following the date of the patient visit or, for the patient test results, in the 3 days following the reception of the results of such tests.
6. That the Investigator resolves and returns to GSK the data queries issued by GSK or a service provider designated by GSK within 7 days after the reception of the request of clarification or in a period of one (1) day during the final stage of clarification of the data base or in such other period as provided by GSK and/or a company designated by GSK.
7. To be responsible for the installation and payment of the required Internet connections needed for the use of the IT Equipment, Computer systems and/or access codes.
8. To return at the end of the Study the IT Equipment and/or access codes to GSK or to any company designated by GSK and any training material and documentation. The IT Equipment cannot under any circumstances be kept by the Health Institution or the Investigator for any reason whatsoever.

Concerning Clinical Trials Register (CTR) publication

- It is expressly specified that GSK and/or the Sponsor can make available to the public the results of the Study by the posting of the said results on a website of the GSK Group named CTR including the registration of all the clinical trials conduct by the GSK Group and this before or after the publication of such results by any other process.

Concerning Data Protection French Law of 6 January 1978 (CNIL)

- In accordance with the Data Protection French Law of 6 January 1978 as modified, computer files used by GSK to monitor and follow the implementation and the progress of the Study are declared with the CNIL by GSK. The Investigator has regarding the processing data related to him a right of access, of rectification and of opposition with GSK in accordance with the legal provisions. This information can be transferred or be accessed to other entities of GSK Group in France, Britain or United States, what the Investigator agrees by the signature of the present Protocol.

12.2. 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 safety of the GSK Biologicals' HZ/su vaccine.

  Note: The study can only enrol placebo subjects from ZOSTER-006/ZOSTER-022 studies who are willing to return for vaccination with HZ/su, regardless of gender, race or male/female ratio.

12.3. Requirements for Japan (Amended 30 May 2017)

Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (Ministry of Health and Welfare/Ministry of Health, Labour and Welfare Notification No.28 dated 27th March, 1997)" GCP, Article 14-3 and 80-2 of the Pharmaceutical Affairs Law and Evaluation and Licensing Division, Pharmaceutical Safety Bureau of MHW, Notification No. 1061, 1998.

Clinical Trial Notification to Regulatory Authority

Japan Vaccine Co.,Ltd. will submit the CTN to the regulatory authorities in accordance with Article 80-2 of the Pharmaceutical Affairs Law before conclusion of any contract for the conduct of the study with study sites.

Informed Consent of Subjects

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

Informed Consent

Prior to the start of the study, the investigator (or sub-investigator) should fully inform the potential subject of the study including the written information given approval by the IRB. The investigator (or sub-investigator) should provide the subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. After giving informed consent based on his/her free will, the subject should sign and personally date the consent form. If the subject wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion should sign and personally date the consent form. If the subject is unable to read, an impartial witness should be present during the entire informed consent discussion, and the witness should sign and personally date the consent form. The investigator (or sub-investigator) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject.

If information becomes available that may be relevant to the subject's willingness to continue participation in the study (revision of ICF and other written information)

If information becomes available that may be relevant to the subject's willingness to continue participation in the study, the investigator (or sub-investigator) should immediately inform the subject of it to confirm the willingness to continue participation in the study, and document the communication of this information (in medical records). If necessary, the investigator should revise the written information to be provided to subjects, promptly report it to the sponsor, and obtain approval from the IRB. The investigator should not enrol any new subject in the study before the IRB's approval. After the IRB approves the revision of the written information to be provided to subjects, the investigator (or sub-investigator) should inform each subject participating in the study of the revised written information, and obtain written informed consent.

Study Monitoring

By monitoring the parties involved in the study including medical institutions, investigators, sub-investigators, study collaborators, and storage managers, monitors will:

1. Oversee the process of obtaining written informed consent, the control of investigational products and the progress of the study (including withdrawals and adverse events, and ensure that the conduct of the study is in compliance with GCP, Revised GCP, this protocol, and any other written agreement between the sponsor and the investigator/institution.
2. Collect and provide information that is necessary to conduct the study properly (information on investigational products' safety, efficacy and quality).
3. Verify that the investigator/institution has adequate qualifications and resources and remain adequate throughout the study period, and that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the study and remain adequate throughout the study period.

4. Verify that source documents and other study records are accurate, complete, kept up-to-date and maintained.
5. Determine whether the person responsible for retaining records is maintaining the essential documents at each medical institution.
6. Check the accuracy and completeness of the CRF entries, source documents and other study-related records against each other.

The investigator and institution should agree to allow the monitor direct access to essential documents and other relevant documents.

Direct access to essential documents by monitors and the scope of those documents will be specified separately in the written procedures for monitoring prepared for this study.

Source Data Recorded Directly on CRF

The following data may be recorded directly on the CRFs and considered to be source data.

1. Assessment of causality between adverse events and the investigational product.

Deviations from and Changes of Protocol

Deviations from Protocol

The investigator (or sub-investigator) may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to subjects without agreement by the sponsor or prior IRB approval. As soon as possible, the implemented deviation or change and the reasons for it should be submitted to the head of the medical institution and the IRB for approval, and via the head of the medical institution to the sponsor for agreement.

The investigator (or sub-investigator) should document all deviations from the approved protocol. The investigator should document the reason only for the deviation from, or the change of, the protocol to eliminate an immediate hazard(s) to subjects, and submit it to the sponsor and the head of the medical institution, and retain its copy.

Changes of Protocol

1. If it becomes necessary to make any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects, the sponsor should promptly document the changes and reasons for them and amend the protocol after discussion with the (coordinating [investigator, committee members] and) investigators, and notify the heads of the medical institutions and investigators of the changes of the protocol (sample ICF and other written information, if necessary). The investigator should not implement any significant changes without approval from the IRB.

2. For changes other than the above 1), the sponsor should document the changes and reasons for them and inform the heads of the medical institutions and investigators of the changes of the protocol. Such changes require prior approval from the IRB, except where necessary to eliminate an immediate hazard(s), or when the change(s) involves only logistical or administrative aspects of the study. The investigator should promptly report the changes implemented without prior approval to the IRB for approval.

Study Period

The study period has not been confirmed at the time of this protocol. When needed and available, the study period can be communicated at local level, outside of this protocol.

If during the conduct of the study the HZ/su vaccine (GSK 1437173A) is approved in Japan, the study will then be locally amended to be conducted as a post-marketing study.

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APPENDIX A AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccine Value & Health Science (VVHS) **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	204486 (ZOSTER-056)
IND number	BB-IND-13857
EudraCT number	2015-000965-30
Amendment number:	Amendment 1
Amendment date:	17 December 2015
Co-ordinating author:	PPD, Scientific Writer (XPE Pharma and Science for GSK Biologicals)

Rationale/background for changes:

- Occurrence of suspected Herpes Zoster (HZ) episodes during the entire study period will be evaluated as secondary objective. Therefore, wording related to collection, reporting and recording of HZ was added where applicable throughout the protocol.
- Other minor changes were done.

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

Cover page:

Contributing authors • PPD***, Study Delivery Manager***

SYNOPSIS and Section ***2.2. Secondary objective***

- ***To evaluate the incidence of suspected HZ episodes (self-reported or medically diagnosed) during the entire study period***.

SYNOPSIS and Section ***10.2. Secondary endpoints***

- ***Occurrence of suspected HZ cases.***
  - ***Occurrence of suspected HZ cases from Month 0 to study end***.

LIST OF ABBREVIATIONS

QS-21	***Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)***

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., a Delaware, USA corporation)~~	~~Triterpene glycoside immune enhancer~~

Section ***2.2. Secondary objective***

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

Section 5.4.1. Data collection

After Visit 2, there will be 3 contacts between the subject/subject's LAR/caregiver and the investigator and/or his delegate for the purpose of collecting information on any event of interest (see Table 4 and Section 5.6.14 for details). Month 3 contact will either be a site visit or a phone contact depending on the needs of the subject. Logistical details pertaining to Month 3 contact will be included in the SPM. ***Months 8 and 14 will be phone contacts.*** The phone contacts will take place using the most convenient method suited for the sites (e.g., telephone calls by site staff or designee, and/or by call centre). 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 LAR/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.

30-day diary cards will be completed by all subjects/subject's LAR/caregiver for unsolicited AEs (from Day 0 to Day 29 after each vaccination), ***including episodes of suspected HZ (self-reported or medically diagnosed)*** and any concomitant medication and vaccination taken from Day 0 to Day 29 after each vaccination.

Episodes of suspected HZ occurring from Day 0 to Day 29 after each vaccination should be collected in the diary cards (by subject/LAR/caregiver) and in the HZ section of the eCRF (if considered an AE by the investigator and/or his delegate) or in the SAE and HZ section of the eCRF (if considered an SAE by the investigator and/or his delegate). Episodes of suspected HZ occurring outside of this period should be reported in the HZ section (if a Non-Serious AE) or in the SAE and HZ section of the eCRF (if an SAE). If the investigators become aware of an HZ episode between study visits, they should report it at that time in the eCRF, as per above.

Section 5.5. Outline of study procedures

Table 4 List of study procedures

Epoch	*Primary*				
Type of contact	**visit**	**visit**	**contact [1]**	**phone contact**	**phone contact**
Timepoint identification	**Visit 1**	**Visit 2**	**Visit 3/Month 3 Phone contact**	**Month 8 Phone contact**	**Month 14* Phone contact**
Time value	**Month 0**	**Month 2**	**Month 3**	**Month 8**	**Month 14***
Sampling timepoints	**Vacc 1**	**Vacc 2**	**Post-Vacc 2**	**SFU**	**SFU**
Training on self-reporting by subjects/LAR/caregiver [5]	O	O	***O***	***O***	
Training on signs/symptoms of typical HZ	***O***	***O***	***O***	***O***	***O***
Recording of suspected HZ episodes	●	●	●	●	●

Section 5.6.4. Medical history

In addition history of prior HZ episodes must be recorded ***(from HZ collected during the ZOSTER-006/ZOSTER-022 studies until the first visit in the study ZOSTER-056)***

Section 5.6.11.Training on self-reporting by subjects was moved (previously having been section 5.6.13)

Section 5.6.12. ***Training and reporting signs/symptoms of typical HZ***

Subjects/subject's LAR/caregiver will be instructed at Visit 1 and Visit 2 to:

- ***recognize the signs and symptoms of typical HZ***
- ***to record in the diary card information related to suspected HZ (Day 0 to Day 29 post-vaccination)***

At each subsequent visit and contact until study end at Month 14, subjects will be reminded of the signs and symptoms of typical HZ and will be questioned about occurrence of a suspected HZ episode from previous study visit or contact.

Section ***5.6.15. Recording of suspected HZ episodes*** was added with the wording below:

5.6.15.1. Suspected HZ

A suspected case of HZ is defined as a new rash characteristic of HZ (e.g., unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations).

A diagnosis of suspected HZ will be based upon investigator or the attending physician judgment. The occurrence of suspected HZ will be reported as an AE/SAE, as appropriate. The reporting period for cases of suspected HZ will be from Day 0 to study end.

5.6.15.2. Study procedures in case of suspected HZ

The subject card will include a request to the attending physician to provide information about the clinical diagnosis of a case of suspected HZ, when contacted by the investigator or delegate. When a clinical diagnosis of suspected HZ has been made by an attending physician, the subject should ensure the study site is informed about the case.

When the investigator or delegate becomes aware that a clinical diagnosis of suspected HZ has been made by an attending physician, he/she will contact the attending physician. The investigator or delegate will obtain the relevant information from the attending physician and this information will be recorded in the HZ section or SAE and HZ section of eCRF, as applicable.

When the suspected HZ cases is self-reported, the investigator or his delegate will collect all information regarding the suspected HZ episode and this will be recorded in the HZ section or SAE and HZ section of eCRF, as applicable.

Note: Non-serious episodes of suspected HZ do not require immediate reporting to the site. The investigator/study staff will question the subject at each scheduled visit and contact regarding the onset of signs and symptoms of the suspected HZ.

Section 5.6.16. Reminder for follow-up contact

The subject/subject's LAR/caregiver will be reminded that, after Visit 2, three contacts between the subjects/subject's LAR/caregiver and the investigator and/or his delegate will take place in order to collect all relevant information on any event of interest that may have occurred (including SAEs, pIMDs, ***suspected HZ*** [Section 8.3], the use of concomitant medications and/or vaccinations (Section 6.6) or pregnancy [Section 8.3]), and that information will be recorded in the appropriate section of the subject's eCRF.

Section 5.6.17. Study conclusion

At the study conclusion contact, the following procedures will take place:

Recording of all ***suspected HZ episodes and*** SAEs (including related to study participation, or to a concurrent GSK medication/vaccine).

Section 6.5. Contraindications to subsequent vaccination

An episode of ***suspected*** HZ ***at*** ~~between~~ Visit 1 (Month 0, Vaccination 1) and***/or*** Visit 2 (Month 2, Vaccination 2).

Section 8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

The occurrence of suspected HZ will constitute an AE or SAE, as appropriate (and shall be reported in the HZ section of the eCRF [if an AE] or in the SAE and HZ section of the eCRF [if an SAE]). During the study, the time period for collecting and

recording of suspected HZ will range from first receipt of study vaccine to study end. When a suspected HZ episode has been reported, specific clinical information about the case, following the first vaccination visit (Month 0) until study end (Month 14), will be entered into the eCRF. Please refer to the SPM for information about recording the details of suspected HZ cases.

Table 10 Reporting periods for collecting safety information

Study activity	**Pre-Vacc 1***	**Visit 1 (Vacc 1)**			**Visit 2 (Vacc 2)**		**Visit 3/Month 3 phone contact (Post-vacc 2)**		**Month 8 phone contact SFU**	**Month 14# phone contact SFU**
Time of reporting		**Day 0/ Month 0**	**Day 29 post Dose 1**		**Day 0/ Month 2**	**Day 29 post Dose 2**	**Month 3**		**Month 8**	**Month 14#**
Reporting of suspected HZ[2]										
Reporting of all SAEs[2]										

[2] At pre-vaccination, suspected HZ episodes will be collected as medical history (see section 5.6.4.). Post vaccination, suspected HZ will be recorded in the diary card as an AE/SAE within the Day 0 –Day 29 period and will also be reported during the Month 3, 8 and 14 contacts.

Type	Unsolicited adverse events/SAEs, SAEs related to study participation or to GSK concomitant medication/vaccine; AEs/SAEs leading to withdrawal from the study.
Method of 'unsolicited' follow-up ***including suspected HZ***	Diary cards
Method for reporting SAEs, SAEs related to study participation or to GSK concomitant medication/vaccine, ***Serious suspected HZ cases*** *and pIMDs,*	Electronic Expedited Adverse Events Report.
Suspected HZ cases (non serious or serious)	***HZ (if an AE)/HZ and SAE (if an SAE) screen of the eCRF***
AEs/SAEs leading to withdrawal from the study	AEs/SAE screen of the eCRF

Section 8.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals

Note: the procedure described in this section will also apply to suspected HZ episodes qualifying as SAEs.

Section ***10.8. Analysis of suspected HZ incidence*** was added with the wording below:

Descriptive statistics

The number of suspected HZ cases will be tabulated.

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 2**	
eTrack study number and Abbreviated Title	204486 (ZOSTER-056)
IND number	BB-IND-13857
EudraCT number	2015-000965-30
Amendment number:	Amendment 2
Amendment date:	11 January 2017
Co-ordinating author:	PPD Scientific Writer (XPE Pharma and Science for GSK Biologicals)

Rationale/background for changes:

- This Country Specific Protocol Amendment was developed in order to implement the Voice of the Patient initiative in Japan.
- The following statement was added in Section 12.3: "If during the conduct of the study the HZ/su vaccine (GSK 1437173A) is approved in Japan, the study will then be locally amended to be conducted as a post-marketing study".
- The list of the contributing authors was updated.

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

Cover page:

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- ~~PPD , Clinical Research and Development Lead (Chiltern International for GSK Biologicals)~~
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- PPD ***, Vice President, VDL***
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LIST OF ABBREVIATIONS

PA:	***Polling Agency***
VCSP:	***Vaccines Clinical Safety and Pharmacovigilance***

12.3. Requirements for Japan

Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (Ministry of Health and Welfare/Ministry of Health, Labour and Welfare Notification No.28 dated 27th March, 1997)" GCP ~~and~~, Article 14-3 and 80-2 of the Pharmaceutical Affairs Law ***and Evaluation and Licensing Division, Pharmaceutical Safety Bureau of MHW, Notification No. 1061, 1998***.

Study Period

The study period has not been confirmed at the time of this protocol. When needed and available, the study period can be communicated at local level, outside of this protocol.

If during the conduct of the study the HZ/su vaccine (GSK 1437173A) is approved in Japan, the study will then be locally amended to be conducted as a post-marketing study.

Voice of the Patient (VoP) Initiative

Subjects who are participating in the Zoster-056 study will be invited for a qualitative survey conducted by Polling Agency (PA) to better understand their own experience after the administration of HZ/su vaccine and what impact it may have had on their daily life, their perception of HZ/su and stated willingness to receive additional dose.

Contact details of the PA will be provided to the subjects by the investigators. Subjects who are willing to participate in this survey, can contact the PA at all stages during the study - after the first, second dose and also when full vaccination course was not completed.

Participation in the survey will be optional and will not impact subject's participation in the study.

Results of this research as well as proposal, interviews and market research material (questionnaire) are for internal use only and will not be published.

The survey is likely to elicit safety information and robust safety reporting process will be followed.

Safety reporting process:

Adverse Event (AE) Reporting:

Any AE linked to the HZ/su vaccine reported by the interviewees must be reported by the PA to the trial investigator within 24 hours of initial receipt (or next working day if over a weekend or a national holiday).

Investigator's responsibilities are as follows:

- ***The investigator will have the responsibility to review the AE reported by the PA and reconcile with the AE/SAE reported in the eCRF. In case of discrepancy between the AE/SAE reported through the PA and the AE/SAE reported in the eCRF, the Investigator will have to contact the subject to request more information regarding the reported AE/SAE and correct the eCRF, if needed (see Section 8).***
- ***The Investigator will have to assess whether the AE/SAE reports should be submitted within eCRF according to protocol requirements (see Section 8).***
- ***Each investigator site will have to track and document the AE/SAE reconciliation.***

Any AE linked to other GSK vaccine/product must be reported to Vaccines Clinical Safety and Pharmacovigilance (VCSP) Department according to spontaneous reporting process. VCSP will process such AE/SAE (linked to marketed products) according to standard processes.

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 3**	
eTrack study number and Abbreviated Title	204486 (ZOSTER-056)
IND number	BB-IND-13857
EudraCT number	2015-000965-30
Amendment number:	Amendment 3
Amendment date:	30 May 2017
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

- This country specific protocol amendment was developed in order to remove the Voice of the Patient (VoP) initiative text from Section 12.3 since this initiative was not adopted in Japan.
- This is a country specific administrative change for the US since the back-up study contact telephone number for reporting SAEs, pregnancies and pIMDs in the US was removed from Section 8.4.2. This US telephone number, which was originally provided to the US sites as a courtesy, became inactivated over the course of the study and the US Fax number is retained as the back-up study contact number for reporting SAEs, pregnancies and pIMDs.

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

LIST OF ABBREVIATIONS

~~**PA:**~~	~~Polling Agency~~
~~**VCSP:**~~	~~Vaccines Clinical Safety and Pharmacovigilance~~

Section 8.4.2 Contact information for reporting serious adverse events, pregnancies and pIMDs

Study Contact for Reporting SAEs, pIMDs and pregnancies
Back-up Study Contact for Reporting SAEs, pIMDs and pregnancies
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** US sites only: Fax: PPD ~~Tel:~~ PPD

12.3. Requirements for Japan

Voice of the Patient (VoP) Initiative

Subjects who are participating in the Zoster-056 study will be invited for a qualitative survey conducted by Polling Agency (PA) to better understand their own experience after the administration of HZ/su vaccine and what impact it may have had on their daily life, their perception of HZ/su and stated willingness to receive additional dose.

Contact details of the PA will be provided to the subjects by the investigators. Subjects who are willing to participate in this survey, can contact the PA at all stages during the study - after the first, second dose and also when full vaccination course was not completed.

Participation in the survey will be optional and will not impact subject's participation in the study.

Results of this research as well as proposal, interviews and market research material (questionnaire) are for internal use only and will not be published.

The survey is likely to elicit safety information and robust safety reporting process will be followed.

Safety reporting process:

Adverse Event (AE) Reporting:

Any AE linked to the HZ/su vaccine reported by the interviewees must be reported by the PA to the trial investigator within 24 hours of initial receipt (or next working day if over a weekend or a national holiday).

Investigator's responsibilities are as follows:

- The investigator will have the responsibility to review the AE reported by the PA and reconcile with the AE/SAE reported in the eCRF. In case of discrepancy between the AE/SAE reported through the PA and the AE/SAE reported in the eCRF, the Investigator will have to contact the subject to request more information regarding the reported AE/SAE and correct the eCRF, if needed (see Section 8).
- The Investigator will have to assess whether the AE/SAE reports should be submitted within eCRF according to protocol requirements (see Section 8).
- Each investigator site will have to track and document the AE/SAE reconciliation.

Any AE linked to other GSK vaccine/product must be reported to Vaccines Clinical Safety and Pharmacovigilance (VCSP) Department according to spontaneous reporting process. VCSP will process such AE/SAE (linked to marketed products) according to standard processes.