Protocol

Study ID: 214461

Official Title of Study: A Phase 3, Randomised, Observer-blind, Placebo-controlled, Multi-centre Study to Evaluate the Immune Response and Safety of the Herpes Zoster Subunit Vaccine When Administered Intramuscularly on a 2-dose Schedule in Adults Aged 50 Years and Older in India

NCT ID: NCT05219253

Date of Document: 25 May 2022

Clinical Study Protocol

Sponsor:
GlaxoSmithKline Biologicals SA (GSK)
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Primary study intervention(s) and number(s)	GlaxoSmithKline Biologicals SA (GSK) lyophilised formulation of the Herpes Zoster subunit vaccine (HZ/su) (GSK1437173A)
Other study intervention(s)	Placebo (lyophilised sucrose reconstituted with saline [NaCl] solution)
eTrack study number and abbreviated title	214461 (ZOSTER-081)
Date of protocol	Final: 8 June 2021
Date of protocol amendment	Amendment 1 Final: 25 May 2022
Title	A phase 3, randomised, observer-blind, placebo- controlled, multi-centre study to evaluate the immune response and safety of the Herpes Zoster subunit vaccine when administered intramuscularly on a 2-dose schedule in adults aged 50 years and older in India.
Brief title	A study on the immune response and safety of a vaccine against Herpes Zoster in adults aged 50 years and older in India.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.1

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and abbreviated title	214461 (ZOSTER-081)
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Title	A phase 3, randomised, observer-blind, placebo- controlled, multi-centre study to evaluate the immune response and safety of the Herpes Zoster subunit vaccine when administered intramuscularly on a 2-dose schedule in adults aged 50 years and older in India.
Sponsor signatory	Agnes Mwakingwe-Omari, Clinical and Epidemiology Project Leader, Zoster Program, Research and Development Centre - United States, GlaxoSmithKline Biologicals SA.
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

Protocol Amendment 1 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline 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 intervention 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 participant.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) 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 intervention(s), 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 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 all other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	214461 (ZOSTER-081)
Date of protocol	Final: 8 June 2021
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Title	A phase 3, randomised, observer-blind, placebo- controlled, multi-centre study to evaluate the immune response and safety of the Herpes Zoster subunit vaccine when administered intramuscularly on a 2-dose schedule in adults aged 50 years and older in India.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

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 Events

GSK central back up study contact for reporting SAEs: refer to the protocol Section 8.3.3.1.

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

5. GSK Helpdesk for emergency unblinding

Refer to the protocol section 6.3.4.1.

PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES TABLE

Amendment 1 (25 May 2022)

Overall rationale for the current Amendment

The protocol was amended to update regarding the licensure of HZ/su in India for adults ≥50 years of age, and for inclusion of an early supportive safety report to fulfil the post-approval commitment to the Indian regulatory authority.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 1.1 - Synopsis	The sections were revised to specify the recent update regarding the licensure of HZ/su in India for adults ≥50 YOA, and to describe the regulatory requirement of the early supportive safety data.	The protocol amendment 1 was made to provide an update regarding the recent licensure of HZ/su in India for adults ≥50 YOA, and for inclusion of an early supportive safety report to fulfil the post-approval commitment to the Indian regulatory authority.
Section 2.1 - Study rationale		
Section 9.5 - Interim Analysis	To fulfil the post-approval commitment to the Indian regulatory authority, a blinded early safety assessment report after completion of 30 days safety follow-up post HZ/su dose 2 (i.e., Visit 3, Month 3) for the initial 200 randomised participants will be provided	
Section 6.8 - Concomitant Therapy	All concomitant medications ongoing once randomized at Visit 1 (Day 1).	The sentence was included to further clarify the requirement for recording concomitant medications ongoing at Visit 1 (Day 1), which remains indicated as such on Table 1- Schedule of Activities.
Section 8.3.3.1 - Contact information for reporting SAEs, pIMDs and pregnancies	Change in email ID to report SAEs, pIMDs and pregnancies	The email ID to report SAEs, pIMDs and pregnancies was updated by GSK since the previous protocol version. Thus, the email ID has been replaced.
Table 5 - Study intervention(s) administered	Presentation of placebo was updated	As the reconstituted Sucrose and Sodium Chloride (NaCl) pharmaceutical product is a solution for injection, the dose form of the NaCl solution was revised as “solution for solution for injection”.
Table 17 - List of potential immune-mediated diseases (pIMDs)	The list of pIMDs was updated	The list of pIMDs was updated by GSK since the previous protocol version. Thus, the table was replaced to further assist investigators.

All changes are tracked in Section 10.8, deleted text is in strikethrough and newly added text is in bold italics.

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1. PROTOCOL SUMMARY

1.1. Synopsis (Amended, 25 May 2022)

Rationale:

GlaxoSmithKline Biologicals SA's (GSK's) Herpes Zoster subunit vaccine (HZ/su) is an adjuvanted recombinant envelope glycoprotein E (gE) subunit vaccine. The HZ/su was first licensed for use in October 2017 and is currently approved around the world under the tradename *Shingrix*, including in Canada, the United States (US), the European Economic Area (EEA) countries, Japan, Australia, New Zealand and China for the prevention of Herpes Zoster (HZ) in adults ≥50 years of age (YOA). In addition, in the EEA and Australia, *Shingrix* is also indicated for the prevention of HZ related complications, such as post-herpetic neuralgia (PHN) in adults ≥50 YOA. In the EEA, *Shingrix* is also indicated for the prevention of HZ and PHN in adults ≥18 YOA, who are at increased risk of HZ.

When this ZOSTER-081 study began, HZ/su was not approved for use in India***. While the study was ongoing, HZ/su was licensed for use in India for adults ≥50 YOA on 21 April 2022. Despite this licensure, HZ/su is not currently available in the Indian market; however, when it does become available, the study participants will be notified by the investigators***. To meet the ***post-approval*** requirements of ***the*** Indian regulatory authorit***y, this study will continue as originally planned*** to demonstrate the immunogenicity and safety of HZ/su in the Indian population. This study ***is designed to*** evaluate the humoral immunogenicity and safety of 2 doses of HZ/su, for the prevention of HZ in adults ≥50 YOA***. In addition, as also required by the Indian regulatory authority, a safety report describing the early supportive safety data will be provided once these data (up to Visit 3, Month 3) on the initial 200 study participants randomized are available.***

Objectives and endpoints:

Refer to Table 3 for study objectives and endpoints.

1.2. Schema

This is a phase 3, observer-blind, randomised, placebo-controlled, multi-centre study to assess the immunogenicity and safety of HZ/su when administered intramuscularly (IM) on a 2-dose schedule (Day 1 and Month 2), in adults aged 50 years and older in India. Approximately, 288 eligible participants will be randomised 1:1 to the HZ/su or Placebo group (144 participants per study group) and followed in an observer-blind design. Use of the placebo control, observer-blind and randomised study design aims to minimise the potential biases in study results.

Blood samples for humoral immunogenicity will be collected from all participants at Visit 1 (pre-study intervention at Day 1) and Visit 3 (Month 3). The primary immunogenicity analysis will be based on the Per Protocol Set (PPS) for immunogenicity. A second analysis of immunogenicity based on the Exposed Set (ES) may be performed to complement the per protocol analysis (see Section 9.4 for details).

All participants who receive the study intervention will be followed for safety-solicited administration site adverse events (AEs) and solicited systemic AEs within 7 days of each study intervention , unsolicited AEs within 30 days of each intervention, serious adverse events (SAEs), potential immune- mediated diseases (pIMDs), intercurrent medical conditions (IMC) and suspected HZ cases throughout the study period.

Section 4 provides an overview of the study design.

1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities

Type of contact	Visit 1	Visit 2	Visit 3	Phone Contact†	Notes
Timepoints	**Day 1**	**Month 2**	**Month 3**	**Month 8/Study Conclusion**	
Informed consent	●				Refer to Section 10.1.3
Check inclusion/exclusion criteria	●				Refer to Sections 5.1 and 5.2
Collect demographic data	●				Refer to Section 8.2.1.2
Collect medical and vaccination history	●				Refer to Section 8.2.1.3
History directed physical examination	O	O			Refer to Section 8.2.1.4
Urine Pregnancy test (if applicable)	●	●			Refer to Section 8.2.1.5
Randomisation	O				Refer to Section 6.3
Check contraindications to vaccination	O	O			Refer to Sections 7.1.1 and 8.2.1.6
Check criteria for temporary delay for randomisation and/or study intervention administration	O	O			Refer to Section 5.5
Body temperature before study intervention administration	●	●			Fever is defined a temperature ≥38°C. The preferred route for temperature measurement is oral. Refer to Section 8.2.1.7
Study intervention					
Study group and study intervention number allocation	O				Refer to Sections 6.3.2 and 6.3.3
Blood sampling for antibody determination (approximately 5 mL from all participants)	●		●		Refer to Section 8.1.1
Administration of study intervention	●	●			Refer to Section 6.1
Record administered study intervention number	●	●			Refer to Section 6.3.2
Post- study intervention administration observation (minimum 30 mins)	O	O			Refer to Section 6.1
Study intervention number allocation for subsequent dose		O			Refer to Sections 6.3.2 and 6.3.3
Safety assessments					
Distribution and training on use of diary card	O	O			
Inform participants on signs/symptoms of HZ	O	O	O		Refer to Section 10.3
Recording solicited AEs (Days 1–7) post-study intervention administration by participants on diary cards	O	O			Refer to Section 10.3.8

Type of contact	Visit 1	Visit 2	Visit 3	Phone Contact†	Notes
Timepoints	**Day 1**	**Month 2**	**Month 3**	**Month 8/Study Conclusion**	
Recording non-serious unsolicited AEs (Days 1-30) post- study intervention administration by participants on diary cards	O	O			Refer to Section 10.3.8
Record medically-attended visits (Days 1-30)	●	●			Refer to Section 10.3.9.3
Return of diary cards		O	O		Refer to Section 10.3.8
Diary card transcription		●	●		Refer to Section 10.3.8
Record suspected HZ cases	●	●	●	●	Refer to Section 10.3
Record any concomitant medications/vaccinations	●	●	●	●	Refer to Section 6.8
Record IMC	●	●	●	●	Refer to Section 9.3.1
Record SAEs, pregnancies and pIMDs	●	●	●	●	Refer to Section 10.3.8
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine#	●	●	●	●	Refer to Section 10.3.8
Record AE/SAEs leading to withdrawal	●	●	●	●	Refer to Section 7.2
Study Conclusion				●	Refer to Section 4.4

AE=Adverse Event; HZ=Herpes Zoster; IMC=Intercurrent Medical Conditions; 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.

Zones of the table where the activity is not performed are greyed.

#SAEs related to study participation or GSK concomitant medication/vaccine are to be recorded from the time the participant consents to participate in the study. All other SAEs are to be reported after administration of the first dose of study intervention.

Table 2 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Visit 1→Visit 2	60 days/2 Months	49 days-83 days[#]
Visit 2→Visit 3	30 days/1 Month	28 days-48 days[#]
Visit 2→Phone contact	180 days/6 Months	160-210 days

[#]subjects may not be eligible for inclusion in the PPS, if study visits occur outside the allowed interval.
See Section 8.9 for allowed interval during special circumstances.

2. INTRODUCTION

2.1. Study rationale (Amended 25 May 2022)

GSK's HZ/su is an Adjuvant System 01_B ($AS01_B$) adjuvanted recombinant subunit vaccine consisting of Varicella Zoster Virus (VZV) gE as antigen.

The vaccine has been evaluated in several studies in older 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 clinically acceptable [Bastidas, 2019; Berkowitz, 2015; Chlibek, 2013; Chlibek, 2014; Cunningham, 2016; Dagnew, 2019; Leroux-Roels, 2012; Lal, 2015; Lecrenier, 2018; López-Fauqued, 2019; Stadtmauer, 2014; Vink, 2019; Vink, 2020].

When this ZOSTER-081 study began, HZ/su was not approved for use in India. While the study was ongoing, HZ/su was licensed for use in India for adults ≥50 YOA on 21 April 2022. Despite this licensure, HZ/su is not currently available in the Indian market; however, when it does become available, the study participants will be notified by the investigators. To meet the post-approval requirements of the Indian regulatory authority, this study to demonstrate the immunogenicity and safety of HZ/su in the Indian population is to continue as originally planned. This study is designed to evaluate the humoral immunogenicity and safety of 2 doses of HZ/su, for the prevention of HZ in adults ≥50 YOA. In addition, as also required by the Indian regulatory authority, a safety report describing the early supportive safety data will be provided once these data (up to Visit 3, Month 3) on the initial 200 study participants randomized are available.

2.2. Background

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

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]. Sensory symptoms can also include numbness, dysesthesias, pruritus, and allodynia in the affected dermatome. Other complications of HZ include ophthalmologic, neurological, cutaneous and visceral disease, which can result in severe disability.

The incidence of HZ increases with age due to immune-senescence and waning of VZV immunity over time following primary varicella infection.

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

2.3. Benefit/Risk assessment

Detailed information about the known and expected benefits and risks and expected AEs of HZ/su can be found in the IB. The important potential risks identified, and the mitigation strategy associated with study interventions/ procedures are listed below.

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Study vaccine: HZ/su		
Risk of potential immune-mediated diseases (pIMDs) following the HZ/su vaccination	Based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, pIMDs are adverse events of special interest (AESI) undergoing special safety monitoring for all GSK vaccines containing Adjuvant Systems. pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology. To date, there is no evidence of an increased risk of pIMDs following vaccination with HZ/su in evaluated adults 50 YOA or older [López-Fauqued, 2019]	Close monitoring of pIMDs will be conducted per study protocol and analysis of safety data generated through clinical trials and other sources. The potential risk of events of possible autoimmune aetiology to occur is mentioned in the Informed Consent Form (ICF). In addition, the ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered serious. pIMDs will be collected up to study end (Month 8/6 months post last intervention).
Guillain-Barré Syndrome (GBS)	New available information on GBS emerged from a post-marketing observational study where the risk of GBS following vaccination with HZ/su was assessed in adults aged ≥65 YOA enrolled in the Medicare health insurance in the US. An increased risk of GBS during the 42 days following vaccination was estimated as an excess of 3.13 cases per million doses administered. Based on the review of the accumulated body of the information that is currently available, GSK considers that the strength of the collective evidence is insufficient to determine a causal relationship between HZ/su vaccination and GBS, owing to substantial limitations and confounding variables.	Close monitoring of GBS will be conducted per study protocol and analysis of safety data generated through clinical trials and other sources as part of pIMDs (including GBS). The potential risk of events of possible autoimmune aetiology to occur is mentioned in the ICF. In addition, the ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered serious. pIMDs (including GBS) will be collected up to study end (Month 8/6 months post last intervention).
Hypersensitivity reactions (including anaphylaxis)	Hypersensitivity reactions may occur following exposure to allergens from a variety of sources including food, aeroallergens, venom, drugs and immunisations. Vaccines are a mixture of compounds and allergic sensitisation can occur to any component. While cutaneous reactions, such as rash or urticaria, are common, anaphylactic reactions are very rare.[Ruggerberg, 2007]	Administration of the study intervention is to be preceded by a review of the participant's 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 study intervention. The onset of serious vaccine-related allergic symptoms is typically immediate. In order to assess and

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
		adequately treat participants who may have an allergic reaction to the study intervention, all participants will need to remain under observation (i.e. visibly followed; no specific procedure required) at the study clinic site for at least 30 minutes after each study intervention dose is administered.
Study Procedures		
Risk from blood sampling	Blood sampling associated risk of discomfort, syncope, dizziness, infection at the site after or during venipuncture.	Blood samples will be obtained in seated or supine position by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the participant's health.

Benefits include:

- Participants receiving HZ/su during the study are very likely to have a reduced risk of HZ since HZ/su is shown to be efficacious in many other populations.
- Medical evaluation/assessments associated with study procedures (e.g. physical examination).

Overall, taking into account the measures to minimise risk to the participants, the potential or identified risks in association with HZ/su vaccine and study procedures are offset by the anticipated benefits to participants receiving HZ/su.

The benefit-risk profile of HZ/su for the prevention of HZ in adults ≥50 YOA continues to be favourable.

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives and endpoints (Amended 25 May 2022)

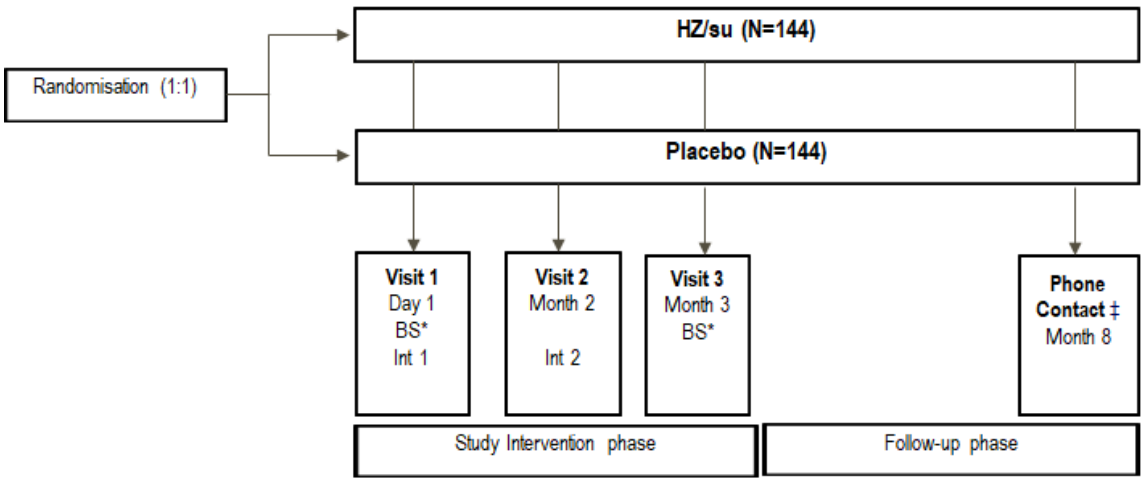
Objectives	Endpoints
Primary	
To determine the vaccine response rate (VRR) for anti-gE humoral immune response at 1-month post-dose 2 (Month 3) of administration of HZ/su*.	Percentage of participants showing a vaccine response for anti-gE antibody concentrations,) at 1-month post-dose 2 (Month 3).
Secondary	
To evaluate the anti-gE humoral response at 1-month post-dose 2 (Month 3) in recipients of HZ/su compared to Placebo**.	Anti-gE antibody concentration expressed as group geometric mean concentration (GMC) ratio at 1-month post-dose 2 (Month 3).
To evaluate safety and reactogenicity following administration of HZ/su or placebo from first dose up to 30 days post last dose.	**Solicited AEs:** Number and percentage of participants reporting each solicited administration site (injection site redness, pain, swelling and prurit***u***s) and solicited systemic AEs (fever, myalgia, fatigue, gastrointestinal [GI] symptoms, headache and shivering) within 7 days (Day 1 to Day 7) after each dose and overall. **Unsolicited AEs**: Number and percentage of participants reporting unsolicited AEs within 30 days (Day 1 to Day 30) after any dose. **SAEs:** Number and percentage of participants reporting SAEs from Dose 1 (Day 1) up to 30 days post last dose. **pIMDs:** Number and percentage of participants reporting pIMDs from Dose 1 (Day 1) up to 30 days post last dose.
To evaluate safety following administration of HZ/su or placebo during the entire study period.	**SAE**- Number and percentage of participants reporting SAEs from Dose 1 (Day 1) up to study end (phone contact Month 8). **pIMDs**- The number and percentage of participants reporting pIMDs from Dose 1 (Day 1) up to study end (phone contact Month 8).
To characterise anti-gE humoral immunogenicity response prior to the first study intervention administration (Day 1) and at 1-month post-second study intervention administration (Month 3) in both groups.	Anti-gE antibody geometric mean concentrations (GMC) and seropositivity rate at pre-study intervention administration (Day 1) and 1-month post-dose 2 (Month 3). Mean geometric increase (MGI) at 1-month post- dose 2 (Month 3) compared to pre-study intervention administration (Day 1).

* The success criteria for the primary objective and VRR definition are presented in Section 9.4.1.
** The success criteria for the secondary objective are presented in Section 9.4.2.2

4. STUDY DESIGN

4.1. Overall design

Figure 1 Study design overview



*BS=Blood Sampling; Int=study intervention, N=number of participants planned to be randomised;
‡ Each participant will be followed up for 6 months post last dose/Month 8.

- **Type of study**: Self-contained.
- **Experimental design**: Phase 3, randomised, observer-blind, placebo-controlled, multi-centric, single country study with 2 parallel groups (see Figure 1).
- **Duration of the study**: Approximately 8 months for each participant.
- **Control**: Placebo-controlled.
- **Blinding**: Observer-blind.
- **Study intervention schedule**: 0 and 2 months (Day 1 and Month 2).
- **Biological samples**: Blood samples will be collected at Day 1 and Month 3 (1-month post-dose 2).
- **Follow-up contact**: Phone contact at Month 8 (6 months post last study intervention administration).
- **Primary completion date (PCD)**: Month 3 (1-month post-dose 2). Refer to glossary of terms for the definition of PCD.
- **Data collection**: Standardised electronic Case Report Form (eCRF). Solicited AEs and unsolicited AEs will be collected using a Participant Diary card (paper diary card).
- **Study groups**: Refer to Table 4 for an overview of the study groups.

Table 4 Study groups, intervention and blinding

Study Groups	Number of participants	Age	Study intervention	Blinding
				Visit 1→Phone contact (Observer-blind)
HZ/su	144	≥50 years	VZV gE $AS01_B$	X
Placebo	144	≥50 years	Lyophilised sucrose Saline (NaCl) solution for reconstitution	X

4.2. Scientific rationale for study design

ZOSTER-081 study will be conducted to evaluate immunogenicity and safety of HZ/su in participants ≥50 YOA in India. The study will enrol approximately 288 participants who will be randomised 1:1 to the HZ/su or Placebo group of equal size to receive 2 doses of study interventions administered intramuscularly 2 months apart.

The randomisation algorithm will use a minimisation procedure accounting for age (50- 69 YOA, ≥70 YOA). Minimisation factors will have equal weight in the minimisation algorithm.

A lyophilised sucrose cake reconstituted with saline (NaCl) solution is included as a control (placebo) in this study evaluating the humoral immunogenicity and safety of HZ/su in this population. The inclusion of placebo control and the use of observer-blind, randomised study design aims to minimise the potential biases in study results.

4.3. Justification for dose

The approved dose regimen for *HZ/su* (2-dose vaccination) with an interval of 2 months between doses, will be followed in this study. Refer to Section 8.9 for interval between doses during special circumstances.

4.4. End of Study definition

A participant is considered to have completed the study if he/she is available for the last scheduled contact as described in the protocol.

End of Study (EoS): Last subject* last visit (LSLV=Phone contact at Month 8) or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints (whichever is later). EoS must be achieved no later than 8 months after LSLV. Refer to glossary of terms for the definition of EoS.

*subject=participant

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardise the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

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

- Participants and/or participant's legally acceptable representative(s) (LAR) 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 participant and/or participant's LAR(s) after the study has been explained according to local regulatory requirements and prior to performance of any study-specific procedure.
- A male or female aged 50 YOA or older at the time of the first study intervention.
- Healthy participants or medically stable patients as established by medical history and clinical examination before entering into the study.
- Female participants of non-childbearing potential may be enrolled in the study. Please refer to Section 10.4.1.1.1 for definitions of women of non-childbearing potential.
- Female participants of childbearing potential may be enrolled in the study, if the participant:
  - has practiced adequate contraception for 1 month prior to study intervention administration, and
  - has a negative pregnancy test on the day of study intervention administration, and
  - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the study intervention administration series.

Refer to Section 10.4.1 for definitions of woman of childbearing potential and adequate contraception.

5.2. Exclusion criteria

The following criteria should be checked at the time of study entry. The potential participant MAY NOT be included in the study if ANY exclusion criterion applies:

5.2.1. Medical conditions

- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s) or study materials or equipment.
- Acute or chronic clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by medical history, physical examination or laboratory screening tests.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- 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).

5.2.2. Prior/Concomitant therapy (Amended 25 May 2022)

- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before first dose and ending 30 days after the last dose of study intervention administration with the exception of licensed pneumococcal vaccines and non-replicating vaccines (i.e. inactivated and subunit vaccines, including inactivated and subunit influenza vaccines, with or without adjuvant for seasonal or pandemic flu) may be administered up until 8 days prior to Dose 1 and/or Dose 2 and/or at least 14 days after any dose of study intervention.

  /In case an emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is recommended and/or organised by the public health authorities, outside the routine immunisation programme, the time period described above can be reduced if necessary for that vaccine provided it is used according to local governmental recommendations and that the Sponsor is notified accordingly**/**.
- Planned 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 intervention up to 1-month post-dose 2 (Month 3) or planned administration during the study period.
- 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 study intervention dose. For corticosteroids, this will mean prednisone equivalent ≥20 mg/day or equivalent is not allowed. Inhaled, intra- articular and topical steroids are allowed.
- Previous vaccination against varicella or HZ.

5.2.3. Prior/Concurrent clinical study experience

Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non- investigational intervention (drug/invasive medical device).

5.2.4. Other exclusions

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions within 2 months of last study intervention administration.
- Indications of drug abuse or excess alcohol use as deemed by investigator to potentially confound safety assessments or render participant unable or unlikely to adhere to protocol requirements.

5.3. Lifestyle considerations

Not applicable.

5.4. Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are determined ineligible and subsequently not enrolled (i.e. not randomised, have not undergone any invasive procedure and not administered a study intervention).

Limited data for screening failures (for example any SAEs that occurred at the visit) will be collected and reported in the eCRF.

5.5. Criteria for temporarily delaying randomisation/study intervention administration

Study intervention administration may be postponed until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of study intervention administration. Refer to the SoA for definition of fever and preferred location for measuring temperature in this study.
- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) (e.g. fever, cough, etc.) at the time of study intervention administration.
- Participants with known COVID-19 diagnosed contacts may be administered study intervention at least 14 days after the exposure, provided that the participant remains symptom-free, and at the discretion of the investigator.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study intervention(s) administered

Table 5 Study intervention(s) administered (Amended 25 May 2022)

Study Intervention Name:	**HZ/su**		**Placebo**	
Study Intervention /Product name	VZV gE	$AS01_B$	Lyophilised sucrose	Saline (NaCl) solution
Study Intervention formulation:	VZV gE (50 µg)	$AS01_B$: QS-21 (50 µg), MPL (50 µg), liposomes; Water for injections	Sucrose (20 mg)	Sodium chloride (NaCl) (0.9%); Water for injections
Presentation:	Powder for suspension for injection	Suspension for suspension for injection	Powder for solution for injection	Solution for ***solution*** for injection
Container	Vial	Vial	Vial	Syringe
Type:	Biologic		Not applicable	
Administration site:	Intramuscular use		Intramuscular use	
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, Labelling and TM:	Refer to SPM			
Manufacturer:	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=Quantum satis
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.

If the investigator or delegate determines that the participant's health on the day of administration temporarily precludes study intervention administration, the visit will be rescheduled.

Study participants must be observed closely for at least 30 minutes after the administration of the study intervention. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

6.2. Preparation/Handling/Storage/Accountability

The study intervention must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorised study personnel should be allowed access to the study intervention. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the Study Procedures Manual (SPM) for more details on storage and handling of the study intervention.

6.3. Measures to minimise bias: randomisation and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the individuals who have consented to participate in the study. Each study centre will be allocated a range of participant identification numbers.

6.3.2. Randomisation to study intervention

Approximately 288 eligible participants will be randomly assigned (1:1) to the study groups (144 participants per study group).

The randomisation 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, United States [US]) 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 thus to reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

6.3.3. Intervention allocation to the participant

An automated internet-based system, Source data Base for Internet Randomisation (SBIR) will be used for randomisation and for identification of intervention material.

The randomisation algorithm will use a minimisation procedure accounting for age (50- 69 YOA, ≥70 YOA). Minimisation factors will have equal weight in the minimisation algorithm.

Once a participant identification number is allocated, the randomisation system will determine study group and will provide the study intervention number to be used for the first dose. The study intervention number to be used for subsequent dosing will be provided by the same automated internet-based system, SBIR.

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

Refer to the SPM for additional information about the study intervention number allocation.

6.3.4. Blinding and unblinding

Data will be collected in an observer-blind manner. To do so, study intervention will be prepared and administered by qualified unblinded study personnel who will not participate in data collection, evaluation, review or the entry of any study endpoint (e.g. reactogenicity, safety).

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no visible link between the study intervention and the identity of the participant.

6.3.4.1. Emergency unblinding

Unblinding a participant's individual study intervention number should occur ONLY in case of a medical emergency when this information is essential for the clinical management or welfare of the participant.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via SBIR.

The investigator may contact a GSK Helpdesk (refer to the Table 6) if he/she needs help to perform the unblinding process (i.e. if the investigator is unable to access the SBIR).

A physician other than the investigator (e.g. an emergency room physician) or participant/care giver/family member may also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back up option). The participant card provides contact information for the investigator, his/her back up and GSK Helpdesk.

Table 6 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Toll-free phone number: 000800 919 0928 Fax: +32.2.401.25.75 Email: rix.ugrdehelpdesk@gsk.com

6.3.4.2. Unblinding prior to regulatory reporting of SAEs

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to the Section 10.3.10.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or SAE that is fatal or life-threatening. For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study intervention compliance

Participants will receive the study intervention directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose in the study clinic site will be recorded in the eCRF.

6.5. Dose modification

Not applicable.

6.6. Continued access to study intervention after the end of the study

No study intervention is planned after the end of this study. However, participants in the placebo group may be offered HZ/su, after the study is completed, depending on the study results, local standards and regulations.

6.7. Treatment of overdose

Not applicable.

6.8. Concomitant therapy (Amended 25 May 2022).

At each study contact, the investigator or his/her delegate should question the participant and/or participant's LAR(s) about all medications/products taken, and vaccinations received by the participant.

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

- ***All concomitant medications ongoing once randomized at Visit 1 (Day 1)***.
- All concomitant medication associated with an AE, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines (refer to the sections 5.2.2 and 9.3.1 for further details).
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD including vaccines/products, as defined in Sections 8.3.1 and 10.3.8.2. These must also be recorded in the Expedited Adverse Event Report.

- 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.
- Any medication used during the assessment or treatment of suspected HZ or its complications during the study.

The Local Medical Lead (LML) should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

'Discontinuation' of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g. safety or immunogenicity), planned in the study protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

- AE requiring expedited reporting to GSK
- Unsolicited non-serious AE
- Solicited AE
- Not willing to be vaccinated
- Other (specify).

7.1.1. Contraindications to subsequent study intervention(s) administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigators' discretion (Section 10.3.8.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.

- Anaphylaxis following the administration of study intervention.
- Any condition that in the judgement of the investigator would make intramuscular injection unsafe.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the participant 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 study intervention. Refer to Section 10.3.5.1 for the definition of pIMDs.
- Occurrence of a suspected HZ between the first and second study intervention dose.
- Receipt of vaccine against HZ or VZV outside of the study.

7.2. Participant discontinuation/withdrawal from the study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for him/her since the date of withdrawal/last contact.

From an analysis perspective, a study 'withdrawal' refers to any participant who was not available for the concluding contact planned in the protocol.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

The primary reason for study withdrawal will be documented in the eCRF, based on the list below:

- AE requiring expedited reporting to GSK
- Unsolicited non-serious AE
- Solicited AE
- Withdrawal by participant, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*If a participant is withdrawn from the study because he/she/participant's LAR(s) has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.8.2).

7.3. Lost to follow-up

A participant will be considered 'lost to follow-up' if he/she fails to return for scheduled visits and cannot be contacted by the study site.

Please refer to the SPM for a description of actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarised in the SoA (Section 1.3).

All screening evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria.

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

Procedures conducted as part of routine clinical management (e.g. haematologic profiles), and obtained before the participant and/or participant's LAR(s) signed the Informed Consent Form (ICF), may be used for screening and/or for establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA (Section 1.3).

The SPM provides the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

8.1. Immunogenicity assessments

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant.

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit/contact. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.1. Biological samples

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoint	Subset name
Blood for antibody determination	~ 5	mL	Day 1 and Month 3	All participants

8.1.2. Laboratory assays

Table 8 Laboratory assays

Assay type	System	Component	Method	Laboratory*
Humoral Immunity (Antibody determination)	Serum	VZV Glycoprotein E Ab.IgG	ELISA	GSK **

*Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium; Marburg, Germany. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy.

Please refer to the Section 10.2 for a brief description of the assay performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

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

8.1.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint Type of contact and timepoint	Subset name	No. participants	Component
Visit 1 (Day 1)	All participants	288	Antibody gE ELISA
Visit 3 (Month 3)	All participants	288	Antibody gE ELISA

8.1.4. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the antigen(s) used in the study intervention.

8.2. Safety assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention or study.

8.2.1. Pre-study intervention procedures

8.2.1.1. Informed consent

Before performing any study procedure, the signed informed consent of the participant and/or participant's LAR(s) needs to be obtained in accordance to local regulatory requirement. Refer to Section 10.1.3 for the requirements on how to obtain informed consent.

8.2.1.2. Collection of demographic data

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

8.2.1.3. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and/or participant's LAR(s) and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention in the eCRF.

8.2.1.4. History-directed physical examination

Perform a history-directed physical examination. If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.5 for the list of criteria for temporary delay of study intervention administration.

Treatment of any pre-existing or new onset condition 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.

8.2.1.5. Pregnancy test

Female participants of childbearing potential must perform a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

Refer to the Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.6. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention.

8.2.1.7. Pre-study intervention administration body temperature

The body temperature of each participant needs to be measured prior to any study intervention administration and recorded in the eCRF. The preferred route for measuring temperature is oral. If the participant has fever (fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement) on the day of study intervention administration, the study intervention administration visit will be rescheduled.

8.2.2. Post-study intervention administration procedures

All participants post-intervention will be followed up for AE/SAE/pIMD/IMC/pregnancy or any other event of interest and instructed to contact the investigator immediately should they manifest any symptoms/signs they perceive as a concern. Refer to Section 1.3 and Section 10.3 for details.

8.3. Adverse Events, Serious Adverse Events and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE and other safety information

Table 10 Timeframes for collecting and reporting of AE, SAE and other safety information

Event	Dose 1				Dose2				6 Months after last dose Study Conclusion
Timing of reporting	D1	D7	D31		D1	D7	D31		
Administration site and systemic solicited events									
Unsolicited AEs									
AEs/SAEs leading to withdrawal from the study									
SAEs									
SAEs related to the study intervention									
SAEs related to study participation or concurrent GlaxoSmithKline medication/ vaccine [a]									
Suspected HZ episodes, IMC, Pregnancy[δ]									
pIMDs									

D: Day, M: Month; HZ=Herpes Zoster, IMC=Intercurrent Medical Conditions

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

[a] SAEs related to study participation or GSK concomitant medication/vaccine are to be recorded from the time the participant consents to participate in the study. All other SAEs are to be reported after administration of the first dose of study intervention.

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

The investigator or designee will record and immediately report all SAEs to the sponsor or designee via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10. 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 outside of the AE/SAE reporting periods defined in Table 10. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 12.

8.3.2. Method of detecting AEs and SAEs, pregnancies and other events

Detection and recording of AE/SAE/pIMDs/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

Open-ended and non-leading verbal questioning of participants and/or participant's LAR(s) is the preferred method of acquiring information related to an AE/SAE/pIMD/pregnancy.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMDs/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 11. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of SUSAR must be followed. These reports will be forwarded to investigators as necessary.

The sponsor has the legal responsibility to notify local authorities/regulatory agencies about the safety of an investigational study intervention. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC and investigators.

Please refer to the Section 10.3.10 for further details regarding the reporting of SAEs/pIMDs/pregnancies.

Table 11 Timeframes for submitting SAE, pregnancy and other events reports to GSK

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	24 hours	electronic pregnancy report	24 hours	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 by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of an pIMD.
‡ Paper Expedited Adverse Events Report will be dated and signed by the investigator (or designee)
‡‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.

8.3.3.1. Contact information for reporting SAEs, pIMDs and pregnancies

Table 12 Contact information for reporting SAEs, pIMDs and pregnancies

Study contact for questions regarding SAEs, pIMDs, pregnancies
Refer to the local study contact information document
Back up study contact for reporting SAEs, pIMDs, pregnancies
Available 24/24 hours and 7/7 days:
GSK Clinical Safety & Pharmacovigilance
Fax: +32 2 656 51 16 or +32 2 656 80 09
Email address: ***ogm28723@gsk.com***

8.3.4. Treatment of adverse events

Any medication administered for the treatment of an SAE/pIMD should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to the Section 10.3.10.1).

8.3.5. Participant card

The investigator (or designee) must provide the participant and/or participant's LAR(s) with a "participant card" containing information about the clinical study. The participant and/or participant's LAR(s) must be instructed to always keep the participant card in his/her/their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back up.

8.4. Pharmacokinetics

Not applicable in this study.

8.5. Genetics

Not being evaluated in the current study.

8.6. Biomarkers

Not applicable in this study.

8.7. Immunogenicity

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

Not being evaluated in the current study.

8.9. Study procedures to be followed during special circumstances

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

- 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 participant'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 International Conference on Harmonisation-Good Clinical Practice (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 local requirements.

- If despite best efforts, it is not possible to collect the biological samples within the interval pre-defined in the protocol (see Table 2), then the interval may be extended as outlined in Table 13.
- If despite best efforts, it is not possible to administer the second dose of study intervention as defined in the protocol (see Table 2), then the interval may be extended as outlined in Table 13.

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 13 Intervals between study visits during special circumstances

Interval	Planned visit 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–60 days
Visit 2→Phone contact	180 days (6 months)	160-210 days	160–210 days

Note: Investigator should prioritise conducting the visit as close to the planned visit interval as possible.

Impact on the PPS for immunogenicity 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 8.3.

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

The study has one primary and one secondary immunogenicity confirmatory objective and will be assessed in hierarchical manner. The null hypothesis related to primary objective under consideration is VRR for anti-gE antibody concentration after second HZ/su dose is <60%.

The primary objective will be met if the lower limit (LL) of the 95% Confidence Interval (CI) of the VRR for anti-gE antibody concentration after second HZ/su dose is ≥60%.

The null hypothesis related to secondary confirmatory objective under consideration is adjusted GMC ratio between HZ/su and Placebo group for anti-gE antibody concentration after second study intervention dose is <3.

The secondary confirmatory objective will be met if the LL of the 95% CI of the adjusted GMC ratio between HZ/su and Placebo group for anti-gE antibody concentration after second study intervention dose is ≥3.

All the safety analyses under secondary objective are descriptive.

9.2. Sample size determination

Approximately 288 (144 participants per study group) eligible participants will be randomised to achieve 200 (100 participants per study group) evaluable participants for the evaluation of the primary objective assuming that approximately 30% of the enrolled participants will not be evaluable. Participants who withdraw from the study will not be replaced.

Considering a 95% VRR in the HZ/su group, the study has at least 99% power to meet the primary objective.

Null hypothesis: The VRR for anti-gE ELISA at 1 month after second HZ/su dose in participants from India is less than 60%.

Alternative hypothesis: The VRR for anti-gE ELISA at 1 month after second HZ/su dose in participants from India is at least 60%.

Power to show the LL of the 95% CI for VRR at one month after second HZ/su dose.

Endpoint	NI criteria	N1:N2 (evaluable)	Reference**	Power*
Vaccine response rate – anti-gE ELISA	LL of 95% CI for VRR ≥60%	100:100	95%	≥99%

*Power computed using PASS 2019 software, Non-Inferiority Test for one proportion, 1-sided alpha=2.5%;
**References used for the sample size calculation: ZOSTER-006 study.

Considering the adjusted GMC ratio of 44.31 between HZ/su and Placebo group and SD of 0.30 and 0.46 for HZ/su and Placebo group, respectively, the study has at least 99% power to meet the secondary confirmatory objective.

Null hypothesis: The adjusted GMC ratio for anti-gE ELISA at 1 month after second study intervention dose in participants from India is less than 3.

Alternative hypothesis: The adjusted GMC ratio for anti-gE ELISA at 1 month after second study intervention dose in participants from India is greater than or equal to 3.

Power to show the LL of the 95% CI for adjusted GMC ratio at one month after second dose.

Endpoint	Criteria for evaluation	N1:N2 (evaluable)	Reference**	Power*
Adjusted GMC ratio	LL of 95% CI for adjusted GMC ratio ≥3	100:100	Adjusted GMC ratio – 44.31 SD for HZ/su group – 0.30 SD for Placebo group – 0.46	≥ 99%

*Power computed using PASS 2019 software, Two-Sample T-Tests for Superiority by a Margin Allowing Unequal Variance
, 1-sided alpha=2.5%;
**References used for the sample size calculation: ZOSTER-006 study.

9.3. Analysis sets

Table 14 Analysis sets

Analysis Set	Description
Enrolled Set	Eligible participants who have signed an informed consent and were randomised or undergone an invasive procedure.
Exposed Set	All participants who received at least 1 dose of the study intervention. Analysis per group using the enrolled set is based on the administered intervention.
Per Protocol Set	All eligible participants who received all doses as per protocol, had immunogenicity results pre and post-dose 2, complied with allowed dosing/blood draw intervals (Table 2), without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. The analysis will be done according to the study intervention that participants received at dose 1.

9.3.1. Criteria for elimination from analysis

If the participant meets one of the criteria mentioned below or ones listed in the Section 7.1.1 (contraindication to subsequent vaccination) or Section 5.2.1 (medical conditions) or Section 5.2.2 (concomitant therapy), he/she may be eliminated from per protocol analysis.

Participants may be eliminated from the PPS for immunogenicity if, during the study up to blood sampling timepoint post-dose 2, they incur a condition that has the capability of altering their immune response (IMC) or are confirmed to have an alteration of their initial immune status. Refer to Glossary of terms for the definition of IMC.

9.4. Statistical analyses

The statistical analysis plan (SAP) will be finalised prior to the first subject* first visit (FSFV) and it will include a more technical and detailed description of the statistical analyses including the supportive analyses and demography summaries. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

Unless otherwise mentioned, for all the planned analyses with CI, a 95% CI will be computed.

*subject= participant

9.4.1. Primary endpoint

The primary immunogenicity analysis will be performed on PPS and if more than 5% participants are eliminated from PPS then complementary analysis will be performed on ES.

The VRR and 95% CI for anti-gE antibody concentration as assessed by ELISA will be calculated in all participants at 1-month post-dose 2 (Month 3).

Success criterion*: The objective is met if the LL of the 95% CI of the VRR for anti-gE antibody concentration after second HZ/su dose is at least 60%.*

The VRR is defined as the percentage of subjects who has at least:

- a 4-fold increase in the post last vaccination anti-gE Ab concentration as compared to the pre-vaccination anti-gE Ab concentration for participants who are seropositive at baseline.

  OR

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

Two-sided 95% CIs for VRR will be computed by Clopper-Pearson method [Clopper, 1934].

9.4.2. Secondary endpoints

Descriptive analyses of demography and more detailed safety analysis will be presented in the SAP.

9.4.2.1. Secondary immunogenicity endpoints

The analysis will be performed on PPS and if more than 5% participants are eliminated from PPS then complementary analysis will be performed on ES.

For the secondary confirmatory group comparison, the GMC ratio with nominal 95% CI will also be provided. This will be obtained using an analysis of variance (ANOVA) model on log-transformed concentrations adjusted for age-strata (50-69 YOA and ≥ 70 YOA) and baseline titres as continuous covariate and will use Satterthwaite method for adjusting the degree of freedom for unequal variance.

Descriptive immune response with respect to anti-gE assessed by ELISA at each timepoint and by study group will be presented:

- Number and percentage of participants with anti-gE assessed by ELISA above seropositivity cut-off will be tabulated with 95% CI.
- GMCs will be tabulated with 95% CI.
- Geometric mean of ratios of antibody concentrations at 1- month post-dose 2 timepoint over pre-study intervention administration will be tabulated with 95% CI.

9.4.2.2. Secondary Safety endpoints

The analyses for safety will be descriptive and based on the ES. The analysis will be performed by group.

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

- Solicited administration site AEs and solicited systemic AEs
  - Number and percentage of participants reporting each solicited administration site AE (any grade, grade 3, resulting in a medically-attended visit) during the 7-day follow-up period after each dose and overall will be tabulated with exact 95% CIs.
  - Number and percentage of participants reporting each solicited systemic AE (any grade, grade 3, resulting in a medically-attended visit) during the 7-day follow-up period after each dose and overall will be tabulated with exact 95% CIs.
- Unsolicited AEs: Number and percentage of participants reporting unsolicited AE (any grade, grade 3, any related, grade 3 related, resulting in a medically-attended visit) within 30 days after any dose coded by the Medical Dictionary for Regulatory Activities (MedDRA) by primary system organ class (SOC) and preferred term (PT) with exact 95% CIs will be tabulated.
- SAEs and pIMDs: Number and percentage of participants reporting SAEs (any and related), fatal SAEs (any and related) and pIMDs (any and related) from Dose 1 (Day 1) up to 30 days post last dose and from Dose 1 (Day 1) up to study end coded by the MedDRA primary SOC and PT with exact 95% CIs will be tabulated.

9.5. Interim analyses (Amended 25 May 2022)

No interim analysis is planned for this study. An EoS analysis with all data including the safety data obtained until study end (6 months post-dose 2) will be performed. A Clinical Study Report (CSR) containing all available data will be written and made available to the investigators. Individual listings will only be provided at this stage.

To fulfil the post-approval commitment to the Indian regulatory authority, a blinded early safety assessment report after completion of 30 days safety follow-up post HZ/su dose 2 (i.e., Visit 3, Month 3) for the initial 200 randomised participants will be provided.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. 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-GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, 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 protocol amendments 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 participants.
- 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.

10.1.2. Financial disclosure

Investigators and sub-investigators must provide the sponsor with full and accurate financial disclosure, as requested, to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators must provide their financial interest information before initiation of the study centre and again at the end of the study. Investigators are responsible for providing a financial disclosure update if their financial interests change at any point during study participation and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator or his/her representative must fully explain the nature of the study to the participant and/or his/her LAR(s) and answer all questions regarding the study.

Participants and/or participant's LAR(s) must be informed that their participation is voluntary.

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

The content of the ICF 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 or witnessed/ thumb printed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the participants and/or participant's LAR(s).

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

10.1.4. Data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets transferred to the sponsor will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

The participants and/or participant's LAR(s) must be informed that:

- His/her personal study-related data will be used by the sponsor in accordance with local data protection law.
- 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 ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

The participants and/or participant's LAR(s) must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

10.1.5. Committees structure

GSK will obtain necessary approvals for conduct of the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study. This includes IRBs/IECs for review and approval of the protocol and subsequent amendments, ICF and any other documentation.

An internal GSK Safety Review Team (SRT) will oversee the safety of the study. All safety data, i.e. AEs, SAEs, fatal SAEs and pIMDs 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.

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

Where required by regulation, summaries will also be posted on applicable national or regional clinical trial registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and 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 participants, as appropriate.

GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.

GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents, including source documents. The document 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 trial documents may be added or removed where justified (in advance of trial initiation) based on their importance and relevance to the trial. When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfil the requirements for certified copies.

All participant data related to the study will be recorded on printed or electronic CRF 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 participants that supports 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 for such review and inspection.

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 in the eCRF by authorised site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g. via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

Quality tolerance limits (QTLs) will be pre-defined in the Study Management Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarised in the CSR.

Trial records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final 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.

10.1.8. Source documents

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any 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.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur 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 enough notice 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 participants by the investigator
- Discontinuation of further study intervention development.

10.1.10. Publication policy

GSK aims to submit the results of the study for publication in searchable, peer reviewed scientific literature within 18 months from the LSLV for interventional studies and follows the guidance from the International Committee of Medical Journal Editors (ICMJE).

10.2. Appendix 2: Clinical laboratory tests

Anti-gE ELISA: Anti-gE Ab concentrations will be measured using an anti-gE ELISA.

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

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting Definition of AE

10.3.1. Definition of an adverse event

An AE is any untoward medical occurrence (an unfavourable/unintended sign – including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. 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 administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g. hospital stays, physician visits and emergency room visits).
- Significant failure of an expected pharmacologic or biological action.
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen). Note the exception made here for pre-intervention events to the AE definition.
- 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.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. 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 participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF. • Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

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

• Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy).
• Other situations – Medical or scientific judgement must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition should 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; and convulsions that do not result in hospitalisation.

10.3.3. Solicited events

- Solicited administration site events

The following administration site events will be solicited:

Table 15 Solicited administration site events (Amended 25 May 2022)

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

- **Solicited systemic events**

The following systemic events will be solicited as per GSK's routine practice for HZ/su in older adults:

Table 16 Solicited systemic events

Fatigue
Fever
GI symptoms†
Headache
Myalgia
Shivering

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

Note: participant's and/or participant's LAR(s) will be instructed to measure and record the oral temperature in the evening. If additional temperature measurements are taken at other times of the day, participants and/or participant's LAR(s) will be instructed to record the highest temperature in the diary card.

10.3.4. Unsolicited adverse events

An unsolicited AE is an AE that was not included in a list of solicited events using a Participant Diary. Unsolicited events must have been spontaneously communicated by a participant and/or participant's LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.

Potential unsolicited AEs may be medically-attended (i.e., symptoms or illnesses requiring a hospitalisation, or an emergency room visit, or visit to/by a health care provider). The participants and/or participant's LAR(s) will be instructed to contact the site as soon as possible to report medically-attended event(s), as well as any events that, though not medically-attended, are of participant and/or participant's LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically-attended or perceived as a concern by the participant and/or participant's LAR(s) will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. Adverse events of special interest

pIMDs are the only AESI collected during this study.

10.3.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 17 (Please refer to the Section 10.3.8.1 for reporting details).

The investigator must exercise his/her medical/scientific judgement to determine 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 17 List of potential immune-mediated diseases (pIMDs) (Amended, 25 May 2022)

Medical Concept	*Additional Notes*
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• ***Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia***
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• ***Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", "primary immune thrombocytopenia".***
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• ***Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"***
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	***Including but not limited to:*** • ***Autoimmune / Immune-mediated myocarditis*** • ***Autoimmune / Immune-mediated pericarditis*** • ***Giant cell myocarditis***
Idiopathic pulmonary fibrosis	***Including but not limited to:*** • ***Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis")*** • ***Pleuroparenchymal fibroelastosis (PPFE)***
Pulmonary alveolar proteinosis (PAP)	• ***Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"***
Endocrine disorders	
Addison's disease	
Autoimmune / Immune-mediated thyroiditis	***Including but not limited to:*** • ***Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)*** • ***Atrophic thyroiditis*** • ***Silent thyroiditis*** • ***Thyrotoxicosis***

Medical Concept	*Additional Notes*
Autoimmune diseases of the testis and ovary	• *Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis*
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• *Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy*
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• *Includes Polyglandular autoimmune syndrome type I, II and III*
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	*Including but not limited to:* • *Acute macular neuroretinopathy (also known as acute macular outer retinopathy)* • *Autoimmune / Immune-mediated retinopathy* • *Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia* • *Cogan's syndrome: an oculo-audiovestibular disease* • *Ocular pemphigoid* • *Ulcerative keratitis* • *Vogt-Koyanagi-Harada disease*
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	*Including but not limited to:* • *Crohn's disease* • *Microscopic colitis* • *Terminal ileitis* • *Ulcerative colitis* • *Ulcerative proctitis*
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• *Includes gouty arthritis*

Medical Concept	*Additional Notes*
Idiopathic inflammatory myopathies	*Including but not limited to:* • *Dermatomyositis* • *Inclusion body myositis* • *Immune-mediated necrotizing myopathy* • *Polymyositis*
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	*Including but not limited to:* • *Rheumatoid arthritis associated conditions* • *Juvenile idiopathic arthritis* • *Palindromic rheumatism* • *Still's disease* • *Felty's syndrome*
Sjögren's syndrome	
Spondyloarthritis	*Including but not limited to:* • *Ankylosing spondylitis* • *Juvenile spondyloarthritis* • *Keratoderma blenorrhagica* • *Psoriatic spondylitis* • *Reactive Arthritis (Reiter's Syndrome)* • *Undifferentiated spondyloarthritis*
Systemic Lupus Erythematosus	• *Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)*
Systemic Scleroderma (Systemic Sclerosis)	• *Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)*
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory demyelinating variants	*Includes the following:* • *Acute necrotising myelitis* • *Bickerstaff's brainstem encephalitis* • *Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)* • *Myelin oligodendrocyte glycoprotein antibody-associated disease* • *Neuromyelitis optica (also known as Devic's disease)* • *Noninfective encephalitis / encephalomyelitis / myelitis* • *Postimmunization encephalomyelitis*

Medical Concept	*Additional Notes*
Guillain-Barré syndrome (GBS)	• *Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)*
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	*Including but not limited to:* • *Cranial nerve neuritis (e.g. Optic neuritis)* • *Idiopathic nerve palsies/paresis (e.g. Bell's palsy)* • *Melkersson-Rosenthal syndrome* • *Multiple cranial nerve palsies/paresis*
Multiple Sclerosis (MS)	*Includes the following:* • *Clinically isolated syndrome (CIS)* • *Malignant MS (the Marburg type of MS)* • *Primary-progressive MS (PPMS)* • *Radiologically isolated syndrome (RIS)* • *Relapsing-remitting MS (RRMS)* • *Secondary-progressive MS (SPMS)* • *Uhthoff's phenomenon*
Myasthenia gravis	• *Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome*
Narcolepsy	• *Includes narcolepsy with or without presence of unambiguous cataplexy*
Peripheral inflammatory demyelinating neuropathies and plexopathies	*Including but not limited to:* • *Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy)* • *Antibody-mediated demyelinating neuropathy* • *Chronic idiopathic axonal polyneuropathy (CIAP)* • *Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)* • *Multifocal motor neuropathy (MMN)*
Transverse myelitis (TM)	• *Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)*
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	*Including but not limited to:* • *IgA nephropathy* • *IgM nephropathy* • *C1q nephropathy* • *Fibrillary glomerulonephritis* • *Glomerulonephritis rapidly progressive* • *Membranoproliferative glomerulonephritis* • *Membranous glomerulonephritis*

Medical Concept	*Additional Notes*
	• *Mesangioproliferative glomerulonephritis* • *Tubulointerstitial nephritis and uveitis syndrome*
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	*Including but not limited to:* • *Bullous Dermatitis* • *Bullous Pemphigoid* • *Dermatitis herpetiformis* • *Epidermolysis bullosa acquisita (EBA)* • *Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease* • *Pemphigus*
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	*Including but not limited to* • *Interstitial granulomatous dermatitis* • *Palisaded neutrophilic granulomatous dermatitis*
Lichen planus	• *Includes liquen planopilaris*
Localised Scleroderma (Morphoea)	• *Includes Eosinophilic fasciitis (also called Shulman syndrome)*
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	*Including but not limited to:* • *Toxic Epidermal Necrolysis (TEN)* • *SJS-TEN overlap*
Sweet's syndrome	• *Includes Acute febrile neutrophilic dermatosis*
Vitiligo	
Vasculitis	
Large vessels vasculitis	*Including but not limited to:* • *Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)* • *Giant cell arteritis (also called temporal arteritis)* • *Takayasu's arteritis*
Medium sized and/or small vessels vasculitis	*Including but not limited to:* • *Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)* • *Behcet's syndrome* • *Buerger's disease (thromboangiitis obliterans)* • *Churg–Strauss syndrome (allergic granulomatous angiitis)*

Medical Concept	*Additional Notes*
	• *Erythema induratum (also known as nodular vasculitis)* • *Henoch-Schonlein purpura (also known as IgA vasculitis)* • *Microscopic polyangiitis* • *Necrotizing vasculitis* • *Polyarteritis nodosa* • *Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)* • *Wegener's granulomatosis*
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• *Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"*
Goodpasture syndrome	• *Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"*
Immune-mediated enhancement of disease	• *Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)*
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	*Including but not limited to:* • *Kawasaki's disease* • *Multisystem inflammatory syndrome in adults (MIS-A)* • *Multisystem inflammatory syndrome in children (MIS-C)*
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• *Includes Loefgren syndrome*
Susac's syndrome	

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments or other abnormal results (e.g. physical examination) the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to the Sections 10.3.1 and 10.3.2).

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

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to the Section 10.3.2 for definition of SAE.

10.3.8. Recording and follow-up of AEs, SAEs, pIMDs and pregnancies

The participants and/or participant's LAR(s) will be instructed to contact the investigator immediately should they experience any signs or symptoms they perceive as serious.

When an AE/SAE occurs, it is the investigator's responsibility to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on 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 instead of individual signs/symptoms.

A Paper Diary (pDiary), hereafter referred to as Participant Diary, will be used in this study to capture details of solicited administration site or systemic events (i.e. on the day of study intervention administration and during the next 6 days) or any unsolicited AEs (i.e. on the day of study intervention administration and during the next 29 days) occurring after dosing. For solicited events continuing after 7 days, the participant and/or participant's LAR(s) will be instructed to record events until resolution. The participant and/or participant's LAR(s) will be instructed to return the completed diary card to the investigator at the next study visit. The participant should be trained on how and when to complete the Participant Diary.

Anyone who measures administration site or systemic events and who will record the event in the Participant Diary should be trained on using the diary. This training must be documented in the participant's source record. If any individual other than the participant is making entries in the Participant Diary, their identity must be documented in the Participant Diary/participant's source record.

The investigator or delegate will transcribe the required information into the eCRF in English.

10.3.8.1. Time period for collecting and recording AEs, SAEs, pIMDs and pregnancies

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

The time period for collecting and recording all SAEs will begin at the first receipt of study vaccine and will end 6 months following administration of the last dose of study vaccine for each participant. See Section 10.3.10 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first 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 participant 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 participant 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 8.3 for instructions on reporting of pregnancies. This applies to pregnancy cases with exposure to the study intervention at any age of gestation. The timing of exposure to the study intervention during pregnancy is estimated in relation to the first day of the last menstrual period, ultrasound or known date of fertilisation (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 6 months following administration of the last dose of study vaccine. See Section 8.3 for instructions on reporting of pIMDs.

10.3.8.2. Follow-up of AEs, SAEs, pIMDs, IMCs and pregnancies

After the initial AE/SAE/pIMD/IMCs/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, pIMDs (serious and non-serious), IMCs and pregnancies will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

Other non-serious AEs must be followed until 30 days following administration of last dose or until the participant is lost to follow-up.

10.3.8.2.1. Follow-up during the study

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

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 participant.

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.

If a participant dies during their participation in the study or during a recognised follow- up period, GSK will be provided with any available post-mortem findings, including histopathology.

10.3.8.2.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE/pIMD using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the SAE/pIMD as fully as possible.

10.3.8.2.3. Follow-up of pregnancies

Pregnant participants 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 does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

Furthermore, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND it is considered by the investigator to be reasonably related to the study intervention, he/she must report this information to GSK as described in the Section 10.3.10.

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

When additional SAE, pIMD or pregnancy information is received after write access to the participant's eCRF is removed, 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 Section 8.3.3.1 or to GSK VCSP department within the defined reporting time frames specified in the Table 11.

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

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

Table 18 Intensity scales for solicited events (Amended 25 May 2022)

Adults (≥50 years)		
Event	**Intensity grade**	**Parameter**
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
Pruritus at administration site	0	None
	1	Mild: Itchy sensation that neither interferes with nor preventing normal everyday activities.
	2	Moderate: Itchy sensation that interferes with normal everyday activities.
	3	Severe: Itchy sensation that prevents normal everyday activities.
Temperature*		Temperature in °C/°F (with 1 decimal)
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	None
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms	0	None
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	None
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Shivering	0	None
	1	Shivering that is easily tolerated
	2	Shivering that interferes with normal activity
	3	Shivering that prevents normal activity

* Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.

The maximum intensity of injection administration site redness/swelling and fever will be scored at GSK as follows:

	Redness/swelling	Fever
0:	≤20 mm	<38.0°C (100.4°F)
1:	>20-≤50 mm	≥38.0°C (100.4°F)- ≤38.5°C (101.3°F)
2:	>50-≤100 mm	>38.5°C (101.3°F)- ≤39.0°C (102.2°F)
3:	>100 mm	>39.0°C (102.2°F)

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 participant, 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 likely necessitate the administration of corrective therapy.

An AE that is assessed as grade 3 (severe) should not be confused with an 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 the Section 10.3.2.

10.3.9.2. Assessment of causality

All solicited administration site and systemic events occurring within 7 days of study intervention administration will be considered causally related to the study intervention.

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgement.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB and/or Prescribing Information for marketed products to assist in making his/her assessment.

Causality should be assessed by the investigator using the following question:

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

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

If an event meets the criteria to be determined 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator 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 study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically-attended visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if the participant received medical attention (defined as hospitalisation, 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.

10.3.9.4. 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).

10.3.10. Reporting of SAEs, pIMDs, pregnancies and other events

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred, the investigator (or designee) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event. The report must be dated and signed by the investigator (or designee).

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 11 for the details on timeframes for reporting of SAEs/pIMDs/pregnancies.

The investigator will be required to confirm the review of SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

Refer to the Section 10.3.10.2 for information on back up systems in case the electronic reporting system does not work.

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

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to the Sponsor Information) or to GSK VCSP department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.3.10.3. Completion and transmission of pregnancy reports to GSK

Once the investigator becomes aware that a participant is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 24 HOURS.

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.

10.3.10.4. Reporting of pIMD to GSK

Once a pIMD is diagnosed (serious or non-serious) in a study participant, 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.

Refer to Section 10.3.10.2 for back up system in case the electronic reporting system does not work.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

10.4.1.1.1. Women not considered as women of childbearing potential

- Premenarchal

  Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Current bilateral tubal ligation or occlusion

Note: Documentation can come from the site personnel's: review of participant'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 a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 19).

Table 19 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 • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomised partner *(A vasectomised 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 sterilisation prior to the female participant's entry into the study, and this male is the sole partner for that participant, *(The information on the male sterility can come from the site personnel's review of the participant'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 participant.)*

10.4.3. Collection of pregnancy information

10.4.3.1. Female participants who become pregnant

Refer to the Sections 8.3.1, 8.3.2, 10.3.8.1 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will be discontinued from the study treatment.

10.5. Appendix 5: Genetics

Not Applicable

10.6. Appendix 6: Country-specific requirements

Investigators should comply with all requirements of the National Ethical guidelines for Biomedical and Health research involving human participants 2017 guidelines by Indian Council of Medical Research, New Drugs Clinical Trial Rules 2019 of India, ICH-GCP Guideline E6 (R2), IRB/IEC standard operating procedures, local regulations, provide written status to the IRB/IEC annually or more frequent in accordance with procedures and policies established by the IRB/IEC and regulatory authority.

10.7. Appendix 7: Abbreviations and glossary of terms

10.7.1. List of abbreviations

Ab:	Antibody
AE:	Adverse Event
AESI:	Adverse Event of Specific Interest
AS01$_B$:	Adjuvant System 01$_B$ -MPL, QS21, liposome based Adjuvant System (50 µg MPL and 50 µg QS21)
CI:	Confidence Interval
CIOMS:	Council for International Organisations of Medical Sciences
CLS:	Clinical Laboratory Sciences
CoP:	Correlate of Protection
COVID-19:	Coronavirus Disease 2019
CSR:	Clinical Study Report
eCRF:	electronic Case Report Form
EDD:	Estimated Date of Delivery
EEA:	European Economic Area
EGA:	Estimated Gestational Age
ELISA:	Enzyme-linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed Set
FSH:	Follicle Stimulating Hormone
GCP:	Good Clinical Practice
gE:	VZV Glycoprotein E

GI:	Gastrointestinal
GMC:	Geometric Mean Concentration
GSK:	GlaxoSmithKline Biologicals SA
HIPAA:	Health Insurance Portability and Accountability Act
HRT:	Hormonal Replacement Therapy
HZ/su:	Herpes Zoster subunit vaccine
HZ:	Herpes Zoster
IB:	Investigator Brochure
IC:	Immunocompromised
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
ICMJE:	International Committee of Medical Journal Editors
IEC:	Independent Ethics Committee
IgG:	Immunoglobulin G
IM:	Intramuscular/Intramuscularly
IMC	Intercurrent Medical Conditions
IRB:	Institutional Review Board
IUD:	Intrauterine device
IUS:	Intrauterine hormone-releasing system
LAR:	Legally Acceptable Representative
LL:	Lower Limit
LML:	Local Medical Lead
LMP:	Last Menstrual Period
LSLV:	Last Subject* Last Visit (*Subject=Participant)
MedDRA:	Medical Dictionary for Regulatory Activities
MGI:	Mean Geometric Increase
MPL:	3-O-desacyl-4'-monophosphoryl lipid A
NaCl:	Saline solution
PCD:	Primary Completion Date
pDairy:	Paper Dairy
PHN:	Post-Herpetic Neuralgia
pIMD:	Potential Immune-Mediated Disease
PPS:	Per Protocol Set

PT:	Preferred Term
QS21:	*Quillaja saponaria* Molina, fraction 21 (purified saponin extract from the South American tree)
QTL:	Quality Tolerance Limit
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SAS:	Statistical Analysis System
SBIR:	Source data Base for Internet Randomisation
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SoA:	Schedule of Activities
SOC:	System Organ Class
SPM:	Study Procedures Manual
SRT:	Safety Review Team
SUSAR:	Suspected Unexpected Serious Adverse Reactions
US	United States
VCSP:	Vaccine Clinical Safety and Pharmacovigilance
VRR:	Vaccine Response Rate
VZV:	Varicella Zoster Virus
WHO:	World Health Organisation
WOCBP:	Woman of Childbearing Potential
YOA:	Years of Age

10.7.2. Glossary of terms

Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant, 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 intervention 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 SAE. In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.
Caregiver	A ‘caregiver’ is someone who – lives in the close surroundings of a participant and has a continuous caring role or – has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g. a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study **(Synonym of End of Trial)**	For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological

	Samples or imaging data, related to primary and secondary endpoints/outcomes. EoS must be achieved no later than 8 months after Last Subject* Last Visit (*Subject=Participant).
Enrolled participant	'Enrolled' means a participant's and/or participant's LAR(s) agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 of the protocol for the definition of 'enrolled set' applicable to the study.
eTrack	GSK's tracking tool for clinical trials.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intercurrent medical condition	A condition that has the capability of altering the immune response to the study intervention or is confirmed to have an alteration of the participant's initial immune status.
Intervention	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 participant.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
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.

Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date	The date that the final participant 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.
Protocol amendment	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomisation	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study	Study with objectives not linked to the data of another study.
Site Monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited event	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
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 legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participant's 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, participant files, and records kept at the pharmacy, laboratories and at medico- technical departments involved in the clinical trial).
Study intervention	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Unsolicited adverse event	Any AE (non-serious and serious) 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 AE.

10.8. 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 1	25 May 2022
Protocol	8 June 2021

Detailed description of the current Protocol amendment:

All changes made from the previous protocol version are detailed in this section. Deleted text is in strikethrough and newly added text is in bold italics.

Section 1.1 Synopsis

The section was updated to specify regarding the licensure of HZ/su in India for adults ≥50 YOA, and for inclusion of an early supportive safety report to fulfil the post-approval commitment to the Indian regulatory authority. The edits are as below.

~~Currently~~ ***When this ZOSTER-081 study began, HZ/su was*** ~~is~~ not approved for use in India***. While the study was ongoing, HZ/su was licensed for use in India for adults ≥50 YOA on the 21 April 2022. Despite this licensure, HZ/su is not currently available in the Indian market; however, when it does become available, the study participants will be notified by the investigators***. To meet the ***post-approval*** requirements of ***the*** Indian regulatory authorit~~ies~~***y*** ~~for licensure and~~ ***this study will continue as originally planned*** to demonstrate the immunogenicity and safety of ~~of~~ HZ/su in the Indian population, ~~ZOSTER-081 study~~ is ~~planned~~. This study ~~will~~ ***is designed to*** evaluate the humoral immunogenicity and safety of 2 doses of HZ/su, for the prevention of HZ in adults ≥50 YOA***. In addition, as also required by the Indian regulatory authority, a safety report describing the early supportive safety data will be provided once these data (up to Visit 3, Month 3) on the initial 200 study participants randomized are available.***

Section 2.1 Study Rationale:

The section was updated to specify regarding the licensure of HZ/su in India for adults ≥50 YOA, and for inclusion of an early supportive safety report to fulfil the post-approval commitment to the Indian regulatory authority. The edits are as below.

When this ZOSTER-081 study began, HZ/su was not approved for use in India. While the study was ongoing, HZ/su was licensed for use in India for adults ≥50 YOA on 21 April 2022. Despite this licensure, HZ/su is not currently available in the Indian market; however, when it does become available, the study participants will be notified by the investigators. To meet the post-approval requirements of the Indian regulatory authority, this study to demonstrate the immunogenicity and safety of HZ/su in the Indian population is to continue as originally planned. This study is designed to evaluate the humoral immunogenicity and safety of 2 doses of HZ/su, for the prevention of HZ in adults ≥50 YOA. In addition, as also required by the Indian regulatory authority, a safety report describing the early supportive safety data will be

provided once these data (up to Visit 3, Month 3) on the initial 200 study participants randomized are available.

~~Currently, HZ/su is not approved for use in India. To meet the requirements of Indian regulatory authorities for licensure and to demonstrate the immunogenicity and safety of HZ/su in the Indian population, ZOSTER-081 study is planned. This study will evaluate the humoral immunogenicity and safety of 2 doses of GSK's HZ/su for the prevention of HZ in Indian adults ≥50 YOA~~.

Section 5.2.2: Prior/Concomitant therapy

The below paragraph was presented as a separate bullet point, wherein the text was an explanation to the bullet point above it, thus the bullet was removed and text was placed in between brackets.

> ***[***In case an emergency mass vaccination for an unforeseen public health threat (e.g. a pandemic) is recommended and/or organised by the public health authorities, outside the routine immunisation programme, the time period described above can be reduced if necessary for that vaccine provided it is used according to local governmental recommendations and that the Sponsor is notified accordingly***]***.

Table 5: Study Intervention administered

As the reconstituted Sucrose and Sodium Chloride (NaCl) pharmaceutical product is a solution for injection, the dose form of the NaCl solution was revised as "solution for solution for injection". Changes to the table from the previous version of the protocol are shown in the below table, deleted text is in strikethrough and newly added text is in bold italics.

Study Intervention Name:	**HZ/su**		**Placebo**	
Study Intervention /Product name	VZV gE	$AS01_B$	Lyophilised sucrose	Saline (NaCl) solution
Study Intervention formulation:	VZV gE (50 µg)	$AS01_B$: QS-21 (50 µg), MPL (50 µg), liposomes; Water for injections ~~q.s.0.5 ml~~	Sucrose (20 mg)	Sodium chloride (NaCl) (0.9%); Water for injections ~~q.s.0.5 ml~~
Presentation:	Powder for suspension for injection	Suspension for suspension for injection	Powder for solution for injection	Solution for ~~suspension~~ ***solution*** for injection
Container	Vial	Vial	Vial	Syringe
Type:	Biologic		Not applicable	
Administration site:	Intramuscular use		Intramuscular use	
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, Labelling and TM:	Refer to SPM			
Manufacturer:	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=Quantum satis

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.

Section 6.8: Concomitant therapy.

The below sentence was included to further clarify the requirement for recording concomitant medications ongoing at Visit 1 (Day 1), which remains indicated as such on Table 1-Schedule of Activities.

- ***All concomitant medications ongoing once randomized at Visit 1 (Day 1).***

Section 8.3.3.1: Contact information for reporting SAEs, pIMDs and pregnancies

The email ID to report SAEs, pIMDs and pregnancies was updated by GSK since the previous protocol version. The changes are as below.

Email address: ~~Rix.CT-safety-vac@gsk.com~~ ***ogm28723@gsk.com***

Section 9.5: Interim Analysis

The below addition was made to describe the early safety assessment report requirement.

To fulfil the post-approval commitment to the Indian regulatory authority, a blinded early safety assessment report after completion of 30 days safety follow-up post HZ/su dose 2 (i.e., Visit 3, Month 3) for the initial 200 randomised participants will be provided.

Table 3, Table 15 and Table 18:

Typographical error pruriti~~s~~ was corrected to prurit***u***s.

Table 17 List of Potential Immune-Mediated Diseases (pIMDs)

The list of pIMDs was updated by GSK since the previous protocol version. Thus, the table was replaced to further assist investigators. The deleted table is presented in strikethrough and the updated table is presented in bold italics below.

~~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.~~
	• ~~Autoimmune haemolytic anaemia.~~
	• ~~Autoimmune thrombocytopenia.~~
	• ~~Antiphospholipid syndrome.~~
		• ~~Autoimmune glomerulonephritis including:~~
		  ○ ~~IgA nephropathy,~~
		  ○ ~~Glomerulonephritis rapidly progressive,~~

• 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.
	• Pernicious anaemia.
	• Autoimmune aplastic anaemia.
	• Autoimmune neutropenia.
	• Autoimmune pancytopenia.
		○ 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.

Table 17 List of potential immune-mediated diseases (pIMDs) (Amended, 25 May 2022)

Medical Concept	*Additional Notes*
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• *Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia*
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• *Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", "primary immune thrombocytopenia".*
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• *Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"*
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	*Including but not limited to:* • *Autoimmune / Immune-mediated myocarditis* • *Autoimmune / Immune-mediated pericarditis* • *Giant cell myocarditis*
Idiopathic pulmonary fibrosis	*Including but not limited to:* • *Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis")* • *Pleuroparenchymal fibroelastosis (PPFE)*
Pulmonary alveolar proteinosis (PAP)	• *Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"*
Endocrine disorders	
Addison's disease	
Autoimmune / Immune-mediated thyroiditis	*Including but not limited to:* • *Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)* • *Atrophic thyroiditis* • *Silent thyroiditis* • *Thyrotoxicosis*

Medical Concept	*Additional Notes*
Autoimmune diseases of the testis and ovary	• *Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis*
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• *Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy*
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• *Includes Polyglandular autoimmune syndrome type I, II and III*
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	*Including but not limited to:* • *Acute macular neuroretinopathy (also known as acute macular outer retinopathy)* • *Autoimmune / Immune-mediated retinopathy* • *Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia* • *Cogan's syndrome: an oculo-audiovestibular disease* • *Ocular pemphigoid* • *Ulcerative keratitis* • *Vogt-Koyanagi-Harada disease*
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	*Including but not limited to:* • *Crohn's disease* • *Microscopic colitis* • *Terminal ileitis* • *Ulcerative colitis* • *Ulcerative proctitis*
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• *Includes gouty arthritis*

Medical Concept	*Additional Notes*
Idiopathic inflammatory myopathies	*Including but not limited to:* • *Dermatomyositis* • *Inclusion body myositis* • *Immune-mediated necrotizing myopathy* • *Polymyositis*
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	*Including but not limited to:* • *Rheumatoid arthritis associated conditions* • *Juvenile idiopathic arthritis* • *Palindromic rheumatism* • *Still's disease* • *Felty's syndrome*
Sjögren's syndrome	
Spondyloarthritis	*Including but not limited to:* • *Ankylosing spondylitis* • *Juvenile spondyloarthritis* • *Keratoderma blenorrhagica* • *Psoriatic spondylitis* • *Reactive Arthritis (Reiter's Syndrome)* • *Undifferentiated spondyloarthritis*
Systemic Lupus Erythematosus	• *Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)*
Systemic Scleroderma (Systemic Sclerosis)	• *Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)*
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory demyelinating variants	*Includes the following:* • *Acute necrotising myelitis* • *Bickerstaff's brainstem encephalitis* • *Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis)* • *Myelin oligodendrocyte glycoprotein antibody-associated disease* • *Neuromyelitis optica (also known as Devic's disease)* • *Noninfective encephalitis / encephalomyelitis / myelitis* • *Postimmunization encephalomyelitis*

Medical Concept	*Additional Notes*
Guillain-Barré syndrome (GBS)	• *Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)*
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	*Including but not limited to:* • *Cranial nerve neuritis (e.g. Optic neuritis)* • *Idiopathic nerve palsies/paresis (e.g. Bell's palsy)* • *Melkersson-Rosenthal syndrome* • *Multiple cranial nerve palsies/paresis*
Multiple Sclerosis (MS)	*Includes the following:* • *Clinically isolated syndrome (CIS)* • *Malignant MS (the Marburg type of MS)* • *Primary-progressive MS (PPMS)* • *Radiologically isolated syndrome (RIS)* • *Relapsing-remitting MS (RRMS)* • *Secondary-progressive MS (SPMS)* • *Uhthoff's phenomenon*
Myasthenia gravis	• *Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome*
Narcolepsy	• *Includes narcolepsy with or without presence of unambiguous cataplexy*
Peripheral inflammatory demyelinating neuropathies and plexopathies	*Including but not limited to:* • *Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy)* • *Antibody-mediated demyelinating neuropathy* • *Chronic idiopathic axonal polyneuropathy (CIAP)* • *Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)* • *Multifocal motor neuropathy (MMN)*
Transverse myelitis (TM)	• *Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)*
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	*Including but not limited to:* • *IgA nephropathy* • *IgM nephropathy* • *C1q nephropathy* • *Fibrillary glomerulonephritis* • *Glomerulonephritis rapidly progressive* • *Membranoproliferative glomerulonephritis* • *Membranous glomerulonephritis*

Medical Concept	*Additional Notes*
	• *Mesangioproliferative glomerulonephritis* • *Tubulointerstitial nephritis and uveitis syndrome*
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	*Including but not limited to:* • *Bullous Dermatitis* • *Bullous Pemphigoid* • *Dermatitis herpetiformis* • *Epidermolysis bullosa acquisita (EBA)* • *Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease* • *Pemphigus*
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	*Including but not limited to* • *Interstitial granulomatous dermatitis* • *Palisaded neutrophilic granulomatous dermatitis*
Lichen planus	• *Includes liquen planopilaris*
Localised Scleroderma (Morphoea)	• *Includes Eosinophilic fasciitis (also called Shulman syndrome)*
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	*Including but not limited to:* • *Toxic Epidermal Necrolysis (TEN)* • *SJS-TEN overlap*
Sweet's syndrome	• *Includes Acute febrile neutrophilic dermatosis*
Vitiligo	
Vasculitis	
Large vessels vasculitis	*Including but not limited to:* • *Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)* • *Giant cell arteritis (also called temporal arteritis)* • *Takayasu's arteritis*
Medium sized and/or small vessels vasculitis	*Including but not limited to:* • *Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)* • *Behcet's syndrome* • *Buerger's disease (thromboangiitis obliterans)* • *Churg–Strauss syndrome (allergic granulomatous angiitis)*

Medical Concept	*Additional Notes*
	• *Erythema induratum (also known as nodular vasculitis)* • *Henoch-Schonlein purpura (also known as IgA vasculitis)* • *Microscopic polyangiitis* • *Necrotizing vasculitis* • *Polyarteritis nodosa* • *Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)* • *Wegener's granulomatosis*
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• *Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"*
Goodpasture syndrome	• *Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"*
Immune-mediated enhancement of disease	• *Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)*
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	*Including but not limited to:* • *Kawasaki's disease* • *Multisystem inflammatory syndrome in adults (MIS-A)* • *Multisystem inflammatory syndrome in children (MIS-C)*
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• *Includes Loefgren syndrome*
Susac's syndrome	

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