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212340 (ZOSTER-073 EXT:041 Y4-10)
Protocol Amendment 1 Final

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

Primary Study vaccine and number	GlaxoSmithKline Biologicals SA (GSK) Lyophilized formulation of the Herpes Zoster subunit vaccine (GSK1437173A)
eTrack study number and abbreviated title	212340 (ZOSTER-073 EXT:041 Y4-10)
Investigational New Drug (IND) number	BB-IND 13879
EudraCT number	2019-001815-21
Date of protocol	Final Version 1: 07 June 2019
Date of protocol amendment	Amendment 1 Final: 15 June 2020
Title	Long-term immunogenicity study of Herpes Zoster subunit vaccine (GSK 1437173A) and immunogenicity and safety assessment of revaccination with two additional doses in adults with renal transplant from study ZOSTER-041.
Detailed title	A phase IIIB, open label, long term follow-up study to assess persistence of immune responses to GSK's HZ/su vaccine 4-7 years after primary vaccination; and immunogenicity and safety assessment of revaccination with 2 additional doses of HZ/su vaccine, administered 1-2 months apart, 6-8 years after primary vaccination of adults with renal transplant from study ZOSTER-041.
Co-ordinating author	PPD (Modis Life Sciences, contractor for GSK)
Contributing authors **(Amended: 15 June 2020)**	• PPD, PPD, Senior Clinical Expert, Zoster • PPD, Clinical Research and Development Lead, Zoster • PPD, Study Statistician • PPD, Lead Statistician • PPD, Study Delivery Leads • PPD Laboratory Study Manager

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Contributing authors (Contd.) **(Amended: 15 June 2020)**	• PPD, Clinical Readout Team Leads • PPD, SERM Expert Scientists • PPD, Oversight Data Managers • PPD, Senior Manager, Global Regulatory Affairs • PPD, Global Patent • PPD Clinical and Epidemiology Project Lead, Zoster Program, US RDC

GSK Protocol WS v 16.0.1

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	212340 (ZOSTER-073 EXT:041 Y4-10)
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Sponsor signatory	Anne Schuind, Clinical and Epidemiology Project Lead (CEPL) for Zoster, Clinical R&D
Signature	
Date	

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 vaccine and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the subject.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

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

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

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

GSK Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 12.5.10.3

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

GSK Central Safety Physician and Back-up Phone contact: refer to protocol Section 8.4.4.1.

PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES TABLE

Table 1 Document history

Document	Date
Amendment 1	15-JUN-2020
Protocol Version 1	07-JUN-2019

Amendment 1: 15-JUN-2020

Overall rationale for the current Amendment:

The purpose of the amendment is to:

- **Outline measures to be applied during special circumstances (e.g., COVID-19 pandemic), to protect participant's welfare and safety, and, as far as possible, to ensure the potential benefit to the participant and promote study integrity.**
- Define study procedures / assessments to allow participation of non-revaccinated subjects in an extended long-term follow-up phase.
- Minor corrections and clarifications

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

Section # and Name	Description of Change	Brief rationale
Section 8.1.16 Study procedures during special circumstances	Added new	To provide guidance on adapting study procedures during special circumstances, such as COVID-19 pandemic
Across the document, including objectives and endpoints sections	Revised text or added new text for non-revaccinated subjects	To nuance differences in study procedures / assessments for non-revaccinated subjects

Amended text is indicated in ***bold italics*** in the body of the protocol. Detailed description of the main change is provided in *Appendix 9*.

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1. SYNOPSIS

Indication:

The target indication for *Shingrix* is prevention of Herpes Zoster (HZ) and related complications in adults aged 50 years and older, and in immunocompromised adults aged 18 years and older.

Rationale:

In the study ZOSTER-041, GSK's adjuvanted recombinant HZ subunit vaccine (HZ/su) demonstrated a clinically acceptable safety profile and induced significant and durable humoral and cell-mediated immune responses up to 1 year of follow-up when given as a 2-dose primary vaccination series, 1 to 2-month apart, in renal transplant (RT) subjects (≥18 years of age [YOA]) taking daily chronic immunosuppressive (CIS) therapy [Vink, 2019].

Study ZOSTER-073 is designed to provide data on the persistence of HZ/su vaccine-induced immune response at 4 – 7 years after a 2-dose primary HZ/su vaccination in RT subjects on CIS therapy. This study will also investigate the immune response after revaccination with HZ/su vaccine.

In studies in subjects ≥50 YOA, a single revaccination dose of HZ/su was shown to boost the HZ/su immune responses when given at 10 years after the 2-dose primary vaccination series [ZOSTER-060 study]. In a CIS-treated IC population, a single revaccination dose might be insufficient and 2 additional doses may be required to boost and maintain the immune response to HZ.

Therefore, study ZOSTER-073 is designed to assess the immunogenicity and safety of two revaccination doses of HZ/su, when given 1-2 month apart, approximately 7 years after primary vaccination of RT subjects taking daily CIS therapy.

Study ZOSTER-073 will provide insights into HZ/su-induced immune responses in the RT population and, potentially, in other immunocompromised populations including SOT, AID, IID subjects receiving CIS.

Objectives and Endpoints (Amended: 15 June 2020):

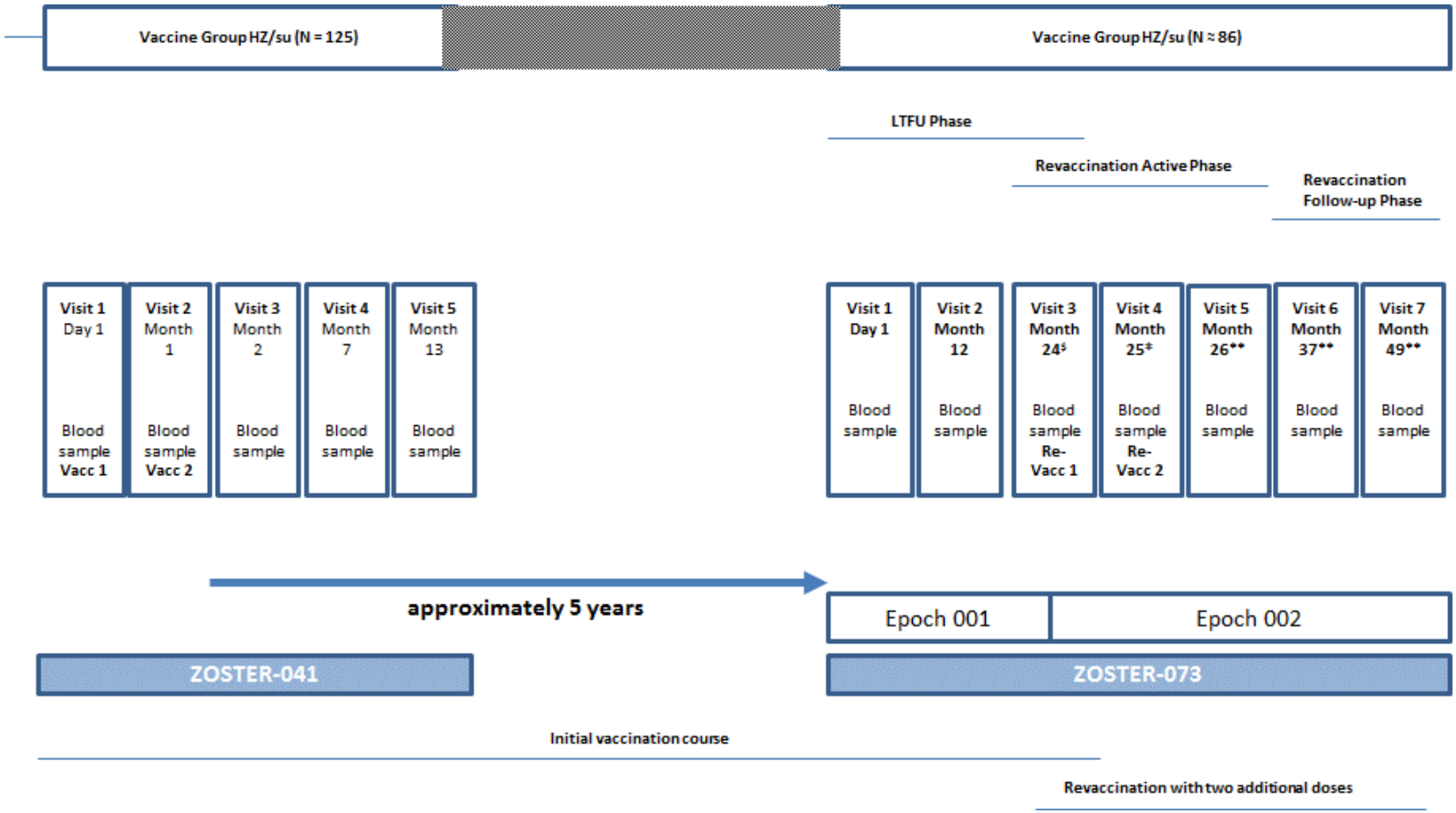
Objectives	Endpoints
Primary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of humoral immunity after primary vaccination course.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 12 and Month 24.
Revaccination active phase - Immunogenicity assessment • To evaluate humoral immunity of HZ/su vaccine post-revaccination Doses 1 & 2.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at pre-revaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
Secondary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of cellular immunity after primary vaccination course.	***In CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at Day 1, Month 12 and Month 24.
LTFU phase - safety assessment • To evaluate safety of HZ/su vaccine from the study ZOSTER-041 last visit to study ZOSTER-073 Visit 3.	***In all subjects:*** • Related-SAEs – Occurrence of SAEs related to primary vaccination as assessed by the investigator from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • HZ episodes – Occurrence of suspected or confirmed HZ cases from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of confirmed HZ cases from Day 1 through Month 24. • AESIs – Occurrence of suspected or biopsy-proven allograft rejections from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of biopsy-proven allograft rejections from Day 1 through Month 24. • Allograft function for episode(s) of allograft rejection. – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic immunosuppressive therapy for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ rash resolution for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24).

Objectives	Endpoints
Revaccination active phase - Immunogenicity assessment • To evaluate cell-mediated immunity post- revaccination Doses 1 & 2.	***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at pre-vaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
Revaccination follow-up phase – Immunogenicity assessment • To evaluate persistence of humoral and cell-mediated immune responses post-revaccination Dose 2.	***In all revaccinated subjects:*** • Anti-gE antibody concentrations as determined by ELISA at 12 months and 24 months post-revaccination Dose 2. ***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T- cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at 12 months and 24 months post-revaccination Dose 2 in a CMI sub-cohort of subjects.
Revaccination active and follow-up phases - Safety assessment • To evaluate reactogenicity and safety of the HZ/su vaccine after each revaccination.	***In all revaccinated subjects:*** • Solicited local and general AEs: – Occurrence, duration and intensity of solicited local AEs within 7 days after each revaccination (i.e., the day of revaccination and 6 subsequent days); – Occurrence, duration and intensity of solicited general AEs within 7 days after each revaccination dose (i.e., the day of revaccination and 6 subsequent days) and causal relationship to revaccination by investigator assessment. • Unsolicited AEs – Occurrence, intensity of unsolicited AEs during 30 days after each revaccination (i.e., the day of revaccination and 29 subsequent days) and causal relationship to revaccination by investigator assessment. • SAEs – Occurrence of SAEs (including fatal SAEs) from Dose 1 of revaccination (Month 24) until 12 months post-last revaccination dose (Month 37). – Occurrence of related-SAEs (including related-fatal SAEs) as per investigator assessment from Dose 1 of revaccination (Month 24) up to study end (Month 49). • AESIs – Occurrence of all biopsy-proven allograft rejections from Dose 1 of revaccination (Month 24) up to study end (Month 49) and causal relationship to revaccination by investigator assessment. – Occurrence of pIMDs from Dose 1 of revaccination (Month 24) up to 12 months post-last revaccination dose (Month 37) and causal relationship by investigator assessment. • HZ episodes – Occurrence of confirmed HZ cases from Dose 1 of revaccination (Month 24) up to study end (Month 49). • Allograft function following revaccination – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 3 months before the first revaccination dose until 3 months after the last revaccination dose.

Objectives	Endpoints
	• Allograft function for episode(s) of allograft rejection – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic of immunosuppressive therapy. • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ resolution.
CCI [redacted]	

CMI = Cell-Mediated Immunity CCI [redacted] **ELISA** = Enzyme Linked Immunosorbent Assay; **gE** = glycoprotein E; CCI [redacted]; **ICS** = Intracellular Cytokine Staining; **IL-2** = Interleukin 2; CCI [redacted]; CCI [redacted]; CCI [redacted]
TNFα = Tumor Necrosis Factor-alpha; **IFNγ** = Interferon-gamma; AE = Adverse Event; **SAE** = Serious Adverse Event; **HZ** = Herpes Zoster; **AESI** = Adverse Event of Special Interest; **pIMDs** = potential Immune-Mediated Diseases
*To be performed by *a* central laboratory if deemed necessary.
(Amended: 15 June 2020)

Overall Design:



HZ/su = Herpes zoster subunit; **LTFU** = Long term follow-up; **Vacc 1-2** = Vaccination dose 1 & 2; **re-Vacc** 1-2 = Revaccinations dose 1 & 2
*The second dose of revaccination (Visit 4, Month 25) will be administered 1 to 2 months after the first revaccination dose.
**Visit 5 (Month 26), Visit 6 (Month 37) and Visit 7 (Month 49) will occur 1, 12 and 24 months after the second revaccination, respectively.
$Phone contact will occur about 35 days before Visit 3 (Month 24) to remind female subjects of childbearing potential to use adequate contraception.

2. SCHEDULE OF ACTIVITIES (SOA)

Table 3 Schedule of activities

Epoch	*Epoch 001*			*Epoch 002*					
Study Phase	**Long-Term Follow-up Phase**			**Revaccination Phase**			**Follow-up Phase**		
Type of contact	**Visit 1**	**Visit 2**	**PC1[a]**	**Visit 3[b]**	**Visit 4[c, h]**	**Visit 5[c, h]**	**Visit 6[c]**	**Visit 7[c]**	***Ad-hoc* HZ Visit [d]**
Timepoints by study Year	**Day 1**	**Year 1**	**35 days prior Year 2**	**Year 2**	**Year 2 + 1 month**	**Year 2 + 2 months**	**Year 3 + 2 months**	**Year 4 + 2 months**	
Timepoints by study Month	**Day 1**	**Month 12**	**Day 695**	**Month 24**	**Month 25**	**Month 26**	**Month 37**	**Month 49**	**Event driven**
Timepoints associated to Long-Term Follow-up Phase (Post-primary vaccination in study ZOSTER-041)	**About 4-5 years post-last HZ/su dose**	**About 5-6 years post-last HZ/su dose**	**About 6-7 years post-last HZ/su dose**						
Timepoints associated to Revaccination Phase in study ZOSTER-073				**Pre-Revacc 1**	**Post-Revacc 1**	**Post-Revacc 2**			
Informed consent (section 12.4.3)	●			●* [f]					
Collect demographic data (section 8.1.2)	●								
Check inclusion/exclusion criteria for enrollment (section 6.1.1 and 6.2.1)	●								
Check inclusion/exclusion criteria for revaccination (section 6.1.2 and 6.2.2)				●*					
Medical history including medications, vaccinations, HZ cases, pIMDs and RT rejections (section 8.1.3)	●								
Interim medical history (section 8.1.4) **(Amended: 15 June 2020)**		O		O	O	O	O	O	
Record transplant specific information, if subject received a new transplant since the last visit in ZOSTER-041 (section 8.1.5)	●								

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Epoch	*Epoch 001*			*Epoch 002*					
Study Phase	**Long-Term Follow-up Phase**			**Revaccination Phase**			**Follow-up Phase**		
Type of contact	**Visit 1**	**Visit 2**	**PC1[a]**	**Visit 3[b]**	**Visit 4[c, h]**	**Visit 5[c, h]**	**Visit 6[c]**	**Visit 7[c]**	***Ad-hoc* HZ Visit [d]**
Timepoints by study Year	**Day 1**	**Year 1**	**35 days prior Year 2**	**Year 2**	**Year 2 + 1 month**	**Year 2 + 2 months**	**Year 3 + 2 months**	**Year 4 + 2 months**	
Timepoints by study Month	**Day 1**	**Month 12**	**Day 695**	**Month 24**	**Month 25**	**Month 26**	**Month 37**	**Month 49**	**Event driven**
Physical examination (section 8.1.6)	●			●*					
History directed physical examination (section 8.1.6)		●			●*	●	●	●	●
Record weight (section 8.1.6)	●	●		●	●	●	●	●	●
Remind females of childbearing potential to use adequate contraception.			O	O	O				
Check contraindications to subsequent vaccination (section 7.7)					O*				
Check criteria for temporary delay for re-vaccination (section 6.3)				O*	O*				
Urine pregnancy test for females of childbearing potential [g]				●*	●*				
Record pre-revaccination temperature				●*	●*				
Biological sampling Phlebotomy for a:									
Blood sample for humoral immune response from all subjects (~5 mL)	●	●		●*	●*	●	●	●	
Blood sample for CMI response from CMI sub-cohort (~30 mL)	●	●		●*	●*	●	●	●	
CCI [redacted]				●*	●*	●	●	●	
Vaccine									
Record treatment number				●	●				
Vaccine administration				●	●				

Epoch	*Epoch 001*			*Epoch 002*					
Study Phase	**Long-Term Follow-up Phase**			**Revaccination Phase**			**Follow-up Phase**		
Type of contact	**Visit 1**	**Visit 2**	**PC1[a]**	**Visit 3[b]**	**Visit 4[c, h]**	**Visit 5[c, h]**	**Visit 6[c]**	**Visit 7[c]**	***Ad-hoc* HZ Visit [d]**
Timepoints by study Year	**Day 1**	**Year 1**	**35 days prior Year 2**	**Year 2**	**Year 2 + 1 month**	**Year 2 + 2 months**	**Year 3 + 2 months**	**Year 4 + 2 months**	
Timepoints by study Month	**Day 1**	**Month 12**	**Day 695**	**Month 24**	**Month 25**	**Month 26**	**Month 37**	**Month 49**	**Event driven**
Safety assessments									
Record clinically and locally obtained serum creatinine measures (section 8.1.9)	●	●		●	●	●	●	●	●
CCI [redacted]	●	●		●	●	●	●	●	
Record any medications / vaccinations 30 days before each study visit (section 7.5)	●	●							
Record any concomitant medications/ vaccinations (section 7.5)				●	●	●	●	●	●
Distribution of HZ-specific diary cards and ZBPI questionnaires and Train subjects on completion of the HZ-specific diary card and ZBPI questionnaire (section 8.1.12.1).	O	O		O			O		O
Distribution of diary cards for recording of solicited and unsolicited AE (and train on completion as necessary) (section 8.1.12.1)				O	O				
Return of diary cards					O	O			
Transcription of solicited AEs reported within 7 days post-vaccination					●	●			
Transcription of non-serious unsolicited AEs reported within 30 days post-vaccination					●	●			
Record AEs/SAEs leading to withdrawal from study	●	●		●	●	●	●	●	

Epoch	*Epoch 001*			*Epoch 002*					
Study Phase	**Long-Term Follow-up Phase**			**Revaccination Phase**			**Follow-up Phase**		
Type of contact	**Visit 1**	**Visit 2**	**PC1[a]**	**Visit 3[b]**	**Visit 4[c, h]**	**Visit 5[c, h]**	**Visit 6[c]**	**Visit 7[c]**	***Ad-hoc* HZ Visit [d]**
Timepoints by study Year	**Day 1**	**Year 1**	**35 days prior Year 2**	**Year 2**	**Year 2 + 1 month**	**Year 2 + 2 months**	**Year 3 + 2 months**	**Year 4 + 2 months**	
Timepoints by study Month	**Day 1**	**Month 12**	**Day 695**	**Month 24**	**Month 25**	**Month 26**	**Month 37**	**Month 49**	**Event driven**
Record SAEs and pIMDs post- revaccination (section 12.5.9)				•	•	•	•		
Record pregnancies and pregnancy outcomes (sections 8.1.13 and 12.5.9.1)	•	•		•	•	•	•	•	
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	•	•		•	•	•	•	•	
Record SAEs related to study vaccine (section 12.5.9)	•	•		•	•	•	•	•	
Record intercurrent medical conditions, including HZ cases (section 7.6)	•	•		•	•	•	•	•	
Record AESI: biopsy-proven allograft rejection (section 8.1.14)	•	•		•	•	•	•	•	
HZ assessments only in case of a clinically diagnosed suspected HZ									
Return HZ-specific diary cards and ZBPI questionnaires to study staff/investigator									O
Transcription of the HZ-specific diary card and ZBPI questionnaires by study staff/investigator [e]		•		•	•	•	•	•	•
Take digital photographs of HZ rash and upload to e-Clinipix (section 8.1.15)									•
Collect HZ lesion samples (from 3 separate lesions) for confirmation by PCR (section 8.1.15)									•
Record relevant information regarding HZ [e]		•		•	•	•	•	•	•
Record any medical attention received for HZ or any HZ-related complication									•

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Epoch	*Epoch 001*			*Epoch 002*					
Study Phase	**Long-Term Follow-up Phase**			**Revaccination Phase**			**Follow-up Phase**		
Type of contact	**Visit 1**	**Visit 2**	**PC1[a]**	**Visit 3[b]**	**Visit 4[c, h]**	**Visit 5[c, h]**	**Visit 6[c]**	**Visit 7[c]**	***Ad-hoc* HZ Visit [d]**
Timepoints by study Year	**Day 1**	**Year 1**	**35 days prior Year 2**	**Year 2**	**Year 2 + 1 month**	**Year 2 + 2 months**	**Year 3 + 2 months**	**Year 4 + 2 months**	
Timepoints by study Month	**Day 1**	**Month 12**	**Day 695**	**Month 24**	**Month 25**	**Month 26**	**Month 37**	**Month 49**	**Event driven**
Phone contact follow-up of HZ rash and HZ pain resolution (section 8.1.15) [e]		O		O	O	O	O	O	
Record the resolution date of HZ rash [e]		●		●	●	●	●	●	●
Primary Study Conclusion						●			
Final Study Conclusion								●	

Note: The double-line borders indicate analyses that will be performed on all data obtained up to this time point (refer to section 10.4).
● is used to indicate a study procedure that requires documentation in the individual electronic Case Report Form (eCRF).
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
Vacc = Vaccination; **PC** = Phone Contact; **AEs** = Adverse Events; **CMI** = Cell- Mediated Immunity; **SAEs** = Serious Adverse Events; **pIMDs** = potential Immune-Mediated Diseases; **HZ** = Herpes Zoster; **AESI** = Adverse Events of Special Interest; **RT** = Renal Transplant; **ZBPI** = Zoster Brief Pain Inventory.
* Before vaccine administration.
a Phone contact 1 (PC1) will occur about 35 days before Visit 3 (Month 24) to remind female subjects of childbearing potential to use adequate contraception.
b Visit 3 is the day of the first revaccination. Pre-revaccination and post-revaccination activities at Visit 3 are part of Epoch 001 and Epoch 002, respectively.
c Visit 4 is the day of the second revaccination that will be administered 1 to 2 months after the first revaccination. The subsequent visits (Visit 5, Visit 6 and Visit 7) will occur within 1, 12 and 24 months after the second revaccination, respectively.
d An *ad-hoc* HZ Visit will be planned in case of suspected HZ and will be scheduled preferably within 3 calendar days from appearance of HZ symptom(s).
e Study activity to be performed at the next scheduled visit, if this has not been performed during the *ad-hoc* HZ visit.
f A second written informed consent will only be obtained prior to performance of any revaccination procedures, if required by local regulatory authorities or Institutional Review Boards (IRB)/Independent Ethics Committees (IEC).
g Blood sample ***is substituted for urine sample*** for pregnancy ***testing as*** required by country, local or ethics committee regulations. ***Pregnancy testing should be completed, and results reviewed prior to revaccination.***
[h] For non-revaccinated subjects (see Glossary of terms ***for the definition and Section 8.1, for details), Visit 4 and 5 will not occur.***
For non-revaccinated subjects, see Section 8.1.
Note:
In times of special circumstances, refer to Section 8.1.16 for study procedures.
(Amended: 15 June 2020)

Whenever possible, the investigator should arrange study visits within the intervals described in Table 4.

Table 4 Intervals between study visits

Interval	Optimal length of interval [a]	Allowed interval (days) [b]
Visit 1 (Day 1) →Visit 2 (Month 12)	12 months (360 days)	330 - 415
Visit 1 (Day 1) → Visit 3 (Month 24)	24 months (720 days)	690 - 775
PC 1 (Day 695) →Visit 3 (Month 24)	35 days	31 - 40
Visit 3 (Month 24) →Visit 4 (Month 25)	30[c] days	30 - 60
Visit 4 (Month 25) → Visit 5 (Month 26)	30 days	30 - 48
Visit 4 (Month 25) → Visit 6 * (Month 37)	12 months (360 days)	330 - 415
Visit 4 (Month 25) → Visit 7 * (Month 49)	24 months (720 days)	690 - 775

PC 1 = Phone Contact 1

a. Whenever possible the investigator should arrange study visits within this interval.

b. The investigator should endeavour to have the subjects come in for the visits within this interval. However, subjects may not necessarily be excluded from the PPS for analysis of immunogenicity if they make the study visit outside this interval.

c. The second dose will be administered 1 to 2 months (30 to 60 days, inclusive) after the first dose.

**** The allowed interval for Visits 6 and 7 should be the same for both the re-vaccinated and non-revaccinated subjects.***

In times of special circumstances, refer to Section 8.1.16 for allowed interval between study visits.

(Amended: 15 June 2020)

3. INTRODUCTION

3.1. Study rationale

Despite significant medical need, currently no prophylactic vaccine is available for prevention of HZ in immunocompromised subjects aged 18-49 YOA, including RT subjects taking daily CIS therapy.

Live attenuated VZV vaccines are contraindicated in immunodeficient or immunosuppressed individuals due to underlying disease or IS therapy [Zostavax US Prescribing Information, 2013; Zostavax Summary of Product Characteristics, 2013].

Shingrix (GSK), an adjuvanted recombinant VZV-gE subunit vaccine (gE/AS01$_B$), hereafter referred to as HZ/su, is licensed in multiple countries for the prevention of HZ and post-herpetic neuralgia (PHN) in older adults (≥ 50 YOA). Since HZ/su vaccine does not contain live virus, it is not contraindicated in case of immunosuppression or immunodeficiency.

The HZ/su vaccine is immunogenic and has demonstrated vaccine efficacy of > 90% in older subjects (≥ 50 YOA) [Lal, 2015; Cunningham, 2016] and 68% in IC subjects (≥ 18 YOA) with autologous hematopoietic stem cell transplantation (HSCT) [ZOSTER-002]. The safety profile of HZ/su vaccine was clinically acceptable in these populations [Lal, 2015; Cunningham, 2016; Dagnew, 2018; de la Serna, 2018; Stadtmauer, 2014; Sullivan, 2018, Cunningham, 2018; López-Fauqued, 2019].

Studies using non-adjuvanted vaccines against common infectious diseases have shown variable and often suboptimal humoral and CD4+T-cell responses when administered in the presence of daily CIS therapy, regardless of the underlying disease, e.g. SOT, AID or other IID. The variable immune response has been suggested to be secondary to direct interference by CIS therapies [Mulley, 2012; Salles, 2010; Orcurto, 2012].

Reports describing alloimmunity in SOT subjects temporally associated with administration of AS03-adjuvanted pandemic H1N1 vaccine prompted an in-depth investigation of this potential safety signal, including the conduct of a retrospective pharmaco-epidemiological study. Based on all accumulated evidence, SOT rejection was not considered a potential risk following vaccination with AS03-adjuvanted A/H1N1 pandemic influenza vaccines [Dos Santos, 2017].

A placebo-controlled study to ascertain the effect of vaccination with HZ/su on both the immune responsiveness of chronically immunosuppressed SOT subjects and on their allografts' safety was conducted [Vink, 2019].

Study ZOSTER-041 assessed safety and humoral and cell-mediated immunogenicity induced by two doses of HZ/su vaccine given 1 to 2-month apart in RT subjects (≥ 18 YOA) taking daily CIS therapy. This study, in which 132 subjects received the HZ/su vaccine, has shown that HZ/su vaccine can induce a strong and persistent immune response up to one-year post-vaccination without increasing the risk of allograft rejection or allograft dysfunction. No safety concerns, including biopsy-proven allograft rejections, were identified in comparison to placebo subjects [Vink, 2019].

In studies in subjects ≥ 50 YOA, a single revaccination dose of HZ/su was shown to boost the HZ/su immune responses when given at 10 years after the 2-dose primary vaccination series [ZOSTER-060]. In a CIS treated-IC population, a single revaccination dose might be insufficient and 2 additional doses may be required to boost and maintain the immune response to HZ.

Study ZOSTER-073 is designed to provide data on the persistence of HZ/su vaccine-induced immune response at 4 – 7 years after a 2-dose primary HZ/su vaccination in RT subjects on CIS therapy. This study will also investigate the immune response after revaccination of RT subjects on CIS therapy with HZ/su.

Eligible RT subjects who participated in the HZ/su treatment group of study ZOSTER-041 and who had a complete vaccination course (2 doses of HZ/su vaccine) will be offered enrollment into study ZOSTER-073, approximately 5 years after their primary vaccination course. Medical history of subjects will be collected to assess HZ cases and RT rejections from last visit in study ZOSTER-041 to time of enrollment in study ZOSTER-073. Confirmed HZ cases and RT biopsy-proven rejections will be collected prospectively throughout study ZOSTER-073. Cell-mediated and humoral immunogenicity will be assessed in the long-term follow-up and revaccination phases.

Even though an immunologic threshold of protection has not been identified, these data will evaluate the potential of HZ/su vaccine in providing long-term immunity against HZ in RT subjects (≥18 years) on daily CIS therapy. This study may also provide insight on the use of HZ/su vaccine in other populations receiving daily CIS therapy, such as other SOT subjects and, potentially, subjects with AID and IID under CIS therapy.

3.2. Background

VZV causes two distinct diseases. Varicella (chickenpox) occurs shortly after primary VZV infection and is characterized by systemic illness and a widely disseminated rash. HZ (shingles) occurs when VZV reactivates from latency. Vaccination as a means of reducing the risk of HZ has been examined in both ≥50 YOA and IC subjects ≥18 YOA.

Shingrix (GSK), a licensed vaccine for prevention of HZ in adults ≥50 YOA, is a recombinant subunit (su) vaccine (HZ/su) consisting of VZV glycoprotein E (gE) as antigen (50 µg) and the adjuvant $AS01_B$ [liposomes in combination with 50 µg 3-O-desacyl-4'-Monophosphoryl Lipid A (MPL) and 50 µg *Quillaja saponaria* Molina, fraction 21 (QS21) per 0.5 mL dose].

HZ/su vaccine induces strong gE-specific humoral and CD4+ T-cell responses through its adjuvant system $AS01_B$, and is efficacious in subjects with weakened immune system, in particular subjects ≥ 50YOA and IC population ≥ 18YOA.

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

3.2.1. Herpes Zoster

HZ is characterized by rash, pain, and pruritus. The typical HZ rash, generally blisters in a localized, dermatomal band on one side of the body, lasts 2 to 4 weeks and is accompanied by severe pain that is often described as burning, shooting, or stabbing. In some subjects, even light touching of the affected area may cause pain, a phenomenon known as allodynia. Pruritus, which can also be severe, may be as common as pain. Pain that persists after the resolution of the HZ rash is called PHN.

While it is not known what triggers the reactivation of VZV and the subsequent development of HZ, it is clear that subjects with impaired cell-mediated immunity (CMI) due to advanced age, malignancy, including hematologic malignancy, HIV infection, organ transplantation, immunodeficiency, autoimmune disease, and treatment with immunosuppressive therapies, are at increased risk for the development of HZ [Cohen, 2007; Schmipff, 1972; Rusthoven, 1988; Hata, 2011].

3.2.2. Herpes Zoster in Solid Organ Transplant subjects

SOT subjects represent a distinct group of subjects with regard to their CMI. Most SOTs are allogeneic, that is the transplantation of organs with a different genotype from one individual to another. Transplant subjects receive immunosuppressive therapy,

chronically, to prevent rejection of these genetically different engrafted organs [EMA, 2008].

Secondary to their CIS, SOT subjects are at increased risk of developing HZ. Three large SOT studies from North America indicate HZ incidence rates in transplant subjects of approximately 8 to 9 times the 3.2 per 1000 person-years estimated for the general US population [Insinga, 2005]. A large single center study from the University of Alberta Hospital, Edmonton, Canada, which included 869 SOT subjects, reported the percentage of subjects with HZ following transplantation of 8.6% for overall SOTs and 7.4% for RTs. The mean time of HZ onset post-transplantation was 13.9 months for SOTs and 15.5 months for RT subjects. The overall HZ incidence rate in SOT subjects was 27.2 per 1000 person-years [Gourishankar, 2004]. Another single center study, conducted at the Mayo Clinic, in Rochester, Minnesota, of 612 RTs, reveals a HZ incidence rate of 28 per 1000 person-years following transplantation. Furthermore, subjects younger than 60 years had an incidence rate of 23 per 1000 person-years whereas subjects of 60 years or more had an incidence rate of 41 per 1000 person-years [Arness, 2008]. A large multicenter study conducted by the US Department of Veterans Affairs of 1077 SOT subjects reported the percentage of HZ of 8.3% overall and 9.0% for RTs. The HZ incidence rate for SOT was 22.2 per 1000 patient-years and for RT subjects was 24.4 per 1000 patient-years. Multivariate modelling revealed that African Americans and older transplant subjects had increased relative hazards of HZ [Pergam, 2011].

The increased incidence rate of HZ within SOT subjects on CIS establishes the basis for evaluating GSK's candidate HZ/su vaccine in this population.

3.3. Benefit/Risk assessment

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

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

3.3.1. Risk assessment

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational vaccine		
Hypersensitivity including allergic reaction such as anaphylaxis	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied [Ruggerberg, 2007].	History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine is a contraindication to vaccination. The onset of vaccine-related allergic symptoms is typically quite prompt. In order to treat subjects with a serious allergic reaction to vaccination, all subjects will need to remain under observation (i.e. visibly followed; no specific procedure) at the vaccination center for at least 30 minutes after revaccination where medical equipment to treat any serious reactions is available.
Potential immune-mediated diseases (pIMDs) are a theoretical concern with adjuvanted vaccines.	Based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, pIMDs are adverse events of special interest undergoing special safety monitoring for all GSK vaccines containing Adjuvant Systems. pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology. To date, there is no evidence of an increased risk of pIMDs following vaccination with HZ/su in the populations evaluated (IC adults, adults 50 YOA or older) [López-Fauqued, 2019].	During the informed consent process, subjects will be informed of this potential risk and the need to attend the clinic for change in health status. pIMDs will be collected up to 12 months after administration of the last dose of study vaccine. The occurrence of pIMD cases during the study will be described.
Potential allograft rejection as a theoretical concern with adjuvanted vaccines in solid organ transplant subjects	To date, there is no evidence of an increased risk of allograft rejection as demonstrated in ZOSTER-041 [Vink, 2019]. Refer to section 3.1 for details.	During the informed consent process for revaccination, the subjects will be informed of this potential risk and the need to inform the clinic and seek medical attention if unwell after revaccination. Clinically management of allograft rejection will be per local standard of care and recorded as AE/SAE, as appropriate. Any renal biopsy results will be recorded to study end. The occurrence of biopsy-proven allograft rejection during the study will be described.

Important/Potential/Identified/Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Intramuscular (IM) injection	Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, redness, and swelling	All subjects will remain under observation at the vaccination center for at least 30 minutes after revaccination. Solicited local adverse events (AE) will be collected and reviewed up to Day 7.
Pain and bruising	Pain or bruising at the site where blood is drawn.	A topical analgesic may be applied to the site where blood will be taken.
Syncope	Syncope (fainting) can occur following or even before any vaccination and/or blood draw as a psychogenic response to the needle insertion.	Subject Monitoring All subjects will remain under observation at the clinical center for at least 30 minutes after revaccination.
Nerve Injury	There is a possibility that in the process of collecting blood a nerve may be injured.	Procedure to be performed by qualified personnel.
Risks from HZ rash lesion sampling	Discomfort / pain / secondary infection associated with swabbing of HZ lesions/crusts	HZ lesion samples will be obtained by a trained professional and anti-bacterial ointment may be applied to minimize the potential for secondary infection.

3.3.2. Benefit assessment

Benefits include:

- Receipt of two additional doses of HZ/su vaccine that may provide a potential clinical benefit in reducing the risk of developing HZ at long-term.
- Medical evaluations/assessments associated with study procedures (e.g. physical examination).

3.3.3. Overall Benefit: Risk conclusion

Considering the measures taken to minimise risk to subjects participating in this study, the potential or identified risks identified in association with the study HZ/su vaccine are justified by the potential benefits (prevention/treatment) that may be afforded to subjects receiving two additional doses of HZ/su vaccine.

4. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 5.

Table 5 Study objectives and endpoints (Amended: 15 June 2020)

Objectives	Endpoints
Primary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of humoral immunity after primary vaccination course.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 12 and Month 24.
Revaccination active phase - Immunogenicity assessment • To evaluate humoral immunity of HZ/su vaccine post-revaccination Doses 1 & 2.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at pre-revaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
Secondary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of cellular immunity after primary vaccination course.	***In CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at Day 1, Month 12 and Month 24.
LTFU phase - safety assessment • To evaluate safety of HZ/su vaccine from the study ZOSTER-041 last visit to study ZOSTER-073 Visit 3.	***In all subjects:*** • Related-SAEs – Occurrence of SAEs related to primary vaccination as assessed by the investigator from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • HZ episodes – Occurrence of suspected or confirmed HZ cases from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of confirmed HZ cases from Day 1 through Month 24.

Objectives	Endpoints
	• AESIs – Occurrence of suspected or biopsy-proven allograft rejections from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of biopsy-proven allograft rejections from Day 1 through Month 24. • Allograft function for episode(s) of allograft rejection. – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic immunosuppressive therapy for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ rash resolution for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24).
<u>Revaccination active phase - Immunogenicity assessment</u> • To evaluate cell-mediated immunity post- revaccination Doses 1 & 2.	***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at pre-vaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
<u>Revaccination follow-up phase – Immunogenicity assessment</u> • To evaluate persistence of humoral and cell-mediated immune responses post-revaccination Dose 2.	***In all revaccinated subjects:*** • Anti-gE antibody concentrations as determined by ELISA at 12 months and 24 months post-revaccination Dose 2. ***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T- cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at 12 months and 24 months post-revaccination Dose 2 in a CMI sub-cohort of subjects.
<u>Revaccination active and follow-up phases - Safety assessment</u> • To evaluate reactogenicity and safety of the HZ/su vaccine after each revaccination.	***In all revaccinated subjects:*** • Solicited local and general AEs: – Occurrence, duration and intensity of solicited local AEs within 7 days after each revaccination (i.e., the day of revaccination and 6 subsequent days); – Occurrence, duration and intensity of solicited general AEs within 7 days after each revaccination dose (i.e., the day of revaccination and 6 subsequent days) and causal relationship to revaccination by investigator assessment. • Unsolicited AEs – Occurrence, intensity of unsolicited AEs during 30 days after each revaccination (i.e., the day of

Objectives	Endpoints
	revaccination and 29 subsequent days) and causal relationship to revaccination by investigator assessment. • SAEs – Occurrence of SAEs (including fatal SAEs) from Dose 1 of revaccination (Month 24) until 12 months post-last revaccination dose (Month 37). – Occurrence of related-SAEs (including related-fatal SAEs) as per investigator assessment from Dose 1 of revaccination (Month 24) up to study end (Month 49). • AESIs – Occurrence of all biopsy-proven allograft rejections from Dose 1 of revaccination (Month 24) up to study end (Month 49) and causal relationship to revaccination by investigator assessment. – Occurrence of pIMDs from Dose 1 of revaccination (Month 24) up to 12 months post-last revaccination dose (Month 37) and causal relationship by investigator assessment. • HZ episodes – Occurrence of confirmed HZ cases from Dose 1 of revaccination (Month 24) up to study end (Month 49). • Allograft function following revaccination – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 3 months before the first revaccination dose until 3 months after the last revaccination dose. • Allograft function for episode(s) of allograft rejection – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic of immunosuppressive therapy. • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ resolution.

CMI = Cell-Mediated Immunity; CCI ; **ELISA** = Enzyme Linked Immunosorbent Assay; **gE** = glycoprotein E; CCI ; **ICS** = Intracellular Cytokine Staining; **IL-2** = Interleukin 2; CCI ; CCI ; CCI
TNFα = Tumor Necrosis Factor-alpha; **IFNγ** = Interferon-gamma; **AE** = Adverse Event; **SAE** = Serious Adverse Event; **HZ** = Herpes Zoster; **AESI** = Adverse Event of Special Interest; **pIMDs** = potential Immune-Mediated Diseases.
*To be performed by *a* central laboratory if deemed necessary.
(Amended: 15 June 2020)

5. STUDY DESIGN

5.1. Scientific rationale for study design

This study will evaluate the persistence of gE-specific immunogenicity after the primary 2-dose HZ/su vaccination in study ZOSTER-041 and the effect on immunogenicity and safety of revaccination with two additional doses of HZ/su vaccine after approximately 7 years in ZOSTER-041 in RT subjects taking daily CIS therapy. Study ZOSTER-073 will provide insights into HZ/su-induced immune responses in the RT population and, potentially, in other immunocompromised populations including SOT, AID, IID subjects receiving CIS.

Former study ZOSTER-041 subjects who received two doses of HZ/su vaccine will be offered enrollment into study ZOSTER-073 at participating centers.

Study ZOSTER-073 has three distinct phases:

- In the long-term follow-up (LTFU) phase, subjects will be followed for two years* (Day 1 to Month 24). Over the same time period, the occurrences of confirmed HZ cases and biopsy-proven RT rejections will be prospectively collected. Whereas, the occurrences of confirmed/suspected HZ cases; and RT rejections will be retrospectively collected back to subjects' study ZOSTER-041 last visit. **(Amended: 15 June 2020)**

  **** Subjects who are ineligible for revaccination or unwilling to receive revaccination (hereafter referred to as non-revaccinated subjects, see*** Glossary of terms***) will be invited to be followed in an extension of the LTFU phase for a total of 4 years (Day 1 to Month 49), with safety and immunogenicity assessments at Months 37 and 49.***

- In the revaccination active phase (Months 24 through 26), subjects will receive two additional doses of HZ/su vaccine, administered on a 1 to 2-month apart schedule at Months 24 and 25. Safety and immunogenicity assessments will be performed 1 month post-revaccination Doses 1 and 2 at Months 25 and 26, respectively.
- In the revaccination follow-up phase (Month 26 to study end), safety and immunogenicity following revaccination will be prospectively monitored at Months 37 and 49 (i.e. 12 and 24 months post-revaccination Dose 2).

In study ZOSTER-073, the occurrence of HZ episodes will be collected and confirmed by molecular biology tests (HZ PCR testing) and the HZ Ascertainment Committee (HZAC) decision (see section 12.2.2 for details).

5.2. Scientific rationale for the non-use of control group

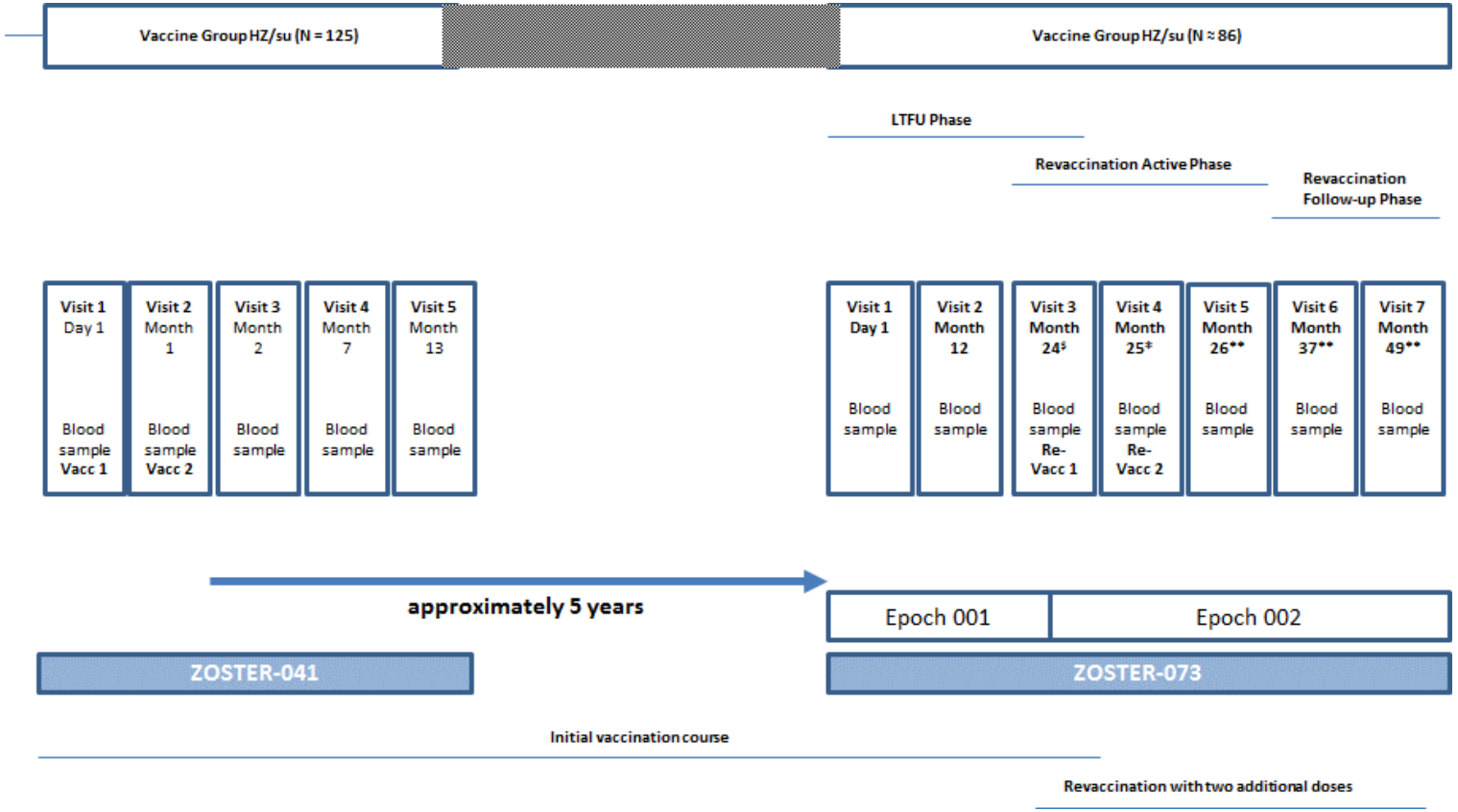
Study ZOSTER-073 has no control group for the following reasons:

- The use of varicella zoster virus live-virus vaccines (ZVLs) is contraindicated in RT subjects.

  This is an extension study of the study ZOSTER-041 in which the immunogenicity and safety of HZ/su vaccine were tested in 264 RT subjects who either received HZ/su vaccine or placebo on a 0, 2-month schedule. The immunogenicity of the placebo group showed consistent baseline values up to 1 year of follow-up and in both study groups, no safety concerns, including biopsy-proven rejections, were identified [Vink, 2019].

5.3. Overall design

Figure 1 Study design overview



HZ/su = Herpes zoster subunit; LTFU = Long term follow-up; Vacc 1-2 = Vaccination dose 1 & 2; re-Vacc 1-2 = Revaccinations dose 1 & 2
*The second dose of revaccination (Visit 4, Month 25) will be administered 1 to 2 months after the first revaccination dose.
**Visit 5 (Month 26), Visit 6 (Month 37) and Visit 7 (Month 49) will occur 1, 12 and 24 months after the second revaccination, respectively.
$Phone contact will occur about 35 days before Visit 3 (Month 24) to remind female subjects of childbearing potential to use adequate contraception.

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (SoA) (see Section 2), are essential and required for study conduct. ***In times of special circumstances, refer to Section 8.1.16 for study procedures.*** **(Amended: 15 June 2020)**

- **Type of study:** extension of other protocol(s); ZOSTER-041 for the analysis of long term immunogenicity and safety.
- **Experimental design**: Phase IIIB, open-label, uncontrolled, multi-centric, single group study.
- **Duration of the study:** The study duration per subject will be approximately 49 months.
  - Epoch 001: LTFU phase starting at Visit 1 (Day 1) and ending at Visit 3 (Month 24)
  - Epoch 002: Revaccination phase starting at Visit 3 (Month 24) and ending at Visit 7 (Month 49)
- **Primary completion Date (PCD):** Visit 5 (Month 26).

  Refer to glossary of terms for the definition of PCD.
- **End of Study (EoS):** Release of laboratory results through Visit 7 (Month 49).

  Refer to glossary of terms for the definition of EoS.
- **Study group:**

Table 6 Study group, treatment and epochs foreseen in the study

Study groups*	Number of subjects	Age (Min-Max)**	Treatment name	Epochs	
	From ZOSTER-041 primary study			Epoch 001 (open)	Epoch 002 (open)
HZ/su	86	20 years - 82 years	HZ/su	●	●

HZ/su = Herpes Zoster subunit vaccine.
*HZ/su Group name for subjects who were vaccinated with 2 doses of HZ/su in study ZOSTER 041.
**Age at the first vaccination in study ZOSTER-041.

- **Control**: uncontrolled.
- **Revaccination schedule**: Subjects will receive two additional doses of the HZ/su vaccine, at Visit 3 (Month 24) and at Visit 4 (Month 25) in the revaccination phase.
- **Treatment allocation:** All eligible subjects will be enrolled into HZ/su group.
- **Blinding:** Open-label

  For a detailed description of treatment allocation, refer to section 7.2.

- **Sampling schedule**:
  - Blood samples to assess humoral immunogenicity will be collected ***from*** all subjects at Visit 1 (Day 1), Visit 2 (Month 12), Visit 3 (Month 24), Visit 4 (Month 25)*, Visit 5 (Month 26)*, Visit 6 (Month 37) and Visit 7 (Month 49). **(Amended: 15 June 2020)**
  - Blood samples to assess CMI responses will be collected in the CMI sub-cohort at Visit 1 (Day 1), Visit 2 (Month 12), Visit 3 (Month 24), Visit 4 (Month 25)*, Visit 5 (Month 26)*, Visit 6 (Month 37) and Visit 7 (Month 49). **(Amended: 15 June 2020)**

CCI [redacted]

Blood samples will not be collected at Visit 4 and Visit 5 from non-revaccinated subjects. Refer to Section 7 for more details.

  - Clinical specimens of HZ lesions (from 3 separate lesions) will be collected from subjects clinically diagnosed as having a suspected case of HZ.
  - A urine sample (blood sample only if required by country, local or ethics committee regulations) will be collected from all female subjects of childbearing potential before revaccination at Visit 3 (Month 24) and Visit 4 (Month 25) for pregnancy testing.
- **Data collection**: electronic Case Report Form (eCRF).
  - Solicited and unsolicited AEs will be collected using a subject Diary (paper Diary) and transcribed into eCRF.
  - In the event of suspected HZ, the HZ clinical course will be collected using a HZ-specific Diary and Zoster Brief Pain Inventory (ZBPI) questionnaire and transcribed into eCRF.
- **Safety monitoring**: An internal safety review team (SRT, study team members) will review available safety data on a regular basis throughout the study. Any potential safety concern identified will be escalated to higher governing bodies as per internal GSK process.

5.4. Number of subjects

Former study ZOSTER-041 subjects, who have a complete primary vaccination course (2 doses of HZ/su vaccine) will be offered enrollment into study ZOSTER-073 at participating centers.

Up to a maximum of 86 subjects will be targeted for enrollment. Assuming full enrollment and considering a 15% drop-out rate (including subjects not eligible in the per-protocol set), approximately 73 evaluable subjects are expected to complete the study.

Refer to Section 10.1 for further information on sample size determination.

Withdrawals will not be replaced.

Overview of the recruitment plan

The study will include subjects in multiple centers in countries that previously participated in study ZOSTER-041.

At the time of initiation of study ZOSTER-073, the investigator will contact ONLY those subjects who had a complete HZ/su vaccination course (2 doses of HZ/su vaccine) in study ZOSTER-041 and who expressed a willingness to participate at a potential follow-up study when questioned at the conclusion of the primary study. The reason for non-participation in study ZOSTER-073 will be documented in the site's screening log.

5.5. Subject and study completion

A subject is considered to have completed the study if he/she returns for the concluding visit (Visit 7; Month 49) as described in the protocol.

Global completion of the study is required in order to provide sufficient subjects as defined in Section 10.1 Sample Size Determination.

6. STUDY POPULATION

6.1. Inclusion criteria

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

6.1.1. Inclusion criteria for enrollment (to be checked at Visit 1)

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits). Or/and subjects' Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject/LAR(s) of the subject prior to performance of any study-specific procedure.
- Subjects who previously participated in study ZOSTER-041 and completed the full 2 dose HZ/su primary vaccination course.

6.1.2. Inclusion criteria for revaccination (to be checked at Visit 3)

All subjects must satisfy ALL enrollment criteria and the following criteria at revaccination Visit 3:

- Subjects receiving maintenance CIS therapy for the prevention of allograft rejection for a minimum of one month (30 days) prior to the first revaccination.
- Subjects without an episode of allograft rejection within 90 days prior to the first revaccination visit.
- Female subjects of non-childbearing potential may be revaccinated. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause.

  Refer to Glossary of terms for definitions of menarche and menopause.
- Female subjects of childbearing potential may be revaccinated, if the subject:
  - has practiced adequate contraception for 30 days prior to revaccination, and
  - has a negative pregnancy test on the day of revaccination, and
  - has agreed to continue adequate contraception up to 2 months after completion of the revaccination series.

  Refer to Glossary of terms for definitions of woman of child bearing potential and adequate contraception.

Note: Subjects not meeting the above inclusion criteria for revaccination may continue to participate in the study for long-term immunogenicity and safety evaluations at study Visits 6 and 7.

6.2. Exclusion criteria

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

6.2.1. Exclusion criteria for enrollment (to be checked at Visit 1)

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

6.2.1.1. Medical conditions

- Vaccination against HZ since completion of study ZOSTER-041.
- Significant underlying illness that, in the opinion of the investigator, is expected to prevent completion of the study.
- Any other condition that, in the opinion of the investigator, would interfere with the evaluations required by the study.

6.2.1.2. Prior/Concurrent clinical study experience

- Concurrently participating in another interventional vaccine or immunosuppressive clinical study, in which the subject ***is*** exposed to an investigational or a non-investigational vaccine/product* (drug) ***at any time during the ZOSTER-073 study.*** **(Amended: 15 June 2020)**

  *Allowed products: Immunosuppressant(s), which are investigational or non-registered product(s) at the local/country level, may be used if they are specifically prescribed for the prevention of allograft rejection and are:

  – available locally through compassionate use programs,

  – submitted for and pending local/country registration,

  – approved and registered for use in one or more of the other participating countries with well-documented Summary of Product Characteristics (SPC) or Prescribing Information (PI).

  The name of the active component(s) of these immunosuppressants must be provided in the concomitant medication listing.

6.2.2. Exclusion criteria for revaccination (to be checked at Visit 3)

All enrollment exclusion criteria and the following criteria should be checked at Visit 3. If ANY exclusion criterion applies, the subject must not be revaccinated.

6.2.2.1. Medical conditions

- History of confirmed HZ within one year before revaccination visit (Visit 3), i.e. HZ between Visit 2 (Month 12) and Visit 3 (Month 24).
- More than one organ transplanted (i.e. kidney-liver**,** double kidney, or kidney plus another organ(s) transplanted).
- Any additional confirmed or suspected immunosuppressive or immunodeficient condition (e.g., malignancy, HIV infection, systemic infection).
- History of any reaction or hypersensitivity (e.g. anaphylaxis) likely to be exacerbated by any component of the vaccine.
- Any other condition that, in the opinion of the investigator, would interfere with the evaluations required by the study or make vaccination unsafe.

6.2.2.2. Prior/Concomitant therapy

- Administration or planned administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months (90 days) before the first revaccination dose of study vaccine and ending at Visit 5 (Month 26).

- Use of anti-CD20 or other B-cell monoclonal antibody agents (e.g., rituximab, ocrelizumab) as maintenance and/or therapeutic immunosuppressive therapy for the prevention of allograft rejection within 9 months (274 days) of first revaccination dose of study vaccine.
- Evidence or high suspicion, in the opinion of the investigator, of noncompliance or nonadherence to use of maintenance immunosuppressive therapies.
- Planned administration/administration of a live vaccine in the period starting 30 days before the first dose and ending 30 days after the last dose of study vaccine administration.
- Planned administration/administration of a non-replicating or subunit vaccine,* not foreseen by the study protocol, in the period starting 8 days before and ending 30 days after each dose of study vaccine.

  *E.g. inactivated and subunit vaccines, including inactivated and subunit influenza vaccines and pneumococcal conjugate vaccines.

6.2.3. Other exclusion criteria for revaccination

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions up to 2 months post-revaccination Dose 2.
- Any condition which, in the judgment of the investigator, would make intramuscular (IM) injection unsafe.

If any of the above exclusion criteria are met, the subject should be encouraged to remain in the study withdrawing only from revaccination, while continuing other study procedures (see section 8.4.5). Alternatively, at the discretion of the investigator, the subject may be withdrawn from the study (see section 12.5.12).

6.3. Criteria for temporary delay for revaccination

Revaccination may be postponed within the allowed time interval (see Table 4) until transient circumstances cited below have been resolved:

- Acute disease and/or fever at the time of revaccination. Fever is defined as temperature ≥38.0°C. The preferred route for measuring temperature in this study is oral. Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be revaccinated at the discretion of the investigator.
- Allograft instability [greater than 20% variability between last two clinically obtained creatinine measurements or calculated glomerular Filtration Rates (GFR)].
- Any condition which, in the judgment of the investigator, would make IM injection unsafe.

7. TREATMENTS

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

7.1. Treatments administered

All ***eligible and willing*** subjects will receive HZ/su vaccine (for details see Table 7).
(Amended: 15 June 2020)

Table 7 Treatments administered

Study Treatment Name:	**HZ/su**
Vaccine name	VZV gE
	AS01B
Presentation	Lyophilized pellet in a monodose vial
	Liquid in a monodose vial
Vaccine formulation:	gE=50µg
	MPL=50µg; QS21=50µg; Liposomes *
Route of Administration	IM injection
Administration site:	
Location	Deltoid
Laterality **	Non-dominant
Number of doses to be administered:	2
Volume to be administered ***	0.5 ml
Packaging and Labelling	Refer to SPM for more details
Manufacturer	GSK

*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 site 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.

Refer to the Study Procedures Manual (SPM) for detailed instructions on study vaccine reconstitution.

After completing all prerequisite procedures prior to the first revaccination (including the review of inclusion and exclusion criteria [see sections 6.1 and 6.2, respectively]), one dose of study vaccine will be administered intramuscularly in the deltoid of preferably the non-dominant arm at Visit 3 (Month 24) (refer to Table 7 for details regarding the treatment administered).

After completing all prerequisite procedures prior to the second revaccination (see section 7.7 regarding the contraindications to subsequent vaccination), one dose of study vaccine will be administered intramuscularly in the deltoid of preferably the non- dominant arm at Visit 4 (Month 25) (see Table 7 for details regarding the treatment administered).

If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 4).

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

7.2. Method of treatment assignment

7.2.1. Subject identification

Subjects will receive the same subject identification numbers as in primary study ZOSTER-041.

7.2.2. Randomization of treatment

This is a single arm, open-label, non-randomized study.

7.2.2.1. Treatment Allocation to the Subject

The number of each administered treatment assigned by Source data Base for Internet Randomisation (SBIR) must be recorded in the eCRF on the Vaccine Administration screen.

7.2.3. Allocation of subjects to CMI sub-cohort

At participating centers, that have access to Peripheral Blood Mononuclear Cell (PBMC) processing facility, up to a maximum of 40 subjects will be targeted for CMI collection such that approximately 34 evaluable subjects are available for CMI analyses, considering a 15% drop-out rate (including subjects not eligible in the per-protocol set).

The CMI analyses will be performed at specified timepoints for subjects included in the CMI-sub-cohort. CMI subjects from ZOSTER-041 (n = 28) will be targeted for enrollment into the ZOSTER-073 CMI sub-cohort. The balance of CMI subjects to be enrolled will be selected at random from CMI participating centers to complete the sub-cohort up to 40 subjects at Visit 1.

7.3. Blinding and unblinding

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

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

7.4. Handling, storage and replacement of study vaccine

The study vaccine has been developed and manufactured by GSK.

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

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

For information on dosage and administration of the study vaccine, refer to Table 7. The study vaccine will be administered on Visit 3 (Month 24) and Visit 4 (Month 25).

7.4.1. Storage and handling of study vaccine

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

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

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

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

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

7.4.2. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 20% additional vaccine doses will be supplied to replace those that are unusable.

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

7.5.1. Recording of concomitant medications/products and concomitant vaccinations

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

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

- All medications/products/vaccines, except vitamins and dietary supplements, administered or taken
  - at ANY time during the period starting with the administration of revaccination Dose 1 (Month 24) and ending 30 days after revaccination Dose 2 (Month 26), and
  - for 30 days before each study visit.
- Any immunoglobulins and blood or blood products administered at and within for 90 days before any visit.
- Any long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Any use of anti-CD20 or other B-cell monoclonal antibody agents (e.g., rituximab, ocrelizumab) administered at any time during the study period.
- Any investigational medication or vaccine administered throughout the study (i.e. from Visit 1 up to study conclusion).
- Prophylactic medication is defined as medication administered in the absence of ANY symptom and in anticipation of a reaction to the revaccination.

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring at the time of revaccination.
- Medications, administered for the treatment of HZ or any related HZ complications, from Visit 1 until study conclusion.
- Following medications for biopsy-proven rejections from Visit 1 until study conclusion:
  - Maintenance IS therapy in use prior to rejection
  - Therapeutic IS therapy
  - Maintenance IS therapy resumed post-rejection
- Any concomitant medications/products/vaccines leading to the withdrawal or non-eligibility of the subject from the study (see section 7.5.2 for further details).

- Any concomitant medications/products/vaccines relevant to an SAE/Adverse Event of Special Interest (AESI) to be reported as per protocol or administered at any time during the study period for the treatment of an SAE/AESI's. In addition, concomitant medications relevant to SAEs and AESI's need to be recorded on the Expedited Adverse Event report.

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

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See section 10.2 for populations to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- Any anti-CD20 or other B-cell monoclonal antibody agents (e.g., rituximab, ocrelizumab) used at any time during the study period.
- A vaccine against HZ (including an investigational or non-registered vaccine) other than the study vaccine during the study period.
- A live vaccine administered during the period starting 30 days before the first revaccination dose and ending 30 days after the last revaccination dose*.
- An inactivated/subunit vaccine, including influenza vaccine, administered during the period starting 8 days before the first revaccination dose and ending 30 days after each revaccination*.

  *In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Summary of Product Characteristics (SmPC) or PI and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the period starting 90 days before any scheduled visit.
- Drug and/or alcohol abuse.

A detailed, comprehensive list of reasons for elimination from per-protocol analyses will be established prior to data cleaning.

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

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

IMCs are clinical events occurring in the course of the study which might alter or confound the interpretation of the immunologic (not safety) assessments of the protocol. With regards to humoral gE assessments, this includes any clinical event that might increase or decrease the level of anti-gE antibodies, such as protein losing conditions in which the loss of gamma-globulin or total proteins might underestimate the subject's gE response (e.g. protein loss conditions associated with proteinuria). Additional examples would be conditions that would cause the administration of exogenous anti-gE antibodies, resulting in an overestimate the subject's anti-gE response, such as conditions requiring the use of immunoglobulin (IV Ig) or blood products. For the CMI assessments, IMCs would be active viral infections that may alter CD4+ T cell counts and/or responses. Examples, although not exhaustive, of such acute viral infections would include acute Hepatitis A, acute Hepatitis B, new onset human immunodeficiency virus (HIV), and potentially acute cytomegalovirus (CMV) and/or Epstein Barr virus (EBV) infections.

The occurrence of an episode of HZ is an IMC, as the anti-gE antibody formed during active shingles in response to reactivation of VZV cannot be distinguished from the anti-gE antibody formed in response to vaccination. At Visit 1, all subjects will be informed of the signs and symptoms of typical HZ, provided a HZ-specific diary card and ZBPI questionnaire, and instructed to call for an appointment if HZ develops. The reporting period for cases of HZ will be from enrollment visit to study end. HZ cases will be collected in HZ specific screen in the eCRF. Note that all suspected or confirmed HZ that occurred since the primary follow-up study ZOSTER-041 will be collected retrospectively as part of the medical history.

ZOSTER-073 IMCs will be reported either as AE or SAEs (as appropriate) in the eCRF from enrollment visit (Visit 1) up to study end (Visit 7).

7.7. Contraindications to subsequent vaccine administration

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

If subjects meet any of the original exclusion criteria for revaccination or the criteria listed below, they should not receive additional dose of the HZ/su vaccine. However, the subjects should be encouraged to continue other study procedures at the discretion of the investigator (see section 8.4.5).

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

- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to section 12.5.5 for the definition of pIMDs and to Table 23 for the pIMD listing.
- Anaphylaxis, following the administration of any previous dose of HZ/su vaccine.
- Pregnancy (see section 12.5.7).
- Allograft rejection, biopsy-proven between Visits 3 and 4.
- An episode of HZ between Visits 3 and 4.

7.8. Treatment after completion of the study

During the study conclusion visit, the investigator will ask each subject/subject's LAR(s) if they are interested in participating in a long-term study. If a subject/subject's LAR(s) is not interested in participating in the long-term study the reason for refusal will be documented, when available, in the subject's eCRF.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

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

Procedures conducted as part of the subject's routine clinical management (e.g. blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

In times of special circumstances, refer to Section 8.1.16 for study procedures.
(Amended: 15 June 2020)

8.1. General study aspects

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

The SoA is provided in Table 3 and time intervals between visits are presented in Table 4.

Non-revaccinated subjects (see Glossary of terms for the definition) are not required to return for Visit 4 and Visit 5.

For these subjects, the following Visit 3 procedures will not occur:

- ***Pregnancy testing in participants unwilling to be revaccinated (see Section 8.1.7)***
- ***Temperature measurement***
- ***Revaccination***
- ***Post-revaccination solicited and unsolicited diary cards (see Section 8.1.12.1)***

(Amended: 15 June 2020)

8.1.1. Informed consent

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

Informed consent given at the enrollment visit will be reconfirmed at Visit 3 before revaccination if needed as per local requirements.

8.1.2. Collection of demographic data

Collect each subject's year of birth and record in the subject's eCRF at the enrollment visit.

Full demographic data will be utilized from the primary study, ZOSTER-041.

8.1.3. Medical history

At the enrollment visit, obtain the subject's medical and vaccination history, since the last study ZOSTER-041 visit, by interview and/or review of the subject's medical records and record in the eCRF any pre-existing conditions or signs and/or symptoms present in a subject prior to the study start.

The following medical conditions, medication(s)/product(s)/vaccine(s) will be collected and recorded:

- Chronic disorders (e.g. diabetes mellitus, chronic obstructive pulmonary disease, stroke, cardiovascular disorders, gout).
- pIMDs.
- HZ (suspected or confirmed).
- Allograft rejection(s) (suspected or biopsy-proven).
- Medications/products/vaccines (except vitamins and dietary supplements) being taken within 1 month (30 days) before the enrollment visit.
- Any immunoglobulins and blood or blood products administered at and within for 90 days before enrollment visit.
- Any long-acting immune-modifying drugs administered at and within 360 days before enrollment visit (e.g. infliximab).
- Any use of anti-CD20 or other B-cell monoclonal antibody agents (e.g., rituximab, ocrelizumab) administered at and within 360 days before enrollment visit.

8.1.4. Interim medical history

From Visit 2 to Visit 7, obtain the subject's interim medical history (history since the last study visit) by interview and/or review of the subject's medical records and record new findings or exacerbations of previous recorded conditions in source documents.

8.1.5. Record transplant-specific information in case of new transplant received since the last visit in ZOSTER-041.

In the event a subject has received a new allograft since ZOSTER-041, transplant-specific information on the new transplant must be collected.

The transplant time points of interest will be:

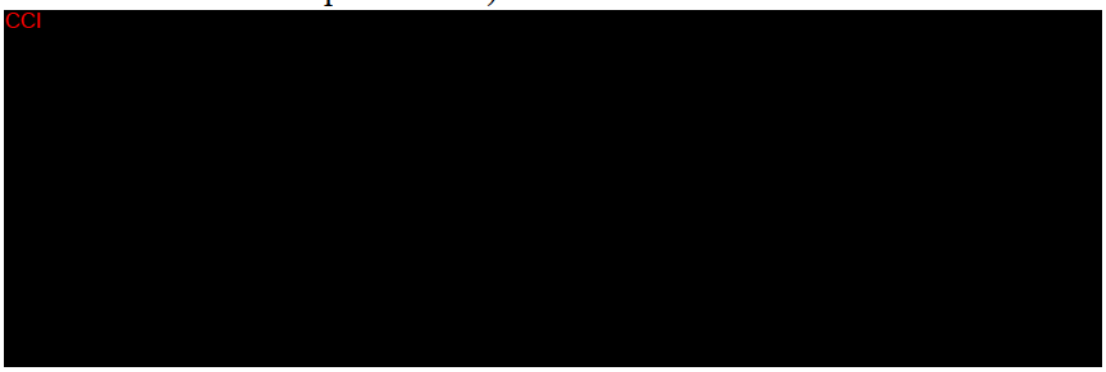
- Pre-transplantation (from a minimum of at least 6 months prior to transplantation).
- At transplantation (day prior to and day of implantation of allograft, unless otherwise specified).
- Post-transplantation (from transplant to time of re-enrollment).

Record the following transplant information (based on medical history) in the eCRF at Visit 1:

- Date of new renal transplant.

- Allograft factors:
  - Age of the allograft (years)
  - Allograft source

    Non-heart beating donations (Yes/No)
  - Allograft's class I and class II HLA antigens
- Recipient factors:
  - Primary kidney disease as indication for transplantation
  - Smoking history (cigarettes, cigars and/or pipes per day) – at transplant and post-transplant
  - Induction immunosuppressive agents used with stop dates
  - Recipient's class I and class II HLA antigens
  - Sensitisation:
    1. PRA/cPRA score – historical maximum score and pre-transplant PRA score (historical maximum PRA: maximum percentage of antibodies prior to transplantation; pre-transplant PRA: percentage of antibodies corresponding to last serum sample available)



- Transplantation factors:
  - Cold ischemic time (hours) of the allograft
  - Allograft function:
    1. Serum creatinine at and post-transplantation (see section 8.1.9)
  - Delayed allograft function – will be defined as use of dialysis after first week post-transplantation (record the actual number of days of dialysis occurring post-transplantation, from the time of transplant)
  - Current allograft biopsy(ies):
    1. Number and dates of biopsies
    2. Reason for biopsy(ies): per surveillance protocol or clinical indication
    3. Presence of biopsy confirmed rejection (acute, subclinical acute, chronic) for each biopsy

8.1.6. Physical examinations and history directed physical examination

- At all visits:
  - measure and record the subject's weight.
  - Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.
  - Physical examination/history directed physical examination is to be recorded in the source documents and abnormalities/pertinent diagnoses in eCRF.
- At enrollment visit and at Visit 3, perform a physical examination. At Visit 3, if the investigator determines that the subject's health on the day of revaccination temporarily precludes revaccination, the visit will be rescheduled.
- At the other visits, perform a history directed physical examination. At Visit 4, if the investigator determines that the subject's health on the day of revaccination temporarily precludes revaccination, the visit will be rescheduled.

8.1.7. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test performed and reviewed prior to any study vaccine administration. ***However, pregnancy testing should not be performed if female subjects are unwilling to be revaccinated.*** **(Amended: 15 June 2020)**

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

A urine pregnancy test is sufficient. A serum pregnancy test should only be performed as required by country, local or ethics committee regulations. In case a serum pregnancy test is required, a blood sample will be collected at Visits 3 and 4 and testing performed per local guidance. The result of serum pregnancy tests will be reviewed prior to any study vaccine administration.

The results of applicable test must be recorded in the eCRF. The study vaccine may only be administered if the pregnancy test is negative.

8.1.8. Pre-revaccination body temperature

The oral (preferred route) body temperature of each subject needs to be measured prior to any study vaccine administration and recorded in the eCRF. If the subject has fever [fever is defined as temperature ≥38.0°C ***(100.4°F)*** regardless of route of measurement] on the day of vaccination, the revaccination visit will be rescheduled within the allowed interval for this visit (see Table 4). ***Pre-revaccination temperature measurements should not be performed for non-revaccinated subjects.*** **(Amended: 15 June 2020)**

8.1.9. Record serum creatinine measures

As the detection of kidney allograft function is paramount to the management of allograft health and prevention of allograft rejection, transplant centers have established vigorous routine clinical surveillance protocols for the monitoring of the allograft. This study will rely on these per site "surveillance protocols" and will not mandate the type or timing of tests to participating study sites.

To follow allograft function, the available serum creatinine measurements, obtained per the site's "surveillance protocol" or for "clinical indication" (locally available), will be recorded in the eCRF.

Record ALL serum creatinine obtained:

- **For Allograft rejection**
  - For 2 months prior to a biopsy-proven allograft rejection, as event baseline. If not 2 or more measurements in 2 months, then go back to 3 or 4 months prior to biopsy to have a minimum of 2 measurements.
  - From onset of allograft rejection through resolution.
  - For 2 months after resolution of the biopsy-proven rejection and the cessation of therapeutic immunosuppressive therapy, so that 2 or more additional post-rejection measurements are recorded.

  Post-allograft rejection serum creatinine measurements will be evaluated in comparison to the subject's baseline pre-allograft rejection measurements.
- **For revaccination**
  - For 3 months prior to first revaccination, Visit 3 (Month 24), as pre-vaccination baseline. If not 3 or more measurements in 3 months, then go back to 4 or 5 months prior to revaccination to have a minimum of 3 measurements.
  - From Visit 3 (Month 24) through Visit 5 (Month 26).
  - For 3 months after last revaccination, Visit 5 (Month 26), so that 3 or more additional post-revaccination measurements are recorded.

  Post-revaccination serum creatinine measurements will be evaluated in comparison to the subject's baseline pre-revaccination measurements.
- **For episode of HZ cases**
  - For 2 months prior to a HZ episode, as event baseline. If not 2 or more measurements in 2 months, then go back to 3 or 4 months prior to HZ episode to have a minimum of 2 measurements.
  - From onset of HZ episode until the HZ rash resolution.
  - For 2 months after HZ episode rash resolution, so that 2 or more post-HZ resolution measurements are recorded.

Post-HZ serum creatinine measurements will be evaluated in comparison to the subject's baseline pre-HZ rejection measurements.

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

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

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 7.6.

8.1.12. Data collection

8.1.12.1. Diary cards and questionnaires

Diary cards and the ZBPI questionnaire will be distributed and explained to subject or subject's LAR(s) (or subject's caregiver) by the investigator or his/her delegate. Any supplied diary cards or questionnaires should be completed by the subject themselves or a site trained assistant.

If assistance is needed, a site trained and designated assistant (such as LAR, a family member or a caregiver) should aid with reading the questions (verbatim) and/or transcribing the subject's responses on the questionnaires and/or diary cards. This assistance should be provided at the time the subject is required to complete the questionnaire or diary card (i.e. in "real time", not retrospectively). The possibility of assistance by a trained and designated person is to be taken into account for all study procedures related to the completion of diary cards and questionnaires. Training the

assistant is to be given by the study staff (see Table 3). Study staff will ask the subject (at the time of return or at subsequent contact) if he/she received any assistance in completing diary cards or questionnaires. If the subject had assistance completing the diary card and/or questionnaires, it should be noted in the eCRF. In case questionnaires are completed at the study site, study staff can assist in reading the questions (verbatim).

All ***revaccinated*** subjects will receive:

- **Diary cards:** To be completed by the subject or subject's trained assistant after each revaccination for recording of solicited AEs (from day of revaccination to subsequent 6 days), unsolicited AEs (from day of revaccination to subsequent 29 days), any medically attended visits and all concomitant medications / vaccinations taken from day of revaccination to subsequent 29 days or to next study visit.

  Diary cards should not to be provided to non-revaccinated subjects.

***All subjects will receive*:**

- **HZ-specific diary card:** To be completed by the subjects or subject's trained assistant beginning immediately (and only) upon development of any symptoms suggestive of HZ and prior to visiting the study site for evaluation of suspected HZ.
- **ZBPI questionnaire**: To be completed by the subject with suspected HZ or subject's trained assistant beginning immediately (and only) upon development of any symptoms suggestive of HZ to collect information on the severity and duration of the HZ-associated pain and the impact of the HZ-episode on the subject's quality of life (QoL). The study staff/investigator will provide instructions to the subject or subject's trained assistant for completing the ZBPI questionnaires and explain the importance of completing and returning the questionnaires to the site in order to provide information on HZ episode.

(Amended: 15 June 2020)

8.1.13. Record pregnancies and pregnancy outcomes

Pregnancies and pregnancy outcomes in study ZOSTER-073 will be collected and recorded from Visit 1 (Day 1) through study conclusion Visit 7 (Month 49).

Please refer to section 12.5.9.1 for details.

8.1.14. Renal allograft rejection

At all visits, subjects will be instructed to contact the study site or their private health care provider if they develop signs or symptoms perceived as renal allograft dysfunction, rejection, or failure, as explained by their transplant physician(s).

Subjects, after notifying the study site of possible allograft dysfunction, rejection, or failure, will undergo the study site's standard clinical procedures for the diagnosis of possible rejection. These allograft diagnostic tests, including any biopsies, will be considered "clinically indicated."

In addition to clinically indicated testing and as part of the management of the transplant, allograft function testing and biopsies may be routinely performed, per a center defined protocol and timetable for surveillance. These tests will be considered as performed per "surveillance protocol" and recorded into eCRF screen.

For study purposes, rejection must be biopsy-proven pathophysiological changes of rejection (acute or chronic glomerulitis, tubulitis, intimal arteritis, interstitial infiltration, hyaline arteriolar thickening, peritubular capillaritis and/or total interstitial inflammation) with or without C4d-staining of biopsy. The rejection will be graded for type and severity by means of the Banff criteria [Racusen, 1999; Sis, 2010; Solez, 2008; Solez, 2012; Mengel, 2012].

Biopsy proven rejection will be recorded on the following eCRF screens; Expedited Adverse Events Report and Renal Biopsy screens. The reporting period for "biopsy proven" rejections will be from Visit 1 (Day 1) to the study end (Month 49). The following information on allograft rejection is to be included in eCRF screens:

- Start date as based on:
  - Date of first appearance of clinical symptoms indicative of rejection, resulting in a "clinically indicated" biopsy or
  - Date of "surveillance protocol" biopsy.
- Pertinent medical evaluations with results, including:
  - Allograft biopsy - date, histological results, the Banff criteria grading and specimen adequacy
  - Clinical laboratories, e.g. proteinuria, serum creatinine, estimated GFR, urinary creatinine clearance.
  - Clinical cultures
  - Ultrasounds
- Medical management including but not limited to:
  - procedures (plasmapheresis, immunoadsorption, splenectomy, other surgical intervention);
  - changes in immunosuppressive medications (intravenous immunoglobulin, high-dose glucocorticoids, antiproliferative agents, anti-B cell agents, anti-plasma cell agents, anti-T cell agents, terminal-complement pathway inhibitor);
  - initiation of dialysis.
- End date of the rejection event.
- Outcome: not recovered/not resolved (ongoing, stabilised, progressing [e.g. allograft rejection progressing to failure]), recovering/resolving/disappearing, recovered/resolved.

8.1.15. *Ad-hoc* HZ visit and phone call for evaluation of suspected HZ

Subject or subject's LAR(s) (or subject's caregiver) will be instructed to call as soon as possible and schedule an *ad-hoc* HZ visit preferably within 3 calendar days from appearance of any symptom suggestive of HZ.

Subject or subject's trained assistant will also be instructed to complete HZ-specific diary card and ZBPI questionnaire daily, starting within 24 hours from appearance of HZ symptom until the day of the ad-hoc HZ Visit. Subject or subject's LAR(s) (or subject's caregiver) will also be instructed to bring the completed HZ-specific diary card and ZBPI questionnaires to the ad-hoc HZ Visit.

During the *ad-hoc* HZ Visit, the study staff/investigator will be instructed to:

- ***Document clinical history of suspected HZ and perform physical exam;*** **(Amended: 15 June 2020)**
- Transcribe all information from the HZ-specific diary card and ZBPI questionnaire completed by the subject or subject's trained assistant into the eCRF in HZ-specific screens;
- Record concomitant medications/vaccinations, including concomitant medication the subject has already received and/or will receive for HZ treatment or treatment of any HZ-related complications;
- Check if the subject received any medical attention [hospitalisation, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication.
- Take digital photographs of HZ rash and upload to e-Clinipix. Please refer to the SPM for specific instructions. At the discretion of the investigator, additional *ad-hoc* HZ follow-up visit(s) may be necessary to manage the progression of the rash, additional photographs of HZ rash may be appropriate.
- If during clinical evaluation the investigator determines that adequate rash lesion samples from at least 3 separate lesions cannot be collected (i.e., <3 lesions present, or if only papules are present), ask the subject to return to the study site for collection of three additional lesion samples (from at least 3 separate lesions).
- Provide an additional supply of ZBPI questionnaires and HZ-specific diary cards to the subjects at *ad-hoc* HZ visit(s). ***Concomitant medications section of*** HZ-specific diary cards ***should be updated as necessary for medication changes, including start/stop dates***. ZBPI questionnaires should be completed by subjects or subject's trained assistant daily for 30 days from onset of HZ symptoms and then weekly until the resolution of the rash. **(Amended: 15 June 2020)**
- Remind subjects or subject's LAR(s) (or subject's caregiver) to return the HZ-specific diary cards and ZBPI questionnaires completed after the initial *ad-hoc* HZ visit, at the next visit or by mail after resolution of rash. Once the additional completed HZ-specific diary cards and ZBPI questionnaires are available, the investigator will transcribe the information into the subject's eCRF.

- Ask/remind the subjects or subject's LAR(s) (or subject's caregiver) to make a phone call to study sites to communicate the resolution date of HZ rash and HZ pain.
- In case subjects do not make a phone call to study sites, make a phone contact with the subjects within 3 months (90 days) of the last *ad-hoc* HZ visit for collecting the resolution date of HZ rash and confirming whether the HZ pain has resolved or is ongoing.
- In the event, the resolution dates for the HZ rash and HZ pain have not otherwise been collected, this information is to be captured at next scheduled visit(s).

8.1.16. Study procedures during special circumstances (Amended: 15 June 2020)

During special circumstances** (e.g., COVID-19 pandemic)**, specific guidance from local public health and other competent authorities regarding the protection of subjects' welfare must be applied.

The following measures may be implemented, at the discretion of the Sponsor, during special circumstances.

For potential subjects unable to be enrolled due to special circumstances:

- ***Potential subjects, who were not able to enroll between 09 December 2019 and 18 March 2020, will be offered enrollment to coincide with the Visit 2 calendar period.***
  - ***Enrollment, Visit 1 and Visit 2 study procedures will be scheduled on the same day.***
  - ***Visit 2 blood samples will be collected and recorded on Visit 2 eCRF per SoA (see Table 3). No Visit 1 blood samples will be collected.***
- ***All subjects will be scheduled together for re-vaccination at Visit 3 (see Table 8 and SPM, for details).***

For all enrolled subjects:

- ***For the duration of COVID-19 pandemic, suspected, probable, and confirmed cases of COVID-19 will be recorded at the next scheduled visit on the COVID-19 specific eCRF.***
- ***Individual subject revaccination visits may be delayed, to allow for treatment of, or vaccination for, COVID-19 (or other special circumstances). Such delay will allow for completion of the therapies and resolution of any therapy-associated AEs and immune-modifying effects (see Section 6.2.2) prior to revaccination.***
- ***As necessary and appropriate, safety follow-up may be made by a telephone call, other means of virtual contact or home visit.***
- ***Diary cards and ZBPI questionnaire may be transmitted from and to the site by conventional mail and/or electronic means.***

- ***Visits for suspected HZ may take place away from the study site, such as in a different location* or at participant's home. If an in-person visit is not feasible, then the medical evaluation of suspected HZ may take place virtually (e.g. video call) with documentation of rash and pain by investigator notes, and by subject-submitted photographs (as possible), diary cards, and ZBPI.***

- ***Biological samples may be collected away from the study site, such as in a different medical location* or at subject's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use (see SPM, for details).***

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

- ***If despite best efforts, it is not possible to collect blood samples within the interval predefined in the protocol (see* Table 4*), then the interval may be extended as defined in Table 8.***

- ***If despite best efforts, it is not possible to administer the second dose of study vaccine as defined in the protocol (see* Table 4*), a maximum dose interval of up to 6 months after the first revaccination dose may be used. If the maximum dose interval length is exceeded, then vaccination should be discontinued*.

Impact on the per protocol set (PPS) for immunogenicity will be determined on a case by case basis.

Table 8 Intervals between study visits during special circumstances (Amended: 15 June 2020)

Visits	*At the discretion of Sponsor, during special circumstances*		*Notes*
	Visit(s) may be delayed	*Allowed interval (days)*	
Visit 2	*Up to 6 months*		*The length of the allowed interval (85 days) remains, but the start of the interval may be moved by up to 6 months (starting no later than 18 months post-Visit 1), e.g. to avoid potential seasonal recurrence of COVID-19*
PC 1		*30 – 40 days before Visit 3*	
Visit 3	*Up to 6 months*		*The length of the allowed interval (85 days) remains, but the start of the interval may be moved by up to 6 months (starting no later than 30 months post-Visit 1), e.g. to avoid potential seasonal recurrence of COVID-19*
Visit 4		*30 – 182 post-Visit 3*	*Optimally 30 - 60 days after Visit 3 (Table 4)*
Visit 5		*30 – 90 post-Visit 4*	*Optimally 30 – 48 days after Visit 4 (Table 4)*
*Visit 6**		*330 – 445 post-Visit 4*	
*Visit 7**		*690 – 805 post-Visit 4*	*Visit 7 may be:* • *Scheduled earlier to make up for delays incurred during times of special circumstance, in order to maintain planned duration of the study.* • *Delayed or cancelled if special circumstances preclude the original planned visit.*

Note: Investigator should prioritize conducting the visit as close to the optimal window as possible.
**** The allowed interval for Visits 6 and 7 should be the same for both the re-vaccinated and non-revaccinated subjects.***

(Amended: 15 June 2020)

8.2. Efficacy assessments

Not applicable.

8.3. Immunogenicity assessments

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

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

Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the

maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.

It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

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

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

Refer also to the Amendment 1 Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

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

8.3.1. Use of specified study materials

When materials are provided by GSK, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the per-protocol analysis (See section 10.2 for the definition of populations for analyses). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

8.3.2. Biological samples

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

8.3.2.1. Blood sampling for immunogenicity response and safety assessments

Blood samples will be taken at each study visit as specified in section 2. Blood draws scheduled on the days of revaccination (Visits 3 and 4) must be done before vaccination.

- A volume of approximately 5.0 mL of whole blood (to provide approximately 2.0 mL of serum) should be drawn from each subject for analysis of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C or below until shipment. Refer to the SPM for more details on sample storage conditions.
- A volume of approximately 30 mL of whole blood should be drawn from subjects included in the CMI sub-cohort for analysis of cell-mediated immune response at each pre-defined timepoint. The blood should be stored at the investigator's site at room temperature and it must not be centrifuged. Samples will be shipped at room temperature (15 to 25°C) to the designated laboratory for cell separation to be performed within 24 hours. Refer to the SPM for more details on sample storage conditions.

CCI [redacted]

For each subject not in the CMI subcohort, an overall volume of approximately 75 mL will be collected during the entire study period (approximately 49 months).

For each subject in the the CMI subcohort, an overall volume of approximately 285 mL will be collected, during the entire study period (approximately 49 months).

Blood samples will be collected in the following order:

1. Anti-gE antibody (5 mL)
2. CMI (30 mL)

CCI [redacted]

8.3.2.2. HZ lesions sampling

In the event there is a case of suspected HZ, subjects will return for an *ad hoc* HZ Visit for the collection of three (3) rash lesions samples. Sampling will be targeted by the highest priority lesion type available, as 1) vesicle fluid; 2) crust; 3) crust swab; and 4) papule swab (see section 8.1.15 for more details on collecting HZ lesion samples). HZ lesion samples should be kept at –20°C or below until shipment. Refer to the SPM for more details on sample storage conditions.

Table 9 Biological samples

Sample type	Quantity	Unit	Timepoint	Sub-cohort Name*
Blood for humoral response	approximately 5	mL	Visits 1, 2, 3, 4**, 5**, 6 and 7	All subjects
Blood for CMI response	approximately 30	mL	Visits 1, 2, 3, 4**, 5**, 6 and 7	CMI sub-cohort
CCI [redacted]				
Clinical specimens of rash lesions for confirmation of HZ by PCR	3 samples (from 3 separate lesions)	NA	Event-driven	Subjects clinically diagnosed as having a suspected case of HZ.

CMI = Cell-Mediated Immunogenicity; HZ = Herpes Zoster; PCR = Polymerase Chain Reaction; NA = Not Applicable;
CCI [redacted]
* Refer to Section 10.1 for subset description.
** ***Refer to Section 5.3 for non-revaccinated subjects. These subjects will not have Visit 4 and Visit 5 blood draws. (Amended: 15 June 2020)***

8.3.3. Laboratory assays

Please refer to Appendix 2 for a detailed description of the assays performed in the study. Please refer to Appendix 3 for the address of the clinical laboratories used for sample analysis.

8.3.3.1. Immunological assays

gE-specific humoral immune response

Assays for the determination of gE-specific antibodies will be performed by Enzyme Linked Immunosorbent Assay (ELISA) at a GSK laboratory using standardized and validated procedures (refer to Table 10).

Table 10 Humoral Immunity (Antibody determination)

System	Component	Method	Kit/Manufacturer	Laboratory*
Serum	Varicella Zoster Virus.Glycoprotein E Ab.IgG	ELISA	NA	GSK and/or lab designated by GSK

Ab = Antibody; IgG = Immunoglobulin class G; ELISA = Enzyme-linked Immunosorbent Assay;
NA = Not applicable;
*Refer to Appendix 3 for the laboratory addresses.

gE-specific CMI response

Assays for the determination of gE-specific CD4+ T-cells expressing at least 2 activation markers (from among IFN-γ, IL-2, TNF-α and CD40L) will be performed by intracellular cytokine staining (ICS) as measured by cytokine flow cytometry (CFC) in a laboratory designated by GSK using standardized and validated procedures (refer Table 11).

Table 11 Cell-mediated Immunity (CMI) using cytokine flow cytometry

System	Component Family	Challenge	Method	Laboratory*
PBMC	CD4.polypositives CD40L+IL-2+TNFα+IFNγ**	gE	ICS	GSK and/or lab designated by GSK

gE = recombinant purified Glycoprotein E; ICS = Intracellular Cytokine Staining as measured by cytokine flow cytometry
*Refer to Appendix 3 for the laboratory addresses.
**CD4.polypositives CD40L+IL-2+TNFα+IFNγ = CD4+ T-cells expressing at least 2 activation markers (from among IFNγ, IL-2, TNFα and CD40L).

Varicella zoster virus (VZV) molecular biology

For clinically diagnosed suspected HZ cases, the potential of HZ infection will be assessed by real-time PCR (PCR) testing for VZV DNA (see Table 12).

Table 12 Molecular Biology (PCR tests)

System	Component	Method	Laboratory*
HZ lesion sample	Varicella Zoster Virus.DNA	PCR	GSK and/or lab designated by GSK
HZ lesion sample	β -Actin Gene.DNA	PCR	GSK and/or lab designated by GSK

PCR: Polymerase Chain Reaction
*Refer to Appendix 3 for the laboratory addresses.

CCI

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

The 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.

8.3.4. Biological samples evaluation

The blood samples will be analyzed according to immunological read-outs provided in Table 14.

Table 14 Immunological read-outs

Blood sampling timepoint		Sub-cohort name*	Targeted No. subjects (i.e. maximum)	Sample type	Components
Type of contact and timepoint	Sampling timepoint				
Visit 1 (Day 1)	Post-primary Vacc 2	All subjects	86	Serum	Anti-gE Ab
		CMI subjects**	40	PBMC	gE-specific CD4+ T-Cells
Visit 2 (Month 12)	Post- primary Vacc 2	All subjects	86	Serum	Anti-gE Ab
		CMI subjects	40	PBMC	gE-specific CD4+ T-Cells
Visit 3 (Month 24)	pre-reVacc 1	All subjects	86	Serum	Anti-gE Ab
		CMI subjects	40	PBMC	gE-specific CD4+ T-Cells
		All subjects	86	Serum	CCI [redacted]
Visit 4 (Month 25) ***	Post-reVacc 1	All subjects	86	Serum	Anti-gE Ab
		CMI subjects	40	PBMC	gE-specific CD4+ T-Cells
		All subjects	86	Serum	CCI [redacted]
Visit 5 (Month 26) ***	Post-reVacc 2	All subjects	86	Serum	Anti-gE Ab
		CMI subjects	40	PBMC	gE-specific CD4+ T-Cells
		All subjects	86	Serum	CCI [redacted]
Visit 6 (Month 37)	Post-reVacc 2	All subjects	86	Serum	Anti-gE Ab
		CMI subjects	40	PBMC	gE-specific CD4+ T-Cells
		All subjects	86	Serum	CCI [redacted]
Visit 7 (Month 49)	Post-reVacc 2	All subjects	86	Serum	Anti-gE Ab
		CMI subjects	40	PBMC	gE-specific CD4+ T-Cells
		All subjects	86	Serum	CCI [redacted]

reVacc = reVaccination; **CMI** = Cell- Mediated Immunogenicity; **Ab** = Antibody; **gE** = recombinant purified Glycoprotein E; CCI [redacted] **NA** = not applicable.

*For subjects in CMI sub-cohort a whole blood sample for gE-specific CD4 T-cell testing will be taken at all study visits.

CCI [redacted]

**refer to section 7.2.2 for the definition of the subsets and method of selection.

*** ***Refer to Section 5.3 for non-revaccinated subjects. These subjects will not have Visit 4 and Visit 5 blood draws.*** **(Amended: 15 June 2020)**

8.3.4.1. Molecular biology on suspected HZ skin lesions

Table 15 Evaluation of suspected HZ cases

Type of contact and timepoint	Sampling timepoint	Sub-cohort	Targeted No. subjects (i.e maximum)	Component
Event driven	Suspected HZ skin lesions	Event-driven	Event-driven	VZV PCR
Event driven	Suspected HZ skin lesions	Event-driven	Event-driven	Beta-actin PCR

HZ = Herpes Zoster; **VZV** = Varicella Zoster Virus; **PCR** = Polymerase Chain Reaction

8.3.5. Immunological correlates of protection

No generally accepted immunological CoP has been demonstrated for HZ/su vaccine.

8.4. Safety Assessments

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

8.4.1. Safety definitions

Please refer to section 12.5 for safety definitions.

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

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 16. Refer to the section 12.5.9.1 for details on the time period for recording safety information.

Table 16 Reporting periods for collecting safety information

Event	Visit 1*	Visit 2	Visit 3			Visit 4			Visit 5	Visit 6	Visit 7
Timepoint	Day 1	Month 12	Month 24			Month 25	Post reVacc	Post reVacc	Month 26	Month 37	Month 49
			reVacc 1	6 days post reVacc 1	29 days post reVacc 1	reVacc 2	6 days post reVacc 2	29 days post reVacc 2			Study conclusion
Solicited local and general AEs **											
Unsolicited AEs **											
AEs/SAEs leading to withdrawal from the study											
SAEs and pIMDs											
SAEs related to the study vaccine $											
SAEs related to study participation or concurrent GSK medication/vaccine											
Intercurrent medical conditions, including HZ cases											
AESI: Biopsy-proven allograft rejections											
Pregnancies and pregnancy outcomes											

* i.e. consent obtained. reVacc 1: revaccination Dos 1; reVacc 2: revaccination Dos 2

***** Applicable for revaccinated subjects only (Amended: 15 June 2020)***

$ SAEs related to study vaccine include SAEs occurring before the first revaccination Visit 3 (Month 24) considered as related to primary vaccination in study ZOSTER-041, and SAEs related to revaccination course occurring after administration of the first dose from revaccination course in study ZOSTER-073

All SAEs will be recorded and reported via Expedited AE Reporting Form to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after the investigator became aware of it, as indicated in Appendix 5. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 16. Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.4.3. Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing intensity, causality and outcome of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in section 12.5.9.

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

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

Table 17 Timeframes for submitting serious adverse event, 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	2 weeks*	electronic pregnancy notification report	2 weeks*	electronic pregnancy follow-up report
AESIs (pIMDs and allograft rejection)	24 hours** ‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

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

8.4.4.1. Contact information for reporting of serious adverse events (SAEs), AESIs and pregnancies

Table 18 Contact information for reporting of serious adverse events (SAEs), AESIs and pregnancies

Study contact for questions regarding SAEs, AESIs and pregnancies
Refer to the local study contact information document
Back-up Study Contact for Reporting SAEs, AESIs and pregnancies
24/24 hour and 7/7 day availability: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: Rix.CT-safety-vac@gsk.com Canadian sites only: Fax: 1-866-903-4718

8.4.4.2. Regulatory reporting requirements for SAEs

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

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

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

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

8.4.5. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AESIs (serious or non-serious, as defined in section 8.4.1), will be followed until the event is resolved, stabilized, otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is given in section 12.5.12.

8.4.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE/AESI should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to section 7.5).

8.4.7. Subject card

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

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

Subjects/subject's LAR(s) must be instructed to keep subject cards in their possession at all times during the study duration.

8.4.8. Evaluation and confirmation of suspected HZ cases

8.4.8.1. Suspected Herpes Zoster

Suspected HZ is defined as a new rash characteristic of HZ (i.e. unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations), or a vesicular rash suggestive of VZV infection regardless of the dermatomal distribution and without alternative diagnosis.

Additionally, sometimes HZ cases do not present with the characteristic HZ or VZV rash, but have a clinical presentation and specific laboratory findings* suggestive of VZV infection. These cases should also be considered as occurrences of HZ.

* Specific laboratory findings include VZV-positive polymerase chain reaction (PCR) culture, immunohistochemistry, or other tests that strongly suggest VZV-infection, which have been performed in the course of a medical evaluation.

A suspected case of HZ is to be evaluated in the clinic by the investigator, within days of onset, ideally while vesicles or ulcerations are present.

Complications of HZ include, but are not limited to, PHN, HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, and visceral disease.

The occurrence of HZ and/or HZ complications will constitute an AE/SAE, as appropriate. The occurrence of HZ is also an intercurrent medical condition (IMC) (see section 7.6).

The reporting period for events of HZ will be from Visit 1 (Day 1) to study end (Month 49). At Visit 1, all subjects will be informed of the signs and symptoms of typical HZ.

8.4.8.2. Confirmed HZ

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

- **By Polymerase Chain Reaction**

Whenever possible, HZ lesion samples will be collected from subjects clinically diagnosed as having a suspected case of HZ (see section 8.1.15). The samples will be transferred to GSK or a validated laboratory designated by GSK and tested using standardised and validated procedures for laboratory diagnosis of HZ by PCR.

Refer to section 12.2.1 for details of PCR assay to be performed on HZ lesion samples.

Refer to section 12.2.2 for details of the PCR testing algorithm to classify suspected cases of HZ.

- **By the HZ Ascertainment Committee**

All suspected HZ cases not confirmed by PCR will be referred to the HZ Ascertainment Committee (HZAC). The HZAC will classify all referred cases as either “HZ” or “not HZ”. However, the HZAC classification will serve as the final case definition only when the case cannot be confirmed or excluded by PCR results obtained by GSK or a validated laboratory designated by GSK, e.g., when all samples from a given subject are inadequate (as when both VZV and β-actin PCR results are negative), or when no samples are available for a given subject (including when suspected HZ occurs in the absence of a characteristic HZ or VZV rash). Therefore, definitive PCR results obtained by GSK or a validated laboratory designated by GSK, when available, will determine the final HZ case assignment. In such cases, the HZAC classification will not contribute to HZ case determination decision.

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

Please note that PCR test results or HZAC classification as described above will not serve as the final case definition if the following applies.

Cases of suspected HZ will not be considered a confirmed case of HZ if they potentially could constitute a primary VZV infection (varicella).

8.4.8.3. HZ complications

Any HZ complications, according to the definitions below, will be recorded by the investigator. HZ complications will be considered as AEs or SAEs. HZ complications associated with confirmed HZ include:

Ophthalmic disease:	Defined as HZ affecting any eye structure as per the investigator's judgment.
PHN:	Defined by the presence of HZ-associated 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash.
Others	HZ vasculitis, disseminated disease, neurologic disease, visceral disease

8.4.8.4. Terms related to evaluation of suspected HZ

- **Duration of a HZ episode**

In case of suspected HZ, the HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash is first noted. The dates of these two events are recorded in the eCRF. The end date of the HZ episode is defined as the first time at which a subject had no rash (papules, vesicles, ulcers or crusts) present. This end date will be recorded in the eCRF.

In case of suspected HZ with absence of the characteristic rash, the HZ onset date is the date on which the signs/symptoms related to the clinical diagnosis of suspected HZ were first noted. The end date of the HZ episode is defined as the date on which the investigator or an attending physician considered the case as resolved. The onset and end date will be recorded in the eCRF.

- **Severity of HZ-associated pain using the Zoster Brief Pain Inventory**

The ZBPI is an assessment tool in the form of a questionnaire completed by the subject that is specifically designed to assess the severity of HZ-associated pain during an HZ episode [Coplan, 2004]. The ZBPI also takes into account the effect of HZ treatment on subject's pain and general health status.

In each case of suspected HZ, the subjects will be asked to assess their HZ-associated pain by completing the ZBPI questionnaire, either themselves or or subject's trained assistant, until the rash is resolved.

HZ occurrence, intensity (severity) and duration will be derived from the data recorded in the ZBPI.

9. DISCONTINUATION CRITERIA

Refer to the section 7.7 for contraindications to subsequent vaccination.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from enrollment visit up to study end (refer to Appendix 5).

Subjects who participate to study ZOSTER-073 but do not consent to revaccination will be encouraged to continue other study procedures for long term immunogenicity and safety assessments.

9.1. Discontinuation from the study

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

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

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

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

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

- Adverse events requiring expedited reporting, including SAEs, biopsy-proven allograft rejections and pIMDs
- HZ episodes
- Unsolicited non-serious adverse event
- Solicited adverse event
- Protocol deviation
- Withdrawal by subject, not due to an adverse event*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

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

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see section 12.5.12).

9.2. Discontinuation of study vaccine

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

A subject withdrawn from the study vaccine may continue and should be encouraged to continue further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

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

- Adverse event requiring expedited reporting, including SAEs, biopsy-proven rejections and pIMDs
- HZ episodes
- Non-serious adverse event (specify)
- Unsolicited non-serious adverse event
- Solicited adverse event
- Not willing to be revaccinated
- Other (specify).

9.3. Lost to follow-up

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample size determination

10.1.1. Sample size calculation

Former ZOSTER-041 subjects, who had a complete vaccination course (2 doses of HZ/su vaccine) will be offered enrollment into study ZOSTER-073 at participating centers.

Up to a maximum of 86 subjects meeting the eligibility criteria for enrollment (2 doses of HZ/su vaccine ***in ZOSTER-041***) will be targeted for enrollment in participating centers. Approximately 15% of the enrolled subjects might withdraw or not be evaluable for immunogenicity, therefore the target sample size will be approximately 73 subjects evaluable for humoral immunogenicity in per-protocol set (as defined in section 10.2). **(Amended: 15 June 2020)**

Up to a maximum of 40 subjects will be targeted for the CMI sub-cohort in participating centers having CMI capabilities in order to reach 34 evaluable subjects for CMI analyses assuming a 15% of drop-out and non-evaluability rate. CMI subjects from ZOSTER-041 will be enrolled into the ZOSTER-073 CMI sub-cohort. Also, the balance of CMI subjects to be enrolled will be selected at random from CMI participating centers (having CMI capabilities) to complete the sub-cohort up to 40 subjects at ZOSTER-073 Visit 1.

10.2. Populations for analyses

For purposes of analysis, the following analysis sets are defined [more detailed description will be provided in the statistical analysis plan (SAP)].

Analysis Set	Description
Enrolled Set	All subjects with a complete vaccination course (2 doses of HZ/su vaccine) in study ZOSTER-041 who met the eligibility criteria and signed informed consent in the current study.
PPS for analysis of persistence (LTFU phase from Visit 1 to Visit 3) (Amended: 15 June 2020)	The PPS for analysis of persistence will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the Enrolled set for whom persistence immunogenicity endpoints measures after primary vaccination course are available ***from*** Visit 1 (Day 1) ***to*** Visit 3 (Month 24). **(Amended; 15 June 2020)**
ES for revaccination phase	The ES for analysis of safety will include all subjects with at least one HZ/su vaccine dose administered in the study ZOSTER-073.
PPS for Immunogenicity after revaccination course (revaccination active phase)	The PPS for analysis of immunogenicity after revaccination will be defined by time-point and will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the ES for revaccination who have received one or two doses of revaccination schedule up to the time point considered ***from*** Visit 3 ***to*** Visit 5 (Month 26). **(Amended: 15 June 2020)**
PPS for persistence after revaccination course (revaccination follow-up phase)	The PPS for persistence for analysis of immunogenicity after revaccination will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the ES for revaccination for whom persistence immunogenicity endpoints measures after revaccination course are available ***from*** Visit 6 (Month 37) ***to*** Visit 7 (Month 49). **(Amended: 15 June 2020)**

PPS = per protocol set, ES = exposed set

For non-revaccinated subjects, the enrolled set will be used for analyses of safety and immunogenicity. Details will be described in the statistical analysis plan (SAP). **(Amended: 15 June 2020)**

10.3. Statistical analyses

All statistical analyses will be descriptive and detailed in the SAP.

10.3.1. Subjects disposition

Number of enrolled and revaccinated subjects (by dose received) will be tabulated overall.

Number of subjects per protocol and exposed sets will be tabulated, overall.

10.3.2. Demography and baseline characteristics analyses

Demographic and baseline characteristics (e.g., in study ZOSTER-041, age in years at the time of primary vaccination; in study ZOSTER-073, age in years at the time of enrollment and of first revaccination) will be summarized using descriptive statistics:

- Frequency tables will be generated for categorical variables such as center.
- Mean, standard deviation (SD), median, minimum and maximum will be provided for continuous data such as age

Analysis of demographic and baseline characteristics will be performed overall, and by age and maintenance immunosuppressive therapy.

10.3.3. Immunogenicity analyses

LTFU phase

Analyses will be based on the Per Protocol Set (PPS) for persistence after primary vaccination course.

If, the percentage of subjects with serological results excluded from the PPS for analysis of persistence after primary vaccination course is 5% or more, a second analysis based on the Enrolled set will be performed to complement the PPS analysis.

All analyses will be performed overall; additional analyses by age and type of maintenance immunosuppressive therapy strata (at the time of primary vaccination in study ZOSTER-041) will be performed if deemed necessary and appropriate.

Endpoint	Statistical Analyses for LTFU phase
Primary	**For persistence of humoral immunity after the primary vaccination course, the following parameters will be tabulated:** • GMCs of anti-gE antibody and anti-gE antibody seropositivity rates with 95% CI at Day 1, Month 12 and Month 24; • Descriptive statistics on anti-gE antibody concentrations (mean, SD, min, Q1, median, Q3, max) at Day 1, Month 12 and Month 24; • Vaccine response rates to ZOSTER-041 primary vaccination for anti-gE antibody concentrations at ZOSTER-073 Day 1, Month 12 and Month 24; • Descriptive statistics of the fold increase over ZOSTER-041 pre-vaccination timepoint at ZOSTER-073 Day 1, Month 12 and Month 24 (mean, SD, min, Q1, median, Q3, max); • Distribution of the fold over ZOSTER-041 pre-vaccination timepoint at ZOSTER-073 Day 1, Month 12 and Month 24; • MGI, i.e. geometric mean of the ratio post-vaccination timepoint over pre-vaccination timepoint in ZOSTER-041 with 95% CI at ZOSTER-073 Day 1, Month 12 and Month 24; The distribution of antibody titers at Day 1, Month 12 and Month 24 will be tabulated and also presented using reverse cumulative curves.
Secondary	**For persistence of cellular immunity after the primary vaccination course, the following parameters will be tabulated:** • Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max): – the frequency of gE specific CD4+T-cells secreting at least 2 activation markers (among IFN-γ, IL-2, TNF-α, CD40L) at Day 1, Month 12 and Month 24; – the fold increase over ZOSTER-041 pre-vaccination timepoint for the frequency of gE-specific CD4(2+) T-cells at ZOSTER-073 Day 1, Month 12 and Month 24; Vaccine response rates to ZOSTER-041 primary vaccination for frequency of gE-specific CD4(2+) T-cells will be tabulated with 95% CI at ZOSTER-073 Day 1, Month 12 and Month 24.

GMC = Geometric Mean Concentration, **MGI** = Mean Geometric Increase, **N** = Number, **SD** = Standard Deviation, **Q1** = Quartile 1, **Q3** = Quartile 3, **Min** = Minimum, **Max** = Maximum, **IFN-γ** = Interferon gamma, **IL-2** = Interleukine 2, **TNF-α** = Tumor Necrosis Factor alpha.

Revaccination active phase

Analyses will be based on the PPS for immunogenicity analysis after revaccination (revaccination active phase).

If the percentage of subjects with serological results excluded from the PPS for analysis after revaccination is 5% or more, a second analysis based on the Exposed Set (ES) for revaccination will be performed to complement the PPS analysis after revaccination.

All analyses will be performed overall; additional analyses by age stratum (at the time of ZOSTER-041 primary vaccination and ZOSTER-073 first revaccination) and by type of maintenance immunosuppressive therapy at the time of revaccination (Visit 3, Month 24) will be performed if deemed necessary and appropriate.

Endpoint	Statistical Analyses for Revaccination active phase
Primary	**For humoral immunity after revaccination for the active phase, at Months 24, 25 and 26, the following parameters will be tabulated:** • GMCs of anti-gE antibody and anti-gE antibody seropositivity rates with 95% CI at Months 24, 25 and 26; • Vaccine response rates for anti-gE antibody concentrations at Months 25 and 26 [post- revaccination timepoint over pre-revaccination timepoint] with 95% CI; • Vaccine response rates to ZOSTER-041 primary vaccination for anti-gE antibody concentrations at ZOSTER-073 Months 25 and 26 with 95% CI; • MGI post-revaccination timepoint over pre-revaccination timepoint at Months 25 and 26 with 95% CI; • MGI post-revaccination timepoint over ZOSTER-041 pre-vaccination timepoint at Months 24, 25 and 26 with 95% CI; • Descriptive statistics of the fold increase of anti-gE antibody concentrations at Month 25 and Month 26 over pre-revaccination timepoint (mean, SD, min, Q1, median, Q3, max). • Distribution of antibody titers at Months 24, 25 and 26 will be tabulated and also presented using reverse cumulative curves.
Secondary	**For cellular immunity after revaccination for the active phase, the following parameters will be tabulated:** • Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max): – the frequency of gE specific CD4+T-cells secreting at least 2 activation markers (among IFN-γ, IL-2, TNF-α, CD40L) at Months 24, 25 and 26; – the fold increase over pre-revaccination timepoint Month 24 in the frequency of gE specific CD4[2+] T-cells at Months 25 and 26. – the fold increase over ZOSTER-041 pre-vaccination timepoint in the frequency of gE specific CD4[2+] T-cells at Months 24, 25 and 26 in the current study. • Vaccine response rates for frequency of gE-specific CD4(2+) T-cells at Months 25 and 26 over pre-revaccination timepoint Month 24 will be tabulated with 95% CI. • Vaccine response rates to ZOSTER-041 primary vaccination for frequency of gE-specific CD4(2+) T-cells at ZOSTER-073 Months 24, 25 and 26 will be tabulated with 95% CI.

GMC = Geometric Mean Concentration, **MGI** = Mean Geometric Increase, **N** = Number, **SD** = Standard Deviation, **Q1** = Quartile 1, **Q3** = Quartile 3, **Min** = Minimum, **Max** = Maximum, **IFN-γ** = Interferon gamma, **IL-2** = Interleukine 2, **TNF-α** = Tumor Necrosis Factor alpha.

Revaccination follow-up phase

Analyses will be based on the PPS for persistence after revaccination course (revaccination follow-up phase).

If the percentage of subjects with serological results excluded from the PPS for persistence analysis after revaccination is 5% or more, a second analysis based on the ES for revaccination will be performed to complement the PPS for persistence analysis after revaccination.

All analyses will be performed overall; additional analyses by age stratum (at the time of ZOSTER-041 primary vaccination and ZOSTER-073 first revaccination) and by type of maintenance immunosuppressive therapy at the time of revaccination (Visit 3, Month 24) will be performed if deemed necessary and appropriate.

Endpoint	Statistical Analyses for Revaccination follow-up phase
Primary	NA.
Secondary	**For humoral immunity after revaccination (revaccination follow-up phase), the following parameters will be tabulated:** • GMC of anti-gE antibody and anti-gE seropositivity rates with 95% CI at Months 37 and 49; • Vaccine response rates for anti-gE antibody concentrations at Months 37 and 49 [over pre-revaccination timepoint] with 95% CI; • Vaccine response rates to ZOSTER-041 primary vaccination for anti-gE antibody concentrations at ZOSTER-073 Months 37 and 49 with 95% CI; • MGI post-revaccination over pre-revaccination timepoint at Months 37 and 49 with 95% CI; • MGI post-revaccination over ZOSTER-041 pre-vaccination timepoint at Months 37 and 49 with 95% CI • Descriptive statistics of the fold increase of anti-gE antibody concentrations at Months 37 and 49 over pre-revaccination timepoint (mean, standard deviation, min, Q1, median, Q3, max). • Descriptive statistics of the fold increase of anti-gE antibody concentrations at Months 37 and 49 over ZOSTER-041 pre-vaccination timepoint (mean, SD, min, Q1, median, Q3, max). • Distribution of antibody titers at Months 37 and 49 will be tabulated and also presented using reverse cumulative curves. **For cellular immunity after revaccination (revaccination follow- up phase), the following parameters will be tabulated:** • Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max): – the frequency of gE specific CD4+T-cells secreting at least 2 activation markers (among IFN-γ, IL-2, TNF-α, CD40L) at Months 37 and 49; – the fold increase over pre-revaccination timepoint in the frequency of gE specific CD4[2+] T-cells at Months 37 and 49. • Vaccine response rates for frequency of gE-specific CD4(2+) T-cells at Months 37 and 49 over pre-revaccination timepoint will be tabulated with 95% CI.

GMC = Geometric Mean Concentration, **MGI** = Mean Geometric Increase, **N** = Number, **SD** = Standard Deviation, **Q1** = Quartile 1, **Q3** = Quartile 3, **Min** = Minimum, **Max** = Maximum, **IFN-γ** = Interferon gamma, **IL-2** = Interleukine 2, **TNF-α** = Tumor Necrosis Factor alpha.

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10.3.4. Safety analyses

Analyses will be performed on the Enrolled and Exposed Sets.

LTFU phase

Endpoint	Statistical Analyses for LFTU phase
Primary	NA
Secondary	• Percentage of subjects reporting history of at least one SAE related to primary vaccination in study ZOSTER-041 classified by MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) from ZOSTER-041 last study visit ***(Month 13)*** to ZOSTER-073 Day 1 will be tabulated with exact 95% CI. • Percentage of subjects reporting at least one SAE related to primary vaccination classified by MedDRA Primary SOC and PT from ZOSTER-041 Day 1 to ZOSTER-073 Month 24 will be tabulated with exact 95% CI. • ***Percentage of subjects with at least one biopsy-proven allograft rejection reported from ZOSTER-073 Day 1 to ZOSTER-073 Month 24 will be tabulated with exact 95% CI.*** • Listing of subjects with history of suspected allograft rejection or history of biopsy-proven allograft rejections from ZOSTER-041 last study visit to ZOSTER-073 Day 1 will be provided. • Listing of subjects with biopsy-proven allograft rejections from ZOSTER-**073** Day 1 to ZOSTER-073 Month 24 will be ***provided***. • Listing of subjects with history a suspected HZ episode from ZOSTER-041 last study visit to ZOSTER-073 Day 1 will be provided. • Listing of subjects with a confirmed HZ episode from ZOSTER-073 Day 1 to ZOSTER-073 Month 24 will be provided. • Number of subjects with declining allograft function, as determined by serum creatinine measurements will be detailed in the SAP. **(Amended: 15 June 2020)**

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All analyses will be performed overall and by age stratum (based on age at the time of primary vaccination in ZOSTER- 041).

Revaccination phase

Endpoint	Statistical Analyses for Revaccination phase
Primary	NA
Secondary	• Percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited), and with any AEs during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each revaccination dose and overall. The same computations will be done for Grade 3 AEs. • Percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 7-day follow-up period (i.e., on the day of revaccination and 6 subsequent days) will be tabulated after each revaccination dose and overall. • Duration of solicited local and general AEs within 7 days and entire duration will be tabulated overall. • Percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e., on the day of revaccination and 29 subsequent days) with its exact 95% CI will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs, for Grade 3 non-serious unsolicited AEs, for Grade 3 causally related non-serious unsolicited AEs and for unsolicited AEs resulting in a medically attended visit. • Percentage of subjects with at least one report of SAE classified by the MedDRA SOC and PTs and reported from revaccination Dose 1 up to 30 days and 12 months post- last revaccination dose will be tabulated with exact 95% CI. SAEs will be also described in detail. • Percentage of subjects with at least one report of causally related-SAE classified by the MedDRA SOC and Preferred Terms and reported from revaccination Dose 1 up to 30 days and 12 months post-last revaccination dose, and up to study end (Month 49) will be tabulated with exact 95% CI. Related-SAE will be also described in detail. • Percentage of subjects with at least one pIMD classified by the MedDRA SOC and Preferred Terms and percentage of subjects with at least one pIMD with causal relationship, reported from Dose 1 up to 30 days and 12 months post- last revaccination dose will be tabulated with exact 95% CI. • Percentage of subjects with at least one biopsy-proven allograft rejection and causal relationship reported from Dose 1 up to study end (Month 49) will be tabulated with exact 95% CI. • Percentage of subjects reporting unsolicited AEs resulting in a medically attended visit from Dose 1 up to 30 days post-last revaccination dose will also be tabulated with exact 95% CI. • Fatal SAEs will be described by onset date of SAE and date of death • SAEs (including fatal SAEs), pIMDs and withdrawal due to AE(s) will be described in detail. • Listing of withdrawals due to AE and SAEs will be provided • Listing of subjects with confirmed HZ episode will be provided. • Listing of subjects with biopsy-proven allograft rejection will be provided.

Endpoint	Statistical Analyses for Revaccination phase
	• Number of subjects with declining allograft function (following revaccination, HZ and allograft rejection), as determined by serum creatinine measurements will be detailed in the SAP.

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All analyses will be performed overall and by age stratum (based on age at the time of revaccination in ZOSTER- 073).

10.3.5. Interim analyses

All analyses are descriptive.

No statistical adjustment will be made for the interim analysis, which is intended to provide outputs related to the different endpoints and timepoints in a phased manner.

10.4. Sequence of analyses

The final study report will contain at least the final analyses of all primary and secondary endpoints.

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The analysis will be performed in the following steps:

- A limited long-term immunogenicity analysis will be performed from ZOSTER-041 Visit 3 (Month 2) to ZOSTER-073 Visit 1 (Day 1). No clinical study report (CSR) will be written at that time.
- A limited long-term immunogenicity analysis will be performed from ZOSTER-041 Visit 3 (Month 2) to ZOSTER-073 Visit 2 (Month 12). No CSR will be written at that time.
- Interim analysis after the revaccination active phase will be performed one month after the second revaccination dose, Month 26 (Visit 5) to assess:
  - Long-term safety from ZOSTER-041 Visit 5 (Month 13) to ZOSTER-073 Visit 3 (Month 24).
  - Persistence of immunogenicity from ZOSTER-041 Visit 3 (Month 2) to ZOSTER-073 Visit 3 (Month 24).
  - Safety and immunogenicity after revaccination from ZOSTER-073 Visit 3 (Month 24) to ZOSTER-073 Visit 5 (Month 26).

  No CSR will be written at that time.
- A final analysis on immunogenicity and safety will be performed at study end (Visit 7), once all data are available and cleaned.

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12. APPENDICES

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

12.1.1. List of abbreviations

AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AID:	Auto-Immune Disorder
CFC:	Cytokine Flow Cytometry
CIS:	Chronic Immunosuppressive
CLS:	Clinical Laboratory Sciences
CMI:	Cell-Mediated Immunity
CMV:	Cytomegalovirus
CoP:	Correlate of Protection
CRF:	Case Report Form
CCI	[redacted]
EBV:	Epstein Barr virus
ELISA:	Enzyme Linked Immunosorbent Assay
EoS:	End of Study
FDA:	Food and Drug Administration, United States of America
GCP:	Good Clinical Practice
GFR:	Glomerular Filtration Rate
GSK:	GlaxoSmithKline Biologicals SA
HIV:	Human Immunodeficiency Virus
HLA:	Human Leukocyte Antigen
HSCT:	Hematopoietic Stem Cell Transplantation

HZ:	Herpes Zoster, shingles
ICF:	Informed Consent Form
ICH:	International Council on Harmonisation
ICS:	Intracellular cytokine staining
IEC:	Independent Ethics Committee
IFNγ:	Interferon-gamma
IID:	Immuno-Inflammatory Disorder
IL-2:	Interleukin 2
IMC:	Intercurrent Medical Condition
IND:	Investigational New Drug
IRB:	Institutional Review Board
LAR:	Legally Acceptable Representative
LSLV:	Last Subject Last Visit
LTFU:	Long-term Follow-up
MedDRA:	Medical Dictionary for Regulatory Activities
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
PBMC:	Peripheral Blood Mononuclear Cells
PCD:	Primary Completion Date
PCR:	Polymerase Chain Reaction
PHN:	Post-herpetic Neuralgia
PI:	Prescribing Information
pIMD:	Potential Immune-Mediated Disease
PP:	Per protocol
RT:	Renal Transplant

SAE:	Serious Adverse Event
SBIR:	Source data Base for Internet Randomisation
SmPC:	Summary of Product Characteristics
SoA:	Schedule of Activities
SOT:	Solid Organ Transplant
SPM:	Study Procedures Manual
TNFα:	Tumor Necrosis Factor-alpha
VE:	Vaccine Efficacy
VZV:	Varicella Zoster Virus
YOA:	Years Of Age
ZBPI:	Zoster Brief Pain Inventory

12.1.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Adverse Events of Special Interest (AESIs):	AESIs are a subset of AEs/SAEs that include specific disorders of interest which may or may not be related to vaccination. For this trial, AESIs will be defined as potential immune-mediated disorders and renal allograft rejection.
Anamnestic:	Relating to a rapid increased production of antibodies in response to a previously experienced immunogenic substance.
Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Donor-specific antibodies:	Anti-HLA antibodies specifically produced against a donor organ's foreign HLA antigens. Other anti-HLA antibodies may be produced against foreign HLA antigens from blood transfusion, child birth, or previous organ transplant.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.

End of Study (EoS) (Synonym of End of Trial)	For studies with collection of human biological samples and/or imaging data, the EoS is defined as Last testing results released of samples collected up to Visit 7* * In this case EoS must be achieved no later than 8 months after LSLV.
Epoch:	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomisation, treatment, follow-up), which applies across all arms of a study. NOTE: Epoch is intended as a standardised term to replace: period, cycle, phase, stage.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis (see section 10.2 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Immunosuppressive therapy:	For protocol purposes, there will be four (4) types of immunosuppressive (IS) therapy.
Induction IS therapy:	For protocol purposes, the "induction" IS therapy will be defined as the combination of all IS therapy used pre-transplant and in the immediate post-transplantation period to specifically prevent hyper-acute and acute allograft rejection. This is sometimes also referred to as initial IS therapy. These medications may include varying combinations of (listing not exhaustive) basiliximab, thymoglobulin, high-dose corticosteroids, high-dose mycophenolate mofetil, high-dose mycophenolate acid, tacrolimus, cyclosporine, and sirolimus. To be considered induction IS therapy for protocol purposes, the IS therapy does not need to include the use of monoclonal or polyclonal antibodies'.
Maintenance IS therapy:	For protocol purposes, the "maintenance" IS therapy will refer to the IS therapy used routinely post-transplantation, at reduced dosages and/or reduced number of medications as compared to the induction IS. Maintenance IS therapy is to prevent host-vs.-graft disease while minimizing potential medication associated adverse events and

	toxicities. This is sometimes also referred to as routine medications. Maintenance medications may include varying combinations of (listing not comprehensive) low-dose corticosteroids, low-dose mycophenolate mofetil, low-dose mycophenolate acid, tacrolimus, cyclosporin and sirolimus.
Therapeutic IS therapy:	For protocol purposes, "therapeutic" IS therapy will refer to any increase in number and/or dosage of IS therapies prescribed for a subject, previously on maintenance IS therapy, for the purpose of acutely treating allograft rejection. This is sometimes also referred to as "Rejection" therapy.
Other IS therapy:	For protocol purposes, "other" IS therapy will refer to the of any IS therapy for purposes other than allograft preservation. E.g. the use of prednisone treatment for a gout flare.
Investigational vaccine: (Synonym of Investigational Medicinal Product)	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions

CCI [redacted]

CCI [redacted]

CCI

[redacted]

Non-revaccinated subjects:	***Subjects who are ineligible or unwilling to receive both revaccination doses*** **(Amended: 15 June 2020)**
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion: date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	***The International Council on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.*** **(Amended: 15 June 2020)**
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Solicited adverse event:	Pre-specified AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents:	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorised use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule…) at the time of enrollment.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the vaccine or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

12.1.3. Trademarks

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

Trademark Information

The following trademarks are used in the present protocol:

Trademarks of the GlaxoSmithKline group of companies	Generic description
Pandemrix	Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (x-179a)
Shingrix	Zoster Vaccine Recombinant, Adjuvanted

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Zostavax (Merck & Co., Inc.)	Herpes zoster vaccine consisting of high titer live attenuated varicella-zoster virus (Oka strain)

12.2. Appendix 2: Clinical laboratory tests

12.2.1. Clinical laboratory tests

Specific antibody (anti-gE) measurements

Anti-gE ELISA: Anti-gE Ab concentrations will be measured using an anti-gE ELISA. Diluted blood serum samples of study subjects will be added to microtiter wells pre-coated with VZV gE recombinant antigen. Secondary peroxidase-conjugated anti-human antibodies will be added, which bind to the primary human anti-gE antibodies. After incubation of the microtiter wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE antibody concentrations are calculated from a standard curve. The assay will be performed on human serum at GSK laboratory or another laboratory designated by GSK.

Intracellular cytokine staining

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

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

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

PCR Assay for confirmation of suspected cases of HZ

HZ cases will be confirmed by a PCR based algorithm that assesses the presence of VZV DNA in samples, and the adequacy of the samples (by assessing the presence of β-actin DNA).

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

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

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

12.2.2. Ascertainment of HZ CASES including PCR testing algorithm to classify suspected HZ cases

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

To classify the suspected case of HZ, samples from the rash lesions (if available) will be collected for laboratory testing by PCR (three samples from separate lesions, collected on the same day, per subject).

If during clinical evaluation at the HZ visit, the investigator determines that adequate rash lesion samples cannot be collected (i.e., less than three lesions present, or if only papules are present), the subject should be asked to return to the study site for collection of additional samples if there is rash progression (i.e., appearance of new/additional lesions if originally less than three lesions present, or appearance of vesicles if originally only papules present) at an *ad-hoc* HZ visit. When the subject returns to repeat sample collection, three samples from separate lesions should be collected. See the SPM for further details on sample collection.

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

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

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

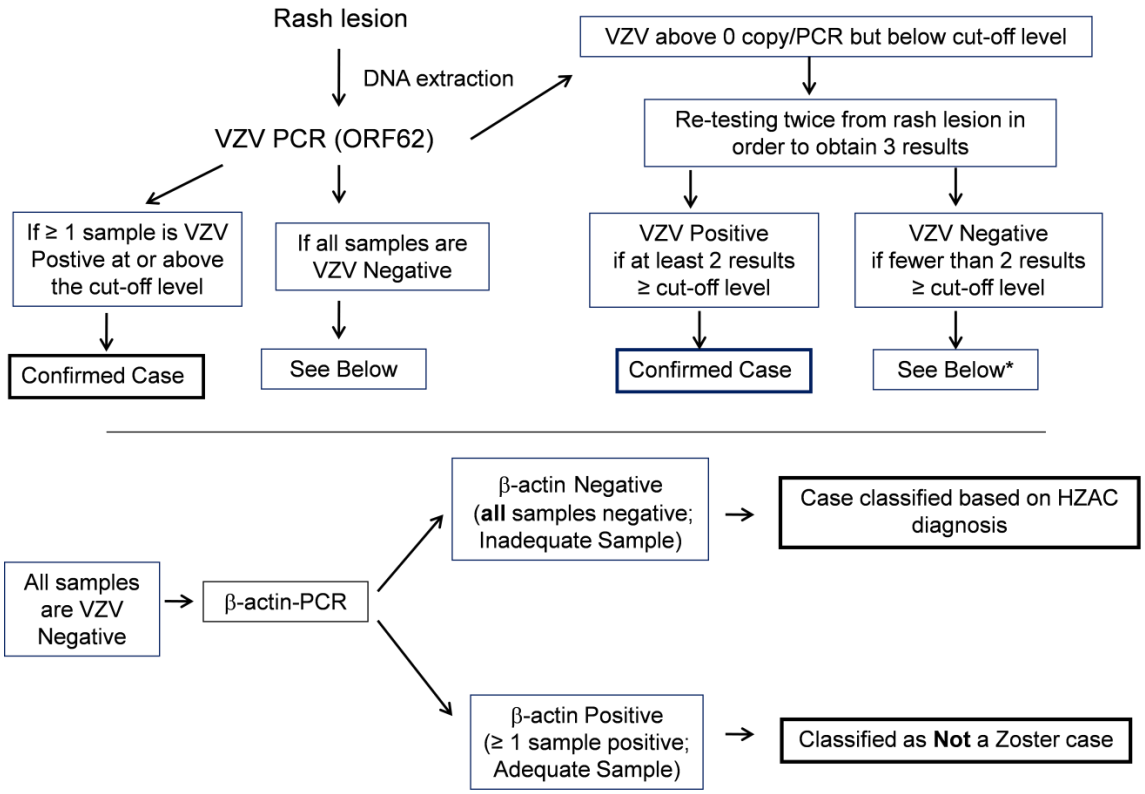
- If PCR results for a particular subject do not confirm or exclude a "suspected HZ case" (i.e. samples coming from a given subject are considered as "inadequate" as both VZV and β-actin PCR results are negative, or no samples are available for the subject), only then will the classification by the HZAC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

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

1. DNA extraction from the rash lesion.
2. VZV PCR assay targeting the orf62 gene is performed to detect VZV in the rash lesion:
    a. If the VZV PCR signal is ≥ the cut-off level, i.e. the technical limit of detection (LOD) of the assay, the sample will be considered as "VZV positive".
    b. If the VZV PCR signal is above 0 copy/ PCR but below the cut-off level of the assay, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain three results per sample. The sample will be considered as "VZV positive" if at least two results out of the three obtained are ≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than two samples are ≥ the cut-off level of the assay.
    c. If the VZV PCR signal is equal to 0 copies/ PCR, the sample will be considered as "VZV negative". If every sample is VZV negative, then extracted DNA from the samples will be assessed for the presence of β-actin DNA to confirm the validity of the rash lesion sampling procedure (see step 3).
3. As described above, if all the samples are VZV negative for a given subject, then β-actin PCR will be performed on "VZV negative" samples to confirm the validity of the sampling procedure.
    a. If the β-actin PCR signal is below the cut-off level of the assay (β-actin Negative), the sample will be considered as "inadequate" as no β-actin DNA from human cells is detected within the rash lesion sample. If all samples are β- actin Negative, then the classification by the HZAC will be used to confirm or exclude the HZ case.
    b. If the β-actin PCR signal is ≥ the cut-off level of the assay (β-actin Positive), the sample will be considered as "valid" but without any VZV DNA. If at least one sample is β-actin Positive, then the HZAC classification of a suspected HZ case will not be part of the decision-making process for HZ case confirmation, and the HZ rash will be considered "VZV negative".

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

Figure 2 Algorithm for HZ case definition by PCR



VZV: Varicella Zoster Virus; PCR: real-time PCR
DNA: Deoxyribonucleic Acid; ORF: Open Reading Frame.
* If the VZV PCR signal is above 0 copy/PCR but below the cut-off level of the assay, it will be considered as "VZV borderline" and will be re-tested twice in order to obtain three results per sample. The sample will be considered as "VZV positive" if at least two results out of the three obtained are ≥ the cut-off level of the assay and it will be considered "VZV negative" if fewer than two samples are ≥ the cut-off level of the assay.
Note: The cut-off level of the VZV PCR assay is defined as the technical limit of detection of the assay (; i.e. lowest concentration that can be detected by PCR in at least 95% of the tests)

12.3. Appendix 3: Clinical laboratories

Table 19 GSK laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Rue de l'Institut, 89 B-1330 Rixensart Belgium
GSK Biological's Clinical Laboratory Sciences, Wavre-Nord Noir Epine	Avenue Fleming, 20 B-1300 Wavre Belgium
GSK Vaccines GmbH Clinical Laboratory Sciences, Marburg, Germany	Emil-von-Behring-Str. 76 35041 Marburg Germany

Table 20 Outsourced laboratories

Laboratory	Address
CEVAC-University of Gent	De Pintelaan, 185 Gent Belgium

12.4. Appendix 4: Study governance considerations

12.4.1. Regulatory and ethical considerations

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

12.4.2. Financial disclosure

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

12.4.3. Informed consent process

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

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

Freely given and written informed consent must be obtained from each subject and/or each subject's LAR(s), as appropriate, prior to participation in the study at Visit 1 (Day 1).

If required by local regulatory authorities or IRB/EC, a second written informed consent will be obtained at Visit 3 (Month 24) prior to performance of any revaccination study procedures.

The content of 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 center.

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

For subjects who become legally emancipated during the course of the study, e.g. become of the legal age of consent, re-consent is sought in accordance with local laws and regulations. The subject can provide consent by signing an ICF, similar to that provided to the parent(s)/LAR(s) at the study start, which summarises the study and includes a consent statement and documents that the subject agrees to continue participating in the study.

Subjects/subjects' LAR(s) must be reconsented 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 subject.

12.4.4. Data protection

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

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

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

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

12.4.5. Committees structure

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

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

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

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

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements as stated in the protocol.

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

Freely given and written informed consent must be obtained from each subject, as appropriate, according to local requirements, prior to participation in the study.

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

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

12.4.6. Publication policy

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

12.4.7. Dissemination of clinical study data

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

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

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

In addition, for studies that are in scope of the EU Clinical Trial Directive, summaries of the results of GSK interventional studies (phase I-IV) in adult population will be posted within defined timelines on the publicly available EU Clinical Trial Register.

If it is not possible to submit a summary of the results within the required timelines in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

	Clinicaltrial.gov	EU
Protocol summary	Before enrollment of subjects	As per CTA submission/Before enrollment of subjects
Results summary	Within 12 months of PCD (Primary and safety endpoint results)/Within 12 months of LSLV* (for secondary endpoint results)	Within 12 months (for adult population studies) of EoS*.

* As defined in the study protocol.

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12.4.8. Data quality assurance

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

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

All subject data relating 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 CRF/eCRF.

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

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

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

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

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

12.4.9. Source documents

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

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

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

12.4.10. Study and site closure

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

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

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

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

The investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.
- Answer data clarification queries from GSK.

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

12.5.1. Definition of AE

12.5.1.1. AE Definition

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

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

12.5.1.2. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).
- Medically attended visits related to adverse events (e.g. Hospital stays, physician visits and emergency room visits).

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

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

12.5.1.3. Events NOT Meeting the AE Definition

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

12.5.2. Definition of SAE

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

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

c. Requires hospitalization or prolongation of existing hospitalization,

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

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

d. Results in disability/incapacity, OR

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

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

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered **serious.**

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

12.5.3. Solicited adverse events

a. Solicited local (injection-site) adverse events

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

Table 21 Solicited local adverse events

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

b. Solicited general adverse events

The following general AEs will be solicited:

Table 22 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

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

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

12.5.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not explicitly solicited using a Subject Diary and that was spontaneously communicated or mentioned in the diary under adverse events by a subject/LAR who has signed the informed consent.

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

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

An unsolicited AE is an AE which includes non-serious and serious AEs unless otherwise specified.

12.5.5. Adverse events of special interest

AESIs for safety monitoring include:

- Allograft rejection, biopsy-proven.
- pIMDs

12.5.5.1. Allograft rejection, biopsy-proven

Biopsy-proven allograft rejection is defined as an AESI. It will be recorded in Expedited Adverse Event Reporting screens, irrespective of the seriousness of the event.

Refer to section 8.1.14 for guidance on the information to be collected for allograft rejections. Refer to section 12.5.10 for reporting details.

12.5.5.2. 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 etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 23. Refer to section 12.5.10 for reporting details.

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

Table 23 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: • Chronic inflammatory demyelinating polyneuropathy, • Multifocal motor neuropathy • Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including: • Diffuse Scleroderma • CREST syndrome • Idiopathic inflammatory myopathies, including: • Dermatomyositis • Polymyositis • Anti-synthetase syndrome. • Rheumatoid Arthritis and associated conditions including: • Juvenile Idiopathic Arthritis • Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: • Ankylosing Spondylitis, • Reactive Arthritis (Reiter's Syndrome), • Undifferentiated Spondyloarthritis, • Psoriatic Arthritis, • Enteropathic arthritis. • Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localized Scleroderma (Morphoea).

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

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

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

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

12.5.6. COVID-19 (Amended: 15 June 2020)

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). When reporting an AE (serious or non-serious as defined in Section 12.5.2) related to COVID-19 infection, the following verbatim terms should be used according to World Health Organisation (WHO) definition (Please refer to Appendix 9):

- ***Suspected COVID-19 infection; or***
- ***Probable COVID-19 infection; or***
- ***Confirmed COVID-19 infection***

Information pertaining to COVID-19 infection should be recorded at the next scheduled visit as medical history on the COVID-19 specific eCRF.

(Amended: 15 June 2020)

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

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to sections 12.5.1 and 12.5.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

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

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

12.5.8.1. Pregnancy

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

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

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

The following should always be considered as SAE and will be reported as described in sections 12.5.10.1 and 12.5.10.4:

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

  Note: the 22 weeks' cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the fetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine will be reported to GSK as described in section 12.5.10. While the investigator is not obligated to actively seek this information from former subjects, he/she may learn of a pregnancy through spontaneous reporting.

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

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

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

Subject Diary training should be directed at the individual(s) who will perform the measurements of AEs and who will enter the information into the Subject Diary. This individual may not be the subject/subjects' LAR(s), but if a person other than the subject/subjects' LAR(s) enters information into the Subject Diary, this person's identity must be documented in the subject's source record. Any individual that makes entries into the Subject Diary must receive training on completion of the Subject Diary at the time of the visit when Subject Diary is dispensed. This training must be documented in the subject's source record.

At each revaccination visit, a Subject Diary card will be provided to the subject or subjects' LAR(s). The subject or subjects' LAR(s) (or subject's caregiver) will be instructed to measure and record the oral body temperature, and any solicited local/general AEs (i.e. on the day of revaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of revaccination and during the next 29 days occurring after revaccination). The subject or subjects' LAR(s) (or subject's caregiver) will be instructed to return the completed Subject Diary card to the investigator at the next study visit.

- Collect and verify completed Subject Diary cards during discussion with the subject on Visit 4 (Month 25) and on Visit 5 (Month 26).
- Any unreturned Subject Diary cards will be sought from the subject through telephone call(s) or any other convenient procedure.
- The investigator will transcribe the collected information into the eCRF in English.

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

All AEs during 30 days following administration of each dose of study vaccine (from day of revaccination and 29 subsequent days) must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine at Visit 3 (Month 24) during revaccination phase and will end at Visit 6 (Month 37) for each subject (See section 12.5.10 for instructions on reporting of SAEs). However, any SAEs assessed as related to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to

a GSK product will be recorded from the time a subject consents to participate in the study until the subject is discharged from the study.

SAEs that are related to the study vaccine administered during revaccination phase will be collected and recorded from the time of the first receipt of study vaccine at Visit 3 (Month 24) until the subject is discharged from the study or until the end of the study (See section 12.5.10 for instructions on reporting of SAEs).

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the enrollment visit [Visit 1 (Day 1)] up to the last study visit [Visit 7 (Month 49)].

After informed consent is obtained, the following events that occurred since the primary follow-up study ZOSTER-041 ***last study visit (Month 13) up to study ZOSTER-073 Visit 1 (Day 1),*** will be collected retrospectively ***and recorded in the medical history:***

- ***all SAEs related to the study vaccine***
- ***all*** suspected ***renal allograft rejections***
- ***all*** biopsy-proven renal allograft rejections
- ***all*** suspected ***episodes of HZ considered as SAEs***
- ***all clinically-***confirmed episodes of HZ considered as SAEs

(Amended: 15 June 2020)

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

The time period for collecting and recording pregnancies will begin at Visit 1 (Day 1) and will end at the last study visit [Visit 7 (Month 49)]. See section 12.5.10 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine at Visit 3 (Month 24) during revaccination phase and will end at Visit 6 (Month 37), approximately 12 months following administration of the last revaccination dose. See section 12.5.10.5 for instructions on reporting of pIMDs.

The time period for collecting and recording of biopsy-allograft rejections will begin at the enrollment visit [Visit 1 (Day 1)] and will end at the last study visit [Visit 7 (Month 49)]. See section 12.5.10.5 for instructions on reporting of renal allograft rejection.

The time period for collecting and recording of IMCs (including HZ) will begin at the enrollment visit [Visit 1 (Day 1)] and will end at the last study visit [Visit 7 (Month 49)]. See section 12.5.10.5 for instructions on reporting of HZ.

Of note, any medical events that occurred since the ZOSTER-041 last study visit (Month 13) up to study ZOSTER-073 Visit 1 (Day 1) will be recorded in medical history section on the eCRF and should not be reported via expedited reporting.
(Amended: 15 June 2020)

Evaluation of adverse events and serious adverse events

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

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

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

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

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

12.5.9.1.2. Assessment of adverse events

Assessment of intensity

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

Table 24 Intensity scales for solicited adverse events

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

*Fever is defined as temperature ≥38.0°C. The preferred location for measuring temperature in this study is the oral cavity.

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

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

The preferred route for recording temperature in this study is oral. When there is no other alternative, the temperature may be recorded by another route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.

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

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (In adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in section 12.5.2.

Assessment of causality

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

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

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

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

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

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

If an event meets the criteria to be determined as 'serious' (see section 12.5.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

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

Assessment of outcomes

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

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

12.5.9.1.3. Medically attended visits

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

12.5.10. Reporting of SAEs, pregnancies, and other events

12.5.10.1. Prompt reporting of SAEs, pregnancies, and other events to GSK

SAEs that occur in the time period defined in section 12.5.9 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in section 12.5.9 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator becomes aware of the pregnancy.

AESIs that occur in the time period defined in section 12.5.9 will be reported promptly to GSK within the timeframes described in Table 17, once the investigator determines that the event meets the protocol definition of a AESIs.

12.5.10.2. Expedited reporting of SAEs to GSK

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

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

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

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

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

12.5.10.4. Completion and transmission of pregnancy reports to GSK

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

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

12.5.10.5. Reporting of AESI's to GSK

Once an AESI is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows specify that the event is an AESI 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 AESIs standard questionnaire provided. Even if the investigator does not have all information regarding an AESI, 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 AESI causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the AESI.

Refer to section 12.5.10.3 for back-up system in case the electronic reporting system does not work.

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

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

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

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

12.5.12.1.1. Follow-up during the study

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

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

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

AESIs of HZ cases 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 resolution of HZ-rash and/or HZ-pain or study conclusion, Visit 7 (Month 49).

AESIs of biopsy-proven allograft rejections documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits until:

- the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or
- study conclusion, Visit 7 (Month 49).

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

The investigator will follow subjects:

- with SAEs, AESIs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

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

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

12.5.12.3. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than 6 to 8 weeks after the estimated date of delivery.

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

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

12.6.1. Definitions

12.6.1.1. Woman of Childbearing Potential (WOCBP)

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

12.6.1.1.1. Women in the following categories are not considered WOCBP

- Premenarchal

  Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non- childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

- Premenopausal female with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

- Postmenopausal female

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

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

12.6.2. Contraception guidance

Female subjects of childbearing potential are eligible to participate if they agree to use an adequate contraception consistently and correctly according to the methods listed in GSK list of highly effective contraceptive methods provided in Table 25.

Table 25 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 (estrogen- 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
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject, *(The information on the male sterility can come from the site personnel's review of the subject's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

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

(Amended: 15 June 2020)

12.6.3. Collection of pregnancy information

12.6.3.1. Female Subjects who become pregnant

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on subject and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in 12.5.10. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Refer to sections 12.5.9, 12.5.10 and 12.5.12.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female subject who is or becomes pregnant while participating from 1 month before Visit 3 to 1 month after Visit 5 will not be revaccinated and will be encouraged to continue other study procedures for long term assessments.

12.7. Appendix 8: Country-specific requirements

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

12.8. Appendix 9: Case Definition for COVID-19 Coronavirus Infection (Amended: 15 June 2020)

WHO Case Definition (Version: March 20, 2020):

- ***Suspected case***
  - ***A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR***
  - ***A patient with any acute respiratory illness AND having been in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; OR***
  - ***A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.***
- ***Probable case***
  - ***A suspect case for whom testing for the COVID-19 virus is inconclusive (inconclusive being the result of the test reported by the laboratory); OR***
  - ***A suspect case for whom testing could not be performed for any reason.***
- ***Confirmed case***
  - ***A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.***

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

- ***Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;***
- ***Direct physical contact with a probable or confirmed case;***
- ***Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR***
- ***Other situations as indicated by local risk assessments.***

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.

(Amended: 15 June 2020)

12.9. Appendix 10: Amendments and Administrative Changes to the Protocol

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

Document history	
Document	**Date**
Amendment 1	15-Jun-2020
Protocol Version 1	07-Jun-2019

Overall rationale for the Amendment 1:

The purpose of the amendment is to:

- **Outline measures to be applied during special circumstances (e.g., COVID-19 pandemic), to protect participant's welfare and safety, and, as far as possible, to ensure the potential benefit to the participant and promote study integrity.**
- Define study procedures / assessments to allow participation of non-revaccinated subjects in an extended long-term follow-up phase.
- Minor corrections and clarifications

List of main changes in the protocol and their rationale:

Section # and Name	Description of Change	Brief rationale
Section 8.1.16 Study procedures during special circumstances	Added new	To provide guidance on adapting study procedures during special circumstances, such as COVID-19 pandemic
Across the document, including objectives and endpoints sections	Revised text or added new text for non-revaccinated subjects	To nuance differences in study procedures / assessments for non-revaccinated subjects

Detailed description of Protocol Amendment 1:

In the following sections, deleted text is indicated in ~~strikethrough~~ and changed text in ***bold italics***:

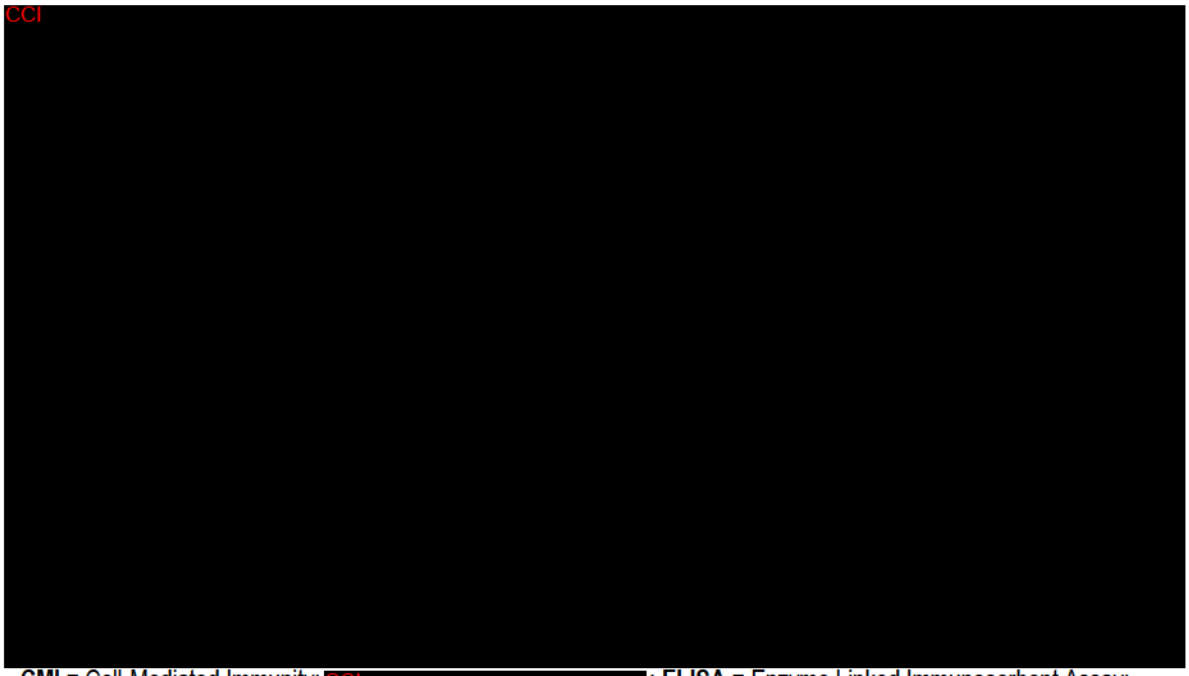
Section 1. SYNOPSIS

Objectives and Endpoints:

Objectives	Endpoints
Primary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of humoral immunity after primary vaccination course.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 12 and Month 24.
Revaccination active phase - Immunogenicity assessment • To evaluate humoral immunity of HZ/su vaccine post-revaccination Doses 1 & 2.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at pre-revaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
Secondary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of cellular immunity after primary vaccination course.	***In CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at Day 1, Month 12 and Month 24~~in a CMI sub-cohort of subjects~~.
LTFU phase - safety assessment • To evaluate safety of HZ/su vaccine from the study ZOSTER-041 last visit to study ZOSTER-073 Visit 3.	***In all subjects:*** • Related-SAEs – Occurrence of SAEs related to primary vaccination as assessed by the investigator from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • HZ episodes – Occurrence of suspected or confirmed HZ cases from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of confirmed HZ cases from Day 1 through Month 24. • AESIs – Occurrence of suspected or biopsy-proven allograft rejections from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of biopsy-proven allograft rejections from Day 1 through Month 24. • Allograft function for episode(s) of allograft rejection. – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic immunosuppressive therapy for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24).

Objectives	Endpoints
	• Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ rash resolution for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24).
Revaccination active phase - Immunogenicity assessment • To evaluate cell-mediated immunity post- revaccination Doses 1 & 2.	***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at pre-vaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26)~~in a CMI sub-cohort of subjects~~.
Revaccination follow-up phase – Immunogenicity assessment • To evaluate persistence of humoral and cell-mediated immune responses post-revaccination Dose 2.	***In all revaccinated subjects:*** • Anti-gE antibody concentrations as determined by ELISA at 12 months and 24 months post-revaccination Dose 2. ***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T- cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at 12 months and 24 months post-revaccination Dose 2 in a CMI sub-cohort of subjects.
Revaccination active and follow-up phases - Safety assessment • To evaluate reactogenicity and safety of the HZ/su vaccine after each revaccination.	***In all revaccinated subjects:*** • Solicited local and general AEs: – Occurrence, duration and intensity of solicited local AEs within 7 days after each revaccination (i.e., the day of revaccination and 6 subsequent days); – Occurrence, duration and intensity of solicited general AEs within 7 days after each revaccination dose (i.e., the day of revaccination and 6 subsequent days) and causal relationship to revaccination by investigator assessment. • Unsolicited AEs – Occurrence, intensity of unsolicited AEs during 30 days after each revaccination (i.e., the day of revaccination and 29 subsequent days) and causal relationship to revaccination by investigator assessment. • SAEs – Occurrence of SAEs (including fatal SAEs) from Dose 1 of revaccination (Month 24) until 12 months post-last revaccination dose (Month 37). – Occurrence of related-SAEs (including related-fatal SAEs) as per investigator assessment from

Objectives	Endpoints
	Dose 1 of revaccination (Month 24) up to study end (Month 49). • AESIs – . – Occurrence of all biopsy-proven allograft rejections from Dose 1 of revaccination (Month 24) up to study end (Month 49) and causal relationship to revaccination by investigator assessment. – Occurrence of pIMDs from Dose 1 of revaccination (Month 24) up to 12 months post-last revaccination dose (Month 37) and causal relationship by investigator assessment. • HZ episodes – Occurrence of confirmed HZ cases from Dose 1 of revaccination (Month 24) up to study end (Month 49). • Allograft function following revaccination – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 3 months before the first revaccination dose until 3 months after the last revaccination dose. • Allograft function for episode(s) of allograft rejection – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic of immunosuppressive therapy. • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ resolution.
CCI [redacted]	



CMI = Cell-Mediated Immunity; CCI ; **ELISA** = Enzyme Linked Immunosorbent Assay; **gE** = glycoprotein E; CCI **ICS** = Intracellular Cytokine Staining; **IL-2** = Interleukin 2; CCI ; CCI ; CCI **TNFα** = Tumor Necrosis Factor-alpha; **IFNγ** = Interferon-gamma; AE = Adverse Event; **SAE** = Serious Adverse Event; **HZ** = Herpes Zoster; **AESI** = Adverse Event of Special Interest; **pIMDs** = potential Immune-Mediated Diseases
* To be performed by ~~a~~the central laboratory if deemed necessary.

The footnotes of the overall design figure have been updated as follows:

HZ/su = Herpes zoster subunit; **LTFU** = Long term follow-up; **Vacc 1-2** = Vaccination dose 1 & 2; **re-Vacc** 1-2 = Revaccinations dose 1 & 2
*The second dose of revaccination (Visit 4, Month 25) will be administered 1 to 2 months after the first revaccination dose.
**Visit 5 (Month 26), Visit 6 (Month 37) and Visit 7 (Month 49) will occur 1, 12 and 24 months after the second revaccination, respectively.
$Phone contact will occur about 35 days before Visit 3 (Month 24) to remind female subjects of childbearing potential to use adequate contraception.
In times of special circumstances, refer to Section 8.1.16.

Section 2. SCHEDULE OF ACTIVITIES (SOA)

The footnotes of Table 3 have been updated as follows:

Interim medical history (section 8.1.4)		O		O	O	O	O	O	~~O~~

Note: The double-line borders indicate analyses that will be performed on all data obtained up to this time point (refer to section 10.4).
● is used to indicate a study procedure that requires documentation in the individual electronic Case Report Form (eCRF).
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
Vacc = Vaccination; **PC** = Phone Contact; **AEs** = Adverse Events; **CMI** = Cell- Mediated Immunity; **SAEs** = Serious Adverse Events; **pIMDs** = potential Immune-Mediated Diseases; **HZ** = Herpes Zoster; **AESI** = Adverse Events of Special Interest; **RT** = Renal Transplant; **ZBPI** = Zoster Brief Pain Inventory.
* Before vaccine administration.
a Phone contact 1 (PC1) will occur about 35 days before Visit 3 (Month 24) to remind female subjects of childbearing potential to use adequate contraception.

b Visit 3 is the day of the first revaccination. Pre-revaccination and post-revaccination activities at Visit 3 are part of Epoch 001 and Epoch 002, respectively.
c Visit 4 is the day of the second revaccination that will be administered 1 to 2 months after the first revaccination. The subsequent visits (Visit 5, Visit 6 and Visit 7) will occur within 1, 12 and 24 months after the second revaccination, respectively.
d An *ad-hoc* HZ Visit will be planned in case of suspected HZ and will be scheduled preferably within 3 calendar days from appearance of HZ symptom(s).
e Study activity to be performed at the next scheduled visit, if this has not been performed during the *ad-hoc* HZ visit.
f A second written informed consent will only be obtained prior to performance of any revaccination procedures, if required by local regulatory authorities or Institutional Review Boards (IRB)/Independent Ethics Committees (IEC).
g Blood sample ***is substituted for urine sample*** for pregnancy ***testing*** ~~only if~~***as*** required by country, local or ethics committee regulations. ***Pregnancy testing should be completed, and results reviewed prior to revaccination.***
[h] For non-revaccinated subjects (see Glossary of terms for the definition and Section 8.1, for details), Visit 4 and 5 will not occur.
For non-revaccinated subjects, see Section 8.1.
Note:
In times of special circumstances, refer to Section 8.1.16 for study procedures.

The footnotes of Table 4 have been updated as follows:

PC 1 = Phone Contact 1
a. Whenever possible the investigator should arrange study visits within this interval.
b. The investigator should endeavour to have the subjects come in for the visits within this interval. However, subjects may not necessarily be excluded from the PPS for analysis of immunogenicity if they make the study visit outside this interval.
c. The second dose will be administered 1 to 2 months (30 to 60 days, inclusive) after the first dose.
**** The allowed interval for Visits 6 and 7 should be the same for both the re-vaccinated and non-revaccinated subjects.***
In times of special circumstances, refer to Section 8.1.16 for allowed interval between study visits.

Section 4 OBJECTIVES AND ENDPOINTS

Table 5 Study objectives and endpoints:

Objectives	Endpoints
Primary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of humoral immunity after primary vaccination course.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 12 and Month 24.
Revaccination active phase - Immunogenicity assessment • To evaluate humoral immunity of HZ/su vaccine post-revaccination Doses 1 & 2.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at pre-revaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
Secondary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of cellular immunity after primary vaccination course.	***In CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at Day 1, Month 12 and Month 24.
LTFU phase - safety assessment • To evaluate safety of HZ/su vaccine from the study ZOSTER-041 last visit to study ZOSTER-073 Visit 3.	***In all subjects:*** • Related-SAEs – Occurrence of SAEs related to primary vaccination as assessed by the investigator from

Objectives	Endpoints
	the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • HZ episodes – Occurrence of suspected or confirmed HZ cases from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of confirmed HZ cases from Day 1 through Month 24. • AESIs – Occurrence of suspected or biopsy-proven allograft rejections from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of biopsy-proven allograft rejections from Day 1 through Month 24. • Allograft function for episode(s) of allograft rejection. – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic immunosuppressive therapy for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ rash resolution for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24).
<u>Revaccination active phase - Immunogenicity assessment</u> • To evaluate cell-mediated immunity post- revaccination Doses 1 & 2.	***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at pre-vaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
<u>Revaccination follow-up phase – Immunogenicity assessment</u> • To evaluate persistence of humoral and cell-mediated immune responses post-revaccination Dose 2.	***In all revaccinated subjects:*** • Anti-gE antibody concentrations as determined by ELISA at 12 months and 24 months post-revaccination Dose 2. ***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T- cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at 12

Objectives	Endpoints
	months and 24 months post-revaccination Dose 2 in a CMI sub-cohort of subjects.
Revaccination active and follow-up phases - Safety assessment • To evaluate reactogenicity and safety of the HZ/su vaccine after each revaccination.	***In all revaccinated subjects:*** • Solicited local and general AEs: – Occurrence, duration and intensity of solicited local AEs within 7 days after each revaccination (i.e., the day of revaccination and 6 subsequent days); – Occurrence, duration and intensity of solicited general AEs within 7 days after each revaccination dose (i.e., the day of revaccination and 6 subsequent days) and causal relationship to revaccination by investigator assessment. • Unsolicited AEs – Occurrence, intensity of unsolicited AEs during 30 days after each revaccination (i.e., the day of revaccination and 29 subsequent days) and causal relationship to revaccination by investigator assessment. • SAEs – Occurrence of SAEs (including fatal SAEs) from Dose 1 of revaccination (Month 24) until 12 months post-last revaccination dose (Month 37). – Occurrence of related-SAEs (including related-fatal SAEs) as per investigator assessment from Dose 1 of revaccination (Month 24) up to study end (Month 49). • AESIs – Occurrence of all biopsy-proven allograft rejections from Dose 1 of revaccination (Month 24) up to study end (Month 49) and causal relationship to revaccination by investigator assessment. – Occurrence of pIMDs from Dose 1 of revaccination (Month 24) up to 12 months post-last revaccination dose (Month 37) and causal relationship by investigator assessment. • HZ episodes – Occurrence of confirmed HZ cases from Dose 1 of revaccination (Month 24) up to study end (Month 49). • Allograft function following revaccination – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 3 months before the first revaccination dose until 3 months after the last revaccination dose. • Allograft function for episode(s) of allograft rejection – Occurrence of allograft dysfunction through assessment of all clinically obtained serum

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Objectives	Endpoints
	creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic of immunosuppressive therapy. • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ resolution.
[redacted]	[redacted]

CMI = Cell-Mediated Immunity; **ELISA** = Enzyme Linked Immunosorbent Assay; **gE** = glycoprotein E; **ICS** = Intracellular Cytokine Staining; **IL-2** = Interleukin 2; **TNFα** = Tumor Necrosis Factor-alpha; **IFNγ** = Interferon-gamma; AE = Adverse Event; **SAE** = Serious Adverse Event; **HZ** = Herpes Zoster; **AESI** = Adverse Event of Special Interest; **pIMDs** = potential Immune-Mediated Diseases
* To be performed ~~aby~~ the central laboratory if deemed necessary.

Section 5.1 Scientific rationale for study design

Study ZOSTER-073 has three distinct phases:

- In the long-term follow-up (LTFU) phase, subjects will be followed for two years* (Day 1 to Month 24). Over the same time period, the occurrences of confirmed HZ cases and biopsy-proven RT rejections will be prospectively collected. Whereas, the occurrences of confirmed/suspected HZ cases; and RT rejections will be retrospectively collected back to subjects' study ZOSTER-041 last visit~~s~~.

  **** Subjects who are ineligible for revaccination or unwilling to receive revaccination (hereafter referred to as non-revaccinated subjects, see Glossary of terms) will be invited to be followed in an extension of the LTFU phase for a total of 4 years (Day 1 to Month 49), with safety and immunogenicity assessments at Months 37 and 49.***

Section 5.3 Overall design

The footnotes of Figure 1 have been updated as follows:

HZ/su = Herpes zoster subunit; **LTFU** = Long term follow-up; **Vacc 1-2** = Vaccination dose 1 & 2; **re-Vacc** 1-2 = Revaccinations dose 1 & 2
*The second dose of revaccination (Visit 4, Month 25) will be administered 1 to 2 months after the first revaccination dose.
**Visit 5 (Month 26), Visit 6 (Month 37) and Visit 7 (Month 49) will occur 1, 12 and 24 months after the second revaccination, respectively.
$Phone contact will occur about 35 days before Visit 3 (Month 24) to remind female subjects of childbearing potential to use adequate contraception.
In times of special circumstances, refer to Section 8.1.16.

Section 5.3 Overall design

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the schedule of activities (SoA) (see Section 2), are essential and required for study conduct. ***In times of special circumstances, refer to Section 8.1.16 for study procedures.***

- **Sampling schedule**:
  - Blood samples to assess humoral immunogenicity will be collected ~~in~~***from*** all subjects at Visit 1 (Day 1), Visit 2 (Month 12), Visit 3 (Month 24), Visit 4 (Month 25)*, Visit 5 (Month 26)*, Visit 6 (Month 37) and Visit 7 (Month 49).
  - Blood samples to assess CMI responses will be collected in ~~a~~the CMI sub-cohort at Visit 1 (Day 1), Visit 2 (Month 12), Visit 3 (Month 24), Visit 4 (Month 25)*, Visit 5 (Month 26)*, Visit 6 (Month 37) and Visit 7 (Month 49).

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****Blood samples will not be collected at Visit 4 and Visit 5 from non-revaccinated subjects. Refer to Section 7 for more details.***

Section 6.2.1.2 Prior/Concurrent clinical study experience

- Concurrently participating in another interventional vaccine or immunosuppressive clinical study, ~~at any time during the study period,~~ in which the subject~~has been or will be~~ ***is*** exposed to an investigational or a non-investigational vaccine/product* (drug) ***at any time during the ZOSTER-073 study.***

Section 7.1 Treatments administered

All ***eligible and willing*** subjects will receive HZ/su vaccine (for details see Table 7).

Section 8 STUDY ASSESSMENTS AND PROCEDURES

In times of special circumstances, refer to Section 8.1.16 for study procedures.

Section 8.1 General study aspects

Non-revaccinated subjects (see Glossary of terms ***for the definition) are not required to return for Visit 4 and Visit 5.***

For these subjects, the following Visit 3 procedures will <u>not</u> occur:

- ***Pregnancy testing in participants unwilling to be revaccinated (see Section 8.1.7)***
- ***Temperature measurement***
- ***Revaccination***

Post-revaccination solicited and unsolicited diary cards (see Section 8.1.12.1)

Section 8.1.7 Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test performed and reviewed prior to any study vaccine administration. ***However, pregnancy testing should not be performed if female subjects are unwilling to be revaccinated.***

Section 8.1.8 Pre-revaccination body temperature

The oral (preferred route) body temperature of each subject needs to be measured prior to any study vaccine administration and recorded in the eCRF. If the subject has fever [fever is defined as temperature ≥38.0°C ***(100.4°F)*** regardless of route of measurement] on the day of vaccination, the revaccination visit will be rescheduled within the allowed interval for this visit (see Table 4). ***Pre-revaccination temperature measurements should not be performed for non-revaccinated subjects.***

Section 8.1.12.1 Diary cards and questionnaires

All ***revaccinated*** subjects will receive:

- **Diary cards:** To be completed by the subject or subject's trained assistant after each revaccination for recording of solicited AEs (from day of revaccination to subsequent 6 days), unsolicited AEs (from day of revaccination to subsequent 29 days), any medically attended visits and all concomitant medications / vaccinations taken from day of revaccination to subsequent 29 days or to next study visit.

  Diary cards should not to be provided to non-revaccinated subjects.

***All subjects will receive*:**

- HZ-specific diary card: To be completed by the subjects or subject's trained assistant beginning immediately (and only) upon development of any symptoms suggestive of HZ and prior to visiting the study site for evaluation of suspected HZ.

Section 8.1.15 Ad-hoc HZ visit and phone call for evaluation of suspected HZ

During the *ad-hoc* HZ Visit, the study staff/investigator will be instructed to:

- ***Document clinical history of suspected HZ and perform physical exam;***
- Transcribe all information from the HZ-specific diary card and ZBPI questionnaire completed by the subject or subject's trained assistant into the eCRF in HZ-specific screens;
- Record concomitant medications/vaccinations, including concomitant medication the subject has already received and/or will receive for HZ treatment or treatment of any HZ-related complications;
- Check if the subject received any medical attention [hospitalisation, emergency room visit, or a visit to or from medical personnel (medical doctor)] for HZ or any HZ-related complication.
- Take digital photographs of HZ rash and upload to e-Clinipix. Please refer to the SPM for specific instructions. At the discretion of the investigator, additional *ad-hoc* HZ follow-up visit(s) may be necessary to manage the progression of the rash, additional photographs of HZ rash may be appropriate.
- If during clinical evaluation the investigator determines that adequate rash lesion samples from at least 3 separate lesions cannot be collected (i.e., <3 lesions present, or if only papules are present), ask the subject to return to the study site for collection of three additional lesion samples (from at least 3 separate lesions).
- Provide an additional supply of ZBPI questionnaires and HZ-specific diary cards to the subjects at *ad-hoc* HZ visit(s). ***Concomitant medications section of*** HZ-specific diary cards ~~, specifically the concomitant medications section~~ ***should be updated as necessary for medication changes,*** ~~and~~***including start/stop dates***. ZBPI questionnaires should be completed by subjects or subject's trained assistant daily

for 30 days from onset of HZ symptoms and then weekly until the resolution of the rash.

Section 8.1.16 Study procedures during special circumstances

During special circumstances *(e.g., COVID-19 pandemic)****, specific guidance from local public health and other competent authorities regarding the protection of subjects' welfare must be applied.***

The following measures may be implemented, at the discretion of the Sponsor, during special circumstances.

<u>For potential subjects unable to be enrolled due to special circumstances:</u>

- ***Potential subjects, who were not able to enroll between 09 December 2019 and 18 March 2020, will be offered enrollment to coincide with the Visit 2 calendar period.***
  - ***Enrollment, Visit 1 and Visit 2 study procedures will be scheduled on the same day.***
  - ***Visit 2 blood samples will be collected and recorded on Visit 2 eCRF per SoA (see Table 3). No Visit 1 blood samples will be collected.***
- ***All subjects will be scheduled together for re-vaccination at Visit 3 (see Table 8 and SPM, for details).***

<u>For all enrolled subjects:</u>

- ***For the duration of COVID-19 pandemic, suspected, probable, and confirmed cases of COVID-19 will be recorded at the next scheduled visit on the COVID-19 specific eCRF.***
- ***Individual subject revaccination visits may be delayed, to allow for treatment of, or vaccination for, COVID-19 (or other special circumstances). Such delay will allow for completion of the therapies and resolution of any therapy-associated AEs and immune-modifying effects (see Section 6.2.2) prior to revaccination.***
- ***As necessary and appropriate, safety follow-up may be made by a telephone call, other means of virtual contact or home visit.***
- ***Diary cards and ZBPI questionnaire may be transmitted from and to the site by conventional mail and/or electronic means.***
- ***Visits for suspected HZ may take place away from the study site, such as in a different location* or at participant's home. If an in-person visit is not feasible, then the medical evaluation of suspected HZ may take place virtually (e.g. video call) with documentation of rash and pain by investigator notes, and by subject-submitted photographs (as possible), diary cards, and ZBPI.***
- ***Biological samples may be collected away from the study site, such as in a different medical location* or at subject's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use (see SPM, for details).***

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

- ***If despite best efforts, it is not possible to collect blood samples within the interval predefined in the protocol (see*** Table 4***), then the interval may be extended as defined in Table 8.***
- ***If despite best efforts, it is not possible to administer the second dose of study vaccine as defined in the protocol (see Table 4), a maximum dose interval of up to 6 months after the first revaccination dose may be used. If the maximum dose interval length is exceeded, then vaccination should be discontinued.***

Impact on the per protocol set (PPS) for immunogenicity will be determined on a case by case basis.

Table 8 Intervals between study visits during special circumstances

Visits	*At the discretion of Sponsor, during special circumstances*		*Notes*
	Visit(s) may be delayed	*Allowed interval (days)*	
Visit 2	*Up to 6 months*		*The length of the allowed interval (85 days) remains, but the start of the interval may be moved by up to 6 months (starting no later than 18 months post-Visit 1), e.g. to avoid potential seasonal recurrence of COVID-19*
PC 1		*30 – 40 days before Visit 3*	
*Visit 3**	*Up to 6 months*		*The length of the allowed interval (85 days) remains, but the start of the interval may be moved by up to 6 months (starting no later than 30 months post-Visit 1), e.g. to avoid potential seasonal recurrence of COVID-19*
Visit 4		*30 – 182 post-Visit 3*	*Optimally 30 - 60 days after Visit 3 (Table 4)*
Visit 5		*30 – 90 post-Visit 4*	*Optimally 30 – 48 days after Visit 4 (Table 4)*
*Visit 6**		*330 – 445 post-Visit 4*	
*Visit 7**		*690 – 805 post-Visit 4*	*Visit 7 may be:* *Scheduled earlier to make up for delays incurred during times of special circumstance, in order to maintain planned duration of the study.* *Delayed or cancelled if special circumstances preclude the original planned visit.*

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

*** The allowed interval for Visits 6 and 7 should be the same for both the re-vaccinated and non-revaccinated subjects.**

Section 8.3.2.2 HZ lesions sampling

The footnotes of Table 9 have been updated as follows:

CMI = Cell-Mediated Immunogenicity; HZ = Herpes Zoster; PCR = Polymerase Chain Reaction; NA = Not Applicable; CCI

* Refer to Section 10.1 for subset description.

*** **Refer to Section 5.3 for non-revaccinated subjects. These subjects will not have Visit 4 and Visit 5 blood draws.***

Section 8.3.4 Biological samples evaluation

The footnotes of Table 14 have been updated as follows:

reVacc = reVaccination; **CMI** = Cell- Mediated Immunogenicity; **Ab** = Antibody; **gE** = recombinant purified Glycoprotein E CCI ; **NA** = not applicable.

*For subjects in CMI sub-cohort a whole blood sample for gE-specific CD4 T-cell testing will be taken at all study visits.

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**refer to section 7.2.2 for the definition of the subsets and method of selection.

**** **Refer to Section 5.3 for non-revaccinated subjects. These subjects will not have Visit 4 and Visit 5 blood draws.***

Section 8.4.2 Time period and frequency for collecting AE and serious adverse event (SAE) information

The footnotes of Table 16 have been updated as follows:

* i.e. consent obtained. reVacc 1: revaccination Dos 1; reVacc 2: revaccination Dos 2

*** **Applicable for revaccinated subjects only***

$ SAEs related to study vaccine include SAEs occurring before the first revaccination Visit 3 (Month 24) considered as related to primary vaccination in study ZOSTER-041, and SAEs related to revaccination course occurring after administration of the first dose from revaccination course in study ZOSTER-073

Section 10.1.1 Sample size calculation

Up to a maximum of 86 subjects meeting the eligibility criteria for enrollment (2 doses of HZ/su vaccine ***in ZOSTER-041***) will be targeted for enrollment in participating centers. Approximately 15% of the enrolled subjects might withdraw or not be evaluable for immunogenicity, therefore the target sample size will be approximately 73 subjects evaluable for humoral immunogenicity in per-protocol set (as defined in section 10.2).

Section 10.2 Populations for analyses

Analysis Set	Description
Enrolled Set	All subjects with a complete vaccination course (2 doses of HZ/su vaccine) in study ZOSTER-041 who met the eligibility criteria and signed informed consent in the current study.
PPS for analysis of persistence (LTFU phase from Visit 1 to Visit 3)	The PPS for analysis of persistence will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the Enrolled set for whom persistence immunogenicity endpoints measures after primary vaccination course are available *from* Visit 1 (Day 1) ~~, Visit 2 (Month 12) and~~*to* Visit 3 (Month 24).
ES for revaccination phase	The ES for analysis of safety will include all subjects with at least one HZ/su vaccine dose administered in the study ZOSTER-073.
PPS for Immunogenicity after revaccination course (revaccination active phase)	The PPS for analysis of immunogenicity after revaccination will be defined by time-point and will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the ES for revaccination who have received one or two doses of revaccination schedule up to the time point considered *from* Visit 3 ~~(Month 24, Visit 4 (Month 25) and~~*to* Visit 5 (Month 26).
PPS for persistence after revaccination course (revaccination follow-up phase)	The PPS for persistence for analysis of immunogenicity after revaccination will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the ES for revaccination for whom persistence immunogenicity endpoints measures after revaccination course are available *from* Visit 6 (Month 37) ~~and~~*to* Visit 7 (Month 49).

PPS = per protocol set, ES = exposed set

For non-revaccinated subjects, the enrolled set will be used for analyses of safety and immunogenicity. Details will be described in the statistical analysis plan (SAP).

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Section 10.3.4 Safety analyses

LTFU phase

Endpoint	Statistical Analyses for LFTU phase
Primary	NA
Secondary	• Percentage of subjects reporting history of at least one SAE related to primary vaccination in study ZOSTER-041 classified by MedDRA Primary System Organ Class (SOC) and Preferred Term (PT) from ZOSTER-041 last study visit ***(Month 13)*** to ZOSTER-073 Day 1 will be tabulated with exact 95% CI. • Percentage of subjects reporting at least one SAE related to primary vaccination classified by MedDRA Primary SOC and PT from ZOSTER-041 Day 1 to ZOSTER-073 Month 24 will be tabulated with exact 95% CI. • ***Percentage of subjects with at least one biopsy-proven allograft rejection reported from ZOSTER-073 Day 1 to ZOSTER-073 Month 24 will be tabulated with exact 95% CI.*** • Listing of subjects with history of suspected allograft rejection or history of biopsy-proven allograft rejections from ZOSTER-041 last study visit to ZOSTER-073 Day 1 will be provided. • Listing of subjects with biopsy-proven allograft rejections from ZOSTER-~~041~~***073*** Day 1 to ZOSTER-073 Month 24 will be ***provided*** ~~tabulated with exact 95% CI~~. • Listing of subjects with history a suspected HZ episode from ZOSTER-041 last study visit to ZOSTER-073 Day 1 will be provided. • Listing of subjects with a confirmed HZ episode from ZOSTER-073 Day 1 to ZOSTER-073 Month 24 will be provided. • Number of subjects with declining allograft function, as determined by serum creatinine measurements will be detailed in the SAP.

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Section 12.1.2 Glossary of terms

Non-revaccinated subjects:	***Subjects who are ineligible or unwilling to receive both revaccination doses***
Protocol amendment:	***The International Council on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.***

Section 12.5.6 COVID-19

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). When reporting an AE (serious or non-serious as defined in Section 12.5.2) related to COVID-19 infection, the following verbatim terms should be used according to World Health Organisation (WHO) definition (Please refer to Appendix 9):

- ***Suspected COVID-19 infection; or***
- ***Probable COVID-19 infection; or***
- ***Confirmed COVID-19 infection***

Information pertaining to COVID-19 infection should be recorded at the next scheduled visit as medical history on the COVID-19 specific eCRF.

Section 12.5.9.1 Time period for detecting and recording adverse events, serious adverse events and pregnancies

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the enrollment visit [Visit 1 (Day 1)] up to the last study visit [Visit 7 (Month 49)].

~~All SAEs related to the study vaccine~~ ***After informed consent is obtained, the following events*** that occurred since the primary follow-up study ZOSTER-041 ***last study visit (Month 13) up to study ZOSTER-073 Visit 1 (Day 1),*** will be collected retrospectively ~~after informed consent is obtained.~~***and recorded in the medical history:***

- ***all SAEs related to the study vaccine***
- ***all*** suspected ~~or~~***renal allograft rejections***
- ***all*** biopsy-proven renal allograft rejections ~~considered as SAEs that occurred since the primary follow-up study ZOSTER-041 will be collected retrospectively, after informed consent is obtained.~~
- ***all*** suspected ~~or~~ ***episodes of HZ considered as SAEs***
- ***all clinically-***confirmed episodes of HZ considered as SAEs ~~that occurred since the primary follow-up study ZOSTER-041 will be collected retrospectively, after informed consent is obtained.~~

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

The time period for collecting and recording pregnancies will begin at Visit 1 (Day 1) and will end at the last study visit [Visit 7 (Month 49)]. See section 12.5.10 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine at Visit 3 (Month 24) during revaccination phase and will end at Visit 6 (Month 37), approximately 12 months following administration of the last revaccination dose. See section 12.5.10.5 for instructions on reporting of pIMDs.

The time period for collecting and recording of biopsy-allograft rejections will begin at the enrollment visit [Visit 1 (Day 1)] and will end at the last study visit [Visit 7 (Month 49)]. See section 12.5.10.5 for instructions on reporting of renal allograft rejection.

The time period for collecting and recording of IMCs (including HZ) will begin at the enrollment visit [Visit 1 (Day 1)] and will end at the last study visit [Visit 7 (Month 49)]. See section 12.5.10.5 for instructions on reporting of HZ.

Of note, any medical events that occurred since the ZOSTER-041 last study visit (Month 13) up to study ZOSTER-073 Visit 1 (Day 1) will be recorded in medical history section on the eCRF and should not be reported via expedited reporting.

Section 12.6.2 Contraception guidance

The following footnote has been removed from Table 25:

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

Section 12.8 Appendix 9: Case Definition for COVID-19 Coronavirus Infection

WHO Case Definition (Version: March 20, 2020):

- ***Suspected case***
  - ***A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR***
  - ***A patient with any acute respiratory illness AND having been in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; OR***
  - ***A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.***

- ***Probable case***
  - ***A suspect case for whom testing for the COVID-19 virus is inconclusive (inconclusive being the result of the test reported by the laboratory); OR***
  - ***A suspect case for whom testing could not be performed for any reason.***
- ***Confirmed case***
  - ***A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.***

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

- ***Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;***
- ***Direct physical contact with a probable or confirmed case;***
- ***Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR***
- ***Other situations as indicated by local risk assessments.***

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation.