Protocol Amendment 2

Study ID: 212884

Official Title of Study: A phase IV, randomized, observer-blind, placebo-controlled, multi-center study to assess the prophylactic efficacy against Herpes Zoster, immunogenicity and safety of Shingrix when administered intramuscularly on a 2-dose schedule in Chinese adults aged 50 years and older.

NCT number: NCT04869982

Date of Document: 23 Nov 2020

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

Primary Study vaccine and number	GlaxoSmithKline Biologicals SA (GSK) lyophilized formulation of the Recombinant Zoster Vaccine (RZV) (GSK1437173A)
Other Study vaccine	Placebo (Lyophilized sucrose reconstituted with saline [NaCl] solution)
eTrack study number and abbreviated title	212884 (ZOSTER-076)
Date of protocol	Final: 26 February 2020
Date of protocol amendment	Amendment 1 Final: 23 April 2020 Amendment 2 Final: 23 November 2020
Short Title	Efficacy, immunogenicity and safety study of GSK's Recombinant Zoster Vaccine *Shingrix* (GSK1437173A) in Chinese adults aged ≥50 years.
Detailed title	A phase IV, randomized, observer-blind, placebo-controlled, multi-center study to assess the prophylactic efficacy against Herpes Zoster, immunogenicity and safety of *Shingrix* when administered intramuscularly on a 2-dose schedule in Chinese adults aged 50 years and older.
Co-ordinating author ***(Amended, 23 November 2020)***	PPD ***and*** PPD ***(4Clinics for GSK)***, Scientific Writer***s***
Contributing authors ***(Amended, 23 November 2020)***	• PPD**,** Clinical Research and Development Lead • PPD, Expert Statistician • PPD, Lead Statistician • PPD, Study Delivery Lead • PPD and PPD, ***Safety Evaluation & Risk Management (SERM) Safety physicians*** • PPD**,** ***deputy Qualified Person for Pharmacovigilance (dQPPV) and*** PPD**,** ***Belgium*** • PPD and PPD Oversight Data Manager

eTrack study number and abbreviated title	212884 (ZOSTER-076)
Detailed title	A phase IV, randomized, observer-blind, placebo-controlled, multi-center study to assess the prophylactic efficacy against Herpes Zoster, immunogenicity and safety of *Shingrix* when administered intramuscularly on a 2-dose schedule in Chinese adults aged 50 years and older.

Contributing authors (Cont.) ***(Amended, 23 November 2020)***

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- PPD and PPD, Local Delivery Lead
- PPD ***and*** PPD**,** Clinical and Epidemiology Project Lead (CEPL) for ZOSTER, Clinical R&D.

GSK Protocol WS v 16.0.1

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	212884 (ZOSTER-076)
Date of protocol amendment	Amendment 2 Final: 23 November 2020
Detailed Title	A phase IV, randomized, observer-blind, placebo-controlled, multi-center study to assess the prophylactic efficacy against Herpes Zoster, immunogenicity and safety of *Shingrix* when administered intramuscularly on a 2-dose schedule in Chinese adults aged 50 years and older.
Sponsor signatory	Jasur Danier, Clinical and Epidemiology Project Lead (CEPL) for ZOSTER, Clinical R&D
Signature	
Date	

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 Biologicals SA (GSK).
- 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 study vaccine and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- 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 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 in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- 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 will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK 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 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	212884 (ZOSTER-076)
Date of protocol amendment	Amendment 2 Final: 23 November 2020
Detailed Title	A phase IV, randomized, observer-blind, placebo-controlled, multi-center study to assess the prophylactic efficacy against Herpes Zoster, immunogenicity and safety of *Shingrix* when administered intramuscularly on a 2-dose schedule in Chinese adults aged 50 years and older.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA

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 Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.9.3

Study Contact for Reporting SAEs: refer to the local study contact information document.

5. GSK Contact information for Emergency Unblinding

GSK helpdesk contact: refer to Table 13**.**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Amendment 2	23-NOV-2020
Amendment 1	23-APR-2020
Final Protocol	26-FEB-2020

Amendment 2 (23-NOV-2020)

Overall Rationale for the Amendment:

Based on feedback of the Center for Drug Evaluation (CDE) in China, interim analysis that was originally planned to support license renewal will not be performed. Additionally, wording regarding a secondary endpoint of potential immune-medicated diseases (pIMDs) prior or planned concomitant administration of corticosteroids, and pregnancy reporting was clarified and/or corrected. Study procedures for special circumstances were updated. The definition of the Enrolled Set was modified. Minor edits were made for clarity and consistency (see Section 12.8).

Table 2 List of main changes in the protocol and their rationale

Section # and Name	Description of Change	Brief Rationale
Section 10.3.6 (Interim analyses); Section 10.4 (Sequence of analyses)	No interim analyses will be performed. Information regarding the requirement for an interim report of demography and safety for license renewal requirements has been removed.	Based on feedback of the Center for Drug Evaluation (CDE), an interim analysis will not be performed.
Section 6.2.2 (Prior/Concomitant therapy); Section 7.5.2 (Concomitant medications/products/vaccines that may lead to the elimination of a subject from analyses)	Correction of the corticosteroids dose, considered an exclusion criterion for study participation when administered or planned to be administered during the period starting 3 months prior to the first vaccine, and possibly determining a subject's evaluability in the per-protocol analysis when administered during the study. It is detailed that prednisone ≥20 mg/day, or equivalent, is not allowed (previously stated that prednisone ≥5 mg/day, or equivalent, is allowed).	A correction was made in alignment with the dose detailed in GSK's current document standard.

Section # and Name	Description of Change	Brief Rationale
Section 4, Table 5 (Study objectives and endpoints); Section 3.3.1 (Risk assessment); Section 8.5.2 Table 19 (Reporting periods for collecting safety information); Section 10.3.5 (Safety analyses); Section 12.5.8.1 (Time period for detecting and recording adverse events, serious adverse events and pregnancies); Section 12.5.9.5 (Reporting of pIMD to GSK)	Modification of a secondary endpoint: occurrence of related[#] serious pIMDs after 12 months post last vaccination up to study end (instead of occurrence of all pIMDs from Day 1 to study end). Clarification that all pIMDs are to be reported up to 12 months post last vaccination. Beyond this time period, only related serious adverse events (SAEs) (including related serious pIMDs as per investigator assessment) are to be reported.	A modification was made to clarify that only related serious pIMDs, are to be reported beyond 12 months post last vaccination.
Section 2, Table 3 (Schedule of Activities); Section 8.5.2, Table 19 (Reporting periods for collecting safety information); Section 8.5.4 Table 20 (Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK); Section 8.5.4.1, Table 21 (Contact information for reporting of serious adverse events (SAEs), pIMDs and pregnancies); Section 12.5.8.1 (Time period for detecting and recording adverse events, serious adverse events and pregnancies)	Note on pregnancy reporting: Pregnancies are to be reported and timing of exposure to the study treatment (i.e., RZV or placebo) is considered. Previously only exposure to *Shingrix* was detailed in the note.	A note on reporting of pregnancies was corrected, because applicable in case of vaccination with either RZV or placebo.
Section 8.4 (Study procedures during special circumstances)	Clarification that COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard AE, medically-attended AE or SAE criteria, and should be reported in the eCRF according to the World Health Organization (WHO) Case Definition.	Study procedures for special circumstances were updated to clarify the recording in the eCRF of information on COVID-19 cases.
Section 10.2 (Populations for analyses); Section 10.3.1 (Subjects disposition)	The definition of the Enrolled Set was modified to include eligible subjects who have signed an informed consent and were randomized or undergone an invasive procedure; a Randomized Set will not be applicable for analyses.	A modification was made to better define the subject disposition and the cohorts for statistical analyses.
[#] In the protocol, AEs causally related to the study vaccine as per investigator agreement are also referred to as 'related AEs'.		

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1. SYNOPSIS

Indication:

Shingrix is indicated in China for the prevention of Herpes Zoster (HZ) in adults 50 years of age (YOA) or older.

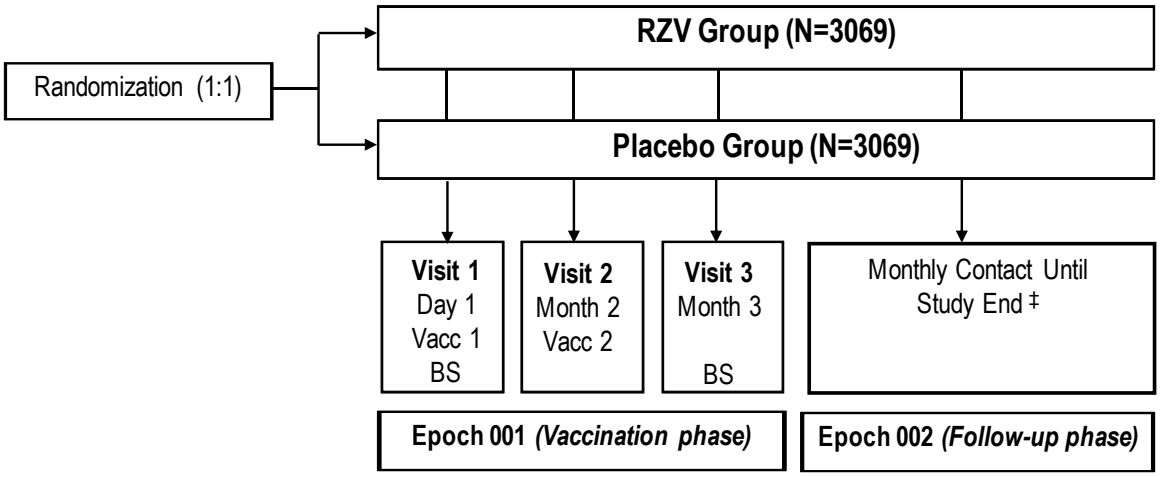
Rationale:

As per requirement of Chinese regulatory authorities, ZOSTER-076 will evaluate the vaccine efficacy (VE), cellular immunogenicity and safety of 2 doses of GlaxoSmithKline Biologicals SA's [GSK's] Recombinant Zoster Vaccine (RZV) vaccine for the prevention of HZ in Chinese adults ≥ 50 YOA.

Objectives and Endpoints:

Refer to Table 7.

Overall Design *(Amended, 23 November 2020)*:



BS= Blood sampling; N= number of subjects planned to be enrolled; Vacc= Vaccination
Note: CCI [redacted]
‡ All subjects will be followed-up until last enrolled subject has completed 1 year of follow-up post last vaccination. In case criteria for vaccine efficacy analyses are not met during this period, the follow-up will be extended.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 3 outlines study procedures and Table 4 presents procedures to be performed for each suspected HZ case.

Table 3 Schedule of Activities *(Amended, 23 November 2020)*

Epoch	Primary (Epoch 001)			Long-term follow-up (Epoch-002)	Notes
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Monthly Contacts†**	
Timepoints	**Day 1**	**Month 2**	**Month 3**	**Month 4 to Study End ***	
Sampling Timepoints	**Pre-Vacc**		**Post-Vacc**		
Informed consent	●				See Section 12.4.3
Check inclusion/exclusion criteria	●				See Sections 6.1 and 6.2 for Inclusion and Exclusion criteria
Record demographic data	●				Refer to Section 8.2.2
Record medical and vaccination history	●				Refer to Section 8.2.3
History directed physical examination	O	O			Refer to Section 8.2.4
Pregnancy test (If applicable)	●	●			Refer to Section 8.2.5
Check contraindications to vaccination	O	O			Refer to Sections 7.7 and 7.8
Pre-vaccination body temperature	●	●			Refer to Section 8.2.7
Study group and treatment number allocation	O				Refer to Section 7.2.2.2.1
Treatment number allocation for subsequent dose		O			Refer to Section 7.2.2.2.2
Record administered treatment number	●	●			Refer to Section 7.2.2
Vaccine administration	●	●			Refer to Section 7.1 for more information 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 (See Section 7.7 for details).
Post-vaccination observation (30 mins)	O	O			
CCI					
Distribute diary cards and train subjects on completion of diary cards	O	O			Diary card will be provided to record solicited local and general AEs, unsolicited AEs and concomitant medication after each vaccination. Additional HZ-specific diary card will be provided to all subjects
Train subjects on signs/symptoms of HZ	O	O	O	O	
Recording solicited AEs (Days 1–7) post-vaccination by subjects on diary cards	O	O			Refer to Section 12.5.8
Recording unsolicited AEs including cellulitis (Days 1-30) post-vaccination by subjects on diary cards	O	O			Refer to Section 12.5.8

Epoch	Primary (Epoch 001)			Long-term follow-up (Epoch-002)	Notes
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Monthly Contacts†**	
Timepoints	**Day 1**	**Month 2**	**Month 3**	**Month 4 to Study End ***	
Sampling Timepoints	**Pre-Vacc**		**Post-Vacc**		
Record medically attended visits (Days1-30) post vaccination	●	●			
Return Diary card		O	O		
Diary card transcription		●	●		
Record and follow-up of HZ cases	●	●	●	●	Refer to Section 8.3.3
Record any concomitant medications/vaccinations	●	●	●	●	Refer to Section 7.5
Record intercurrent medical conditions	●	●	●	●	Refer to Section 7.6
Record SAEs, pIMDs and pregnancies[δ]	●	●	●	●	Refer to Section 12.5.8
Record SAEs related to study participation, or to a concurrent ***GlaxoSmithKline*** medication/vaccine	●	●	●	●	
Record AE/SAEs leading to withdrawal	●	●	●	●	
Study Conclusion				●	Refer to Section 5.4

AE: Adverse Event; CCI [redacted]; HZ: Herpes Zoster; pIMD: potential Immune Mediated Disease; SAE: Serious Adverse Event;

● 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.

†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 14 months (approximately 430 days) from the enrolment date. In case criteria for vaccine efficacy analyses are not met during this period, the follow-up will be extended. The study conclusion visit/ contact for subjects with an ongoing episode of HZ will occur after the resolution of the rash OR when Day HZ-29 follow-up has been completed. The investigator is to record all ongoing HZ-associated symptoms in the eCRF.

[δ] This applies to pregnancy cases with exposure to ***the study treatment*** at any age of gestation. The timing of exposure to ***the study treatment*** during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

*All subjects will be followed-up until last enrolled subject has completed 1 year of follow-up post last vaccination. In case criteria for vaccine efficacy analyses are not met during this period, the follow-up will be extended.

Table 4 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
Timepoints	**Day HZ-1**	**Day HZ-8**	**Day HZ-15**	**Day HZ-22**	**Day HZ-29****
Perform targeted clinical examination	O				
Return HZ-specific diary cards to study staff/investigator	O				
Perform the checks below in the event of clinically diagnosed suspected HZ cases only					
Transcription of the HZ-specific diary card by study staff/investigator	●				
Take digital photographs of HZ rash$^{\alpha}$	●				
Collect HZ lesion samples (3 replicate samples) for confirmation by PCR*	●				
Record relevant information regarding HZ in eCRF	●	●	●	●	●
Record concomitant medication/vaccination	●	●	●	●	●
Record any other intercurrent medical conditions	●	●	●	●	●
Record any medical attention received for HZ	●	●	●	●	●

eCRF = electronic Case Report Form; HZ = Herpes Zoster; PCR = Polymerase Chain Reaction

● 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.

$^{\alpha}$ 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 3 additional samples prior to or at Visit HZ-2 (preferably within 7 days).

** If the HZ rash has not resolved by Day HZ-29, the subject will be seen weekly until the rash resolves. At the time of LSLV, if a subject has an ongoing HZ case, they will be followed up till Day HZ-29.

The investigator should arrange study visits within the intervals described in Table 5.

Table 5 Intervals between study visits *(Amended, 23 November 2020)*

Interval	Optimal length of interval	Allowed interval
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 14 Contact (for the last enrolled subject only)**	365 days (12 months)	344 – 395 days

*including first contact post Visit 3 (Month 3).
** All subjects will be followed-up until last enrolled subject has completed 1 year of follow-up post last vaccination. In case criteria for vaccine efficacy analyses are not met during this period, the follow-up will be extended.
# Subjects may not be eligible for inclusion in the per protocol set (PPS) for [redacted] if study visits occur outside the allowed interval.

Time intervals between study visits/contacts to be performed for follow-up of clinically confirmed suspected HZ are presented in Table 6. If the HZ rash has not resolved by Day HZ-29, the subject will be seen weekly until the rash resolves. At the time of LSLV, if a subject has an ongoing HZ case, they will be followed up till Day HZ-29.

Table 6 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)*

Note: The date of the previous visit/contact is used as reference date to define the interval between the subsequent study visits/contacts.
* If contacted early in the window, then remaining days in the interval will need to be captured with the next contact.

3. INTRODUCTION

3.1. Study rationale

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 vaccine, referred to as recombinant zoster vaccine (RZV) or *Shingrix* 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 [Leroux-Roels, 2012; Chlibek, 2013; Chlibek, 2014; Stadtmauer, 2014; Berkowitz, 2015; Lecrenier, 2018; Lal, 2015; Cunningham, 2016; López-Fauqued, 2019; Vink, 2019(a); Vink, 2019(b); Bastidas, 2019; Dagnew, 2019].

Two large pivotal Phase III trials, ZOSTER-006 [also referred to as ZOE-50] that enrolled subjects ≥ 50 YOA and ZOSTER-022 [also referred to as ZOE-70] that enrolled subjects ≥ 70 YOA, evaluated the vaccine efficacy (VE), immunogenicity and safety of RZV. The combined enrollment in these studies was more than 30 000 subjects who either received RZV or placebo on a 0 and 2 month schedule. Results from ZOSTER-006 and ZOSTER-022 showed a VE of 97.2% and 89.8% against HZ in adults ≥ 50 YOA and ≥ 70 YOA, respectively. In addition, the co-primary objective of a pre-specified pooled analysis of ZOSTER-006 and ZOSTER-022 demonstrated that RZV effectively prevents post-herpetic neuralgia (PHN) with an efficacy of 88.8% in people ≥ 70 YOA. No safety concerns have been raised [Lal, 2015; Cunningham, 2016; López-Fauqued, 2019].

Upon request from Chinese regulatory authorities, the results of these pivotal studies were analyzed in an Asian sub-population. A total of 5 196 subjects were enrolled from Asia; specifically, from China (Taiwan Province and Hong-Kong Special Administrative Region), South Korea and Japan. Despite the fact that ZOSTER-006 and ZOSTER-022 studies were not powered to perform inferential analyses on sub-populations, results from the Asian sub-population analysis showed a VE of 95.55% and 95.26% against HZ in adults ≥ 50 YOA and ≥ 70 YOA, respectively. CCI [redacted]. Further, the reactogenicity and safety profiles of RZV in the Asian sub-population were comparable to the reactogenicity and safety profile in the entire populations of both studies. Please refer to the local prescribing information of RZV for further details.

Shingrix is approved in Canada, the United States, the European Economic Area (EEA) countries, Japan, Australia and China for prevention of HZ in adults ≥50 YOA. In addition, in the EEA and Australia, *Shingrix* is also indicated for prevention of HZ related complications, such as PHN in adults ≥50 YOA.

3.2. Background *(Amended, 23 November 2020)*

VZV causes 2 distinct diseases. Varicella (chickenpox) occurs shortly after primary VZV infection and is characterized by systemic illness and a widely disseminated rash. HZ, commonly called shingles, occurs when VZV reactivates from latency and typically manifests as a localized ***pain and*** dermatomal rash.

The typical HZ rash usually lasts 2 to 4 weeks and is typically accompanied by ***acute neuritis presented as*** 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 PHN***, which*** 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. ***(Amended, 23 November 2020)***

The incidence of HZ increases with age due to immune-senescence and waning of VZV immunity over time following primary varicella infection. While few epidemiological studies have directly assessed the burden of HZ in China, these studies indicate that the risk of HZ in Chinese adults ≥50 YOA is comparable to the risk observed in the Asian regions and the rest of the world. HZ incidence increases with age and is more common in females than in males. Overall, risk of HZ in Chinese adults ≥ 50 YOA ranged from 3.2 per 1000 person years to 8.6 per 1000 person years, which is similar to the rest of the world [Zhu, 2015; Li, 2016; Lu, 2018].

Shingrix is the first shingles vaccine licensed for use in China and is indicated for the prevention of HZ in adults ≥50 YOA. Please refer to the local prescribing information for further details. As per requirement of the Chinese regulatory authorities, this post-licensure study will evaluate VE, cellular immunogenicity and safety of *Shingrix* in adults ≥50 YOA in China.

3.3. Benefit/Risk assessment

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

Please refer to the Prescribing Information and the current Investigator's Brochure (IB) for information regarding the summary potential risks and benefits of *Shingrix*.

3.3.1. Risk assessment *(Amended, 23 November 2020)*

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study vaccine: RZV		
Risk of potential immune mediated diseases (pIMDs) following the RZV 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 (AESI) undergoing special safety monitoring for all GSK vaccines containing Adjuvant Systems. pIMDs are a subset of adverse events (AEs) that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. Up to date, there is no evidence of an increased risk of pIMDs following vaccination with RZV in the populations evaluated adults 50 YOA or older [López-Fauqued, 2019]	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 etiology 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. pIMDs will be collected up to 12 months after administration of the last dose of study vaccine, ***and pIMDs considered serious and related to study vaccine will be collected from 12 months after administration of the last dose of study vaccine until study end***. ***(Amended, 23 November 2020)***
Hypersensitivity reactions (including anaphylaxis)	Hypersensitivity reactions may occur following exposure to allergens from a variety of sources including food, aeroallergens, venom, drugs and immunizations. Vaccines are a mixture of compounds and allergic sensitization can occur to any component. While cutaneous reactions, such as rash or urticaria, are common, anaphylactic reactions are very rare.[Ruggerberg, 2007]	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 history-directed clinical examination. Anaphylaxis following vaccine administration is a contraindication to subsequent vaccination. 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. The onset of serious vaccine-related allergic symptoms is typically immediate. In order to assess and adequately treat subjects who may have allergic reaction to vaccination, all subjects will need to remain under observation (i.e. visibly followed; no specific procedure) at the vaccination center for at least 30 minutes after each vaccination.

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
CCI [redacted]		
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 under aseptic conditions to minimize the potential for secondary infection. The potential risk of some temporary discomfort during the sampling procedure and the risk of infection are mentioned in the ICF.

3.3.2. Benefit assessment

Benefits include:

- Subjects receiving RZV during the study are very likely to have a reduced risk of HZ since RZV is shown to be efficacious.
- Medical evaluation/assessments associated with study procedures (e.g. physical examination, HZ case ascertainment).

3.3.3. Overall Benefit: Risk conclusion

Taking into account the measures to minimize risk to subjects participating in this study, the potential or identified risks in association with RZV and study procedures are offset by the anticipated benefits to subjects receiving RZV.

The benefit-risk profile of *Shingrix* for the prevention of HZ in adults ≥50 YOA continues to be favorable.

4. OBJECTIVES AND ENDPOINTS

Table 7 Study objectives and endpoints *(Amended, 23 November 2020)*

Objectives	Endpoints
Primary	
To evaluate VE in the prevention of HZ compared to placebo in Chinese adults ≥ 50 YOA, as measured by the reduction in HZ risk. *Criterion: The objective is met if the lower limit (LL) of the 2-sided 95% confidence interval (CI) of VE is above 25%.*	Confirmed HZ cases in the modified Exposed Set (mES). *Refer to Section 10.2 for description of mES.*
Secondary	
To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-69 YOA and ≥ 70 YOA, as measured by the reduction in HZ risk	Confirmed HZ cases within each of the following age ranges: 50-69 YOA and ≥ 70 YOA in the mES.
To evaluate vaccine reactogenicity and safety	Solicited local and general adverse events (AEs) ***(Amended, 23 November 2020)*** – Occurrence, intensity ***and*** resulting in medical***ly*** attended visit of each solicited local AE within 7 days (Days 1 - 7) after each vaccination – Occurrence, intensity, resulting in medical***ly*** attended visit and relationship to vaccination of each solicited general AE within 7 days (Days 1 - 7) after each vaccination. Unsolicited AEs – Occurrence, intensity, resulting in a medically-attended visit, and relationship to vaccination of unsolicited AEs (including cellulitis) within 30 days (Days 1 - 30) post-vaccination period, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

Objectives	Endpoints
	Serious Adverse Events (SAEs) ***(Amended, 23 November 2020)*** – Occurrence and relationship to vaccination of SAEs from Day 1 up to 30 days post last vaccination. – Occurrence and relationship to vaccination of SAEs from Day 1 up to 12 months post last vaccination. – Occurrence of SAEs related to study vaccine, from Day 1 up to end of study. – Occurrence of SAEs related to study participation or to ***GlaxoSmithKline*** concomitant medication/vaccine during the entire study period. – Occurrence and relationship to vaccination of fatal SAEs from Day 1 up to 30 days post last vaccination. – Occurrence and relationship to vaccination of fatal SAEs from Day 1 up to 12 months post last vaccination. – Occurrence of related-fatal SAEs from Day 1 up to end of study. pIMDs ***(Amended, 23 November 2020)*** – Occurrence and relationship to vaccination of pIMDs from Day 1 up to 30 days post last vaccination. – Occurrence and relationship to vaccination of pIMDs from Day 1 up to 12 months post last vaccination. – Occurrence of ***related serious*** pIMDs ***after 12 months post last vaccination up*** to study end.
Exploratory	
CCI [redacted]	

5. STUDY DESIGN

5.1. Scientific rationale for study design

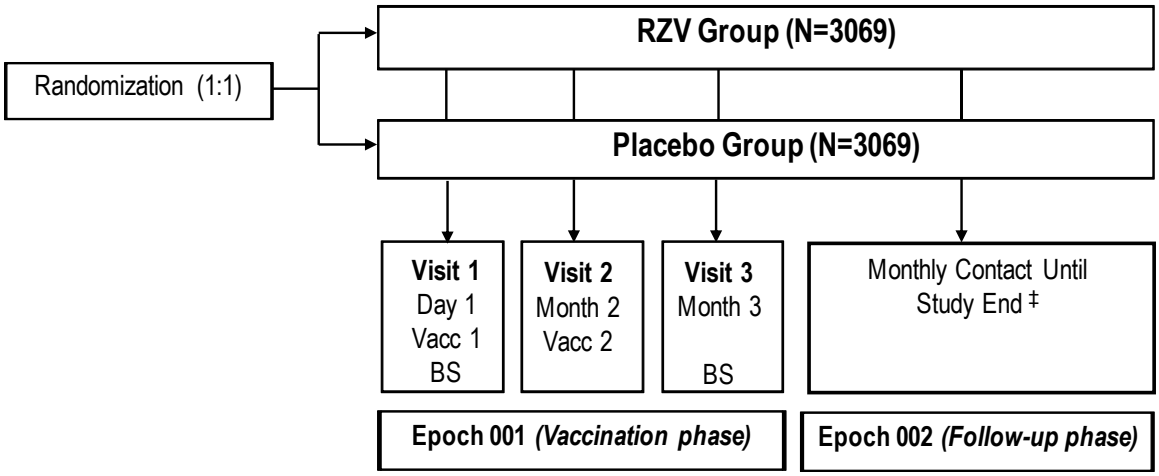
Study ZOSTER-076 will be conducted to evaluate VE, cellular immunogenicity and reactogenicity/safety of RZV in subjects ≥ 50 YOA in China. Subjects will be randomized 1:1 to the RZV or Placebo arm and will be followed in an observer-blind design. Recruitment will be stratified by age, including a minimum of subjects in each age category to ensure recruitment of a broad age range of adults ≥ 50 YOA. Additional minimization factors include center, age (50-59, 60-69, 70-79 and ≥ 80 years - to ensure a

comparable age spectrum in each treatment group), gender and presence of significant medical conditions, for example, diabetes mellitus.

A lyophilized sucrose cake reconstituted with saline (NaCl) solution is included as a control (placebo) in this study evaluating the VE, cellular immunogenicity and reactogenicity/safety of RZV in this population. The use of placebo control and the observer-blind, randomized study design aim to minimize the potential biases in study results.

5.2. Overall design (Amended, 23 November 2020)

Figure 1 Study design overview *(Amended, 23 November 2020)*



CCI [redacted]; N= number of subjects planned to be enrolled; Vacc= Vaccination

CCI [redacted].

‡ All subjects will be followed-up until last enrolled subject has completed 1 year of follow-up post last vaccination. In case criteria for vaccine efficacy analyses are not met during this period, the follow-up will be extended.

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 schedule of activities (Section 2), are essential and required for study conduct.

- Type of study: self-contained
- Experimental design: Phase IV, randomized, observer-blind, placebo-controlled, multi-centric, single-country study with 2 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, 14 months (approximately 430 days) from the enrolment date. Therefore, subjects enrolled early in the trial will be followed for longer duration than the subjects who enrol later in the trial. In case criteria for VE analyses are not met during this period, the follow-up will be extended.

The study conclusion visit/ contact for subjects with an ongoing episode of HZ at the time of last subject last contact will occur at Visit HZ-5 (Day HZ-29).

– **Epoch 001** ***(Vaccination phase)***: CCI [redacted]

– **Epoch 002** ***(Follow-up phase)***: Starting with the first 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, 14 months (approximately 430 days) from the enrolment date of the last enrolled subject. ***(Amended, 23 November 2020)***

- Primary completion Date (PCD): The primary completion date will be when the last subject completes his/her study conclusion contact (within 30 days of the projected study conclusion date of the last enrolled subject, that is, 14 months (approximately 430 days) from the enrolment date. In case criteria for VE analyses are not met during this period, the follow-up will be extended.

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 last enrolled subject, that is, 14 months (approximately 430 days) from the enrolment date of the last subject; In case criteria for VE analyses are not met during this period, the follow-up will be extended 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 8 Study groups, treatment and epochs foreseen in the study

Study groups	Targeted number of eligible subjects	Age (years)	Epochs	
			Epoch 001	Epoch-002
RZV group	3069	≥50 years	●	●
Placebo group	3069	≥50 years	●	●

Table 9 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		RZV	Placebo
RZV	VZV gE	●	
	AS01B	●	
Placebo	Lyophilized 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 RZV group or Placebo group. The randomization algorithm will use a stratification procedure accounting for age (50-69 YOA and ≥ 70 YOA).
- Blinding:

Table 10 Blinding of study epochs

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

- Sampling schedule:
  - CCI [redacted]
  - Clinical specimens of HZ lesions will be collected from all subjects who are clinically diagnosed with a suspected case of HZ (Section 8.3.2).
  - 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).

  Note: The result of the pregnancy test must be obtained before any study vaccination and must be negative.
- **Data collection**: standardized Electronic Case Report Form (eCRF). Solicited and unsolicited AEs will be collected using a subject Diary (paper Diary [pDiary]). In the event of suspected HZ, the HZ clinical course will be collected using a HZ-specific diary card.
- **Safety monitoring**: An internal GSK Safety Review Team (SRT) will oversee the safety of the ZOSTER-076 study. All safety data, i.e. ***suspected HZ cases***, AEs, SAEs, fatal SAEs, pIMDs and cellulitis will be reviewed in a blinded manner by the SRT at regular intervals together with data from other ongoing ZOSTER vaccine studies. Any potential safety concern related to conduct of the study will be escalated to higher governing bodies as per internal GSK process. ***(Amended, 23 November 2020)***

5.3. Number of subjects *(Amended, 23 November 2020)*

Approximately 6138 subjects will be randomized leading to approximately 5524 evaluable subjects for an estimated total of 2762 evaluable subjects per treatment group.

CCI [redacted]

Withdrawals will not be replaced.

5.4. Subject and study completion

A subject is considered to have completed the study if he/she is available for the concluding contact. This corresponds to the last monthly contact that occurs within 30 days of the projected study conclusion date of the last enrolled subject, that is, 14 months (approximately 430 days) from the enrolment date of the last subject. In case criteria for vaccine efficacy analyses are not met during this period, the follow-up will be extended.

6. STUDY POPULATION

6.1. Inclusion criteria for enrolment

Deviations from 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 who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits) or/and subjects' Legally Acceptable Representative(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, return for follow-up visits).
- Written or witnessed/thumb printed informed consent obtained from the subject/subject's LAR prior to performance of any study specific procedure.
- A male or female aged 50 years or older at the time of the first vaccination.
- Medically stable subjects as established by medical history and history-directed clinical examination before entering into the study.
- 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 or post-menopause. Please refer to Section 12.6.1 for definitions 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 during the entire treatment period and for 2 months after completion of the vaccination series.

Refer to Section 12.6.1.1 for definitions of woman of child bearing potential and adequate contraception.

6.2. 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.

6.2.1. Medical conditions

- Any other condition (e.g., extensive psoriasis, chronic pain syndrome, cognitive impairment, severe hearing loss) that, in the opinion of the investigator, might interfere with the evaluations required by the study.
- History of HZ
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 4 years).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine or study materials and equipment.
- Acute clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality as determined by physical examination or laboratory screening tests.
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, Human Immunodeficiency Virus [HIV] infection) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders)

6.2.2. Prior/Concomitant therapy *(Amended, 23 November 2020)*

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine during the period starting 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the study period.
- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before each dose and ending 30 days after the last dose of vaccine administration. However, licensed pneumococcal vaccines and inactivated and subunit influenza vaccines (without adjuvant for seasonal or pandemic flu) may be co- administered with any dose of study vaccine.
- Previous vaccination against varicella or HZ.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g. infliximab).

- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccine up to one month post dose 2 (Month 3).
- Planned or chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine. For corticosteroids, this will mean prednisone ≥***20*** mg/day, or equivalent, is ***not*** allowed. Inhaled, intra-articular and topical steroids are allowed. ***(Amended, 23 November 2020)***

6.2.3. Prior/Concurrent clinical study experience

- 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 (drug or medical device).

6.2.4. Other exclusions

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions within 2 months of last vaccination.
- History of current/chronic alcohol consumption and/or drug abuse.

6.3. Criteria for temporary delay for enrolment and vaccination

Vaccination may be postponed within the allowed time interval until transient circumstances cited below have been resolved:

- Acute disease and/or fever at the time of enrolment. For this study, fever is defined as temperature ≥37.3°C as per guidelines from Chinese authorities for axillary measurement. The preferred location for measuring temperature in this study will be the axillary route.
- Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever maybe enrolled at the discretion of the investigator.

7. TREATMENTS

Study treatment is defined as a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

7.1. Treatments administered

Table 11 Treatments administered

Study Treatment Name:	**RZV**		**Placebo**	
Vaccine/Product name *	VZV gE	$AS01_B$	Lyophilised sucrose Sucrose=20mg	Saline (NaCl) solution
Presentation	Lyophilized pellet in a monodose vial	Liquid in a monodose vial	Lyophilized pellet in a monodose vial	Liquid in a syringe
Vaccine formulation:	gE=50µg per 0.5 ml of reconstituted vaccine	MPL=50µg; QS21=50µg; Liposomes per 0.5 ml of reconstituted vaccine	Sucrose=20mg per 0.5 mL of reconstituted placebo	NaCl=150mM (water for injection)
Route of Administration	IM		IM	
Location	Deltoid		Deltoid	
Laterality **	Non-dominant		Non-dominant	
Number of doses to be administered:	2		2	
Volume to be administered ***	0.5 mL		0.5 mL	
Packaging and Labelling	Refer to SPM for more details		Refer to SPM for more details	
Manufacturer	GSK		GSK	

$AS01_B$= Adjuvant System 01_B; gE= recombinant purified Glycoprotein E; IM= intramuscular MPL= 3-O-desacyl-4'-monophosphoryl lipid A; NaCl= Sodium Chloride; SPM= Study Procedures Manual

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

** 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

*** Refer to the SPM for the volume after reconstitution.

After completing all prerequisite procedures prior to vaccination (refer to Section 7.7 regarding the contraindications to subsequent vaccination), 1 dose of study vaccine will be administered intramuscularly preferably in the deltoid of the non-dominant arm (refer to Table 11 for details regarding the treatment administered).

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 5).

The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis and syncope.

7.2. Method of treatment assignment

7.2.1. 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 center.

7.2.2. Randomization of treatment

7.2.2.1. Randomization of supplies

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

To allow GSK to take advantage of greater rates of recruitment in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

7.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by component.

7.2.2.2.1. Study group and treatment number allocation

The target will be to enrol approximately 6138 eligible subjects who will be randomly assigned to 2 study groups in a (1:1) ratio (approximately 3069 subjects in each group).

The enrolment will be performed to ensure distribution of the population across the 2 age strata (50-69 YOA and ≥70 YOA). Approximately 75-80% and 20-25% subject should be enrolled in 50-69 YOA and ≥70 YOA, respectively. The expected distribution of subjects within these 2 age strata is as shown in Table 12.

To ensure that the collection of date of birth will not jeopardize the privacy of Personally Identifiable Information (PII), only year of birth (YYYY) will be collected.

Table 12 Number of subjects required for enrolment

Age Stratum	Vaccine	Targeted number (%) of subjects
50-69 YOA	RZV	4604-4910 (75-80%)
	Placebo	
≥ 70 YOA	RZV	1228-1534 (20-25%)
	Placebo	

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). Within each age stratum, the randomization algorithm will use a minimization procedure accounting for center, gender, age (50-59, 60-69 for 50-69 YOA stratum, 70-79 and ≥80 YOA for ≥ 70 YOA stratum) 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 study staff in charge of the vaccine administration will access SBIR. Upon 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 Study Procedures Manual (SPM) for specific instructions.

7.2.2.2.2. Treatment number allocation for subsequent dose

For the second dose, the study staff in charge of 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.

7.2.3. Allocation of subjects to assay subsets *(Amended, 23 November 2020)*

CCI [redacted]

CCI [redacted]

7.3. Blinding and unblinding

This study will be conducted in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine(s) recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity and efficacy) 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 outcomes.

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.

7.3.1. 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 a back-up process, the investigator has the option of contacting a GSK Helpdesk (refer to Table 13) if he/she needs support to perform the unblinding (i.e. he/she cannot access the automated Internet-based system).

A 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 available in the patient/subject card.

Table 13 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 from analysis of efficacy if the subject's treatment code is unblinded by the investigator or treating physician but will 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 a regulatory agency, 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.

7.4. Handling, storage and replacement of study vaccine

7.4.1. Storage and handling of study vaccine

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorised 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.

A temperature excursion is any temperature that is not in range of the label storage temperature conditions. Temperatures outside the range of label storage temperature conditions must be reported and/or documented. Temperature excursion impacting study vaccines must be reported and/or documented.

In the frame of the reporting, the lack/absence of temperature monitoring documentation from a device meeting GSK requirements has to be considered as a temperature excursion.

Study vaccine that are impacted by a temperature excursion will not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g. Site Monitor).

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

7.4.2. 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. Concomitant medication(s)/product(s) and concomitant vaccinations

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

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

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 period of 30 days following each dose of study vaccine.
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine until study end.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination) within 24 hours of each dose of study vaccine administration.

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 during the assessment or treatment of HZ or its complications during the study.
- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the subject from the study (See section 7.5.2).
- Any concomitant medications/products/vaccines relevant to an 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 pIMDs need to be recorded on the expedited Adverse Event report.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.5.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from analyses *(Amended, 23 November 2020)*

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 10.2 for definition for populations to be analyzed.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period;
- Administration of a vaccine not foreseen by the study protocol within 30 days prior to dose 2 of vaccine and/or within 30 days after any dose. However, licensed non-replicating vaccines against pneumococcus, seasonal or pandemic flu (without adjuvant) may be co-administered with 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 Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

- Receipt of a vaccine against HZ other than the study vaccine during the study period;
- Prolonged use (> 14 consecutive days) of oral and/or parenteral antiviral agents that are active against VZV (acyclovir, valacyclovir, famciclovir etc.) during the study period for an indication other than to treat suspected or confirmed HZ or an HZ-related complication (topical use of these antiviral agents is allowed);
- ***C***hronic administration (i.e. more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this will mean prednisone ≥***20*** mg/day or equivalent is ***not*** allowed. Inhaled, intra-articular and topical steroids are allowed. ***(Amended, 23 November 2020)***
- Immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the first dose of study vaccine up to one month post dose 2 (Month 3).
- Administration of cytotoxic chemotherapy at any time during the study period.
- Drug and/or alcohol abuse.

A detailed, comprehensive list of reasons for elimination from analyses will be established at the time of data cleaning.

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

At each study visit subsequent to the first vaccination/the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition (IMC) that may lead to elimination from per protocol analysis. If it is the case, the condition(s) must be recorded in the eCRF.

Subjects may be eliminated from the modified exposed set (mES) and/or per protocol set (PPS) for CCI [redacted] if, during the study, they incur a condition that has the potential to impact the effect of the vaccine e.g. they have any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g. malignancy, HIV infection).

CCI [redacted]

Intercurrent conditions should be reported in the AE section of the eCRF.

7.7. Contraindications to subsequent vaccine administration

Prior to receipt of additional study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination.

If subjects meet any of the original exclusion criteria or the criteria listed below, they should not receive additional vaccinations. However, the subjects should be encouraged to continue other study procedures at the discretion of the investigator (Section 8.5.5).

- Anaphylaxis following the administration of vaccine.
- Subjects who experience any SAE judged to be possibly or probably related to study vaccine or non-study vaccines, including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 12.5.5.1 for the definition of pIMDs.
- Occurrence of suspected or confirmed HZ between the first and second vaccine dose.
- Receipt of vaccine against VZV outside of the study.

7.8. Warnings and precautions

Warnings and precautions to vaccination must be checked at the beginning of each vaccination visit.

Refer to the approved product label/package insert.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 2).

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject(s) should discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. 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.

8.1.1. Data Collection

Diary cards will be distributed to subject or subject's LAR/caregiver by the investigator or his/her delegate. The study staff/investigator will provide instructions to the subject or subject's LAR/caregiver for completing the diary cards and explain the importance of timely completion and returning the diary cards to the site. Any supplied diary cards should be completed by the subject themselves or a site trained assistant (such as LAR, a family member or a caregiver).

If assistance is needed, a site trained and designated assistant should aid with reading the questions (verbatim) and/or transcribing the subject's responses on the questionnaires and/or diary cards. This assistance should be provided at the time the subject is required to complete the questionnaire or diary card (i.e. in "real time", not retrospectively). Training of the assistant is to be given by the study staff (see Table 3). 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, it should be noted in the eCRF.

All subjects will receive:

- **Diary cards:** To be completed by the subject or subject's LAR/caregiver after each vaccination for recording of solicited AEs (from day of vaccination to subsequent 6 days), unsolicited AEs including medically attended visits (from day of vaccination to subsequent 29 days), and all concomitant medications/vaccinations taken from day of vaccination to subsequent 29 days or to next study visit.
- **HZ-specific diary card:** At Visit 1, all subjects/subject's LAR/caregiver will receive a HZ-specific diary card. This is to be completed by the subjects/subject's LAR/caregiver beginning immediately (and only) upon development of any signs/symptoms suggestive of HZ (to record the date of onset of rash and/or pain) and prior to visiting the study site for evaluation of suspected HZ.

8.1.2. Monthly contacts

After Visit 3 (Month 3), monthly contacts between the subjects/ subject's LAR/caregiver and the investigator/delegate will take place to collect information on any event of interest that may have occurred. Also, subjects with suspected HZ will be contacted as outlined in Table 4. The contacts will take place using the most convenient method suited for the sites (e.g., telephone calls by site staff or designee). A guidance document outlining the information that needs to be collected at each contact will be provided to 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. 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.

8.2. Pre-vaccination procedures

8.2.1. Informed Consent

Before performing any study procedure, the signed informed consent of the subject needs to be obtained. Refer to section 12.4.3 for the requirements on how to obtain informed consent.

8.2.2. Collection of demographic data

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

8.2.3. Medical and vaccination history

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

8.2.4. 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.

8.2.5. Pregnancy test

Female subjects of childbearing potential are to have a urine 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.

8.2.6. Check contraindications, warnings and precautions to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 7.7 and 7.8 for more details.

8.2.7. Pre-vaccination body temperature

The subjects' body temperature (axillary route is the preferred route of measurement) needs to be measured prior to any study vaccine administration. If the subject has fever (for this study, fever is defined as temperature ≥37.3°C as per guidelines from the Chinese authorities for axillary measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Section 6.3).

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 (oral, rectal or tympanic), the route should be documented.

8.2.8. Record any concomitant medications/vaccinations and any intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 7.5. IMCs must be checked and recorded in the eCRF as described in Section 7.6.

8.3. Efficacy assessments

8.3.1. Case Definitions

8.3.1.1. Suspected Herpes Zoster

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.

The HZ onset date is the earlier of the following 2 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 investigator is to record in the eCRF if HZ associated symptoms is ongoing at the end-date of HZ rash.

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 8.3.2 for more details on the evaluation and follow-up of suspected HZ cases.

8.3.1.2. Confirmed HZ

A suspected case of HZ can be confirmed by GSK in 2 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 a validated laboratory designated by GSK and analyzed using standardized and validated procedures for laboratory diagnosis of HZ by PCR. Refer to Section 12.2 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.

- 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”. 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 3 to 5 physicians with HZ expertise. 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.

8.3.2. Evaluation of suspected HZ cases

All subjects and/or subjects' LAR/caregiver will be educated with regards to the signs and symptoms of HZ with the characteristic HZ rash. Subjects and/or subject's LAR/caregiver will be instructed to contact the investigator immediately and visit the study site (within 48 hours, if possible) if they develop signs/symptoms suggestive of HZ.

The investigator or delegate will perform a targeted 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 the case is not compatible with the diagnosis of HZ, 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.

The schedule of visits/contacts that will take place for follow-up of clinically diagnosed suspected HZ cases is presented in Table 4.

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

- The investigator or 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 SPM for specific instructions;
- The study staff/investigator will record concomitant medication/vaccination, including concomitant medication for HZ treatment. 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 (3 replicate samples on the same day) will be collected from subjects clinically diagnosed as having a suspected case of HZ;
- After Visit HZ-1 until Visit HZ-5, visits/contacts will take place for follow-up of the HZ episode according to the schedule presented in Table 4. 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 should be continued.
- HZ related complications will be followed as AE/SAE, as appropriate. Please refer to Section 8.5.4.

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; and 3) 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.

8.3.3. Follow up of suspected HZ cases *(Amended, 23 November 2020)*

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 will be collected weekly until Day HZ-29 and weekly from Day HZ-30 until the HZ rash resolves. If the rash hasn't resolved the subject will be seen weekly until the rash resolves. The end date of the pain associated with this HZ episode should be recorded. At the time of LSLV, if a subject has an ongoing HZ case, he/she will be followed up till Day HZ-29.

The investigator will note in the subject's eCRF the end date of HZ rash and if any HZ-associated symptoms are still ongoing. Complications of the HZ episode (for example, PHN, disseminated HZ, ophthalmic disease) should be recorded as AE/SAE, as appropriate. ***(Amended, 23 November 2020)***

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 presence of a new rash will be considered a new episode. Visits/contacts will start from Day HZ-1 defined as the first visit following appearance of the new rash.

8.3.4. Use of specified study materials

When materials are provided by GSK, it is MANDATORY that all clinical 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 10.2 for the definition of populations for analyses). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK 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.

8.3.5. Biological samples *(Amended, 23 November 2020)*

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

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 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 China and will only be performed once an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) has approved this research.

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

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

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***/contact***), 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. ***(Amended, 23 November 2020)***

The biological samples collected in the study, the quantity needed, the unit and the time points are described in Table 14.

Table 14 Biological samples

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

Approx= Approximately; CCI [redacted]; HZ= Herpes Zoster; mL= milliliter

8.3.6. Laboratory assays

Please refer to Section 12.2 for a detailed description of the assays performed in the study. Please refer to Section 12.3 for the address of the clinical laboratories used for sample analysis.

Laboratory assays which will be used in this study are summarized in CCI and Table 16 (Molecular Biology), respectively.

CCI

[redacted]

8.3.6.1. Herpes Zoster lesion samples *(Amended, 23 November 2020)*

Clinical specimens of HZ lesions will be collected from subjects clinically diagnosed as having a suspected case of HZ (see Section 8.3.2). Samples for HZ cases assessment should be kept at –20°C or –70/80°C until shipment.

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

Please refer to Section 12.2 for a detailed description of the assays performed in the study. Please refer to Section 12.3 for the address of the clinical laboratories used for sample analysis.

Table 16 Molecular Biology

System	Component	Method	Unit	Laboratory
HZ lesion sample	Varicella Zoster Virus DNA	PCR	No unit	To be identified
HZ lesion sample	Actin Gene DNA	PCR	No unit	To be identified

HZ= Herpes Zoster; DNA= Deoxyribose nucleic acid; PCR= Polymerase Chain Reaction

The contract research organization's (CRO's) clinical laboratories have established a Quality System supported by procedures. Clinical laboratories contracted by GSK conform to Good ***Clinical*** Laboratory Practice guidelines and operate in compliance with regulatory standards. ***(Amended, 23 November 2020)***

Additional 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.

8.3.7. Biological Sample Evaluation

CCI

[redacted]

8.3.8. Immunological correlates of protection

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

8.4. Study procedures during special circumstances *(Amended, 23 November 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 special circumstances 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 and to refer to the requirements of China authority and the ethical committees.

- If despite best efforts it is not possible to collect the biological samples within the interval predefined in the protocol (see Table 5), then the interval may be extended as outlined in Table 18.

- If despite best efforts it is not possible to administer the second dose of study intervention as defined in the protocol (see Table 5), a maximum dose interval of 180 days may be used (see Table 18).
  - 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 18 Intervals between study visits during special circumstances *(Amended, 23 November 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 14 Contact (for the last enrolled subject only)	365 days (***12*** months)	344-395 days	344 - 395 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 4 and Table 6.
  - 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.

Impact on the modified exposed set for vaccine efficacy analysis and per protocol set for [redacted] will be determined on a case by case basis.

COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard AE, medically-attended AE or SAE criteria, as outlined in Section 8.5.

COVID-19 cases should be reported in the eCRF according to the WHO Case Definition [WHO, 2020]. (Amended, 23 November 2020)

8.5. Safety Assessments

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the study treatment or study.

8.5.1. Safety definitions

Please refer to Section 12.5 for safety definitions.

8.5.2. Time period and frequency for collecting AE and serious adverse event (SAE) information

An overview of the protocol-required reporting periods for safety outcomes is given in Table 19. Refer to the Section 12.5.8.1 for details on the time period for recording safety information.

Table 19 Reporting periods for collecting safety information *(Amended, 23 November 2020)*

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 61	Day 67	Day 91		
Solicited AEs	■	■	■		■	■	■		
Unsolicited AEs (including cellulitis)	■	■	■		■	■	■	■	
Medically attended visits									
	■	■	■		■	■	■		
AEs/SAEs leading to withdrawal from the study									
	■	■	■	■	■	■	■	■	■
All SAEs									
	■	■	■	■	■	■	■	■	
SAEs related to the study vaccine									
	■	■	■	■	■	■	■	■	■
SAEs related to study participation or concurrent ***GlaxoSmithKline*** medication/ vaccine [a]									
	■	■	■	■	■	■	■	■	■
pIMDs [b]									
	■	■	■	■	■	■	■	■	
Pregnancies[δ]									
	■	■	■	■	■	■	■	■	■
HZ episodes									
	■	■	■	■	■	■	■	■	■

AE= Adverse event; HZ= Herpes Zoster; 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 ***GlaxoSmithKline*** 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.

[b] All pIMDs are to be reported up to 12 months post last vaccination. Beyond this time period, only related SAEs (including related serious pIMDs as per investigator assessment) are to be reported.

[δ] This applies to pregnancy cases with exposure to ***the study treatment*** at any age of gestation. The timing of exposure to ***the study treatment*** during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

* Study conclusion will be scheduled based on the projected date of the last contact of the last enrolled subject, that is 14 months (approximately 430 days) from the enrolment date.

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Section 12.5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.5.3. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.5.8.

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the subjects/subject's LAR(s) is the preferred method to inquire about AE occurrence.

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

Table 20 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK *(Amended, 23 November 2020)*

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[δ]	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.

[δ] This applies to pregnancy cases with exposure to ***the study treatment*** at any age of gestation. The timing of exposure to ***the study treatment*** during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

8.5.4.1. Contact information for reporting of SAEs, pIMDs and pregnancies

Table 21 Contact information for reporting of serious adverse events (SAEs), pIMDs and pregnancies *(Amended, 23 November 2020)*

Study contact for questions regarding SAEs, pIMDs and pregnancies[δ]
Refer to the local study contact information document
Back-up Study Contact for Reporting SAEs, pIMDs and pregnancies[δ]
24/24 hour and 7/7 day availability: **GSK Clinical Safety & Pharmacovigilance** Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com Refer to Section 12.5.9.3 for details. [δ] *This applies to pregnancy cases with exposure to **the study treatment** at any age of gestation. The timing of exposure to **the study treatment** during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).*

8.5.4.2. Regulatory reporting requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor is essential for meeting legal obligations and ethical responsibilities for the safety of subjects and the safety of a study treatment under clinical investigation.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Follow-up of AEs, SAEs, pIMDs and pregnancies

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and pIMDs, will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in Section 12.5.11.

8.5.6. 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 7.5).

8.5.7. Subject card

Study subjects/subject's LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a "subject card" to each subject/subject's LAR(s). 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/subject's LAR(s) must be instructed to keep subject cards in their possession at all times during the study duration.

8.6. Genetic Research (Pharmacogenetics)

Human genetics are not evaluated in this study.

9. DISCONTINUATION CRITERIA

9.1. Discontinuation from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who is not available for the concluding contact foreseen in the protocol.

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

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

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up (Refer to Section 9.3).

Primary reason for study 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 subject's LAR(s) or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AEs requiring expedited reporting
- Unsolicited non-serious AE

- Solicited AE
- Protocol deviation
- Withdrawal by subject, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 12.5.11).

9.2. Discontinuation of study vaccine

A 'withdrawal' from the study vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine may continue further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

Primary reason relative to premature discontinuation of the study vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject himself/herself, by subject's LAR (s) or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE requiring expedited reporting
- Non-serious adverse event (specify)
- Unsolicited non-serious AE
- Solicited AE
- Not willing to be vaccinated
- HZ episode
- Vaccination against VZV outside of the study
- Other (specify).

9.3. Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

This study is planned to enroll approximately 6138 subjects equally randomized (approximately 3069 subjects) to the RZV and Placebo groups.

The sample size of the study has been determined to have at least 90% power for the confirmatory VE primary objective of ≥ 25% (LL of the 2-sided 95% CI of VE).

Based on the assumption of a true conservative VE of 85% (reference ZOSTER-006 study) for prevention of confirmed HZ cases during the 12 months of follow-up post second dose, a total number of 27 cases of HZ will be needed to demonstrate with at least 90% power that the lower limit (LL) of the 2-sided 95% confidence interval (CI) for the VE is above 25% (By Pass 2012, One Proportion Power Analysis, one-sided test, one-sided alpha=2.5%). In case the number of confirmed HZ cases required for VE evaluation are not met, the follow-up duration will be extended.

10.1.1. Hypotheses related to primary and secondary objectives

The efficacy of RZV against HZ in this population for primary objective will be demonstrated if the LL of the 2-sided 95% CI of VE is above 25%.

Of note, analyses under secondary objective are descriptive.

10.1.2. Sample size calculation

Table 22 shows the power achieved with the target sample size (2762 evaluable subjects per group) with a randomization ratio of 1:1 to demonstrate the primary objective of VE under the alternative hypothesis that with true VE at 85%, lower limit of 2-sided 95% CI of VE observed will be ≥25% (Pass 2012, One Proportion Power Analysis, one-sided test, one-sided alpha=2.5%.).

An attack rate of HZ of 0.85% per year in the Placebo group, a drop-out rate of 5% and an incidence of 5% for non-compliance to vaccine schedule were assumed for sample size calculations.

Table 22 Sample size and expected number of cases in ZOSTER-076

Endpoints	Vaccine efficacy		Expected Number of HZ confirmed cases			Sample Size		Power
	VE - assumed	VE - LL of 95% CI	Placebo	All	Attack rate in control	Evaluable	Enrolled*	
HZ confirmed	85%	25%	23	27	0.85%	5524	6138	At least 90%

*By PASS 12, One Proportion Power Analysis, one-sided test, one-sided alpha=2.5%. *Assuming 10% drop out or non-evaluable subjects

The following conditions are planned prior to the final HZ VE analyses of the study. The number of HZ cases mentioned refers to the cases in the primary cohort for efficacy (i.e. the mES).

1. At least 27 confirmed HZ cases for the overall HZ VE analysis.
2. All subjects will be followed up till the last enrolled subject completes 12 months follow-up post last vaccination. In case the 27 cases needed for VE analysis are not accrued during this period, the follow-up will be extended.

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10.2. Populations for analyses *(Amended, 23 November 2020)*

For purposes of analysis, the following analysis sets are defined:

Analysis Set *(Amended, 23 November 2020)*	Description *(Amended, 23 November 2020)*
Enrolled	***Eligible subjects who have signed an informed consent and were randomized or undergone an invasive procedure***
Exposed	All subjects who receive at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment. The ES for the analysis of solicited AEs will include all participants who received at least 1 dose of the study treatment who have documented solicited AEs (i.e. diary card for solicited AEs completed and returned). The ES for the analysis of any other AEs other than solicited AEs will include all participants who received at least 1 dose of the study treatment. The ES for the analysis of cellular immunogenicity will include all subjects vaccinated for whom data concerning at least one cellular immunogenicity endpoint measure is available.
Modified Exposed	The modified exposed set excludes subjects from the exposed set who were not administered 2 doses of the study vaccine per protocol, or who developed a confirmed case of HZ prior to 30 days after the second vaccination.
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10.3. Statistical analyses

10.3.1. Subjects disposition *(Amended, 23 November 2020)*

Number of enrolled ***and*** vaccinated (at least 1 vaccination) subjects, included in each group or in total for a given age category or for all age categories will be described.

10.3.2. Demography and baseline characteristics analyses

Demographic and other baseline characteristics will be described by assigned group and for the total for Exposed Set (ES) and modified Exposed Set (mES) and the CCI [redacted]

Demographic characteristics (age at first study vaccination in years, gender, race and ethnicity) will be summarized by overall and vaccine groups using descriptive statistics:

- Frequency tables will be generated for categorical variables such as center.
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age.
- Cohort description and withdrawal status will be summarized by group and overall. All the important protocol deviation will be presented.

All the above analysis will be performed by age strata (50-69 YOA and $\geq$70 YOA) on ES and mES.

10.3.3. Efficacy analyses

The primary analysis of efficacy will be based on the mES. A secondary analysis based on the ES will performed to complement the mES analysis.

10.3.3.1. Case accountability *(Amended, 23 November 2020)*

Rules for HZ cases for efficacy analysis:

- An "event" in the efficacy analysis is defined as an endpoint of interest, i.e., confirmed case of HZ.
- The incidence rate of an "event" is determined with reference to the first "event" observed in the subject, should several "events" occur in the same subject.
- The HZ-free period for a subject is calculated from HZ onset to time zero relative to the cohort considered: first vaccination for ES and beyond the HZ-case exclusion period following the second injection for mES.

The follow-up time for each subject will start:

- at the day after first vaccination (Day 1) if analyses were done on the ES for efficacy, or
- at 30 days after second vaccination if analyses were done on the mES. ***(Amended, 23 November 2020)***

The follow-up time for each subject will end on the:

- Date of the last visit/contact for subjects who did not have an event;
- Last contact date for subjects dropped out if not preceded by an event;
- Date of the event
- Date of vaccination against VZV outside the study.

The follow-up time at risk is computed using the following formula:

- stop – start +1.

The time at risk is expressed in Person-Year and derived from the follow up time (follow up time in days/365.25).

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

Endpoint	Statistical Analysis Methods
Primary	**Confirmed HZ cases for efficacy** The primary analysis of efficacy on the mES will be based on the occurrence of the primary endpoint anytime from 30 days after the administration of the second dose of the study vaccine up to study end. All subjects from the mES will contribute to the comparison. It will consider the exact inference on the relative risk adjusted for age strata conditionally to the total number of HZ cases observed and time at risk. This method computes an exact CI around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the sum of the time at risk of the subjects within each group. Incidence rate and VE with 95% CI will be calculated. The VE will be defined as 1 minus the relative risk (RR). RR is defined as the ratio of the incidence rates of the vaccine group over the placebo group VE= (1 – relative risk) x 100 The VE of RZV against HZ will be demonstrated if the LL of the two-sided 95% CI of VE is above 25%. All p-values reported will be related to the null hypothesis test VE = 0. The CI for VE will be derived from the exact CI from RR [Miettinen, 1985].
Secondary	**Confirmed HZ cases during the study in each age category (Descriptive)** The number of confirmed HZ cases, follow-up days, associated rate, VE with 95% CI will be presented by each age category, descriptively, as for the primary endpoint.

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CCI [redacted]

Endpoint	Statistical Analysis Methods
Exploratory	CCI [redacted]

10.3.5. Safety analyses *(Amended, 23 November 2020)*

The primary analysis of safety will be performed on the Exposed Set.

All analyses will also be performed by age strata (50-69 YOA and ≥70 YOA).

Endpoint	Statistical Analysis Methods
Secondary	The percentage of subjects with at least 1 local AE (solicited and unsolicited), with at least 1 general AE (solicited and unsolicited) and with any AE during the solicited follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The percentage of doses followed by at least 1 local AE (solicited and unsolicited), by at least 1 general AE (solicited and unsolicited) and by any AE will be tabulated, with exact 95% CI. The percentage of subjects with at least 1 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 same calculations will be performed for AEs rated as grade 3. The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE will be tabulated, with exact 95% CI. Fever will be reported per 0.5°C cumulative increments and the same tabulation will be performed for fever with causal relationship to the study vaccine. For all other solicited AE, the same tabulation will be performed for grade 1, grade 2 and grade 3 AEs and for any and grade 3 general AEs with relationship to the study vaccine. The proportion of solicited AEs resulting in a medically attended visit will be tabulated. Duration of each individual solicited local and general AE during the solicited follow-up period will be presented. Total duration of each individual solicited local and general AE will be tabulated.

Endpoint	Statistical Analysis Methods
	The percentage of subjects with at least 1 report of unsolicited AE (including cellulitis) classified by MedDRA and reported within 30 days (Days 1-30) post-vaccination period will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs, for unsolicited AEs with a relationship to vaccination, grade 3 unsolicited AEs with a relationship to vaccination. Number and percentage of any, grade 3, related, grade 3 related and medically-attended adverse events reported within 30 days (Days 1-30) post-vaccination period according to MedDRA primary preferred terms. Number and percentage of SAEs from first vaccination up to 12 months post last vaccination will be presented with 95% CI. The same tabulation will also be done for the interval starting from first vaccination up to 30 days post last vaccination. Number and percentage of SAEs causally related to vaccination for the interval starting from first vaccination up to 30 days post last vaccination and from first vaccination up to 12 months post last vaccination and from study start up to study end will be presented with 95% CI. Number and percentage of subjects experiencing fatal SAEs, classified by MedDRA Primary System Organ Class and Preferred Term will be tabulated using date of onset of SAE for the time periods–from first vaccination up to 30 days post last vaccination and first vaccination up to 12 months post last vaccination and from study start up to study end will be presented with 95% CI. Fatal SAEs will also be tabulated using the date of death within the same time periods. Number and percentage of fatal SAEs causally related to vaccination for the interval- starting from first vaccination up to 30 days post last vaccination and from first vaccination up to 12 months post last vaccination and from study start up to study end will be presented with 95% CI. Number and percentage of pIMDs from first vaccination up to 12 months post last vaccination will be presented with 95% CI. The same tabulation will also be done for the interval, starting from first vaccination up to 30 days post last vaccination. Number and percentage of pIMDs causally related to vaccination from first vaccination up to 12 months post last vaccination will be presented with 95% CI. The same tabulation will also be done for the interval starting from first vaccination up to 30 days post last vaccination and, ***for serious pIMDs causally related to vaccination, after 12 months post last vaccination up*** to study end. ***(Amended, 23 November 2020)*** The proportion of subjects with concomitant medication will be tabulated, within 30 days post vaccination and overall, with exact 95% CI. Listing of fatal SAEs, SAEs, pIMDs and withdrawals (from the study or from vaccination) due to AEs, SAEs, solicited and unsolicited AEs will be generated for corresponding follow-up period. Listing of pregnancy during the entire study period will be generated. Listing for all the suspected HZ episodes will be generated.

10.3.6. Interim analyses (Amended, 23 November 2020)

No interim analyses will be performed.

10.4. Sequence of analyses *(Amended, 23 November 2020)*

The final analysis covering all primary and secondary endpoints will be performed when all data up to study conclusion are available. A clinical study report will be written at this stage and individual listings will be included. If the data for exploratory endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These analyses will be documented in annex(es) to the study report.

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12. APPENDICES

12.1. Appendix 1: Abbreviations, glossary of terms and trademarks

12.1.1. List of abbreviations

AE:	Adverse event
AESI	Adverse Event of Specific Interest
AS01B:	MPL, QS21, liposome based Adjuvant System (50 µg MPL and 50 µg QS21)
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CCI [redacted]	
CMV	Cytomegalovirus
CRO:	Contract Research Organization
CSR	Clinical Study Report
DNA:	Deoxyribonucleic acid
EBV	Epstein Barr virus
eCRF:	electronic Case Report Form
EGA	Estimated Gestational Age
EoS:	End of Study
ES:	Exposed Set
(e)TDF:	Electronic Temperature excursion Decision Form
FSH	Follicle Stimulating Hormone
GCP:	Good Clinical Practice
gE:	VZV glycoprotein E
GSK:	GlaxoSmithKline Biologicals SA
HIV:	Human Immunodeficiency Virus

HRT	Hormonal Replacement Therapy
HZ:	Herpes Zoster
HZAC:	Herpes Zoster Ascertainment Committee
IB:	Investigator Brochure
IC:	Immunocompromised
ICF:	Informed Consent Form
IEC	Independent Ethics Committee
IM:	Intramuscular/Intramuscularly
IMC	Intercurrent Medical Condition
IRB	Institutional Review Board
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
mL:	Milliliter
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
pDiary	Paper Diary Card

PHN:	Postherpetic Neuralgia
pIMD:	Potential Immune-Mediated Disease
PPS	Per Protocol Set
QS-21:	*Quillaja 68aponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
RR	Relative Risk
RZV	Recombinant Zoster Vaccine
SAE:	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS:	Statistical Analysis System
SBIR:	Source data Base for Internet Randomization
SD	Standard Deviation
SoA	Schedule of Activities
SPM:	Study Procedures Manual
SRT	Safety Review Team
su:	Subunit
TBC	To Be Confirmed
VE:	Vaccine Efficacy
VZV:	Varicella Zoster Virus
YOA:	Years of Age

12.1.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 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 (see Section 7.3 for details on observer-blinded studies).
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.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
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 with collection of human biological samples and/or imaging data, the EoS is defined as Last testing results released of samples collected at Visit Month 13* * In this case 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.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
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 (see Section 10.2 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
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 authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
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 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.
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.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine:	Any investigational vaccine/product being tested and/or any authorised 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.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Study procedures manual (SPM):	Manual that provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the patients.
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.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

12.1.3. Trademarks

Trademark Information

Trademarks of the GSK group of companies	Generic description
Shingrix	Zoster vaccine recombinant, Adjuvanted

12.2. Appendix 2: Clinical laboratory tests

The tests detailed in Section 8.3.5 will be performed by the laboratory designated by the sponsor.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6 of the protocol.

The investigator is not allowed to do extra testing on samples outside of what has been agreed upon by the ethic committees**.**

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- **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. β-actin PCR will be performed on VZV negative samples only, to confirm the adequacy of the sampling procedure by demonstrating the presence of human material in the collected

sample and rule out false VZV negative results. Samples found negative by both VZV and β-actin–PCRs negative, will be deemed inadequate.

In the Taqman-based PCR experiments, the amplification of a PCR product is monitored in real-time 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 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 VZV illness including the GSK PCR testing algorithm to classify suspected cases**

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

Each rash lesion will be tested using standardized 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 Shingles Prevention Study (*Zostavax* efficacy study) [Oxman, 2005] will be used to classify each suspected case of VZV illness as a confirmed case or not.

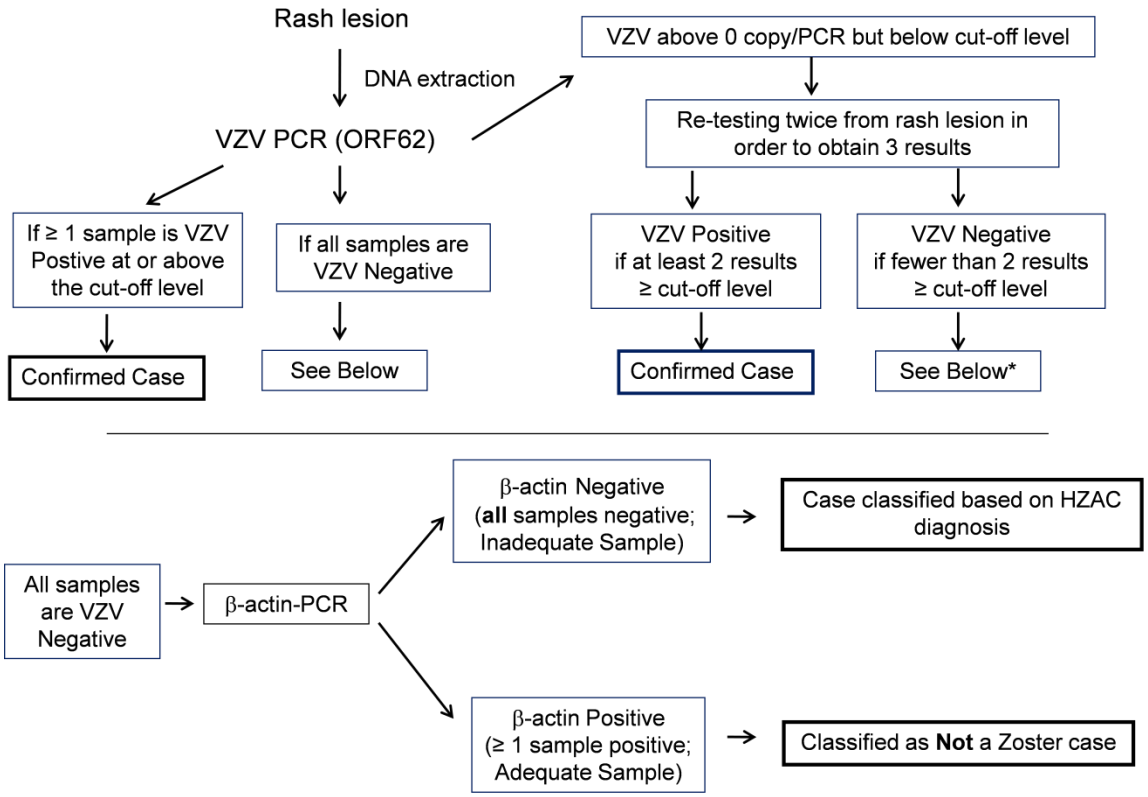
- If at least 1 sample coming from a given subject is "VZV positive" by PCR (as defined below), the PCR algorithm will classify the "suspected VZV illness" as a "confirmed case".
- If all the samples coming from a given subject are "VZV negative" (as defined below), then β-actin PCR will be performed.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

- If PCR results for a particular subject do not confirm or exclude a "suspected VZV illness 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 case of VZV illness.
  This algorithm includes the following steps (see Figure 2):

1. DNA extraction from the rash lesion.
2. VZV real-time PCR assay targeting the ORF62 gene is performed to detect VZV in the rash lesion:
   a. If the VZV PCR signal is ≥ the cut-off level, that is, the technical limit of detection (LOD) of the assay, the sample will be considered as "VZV positive".
   b. 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 3 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.
   c. 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.
   a. 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 VZV illness.
   b. 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 case, will not be part of the decision-making process for 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 GSK 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; that is, lowest concentration that can be detected by PCR in at least 95% of the tests)

12.3. Appendix 3: Clinical laboratories

Laboratory for human biological samples management, PCR testing and CCI testing is listed below:

Laboratory	Address
Covance Pharmaceutical Research and Development Shanghai	Building N°338, Jialilue Road, Zhangjiang Hi-Tech Park Shanghai 201203 China

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted, to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

12.4.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interest prior initiation of the centre and at the end of the study. Investigators are responsible for providing an update of Financial Disclosure if their financial interest changes at any point during their participation in a study and for 1 year after completion of the study.

12.4.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects/subject's LAR(s) must be informed that their participation is voluntary.

Freely given and written or witnessed/thumb printed informed consent must be obtained from each subject and/or subject's LAR(s), as appropriate, prior to participation in the study.

The content of informed consent form must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the subject or the subject's LAR(s).

Subjects who are rescreened are required to sign a new ICF.

12.4.4. Data protection

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject's names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

GSK will also ensure the protection of personal data of investigator and the site staff which will be collected within the frame and for the purpose of the study.

12.4.5. Publication policy

GSK aims to publish the results of this study in searchable, peer reviewed scientific literature. GSK will target to submit within 18 months from LSLV for interventional studies and from the completion of the analysis for non-interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

12.4.6. Dissemination of clinical study data

The key design elements of this protocol will be posted on the GSK Clinical Study Register and on publicly accessible registers including ClinicalTrials.gov. Where required, protocol summaries will also be posted on national or regional clinical trial registers or databases in compliance with the applicable regulations.

GSK also assures that results will be submitted to ClinicalTrials.gov within the required time-frame, in compliance with the current regulations mentioned in the table below.

At the time of study results posting, the full study protocol and statistical analysis plan will also be posted on ClinicalTrials.gov.

	Clinicaltrial.gov
Protocol summary	Before enrolment of subjects
Results summary	Within 12 months of PCD (Primary and safety endpoint results)/Within 12 months of LSLV* (for secondary endpoint results)

* As defined in the study protocol.

Under the framework of the SHARE initiative, anonymized patient-level data from GSK sponsored interventional studies that evaluate products will be made available within 6 months of this publication to independent researchers whose research proposals have been approved by an independent panel. Requests for access may be made through www.clinicalstudydatarequest.com.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK 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.

12.4.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial may be added or reduced where justified (in advance of trial initiation) based on the importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, eCRF), the copy should fulfil the requirements for certified copies.

All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail). Safety and rights of subjects must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.4.8. Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and source documents can be found in the glossary of terms.

12.4.9. Study and site closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will be upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

The investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen eCRF.

  After study conclusion, placebo recipients may be offered RZV, if supported by study results.

12.5. Appendix 5: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

12.5.1. Definition of AE

12.5.1.1. AE Definition

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

NOTE: 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 study treatment.

12.5.1.2. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- 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.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).
- Medically attended visits related to adverse events (e.g. Hospital stays, physician visits and emergency room visits).

AEs to be recorded as endpoints (solicited AEs) are described in Section 12.5.3. All other AEs will be recorded as UNSOLICITED AEs.

"Lack of efficacy" or "vaccination failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

12.5.1.3. Events NOT Meeting the AE Definition

- 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.

12.5.2. Definition of SAE

A SAE 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 hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered

serious. When in doubt as to whether 'hospitalisation' occurred, or was necessary, the AE should be considered serious.

- 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, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- 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 hospitalization but may jeopardize 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 hospitalization.

Any HZ complications listed below will be recorded by the investigator/the study staff in the HZ-specific eCRF screens and on the AE/SAE reporting screens, as applicable.

The reporting period for HZ complications will be from Day 1 to study end. Recorded complications not ultimately associated with a confirmed HZ case will not be considered as complication of HZ.

Post-herpetic neuralgia	PHN is defined by the presence of HZ-associated severe pain persisting or appearing more than 90 days after onset of the HZ rash.
Disseminated disease	Defined as ≥ 6 HZ lesions clearly outside the primary dermatome as per the investigator's judgment.
Ophthalmic disease	Defined as HZ affecting any eye structure as per the investigator's judgment.
Neurologic disease	Defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis, stroke, etc. that is temporally associated with an episode of HZ and, in the opinion of the investigator, is caused directly by VZV infection arising from the HZ episode.

Visceral disease	Defined as an abnormality of one or more internal organs (e.g., hepatitis, pneumonitis, gastroenteritis, etc.) that is temporally associated with an episode of HZ and, in the opinion of the investigator, is caused directly by VZV infection arising from the HZ episode.
HZ vasculitis	Vasculopathy or vasculitis (based on clinical, laboratory or radiologic findings) that is temporally associated with an episode of HZ and, in the opinion of the investigator, is caused directly by the VZV infection arising from the HZ episode.
Stroke	A diagnosis of stroke requires that criteria 1, 2 and 3 are fulfilled or criteria 1 and 4 and in the opinion of the investigator is temporally associated with an episode of HZ Criterion 1: Rapid onset of localizing neurological deficit and/or change in level of consciousness; Criterion 2: Localizing neurological deficit or change in level of consciousness that lasts greater than 24 hours; Criterion 3: No other cerebral process, peripheral lesion, or other disorder is the cause of the localizing neurological deficit or change in level of consciousness; Criterion 4: Computerized Tomography (CT) scan or Magnetic Resonance Imaging (MRI) scan evidence of an acute thrombotic or hemorrhagic lesion.

12.5.3. Solicited adverse events

a. Solicited local (injection-site) adverse events

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

Table 23 Solicited local adverse events

All age groups
Pain at injection site
Redness at injection site
Swelling at injection site

b. Solicited general adverse events

The following general AEs will be solicited:

Table 24 Solicited general adverse events

Fatigue
Fever
Nausea
Vomiting
Diarrhoea
Abdominal pain*
Headache
Myalgia
Shivering*

*Abdominal pain and shivering are not listed in the solicited general AEs as per the grading criteria for AEs in clinical trials of preventive vaccines in China. However, they are solicited as per GSK routine practice for RZV in older adults.

For analysis purpose, the symptoms of nausea, vomiting and diarrohea will be presented separately as per guidelines in China. In addition, nausea, vomiting, diarrhoea and/or abdominal pain will be collectively presented as "Gastrointestinal symptoms "as per GSK standard method of reporting solicited general AEs

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

12.5.4. Unsolicited adverse events

An unsolicited AE is an AE that is not a specific symptom solicited using a Subject Diary and that is spontaneously recorded by a subject/subject's LAR(s) who has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider) or were of concern to the subjects/subject's LAR(s). In case of such events, subjects/subject's LAR(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects/subject' LAR(s) will be collected during interview with the subjects/subject's LAR(s) and by review of available medical records at the next visit.

12.5.5. Adverse events of special interest (AESIs)

12.5.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) 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 the Table 25.

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

Table 25 List of potential immune-mediated diseases (pIMDs)

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), • Necrotising vasculitis (cutaneous or systemic), • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), • Henoch-Schonlein purpura (IgA vasculitis), • Behcet's syndrome, • Leukocytoclastic vasculitis.	• Autoimmune haemolytic 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.

12.5.6. 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. physical examination) 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 12.5.1 and 12.5.2). 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

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

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

12.5.7.1. Pregnancy

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

While pregnancy 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 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 12.5.9.1 and 12.5.9.4:

- 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 (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect 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 as described in Section 12.5.9. While the investigator is not obligated to actively seek this information from former subjects, he/she may learn of a pregnancy through spontaneous reporting.

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

A Paper Diary (pDiary) hereafter referred to as Subject Diary will be used in this study to capture solicited AEs and unsolicited AEs. The subject should be trained on how and when to complete each field of the Subject Diary.

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

Subject Diary training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary. If a person other than the subject/subject's/LAR(s) enters information into the Subject Diary, this person's identity must be documented in the Subject Diary. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit when Subject Diary is dispensed. This training must be documented in the subject's source record**.**

At each vaccination visit, diary cards will be provided to the subject. The subject will be instructed to measure and record the axillary body temperature, any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination. The subject will be instructed to return the completed diary card to the investigator at the next study visit.

- Collect and verify completed diary cards during discussion with the subject on Visit 2 (Month 1) and Visit 3 (Month 3).
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure.

The investigator will transcribe the collected information into the eCRF in English.

12.5.8.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies *(Amended, 23 November 2020)*

All AEs during 30 days following administration of each dose of study vaccine (Day 1 to Day 30) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording ***all*** SAEs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine for each subject. See Section 12.5.9 for instructions on reporting of SAEs. However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ***GlaxoSmithKline*** product will be recorded from the time a subject consent to participate in the study.

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

SAEs that are related to the study vaccine will be collected and recorded from the time of the first receipt of study vaccine 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 (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent ***GlaxoSmithKline*** medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine until study end. See section 12.5.9 for instructions on reporting of pregnancies. This applies to pregnancy cases with exposure to ***the study treatment*** at any age of gestation. The timing of exposure to ***the study treatment*** during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine. ***Beyond this time period, only serious pIMDs that are related to the study vaccine are to be reported.*** See section 12.5.9.5 for instructions on reporting of pIMDs. ***(Amended, 23 November 2020)***

12.5.8.2. Evaluation of adverse events and serious adverse events

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

As a consistent method of collecting AEs, the subject/subject's LAR(s) should be asked a non-leading question such as:

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

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

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.

12.5.8.2.2. Assessment of adverse events

Assessment of intensity

Solicited local and general AEs are listed in Section 12.5.3. The intensity scales described below are based on guidelines in China where possible, and as per GSK standard grading for events which do not have an intensity scale in China e.g. abdominal pain (gastrointestinal symptoms) and shivering.

From an analysis perspective, the intensity of nausea, vomiting and diarrhoea will be presented separately as per the guidelines of Chinese authorities. In addition, as per GSK standard grading, the solicited general AEs of nausea, vomiting, diarrhoea and/or abdominal pain will be presented collectively as "gastrointestinal symptoms". For analysis as per GSK standard grading, the maximum intensity of any one of these solicited general AEs (i.e. nausea, vomiting and diarrhoea) reported by a subject will be attributed as maximum intensity of "gastrointestinal symptoms" for that subject.

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

Table 26 Intensity scales for solicited symptoms in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Do not influence or do slightly influence limb activities.
	2	Moderate Influence limb activities.
	3	Severe: Influence daily life.
	4	Lose the basic selfcare ability, or hospitalization
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C (with 1 decimal)
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
	4	Refractory; require emergency presentation or hospitalization
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
	4	Emergency presentation or hospitalization
Gastrointestinal symptom (Diarrhea)	0	Normal
	1	Slight or transient, 3-4 times/day, stool with abnormal properties, or slight diarrhea persisting for not more than 1 week
	2	Moderate or persistent, 5-7 times/days, stool with abnormal properties, or diarrhea >1 week
	3	>7 times/day, stool with abnormal properties, or bloody diarrhea, orthostatic hypotension, electrolyte imbalance, and requiring intravenous fluid >2 L
	4	Hypotensive shock, requiring hospitalization for treatment
Gastrointestinal symptom (Nausea)	0	Normal
	1	Transient (<24 h) or intermittent, while food intake basically normal
	2	Persistent nausea, leading to decreased food intake (24-48 h)
	3	Persistent nausea, leading to little food intake (>48 h) or require intravenous fluid infusion
	4	Life-threatening (such as hypotensive shock)
Gastrointestinal symptom (Vomiting)	0	Normal
	1	1-2 times/24 h and do not influence activities
	2	3-5 times/24 h or activities restricted
	3	>6 times within 24 h or require intravenous fluid infusion
	4	Due to hypotension, require hospitalization or nutrition by other routes
Gastrointestinal symptom	0	Normal
(Abdominal pain)	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
	4	Emergency presentation or hospitalization

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Shivering	0	None
	1	Shivering that is easily tolerated
	2	Shivering that interferes with normal activity
	3	Shivering that prevents normal activity

* For this study, fever is defined as temperature ≥ 37.3°C as per guidelines from the Chinese authorities for axillary measurement. The preferred location for measuring temperature in this study will be the axilla.

The maximum intensity of local injection site redness/swelling will be scored at GSK using GSK's standard grading scale (based on the US Food and Drug Administration (FDA) guidelines [FDA, 2007]) and the guidelines of grading standards for AEs set by the Chinese authorities as follows.

		GSK standard grading scale	**Grading scale defined by Chinese authorities**
0	:	< 20 mm diameter	Absent
1	:	≥ 20 mm to ≤50 mm diameter	25 mm to <50 mm
2	:	> 50 mm to ≤100 mm diameter	50 mm to <100 mm
3	:	> 100 mm diameter	>100 mm
4		Not defined	Abscess, exfoliative dermatitis, and dermis or deep tissue necrosis

Fever will be graded as:

		GSK standard grading scale	**Grading scale defined by Chinese authorities (for axillary measurement)**
0	:	<38.0°C	<37.3°C
1	:	≥38.0°C – ≤38.5°C	37.3°C – <38°C
2	:	>38.5°C – ≤39.0°C	38.0°C -<38.5°C
3	:	>39.0°C	38.5°C - <39.5°C
4		Not defined	≥ 39.5°C

The preferred location for measuring temperature in this study will be the axilla. If temperature is measured by other routes (such as oral or rectal), fever grading as per GSK scale will remain the same irrespective of route of measurement. For the grading scale as per Chinese authorities, the following conversion will be used:

- Axillary temperature = Oral temperature minus 0.2°C;
- Axillary temperature = Rectal temperature minus 0.5°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 1 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; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in Section 12.5.2**.**

Assessment of causality

The investigator is obligated to assess the relationship between study vaccine and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e. investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine cannot be determined, the investigator should indicate the AE to be related to all products.

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 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. 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. 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 12.5.2), 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).

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).

12.5.8.2.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject/subject's LAR(s) will be asked if he/she/the subject received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

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

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

SAEs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 20, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 20, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 12.5.8 will be reported promptly to GSK within the timeframes described in Table 20, once the investigator determines that the event meets the protocol definition of a pIMDs.

12.5.9.2. SAEs requiring expedited reporting to GSK

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.

12.5.9.3. 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 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.

12.5.9.4. Completion and transmission of pregnancy reports to GSK

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.

12.5.9.5. Reporting of pIMD to GSK *(Amended, 23 November 2020)*

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 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.

The seriousness assessment of the pIMDs will use the same criteria as apply for SAEs (see Section 12.5.2). (Amended, 23 November 2020)

Refer to Section 12.5.9.3 for back-up system in case the electronic reporting system does not work.

12.5.10. 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 Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 20.

12.5.11. Follow-up of adverse events, serious adverse events, pIMDs and pregnancies

12.5.11.1. 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 (within 24 hours for SAEs; refer to Table 20).

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 30 days after the last vaccination.

12.5.11.2. 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 or until 30 days after last vaccination.

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

GSK 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 will be provided with any available post-mortem findings, including histopathology.

12.5.11.3. 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 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 6 to 8 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.

12.6. Appendix 6: Contraceptive guidance and collection of pregnancy information

12.6.1. Definitions

12.6.1.1. Woman of Childbearing Potential (WOCBP)

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

12.6.1.1.1. 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

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.

12.6.2. Contraception guidance

- Female subjects of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in GSK list of highly effective contraceptive methods provided in Table 27.

Table 27 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] ***Failure rate of <1% per year when used consistently and correctly***.
Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
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; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days before vaccination and 2 months after the last dose of study treatment

12.6.3. Collection of pregnancy information

12.6.3.1. Female Subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in 12.5.9. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be discontinued from study treatment.

12.7. Appendix 7: Country-specific requirements

Not Applicable.

12.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	Date of Issue
Amendment 2	23-NOV-2020
Amendment 1	23-APR-2020
Final Protocol	26-FEB-2020

Overall Rationale for Amendment 1:

eTrack study number and Abbreviated Title	***212884 (ZOSTER-076)***
Amendment number:	Amendment 1
Amendment date:	23 April 2020
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

In this protocol amendment, Section 8.4 has been added as a precautionary measure in case of a public health crisis/special circumstances (e.g., COVID-19 pandemic).

Section 8.4 outlines the measures which include allowing flexibility in schedule and procedures to optimize site staff safety, patient safety and to preserve study integrity. 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.

Other minor changes include:

- In section 8.3.3, for each suspected case of HZ that the investigator concludes is clinically consistent with HZ, data will be collected 'weekly' instead of 'daily'to align with the eCRF.
- In Table 6, the term 'group' has been added to RZV and Placebo to denote the study groups.

In section 5.1 and 7.2.2.2.1, the '>'80 YOA has been changed to '≥'80 YOA to avoid a gap in the age.

Detailed description of Protocol Amendment 2:

Note: Two additional tables, Table 1 (Document history) and Table 2 (List of main changes in the protocol and their rationale), were included. The table numbering was updated accordingly.

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

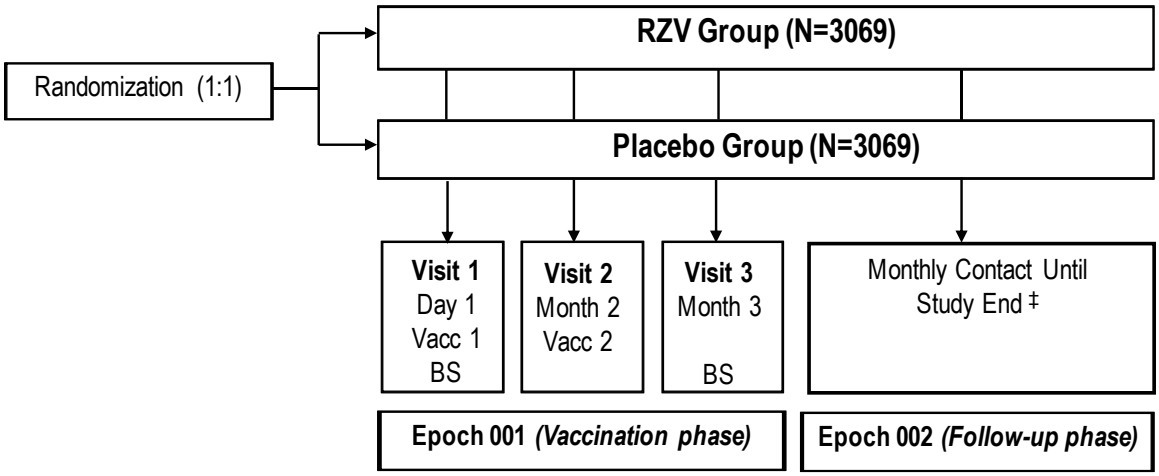
Title page

Co-ordinating author	PPD ***and*** PPD ***(4Clinics for GSK)***, Scientific Writer***s***
Contributing authors	•
	• PPD and PPD , ~~Clinical Safety Representatives~~ ***Safety Evaluation & Risk Management (SERM) Safety physicians***
	• PPD ***, deputy Qualified Person for Pharmacovigilance (dQPPV) and*** PPD ***, Belgium***
	•
	• PPD ***and*** PPD ***,*** Global Regulatory Affairs
	• PPD ***and*** PPD Clinical Trial Supply Managers
	• PPD ***and*** PPD , Global Patents
	• PPD ~~/~~***and*** PPD , Clinical Laboratory Science Readout Team Leader***s***
	•
	• PPD ***and*** PPD ***,*** Clinical and Epidemiology Project Lead (CEPL) for ZOSTER, Clinical R&D.

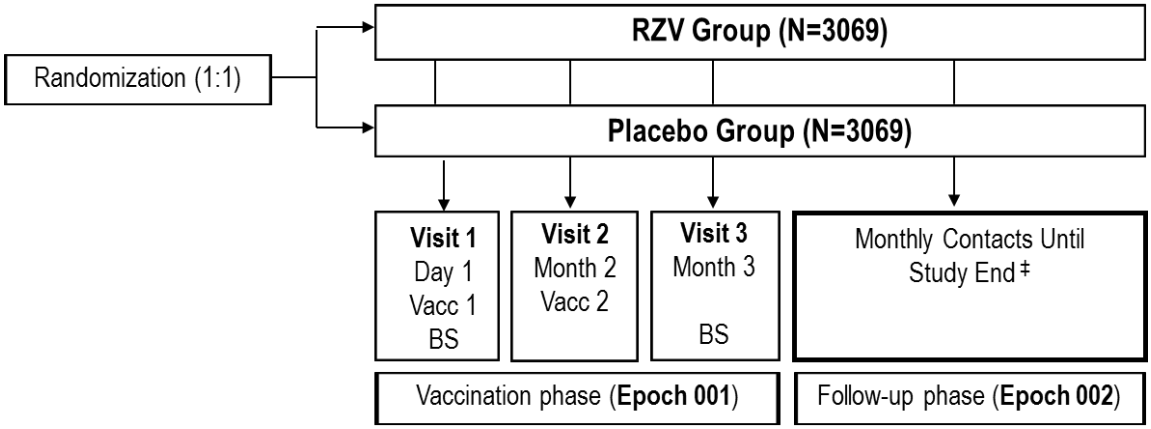
Section 1 Synopsis

Overall Design

New diagram:



Original diagram:



Section 2: Schedule of Activities (SoA)

Table 3 Schedule of Activities

Epoch
Type of contact
Timepoints
Sampling Timepoints
Record SAEs, pIMDs and pregnancies[δ]
Record SAEs related to study participation, or to a concurrent ***GlaxoSmithKline*** ~~GSK~~ medication/vaccine

[δ] This applies ~~only~~ to pregnancy cases with exposure to ***the study treatment*** ~~*Shingrix*~~ at any age of gestation. The timing of exposure to ***the study treatment*** ~~*Shingrix*~~ during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

Table 5 Intervals between study visits

Interval	Optimal length of interval	Allowed interval
Visit 1 → Visit 2		49 days - 83 days[#]
Visit 2 → Visit 3		28 days- 48 days[#]

[#] Subjects may not be eligible for inclusion in the ~~modified Exposed Set (mES) and/or~~ per protocol set (PPS) for CCI [redacted] if study visits occur outside the allowed interval.

Section 3.2 Background

VZV causes 2 distinct diseases. Varicella (chickenpox) occurs shortly after primary VZV infection and is characterized by systemic illness and a widely disseminated rash. HZ, commonly called shingles, occurs when VZV reactivates from latency and typically manifests as a localized~~,~~ ***pain and*** dermatomal rash.

The typical HZ rash usually lasts 2 to 4 weeks and is typically accompanied by ***acute neuritis presented as*** 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 PHN***, which*** ~~. PHN~~ is defined as pain that persists after the resolution of the HZ rash.

Section 3.3.1 Risk assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study vaccine: RZV		
Risk of potential immune mediated diseases (pIMDs) following the RZV 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 (AESI) undergoing special safety monitoring for all GSK vaccines containing Adjuvant Systems. pIMDs are a subset of adverse events (AEs) that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. Up to date, there is no evidence of an increased risk of pIMDs following vaccination with RZV in the populations evaluated adults 50 YOA or older [López-Fauqued, 2019]	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 etiology 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. pIMDs will be collected up to 12 months after administration of the last dose of study vaccine, ***and pIMDs considered serious and related to study vaccine will be collected from 12 months after administration of the last dose of study vaccine until study end***. ~~The occurrence of pIMD cases will be described in the clinical study report (CSR)~~.

Section 4 Objectives and endpoints

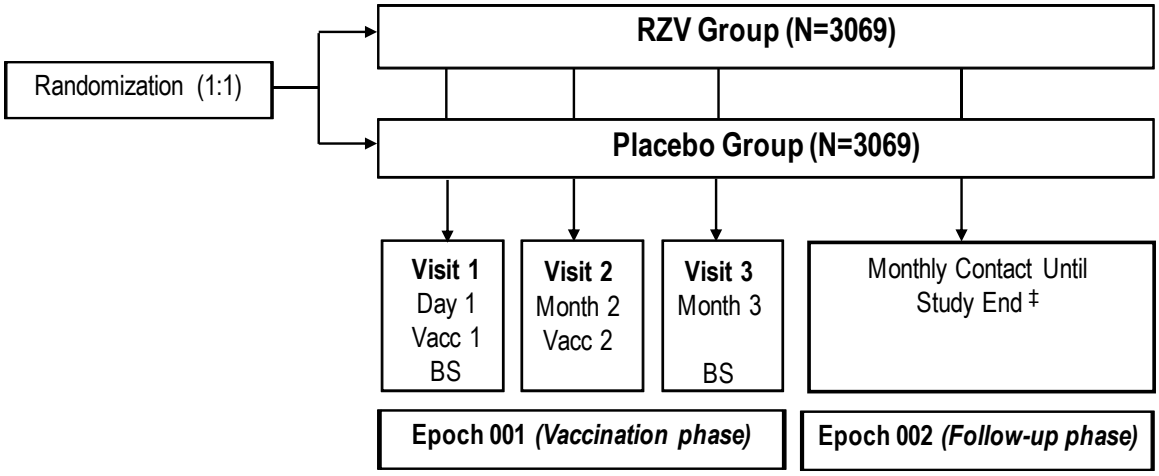
Table 7 Study objectives and endpoints

Objectives	Endpoints
Secondary	
To evaluate vaccine reactogenicity and safety	Solicited local and general adverse events (AEs) – Occurrence, intensity~~,~~ ***and*** resulting in medical***ly*** attended visit ~~and duration~~ of each solicited local AE within 7 days (Days 1 - 7) after each vaccination – Occurrence, intensity, resulting in medical***ly*** attended visit ~~and duration~~ and relationship to vaccination of each solicited general AE within 7 days (Days 1 - 7) after each vaccination. Serious Adverse Events (SAEs) – – Occurrence of SAEs related to study participation or to ***GlaxoSmithKline*** ~~GSK~~ concomitant medication/vaccine during the entire study period. pIMDs – Occurrence ~~and relationship to vaccination~~ of ***related serious*** pIMDs ***after 12 months post last vaccination up*** ~~from Day 1~~ to study end.

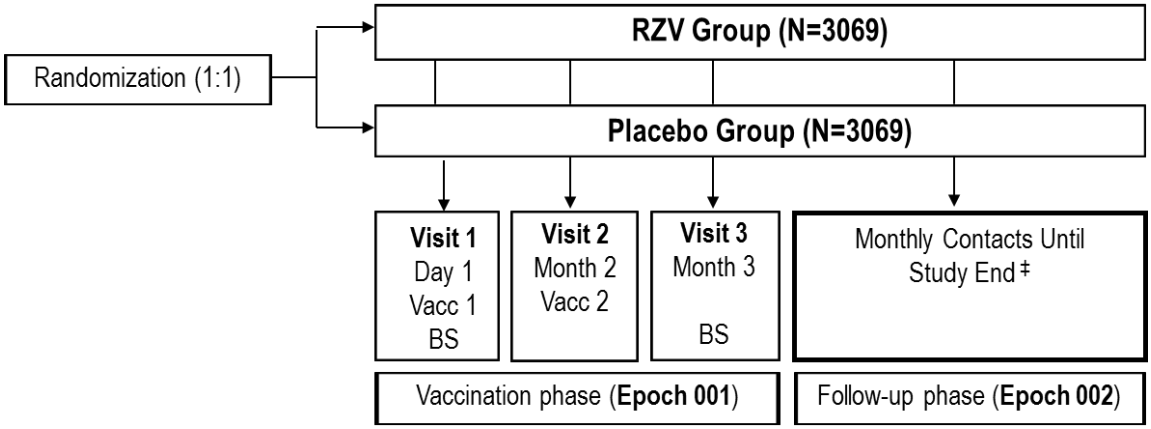
Section 5.2 Overall design

Figure 1 Study design overview

New diagram:



Original diagram



- **Epoch 001** ***(Vaccination phase)***: CCI [redacted]

- **Epoch 002** ***(Follow-up phase)***: Starting with the first 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, 14 months (approximately 430 days) from the enrolment date of the last enrolled subject.

- **Safety monitoring**: An internal GSK Safety Review Team (SRT) will oversee the safety of the ZOSTER-076 study. All safety data, i.e. ***suspected HZ cases***, AEs, SAEs, fatal SAEs, pIMDs and cellulitis will be reviewed in a blinded manner by the SRT at regular intervals together with data from other ongoing ZOSTER vaccine studies.

Section 5.3 Number of subjects

Approximately 100 subjects (50 subjects in each of ~~HZ/su~~ ***RZV*** and Placebo group) will be part of the CCI [redacted]

Section 6.2.2 Prior/Concomitant therapy

- Planned or chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first vaccine. For corticosteroids, this will mean prednisone ≥***20***~~5~~ mg/day, or equivalent, is ***not*** allowed. Inhaled, intra-articular and topical steroids are allowed.

Section 7.2.3 Allocation of subjects to assay subsets

Around 100 subjects (50 in each of ~~HZ/su~~ ***RZV*** and Placebo group) enrolled at the designated site(s) will be included in the CCI [redacted].

Section 7.5.2 Concomitant medications/products/vaccines that may lead to the elimination of a subject from analyses

- ~~Planned or~~***C***~~c~~hronic administration (i.e. more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this will mean prednisone ≥***20***~~5~~ mg/day or equivalent is ***not*** allowed. Inhaled, intra-articular and topical steroids are allowed.

Section 8.3.3 Follow up of suspected HZ cases

The investigator will note in the subject's eCRF the end date of HZ rash and if any HZ-associated symptoms are still ongoing. Complications of the HZ episode (for example, PHN, disseminated HZ, ophthalmic disease) ~~HZ~~ should be recorded as AE/SAE, as appropriate.

Section 8.3.5 Biological samples

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit***/contact***), 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

Section 8.3.6.1 Herpes Zoster lesion samples

The contract research organization's (CRO's) clinical laboratories have established a Quality System supported by procedures. Clinical laboratories contracted by GSK conform to Good ***Clinical*** Laboratory Practice guidelines and operate in compliance with regulatory standards.

Section 8.4 Study procedures during special circumstances

Table 18 Intervals between study visits during special circumstances

Interval	Optimal length of interval
Visit 2→Month 14 Contact (for the last enrolled subject only)	365 days (***12***~~2~~24 months)

COVID-19 cases identified during the study (as per standard of care) will be captured and reported using standard AE, medically-attended AE or SAE criteria, as outlined in Section 8.5.

COVID-19 cases should be reported in the eCRF according to the WHO Case Definition [WHO, 2020].

Section 8.5.2 Time period and frequency for collecting AE and serious adverse event (SAE) information

Table 19 Reporting periods for collecting safety information

Events	Timing of reporting
SAEs related to study participation or concurrent ***GlaxoSmithKline*** ~~GSK~~ medication/ vaccine [a]	
pIMDs [b]	
Pregnancies[δ]	

[a] SAEs related to study participation or ~~GSK~~ ***GlaxoSmithKline*** 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.

[b] All pIMDs are to be reported up to 12 months post last vaccination. Beyond this time period, only related SAEs (including related serious pIMDs as per investigator assessment) are to be reported.

[δ] This applies ~~only~~ to pregnancy cases with exposure to ***the study treatment*** ~~*Shingrix*~~ at any age of gestation. The timing of exposure to ***the study treatment*** ~~*Shingrix*~~ during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

Section 8.5.4 Reporting of serious adverse events, pregnancies, and other events

Table 20 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK

Type of Event
Pregnancies[δ]

[δ] This applies ~~only~~ to pregnancy cases with exposure to ***the study treatment*** ~~*Shingrix*~~ at any age of gestation. The timing of exposure to ***the study treatment*** ~~*Shingrix*~~ during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

Section 8.5.4.1 Contact information for reporting of SAEs, pIMDs and pregnancies

Table 21 Contact information for reporting of serious adverse events (SAEs), pIMDs and pregnancies

Study contact for questions regarding SAEs, pIMDs and pregnancies[δ]
Back-up Study Contact for Reporting SAEs, pIMDs and pregnancies[δ]
[δ] *This applies ~~only~~ to pregnancy cases with exposure to **the study treatment** ~~Shingrix~~ at any age of gestation. The timing of exposure to **the study treatment** ~~Shingrix~~ during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology)*.

Section 10.2 Populations for analyses

Analysis Set	Description
Enrolled	~~All subjects who sign informed consent.~~ ***Eligible subjects who have signed an informed consent and were randomized or undergone an invasive procedure***
~~**Randomized**~~	~~All subjects for whom valid signed informed consent form is available and treatment is allocated.~~

Section 10.3.1 Subject disposition

Number of enrolled, ~~randomized,~~ ***and*** vaccinated (at least 1 vaccination) subjects, included in each group or in total for a given age category or for all age categories will be described.

Section 10.3.3.1 Case accountability

The follow-up time for each subject will start:

- at 30 days after second vaccination ~~(Month 3)~~ if analyses were done on the mES.

Section 10.3.5 Safety analyses

Endpoint	Statistical Analysis Methods
Secondary	Number and percentage of pIMDs causally related to vaccination from first vaccination up to 12 months post last vaccination will be presented with 95% CI. The same tabulation will also be done for the interval starting from first vaccination up to 30 days post last vaccination and, ***for serious pIMDs causally related to vaccination, after 12 months post last vaccination up*** ~~from first vaccination~~ to study end.

Section 10.3.6 Interim analyses

~~Interim report of demography and safety will be produced for license renewal requirements; no statistical adjustment will be performed. The cut-off date for the interim report will be based on the regulatory requirement for license renewal. To ensure the study team remains blinded, any analysis will be performed by an unblinded statistician outside GSK. This will be done on data as clean as possible.~~

~~No formal interim analyses of efficacy will be performed.~~

~~Individual data will not be available.~~***No interim analyses will be performed.***

Section 10.4 Sequence of analyses

~~For the license renewal requirement in China, an interim report on data as clean as possible on safety/reactogenicity data will be performed as mentioned in Section 10.3.6.~~

Section 11 References

World Health Organization (WHO). Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim guidance. 20 March 2020.

Section 12.5.8.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

The time period for collecting and recording ***all*** SAEs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine for each subject. See Section 12.5.9 for instructions on reporting of SAEs. However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ~~GSK~~ ***GlaxoSmithKline*** product will be recorded from the time a subject consent to participate in the study.

SAEs that are related to the study vaccine will be collected and recorded from the time of the first receipt of study vaccine 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 (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent ~~GSK~~ ***GlaxoSmithKline*** medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine until study end. See section 12.5.9 for instructions on reporting of pregnancies. This applies ~~only~~ to pregnancy cases with exposure to ***the study treatment*** ~~*Shingrix*~~ at any age of gestation. The timing of exposure to ***the study treatment*** ~~*Shingrix*~~ during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilization (e.g., assisted reproductive technology).

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine. ***Beyond this time period, only serious pIMDs that are related to the study vaccine are to be reported.*** See section 12.5.9.5 for instructions on reporting of pIMDs.

Section 12.5.9.5 Reporting of pIMD to GSK

The seriousness assessment of the pIMDs will use the same criteria as apply for SAEs (see Section 12.5.2).

Section 12.8. Appendix 8: Protocol Amendment History

eTrack study number and Abbreviated Title	~~204939 (ZOSTER-062)~~ ***212884 (ZOSTER-076)***
~~**IND number**~~	~~BB-IND-13857~~
~~**EudraCT number**~~	~~2016-000744-34~~
Amendment number:	Amendment 1