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

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' lyophilized formulation of the Herpes Zoster subunit vaccine (HZ/su) (GSK1437173A)
Other Study vaccine	Placebo (Lyophilized sucrose reconstituted with saline [NaCl] solution)
eTrack study number and Abbreviated Title	204939 (ZOSTER-062)
Investigational New Drug (IND) number	BB-IND-13857
EudraCT number	2016-000744-34
Date of protocol	Final Version 2: 14 June 2018
Date of protocol amendment	Amendment 1 Final: 18 March 2019 Amendment 2 Final: 14 April 2020
Title	Safety and immunogenicity study of GSK Biologicals' Herpes Zoster subunit vaccine (HZ/su) GSK1437173A on a two-dose schedule in adults ≥ 50 years of age with a prior episode of Herpes Zoster
Detailed Title	A phase III, randomized, observer-blind, placebo controlled, multicenter clinical trial to assess Herpes Zoster recurrence and the reactogenicity, safety and immunogenicity of GSK Biologicals' Herpes Zoster vaccine (HZ/su) when administered intramuscularly on a 0 and 2 month schedule to adults ≥ 50 years of age with a prior episode of Herpes Zoster.
Co-ordinating author	PPD and PPD, Scientific Writer
Contributing authors (*Amended 14 April 2020*)	• PPD Clinical Research and Development Leads • PPD Lead Statisticians • PPD ***Statistician*** • PPD Study Delivery Leads .

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Contributing authors (*Amended 14 April 2020*)	• PPD Clinical Safety Representatives • PPD Oversight Data Manager • PPD Global Regulatory Affairs • PPD US Regulatory Affairs • PPD Clinical Trial Supply Manager • PPD Global Patents • PPD Clinical Laboratory Science Readout Team Leaders • PPD Clinical Laboratory Science Study Managers • PPD ***ACE and Local Delivery Leads*** • PPD Clinical and Epidemiology Project Lead (CEPL) for ZOSTER, Clinical R&D.

GSK Biologicals' Protocol DS v15.0

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204939 (ZOSTER-062)
IND number	BB-IND-13857
EudraCT number	2016-000744-34
Date of protocol amendment	Amendment 2 Final: 14 April 2020
Detailed Title	A phase III, randomized, observer-blind, placebo controlled, multicenter clinical trial to assess Herpes Zoster recurrence and the reactogenicity, safety and immunogenicity of GSK Biologicals' Herpes Zoster vaccine (HZ/su) when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of Herpes Zoster.
Sponsor signatory	Anne Schuind, Clinical and Epidemiology Project Lead (CEPL) for ZOSTER, Clinical R&D
Signature	_____
Date	_____

Protocol Amendment 2 Rationale

Amendment number:	Amendment 2

Rationale/background for changes:

This protocol amendment 2 outlines measures that may be applicable during special circumstances (e.g., during COVID-19 pandemic). The purpose of the amendment is to introduce measures that may allow protection of subject's welfare and safety, as well as maintaining the integrity of the study.

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety of subjects or/nor the scientific value of the study.

As much as possible all study specified visits and procedures should be completed according to the protocol, taking into account clinical judgment and local public health guidance to protect the safety of staff and subjects.

Section 6.7 outlines the measures which include allowing flexibility in schedule and procedures to optimize site staff safety, patient safety and to preserve study integrity

Other change includes:

- CCI [redacted]

Please refer to Appendix C for a list of all the changes.

Protocol Amendment 2 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' study vaccines 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	204939 ((ZOSTER-062))
IND number	BB-IND-13857
EudraCT number	2016-000744-34
Date of protocol amendment	Amendment 2 Final: 14 April 2020
Detailed Title	A phase III, randomized, observer-blind, placebo controlled, multicenter clinical trial to assess Herpes Zoster recurrence and the reactogenicity, safety, and immunogenicity of GSK Biologicals' Herpes Zoster vaccine (HZ/su) when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of Herpes Zoster.
Investigator name	_____
Signature	_____
Date	_____

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 9.4.2**.**

SYNOPSIS

Detailed Title

A phase III, randomized, observer-blind, placebo controlled, multicenter clinical trial to assess Herpes Zoster recurrence and the reactogenicity, safety and immunogenicity of GSK Biologicals' Herpes Zoster vaccine (HZ/su) when administered intramuscularly on a 0 and 2 month schedule to adults ≥ 50 years of age with a prior episode of Herpes Zoster.

Indication

Worldwide, indications for *Shingrix* include the prevention of herpes zoster (HZ) and the prevention of HZ-related complications, such as postherpetic neuralgia (PHN), in adults 50 years of age (YOA) or older.

Rationale for the study and study design

- **Rationale for the study**

GlaxoSmithKline Biologicals SA (GSK) vaccine for the prevention of HZ is a recombinant subunit (su) vaccine consisting of Varicella Zoster Virus (VZV) glycoprotein E (gE) as antigen and the adjuvant system $AS01_B$. The final vaccine formulation (HZ/su) has been evaluated in several studies in healthy elderly adults (≥ 50 YOA) and immunocompromised (IC) adults (≥18 YOA). In these studies, it was shown to be efficacious and elicit strong cellular and humoral immune responses. Furthermore, the safety and reactogenicity profile of the vaccine was acceptable.

Two large pivotal Phase III trials, ZOSTER-006 [also referred to as ZOE-50] enrolled subjects ≥ 50 YOA and ZOSTER-022 [also referred to as ZOE-70] enrolled subjects ≥ 70 YOA, evaluated the vaccine efficacy and safety of HZ/su. These trials enrolled more than 30,000 subjects who either received HZ/su or placebo on a 0, 2-month schedule. Results from ZOSTER-006 and ZOSTER-022 showed a vaccine efficacy of 97.2% and 89.8% against HZ in adults ≥ 50 YOA and ≥ 70 YOA, respectively. In addition, the second primary objective of pre-specified pooled analysis of ZOSTER-006 and ZOSTER-022 demonstrated that HZ/su effectively prevents PHN with an efficacy of 88.8% in people ≥ 70 YOA. No safety concerns have been raised.

An indication in adults ≥ 50 YOA was filed for registration. HZ/su (trade name *Shingrix*) was first approved in Canada and the United States in October 2017.

The majority of completed HZ/su studies in older adults excluded people with a history of HZ in order to avoid

introducing bias in efficacy, immunogenicity or safety evaluations. In an open label, single arm (uncontrolled) study (ZOSTER-033) conducted in adults ≥ 50 YOA with a history of previous HZ, 6 participants (6.3%) reported a total of 9 suspected HZ cases. This observation was unexpected, assuming a recurrence rate of HZ is <1% per year and the efficacy of HZ/su shown in the ZOSTER-006 and ZOSTER-022 studies.

Study ZOSTER-062 is an observer-blind, randomized, placebo-controlled study to assess the rate of HZ-recurrence as well as the reactogenicity, safety and immunogenicity of HZ/su in a population with a history of HZ. In contrast to the ZOSTER-033 study, the study design incorporates a placebo arm to better understand the rate of HZ recurrence in this population, CCI [redacted] as well as HZ case ascertainment using the procedures applied in the ZOSTER-006 and ZOSTER-022 efficacy studies.

- **Rationale for the study design**

Study ZOSTER-062 will evaluate HZ recurrence and the reactogenicity, safety and immunogenicity of HZ/su in subjects ≥ 50 YOA with a prior episode of HZ. Subjects will be randomized (1:1) to the HZ/su or placebo arm and will be followed in an observer-blind design. Recruitment will be stratified by age, including a minimum of subjects in each age category to ensure recruitment of a broad age range of adults ≥ 50 YOA. A stratified enrolment, including a minimum of subjects in each category, will also be used to account for 'time since previous HZ episode' (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago). Additional minimization factors include: center, (female) gender, family (first degree blood relative) history of HZ, history of PHN and a combined minimization factor to reflect the presence of any of the following conditions: type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic kidney disease and depression.

The placebo-control design and rigorous HZ case ascertainment aligned with previous HZ/su studies provides study design elements not present in the prior ZOSTER-033 study, that will support the assessment of HZ recurrence in the ZOSTER-062 study population. In addition to humoral immunity in all subjects, CCI [redacted]

- **Rationale for the use of placebo**

A lyophilized sucrose cake reconstituted with saline (NaCl) solution is included as a control (placebo) in this study evaluating the rate of HZ recurrence, reactogenicity, safety and immunogenicity of HZ/su in people with a history of HZ. Use of the placebo control and the observer-blind, randomized study design, aims to minimize potential bias in study results.

Objectives

Primary

To compare the incidence of HZ recurrence in the HZ/su group to the placebo group.

A formal non-inferiority analysis with non-inferiority margin of 5 will be performed.

- *Criterion: The objective is met if the upper limit (UL) of the 95% CI of the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below **5**.*

Secondary

- To evaluate the rate of HZ recurrence in HZ/su and placebo groups during the entire study period.
- To evaluate safety and reactogenicity following administration of HZ/su vaccine or placebo within 30 days after each dose.
- To evaluate safety following administration of HZ/su vaccine or placebo during the entire study period.
- To characterize the anti-gE humoral immunogenicity response prior to the first vaccination (Day 1), at two months post first vaccination (Month 2) and at one month post last vaccination (Month 3) in both groups.

CCI

- CCI [redacted]
- [redacted]

Study design

- **Experimental design**: Phase III, observer-blind, randomized, placebo controlled, multicenter, multi-country study with two parallel groups.
- **Duration of the study**: The duration of the study will vary for each subject. The duration of the study will be up to the study conclusion contact that occurs within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months (790 days) from the enrolment date. Therefore, subjects enrolled early in the trial could be followed for longer duration than the subjects who enrol later in the trial.
  - **Epoch 001**: Starting at Visit 1 (Day 1), followed by Visit 2 at two months post first vaccination (Month 2), and then Visit 3 at one month post last vaccination (Month 3).
  - **Epoch-002**: Starting with monthly contact after Visit 3 (Month 3) and ending at the monthly contact that occurs within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months (790 days) from the enrolment date.
- **Primary completion Date (PCD):** The primary completion date will be when the last subject completes their study conclusion contact (within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months [790 days] from the enrolment date).
- **End of Study (EoS):** 1) After all the subjects complete their study conclusion contact, occurring within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months (790 days) from the enrolment date and 2) the release of all polymerase chain reaction (PCR) test results for the HZ rash lesion samples collected.

- **Study groups:**

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of eligible subjects	Age (years)	Epochs	
			Epoch 001	Epoch 002
HZ/su	713	≥50 years	●	●
Placebo	713	≥50 years	●	●

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		HZ/su	Placebo
HZ/su	VZV gE	●	
	AS01B	●	
Placebo	Lyophilised sucrose		●
	Saline (NaCl) solution for reconstitution		●

- **Control**: placebo control.
- **Vaccination schedule**: 0 and 2 months.
- **Treatment allocation**: Eligible subjects will be randomized (1:1) to the HZ/su or placebo group. The randomization algorithm will use a stratification procedure accounting for age (50-59 YOA; 60-69 YOA and ≥70 YOA) and also a stratification procedure accounting for 'time since previous HZ episode' (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago). Additional minimization factors include: (female) gender, center, family (first degree blood relative) history of HZ, history of PHN and a combined minimization factor to reflect the presence of any of the following conditions- type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic kidney disease and depression
- Blinding:

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch-002	observer-blind

	• **Sampling schedule**: – Blood samples for humoral immunity (approximately 5 ml per visit) will be collected from all subjects at Visit 1 (Day 1), Visit 2 (Month 2), and Visit 3 (Month 3). – CCI [redacted] – Clinical specimens of HZ lesions will be collected from all subjects who are clinically diagnosed with a suspected case of HZ. – A urine specimen will be collected from all female subjects of child-bearing potential at Visit 1 (Day 1) and Visit 2 (Month 2). Please refer to glossary of terms for definition of woman of child bearing potential. If a serum pregnancy test instead of a urine pregnancy test is required by country, local or ethics committee regulations, a blood sample will be collected from women of child-bearing potential at Visit 1 (Day 1) and Visit 2 (Month 2) and used for the test as per local guidance. Note: The result of the pregnancy test must be obtained before any study vaccination and must be negative. • **Type of study**: self-contained • **Data collection**: eCRF (electronic Case Report Form) • **Safety monitoring:** An internal GSK Safety Review Team (SRT) will oversee the safety of the ZOSTER-062 study. Serious adverse events (SAEs), adverse events (AEs) including potential immune mediated diseases (pIMDs) and accrual of HZ cases will be reviewed in a blinded manner by the SRT at regular intervals. Any potential safety concern related to conduct of the study will be escalated to higher governing bodies as per internal GSK process.

Case definition	• **Suspected HZ** A suspected case of HZ is defined as a new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. Subjects clinically diagnosed as having a suspected case of HZ by the investigator will be referred to as a case of 'suspected HZ' and followed up. If a case is not clinically diagnosed as suspected HZ, the investigator should not progress further with evaluation of the case. The HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted. • **Confirmed HZ** A suspected case of HZ can be confirmed in two ways by GSK: – By PCR; – By the HZ Ascertainment Committee (HZAC). CCI 
Number of subjects	Target enrolment is 1426 eligible subjects (713 per treatment group) with a previous HZ episode to reach approximately 606 evaluable subjects per group.

Endpoints	**Primary** Occurrence of confirmed HZ episodes from 30 days post second vaccination until study end.
	Secondary • Occurrence of confirmed HZ episodes from first study vaccination until study end. • Reactogenicity and safety, in all subjects – Occurrence, intensity and duration of each solicited local AE within 7 days (Day 1-7) after each vaccination. – Occurrence, intensity, duration and relationship to vaccination of each solicited general AE within 7 days (Days 1-7) after each vaccination. – Occurrence, intensity, duration and relationship to vaccination of unsolicited AEs within 30 days (Days 1-30) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. – Occurrence and relationship to vaccination of all SAEs from dose 1 up to 30 days post last vaccination. – Occurrence and relationship to vaccination of any pIMDs from dose 1 up to 30 days post last vaccination. – Occurrence and relationship to vaccination of all SAEs within the period starting after 30 days post last vaccination until 1 year post last vaccination. – Occurrence and relationship to vaccination of any pIMDs within the period starting after 30 days post last vaccination until 1 year post last vaccination. – Occurrence of SAEs related to investigational vaccine, related to study participation or to GSK concomitant medication/vaccine during the entire study period.

	• Immunogenicity, in all subjects – Vaccine response for anti-gE humoral immunogenicity as determined by ELISA at Month 2 and Month 3. – Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 2 and Month 3.
	CCI [redacted]

	CCI [redacted]

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LIST OF ABBREVIATIONS

CCI [redacted]

Ab:	Antibody
AE:	Adverse event
AS01$_B$:	MPL, QS21, liposome based Adjuvant System (50 µg MPL and 50 µg QS21)

CCI [redacted]

CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CMI:	Cell-Mediated Immunity
COVID-19	***Coronavirus Disease 2019 (Amended 14 April 2020)***
CRO:	Contract Research Organization
eCRF:	electronic Case Report Form
(e)TDF:	Electronic Temperature excursion Decision Form
DNA:	Deoxyribonucleic acid
ELISA:	Enzyme Linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed Set
gE:	VZV glycoprotein E
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GSK:	GlaxoSmithKline
HIV:	Human Immunodeficiency Virus

HZ:	Herpes Zoster
HZAC:	Herpes Zoster Ascertainment Committee
HZ/su:	Herpes Zoster subunit vaccine
IB:	Investigator Brochure
IC:	Immunocompromised
ICF:	Informed Consent Form
CCI [redacted]	
IgG:	Immunoglobulin class G
CCI [redacted]	
IM:	Intramuscular/Intramuscularly
IMC:	Intercurrent Medical Condition
IND:	Investigational New Drug
LAR	Legally Acceptable Representative
LL:	Lower Limit
LMP:	Last Menstrual Period
LOD	Limit of Detection
M:	Month
MedDRA:	Medical Dictionary for Regulatory Activities
mES	modified Exposed Set
mIU:	Milli-International Unit
ml:	Millilitre
MPL:	3-O-desacyl-4'-Monophosphoryl Lipid A

NA:	Not Applicable
NaCl:	Sodium Chloride (saline)
PBMC:	Peripheral Blood Mononuclear Cells
PCD:	Primary Completion Date
PCR:	Polymerase Chain Reaction
PHN:	Postherpetic Neuralgia
PI:	Prescribing Information
PPS:	Per Protocol Set
pIMD:	Potential Immune-Mediated Disease
Pre-Vacc:	Pre-Vaccination
Post-Vacc:	Post-Vaccination
QS21:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
SAP:	Statistical Analysis Plan
SAS:	Statistical Analysis System
SAE:	Serious Adverse Event
SBIR:	Source data Base for Internet Randomization
SD:	Standard Deviation
SDV:	Source Data Verification
SmPC:	Summary of Product Characteristics
SMS:	Short Message Service
SPM:	Study Procedures Manual
SRT:	Safety Review Team
su:	Subunit

CCI [redacted]

VRR:	Vaccine Response Rate
VZV:	Varicella-Zoster Virus
YOA:	Years of Age
ZBPI:	Zoster Brief Pain Inventory

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 Contraceptive, either combined or progestogen alone.
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- Contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization 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), and/or progesterone alone oral contraceptive.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, 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 (that is, 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 observer-blind study, the subject and the site and sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment assignment.
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.
End of Study (EoS): **(Synonym of End of Trial)**	For studies without collection of human biological samples or imaging data, EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biological Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardized term to replace: period, cycle, phase, stage.
eTrack:	GSK’s tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis.

Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization 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.
Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to a qualified individual or party to perform those trial-related duties and functions.
Legally acceptable representative (LAR): **(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.
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 all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study vaccine:	Any investigational vaccine being tested and/or any authorized use of a vaccine/ product /placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule,) at the time of enrolment.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
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.
Treatment number:	A number identifying a treatment to a subject, according to the treatment allocation.
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.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

Woman of child bearing potential (WOCBP):

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal: 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).
- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Documented tubal ligation

Note: Documentation can come from the site personnel's: review of subject's medical records, medical examination, or medical history interview.

- Postmenopausal female: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

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 of the GSK group of companies	Generic description
Shingrix	Herpes Zoster vaccine non-live recombinant, $AS01_B$ adjuvanted

Trademarks not owned by the GSK group of companies	Generic description
Zostavax (Merck & Co., Inc.)	Herpes Zoster vaccine consisting of high-titer live attenuated Varicella-Zoster Virus (Oka strain)

1. INTRODUCTION

1.1. Background

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

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

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

Age is the most common risk factor for developing HZ. The incidence of HZ is relatively constant at 2-3 cases per 1000 persons per year until age 40, and then increases progressively with age: at 50-59 years of age (YOA) the incidence is about 5 cases per 1000 persons per year, and it increases to 10 cases per 1000 persons per year in people ≥ 60 YOA [CDC, 2008; Oxman, 2005].

Half of all HZ cases occur in patients over the age of 60, and individuals who reach 85 years of age have a 50% chance of having HZ during their lifetime [Oxman, 2005]. Patients with impaired cell-mediated immunity (CMI) due to disease, drug treatment, medical interventions or advanced age are at an increased risk of developing 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 (IC) persons [Oxman, 2005; Sperber, 1992].

GlaxoSmithKline Biologicals SA (GSK) vaccine for the prevention of HZ is a recombinant subunit (su) vaccine consisting of VZV glycoprotein E (gE) as antigen and the adjuvant system AS01$_B$. The vaccine referred to as HZ/su, was shown to be efficacious and elicit strong cellular and humoral immune responses in several studies in healthy elderly adults (≥ 50 YOA) and IC adults (≥ 18 YOA), HZ/su. Furthermore, the safety and reactogenicity profile of the vaccine was acceptable.

Two large pivotal Phase III trials, ZOSTER-006 [also referred to as ZOE-50] enrolled subjects ≥ 50 YOA [Lal, 2015] and ZOSTER-022 [also referred to as ZOE-70] enrolled subjects ≥ 70 YOA [Cunningham, 2016], evaluated the vaccine efficacy and safety of HZ/su. These trials enrolled more than 30,000 subjects who either received HZ/su or placebo on a 0, 2-month schedule. Results from ZOSTER-006 and ZOSTER-022 showed a vaccine efficacy of 97.2% and 89.8% against HZ in adults ≥ 50 YOA and ≥ 70 YOA, respectively. In addition, the second primary objective of pre-specified pooled analysis of ZOSTER-006 and ZOSTER-022 demonstrated that HZ/su effectively prevents PHN with an efficacy of 88.8% in people ≥ 70 YOA. No safety concerns have been raised.

An indication in adults ≥ 50 YOA was filed for registration. HZ/su (trade name *Shingrix*) was first approved in Canada and the United States in October 2017.

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

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

The majority of previously completed HZ/su studies in older adults excluded people with a history of HZ to avoid introducing bias in efficacy, immunogenicity or safety evaluations. However, in an open label, single arm (uncontrolled) study (ZOSTER-033) conducted in adults ≥ 50 YOA with a history of previous HZ, 6 participants (6.3%) reported a total of 9 suspected HZ cases [Godeaux, 2017]. Given the recurrence rate of HZ reported in this population is <1% per year [Tseng, 2012; Yawn, 2011] and the known efficacy of HZ/su in the ZOSTER-006 and ZOSTER-022 studies, this observation was unexpected.

Study ZOSTER-062 is an observer-blind, randomized, placebo-controlled study to assess the rate of HZ-recurrence as well as the reactogenicity, safety and immunogenicity of HZ/su in a population with a history of HZ. In contrast to the ZOSTER-033 study, the study design will incorporate inclusion of a placebo arm to better understand the rate of recurrence,[redacted] of subjects as well as more rigorous HZ case ascertainment (in line with the diagnostic approach used in the ZOSTER-006 and ZOSTER-022 efficacy studies).

1.2.2. Rationale for the study design

Study ZOSTER-062 will be conducted to evaluate HZ recurrence and the safety, reactogenicity and immunogenicity of HZ/su in subjects ≥ 50 YOA with a prior episode of HZ. Subjects will be randomized 1:1 to the HZ/su or placebo arm and will be followed in an observer-blind design. Recruitment will be stratified by age, including a minimum of subjects in each age category to ensure recruitment of a broad age range of adults ≥ 50 YOA. A stratified enrolment, including a minimum of subjects in each category will be used to account for 'time since previous HZ episode' (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago). Additional minimization factors include: (female) gender, center, family (first degree blood relative) history of HZ, history of PHN and a combined minimization factor to reflect the presence of any of the following conditions: type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic kidney disease and depression.

The placebo-control design and rigorous HZ case ascertainment aligned with previous HZ/su studies provides study design elements not present in the earlier ZOSTER-033 study that will support the assessment of HZ recurrence in the ZOSTER-062 study population. In addition to humoral immunity in all subjects, CCI [redacted].

1.2.3. Rationale for the use of placebo

A lyophilized sucrose cake reconstituted with saline (NaCl) solution is included as a control (placebo) in this study evaluating the rate of HZ recurrence, reactogenicity, safety and immunogenicity of HZ/su in people with a history of HZ. Use of the placebo control and the observer-blind, randomized study design aims to minimize the potential biases in study results.

1.3. Benefit : Risk Assessment

Please refer to the current IB and/or the Prescribing Information (PI) for information regarding the summary 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/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study vaccine: HZ/su		
Risk of potential immune mediated diseases (pIMDs) following the HZ/su vaccination	Based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, pIMDs are adverse events of special interest undergoing special safety monitoring for all GSK vaccines containing Adjuvant Systems. pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology.	Close monitoring of pIMDs as per study protocol and analysis of safety data generated through clinical trials and other sources. The potential risk of events of possible autoimmune aetiology to occur is mentioned in the Informed Consent Form (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.
Hypersensitivity reactions (including anaphylaxis)	Hypersensitivity reactions, may occur following exposure to allergens from a variety of sources including food, aeroallergens, venom, drugs, and immunisations. Vaccines are a mixture of compounds and allergic sensitisation can occur to any component. While cutaneous reactions, such as rash or urticaria, are common, anaphylactic reactions are very rare.	Administration of the study vaccination is to be preceded by a review of the subjects' medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.
Virus reactivation in immunocompetent individuals with a history of Herpes Zoster	Following the ZOSTER-033 results, EU Authorities requested to add this as a potential risk. ZOSTER-033 was a phase III, open-label, uncontrolled study which evaluated the safety and immunogenicity of *Shingrix* when administered intramuscularly on a 0, 2-month schedule to 96 subjects with a prior physician-documented history of HZ. The occurrence of HZ was not an endpoint of	This potential risk will be assessed in this randomized, placebo-controlled study.

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
	the study. Six subjects (6.3%), two of whom had reported more than one prior episode of HZ (1 participant with 2 episodes and 1 participant with 3 episodes), reported nine episodes of unconfirmed HZ during the study period of M0 – M14.	
Risk of serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g. optic ischemic neuropathy and inflammatory (non-infective) ocular disease.	Clinical data from pooled analysis of safety reported 3 events of optic ischemic neuropathy (OIN) temporally associated with vaccination in *Shingrix* and none in the Placebo group. Based on this observation, US authorities requested to add this as potential risk.	Close monitoring and analysis of safety data generated through clinical trials and other sources, with focus in identifying serious ocular complications that may be due to vasculitis (such as temporal arteritis) or inflammation, e.g. optic ischemic neuropathy and inflammatory (non-infective) ocular disease.
Study Procedures		
Risk from blood sampling.	Blood sampling associated risk of discomfort, syncope, dizziness, infection at the site after or during venipuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health.
Risk from lesion sampling.	Swab/needle sampling of lesions/crusts associated risk of secondary infection, and discomfort related to the procedure.	Lesion samples will be obtained by a trained professional and anti-bacterial ointment may be applied to minimize the potential for secondary infection. The potential risk of some temporary discomfort during the sampling procedure and the precautionary use of an anti-bacterial ointment to reduce the risk of infection are mentioned in the ICF.

1.3.2. Benefit Assessment

Benefits include:

- The subjects receiving the HZ/su during the study may have reduced risk of HZ recurrence.
- Medical evaluation/assessments associated with study procedures (e.g. physical examination, HZ case ascertainment).

1.3.3. Overall Benefit: Risk Conclusion

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

2. OBJECTIVES

2.1. Primary objective

- To compare the incidence of HZ recurrence in the HZ/su group to the placebo group.

  A formal non-inferiority analysis with non-inferiority margin of 5 will be performed.

  – *Criterion: The objective is met if the upper limit (UL) of the 95% CI of the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below **5**.*

Refer to Section 11.1 for the definition of the primary endpoint.

2.2. Secondary objectives

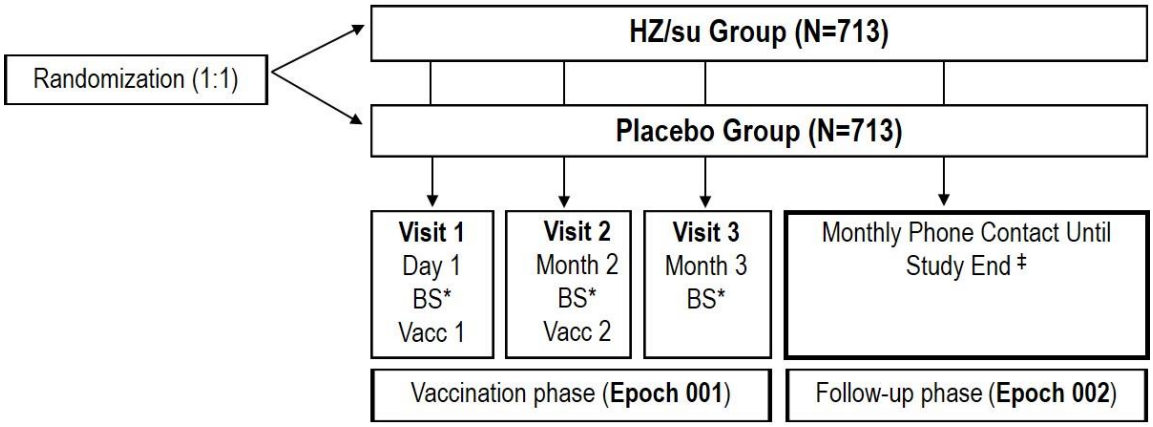
- To evaluate the rate of HZ recurrence in HZ/su and placebo groups during the entire study period.
- To evaluate safety and reactogenicity following administration of HZ/su vaccine or placebo within 30 days after each dose.
- To evaluate safety following administration of HZ/su vaccine or placebo during the entire study period.
- To characterize anti-gE humoral immunogenicity response prior to the first vaccination (Day 1), at two months post first vaccination (Month 2) and at one month post last vaccination (Month 3) in both groups.

Refer to Section 11.2 for the definition of the secondary endpoints.

CCI [redacted]

3. STUDY DESIGN OVERVIEW

Figure 1 Overview of Study Design



BS= Blood sampling; HZ= Herpes Zoster; N= number of subjects planned to be enrolled; Vacc= Vaccination
*A blood sample (approx. 5ml per visit) will be collected from all subjects at Visits 1, 2 and 3. CCI [redacted]

‡ The duration of the study will vary for each subject. Study conclusion will be scheduled based on the projected date of the last contact of the last enrolled subject, that is 26 months (790 days) from the enrolment date. The study conclusion visit/ contact for subjects with an ongoing episode of HZ will occur after a 4-week pain-free period is documented OR after Day HZ-92 follow-up has been completed.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 6.5), are essential and required for study conduct. ***Refer to Section 6.7 for study procedures to be considered during special circumstances (Amended 14 April 2020)***.

- **Experimental design**: Phase III, observer-blind, randomized, placebo controlled, multicenter, multi-country study with two parallel groups.
- **Duration of the study**: The duration of the study will vary for each subject. The duration of the study will be up to the study conclusion contact that occurs within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months (790 days) from the enrolment date. Therefore subjects enrolled early in the trial could be followed for longer duration than the subjects who enrol later in the trial. The study conclusion visit/ contact for subjects with an ongoing episode of HZ at the time of LSLV will occur after a 4-week pain-free period is documented OR after Day HZ-92 follow-up has been completed.
  - **Epoch 001**: Starting at Visit 1 (Day 1) followed by Visit 2 at two months post first vaccination (Month 2), Visit 3 at one month post last vaccination (Month 3).
  - **Epoch-002**: Starting with monthly contact after Visit 3 (Month 3) and ending at the monthly contact that occurs within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months (790 days) from the enrolment date.
- **Primary completion Date (PCD):** The primary completion date will be when the last subject completes their study conclusion contact (within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months [790 days] from the enrolment date.

Refer to glossary of terms for the definition of PCD.

- **End of Study (EoS): 1)** After all the subjects complete their study conclusion contact, occurring within 30 days of the projected study conclusion date of the late enrolled subject, that is, 26 months (790 days) from the enrolment date of the last subject and 2) the release of all polymerase chain reaction (PCR) test results for the HZ rash lesion samples

Refer to glossary of terms for the definition of EoS.

- **Study groups:**

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of eligible subjects	Age (years)	Epochs	
			Epoch 001	Epoch 002
HZ/su	713	≥50 years	●	●
Placebo	713	≥50 years	●	●

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		HZ/su	Placebo
HZ/su	VZV gE	●	
	AS01B	●	
Placebo	Lyophilised sucrose		●
	Saline (NaCl) solution for reconstitution		●

- **Control**: placebo controlled
- **Vaccination schedule**: 0 and 2 months.
- **Treatment allocation**: Eligible subjects will be randomized (1:1) to HZ/su group or placebo group. The randomization algorithm will use a stratification procedure accounting for age (50-59 YOA; 60-69 YOA and ≥ 70 YOA) and also a stratification procedure accounting for 'time since previous HZ episode' (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago). Additional minimization factors include: (female) gender, center, family (first degree blood relative) history of HZ, history of PHN and a combined minimization factor to reflect the presence of any of the following conditions: type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic kidney disease and depression.
- **Blinding**:

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch-002	observer-blind

- **Sampling schedule**:
  - Blood samples for humoral immunity (approximately 5 ml per visit) will be collected from all subjects at Visit 1 (Day 1), Visit 2 (Month 2), and Visit 3 (Month 3).
  - CCI [redacted]
  - Clinical specimens of HZ lesions will be collected from all subjects who are clinically diagnosed with a suspected case of HZ (Section 4.1).
  - A urine specimen will be collected from all female subjects of child-bearing potential (see glossary of terms for definition of woman of child bearing potential) at Visit 1 (Day 1) and Visit 2 (Month 2). If a serum pregnancy test instead of a urine pregnancy test is required by country, local or ethics committee regulations, a blood sample will be collected from women of child-bearing potential at Visit 1 (Day 1) and Visit 2 (Month 2) and used for the test as per local guidance.

  Note: The result of the pregnancy test must be obtained before any study vaccination and must be negative.

- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

- Safety monitoring: An internal GSK Safety Review Team (SRT) will oversee the safety of the ZOSTER-062 study. Serious adverse events (SAEs), adverse events (AEs) including potential immune mediated diseases (pIMDs) and accrual of HZ cases will be reviewed in a blinded manner by the SRT at regular intervals. Any potential safety concern related to conduct of the study will be escalated to higher governing bodies as per internal GSK process.

4. CASE DEFINITION

4.1. Suspected HZ

A suspected case of HZ is defined as a new unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis.

If a case is not clinically diagnosed as suspected HZ, the investigator should not progress further with evaluation of the case. Subjects with 'suspected HZ' should be further evaluated, as below (also refer to Section 4.5).

The HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted.

The end date of a HZ episode is defined as the first time at which a subject had no rash (papules, vesicles, ulcers or crusts) present. This end date will be recorded in the eCRF.

The occurrence of HZ will be recorded in HZ-specific eCRF screens. The reporting period for cases of HZ will be from Day 1 to study end. Refer to Section 4.5 for more details on the evaluation and confirmation of suspected HZ cases.

4.2. Confirmed HZ

A suspected case of HZ can be confirmed by GSK in two ways:

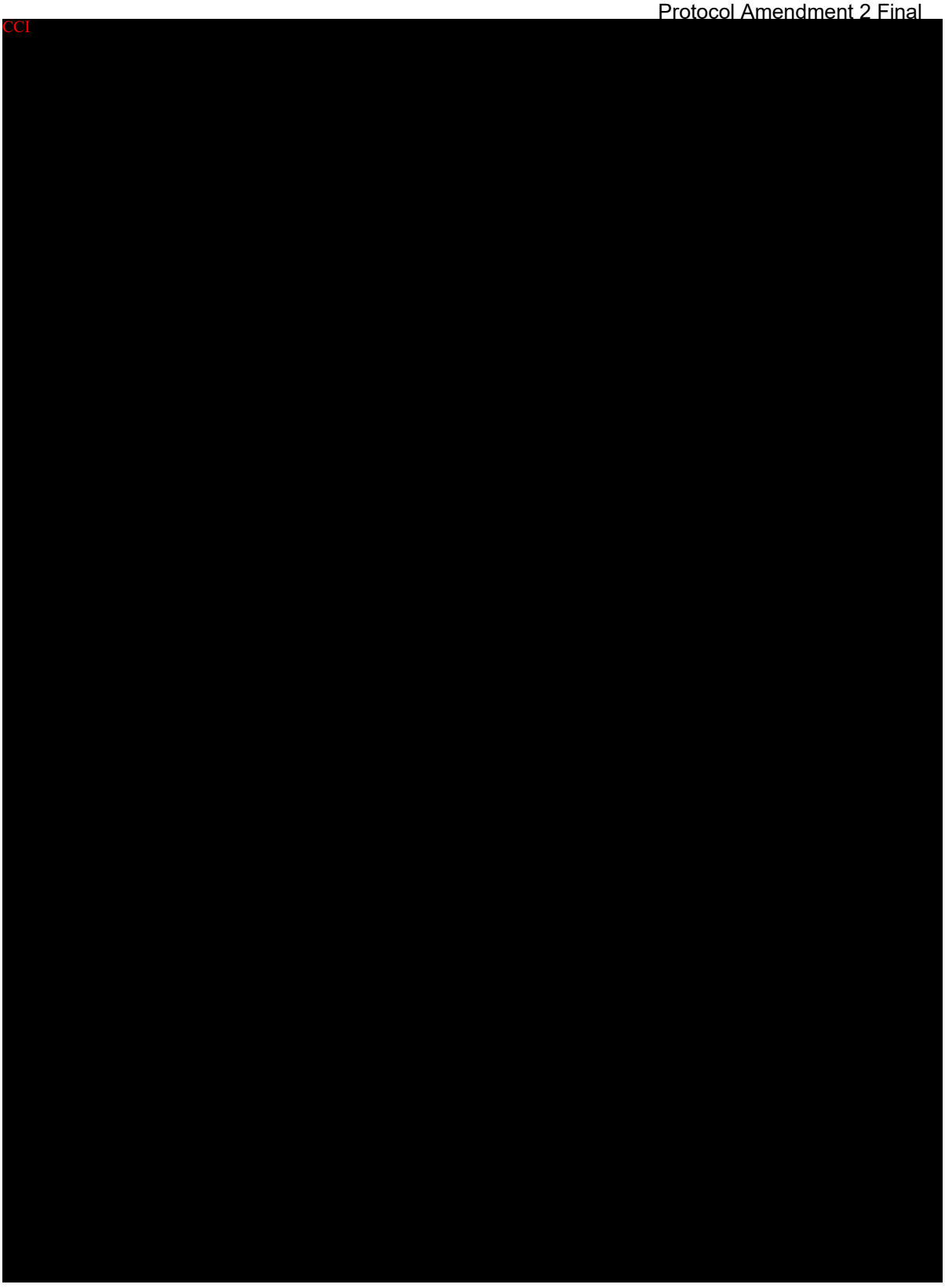
- By PCR:

  Rash lesion samples will be collected from subjects clinically diagnosed as having a suspected case of HZ. The samples will be transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals and analyzed using standardized and validated procedures for laboratory diagnosis of HZ by PCR (see Section 4.5.2.2.1).

- By the HZ Ascertainment Committee (HZAC):

  All suspected HZ cases will be referred to the HZAC. The HZAC will classify all referred cases as either "HZ" or "not HZ" or "not able to decide" (see Section 4.5.2.2.2).

CCI



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[redacted]

4.5. Evaluation and confirmation of suspected HZ cases

4.5.1. Definitions

Refer to Sections 4.1, 4.2, 4.3 and 4.4 for definitions of suspected HZ, confirmed HZ, PHN and other HZ complications, respectively.

For all subjects in case of a suspected or confirmed case of HZ:

HZ-specific diary card: To be completed by subjects (or subject's LAR/caregiver) who develop symptoms suggestive of HZ beginning immediately upon development of these symptoms and prior to visiting the study site for evaluation of the suspected HZ.

ZBPI questionnaire: To be completed by subjects (or subject's LAR/caregiver) with suspected HZ on Day HZ-1(Visit HZ-1) and daily from Day HZ-1 up to Day HZ-29, and weekly from Day HZ-30 onwards until a 4-week pain-free period is documented. For all subjects with ongoing HZ-associated pain at the time of last subject last contact, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-92 (Refer to Section 4.5.2 for more details).

Please refer to Table 7 and Table 8 for information on when diary cards and questionnaires are dispensed to the subjects.

4.5.2. Evaluation of suspected cases of HZ

All suspected HZ cases that occur during the study period will be followed and evaluated. Any symptom/sign suggestive of HZ must be evaluated. At Visit 1 (Day 1), all subjects (and subject's LAR/caregiver, if applicable) will be educated with regard to the signs and symptoms of HZ. The subjects are also given a HZ-specific diary card that they would complete with the date of onset of rash and/or pain. Subjects will be instructed to contact their study site immediately and visit the study site (within 48 hours if possible) for evaluation of the suspected case of HZ. The subject will be asked to bring the completed HZ-specific diary card when he/she visits the study site for evaluation of the suspected HZ. The investigator or delegate will perform a clinical examination when the subject visits the study site for the first evaluation of the suspected case of HZ [Visit HZ-1 at Day HZ-1]. If it is not considered a suspected HZ diagnosis, further evaluation of this event should not progress for the purpose of this study. However, the case should be handled as AE/SAE, if applicable (Section 9.3).

The schedule of visits/contacts that will take place for follow-up of clinically diagnosed suspected HZ cases is presented in Table 8.

For clinically diagnosed suspected HZ cases, the following will take place at Visit HZ-1:

- The investigator or their delegate will verify the completed HZ-specific diary card returned by the subject (or the subject's LAR/caregiver, if applicable). The information from the diary card will be transcribed into the eCRF. The investigator or their delegate will record relevant information regarding the HZ episode in the eCRF (such as date of onset of pain and/or rash, date of clinical diagnosis of HZ, location and nature of HZ lesions, HZ-related complications if any);
- The rash will be documented by digital photography. Please refer to the study procedures manual (SPM) for specific instructions;
- The study staff/investigator will record concomitant medication/vaccination, including concomitant medication for HZ treatment or any HZ-related complications (Section 7.7), and record any other intercurrent medical conditions (IMCs) (Section 7.8). Concomitant medication the subject has already received and/or will receive for HZ treatment will be recorded in the eCRF. The study staff/investigator will check if the subject received any medical attention [hospitalization, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication;
- Rash lesion samples (three replicate samples on the same day) will be collected from subjects clinically diagnosed as having a suspected case of HZ;
- The subject will be given a supply of ZBPI questionnaires to collect information on the severity and duration of HZ-associated pain. The study staff/investigator will provide instructions to the subjects for completing the ZBPI questionnaires and explain the importance of completing and returning the questionnaires to the site.

- The subject/subject's LAR/caregiver will be asked to complete the ZBPI questionnaires on Day HZ-1 (Visit HZ-1) and daily from Day HZ-1 up to Day HZ-29 (ZBPI must be completed to Day HZ-29 at minimum) and weekly from Day HZ-30 onwards until:
  - A 28-day (or 4-week) pain free period is documented (a 'No' answer to the ZBPI question: 'Have you had any pain caused by your shingles in the last 24 hours' (item 1) at each assessment during that entire period);
  - For all subjects with ongoing HZ-associated pain at the time of last subject last contact, completion of ZBPI questionnaires will continue until a 4-week pain-free period is documented OR until at least Day HZ-92.
- After Visit HZ-1 until Visit HZ-7, visits/contacts will take place for follow-up of the HZ episode according to the schedule presented in Table 8. Follow-up of HZ-associated pain and complications will continue irrespective of whether the rash has ended in some cases. When a case initially clinically diagnosed as suspected HZ is subsequently no longer considered by the investigator as suspected HZ, this will be noted in the eCRF. However study procedures to be performed during the follow-up period for a suspected HZ case (see Table 8) should be continued.
- If HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period), the study staff/investigator will inform the subject/subject's LAR/caregiver to stop completing the ZBPI questionnaires and will provide instructions for the subject to return the completed questionnaires to the study site**.**
- If a 4-week pain-free period is achieved and the HZ rash resolves, subsequent follow-up visits or contacts related to this case of HZ will be cancelled meaning that collection of subsequent HZ episode-related information will be stopped and no further information on that particular suspected HZ episode will be encoded in the clinical database. However, if pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. Visits/contacts will restart with Day HZ-1 defined as the first visit of the assigned episode, prior to the pain free period. Follow-up of HZ-associated pain persisting beyond Visit HZ-7 (Day HZ-92) or other complications will be done at monthly contacts between the subject and the investigator and/or investigator's delegate.
- HZ related complications if considered as SAE will be followed as appropriate (Section 9.3.1).

The following will take place at each visit or contact that occurs for each episode:

- The study staff/investigator will: 1) record relevant information regarding the suspected HZ case (such as the location and nature of HZ lesions, the end date of the rash, HZ-related complications, if any); 2) record concomitant medications/vaccinations, including concomitant medication the subject has already received and/or will receive for HZ treatment or treatment of any HZ-related complications (Section 7.7); 3) record any other IMC (Section 7.8); and 4) check if the subject received any medical attention [hospitalization, emergency room visit, or

a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication.

- Additional photographs of HZ lesions may be taken after the first visit for the HZ episode to help note the progression of the rash.
- If the investigator determines that adequate rash samples are not present at the first visit (that is < 3 lesions present or only papules present), the investigator has the option of collecting three additional samples prior to or at the second Visit HZ-2.
- The study staff/investigator will remind subjects/subject's LAR/caregiver to complete the ZBPI questionnaires and return the completed ZBPI questionnaires to the study site according to the instructions given by the study staff/investigator. Once the completed ZBPI questionnaires are available, the investigator will transcribe the information into the subject's eCRF. A new supply of ZBPI questionnaires will be provided to the subjects as necessary.

4.5.2.1. Evaluation of severity of HZ-associated pain using the Zoster Brief Pain Inventory

The ZBPI is an assessment tool in the form of a questionnaire completed by the subject/subject's LAR/caregiver that is specifically designed to assess HZ-associated pain and discomfort during an HZ episode.

In each case of suspected HZ, the subjects will be asked to assess their HZ-associated pain by completing the ZBPI questionnaire either themselves or assisted by an aide (such as a family member or caregiver who is not involved in the study) (Section 6.4.1). At each visit, the subject/subject's LAR/caregiver will be trained (if required) on ways to complete the ZBPI questionnaire.

Information on HZ-associated pain is derived from the ZBPI question: "Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours" (item 3), so called "worst pain" in this protocol.

4.5.2.2. Confirmation of a suspected case of HZ

A suspected case of HZ can be confirmed by GSK in two ways:

4.5.2.2.1. Confirmation of suspected HZ by PCR

Rash lesion samples will be collected from subjects clinically diagnosed as having a suspected case of HZ. The samples will be transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals and analyzed using standardised and validated procedures for laboratory diagnosis of HZ by PCR. Refer to APPENDICES

APPENDIX A for details of PCR assay to be performed on HZ lesion samples and for details of the PCR testing algorithm to classify suspected cases of HZ.

4.5.2.2.2. Confirmation of suspected HZ by the HZAC

All suspected HZ cases will be referred to the HZAC. The HZAC will classify all referred cases as either "HZ" or "not HZ" or "not able to decide". The HZAC classification will serve as the final case definition only when the case cannot be confirmed or excluded by PCR, e.g., when all samples from a given subject are inadequate (as when both VZV and β-actin PCR results are negative), or when no samples are available for a given subject. Therefore, definitive PCR results, when available, will determine the final HZ case assignment. In such cases, the HZAC classification will not contribute to HZ case determination decision.

The HZAC will consist of three to five physicians with HZ expertise. HZAC members, participating as investigators in this study, will not evaluate cases from their own study site. HZAC members will be blinded to group assignments. For every case, each reviewing HZAC member will be asked to make a clinical determination of whether the case is HZ based on review of the available clinical information (e.g., summary of the rash and pain evaluations, digital photographs of the subject's rash, and clinical progress notes). A suspected case of HZ will be considered as "HZ" if the HZAC members concur unanimously; otherwise, it will be classified as "not HZ". A case of "not able to decide" will be classified as "not HZ". As described above, the HZAC case assignment will only be considered as the final case assignment if definitive PCR results are not available. Further details will be provided in the HZAC charter.

4.5.3. Follow up of suspected HZ cases and HZ-associated pain

Data will be collected on all suspected HZ cases that occur from Visit 1 (Day 1) until the study conclusion. For each suspected case of HZ that the investigator concludes is clinically consistent with HZ, data on HZ-associated pain (using ZBPI questionnaires completed by the subject/subject's LAR/caregiver) will be collected ***daily*** until Day- HZ-29, and weekly from Day HZ-30 until the subject has no HZ-associated pain for 4 consecutive weeks. For all subjects with ongoing HZ-associated pain at the time of last subject last contact, ZBPI data will be collected until a 4-week pain-free period is documented OR until Day HZ-92. If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of the ZBPI questionnaire will resume based upon the weekly schedule established at the start of the assigned episode. Visits/contacts will also restart according to the schedule in Table 8 with reference to the established Day HZ-1 at the start of the assigned episode prior to the pain free period. Follow-up ***is*** described in Section 4.5.2.

If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected (that is, less than three lesions present, or if only papules are present), the investigator has the option of collecting three additional samples preferably within 7 days, or at the Visit HZ-2 if there is rash progression (that is, appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present). When the subject returns for repeat sample collection, if possible, three samples from separate lesions should be collected. Refer to the central lab manual for further details on sample collection.

Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash.

5. STUDY COHORT

5.1. Number of subjects/centers

Target enrolment is 1426 eligible subjects (713 per treatment group) with previous HZ episode to reach approximately 606 evaluable subjects per group for statistical analysis assuming a 15% drop out rate. Refer to Sections 5.2 and 5.3 for eligibility criteria.

Subjects will be stratified according to age and time since previous HZ episode. Sample size details are given in Table 4, Table 5 and Section 11.4.

The enrolment strategy will ensure that a minimum of 285 subjects in each of the 50-59 and 60-69 YOA ranges and at least 143 subjects ≥ 70 YOA are expected to be included in the study (Table 4). A minimum of 143 subjects are expected to be enrolled in each sub-group for 'time since previous HZ episode (Table 5). Additional minimization factors include: (female) gender, center, family (first degree blood relative) history of HZ, history of PHN and a combined minimization factor to reflect the presence of any of the following conditions: type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic kidney disease and depression.

Table 4 Expected enrolment based on overall age stratification

Age strata	Sample size	Percentage of total
50-59 YOA	Min 285	Min 20
60-69 YOA	Min 285	Min 20
≥ 70 YOA	Min 143	Min 10
All	1426	100.0

Table 5 Expected enrolment based on time from previous HZ case

Sub-group	Sample size	Percentage of total
≤4 years ago	Min 143	Min 10
5-9 years ago	Min 143	Min 10
≥ 10 years ago	Min 143	Min 10
All	1426	100.0

CCI [redacted]

CCI

Overview of the recruitment plan:

- The target enrolment will be 1426 subjects**.**
- The study is planned to be conducted at multiple sites in multiple countries.
- The recruitment rate will be monitored using a study-specific central randomization system on the internet (SBIR).

5.2. Inclusion criteria for enrolment

Deviations from the inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study 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 and/or subject's LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards and ability to be in regular contact to allow evaluation during the study).
- Written informed consent obtained from the subject/subject's LAR(s) prior to performance of any study specific procedure.
- A male or female ≥ 50 YOA at the time of the first vaccination.
- Subjects with a history of HZ (>6 months prior to enrolment). Confirmation of the prior HZ diagnosis can be done by one of the following three methods:
  - Clinically diagnosed HZ: The subject is eligible for enrolment if there is documentation from a physician or health care provider that establishes a diagnosis of HZ and the date of diagnosis. Examples of documentation include a physician progress note or a hospital discharge summary. The diagnosing physician does not need to be an investigator in the ZOSTER-062 study. Subject recall of having a prior HZ episode in the absence of supporting documentation is not sufficient to meet inclusion criteria.

  OR

  - Laboratory diagnosed HZ: a rash consistent with HZ accompanied by laboratory findings (for example, PCR, viral culture, immunohistochemical staining, etc.) that indicates the presence of VZV in the rash.

OR

- HZ diagnosed by an adjudication committee: HZ diagnosed by an expert committee constituted specifically to diagnose HZ during clinical trials such as the HZAC from previous HZ/su efficacy studies, or comparable committees empanelled during other clinical or epidemiological studies.

- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy, bilateral salpingectomy or post-menopause.

  Please refer to the glossary of terms for the definition of 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 for 2 months after completion of the vaccination series.

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

5.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity regulatory acceptability of the study, 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:

- Subjects who at time of study entry or during the maximum period of anticipated study participation (approximately 4 years) are/will become part of the population recommended to receive a zoster vaccine per existing local or national immunization practices will be excluded from study participation.
- 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 -30 to Day 1), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Onset of HZ in the past 6 months or any ongoing symptoms from a prior HZ episode.
- Chronic antiviral use for HZ prophylaxis.
- History of > 1 prior episode of HZ.

- A history of disseminated HZ, cutaneous or associated with visceral disease (defined as an abnormality of one or more internal organs [e.g., hepatitis, pneumonitis, gastroenteritis, etc] caused by VZV infection) or associated with neurologic disease (defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis or stroke) caused by VZV infection.
- Use or anticipated use of immunosuppressants or immune-modifying drugs during the period starting six months prior to study start and during the whole study period. This includes chronic administration of corticosteroids (> 14 consecutive days of prednisone at a dose of ≥ 20 mg/day [or equivalent]) (intra-articular**,** inhaled and topical steroids are allowed), long-acting immune-modifying agents (e.g., infliximab) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders).
- Administration or planned administration of a vaccine not foreseen by the study protocol within the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose of study vaccine. However, licensed pneumococcal vaccines and non-replicating vaccines (i.e., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flu) may be administered up until 8 days prior to dose 1 and/or dose 2 and/or at least 14 days after any dose of study vaccine.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination against VZV or HZ.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required)
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first dose of study vaccine or planned administration during the study period.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions in the period up to 2 months after completion of the vaccination series.

6. CONDUCT OF THE STUDY

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

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

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

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

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

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject and/or subject's LAR(s) informed consent.
- 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 subject's LAR(s) prior to participation in the study.

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

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF 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.

6.2. Subject identification and randomization

6.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.

6.2.2. Randomization of treatment

6.2.2.1. Randomization of supplies

The randomization of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centers /warehouses.

6.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

6.2.2.2.1. Study group and treatment number allocation

The target will be to enrol approximately 1426 subjects who will be randomly assigned to two study groups in a (1:1) ratio (713 subjects in each group).

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). The randomization algorithm will use a stratification procedure accounting for age and ‘time since previous HZ episode’ as stratification factors.

A minimum of 285 subjects in each of the 50-59 and 60-69 YOA ranges and at least 143 subjects ≥ 70 YOA range are expected to be enrolled. A minimum of 143 subjects are expected to be enrolled in each sub-group (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago) for ‘time since previous HZ episode’. Additional minimization factors include: (female) gender, center, family (first degree blood relative) history of HZ, history of PHN (defined as clinically significant pain or painful abnormal sensations [e.g., allodynia or itch] that persists 90 days or more after HZ rash onset) and a combined minimization factor to reflect the presence of any of the following conditions- type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic kidney disease and depression. Minimization factors will have equal weight in the minimization algorithm.

After obtaining the signed and dated ICF 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 randomization system will determine the study group and will provide the treatment number to be used for the first dose.

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

When SBIR is not available, please refer to the SBIR user guide or the SPM for specific instructions.

6.2.2.2.2. 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 consistent with the allocated study group.

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

6.3. Method of blinding

This is an observer-blind study.

Data will be collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. HZ recurrence, safety, reactogenicity, and immunogenicity) will all be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by authorized medical personnel who will not participate in any of the study clinical evaluation assays.

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

6.4. 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.

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied (refer to Section 6.7 for further details; Amended 14 April 2020).

6.4.1. Diary cards and questionnaires

The diary cards and/or questionnaires to be completed by the subject/subject's LAR/caregiver will be distributed and explained by the investigator or delegate. Any supplied diary cards or questionnaires should be preferably completed by the subject themselves. In case of difficulty in self-completion of the diary cards or questionnaires, a caregiver may provide assistance with reading the questions (verbatim) and/or transcribing the subject's responses on the questionnaires and/or diary cards.

All subjects will receive a diary card on the day of each vaccination. The diary card will be completed by the subjects (or subjects' LAR/caregiver) after each vaccination to record solicited AEs (from Day 1 to Day 7), unsolicited AEs (from Day 1 to Day 30) and any concomitant medication and vaccination taken from Day 1 to Day 30 (Table 7 and Table 22).

In addition, HZ-specific diary card will also be dispensed to be completed by subjects (or subject's LAR/caregiver) who develop symptoms suggestive of HZ, prior to visiting the study site for evaluation of the suspected HZ.

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

6.4.2. Monthly contacts

After Visit 3 (Month 3), monthly contacts between the subjects/ subject's LAR/caregiver and the investigator or delegate will take place to collect information on any event of interest that may have occurred [see Section 6.6.13 for details]. Also, subjects with suspected HZ will be contacted as outlined in Table 8 . The contacts will take place using the most convenient method suited for the sites (e.g., telephone calls by site staff or

designee, or Short Message Service (SMS) text messages through a call centre, or visit by the study staff to the subject's home). A guidance document outlining the information that needs to be collected at each contact will be provided to each country and will serve as a guidance to develop the local script (Refer to the SPM). The logistic details on the set-up of the contacts will be documented by each site/country. At each contact, the subject/subject's LAR/caregiver will respond to a standard set of questions in a language that is understandable to them. The investigator or delegate will transcribe the relevant information on any event of interest in the appropriate language of the subject's eCRF to English. In case of an ongoing HZ case, subjects/subjects' LAR/caregiver will also be reminded to complete ZBPI questionnaires and visit the site (refer to section 4.5.2.1).

6.5. Outline of study procedures

Table 7 presents the list of study procedures and Table 8 presents procedures to be performed for each suspected HZ case.

Table 7 List of study procedures

Epoch	Epoch 001			Epoch-002	
Type of contact	Visit 1	Visit 2	Visit 3	Contact	Monthly Contact until study end[6]
Timepoints	Day 1	Month 2	Month 3	Month 14	Month 26*
Sampling timepoints	Pre-vacc 1	Pre-vacc 2	Post-vacc 2		
Informed consent	●				
Check inclusion/exclusion criteria	●				
Collect demographic data	●				
Medical history including previous HZ history (Section 6.6.4)	●				
History directed physical examination	O	O			
Pregnancy test if applicable[1]	●	●			
Check contraindications and warnings and precautions to vaccination	O	O			
Pre-vaccination body temperature (oral route preferred)	●	●			
Study group and treatment number allocation	O				
Treatment number allocation for subsequent doses		O			
Recording of administered treatment number	●	●			
Vaccine administration [5]	●	●			
Blood sampling for antibody determination (~5 ml) from all subjects [4]	●	●	●		
CCI					
Post-vaccination observation (30 minutes minimum)	O	O			
Distribution of diary cards[2]	O	O			
Training on self-reporting by subjects [3]	O	O	O	O	O
Training on completion of diary cards	O	O			
Training on signs/symptoms of typical HZ	O	O	O	O	O
Reminder for follow-up contact	O	O	O	O	O
Recording of solicited AEs (Days 1–7 post-vaccination) by subjects on diary cards	O	O			
Recording of unsolicited AEs within 30 days (Days 1-30 post-vaccination) by subjects on diary cards	O	O			

Epoch	Epoch 001			Epoch-002	
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Contact**	**Monthly Contact until study end[6]**
Timepoints	**Day 1**	**Month 2**	**Month 3**	**Month 14**	**Month 26***
Sampling timepoints	**Pre-vacc 1**	**Pre-vacc 2**	**Post-vacc 2**		
Return of diary cards		O	O		
Diary card transcription by study staff/investigator		●	●		
Record any intercurrent medical conditions (excluding HZ)	●	●	●	●	●
Record and follow-up of HZ cases [7]	●	●	●	●	●
Record any concomitant medications/vaccinations	●	●	●	●	●
Recording of SAEs, pregnancies, pIMDs	●	●	●	●	
Recording of AE/SAEs leading to withdrawal	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●
Study Conclusion					●

AE: Adverse Event; [redacted]HZ: Herpes Zoster; M: Month; pIMD: potential Immune Mediated Disease; Pre-Vacc: Pre-Vaccination; Post-Vacc: Post-Vaccination; SAE: Serious Adverse Event; VZV: Varicella Zoster Virus

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

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

[1] Only for women of child bearing potential. Please refer to glossary of terms for definition of woman of child bearing potential.

[2] Diary card to collect solicited and unsolicited AEs following each vaccination and HZ specific diary card.

[3] Subjects 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 or HZ symptoms.

[4] Before vaccine administration

[5] Any subject with a clinically diagnosed suspected HZ episode between Visit 1 (Day 1) and Visit 2 (Month 2) is not to receive the second dose.

[6] The duration of the study will vary for each subject. Study conclusion will be scheduled based on the projected date of the last contact of the last enrolled subject, that is 26 months (790 days) from the enrolment date. The study conclusion visit/ contact for subjects with an ongoing episode of HZ will occur after a 4-week pain-free period is documented OR after Day HZ-92 follow-up has been completed.

[7] Refer to Section 4.5 and Table 8 for the brief evaluation and study procedures to be followed in case of suspected HZ.

* For the last enrolled subject only

Table 8 Study procedures to be performed during the follow-up period for each suspected HZ case

Type of contact	Visit HZ-1	Visit HZ-2	Contact HZ-3	Contact HZ-4	Visit HZ-5	Contact HZ-6	Visit HZ-7
Timepoints	**Day HZ-1**	**Day HZ-8**	**Day HZ-15**	**Day HZ-22**	**Day HZ-29**	**Day HZ-57**	**Day HZ-92**
Perform clinical examination	O						
Return HZ-specific diary cards to study staff/investigator	O						
Transcription of the HZ-specific diary card by study staff/investigator	●						
Take digital photographs of HZ rash [α]	●						
Recording of the HZ onset date by study staff/investigator	●						
Collect HZ lesion samples (3 replicate samples) for confirmation by PCR of a case of clinically diagnosed suspected HZ as specified in Section 4.5.2*	●						
Record relevant information regarding HZ in eCRF by study staff/investigator as specified in 4.5.2	●	●	●	●	●	●	●
Record information regarding HZ related complications	●	●	●	●	●	●	●
Record concomitant medication/vaccination according to guidelines in Section 7.7	●	●	●	●	●	●	●
Record any other IMCs according to guidelines in Section 7.8	●	●	●	●	●	●	●
Record any medical attention received for HZ or any HZ-related complication	●	●	●	●	●	●	●
Dispense ZBPI questionnaires to subjects ‡	O	O			O		O
Training on completion of ZBPI questionnaires	O	O			O		O
Completion of ZBPI questionnaires by the subjects (refer to section 4.5.2.1)	O	O	O	O	O	O	O
Return completed ZBPI questionnaires to study staff/investigator		O	O	O	O	O	O
Transcription of ZBPI questionnaires by study staff/investigator	●	●	●	●	●	●	●

● 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.

HZ = Herpes Zoster; PCR = Polymerase Chain Reaction; eCRF = electronic Case Report Form; IMC = Intercurrent Medical Condition; ZBPI = Zoster Brief Pain Inventory.

[α] Additional photographs of HZ lesions may be taken after Visit HZ-1 to help note the progression of the rash.

* If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash samples are not present (that is <3 lesions present or only papules), the investigator has the option of collecting three additional samples prior to or at Visit HZ-2 (preferably within 7 days).

‡ The study staff/investigator will dispense additional questionnaires and provide instructions for the subject to return the completed questionnaires to the study site until the subject has a 4-week pain free or at least Day HZ-92 (for subjects with ongoing pain at the time of last subject last contact).

Time intervals between study visits/contacts related to study procedures performed in subjects participating in the study are provided below. Whenever possible, the investigator should arrange study visits within the interval described in Table 9.

Table 9 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval [2]
Visit 1→Visit 2	60 days (2 months)	49 days - 83 days
Visit 2→Visit 3	30 days (1 month)	28 days- 48 days
Between Monthly Contacts*	30 days (1 month)	20 – 40 days
Visit 2→Month 26 Contact (for the last enrolled subject only)	730 days (24 months)	730- 760 days

*including first contact post Visit 3 (Month 3)

[1] Whenever possible the investigator should arrange study visits according to this interval.

[2] Except the intervals between the Monthly Contacts post Visit 3 (Month 3), subjects may not be eligible for inclusion in the Per Protocol Set if study visits occur outside the allowed interval.

Time intervals between study visits/contacts to be performed for follow-up of HZ are presented in Table 10.

Table 10 Intervals between visits/contacts for subjects in case of suspected HZ

Interval between Visits/ Contacts	Length of interval	Optimal Timing of contact (range of days)
Visit HZ-1 (Day HZ-1) → Visit HZ-2 (Day HZ-8)	7 days	Day HZ-8 (+/- 3 days)*
Visit HZ-2 (Day HZ-8) → Contact HZ-3 (Day HZ-15)	7 days	Day HZ-15 (+/- 3 days)*
Contact HZ-3 (Day HZ-15) → Contact HZ-4 (Day HZ-22)	7 days	Day HZ-22 (+/- 3 days)*
Contact HZ-4 (Day HZ-22) → Visit HZ-5 (Day HZ-29)	7 days	Day HZ-29 (+/- 3 days)*
Visit HZ-5 (Day HZ-29) → Contact HZ-6 (Day HZ-57)	28 days	Day HZ-57 (+/- 7 days)*
Visit HZ-1 (Day HZ-1) → Visit HZ-7 (Day HZ-92)	91 days	Day HZ-92 (+ 7 days)

Note: The date of the previous visit/contact is used as reference date to define the interval between the subsequent study visits/contacts.

Note: If HZ-associated pain ceases (that is, after a 4-week pain-free period is documented) and the HZ rash resolves, subsequent follow-up HZ visits or contacts will be cancelled (see Section 4.5.2). At the time of last subject last contact, follow-up of HZ-associated pain persisting beyond Visit HZ-7 (Day HZ-92) or other complications will end for study purposes and the subject will be followed as per the investigators discretion.

* If contacted early in the window, then remaining days in the interval will need to be captured with the next contact.

Refer to Section 6.7 for study procedures to be considered during special circumstances.

6.6. Detailed description of study procedures

6.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject/subject's LAR(s) must be obtained before study participation. Refer to Section 6.1 for the requirements on how to obtain informed consent.

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

The caregiver can stop participation in the study for any reason at any time, and he/she should be replaced by another caregiver. The former caregiver must not be involved in the consent process and the appointment of a new caregiver. The new caregiver will confirm his/her participation following the same process: by having both subject and him/her-self (re-)signing the annex part of the ICF.

6.6.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 5.2 and 5.3 before enrolment.

6.6.3. Collect demographic data

Record demographic data such as year of birth, sex, race and ethnicity in the subject's eCRF.

6.6.4. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in 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), any pIMDs (see Table 21).

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).

In addition, history of the prior HZ episode must be recorded. Any available information for the diagnosis of HZ episode (clinical diagnosis, PCR, laboratory methods, etc.) must be recorded.

6.6.5. 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.

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.

6.6.6. Pregnancy test

Female subjects of childbearing potential (refer to glossary of terms for definition) are to have a urine/blood pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative.

Note: 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.

6.6.7. Check contraindications, warnings and precautions to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 7.5 and 7.6 for more details.

6.6.8. Assess pre-vaccination body temperature

The body temperature (oral route) of each subject needs to be measured prior to any study vaccine administration. If the subject has fever (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 9).

In rare situations when there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.

6.6.9. Study group and treatment number allocation

Study group and treatment number allocation will be performed as described in Section 6.2.2. The number of each administered treatment must be recorded in the eCRF.

6.6.10. Sampling

Refer to the central lab manual for detailed instructions for the collection, handling and processing of the samples.

6.6.10.1. Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Section 6.5 (List of Study Procedures).

- A volume of at least approximately 5 ml of whole blood (to provide at least 1.5 ml of serum) should be drawn from all subjects for assessment of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the central lab manual for more details on sample storage conditions.
- CCI [redacted]

6.6.10.2. Clinical specimens of HZ lesions for PCR analysis

Clinical specimens of HZ lesions will be collected from subjects clinically diagnosed as having a suspected case of HZ (see Sections 4.5.2.2.1, 4.5.3). Samples for HZ cases assessment should be kept at –20°C/ –4°F or –70/80°C (-94/-112°F) until shipment.

Refer to the central lab manual for more details on sample storage conditions.

6.6.11. Study vaccine administration

- After completing all prerequisite procedures prior to vaccination, the vaccine will be administered IM in the deltoid of the arm according to the administration schedule (refer to Section 7.3 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 9).

- 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.
- Any subjects with an event of HZ between Visit Day 1 and Visit Month 2 vaccine, should not receive the upcoming dose.

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

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 7.7.

IMCs must be checked and recorded in the eCRF as described in Section 7.8.

6.6.13. Training on self-reporting by subjects

Subjects/ subject's LAR/caregiver will be instructed at Visit Day 1 (and will be reminded at subsequent visits and phone contacts) 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).
- should the subject develop any symptoms suggestive of HZ, the subject should be reminded to start completion of the HZ-specific diary card immediately upon development of these symptoms prior to visiting the study site for evaluation of the suspected HZ.

6.6.14. Recording of AEs, SAEs, pregnancies and pIMDs

- Refer to Section 9.3 for procedures for the investigator to record AEs, SAEs, pregnancies and pIMDs. Refer to Section 9.4 for guidelines and how to report SAE, pregnancy and pIMD reports to GSK Biologicals.
- The subjects /subject's LAR(s)/caregiver will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to the subject/subject's LAR/caregiver. The subject will be instructed to measure and record the oral body temperature and any solicited local/general AEs (that is, on the day of vaccination and during the next 6 days) or any unsolicited AEs (that is, on the day of vaccination and during the next 29 days occurring after vaccination). The subject will be instructed to return the completed diary card to the investigator at the next study visit.
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient method.
- The investigator will transcribe the collected information into the eCRF in English.

6.6.15. Monthly contact

After Visit 3 (Month 3), all subjects will be contacted by the study staff on a monthly basis until the study end (that is, until all the subjects complete their last contact, occurring within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months [790 days] from the enrolment date). Therefore, duration of the follow-up will vary for each subject and subjects enrolled early in the trial could be followed for longer duration than the subjects who enrol later in the trial.

6.6.16. Study conclusion

Study conclusion will be scheduled based on the projected date of the last contact of the last enrolled subject, that is, 26 months (790 days) from the enrolment date. All sites will be notified of this date as to schedule the study conclusion contact for all subjects within 30 days of that date.

The study conclusion visit/ contact for subjects with an ongoing episode of HZ will occur after a 4-week pain-free period is documented OR after Day HZ-92 follow-up has been completed (see Table 8).

At the study conclusion contact the investigator will:

- review data collected to ensure accuracy and completeness,
- complete the Study Conclusion screen in the eCRF.

After study conclusion, placebo recipients may be offered cross-over vaccination with HZ/su, if supported by study results.

6.7. Study procedures during special circumstances (Amended 14 April 2020)

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled subjects:

The impact of COVID-19 to the study conduct will be documented in the clinical study report.

- ***Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.***
- ***Diary cards may be transmitted from and to the site by electronic means and/or conventional mail.***
- ***Biological samples may be collected at a different location* other than the study site or at subject's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***

**** It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on subjects by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.***

- ***If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 9), then the interval may be extended as outlined in Table 11.***
- ***If despite best efforts it is not possible to administer the second dose of study intervention as defined in the protocol (see Table 9), a maximum dose interval of 180 days may be used (see Table 11).***
  - ***In case the investigator needs to conduct visits 2 and 3 during the allowed extended interval due to the special circumstances, then the best efforts should be made to conduct a safety follow-up by telephone contact at the time when visits 2 and 3 were initially planned (as close to the optimal window as possible) and approximately monthly thereafter until visits 2 and 3 procedures can be conducted.***

Table 11 Intervals between study visits during special circumstances (Amended 14 April 2020)

Interval	Optimal length of interval	Allowed interval per Protocol	*Allowed interval during special circumstances*
Visit 1 →Visit 2	60 days (2 months)	49 days - 83 days	49 days – ***180 days***
Visit 2→Visit 3	30 days (1 month)	28 days- 48 days	28 days***- 90 days***
Between Monthly Contacts*	30 days (1 month)	20 – 40 days	20 – 40 days
Visit 2→Month 26 Contact (for the last enrolled subject only)	730 days (24 months)	730- 760 days	730- 760 days

Note: Investigator should prioritize conducting the visit as close to the optimal window as possible.

- ***Visits for suspected HZ may take place in a different location* other than the study site or at subject's home. If this is not feasible, then the medical evaluation of suspected HZ may take place virtually with documentation of all the signs and symptoms as outlined in Table 8 and Table 10.***
  - ***If the subject is not able to contact the study staff/investigator to evaluate/ clinically diagnose the suspected HZ case, the subject should be encouraged to document all the signs and symptoms and record the progression of the rash and share it with the investigator when possible.***

- ***Digital photographs can be taken by the study staff/investigator at a different location* other than the study site or at subject's home. If this is not feasible, subjects might be asked to take photographs of their Hz lesions themselves. The photographs will be transferred to the investigator.***
- ***ZBPI questionnaire may be transmitted from and to the site by electronic means and/or conventional mail. If feasible the study staff/investigator can conduct ZBPI questionnaire by telephone contact.***

Impact on the modified exposed set for HZ recurrence analysis and per protocol set for immunogenicity (humoral and CCI) will be determined on a case by case basis.

6.8. Biological sample handling and analysis

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

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

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

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

If additional testing is performed, the marker priority ranking given in Section 6.8.4 may be changed.

Any sample testing will be done in line with the consent of the individual subject/subject's LAR(s).

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

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

6.8.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See Section 11.5 for the definition of cohorts to be analyzed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

6.8.2. Biological samples

The biological samples collected in the study, the quantity needed, the unit and the time points are described in Table 12.

Table 12 Biological samples

Sample type	Quantity	Unit	Timepoint	Sub-set name*
Blood-Humoral	approx 5	ml	scheduled	All subjects
CCI [redacted]				
HZ lesion sample	preferably 3 samples	-	unscheduled	All subjects with suspected HZ episodes during the study

*Refer to Section 5.1 for sub-cohort description
Approx= Approximately; CCI [redacted] HZ= Herpes Zoster; ml= milliliter

6.8.3. Laboratory assays

Please refer to APPENDICES

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

Laboratory assays which will be used in this study are summarised in Table 13 (Humoral Immunogenicity), Table 14 CCI and Table 15 (Molecular Biology), respectively.

Table 13 Humoral Immunity (Antibody determination)

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

Ab: Antibody; ELISA; Enzyme-linked Immunosorbent Assay; IgG: Immunoglobulin class G; mIU: milli-international unit; ml= milliliter; NA: Not applicable

CCI

Table 15 Molecular Biology (PCR tests)

System	Component	Method	Unit	Laboratory
HZ lesion sample	Varicella Zoster Virus DNA	PCR	No unit	GSK Biologicals
HZ lesion sample	Actin Gene DNA	PCR	No unit	GSK Biologicals

DNA= Deoxyribonucleic Acid; HZ= Herpes Zoster; PCR= Polymerase Chain Reaction

Additional exploratory testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These assays may not be represented in the objectives/endpoints of the study protocol.

The GSK Biologicals'/contract research organization's (CRO) clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals'/CRO's clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department. Clinical laboratories contracted by GSK also conform to Good Laboratory Practice guidelines and operate in compliance with regulatory standards.

6.8.4. Biological samples evaluation

6.8.4.1. Immunological read-outs

The plan for immunogenicity testing on samples obtained is shown in Table 16

Table 16 Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	Number of targeted subjects	Component
Type of contact and timepoint	Sampling timepoint			
Day 1 (Visit 1)	Pre-vacc 1	All subjects	1426	Ab gE ELISA
		CCI [redacted]		
Month 2 (Visit 2)	Pre-vacc 2	All subjects	1426	Ab gE ELISA
		CCI [redacted]		
Month 3 (Visit 3)	Post-vacc 2	All subjects	1426	Ab gE ELISA
		CCI [redacted]		

Ab: Antibody; CCI [redacted] ELISA: Enzyme-linked Immunosorbent Assay; gE: recombinant purified Glycoprotein E; CCI [redacted]; Pre-Vacc: pre-vaccination; Post-Vacc: post-vaccination;

6.8.5. Immunological correlates of protection

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

7. STUDY VACCINES AND ADMINISTRATION

7.1. Description of study vaccine

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

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

The vaccine/placebo are labelled and packed according to applicable regulatory requirements.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 17 Study vaccine and Placebo

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
HZ/su	VZV gE	gE=50µg (50µg gE per 0.5ml of reconstituted vaccine)	Lyophilized pellet in a monodose vial	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes per 0.5 ml of reconstituted vaccine	Liquid in a monodose vial		
Placebo	Lyophilised sucrose	Sucrose=20mg (20mg sucrose per 0.5ml of reconstituted placebo)	Lyophilized pellet in a monodose vial	0.5 ml	2
	Saline (NaCl) solution	NaCl=150mM (150mM NaCl solution [salt water for injection])	Liquid in a monodose vial		

$AS01_B$= Adjuvant System 01_B; gE= recombinant purified Glycoprotein E; MPL= 3-O-desacyl-4'-monophosphoryl lipid A; NaCl= Sodium Chloride; QS21: Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)

7.2. Storage and handling of study vaccines

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 vaccines.

7.3. Dosage and administration of study vaccine/placebo

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 (not to exceed the range of 2°C/36°F and 30°C/86°F).

Vaccine will be administered as indicated in Table 18.

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

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

Table 18 Dosage and administration

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

IM: Intramuscular; ml= milliliter

[1] The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

7.4. Replacement of unusable vaccine doses

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

7.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of study vaccine. 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 9.5).

- Anaphylaxis following the administration of vaccine
- Pregnancy (see Section 9.2.1)
- Any SAE judged to be vaccine-related by the investigator.
- Occurrence of HZ between the first and second vaccine dose.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including Human Immunodeficiency Virus (HIV) infection.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 9.1.5.1 for the definition of pIMDs.

The following events constitute contraindications to administration of study vaccine 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 6.5), or the subject may be withdrawn from vaccination at the discretion of the investigator (see Section 9.5).

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

7.6. Warnings and precautions

Refer to the approved product label/package insert, if applicable

7.7. Concomitant medications/products and concomitant vaccinations

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

7.7.1. 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 the 30 day period following each dose of study vaccine (Day 1 to Day 30).
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ending at Visit 3 (Day -30 to Day 90 [that is, 30 days post last vaccination]).
- Prophylactic medication (that is, medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring.
- Any medication used to treat HZ or its complications during the study period.
- Any concomitant medications/products/vaccines listed in Section 7.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE /pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

7.7.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analysis

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 11.5 for cohorts to be analyzed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (that is, more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day or equivalent. Inhaled, topical and intra-articular corticosteroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).

- A vaccine not foreseen by the study protocol administered during the period starting 30 days before and ending 30 days after the last dose of study vaccine administration* with the exception of licensed pneumococcal vaccines and non-replicating vaccines (that is, inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flu) which may be administered up until 8 days prior to either dose and/or at least 14 days after either dose of study vaccine.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed and used according to its Summary of Product Characteristics (SmPC) or PI and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

- Immunoglobulins and/or any blood products administered during the study period.
- Administration of cytotoxic chemotherapy at any time during the study period.
- Receipt of a vaccine against HZ or VZV vaccine other than the study vaccine during the study period.

7.8. Intercurrent medical conditions (IMC) that may lead to elimination of a subject from per-protocol analyses

At each study visit subsequent to the first vaccination visit, it must be verified if the subject has experienced or is experiencing any IMC. If it is the case, the condition(s) must be recorded in the eCRF (Table 22).

An IMC is defined as a condition that has the capability of confounding the immune response to the study vaccine or its interpretation of HZ recurrence. Subjects may be eliminated from the per protocol set (PPS) for immunogenicity if they incur an IMC between dose 1 and one month post last vaccination.

Examples of IMCs include cases of HZ or a confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, HIV infection).

8. HEALTH ECONOMICS

Not applicable

9. SAFETY

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

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

9.1. Safety definitions

9.1.1. 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 (that is 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 study 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 study vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine administration.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (that is invasive procedures, modification of subject's previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 9.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

9.1.2. Definition of a serious adverse event

A SAE is a subset of AEs and is any untoward medical occurrence that:

- Results in death,
- 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.

- Requires hospitalization or prolongation of existing hospitalization,

  Note: In general, hospitalization 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 'hospitalization' occurred or was necessary, the AE should be considered serious.

  Hospitalization 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.

- 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, diarrhea, 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.

- 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.

9.1.3. Solicited adverse events

9.1.3.1. Solicited local (injection-site) adverse events

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

Table 19 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site
Injection site pruritus

9.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 20 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering
Malaise

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

Note: Subjects/subject's LAR (s)/caregiver will be instructed to measure and record the oral temperature in the evening. Should additional temperature measurements be performed at other times of day, subjects/subject's LAR (s)/caregiver will be instructed to record the highest temperature in the diary card.

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

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. imaging studies) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 9.1.1 and 9.1.2). 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 their medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.1.5. Adverse events of specific interest

9.1.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 21.

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

Table 21 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and 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. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy, - Multifocal motor neuropathy - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: - Diffuse Scleroderma - CREST syndrome • Idiopathic inflammatory myopathies, including: - Dermatomyositis - Polymyositis • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: - Juvenile Idiopathic Arthritis - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing Spondylitis, - Reactive Arthritis (Reiter's Syndrome), - Undifferentiated Spondyloarthritis, - Psoriatic Arthritis, - Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localised Scleroderma (Morphoea).

Vasculitis	Blood disorders	Others
• Large vessels vasculitis including: - Giant Cell Arteritis (Temporal Arteritis), - Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: - Polyarteritis nodosa, - Kawasaki's disease, - Microscopic Polyangiitis, - Wegener's Granulomatosis (granulomatosis with polyangiitis), - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), - Buerger's disease (thromboangiitis obliterans), - Necrotizing vasculitis (cutaneous or systemic), - anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), - Henoch-Schonlein purpura (IgA vasculitis), - Behcet's syndrome, - Leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: - IgA nephropathy, - Glomerulonephritis rapidly progressive, - Membranous glomerulonephritis, - Membranoproliferative glomerulonephritis, - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: - Autoimmune uveitis - Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • 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 (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.

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

9.2.1. Pregnancy

Female subjects who are pregnant or lactating may 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 9.4.1 and 9.4.3:

- 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 EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (that is death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] 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 study vaccine will be reported to GSK Biologicals as described in Section 9.4.3. 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.

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

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

All AEs starting within 30 days following administration of each dose of study vaccine (Day 1 to Day 30) must be recorded in the Adverse Event screen in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at Month 14 contact (that is, approximately 12 months following administration of the last dose of the study vaccine for each subject). See Section 9.4 for instructions on reporting of SAEs.

SAEs that are related to the investigational product will be collected and recorded from the time of the first receipt of study vaccine/placebo until the subject is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (that is, protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first study visit until she/he is discharged from the study.

The standard time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end at Month 14 contact (that is, approximately 12 months following administration of the last dose of the study vaccine for each subject). See section 9.4 for instructions on reporting of pregnancies.

The standard time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end at Month 14 contact (that is, approximately 12 months following administration of the last dose of the study vaccine for each subject). See section 9.4 for instructions on reporting of pIMDs.

The time period for collecting and recording of IMCs (including HZ) will begin at the first receipt of study vaccine and will end at the end of the study.

An overview of the protocol-required reporting periods for AEs, SAEs, IMCs and pregnancies is given in Table 22.

Table 22 Reporting periods for collecting safety information

Events	Dose 1 (Visit 1)	7 days Post first Dose	30 days Post first Dose		Dose 2 (Visit 2)	7 days Post last vaccination	30 days Post last vaccination (Visit 3)	One year Post last vaccination	Monthly contact until study end*
	Day 1				Month 2		Month 3	Month 14	
Timing of reporting	Day 1	Day 7	Day 30		Day 1	Day 7	Day 30		
Solicited AEs									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
All SAEs									
SAEs related to the study vaccine									
SAEs related to study participation or concurrent GSK medication/ vaccine [a]									
pIMDs									
Pregnancies									
IMCs (excluding HZ episodes)									
HZ episodes									
HZ related complication (including SAE information)									

AE= Adverse event; HZ= Herpes Zoster; IMC= Intercurrent medical condition; pIMDs= potential immune mediated diseases; SAE= serious adverse event

Note: For each solicited and unsolicited AEs the subject experiences, the subject will be asked if he/she received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in the eCRF.

[a] SAEs related to study participation or GSK concomitant medication/vaccine are to be recorded from the time the subject consents to participate in the study. All other SAEs are to be reported after administration of the first dose of vaccine.
* Study conclusion will be scheduled based on the projected date of the last contact of the last enrolled subject, that is 26 months (790 days) from the enrolment date.

9.3.2. 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 22. 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 study vaccine the investigator will promptly notify the Study Contact for Reporting SAEs.

9.3.3. Evaluation of adverse events and serious adverse events

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

As a consistent method of collecting AEs, the subject or the subject's LAR/caregiver 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.

9.3.3.2. Assessment of adverse events

9.3.3.2.1. Assessment of intensity

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

Table 23 Intensity scales for solicited AEs in adults

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Pruritus at injection site	0	None
	1	Mild: Itchy sensation that neither interferes with nor prevents normal activities
	2	Moderate: Itchy sensation that interferes with normal activity
	3	Severe: Itchy sensation that prevents normal activity
Fever*		Record temperature in °C
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain)	0	None
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	None
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Shivering	0	None
	1	Shivering that is easily tolerated
	2	Shivering that interferes with normal activity
	3	Shivering that prevents normal activity
Malaise	0	None
	1	Malaise that is easily tolerated
	2	Malaise that interferes with normal activity
	3	Malaise that prevents normal activity

*Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred route for measuring temperature in this study will be the oral cavity. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.

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

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

Fever will be graded as:

0	:	<38.0°C
1	:	≥38.0°C – 38.4°C
2	:	≥38.5°C – 39.0°C
3	:	>39.0°C

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 In adults, 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; 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 9.1.2.

9.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccine and the occurrence of each AE/SAE using clinical judgement.

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 study vaccine will be considered and investigated. The investigator will also consult the IB and/or SmPC and/or Prescribing Information for marketed products 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.

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

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

YES	:	There is a reasonable possibility that the study 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 9.1.2), 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).

9.3.3.3. 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).

9.3.3.4. Medically attended visits

For each solicited and unsolicited AE/SAE the subject experiences, the subject/subject's LAR/caregiver will be asked if he/she /the subject received medical attention defined as hospitalization, or an otherwise unscheduled visit ***by*** medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF ***(Amended 14 April 2020).***

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

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

SAEs that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 24, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 24, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 9.3 will be reported promptly to GSK within the timeframes described in Table 24, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 24 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.

9.4.2. 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: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com

9.4.3. 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.

9.4.3.1. 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.

9.4.4. 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.

9.4.5. 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 9.4.3.1 for back-up system in case the electronic reporting system does not work.

9.4.6. 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 24.

9.4.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 9.4.1. 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 study vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

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

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

9.5.1.1. 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 of receipt of information regarding the SAEs; refer to Table 24).

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 last visit of the subject.

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 the last visit of the subject.

9.5.1.2. 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, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- With other non-serious AEs until they are resolved/until study end or they are lost to follow-up. If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper/ electronic Expedited Adverse Events Report 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 recognized follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

9.5.2. 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.

9.6. 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 a SAE / pIMDs should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 7.7).

9.7. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency when knowledge of the treatment is essential for the clinical management or welfare of the subject.

The emergency unblinding process consists of the automated Internet-based system (SBIR) that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

As back up process, the investigator has the option of contacting a GSK Helpdesk if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Non-investigator physician (e.g. physician from emergency room) or subject/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back up process). Contact details of investigator and GSK Helpdesk are reported in the patient/subject card.

GSK Helpdesk 24/24 hour and 7/7 day availability
The Helpdesk is available by phone, fax and email Phone: +32.2.656.68.04 Fax: +32.2.401.25.75 email: rix.ugrdehelpdesk@gsk.com

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician, but can still be followed-up for safety. The relevant event or condition will be recorded in the eCRF.

GSK Vaccines Clinical Safety and Pharmacovigilance (VCSP) staff may unblind the treatment assignment for any subject in case of Suspected Unexpected Serious Adverse Reaction (SUSAR) as well as in case of fatal or life threatening cases. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

9.8. Subject card

Study subjects/subjects' LAR/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/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/caregiver must be instructed to keep subject cards in their possession at all times during the study duration.

10. SUBJECT COMPLETION AND WITHDRAWAL

10.1. Subject completion

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

10.2. Subject withdrawal

Withdrawals will not be replaced.

10.2.1. 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 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/caregiver or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Unsolicited non-serious AE.
- Solicited AE
- HZ episode
- Protocol violation (specify).
- Consent withdrawal, not due to an AE*.
- 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 caregiver has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's LAR/caregiver, 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 9.5.1.2).

10.2.2. Subject withdrawal from study vaccine

A 'withdrawal' from the study vaccine refers to any subject who does not receive the complete treatment, that is when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study 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.

Information relative to premature discontinuation of the study vaccine should 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:

- SAE.
- Unsolicited non-serious AE.
- Solicited AE
- Not willing to be vaccinated
- HZ
- Other (specify).

11. STATISTICAL METHODS

11.1. Primary endpoint

Occurrence of confirmed HZ episodes from 30 days post second vaccination until study end.

11.2. Secondary endpoints

- Occurrence of confirmed HZ episodes from first study vaccination until study end.
- Reactogenicity and safety, in all subjects
  - Occurrence, intensity and duration of each solicited local AE within 7 days (Days 1-7) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of each solicited general AE within 7 days (Days 1-7) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of unsolicited AEs within 30 days (Days 1-30) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
  - Occurrence and relationship to vaccination of all SAEs from dose 1 up to 30 days post last vaccination.
  - Occurrence and relationship to vaccination of any pIMDs from dose 1 up to 30 days post last vaccination.
  - Occurrence and relationship to vaccination of all SAEs within the period starting after 30 days post last vaccination until 1 year post last vaccination.
  - Occurrence and relationship to vaccination of any pIMDs within the period starting after 30 days post last vaccination until 1 year post last vaccination.
  - Occurrence of SAEs related to investigational vaccine, related to study participation or to GSK concomitant medication/vaccine during the entire study period.
- Immunogenicity, in all subjects
  - Vaccine response for anti-gE humoral immunogenicity as determined by ELISA at Month 2 and Month 3.
  - Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 2 and Month 3.

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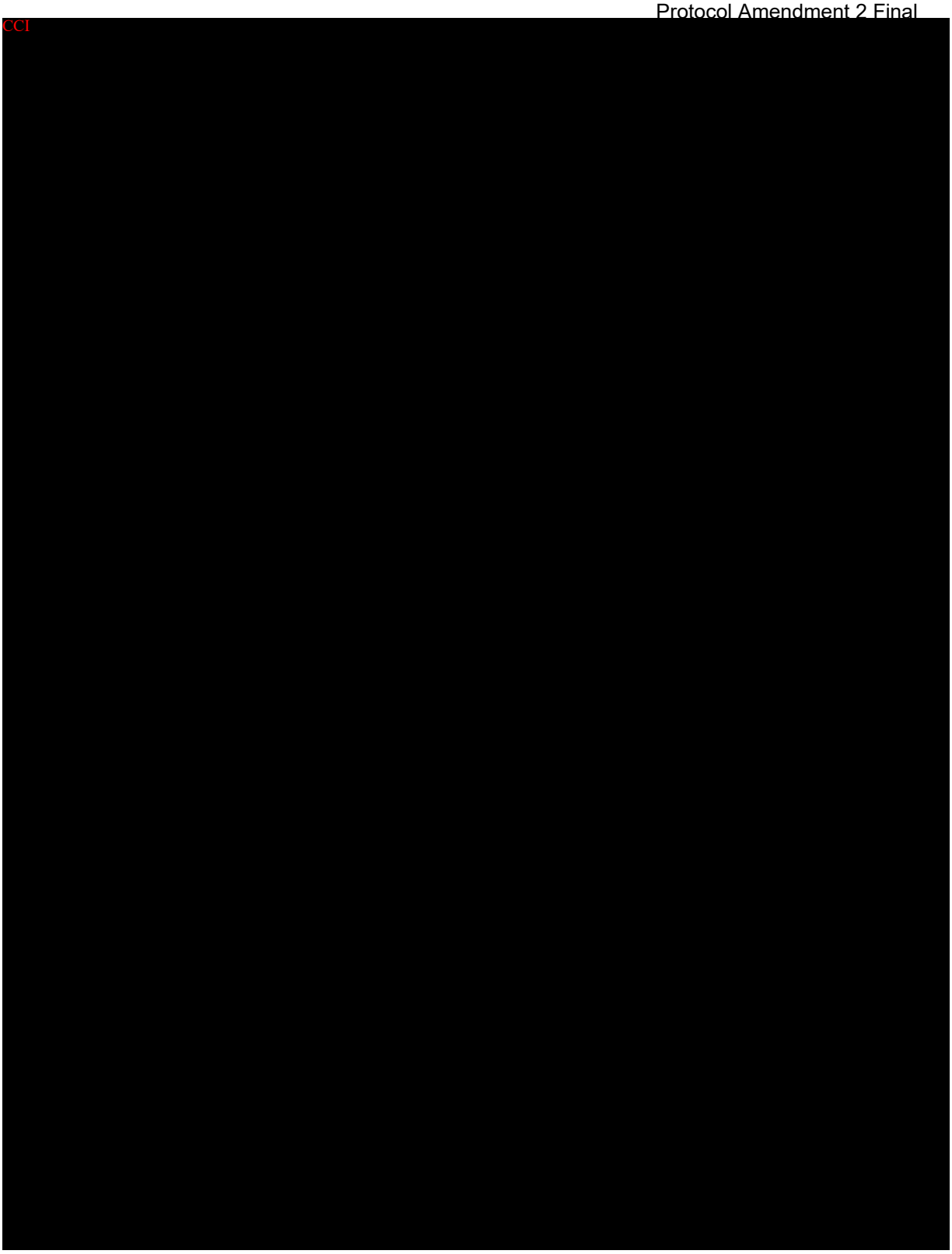

11.4. Determination of sample size

The sample size determination enables the evaluation of the non-inferiority of HZ recurrence incidence rate, and to rule out a ***5***-fold increased risk of HZ recurrence in the HZ/su group compared to the placebo group. The following assumptions were made:

- Incidence rate of HZ recurrence in the placebo group= 0.55% per year.
- Incidence rate of HZ recurrence in the HZ/su group= 0.275% per year, assuming a 50% vaccine efficacy.
- Power of 90% and Type I error of 0.025 (one-sided).
- Criterion for non-inferiority = 5-fold; the 5-fold criterion has been selected as acceptable for ruling out a moderate increased risk of HZ in a clinical trial setting.

Let π be the ratio of incidence rate of HZ recurrence in HZ/su group vs the placebo group, then null hypothesis H0: $\pi \geq 5$ vs. alternative hypothesis Ha: $\pi < 5$. With the assumption that the number of HZ recurrence cases in HZ/su and placebo group follows Poisson distribution independently, conditioning on the total number of cases, the number of cases in HZ/su group would follow the binomial distribution [Lehmann, 1959]. With 1:1 randomization, the parameter p in the binomial distribution (that is, the probability of HZ recurrence in HZ/su group) is expected to be $p=\pi/(1+\pi)$. Therefore, the above hypotheses becomes: H0: $p \geq 0.8333$ vs. Ha: $p < 0.8333$. Under the assumption of VE of 50%, a total number of 10 HZ recurrence cases is needed (PASS 12: Tests for One Proportion using proportions (Exact Test)). With incidence rate of 0.55% per year and two year follow up, 606 evaluable subjects per group are needed. Further assuming a dropout rate of 15% during the 2 year follow up period, 713 subjects per group (a total of 1426 subjects) need to be enrolled.

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11.4.2. Time since previous HZ sub-groups and age category

- To allow a descriptive analysis of the results the target will be to enrol a minimum of:
- 143 subjects in each (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago) “time since previous HZ episode” category.

- 285 subjects in 50-59 and 60-69 YOA category and ***143*** subjects in ≥70 YOA category.

11.5. Cohorts for Analyses

11.5.1. Exposed Set

The exposed set (ES) will include all vaccinated subjects with at least one study vaccine administered.

The ES for analysis of immunogenicity will include all vaccinated subjects for whom data related to immunogenicity endpoints are available.

The ES for analysis of reactogenicity will include all subjects with at least one vaccine administration documented.

11.5.1.1. Modified Exposed Set

The modified exposed set (mES) is the primary population for HZ recurrence analysis. The mES excludes subjects in the ES who were not administered the second dose of the study vaccine or who developed a confirmed case of HZ prior to 30 days after the second vaccination.

11.5.2. Per Protocol Set for immunogenicity

The per protocol set (PPS) for immunogenicity will be defined by time-point (Month 2 and Month 3) and will include evaluable subjects from the ES:

- who meet all eligibility criteria.
- who received 2 doses of the HZ/su study vaccine or placebo according to their random assignment.
- who did not receive forbidden medications as defined in the protocol.
- who had no IMC which may influence immune response.
- who complied with the vaccination schedule as specified in Table 9.
- who complied with the blood sample schedule as specified in Table 9.
- for whom data concerning immunogenicity endpoint measures are available.

11.6. Derived and transformed data

11.6.1. Handling of missing data

For the analysis of solicited AEs, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited AEs based on the ES will include only subjects/doses with documented safety data (that is symptom screen/sheet completed).

For the analysis of HZ recurrence/unsolicited AEs/SAEs/pIMDs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

11.7. Analysis of demographics

Demographic characteristics (age at first study vaccination in years, gender and ethnicity), 'time since previous HZ episode', age stratum and withdrawal status will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as age stratum, 'time from previous HZ episode' and gender.
- Mean, median, Standard Deviation (SD) will be provided for continuous data such as age.
- The analysis will be based on ES.

11.8. Analysis of incidence rate of Herpes Zoster recurrence

For each group, the number of subjects, person-time, number of confirmed HZ cases and incidence rate will be tabulated.

A formal non-inferiority analysis with a non-inferiority margin of 5 will be performed in the final analysis. Non-inferiority assessment will be carried out based on the fact that the distribution of two Poisson variates conditional on their sum is binomial [Lehmann, 1959]. Let n1 and n0 be the number of HZ recurrence cases, T1 and T0 (years) be total follow up, and r1 and r0 be the incidence rate in HZ/su group and placebo group respectively. It is assumed that ni ~ Poisson(λi) (i=0,1) and $\lambda i = Ti \times ri$, and condition on n=n0+n1, n1 ~ binomial(n, p), where $p=\lambda 1/(\lambda 1+\lambda 0)$. A 95% exact CI for p can be derived by using Clopper-Pearson approach, through which a 95% exact CI for $\pi=r1/r0$ (that is, the ratio of incidence rate of HZ recurrence (HZ/su versus placebo)) can be derived. Non-inferiority is met if the upper limit of the 95% CI for π is below 5**.**

In addition to performing a formal non-inferiority analysis, to further quantify the likelihood of the risk increase of HZ following Shingrix vaccination, a probability curve that the ratio of incidence of HZ recurrence (HZ/su versus placebo) is higher than x-fold (x varying from 1 to 5) will be estimated by Bayesian methodology. It will be assumed that the number of HZ cases in the HZ/su and in placebo groups follows Poisson distribution with rate (incidence rate) of λ_{HZ} and λ_p respectively. We further assume that λ_{HZ} and λ_p are random variables both with non-informative Gamma prior distribution: Gamma(0.001, 0.001). Based on the posterior distribution of λ_{HZ} and λ_p, the probability curve of the ratio of incidence of HZ recurrence (HZ/su versus placebo), that is, $Pr(\lambda_{HZ}/\lambda_p > x|$ data, prior), can be calculated for each given value of x. This will be further detailed in the statistical analysis plan (SAP).

The primary analysis of incidence rate of HZ recurrence will be based on the mES. The analysis will be repeated for the ES.

11.9. Analysis of immunogenicity

The primary analysis will be based on the PPS for analysis of immunogenicity. If, in any group, the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.

11.9.1. Humoral immune response

A seronegative subject is a subject whose Ab concentration is below the cut-off value.

A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.

The seropositivity rate is defined as the percentage of seropositive subjects.

The vaccine response rate (VRR) for anti-gE is defined as the percentage of subjects who have at least:

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

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

Within groups assessment

The following descriptive analyses will be performed for each group and by age stratum (50-59 YOA; 60-69 YOA and ≥70 YOA) and by 'time since previous HZ episode' (≤4 years ago, 5-9 years ago, ≥10 years ago):

- Seropositivity rate at Day 1, Month 2 and Month 3 with exact 95% CI
- GMC at Day 1, Month 2 and Month 3 with 95% CI
- VRR at Month 2 and Month 3 with exact 95% CI
- Descriptive statistics of the fold over pre-vaccination at Month 2 and Month 3 (Mean, SD, Min, Q1, Median, Q3, Max).

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11.10. Analysis of safety

The analysis will be performed on the ES. When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g., using windows such as Days 1-7, Days 1-30 and more than 30 days post-vaccination). Safety analyses will also be performed by age stratum (50-59 YOA; 60-69 YOA and ≥70 YOA) and by 'time since previous HZ episode' (≤4 years ago, 5-9 years ago, ≥10 years ago).

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

- The proportion of subjects with at least one local AE (solicited or unsolicited), with at least one general AE (solicited or unsolicited) and with any AE (solicited or unsolicited) during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall.
- The proportion of subjects with at least one local AE (solicited only), with at least one general AE (solicited only) and with any AE (solicited only) during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall.
- The proportion of subjects reporting each individual solicited local and general AE during the solicited 7-day-follow-up period will be tabulated with exact 95% CI.
- For all solicited AEs, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination
- The proportion of solicited AEs resulting in a medically attended visit will be tabulated.
- Total duration of each individual solicited local and general AE will be tabulated.
- The proportion of subjects reporting temperature by half degree (°C) cumulative increments. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for any fever resulting in a medically attended visit.
- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA system organ class (SOC) and preferred term (PT) and reported up to 30 days after each vaccination will be tabulated with exact 95% CI.
- The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The proportion of AEs resulting in a medically attended visit will also be tabulated.
- Total number/percentages of doses (per dose and overall) followed by AEs will be tabulated.
- All pIMDs and related pIMDs occurring from first vaccination up to 30 days post last vaccination will be tabulated.
- All pIMDs and related pIMDs occurring after 30 days post last vaccination until 1 year post last vaccination will be tabulated.
- All SAEs, related SAEs occurring from first vaccination up to 30 days post last vaccination will be tabulated.

- All SAEs, related SAEs occurring after 30 days post last vaccination until one year post last vaccination will be tabulated.
- Fatal SAEs will be tabulated using date of onset of SAE in the following manner – within Day 1-Month 3 (30 days post last vaccination), Day 1 to Month 14 (one year post last vaccination) and Month 3 till study end. Fatal SAEs will also be tabulated using the date of death within the same time periods.
- All SAE related to investigational vaccine, related to study participation or to GSK concomitant medication/vaccine occurring during the entire study period will be tabulated.
- AEs/SAEs leading to withdrawal from the study will be tabulated.

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11.11. Interpretation of analyses

The primary objective of non-inferiority of the incidence of HZ recurrence in the HZ/su and placebo groups is considered met if the upper limit of the 95% CI of the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below 5. For all secondary objectives, analyses will be descriptive with the aim to characterize the differences in reactogenicity, safety and immunogenicity between groups.

11.11.1. 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.

11.11.2. Sequence of analyses

There will be only one final analysis following end of the study.

A clinical study report containing all data will be written and made available to the investigators.

If the data for tertiary endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These data will be documented in annex(es) to the study report.

11.11.3. Statistical considerations for interim analyses

No interim analyses are planned.

12. ADMINISTRATIVE MATTERS

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

12.1. 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 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 validated GSK system to download the final version of the data generated at the investigational site**.**

12.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, the:

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

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

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

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform an eCRF review and a Source Document Verification (SDV). By SDV we verify 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 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.

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.

12.3. 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. 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, otherwise, the minimum retention period will default to 25 years after completion of the study report.

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.

12.4. 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.

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

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in adult populations conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

12.6. 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.

12.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

13. COUNTRY SPECIFIC REQUIREMENTS

Not applicable

14. REFERENCES

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15. APPENDICES

APPENDIX A LABORATORY ASSAYS

Specific Ab (anti-gE) measurements:

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

CCI

PCR assay for confirmation of suspected case of HZ: HZ cases will be confirmed by a PCR based algorithm that assesses the presence of VZV Deoxyribonucleic Acid (DNA) in samples, and the adequacy of the samples (by assessing the presence of β-actin DNA).

VZV and β-actin DNA in HZ clinical specimens will be assessed using real-time PCR detection by the 5’ nuclease assay based on the Taqman probe technology. If the VZV PCR is negative, β-actin PCR will be performed to assess adequacy of the sample and if a specimen is found to be VZV–PCR negative and β-actin–PCR negative, it is considered to be inadequate.

In the Taqman-based PCR experiments, the formation of a PCR product is monitored in real-time during amplification by means of fluorogenic probes that bind specifically to the amplified product. The reporter fluorophore is at the 5' end of the Taqman probe and the quencher is at the 3' end. As long as the probe is intact, no fluorescence is produced by the fluorophore. During the PCR polymerization step, the Taq DNA polymerase displaces the Taqman probe by 3-4 nucleotides, and the 5' nuclease activity of the DNA polymerase separates the fluorophore from the quencher, and a measurable fluorescent signal proportional to the DNA copy number is produced.

As mentioned above, the 5' nuclease-based PCR assay allows the determination of the DNA copy number within samples, but in the present study the VZV and β-actin DNA PCR data on samples from suspected HZ lesions (swabs of vesicles, papules and crusts, and crusts themselves) will be used qualitatively only according to the above mentioned approach.

- **Ascertainment of HZ cases including the PCR testing algorithm to classify HZ suspected cases**

A suspected case of HZ will be documented by digital photography of the rash (if rash is present) and by collecting any relevant information as described in the clinical protocol.

To classify the suspected case of HZ, the samples from the rash lesions (if available) will be collected for laboratory testing by PCR (3 samples, collected on the same day, per subject). If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected (that is, less than three lesions present, or if only papules are present), the investigator has the option of collecting three additional samples preferably within 7 days, or at the Visit HZ-2 if there is rash progression (that is, appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present). When the subject returns for repeat sample collection, if possible, three samples from separate lesions should be collected. Refer to the central lab manual for further details on sample collection.

Each rash lesion will be tested using standardised and validated molecular assays according to the PCR testing algorithm described below.

A hierarchical case definition algorithm used in GSK's Phase III efficacy trials, similar to the algorithm used by Merck in their Shingle Prevention Study (*Zostavax* efficacy study) [Oxman, 2005] will be used to classify each suspected case of HZ as a confirmed HZ case or not.

- If at least 1 sample coming from a given subject is "VZV positive" by PCR (as defined below), the PCR algorithm will classify the "suspected HZ case" as a "confirmed case of HZ".
- If all the samples coming from a given subject are "VZV negative" (as defined below), then β-actin PCR will be performed. If one or more "VZV negative" samples are "β-actin positive", this means that the sampling procedure is valid and that the "suspected HZ case" will be classified as "not a case of HZ."

- If PCR results for a particular subject do not confirm or exclude a "suspected HZ case" (that is, samples coming from a given subject are considered as "inadequate" as both VZV and β-actin PCR results are negative, or no samples are available for the subject), only then will the classification by the HZAC be used to confirm or exclude the suspected HZ case. The HZAC will consist of physicians with HZ expertise. For every suspected HZ case, each HZAC member will be asked to make a clinical determination of whether the case is HZ based on review of the available clinical information. A "suspected HZ case" will be considered as "HZ" if all HZAC members concur (unanimous decision); otherwise, it will be classified as "not HZ".

This algorithm includes the following steps (see Figure 2):

1. DNA extraction from the rash lesion.
2. VZV real-time PCR assay (PCR) targeting the orf62 gene is performed to detect VZV in the rash lesion:

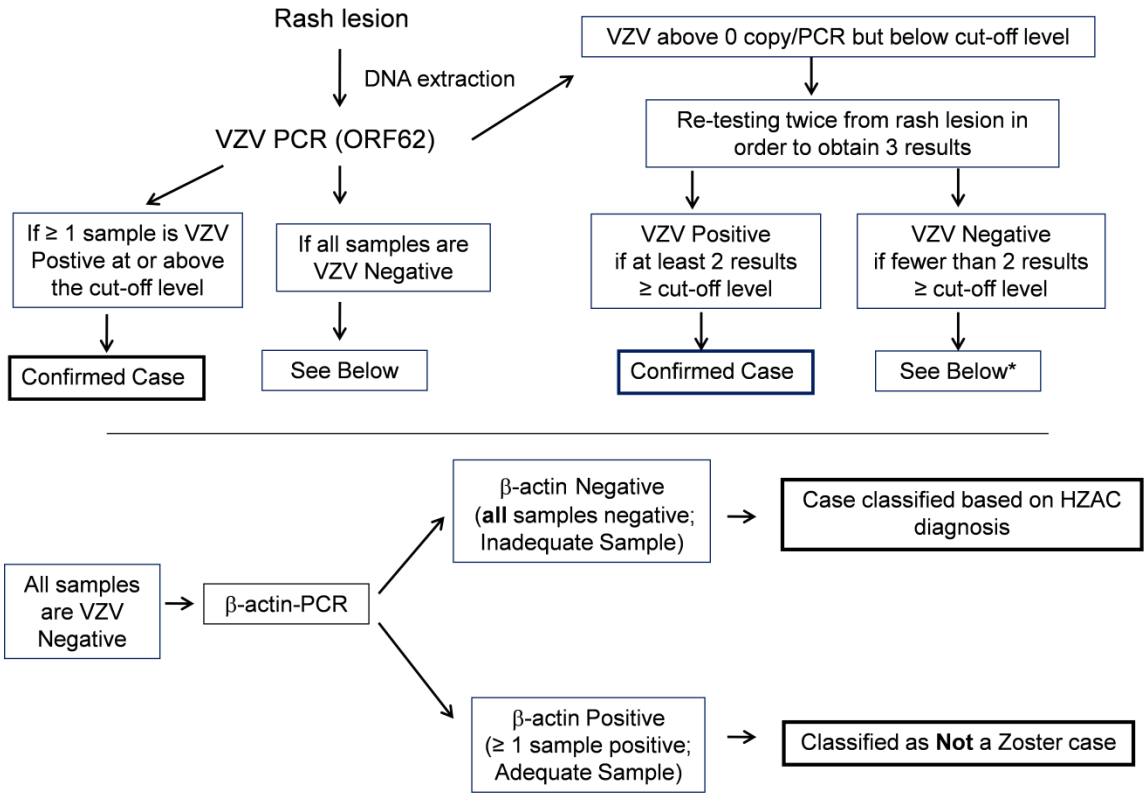
- If the VZV PCR signal is ≥ the cut-off level, that is, the technical limit of detection (LOD) of the assay (10 VZV DNA copies), the sample will be considered as "VZV positive".
- If the VZV PCR signal is above 0 copy/PCR but below the cut-off level of the assay, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain 3 results per sample. The sample will be considered as "VZV positive" if at least 2 results out of the three obtained are ≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than 2 samples are ≥ the cut-off level of the assay.
- If the VZV PCR signal is equal to 0 copies/PCR, the sample will be considered as "VZV negative". If every sample is VZV negative, then extracted DNA from the samples will be assessed for the presence of β-actin DNA to confirm the validity of the rash lesion sampling procedure (see step 3).

3. As described above, if all the samples are VZV negative for a given subject, then β-actin PCR will be performed on "VZV negative" samples to confirm the validity of the sampling procedure.

- If the β-actin PCR signal is below the cut-off level of the assay (β-actin Negative), the sample will be considered as "inadequate" as no β-actin DNA from human cells is detected within the rash lesion sample. If all samples are β-actin Negative, then the classification by the HZAC will be used to confirm or exclude the HZ case.
- If the β-actin PCR signal is ≥ the cut-off level of the assay (β-actin Positive), the sample will be considered as "valid" but without any VZV DNA. If at least one sample is β-actin Positive, then the HZAC classification of a suspected HZ case, will not be part of the decision-making process for HZ case confirmation.

Note: The cut-off level of the VZV PCR and β-actin PCR assays is defined as the technical limit of detection of these assays (LOD; that is, lowest concentration that can be detected by PCR in at least 95% of the tests).

Figure 2 Algorithm for HZ case definition by PCR



VZV: Varicella Zoster Virus; PCR: real-time Polymerase Chain Reaction; DNA: Deoxyribonucleic Acid; ORF: Open Reading Frame; HZAC: Herpes Zoster Ascertainment Committee.

* If the VZV PCR signal is above 0 copy/PCR but below the cut-off level of the assay, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain 3 results per sample. The sample will be considered as "VZV positive" if at least 2 results out of the three obtained are ≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than 2 results are ≥ the cut-off level of the assay. See then below 'All samples are VZV Negative'.

Note: The cut-off level of the VZV PCR assay was defined as the technical limit of detection of the assay (LOD of 10 VZV DNA copies; that is, lowest concentration that can be detected by PCR in at least 95% of the tests)

APPENDIX B CLINICAL LABORATORIES

Table 25 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Clinical Laboratory Sciences, Rixensart	Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

Table 26 Outsourced laboratories

Laboratory	Address
CCI [redacted]	

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	204939 (ZOSTER-062)
IND number	BB-IND-13857
EudraCT number	2016-000744-34
Amendment number:	Amendment 1
Amendment date:	18 March 2019
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

This protocol amendment incorporates feedback from regulatory authorities with the following changes:

- The primary objective has been revised to a formal non-inferiority analysis with revised success criterion for non-inferiority. Consequently, the sample size was adjusted from 986 to 1426 subjects.
- To capture CCI episodes developing after Day HZ-92 according to the protocol definition, the time frame for completing the Zoster Brief Pain Inventory (ZBPI) questionnaire has been clarified. Subjects with suspected herpes zoster (HZ) are required to complete the questionnaire until a 4-week pain-free period is documented. This amendment clarifies procedures for monitoring CCI in subjects who have ongoing symptoms beyond Day HZ-92.
- In the tabulation of safety analyses, the collection period for fatal serious adverse events (SAEs) is updated.

Other changes include:

- The timeframe for primary endpoint (confirmed HZ episodes) is corrected to 30 days post second vaccination instead of 30 days post last vaccination.
- Grading of fever is added to Section 9.3.3.
- The definition of modified exposed set (mES) is clarified.
- Section 9.7 on “Emergency Unblinding” is added as per requirement of new process for observer-blind studies.

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

Title Page:

Contributing authors	• PPD Clinical Research and Development Lead • PPD Study Delivery Leads~~ • PPD Lead Statistician • PPD Oversight Data Manager • PPD Clinical Laboratory Science Study Managers~~ • PPD Clinical and Epidemiology Project Lead, ~~Zoster Program, US RDC~~ ***(CEPL) for ZOSTER, Clinical R&D.***

Glossary of terms

Adequate contraception: ***Oral Contraceptive, either combined or progestogen alone***. ~~Combined estrogen and progesterone oral contraceptives,~~

- **Woman of child bearing potential (WOCBP):** Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - ***Documented tubal ligation***

Synopsis and Introduction

An indication in adults ≥ 50 YOA was filed for registration. HZ/su (trade name *Shingrix*) was first approved in ***Canada and*** in the United States a~~nd Canada~~ in October 2017. ~~and in the European Union and in Japan in March 2018~~.

Primary Objective (Synopsis and Section 2.1)

To compare the incidence of HZ recurrence in the HZ/su group to the placebo group.

~~*The methodology will depend on the number of confirmed HZ cases accrued from one month post last vaccination to study end. If at least 7 confirmed HZ cases are accrued, a*~~ *A formal non-inferiority* ***analysis with non-inferiority margin of 5*** *will be performed.*

- *Criterion: The objective is met if the upper limit (UL) of the 95% CI of the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below* ***5*** *~~10~~.*

~~*If less than 7 confirmed HZ cases are accrued over the study period, the analysis will be descriptive:*~~

- ~~*Ratio of the incidence of HZ recurrence (HZ/su versus placebo) and its 95% CI will be provided.*~~

~~– *A probability curve that the ratio of incidence of HZ recurrence (HZ/su versus placebo) is higher than x-fold (x varying from 1 to 5 10) may be estimated by Bayesian methodology.*~~

Synopsis Table 1 Study groups and epochs foreseen in the study

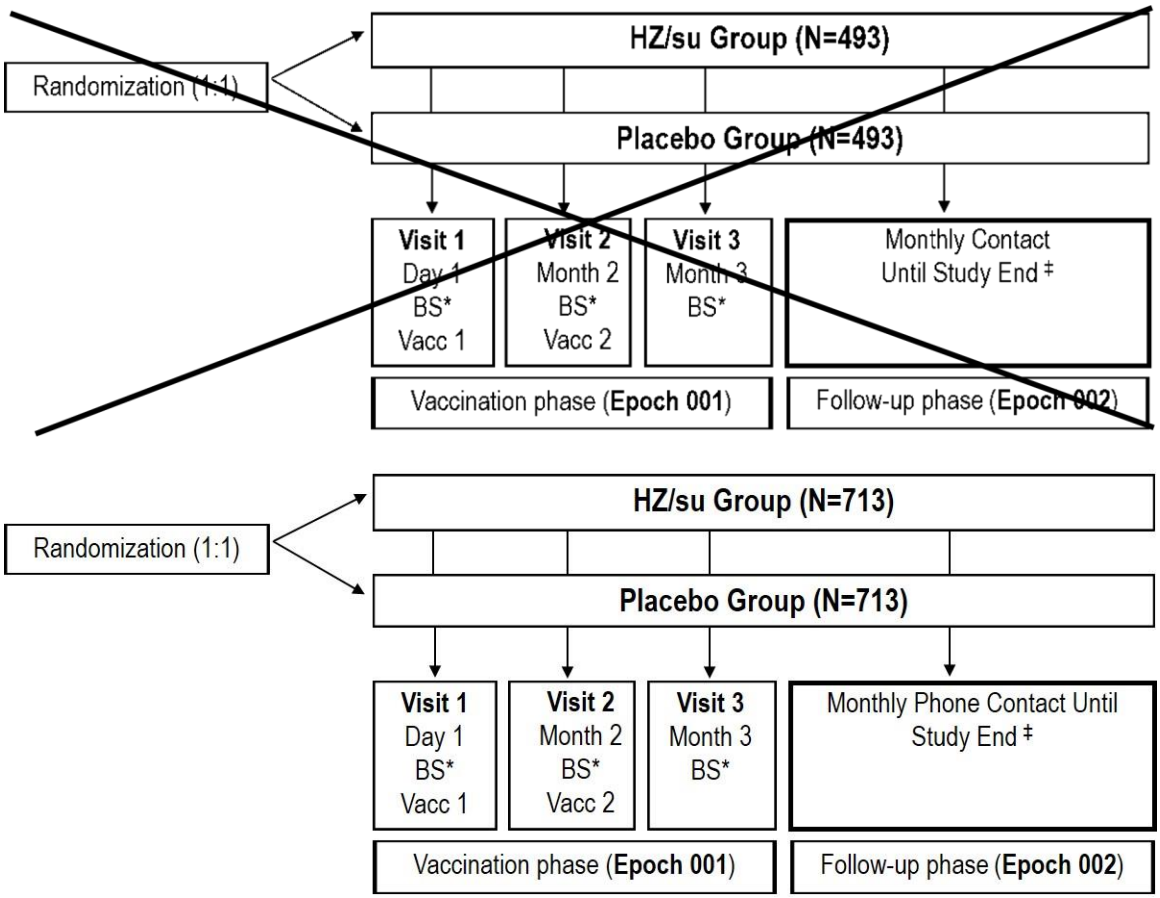
Study groups	Number of *eligible* subjects	Age (years)	Epochs	
			Epoch 001	Epoch 002
HZ/su	~~493~~ ***713***	≥50 years	●	●
Placebo	~~493~~ ***713***	≥50 years	●	●

Number of subjects Target enrolment is ~~986~~ ***1426*** eligible subjects (~~493~~ ***713*** per treatment group) with a previous HZ episode to reach approximately ***606*** ~~419~~ evaluable subjects per group.

Endpoints **Primary**

Occurrence of confirmed HZ episodes from 30 days post ***second*** ~~last~~ vaccination until study end.

– **Section 3: Study design overview**



Duration of the study: The duration of the study will vary for each subject. The duration of the study will be up to the study conclusion contact that occurs within 30 days of the

projected study conclusion date of the last enrolled subject, that is, 26 months (790 days) from the enrolment date. Therefore subjects enrolled early in the trial could be followed for longer duration than the subjects who enrol later in the trial. ***The study conclusion visit/ contact for subjects with an ongoing episode of HZ at the time of LSLV will occur after a 4-week pain-free period is documented OR after Day HZ-92 follow-up has been completed.***

Table 1: Study groups and epochs foreseen in the study

Study groups	Number of eligible subjects	Age (years)	Epochs	
			Epoch 001	Epoch 002
HZ/su	~~493~~ ***713***	≥50 years	•	•
Placebo	~~493~~ ***713***	≥50 years	•	•

Section 4.2: Confirmed HZ

Rash lesion samples will be collected from subjects clinically diagnosed as having a suspected case of HZ. The samples will be transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals ***and analyzed*** using standardized and validated procedures for laboratory diagnosis of HZ by PCR (see Section 4.5.2.2.1).

CCI [redacted]

Section 4.5.1: Definitions

ZBPI questionnaire: To be completed by subjects (or subject's LAR/caregiver) with suspected HZ on Day HZ-1(Visit HZ-1) and daily from Day HZ-1 up to Day HZ-29, and weekly from Day HZ-~~29~~ ***30*** onwards until a 4-week pain-free period is documented ~~or until Day HZ-92~~. For all subjects with ongoing HZ-associated pain at the time of last subject last contact, ZBPI data will be collected until a 4-week pain-free period is documented OR until at least Day HZ-92 (Refer to Section 4.5.2 for more details).

Section 4.5.2: Evaluation of suspected case of HZ

The schedule of visits/contacts that will take place for follow-up of ***clinically diagnosed*** suspected HZ cases is presented in Table 8.

- The subject/subject's LAR/caregiver will be asked to complete the ZBPI questionnaires on Day HZ-1 (Visit HZ-1) and daily from Day HZ-1 up to Day ***HZ***-29 (ZBPI must be completed to Day HZ-29 at minimum) and weekly from Day HZ-30 onwards until:
  - A 28-day (or 4-week) pain free period is documented (a 'No' answer to the ZBPI question: 'Have you had any pain caused by your shingles in the last 24 hours' (item 1) at each assessment during that entire period) ~~or until Day HZ-92~~;

- For all subjects with ongoing HZ-associated pain at the time of last ***subject last*** contact, completion of ZBPI questionnaires will continue until a 4-week pain-free period is documented OR until at least Day HZ-92.

- If HZ-associated pain ceases (defined as a 28-day [or 4-week] pain free period), ~~or until Day HZ-92~~, the study staff/investigator will inform the subject/subject's LAR/caregiver to stop completing the ZBPI questionnaires and will provide instructions for the subject to return the completed questionnaires to the study site.

- If a 4-week pain-free period is achieved and the HZ rash resolves, subsequent follow-up visits or contacts related to this case of HZ will be cancelled ***meaning that collection of subsequent HZ episode-related information will be stopped and no further information on that particular suspected HZ episode will be encoded in the clinical database. However, if pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. Visits/contacts will restart with Day HZ-1 defined as the first visit of the assigned episode, prior to the pain free period. Follow-up of HZ-associated pain persisting beyond Visit HZ-7 (Day HZ-92) or other complications will be done at monthly contacts between the subject and the investigator and/or investigator's delegate.*** ~~If pain continues beyond Day HZ-92, and rash has resolved, collection of information on pain will end for study purposes and the subject will be followed as per the investigator's discretion. Once a pain free period of 4 weeks has been documented or information on pain till Day HZ-92 has been collected, subjects with ongoing symptoms related to suspected HZ episode including ongoing pain will be followed as per the investigator discretion.~~

The study staff/investigator will remind subjects/subject's ***LAR***/caregiver to complete the ZBPI questionnaires and return the completed ZBPI questionnaires to the study site according to the instructions given by the study staff/investigator. Once the completed ZBPI questionnaires are available, the investigator will transcribe the information into the subject's eCRF. A new supply of ZBPI questionnaires will be provided to the subjects as necessary.

Section 4.5.2.2.1: Confirmation of suspected HZ by PCR

The samples will be transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals ***and analyzed*** using standardised and validated procedures for laboratory diagnosis of HZ by PCR.

Section 4.5.3: Follow up of suspected HZ cases and HZ-associated pain

Data will be collected on all suspected HZ cases that occur from Visit 1 (Day 1) until the study conclusion. For each suspected case of HZ that the investigator concludes is clinically consistent with HZ, data on HZ-associated pain (using ZBPI questionnaires completed by the subject/subject's LAR/caregiver) will be collected ***daily*** until Day- HZ-29, and ***weekly*** from Day HZ-30 until the subject has no HZ-associated pain for 4

consecutive weeks, ~~or until Day HZ-92~~. For all subjects with ongoing HZ-associated pain at the time of last subject last contact, ZBPI data will be collected until a 4-week pain-free period is documented OR until Day HZ-92. If pain reappears in the same area after a 4-week pain-free period and is not accompanied by a new HZ rash, it will be assigned to the previous HZ-episode. The completion of the ZBPI questionnaire will resume based upon the weekly schedule established at the start of the assigned episode. Visits/contacts will also restart according to the schedule in Table 8 with reference to the established Day HZ-1 at the start of the assigned episode prior to the pain free period. Follow-up ~~will end at Day HZ-92 as~~ ***is*** described in Section 4.5.2.

When the subject returns for repeat sample collection, if possible, three samples from separate lesions should be collected. Refer to the ~~SPM~~ ***central lab manual*** for further details on sample collection.

Section 5.1: Number of subjects/centers

Target enrolment is ~~986~~ ***1426*** eligible subjects (~~493~~ ***713*** per treatment group) with previous HZ episode to reach approximately ~~419~~ ***606*** evaluable subjects per group for statistical analysis assuming a 15% drop out rate.

The enrolment strategy will ensure that a minimum of ***285*** ~~197~~ subjects in each of the 50-59 and 60-69 YOA ranges and at least ***143*** ~~98~~ subjects ≥ 70 YOA are expected to be included in the study (Table 4). A minimum of ***143*** ~~98~~ subjects are expected to be enrolled in each sub-group for ‘time since previous HZ episode (Table 5).

Table 4: Expected enrolment based on overall age stratification

Age strata	Sample size	Percentage of total
50-59 YOA	Min ***285*** ~~197~~	Min 20
60-69 YOA	Min ***285*** ~~197~~	Min 20
≥ 70 YOA	Min ***143*** ~~98~~	Min 10
All	~~986~~ ***1426***	100.0

Table 5: Expected enrolment based on time from previous HZ case

Sub-group	Sample size	Percentage of total
≤4 years ago	Min ***143*** ~~98~~	Min 10
5-9 years ago	Min ***143*** ~~98~~	Min 10
≥ 10 years ago	Min ***143*** ~~98~~	Min 10
All	***1426*** ~~986~~	100.0

Overview of the recruitment plan:

- The target enrolment will be ~~986~~ ***1426*** subjects.

Section 5.2: Inclusion criteria for enrolment

- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy, ***bilateral salpingectomy*** or post-menopause.

Section 5.3: Exclusion criteria for enrolment

- Use or anticipated use of immunosuppressants or immune-modifying drugs during the period starting six months prior to study start and during the whole study period. This includes chronic administration of corticosteroids (> 14 consecutive days of prednisone at a dose of ≥ 20 mg/day [or equivalent]) (***intra-articular***, inhaled and topical steroids are allowed), long-acting immune-modifying agents (e.g., infliximab).
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.

Section 6.2.2.2.1: Study group and treatment number allocation

- The target will be to enrol approximately ~~986~~ ***1426*** subjects who will be randomly assigned to two study groups in a (1:1) ratio (~~493~~ ***713*** subjects in each group).
- A minimum of ***285*** ~~197~~ subjects in each of the 50-59 and 60-69 YOA ranges and at least ***143*** ~~98~~ subjects ≥ 70 YOA range are expected to be enrolled. A minimum of ***143*** ~~98~~ subjects are expected to be enrolled in each sub-group (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago) for 'time since previous HZ episode'.

Section 6.4.1: Diary cards and questionnaires

All subjects will receive ~~2~~ ***a*** ~~dairy~~ ***diary*** card~~s- 7-day and 30-day diary card~~ on the day of ***each*** vaccination ~~to be completed by the subjects/ subjects' LAR/caregiver~~. ***The diary card will be completed by the subjects (or subjects' LAR/caregiver) after each vaccination to record*** ~~7-day diary cards will be completed for~~ solicited AEs (from Day 1 to Day 7) ~~, after each vaccination)~~ and ~~the 30-day diary cards will be completed for~~ unsolicited AEs (from Day 1 to Day 30 ~~after each vaccination~~) and any concomitant medication and vaccination taken from Day 1 to Day 30 ~~after each vaccination~~ (Table 7 and Table 21).

Section 6.4.2: Monthly contacts

After Visit 3 (Month 3), monthly contacts between the subjects/ subject's ***LAR***/caregiver and the investigator or delegate will take place to collect information on any event of interest that may have occurred [see Section 6.6.13 for details]

Footnote to Table 7: List of study procedures

[2] ~~One diary~~ Diary card ***to collect solicited and unsolicited AEs following each vaccination*** ~~for solicited AEs (Days 1-7) and one for unsolicited AEs (Days 1-30) post each vaccination~~ and HZ specific diary card.

Table 8: Study procedures to be performed during the follow-up period for each suspected HZ case

Type of contact	Visit HZ-1	Visit HZ-2	Contact HZ-3	Contact HZ-4	Visit HZ-5	Contact HZ-6	Visit HZ-7
Timepoints	**Day HZ-1**	**Day HZ-8**	**Day HZ-15**	**Day HZ-22**	**Day HZ-29**	**Day HZ-57**	**Day HZ-92**
Dispense ZBPI questionnaires to subjects‡	O	***O***			***O***		***O***

‡ The study staff/investigator will dispense additional questionnaires and provide instructions for the subject to return the completed questionnaires to the study site ***until the subject has a 4-week pain free or at least Day 92 (for subjects with ongoing pain at the time of last subject last contact).***

Footnote to Table 10: Intervals between visits/contacts for subjects in case of suspected HZ

Note: If HZ-associated pain ceases (that is, after a 4-week pain-free period is documented) and the HZ rash resolves, subsequent follow-up HZ visits or contacts will be cancelled (see Section 4.5.2). ***At the time of last subject last contact, f***ollow-up of HZ-associated pain persisting beyond Visit HZ-7 (Day HZ-92) or other complications will end for study purposes and the subject will be followed as per the investigators discretion.

Section 6.6.10: Sampling

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

Section 6.6.10.1: Blood sampling for immune response assessments

- A volume of at least approximately 5 ml of whole blood (to provide at least 1.5 ml of serum) should be drawn from all subjects for assessment of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the ***central lab manual*** ~~SPM~~ for more details on sample storage conditions.
- CCI [redacted]

Section 6.6.10.2: Clinical specimens of HZ lesions for PCR analysis

Samples for HZ cases assessment should be kept at –20°C/ –4°F or –70/80°C ***(-94/-112°F)*** until shipment.

Refer to the ~~SPM~~ ***central lab manual*** for more details on sample storage conditions.

Section 6.7: Biological sample handling and analysis

Please refer to the ***central lab manual*** ~~SPM~~ for details on biospecimen management (handling, storage and shipment).

Table 15: Immunological read-outs

Blood sampling timepoint		Sub-cohort Name	Number of targeted subjects	Component
Type of contact and timepoint	Sampling timepoint			
Day 1 (Visit 1)	Pre-vacc 1	All subjects	***1426*** ~~986~~	Ab gE ELISA
		CCI [redacted]		
Month 2 (Visit 2)	Pre-vacc 2	All subjects	***1426*** ~~986~~	Ab gE ELISA
		CCI [redacted]		
Month 3 (Visit 3)	Post-vacc 2	All subjects	***1426*** ~~986~~	Ab gE ELISA
		CCI [redacted]		

Section 7.7.2: Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analysis

- ***Administration of cytotoxic chemotherapy at any time during the study period.***

Section 9.3.1: Time period for detecting and recording adverse events, serious adverse events and pregnancies

The standard time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end at ~~study end at~~ Month 14 contact (that is, approximately 12 months following administration of the last dose of the study vaccine for each subject).

The standard time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will ~~end at study end~~ at Month 14 contact (that is, approximately 12 months following administration of the last dose of the study vaccine for each subject).

Section 9.3.3.2.1: Assessment of intensity

~~The preferred route for recording temperature in this study is oral. Fever is defined as temperature ≥ 38.0°C / 100.4°Grade 3 fever will be defined as temperature > 39.0°C.~~

Fever will be graded as:

0	***:***	***<38.0°C***
1	***:***	***≥38.0°C – 38.4°C***
2	***:***	***≥38.5°C – 39.0°C***
3	***:***	***>39.0°C***

Section 9.7 Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency when knowledge of the treatment is essential for the clinical management or welfare of the subject.

The emergency unblinding process consists of the automated Internet-based system (SBIR) that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

As back up process, the investigator has the option of contacting a GSK Helpdesk (refer to Table 24) if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

Non-investigator physician (e.g. physician from emergency room) or subject/care giver/family member can also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back up process). Contact details of investigator and GSK Helpdesk are reported in the patient/subject card.

Table 24 Contact information for emergency unblinding

GSK Helpdesk *24/24 hour and 7/7 day availability*
The Helpdesk is available by phone, fax and email *Phone: +32.2.656.68.04* *Fax: +32.2.401.25.75* *email: rix.ugrdehelpdesk@gsk.com*

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician, but can still be followed-up for safety. The relevant event or condition will be recorded in the eCRF.

GSK Vaccines Clinical Safety and Pharmacovigilance (VCSP) staff may unblind the treatment assignment for any subject in case of Suspected Unexpected Serious Adverse Reaction (SUSAR) as well as in case of fatal or life threatening cases. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

Section 10.2.2.: Subject withdrawal from study vaccine

- SAE.
- Unsolicited non-serious AE.
- Solicited AE
- Not willing to be vaccinated
- ***HZ***
- Other (specify).

Section 11.1: Primary Endpoint

- Occurrence of confirmed HZ episodes from 30 days post ***second*** ~~last~~ vaccination until study end.

Section 11.4: Determination of sample size

The sample size determination enables the evaluation of the non-inferiority of HZ recurrence incidence rate, and to rule out a ***5*** ~~10~~-fold increased risk of HZ recurrence in the HZ/su group compared to the placebo group. The following assumptions were made:

- Criterion for non-inferiority = ~~10~~ ***5***-fold; the ~~10~~ ***5***-fold criterion has been selected as acceptable for ruling out a moderate increased risk of HZ in a clinical trial setting.

Let π be the ratio of incidence rate of HZ recurrence in HZ/su group vs the placebo group, then null hypothesis H0: $\pi \geq 5$ vs. alternative hypothesis Ha: $\pi < 5$. With the assumption that the number of HZ recurrence cases in HZ/su and placebo group follows Poisson distribution independently, conditioning on the total number of cases, the number of cases in HZ/su group would follow the binomial distribution (Lehmann, 1959). With 1:1 randomization, the parameter p in the binomial distribution (that is, the probability of HZ recurrence in HZ/su group) is expected to be $p=\pi/(1+\pi)$. Therefore, the above hypotheses becomes: H0: $p \geq 0.8333$ vs. Ha: $p < 0.8333$. Under the assumption of VE of 50%, a total number of 10 HZ recurrence cases is needed (PASS 12: Tests for One Proportion using proportions (Exact Test)). With incidence rate of 0.55% per year and two year follow up, 606 evaluable subjects per group are needed. Further assuming a dropout rate of 15% during the 2 year follow up period, 713 subjects per group (a total of 1426 subjects) need to be enrolled.

~~Sample size calculations were done using PASS 12 (non-inferiority for two proportions using ratios).~~

- ~~Assuming a dropout rate of 15% during the 2-year follow-up period, 493 subjects are to be enrolled in each group to reach 419 evaluable subjects. Based on the above assumptions, this sample size and a follow-up of at least 2 years will yield 7 confirmed HZ cases which will be needed for final analysis.~~

Section 11.4.2: Time since previous HZ sub-groups and age category

- To allow a descriptive analysis of the results the target will be to enrol a minimum of:
- ***143*** ~~98~~ subjects in each (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago) "time since previous HZ episode" category.
- ***285*** ~~197~~ subjects in 50-59 and 60-69 YOA category and ***143*** ~~98~~ subjects in ≥70 YOA category.

Section 11.5.1.1: Modified Exposed Set

- The modified exposed set (mES) is the primary population for HZ recurrence analysis. ***The mES excludes subjects in the ES who were not administered the second dose of the study vaccine*** , ~~which excludes subjects in the ES who did not receive the 2 doses of the study vaccine according to protocol~~ or who developed a confirmed case of HZ prior to 30 days after the second vaccination.

Section 11.5.2: Per Protocol Set for Immunogenicity

- who complied with the vaccination schedule as specified in ~~Table 10~~ ***Table 9***
- who complied with the blood sample schedule as specified in ~~Table 10~~ ***Table 9.***

Section 11.8: Analysis of incidence rate of Herpes Zoster recurrence

A ***formal*** non-inferiority ***analysis with a non-inferiority margin of 5*** ~~assessment~~ will be performed ~~if the number of accrued confirmed HZ cases (from both study groups combined) is at least 7~~ in the final analysis ~~(in the mES)~~. ~~Non-inferiority is met if the upper limit of the 95% CI for the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below 10~~. Non-inferiority assessment, ~~point estimate and 95% CI for the ratio of the incidence of HZ recurrence (HZ/su versus placebo)~~ will be carried out based on the fact that the distribution of two Poisson variates conditional on their sum is binomial (Lehmann, 1959). ***Let n1 and n0 be the number of HZ recurrence cases, T1 and T0 (years) be total follow up, and r1 and r0 be the incidence rate in HZ/su group and placebo group respectively. It is assumed that ni ~ Poisson(λi) (i=0,1) and λi=Ti×ri, and condition on n=n0+n1, n1 ~ binomial(n, p), where p=λ1/(λ1+λ0). A 95% exact CI for p can be derived by using Clopper-Pearson approach, through which a 95% exact CI for π=r1/r0 (that is, the ratio of incidence rate of HZ recurrence (HZ/su versus placebo)) can be derived. Non-inferiority is met if the upper limit of the 95% CI for π is below 5.***

In addition to performing a formal non-inferiority analysis, to further quantify the likelihood of the risk increase of HZ following Shingrix vaccination, a probability curve that the ratio of incidence of HZ recurrence (HZ/su versus placebo) is higher than x-fold (x varying from 1 to 5) will be estimated by Bayesian methodology. It will be assumed that the number of HZ cases in the HZ/su and in placebo groups follows Poisson distribution with rate (incidence rate) of λ_{HZ} and λ_p respectively. We further assume that λ_{HZ} and λ_p are random variables both with non-informative Gamma prior distribution: Gamma(0.001, 0.001). Based on the posterior distribution of λ_{HZ} and λ_p, the probability curve of the ratio of incidence of HZ recurrence (HZ/su versus placebo), that is, $Pr(\lambda_{HZ}/\lambda_p>x|$ data, prior), can be calculated for each given value of x. This will be further detailed in the statistical analysis plan (SAP).

- ~~If the number of accrued confirmed cases is below 7 in the mES, the descriptive statistics for the incidence ratio will be provided. In addition, the probability that the ratio of incidence of HZ recurrence (HZ/su versus placebo) is higher than x-fold (varying from 1 to 10) may be estimated using Bayesian methodology with different priors. This will be further detailed in the statistical analysis plan (SAP).~~

Section 11.10 : Analysis of safety

- All SAEs, related SAEs ~~and fatal SAEs~~ occurring from first vaccination up to 30 days post last vaccination will be tabulated.
- All SAEs, related SAEs ~~and fatal SAEs~~ occurring after 30 days post last vaccination until one year post last vaccination will be tabulated.
- ***Fatal SAEs will be tabulated using date of onset of SAE in the following manner- within Day 1- Month 3 (30 days post last vaccination), Day 1 to Month 14 (one year post last vaccination) and Month 3 till study end. Fatal SAEs will also be tabulated using the date of death within the same time periods.***

Section 11.11: Interpretation of analyses

- ~~If the number of accrued confirmed HZ cases is at least 7 in the mES,~~ The primary objective of non-inferiority of the incidence of HZ recurrence in the HZ/su and placebo groups is considered met if the upper limit of the 95% CI of the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below ***5*** ~~10~~. ~~If the number of accrued confirmed cases is below 7 in the mES, a descriptive assessment of the incidence of HZ recurrence will be done.~~ For all secondary objectives, analyses will be descriptive with the aim to characterize the differences in reactogenicity, safety and immunogenicity between groups.

Section 12.1: Electronic case report form instructions

- The investigator will be provided with a ***validated GSK system to download*** ~~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~~

Appendix A: Laboratory Assays

- **Ascertainment of HZ cases including the PCR testing algorithm to classify HZ suspected cases**
- To classify the suspected case of HZ, the samples from the rash lesions (if available) will be collected for laboratory testing by PCR (3 samples, collected on the same day, per subject). If during clinical evaluation at Visit HZ-1, the investigator determines that adequate rash lesion samples cannot be collected (that is, less than three lesions present, or if only papules are present), the investigator has the option of collecting three additional samples preferably within 7 days, or at the Visit HZ-2 if there is rash progression (that is, appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present). When the subject returns for repeat sample collection, if possible, three samples from separate lesions should be collected. Refer to the ~~SPM~~ ***central lab manual*** for further details on sample collection.

GlaxoSmithKline Biologicals SA

Vaccines R &D

Protocol Amendment 2

eTrack study number and Abbreviated Title	204939 (ZOSTER-062)
IND number	BB-IND-13857
EudraCT number	2016-000744-34
Amendment number:	Amendment 2
Amendment date:	14 April 2020
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

This protocol amendment 2 outlines measures that may be applicable during special circumstances (e.g., during COVID-19 pandemic). The purpose of the amendment is to introduce measures that may allow protection of subject's welfare and safety, as well as maintaining the integrity of the study.

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the safety of subjects or/nor the scientific value of the study.

As much as possible all study specified visits and procedures should be completed according to the protocol, taking into account clinical judgment and local public health guidance to protect the safety of staff and subjects.

Section 6.7 outlines the measures which include allowing flexibility in schedule and procedures to optimize site staff safety, patient safety and to preserve study integrity

Other change includes:

- Clarification on subjects to be enrolled in the CCI sub-cohort has been added.

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

Section 3. Study design overview

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 6.5), are essential and required for study conduct. ***Refer to Section 6.7 for study procedures to be considered during special circumstances***.

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[redacted]

Section 6.4. General study aspects

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied (refer to Section 6.7 for further details).

Section 6.7. Study procedures during special circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled subjects:

The impact of COVID-19 to the study conduct will be documented in the clinical study report.

- ***Safety follow-up may be made by a telephone call, other means of virtual contact or home visit, if appropriate.***
- ***Diary cards may be transmitted from and to the site by electronic means and/or conventional mail.***
- ***Biological samples may be collected at a different location* other than the study site or at subject's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.***

**** It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on subjects by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.***

- ***If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 9), then the interval may be extended as outlined in Table 11.***
- ***If despite best efforts it is not possible to administer the second dose of study intervention as defined in the protocol (see Table 9), a maximum dose interval of 180 days may be used (see Table 11).***
    - ***In case the investigator needs to conduct visits 2 and 3 during the allowed extended interval due to the special circumstances, then the best efforts should***

be made to conduct a safety follow-up by telephone contact at the time when visits 2 and 3 were initially planned (as close to the optimal window as possible) and approximately monthly thereafter until visits 2 and 3 procedures can be conducted.

Table 11 Intervals between study visits during special circumstances

Interval	Optimal length of interval	Allowed interval per Protocol	*Allowed interval during special circumstances*
Visit 1→Visit 2	60 days (2 months)	49 days - 83 days	49 days – ***180 days***
Visit 2→Visit 3	30 days (1 month)	28 days- 48 days	28 days- ***90 days***
Between Monthly Contacts*	30 days (1 month)	20 – 40 days	20 – 40 days
Visit 2→Month 26 Contact (for the last enrolled subject only)	730 days (24 months)	730- 760 days	730- 760 days

Note: Investigator should prioritize conducting the visit as close to the optimal window as possible.

- ***Visits for suspected HZ may take place in a different location* other than the study site or at subject's home. If this is not feasible, then the medical evaluation of suspected HZ may take place virtually with documentation of all the signs and symptoms as outlined in Table 8 and Table 10.***
  - ***If the subject is not able to contact the study staff/investigator to evaluate/ clinically diagnose the suspected HZ case, the subject should be encouraged to document all the signs and symptoms and record the progression of the rash and share it with the investigator when possible.***
  - ***Digital photographs can be taken by the study staff/investigator at a different location* other than the study site or at subject's home. If this is not feasible, subjects might be asked to take photographs of their Hz lesions themselves. The photographs will be transferred to the investigator.***
  - ***ZBPI questionnaire may be transmitted from and to the site by electronic means and/or conventional mail. If feasible the study staff/investigator can conduct ZBPI questionnaire by telephone contact.***

Impact on the modified exposed set for HZ recurrence analysis and per protocol set for immunogenicity (humoral and CCI) will be determined on a case by case basis.

Section 9.3.3.4. Medically attended visits

For each solicited and unsolicited AE/SAE the subject experiences, the subject/subject's LAR/caregiver will be asked if he/she /the subject received medical attention defined as hospitalization, or an otherwise unscheduled visit ***by*** medical personnel for any reason, including emergency room visits.

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