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

eTrack study number and Abbreviated Title	204878 (ZOSTER-064)
Investigational New Drug (IND) number	BB-IND-13857
Date of protocol	Final: 29 January 2018
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Title	Observational study to assess frailty of subjects during ZOSTER-006 and ZOSTER-022.
Detailed Title	Observational study to assess frailty of subjects during ZOSTER-006 and ZOSTER-022 and HZ efficacy, immunogenicity and safety of HZ/su by frailty status.
Co-ordinating author(s)	• PPD, Lead Scientific Writer • PPD, Senior Scientific Writer • PPD, Scientific Writer, XPE Pharma & Science for GSK Biologicals • PPD, Scientific Writer, XPE Pharma & Science for GSK Biologicals (Administrative Change 3, 11 Feb 2019)
Contributing authors	• PPD, Clinical Research and Development Lead • PPD, Study Delivery Lead • PPD, Lead Statistician • PPD, Lead Statistician • PPD, Oversight Data Management

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Contributing authors (cont.)	• PPD, Director Value Evidence • PPD, Health Economics Biostatistician • PPD, Global Regulatory Affairs (Administrative Change 3, 11 Feb 2019) • PPD, Clinical and Epidemiology Project Lead (CEPL) for Zoster, US RDC

GSK Biologicals' protocol template for observational studies and interventional studies without administration of medicinal products as described in a research protocol based on the Protocol Document Standard version 15.0

Protocol Administrative Change 3 Sponsor Signatory Approval

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IND number	BB-IND-13857
Date of protocol administrative change	Administrative Change 3 Final: 11 February 2019
Detailed Title	Observational study to assess frailty of subjects during ZOSTER-006 and ZOSTER-022 and HZ efficacy, immunogenicity and safety of HZ/su by frailty status.
Sponsor signatory	Anne Schuind, Clinical and Epidemiology Project Lead for Zoster, GlaxoSmithKline Biologicals, US RDC
Signature	_____
Date	_____

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Protocol Administrative Change 3 Rationale

Amendment number: Administrative Change 3
Rationale/background for changes: • The Japan Vaccine Company will no longer be in operation as of 01 April 2019. Therefore, the reference to "Japan Vaccine Co., Ltd." has been changed to "GSK Japan".

Protocol Administrative Change 3 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

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

eTrack study number and Abbreviated Title	204878 (ZOSTER-064)
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Investigator name _____

Signature _____

Date _____

Leiter der klinischen Prüfung name, function and title _____

Signature _____

Date _____

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GSK Japan* **study representative name, function and title**	
Signature	
Date	

***(Administrative Change 3, 11 February 2019)**

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals

Rue de l'Institut 89, 1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

SYNOPSIS

Detailed Title

Observational study to assess frailty of subjects during ZOSTER-006 and ZOSTER-022 and HZ efficacy, immunogenicity and safety of HZ/su by frailty status.

Objective(s)

Primary

- To assess the baseline frailty of subjects enrolled in ZOSTER-006 and ZOSTER-022.

Secondary

- To present the distribution of *SF-36* and *EQ-5D* scores in subjects included in ZOSTER-006 and ZOSTER-022 at b!aseline by country to allow comparison with normative values for those questionnaires in the general population of the countries participating in the study.
- To assess vaccine efficacy against HZ by frailty status.
- To assess HZ burden of illness (BOI) by frailty status.
- To identify predictive factors for individuals developing HZ.
- To describe safety per frailty status.
- To assess humoral immunogenicity by frailty status.

Tertiary

- To describe CMI by frailty status of subjects enrolled in ZOSTER-006 only.

Rationale for the study

In the course of ZOSTER-006 and ZOSTER-022, QoL questionnaires were encoded into the respective trial database only for subjects who developed a suspected HZ episode during the study. This was done to assess the QoL of subjects who developed suspected cases of HZ between the vaccine group and the placebo group. The remaining subjects who did not develop suspected cases of HZ completed the questionnaires; however, these questionnaires were never encoded or analysed as part of ZOSTER-006 and ZOSTER-022. The purpose of this study is to allow for the encoding and analysis of all questionnaires for subjects enrolled in ZOSTER-006 and ZOSTER-022. The aim is to assess the baseline frailty of subjects enrolled in ZOSTER-006 and ZOSTER-022 and to investigate the representativeness of the study population to the general population. Additionally, analysis of efficacy, safety and immunogenicity will be performed by frailty status. The study will also explore if quality of life data and subject characteristics reported by the subjects before the onset of HZ would be predictive of HZ.

	This should help confirm previously hypothesized predictive factors such as age, stress or functional status, and also to assess other potential risk factors such as frailty, fatigue or emotional and mental health.
Study design	• A multi-country, observational, retrospective study. • Study population: All subjects enrolled in ZOSTER-006 and ZOSTER-022. • Type of study: Data to be analysed in this study have been collected in the ZOSTER-006 (eTrack 110390) and ZOSTER-022 (eTrack 113077) and will be combined for assessment of primary, secondary and tertiary objectives. • Data collection: QoL questionnaires and the year of birth of subjects enrolled in ZOSTER-006 and ZOSTER-022. – QoL questionnaires: The *SF-36* is a multi-purpose health survey with 36 questions. The *EQ-5D* is a questionnaire with 5 questions designed as a generic measure of health status that provides a simple descriptive profile and a single index value. The *EQ-5D* defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. • Method: Frailty scores for study subjects in ZOSTER-006 and ZOSTER-022 will be calculated by incorporating the subject's medical history and items from the *SF-36* and *EQ-5D* questionnaires.
Discussion of study design	This is a retrospective, observational study of subjects previously enrolled in ZOSTER-006 and ZOSTER-022, therefore no new subjects will be enrolled in this study and no new ICF will be required from study subjects.
Number of subjects	Approximately 30,000 subjects who were enrolled in ZOSTER-006 and ZOSTER-022
Endpoints	**Primary** • Baseline Frailty Status: – Frailty Status pre-vaccination dose 1 as defined by responses to components of the *SF-36* and *EQ-5D* questionnaire at vaccination day 0 and the subjects coded medical history.

Secondary

- SF-*36* and *EQ-5D* scale scores:
  - At months 0, 14, 26 and 38.
- Confirmed HZ cases:
  - Incidence of HZ cases during ZOSTER-006 and ZOSTER-022 for subjects in the modified Total Vaccinated Cohort (mTVC).
- HZ Burden of Illness:
  - HZ Burden of Illness score for subjects in both ZOSTER-006 and ZOSTER-022 as calculated from the Zoster Brief Pain Inventory (ZBPI).
- Solicited local and general symptoms from ZOSTER-006 and ZOSTER-022:
  - Occurrence, intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset.
- Unsolicited adverse events (AEs) from ZOSTER-006 and ZOSTER-022:
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 - 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects.
- Serious Adverse Events (SAEs) from ZOSTER-006 and ZOSTER-022.
  - Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in all subjects;
  - Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine during the entire study period in all subjects;
  - Occurrence of any fatal SAEs during the entire study period in all subjects.

- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any pIMDs during the entire study period in all subjects.
- Humoral Immunogenicity of the study vaccine in subset of subjects from ZOSTER-006 and ZOSTER-022.
  - Anti-gE and *anti-VZV Ab* concentrations as determined by Enzyme-linked Immunosorbent Assay (ELISA), in a subset of subjects at Months 0, 3, 14, 26 and 38.

Tertiary

- Cell-mediated immunogenicity (CMI) of the study vaccine in subsets of subjects from ZOSTER-006 only.
  - CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38
  - Frequencies of CD4 T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to glycoprotein E (gE) and VZV as determined by intracellular cytokine staining (ICS) in a subset of subjects at Months 0, 3, 14, 26 and 38**.**

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LIST OF ABBREVIATIONS

ATP	According to protocol
BOI	Burden of illness
EQ-5D	EuroQol 5D questionnaire
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HZ	Herpes Zoster
HZ/su	Herpes Zoster Subunit Vaccine (50µg gE/AS01$_B$)
HZAC	Herpes Zoster Ascertainment Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
mTVC	modified Total Vaccinated Cohort
PCR	Polymerase Chain Reaction
PHN	Postherpetic Neuralgia
QoL	Quality of Life
SDV	Source Document Verification
SF-36	Short Form 36 Questionnaire
TTO	Time-Trade-Off
TVC	Total Vaccinated Cohort
VZV	Varicella-Zoster Virus
YOA	Years of Age
ZBPI	Zoster Brief Pain Inventory

GLOSSARY OF TERMS

According to Protocol (ATP)	In ZOSTER-006 and ZOSTER-022, the ATP cohort included all evaluable subjects meeting all eligibility criteria, complying with the procedures and intervals allowed for the analysis, with no elimination criteria during the study.
Case-control study:	A form of epidemiological study where the study population is selected on the basis of whether the subjects do (cases) or do not (controls) have the particular outcome (disease) under study. The groups are then compared with respect to exposure/ characteristic of interest.
Coded:	Data from which personal identifier information has been removed and replaced by a key. These data are not anonymised since a decode listing exists and it is therefore possible to identify the patient under certain circumstances by an authorised or legally appointed third party data custodian, or by the original holder of the data.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all-timepoints within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
modified Total Vaccinated cohort (mTVC)	The mTVC will include only subjects from centres that participate in ZOSTER-064, which will exclude subjects in the TVC who were not administered the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination (i.e. these subjects that were included in the mTVC of ZOSTER-006 and ZOSTER-022.

Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Quality of Life (QoL)	Quality of life is measured, using two questionnaires (*EQ-5D* and *SF-36*) that were completed by the subject. *EQ-5D* and *SF-36* provide multi-dimensional evaluation of the health status.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Total Vaccinated cohort (TVC)	The TVC will include all subjects from centres that participate in ZOSTER-064 and all subjects who had a HZ suspected case in either the ZOSTER-006 or ZOSTER-022 studies. Subjects enrolled in ZOSTER-064 need to have been part of the TVC in ZOSTER-006 or ZOSTER-022.

1. INTRODUCTION

1.1. Background

Varicella-Zoster Virus (VZV) causes two distinct diseases. Varicella (chickenpox) shortly occurs after primary VZV infection and is characterised by systemic illness and a widely disseminated rash. Herpes Zoster (HZ, shingles) occurs when VZV reactivates from latency and typically manifests as a localised, dermatomal rash. The typical HZ rash usually lasts 2 to 4 weeks and is usually accompanied by pain; that is often described as burning, shooting, or stabbing, and pruritus, which can also be severe, may be as common as pain. In some patients, even touching the affected area lightly may cause severe pain, a phenomenon known as allodynia. The most common complication of HZ is postherpetic neuralgia (PHN), defined as pain that persists after the resolution of the HZ rash. Patients affected by PHN typically report constant burning, throbbing, intermittent sharp or electric shock-like pain, or allodynia. PHN tends to improve over a period of months and about 70-80% of cases resolve within 1 year. However, in some persons PHN persists for many years [Dworkin, 2007].

Inclusion of subjects in clinical trials may be biased for various reasons, e.g. inclusion/exclusion criteria, selection of patients by investigators, self-selection of patients. As such, the aim of this study is to explore if the subjects in the ZOSTER-006 and ZOSTER-022 studies were representative of an older adult population. This will be done by exploring the baseline frailty status and quality of life scores of subjects within the studies.

Several studies have demonstrated that the incidence and severity of HZ increases with age [CDC, 2008]. It is also likely that the incidence and severity of HZ is higher in frail subjects. However, as with age vaccine efficacy may somewhat lower in frail subjects. This study will therefore allow a synthesis of the benefit of vaccination in frail subjects, i.e. in terms of increased incidence, vaccine efficacy, safety and immunogenicity.

1.1.1. Risk factors for herpes zoster

Several risk factors for developing HZ have previously been identified, amongst which the age of the individual is the most common. The incidence of HZ is relatively constant at 2-3 cases per 1000 persons per year until age 40, and then increases progressively with age: At 50-59 years of age (YOA) the incidence is about 5 cases per 1000 persons per year, and it increases to 10 cases per 1000 persons per year in people ≥ 60 YOA [CDC, 2008]. Half of all HZ cases occur in subjects over the age of 60, and individuals who reach 85 years old have a 50% chance of having HZ during their lifetime [Oxman, 2005]. Age has also been demonstrated to be a risk factor for the development of PHN amongst patients with HZ [Oxman, 2005; Scott, 2006; Kanbayashi, 2012; Kawai, 2015].

A second factor that has been consistently related to HZ development is the presence of immunosuppressive conditions [Cohen, 2007; Buchbinder, 1992; Langan, 2013]. Other factors have been suggested to be associated with an increase of HZ incidence, including female gender [Fleming, 2004; Jung, 2004; Liu, 2015], race [Fleming, 2004; Schmader, 1998], psychological symptoms such as stress and depression [Irwin, 1998; Schmader, 1998; Lasserre, 2012], or impaired functional status [Wolfe, 2006; Liu, 2015].

Some factors have also been associated with greater incidence of PHN among patients with HZ: psychological symptoms [Clark, 2000; Volpi, 2008], impaired physical and social functional status [Katz, 2005; Drolet, 2010, Kawai, 2015] and severity of the HZ rash and associated pain [Whitley, 1999; Jung, 2004; Opstelten, 2007; Drolet, 2010; Kanbayashi, 2012].

1.1.2 ZOSTER-006 and ZOSTER-022

Two GSK-sponsored Phase III studies investigated the effect of GSK's candidate HZ/su vaccine on the incidence of the disease in subjects 50 YOA and older (ZOSTER-006, eTrack number 110390, NCT01165177, started in 2010) [Lal, 2015] and in subjects 70 YOA and older (ZOSTER-022, eTrack number 113077, NCT01165229, started in 2010), respectively [Cunningham, 2016].

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

As part of the study procedures, each subject enrolled in one of these two studies was asked to complete two quality of life (QoL) questionnaires named respectively *SF-36* and *EQ-5D* at predefined timepoints. These questionnaires were to be completed independently from the fact that subjects had HZ or not and provide relevant information about the QoL (functional status, ability to socialize, mental health, etc.) of subjects before they develop HZ (see APPENDIX A and APPENDIX B for samples of the *SF-36* and *EQ-5D* questionnaires).

1.2. Rationale for the study

In the course of ZOSTER-006 and ZOSTER-022, Quality of Life questionnaires (QoL), *EQ-5D* and *SF-36*, were completed by all study subjects at baseline. Extracting some elements of these questionnaires and combining them with other medical history data allows attributing of frailty scores.

As these questionnaires were encoded into the respective trial databases only for subjects who developed a suspected Herpes Zoster (HZ) episode during the studies, as per the original study protocols, the purpose of ZOSTER-064 is to allow for the encoding of remaining questionnaires of the subjects and analysis of all questionnaires together. This will allow classification in different levels of frailty and therefore will allow baseline frailty assessment of subjects that took part in the ZOSTER-006 and ZOSTER-022 studies. This will inform the representativeness of the study sample to the general population in older adults, i.e. in terms of the proportion of subjects who are pre-frail and frail. In addition, a comparison of the *SF-36* and *EQ-5D* scores in subjects at baseline

with normative values for those questionnaires in the general population of the countries participating in the study (where these values are available) will also provide further insight in the study population and allow to better understand the study population compared to the overall target population for the vaccine.

Analyses pertaining to efficacy, safety and immunogenicity as per frailty score might then also be performed according to the methodology used in the ZOSTER-006 and ZOSTER-022 studies.

Additionally, the data collected can be used to assess if some physical, physiological and/or psychological characteristics reported by the subjects before the onset of HZ would be predictive of HZ. This will help understand the previously hypothesized predictive factors such as stress or functional status, and also to assess other potential risk factors such as frailty, fatigue or emotional and mental health.

2. BENEFIT: RISK ASSESSMENT

ZOSTER-064 study will use data collected as part of the *SF-36* and *EQ-5D* QoL questionnaires completed by subjects in ZOSTER-006 and ZOSTER-022 studies. There are no risks or benefits to subjects in this study because this is a retrospective observational study.

3. OBJECTIVES

3.1. Primary Objective

- To assess the baseline frailty of subjects enrolled in ZOSTER-006 and ZOSTER-022.

3.2. Secondary Objectives

- To present the distribution of *SF-36* and *EQ-5D* scores in subjects included in ZOSTER-006 and ZOSTER-022 at baseline by country to allow comparison with normative values for those questionnaires in the general population of the countries participating in the study.
- To assess vaccine efficacy against HZ by frailty status.
- To assess HZ burden of illness (BOI) by frailty status.
- To identify predictive factors for individuals developing HZ.
- To describe safety per frailty status.
- To assess humoral immunogenicity by frailty status.

3.3. Tertiary Objectives

- To describe CMI by frailty status of subjects enrolled in ZOSTER-006 only.

4. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 8), are essential and required for study conduct.

- Type of design: Observational, retrospective study.
- Study population: Adults aged ≥50 years of age who participated in either ZOSTER-006 or ZOSTER-022.
- Type of study*:* to be combined with other protocols for analysis*:* data to be analysed in this study have been collected in ZOSTER-006 (eTrack 110390) and ZOSTER-022 (eTrack 113077).
- Data collection*:* CRF/eCRF
- Duration of the study: The time between the first and the last information to be encoded will be approximately 8 months.

4.1. Discussion of study design

This is a retrospective, observational study, therefore no new subjects will be enrolled in this study and no new ICF will be required from study subjects (see Section 7.2). In ZOSTER-006 and ZOSTER-022, encoding of QoL questionnaires (*SF-36*, *EQ-5D*) was only performed for subjects who developed a suspected HZ episode during the study. This was done to assess the QoL of subjects who developed suspected cases of HZ between the vaccine group and the placebo group. The remaining study subjects who did not develop suspected cases of HZ completed the questionnaires; however, these questionnaires were never encoded or analysed as part of ZOSTER-006 and ZOSTER-022. The purpose of ZOSTER-064 is to allow for the encoding of the remaining questionnaires to assess the baseline frailty of all the subjects in ZOSTER-006 and ZOSTER-022.

5. HZ CASE DEFINITION

Classification as a HZ confirmed case was done during ZOSTER-006 and ZOSTER-022, after confirmation of all suspected HZ cases by either of the two following ways:

- Polymerase Chain Reaction (PCR):

  Rash lesion samples were collected from subjects clinically diagnosed as having a suspected case of HZ. The samples were transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals using standardised and validated procedures for laboratory diagnosis of HZ by PCR. For more information, please refer to Appendix B of the ZOSTER-006 protocol.

- The HZ Ascertainment Committee:

All suspected HZ cases were referred to the HZ Adjudication Committee (HZAC). The HZAC classified all referred cases as either "HZ", "not HZ", or "not able to decide". However, the HZAC classification was to serve as the final case definition only when the case could not be confirmed or excluded by PCR, e.g., when all samples from a given subject were inadequate (as when both VZV and β-actin PCR results were negative), or when no samples were available for a given subject. If the case could not be confirmed or excluded by PCR and the HZAC final outcome was 'not able to decide', the overall final outcome was "No possible classification"; for analysis the categories "not HZ" and "No possible classification" were considered as "not HZ".

6. STUDY POPULATION

6.1. Number of subjects/ centres

Approximately 30,000 subjects enrolled in ZOSTER-006 and ZOSTER-022

There will be no new subjects enrolled in the ZOSTER-064 study. The protocol is developed to allow for the encoding into the eCRF of all QoL questionnaires of subjects enrolled in ZOSTER-006 and ZOSTER-022 and analysing frailty status.

6.2. Inclusion criteria for the study

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- All subjects enrolled in ZOSTER-006 and ZOSTER-022 (See Section 7.2 and 8.3.1)

6.2.1. Inclusion criteria for the study data encoding

- All subjects enrolled in ZOSTER-006 and ZOSTER-022 (See Section 7.2 and 8.3.1)
- Subjects who died or were lost to follow-up during ZOSTER-006 and ZOSTER-022 will be considered for enrolment in ZOSTER-064 and their data/questionnaires up to that point will be used.

See Section 8.1 for site specific subject lists.

6.3. Exclusion criteria for the study

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- Subjects who were excluded from all analyses from ZOSTER-006 and ZOSTER-022. This will include any subject eliminated following deviations from GCP compliance.

6.3.1. Exclusion criteria for data encoding

- Subjects who developed a suspected HZ case during ZOSTER-006 and ZOSTER-022 (since their QoL questionnaires were encoded in the eCRF for ZOSTER-006 and ZOSTER-022).

7. CONDUCT OF THE STUDY

7.1. Regulatory and ethical considerations

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

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

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Investigator reporting requirements as stated in the protocol.

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

7.2. Informed consent

ZOSTER-064 is a study related to ZOSTER-006 and ZOSTER-022 that allows for encoding and analysis of questionnaires already completed by the subjects who were part of those earlier studies. Not all of the previously completed questionnaires have been encoded and analysed yet. As such, ZOSTER-064 will provide an opportunity to assess the frailty index of all subjects enrolled in ZOSTER-006 and ZOSTER-022.

Every subject considered for inclusion in this study has previously signed an ICF from the investigational sites of ZOSTER-006 or ZOSTER-022. The ICF signed by the patients in ZOSTER-006 and ZOSTER-022 allows for the use of all collected information in new studies. In these ICFs, it was specified that:

"The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines / products / medicines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies you).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future."

Since consent has been obtained in the prior studies (ZOSTER-006 and ZOSTER-022), it is the Sponsor's request to obtain a waiver of informed consent from subjects to be enrolled in ZOSTER-064.

8. DETAILED STUDY PROCEDURES

8.1. Subject identification

Subjects will be identified by the same subject identification number as in ZOSTER-006 and ZOSTER-022, PPD This will prevent from the possibility of having two subjects enrolled in two different studies with the same identification number.

Sites will be provided with a list of subjects for whom questionnaires and data should be encoded. To help the investigator/delegate identify subjects for which data and QoL questionnaires are to be encoded, the list will include (but may not be limited to) the following information for each subject:

- Subject identification number in ZOSTER-006 or ZOSTER-022
- New subject identification number to be used in ZOSTER-064
- Site number
- Date of birth (year)
- Date of subject's consent withdrawal, when applicable
- Occurrence of suspected HZ episode in ZOSTER-006 and ZOSTER-022

8.2. Outline of study procedures

Table 1 List of study procedures

Activity	Epoch-001
Check inclusion/exclusion criteria*	○
Encoding of subject's year of birth**	●
Encoding of QoL questionnaires **	●
Study conclusion (Investigator's signature)**	●

QoL: quality of life
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure performed by GSK and not documented in the eCRF.
* To be performed by GSK.
** Procedure to be performed for subjects with no suspected HZ episode during ZOSTER-006 and ZOSTER-022.
Refer to Section 8.3 for details about the study procedures.

8.3. Detailed description of study procedures

8.3.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 6.2 and 6.3, respectively, before encoding of subject data.

Checking of the eligibility criteria will be performed centrally. Sites will receive a list of subjects for which data and QoL questionnaires should be encoded (see Section 8.1).

8.3.2. Encoding of data in the ZOSTER-064 eCRF

A new eCRF database (using the Inform system) will be created for ZOSTER-064.

8.3.2.1. Demographic characteristics

The list of subjects for which demographic characteristics need to be encoded in the ZOSTER-064 eCRF will be provided to the sites (see Section 8.1).

Demographic characteristics to be encoded in the ZOSTER-064 eCRF include:

- the subject identification number to be used in ZOSTER-064
- the site number,
- the date of birth (year).

These data will be provided in the list of subjects that will be sent to the sites.

To note: Additional subject's information related to (but not limited to) medical history, development of an immune-compromising condition or taking immune-suppressive treatments will be used to perform the analysis. These data **do not** need to be encoded on the ZOSTER-064 eCRF, but will be retrieved centrally from the ZOSTER-006 and ZOSTER-022 databases and linked to perform the required analyses.

8.3.3. Encoding of QoL questionnaires

The list of subjects for which QoL questionnaires (*SF-36* and *EQ-5D)* need to be encoded in the ZOSTER-064 eCRF will be provided to the sites (see Section 8.1).

Reminder: Eligible subject for this study, for which QoL questionnaires and the year of birth should be encoded, were those enrolled in ZOSTER-006 and ZOSTER-022. This includes any subjects that completed the study, data collected up to withdraw of consent for subjects who withdrew from the study, or data collected up to date of death for subjects who died (as documented in the database for ZOSTER-006 and ZOSTER-022), and whose questionnaires were not previously encoded into the eCRF during these studies (subjects who did not have suspected HZ).

8.3.4. Study conclusion

The investigator/delegate will:

- review all the data encoded in eCRF to ensure accuracy and completeness,
- sign the eCRF.

8.4. Biological sample handling and analysis

No samples will be collected as part of this study.

9. SAFETY

Not applicable.

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

- Baseline Frailty Status:
  - Frailty Status pre-vaccination dose 1 as defined by responses to components of the *SF-36* and *EQ-5D* questionnaire at vaccination day 0 and the subjects coded medical history.

10.2. Secondary endpoints

- *SF-36* and *EQ-5D* scale scores:
  - At months 0, 14, 26 and 38.
- Confirmed HZ cases:
  - Incidence of HZ cases during the ZOSTER-006 and ZOSTER-022 studies for subjects in the mTVC.

- HZ Burden of Illness
  - HZ Burden of Illness score for subjects in both the ZOSTER-006 and -022 studies as calculated from the ZBPI.
- Solicited local and general symptoms from ZOSTER-006 and ZOSTER-022:
  - Occurrence, intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset.
- Unsolicited adverse events (AEs) from ZOSTER-006 and ZOSTER-022:
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 - 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects.
- Serious Adverse Events (SAEs) from ZOSTER-006 and ZOSTER-022.
  - Occurrence and relationship to vaccination of all SAEs from Month 0 to Month 14 in all subjects;
  - Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine during the entire study period in all subjects;
  - Occurrence of any fatal SAEs during the entire study period in all subjects.
- Occurrence of pre-defined AEs
  - Occurrence and relationship to vaccination of any pIMDs during the entire study period in all subjects.
- Humoral Immunogenicity of the study vaccine in subset of subjects from ZOSTER-006 and ZOSTER-022.
  - Anti-gE and anti-VZV Ab concentrations as determined by Enzyme-linked Immunosorbent Assay (ELISA), in a subset of subjects at Months 0, 3, 14, 26 and 38.

10.3. Tertiary endpoints

- Cell-mediated immunogenicity (CMI) of the study vaccine in subsets of subjects from ZOSTER-006 only.
  - CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38;
  - Frequencies of CD4 T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to glycoprotein E (gE) and VZV as determined by intracellular cytokine staining (ICS) in a subset of subjects at Months 0, 3, 14, 26 and 38.

10.4. Determination of sample size

Approximately 30,000 subjects were enrolled in ZOSTER-006 and ZOSTER-022. Out of these, approximately 1000 subjects will have developed suspected HZ cases over the course of the studies and their QoL questionnaires were encoded in the eCRF for ZOSTER-006 and ZOSTER-022, according to the protocols of those studies, respectively. Therefore approximately 29,000 subjects whose QoL questionnaires were completed and collected but not encoded in the earlier studies, will be encoded in the ZOSTER-064 study. Data encoded as part of the 064 study will be combined with data from the ZOSTER-006 and ZOSTER-022 studies to ensure that subjects data are available for analysis, as appropriate taking into account inclusion/exclusion criteria (see section 6) and cohorts for analysis (see section 10.5).

10.4.1. Number of subjects in the CMI subset

The CMI analyses was performed for ZOSTER-006 only in the Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that had access to a PBMC processing facility within the acceptable time window from sample collection to PBMC processing. The CMI subset contained approximately 350 subjects. As a consequence, analysis of CMI by frailty status is expected to be limited.

10.4.2. Number of subjects in the Humoral subset

The analysis of humoral immunogenicity was performed in both the ZOSTER-006 and ZOSTER-022 studies. The Humoral subset contained approximately 2800 subjects in total between ZOSTER-006 and ZOSTER-022.

10.5. Cohorts for Analysis

10.5.1. Total Vaccinated cohort

The primary analysis of EQ-5D and SF-36 questionnaires will be performed on the TVC. The TVC will include all subjects from centres that participated in ZOSTER-064 and all subjects who had a HZ suspected event in either the ZOSTER-006 or ZOSTER-022 studies.

Subjects enrolled in ZOSTER-064 need to have been part of the TVC in ZOSTER-006 or ZOSTER-022. Refer to the glossary of terms for the definition of TVC.

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

10.5.2. *modified* Total Vaccinated Cohort

The mTVC will include only subjects from centres that participate in ZOSTER-064 (i.e. these subjects that were included in the mTVC of ZOSTER-006 and ZOSTER-022), which will exclude subjects in the TVC who were not administered the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination.

10.5.3. According to Protocol cohort for analysis of immunogenicity

The analysis of the immunogenicity data from the ZOSTER-064 (i.e. combined immunogenicity data from ZOSTER-006 and ZOSTER-022) will be performed on the ATP cohort for analysis of immunogenicity

In ZOSTER-006 and ZOSTER-022, the ATP cohort for analysis of immunogenicity included all evaluable subjects from the ATP cohort for analysis of safety (i.e., those meeting all eligibility criteria, complying with the procedures and intervals allowed for the analysis, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available.

For the immunogenicity tables where different timepoints were presented, the concept of "**Adapted ATP cohort for immunogenicity**" was used to denote that for each timepoint, the corresponding ATP cohort for immunogenicity was used.

More specifically,

- The analyses on the timepoints Month 0 and Month 3 were based on the ATP cohort for immunogenicity Month 3;
- The analysis on the timepoint Month 14 was based on the ATP cohort for immunogenicity Month 14;
- The analysis on the timepoint Month 26 was based on the ATP cohort for immunogenicity Month 26;
- The analysis on the timepoint Month 38 was based on the ATP cohort for immunogenicity Month 38;

The goal was to include all evaluable subjects in the statistical analysis at a specific timepoint, i.e., by including all the subjects not impacted by the elimination code for a specific Adapted ATP cohort for immunogenicity. For the criterion impacted only a specified timepoint (specified blood sampling interval), the subject was excluded from the analysis at that timepoint. For the criteria impacting a specified timepoint and the subsequent ones (e.g., medication forbidden by the protocol), the subject was excluded from the analyses performed at that timepoint onwards. For the criteria impacting all timepoints (e.g., not received two doses), the subject was excluded from the analyses at all-timepoints.

For the analysis of humoral immunogenicity, ATP cohort was further defined as ATP cohort for immunogenicity – Humoral.

For CMI the analysis will be performed on all the samples available (TVC) due to low number of samples.

Compared to the criteria applicable for the ATP cohort for analysis of safety, additional criteria for the ATP cohort for immunogenicity were the following:

- Administration of any medication forbidden by the protocol
- Underlying medical condition forbidden by the protocol
- Concomitant infection related to the disease under study (VZV) which might have influenced immune response
- Concomitant infection not related to the disease under study (VZV) which might have influenced immune response
- Vaccination done but not compliant with Dose 1- Dose 2 vaccination schedules (dates of vaccination not corresponding to protocol intervals or unknown vaccination dates)
- Blood sample taken but not compliant with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS/vaccination dates)
- Serological results not available for antigens POST vaccination (including lost samples, not done, unable to test, absence of parallelism)
- Subject did not belong to the specified Immunogenicity subset
- The subject did not receive two doses

10.6. Derived and transformed data

10.6.1. Handling of missing data

For a given subject and a given measurement, missing or non-evaluable measurements will not be imputed for the analysis. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missingness being either Completely At Random (MCAR) or Missing At Random (MAR) only.

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

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

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

10.6.2. Humoral and CMI immune response

The derivation of data transformed variables for humoral immunogenicity and CMI will be consistent with the derivation provided in the Zoster-006 and Zoster-022 protocols, and the details will be included in the statistical analysis plan.

10.7. Statistical methods

Age in years will be computed as the difference between the date of completion of the QoL questionnaire collected at Month 0 and the date of birth.

As this is an exploratory analysis, no adjustment will be done for multiple comparisons (i.e. a 2-sided significance level of 0.05 will be used).

Spearman correlations coefficients will be presented to display the relationships between pairs of variables. In addition, particularly for the QoL variables, the variance inflation factor and the condition indices for testing multicollinearity will be estimated.

A bootstrap analysis will be carried out to evaluate the robustness of the results with respect to the selection of variables in the final multivariate model.

All analyses will be carried out using SAS Version 9.1.3 or later.

GSK vaccines will be responsible for performing the statistical analysis.

10.7.1. Quality of Life Questionnaires

The *EQ-5D* and *SF-36* QoL questionnaires have been completed by subjects enrolled in ZOSTER-006 and ZOSTER-022. Questionnaires were completed by all subjects to assess the frailty of subjects enrolled in ZOSTER-006 and ZOSTER-022 and also the existence of predictive factors for the development of HZ. Both the *EQ-5D* and *SF-36* questionnaires are international standards and have been appropriately validated.

10.7.2. *SF-36* questionnaire

The *SF-36* is a multi-purpose health survey with 36 questions underlying the construction of 8 scales [Ware, 2001]. All but one of the 36 items (self-reported health transition) are used to score the eight *SF-36* scales (see Table 2). Each item is used in scoring only one scale. Scale scores are to be constructed following the summated ratings and standardized *SF-36* scoring algorithms. See APPENDIX A for a sample of *SF-36* questionnaire.

Table 2 Construction of the eight scales generated from the *SF-36*

Scale	Items	Response Categories Per Item
Physical Functioning (PF)	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	3
Role Physical (RP)	4a, 4b, 4c, 4d	5
Bodily Pain (BP)	7*, 8*	6, 5
General Health (GH)	1*, 11a, 11b*, 11c, 11d*	5
Vitality (VT)	9a*, 9e*, 9g, 9i	5
Social functioning (SF)	6*, 10	5
Role Emotional (RE)	5a, 5b, 5c	5
Mental Health (MH)	9b, 9c, 9d*, 9f, 9h*	5

* Item Reversed

10.7.3. *EQ-5D* questionnaire

The *EQ-5D* questionnaire is a generic measure of health status that provides a simple descriptive profile and a single index value [Kind, 1996]. The *EQ-5D* defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 items are combined to generate health profiles, i.e. a respondent who responds 1 (no problem\no symptom) to all 5 items has a profile "11111" and similarly a subject who responds with the highest level of difficulty or symptom to all items has a profile "33333". These profiles are subsequently converted to a continuous single index utility score using a one to one matching, e.g. "11111"=1.00, "22222"=0.52 and "33333"= -0.59, using value sets (i.e. matching profiles to single index utility scores). As suggested by the developers, for international studies, the United Kingdom Time-Trade-Off (TTO) value set is to be used for the main analysis. Note: higher scores represent a better QoL. See APPENDIX B for a sample of *EQ-5D* questionnaire.

10.7.4. Definition of Frailty

Frailty status will be measured in relation to the accumulation of deficits using a frailty index (FI) adapted from the model proposed by Mitnitski et al. [Mitnitski, 2001]. The different aspects of frailty composing the FI will be assessed through the medical history and *SF-36* and *EQ-5D* questionnaires recorded pre-vaccination dose 1. The frailty index will be a score between 0 and 41 as detailed in Table 3.

Table 3 Detail of frailty components

Item	Scoring method based on response to question	Max Contribution to Frailty Index
SF-36 Q1	Poor=1, Fair=0.5 Good=0, Very good=0 Excellent=0	1
SF-36 Q11A-11D	**Q11A, Q11C** Definitely true=1 Mostly true=0.5 Don't know=0 Mostly false=0 Definitely false=0	4

Item	Scoring method based on response to question	Max Contribution to Frailty Index
	Q11B, Q11D Definitely true=0 Mostly true=0 Don't know=0 Mostly false=0.5 Definitely false=1	
SF-36 Q3I - Q3J	Limited a lot=1 Limited a little=0.5 Not limited at all=0	10
SF-36 Q9A - Q9I	**Q9A, Q9D, Q9E, Q9H**: All of the Time=0 Most of the time=0 Some of the time=0 A little of the time=0.5 None of the time=1 **Q9B, Q9C, Q9F, Q9G, Q9I** : All of the Time=1 Most of the time=0.5 Some of the time=0 A little of the time=0 None of the time=0	9
SF-36 Q2 Compared to one week before, how did the subject rate his / her health in general?	Much worse=1, Somewhat worse=0.5, Same=0 Somewhat better=0 Better=0	1
EQ-5D Mobility	No Problems=0 Some Problems=0.5 Confined to bed=1	1
EQ-5D Anxiety	No Anxiety=0 Moderate Anxiety=0.5 Extreme Anxiety=1	1
EQ-5D Self care	No Problems=0 Some Problems=0.5 Inability to wash or dress himself /herself=1	1
EQ-5D Usual activities	No Problems=0 Some Problems=0.5 Inability to perform usual activities=1	1
Medical history	Cancer	1
	Diabetes Mellitus	1
	High Blood Pressure	1
	Heart Attack	1
	Congestive Heart Failure	1
	Cerebrovascular Disease	1
	Arthritis	1
	Chronic Lung Disease	1
	Stomach or Intestinal Ulcers	1
	Migraine	1
	Cataract	1
	Glaucoma	1
Total		**41**

The medical history is divided into 12 categories; each category will contribute a score of 0 or 1 to the frailty index. The coded medical history database will be searched and subjects with the relevant preferred terms will be assigned to 1 or more of the above categories. A frailty index will be defined by combining all 41 items into a score from 0 to 1 whereby: frailty index = (accumulation of deficits) / (number of items).

Each subject will then be assigned to one of three categories, Non-Frail, Pre-Frail and Frail.

If the frailty index is less than or equal to 0.08 then the subject is classified as Non-Frail. If the score is greater than 0.08 but less than or equal to 0.25 then the subject is classified as pre-frail. If the score is greater than 0.25 then the subject is classified as Frail.

Further details of the calculation of the frailty index will be provided in the statistical analysis plan (SAP).

10.7.5. HZ burden-of-illness score

For each confirmed case of HZ in ZOSTER-006 and ZOSTER-022, responses to the "worst pain" question in the ZBPI were used to calculate a "HZ burden-of-illness" score, defined as the area under the curve (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of the case. Subjects who developed HZ presented "burden-of-illness" scores ranging from 0 up to, theoretically, 1820. A score of 0 is recorded for subjects in whom HZ did not develop during the study period.

10.7.6. Analysis of Frailty

10.7.6.1. Analysis of primary objective

The number and percentage of subjects in each of the frailty status categories (non-frail, pre-frail and frail) pre-vaccination dose 1 will be presented by vaccination group, overall by age and the following age strata: 50-59, 60-69, 70-79 and ≥ 80 YOA.

10.7.6.2. Analysis of secondary objectives

Descriptive statistics of the 8 derived scales of the *SF-36* and the *EQ-5D* Utility is presented at vaccination day 0 and post-vaccination months 14, 26 and 38.

The analyses will also be presented by country to allow comparison with normative values for those questionnaires in the general population of the countries participating in the study.

10.7.6.2.1. Vaccine efficacy against HZ by frailty status

The primary efficacy endpoint in ZOSTER-006 and ZOSTER-022, vaccine efficacy against HZ, will be summarised by baseline frailty status (non-frail, pre-frail, frail) for subjects in the modified Total Vaccinated cohort.

10.7.6.2.2. Vaccine efficacy against HZ BOI by frailty status

Vaccine efficacy against HZ BOI will be analysed by frailty status (non-frail, pre-frail, frail) for subjects in the modified Total Vaccinated cohort.

10.7.6.3. Predictive factors for individuals developing HZ

Only subjects in the placebo vaccination group will be included in the analysis of potential predictive factors. A Cox proportional hazards regression model allowing for time-dependent covariates will be fitted to identify which factors are predictive of developing HZ. The model will include time to HZ as the outcome variable and as potential predictors: demographic and clinical characteristics, *SF-36* variables and *EQ-5D* variables. Subjects who did not develop HZ will be censored at the time of their last study visit. The proportional hazards regression model will be used for both minimally adjusted analyses and multivariate analyses. All factors will initially be examined in an age- and sex-adjusted model with stratification for the clinical trial (i.e. ZOSTER-006 and ZOSTER-022). Factors will be included in the multivariate model if they are associated ($P < 0.05$ using a two-sided test) with HZ in the minimally adjusted model. The multivariate model will also include age and gender with stratification for the clinical trial (i.e. ZOSTER-006 and ZOSTER-022). A step-down (backward) variable selection procedure will be used to fit the final multivariate model. This model will be fitted using the PHREG procedure of the *SAS/STAT* package.

Spearman correlations coefficients will be presented to display the relationships between pairs of variables. In addition, particularly for the quality of life variables, the variance inflation factor and the condition indices for testing multicollinearity will be estimated.

In the analysis, the impact of excluding "suspected but not confirmed cases" of HZ will be explored. Three analyses will be performed whereby it will be assumed that "suspected but not confirmed cases" are (1) "Not in at risk group" (2) "In at risk group" and event=0, (3) "In at risk group" and event=1.

Due to the multiple measurements of the *EQ-5D* and *SF-36* over time, repartition in the HZ positive or HZ negative will be dynamic. Subjects who did not develop a confirmed HZ before one-timepoint (Day 0, Month 14, Month 26 and Month 38) will be considered HZ negative at that timepoint, and the characteristics and QoL scores reported for this subject at the previous timepoint will be considered as **not leading** to HZ.

Subjects who developed a confirmed HZ during the interval between two timepoints will be considered HZ+ at the later timepoint. Characteristics and QoL scores reported for this subject at the last timepoint before onset of HZ will be considered **leading** to HZ**.**

Example: A subject developed a confirmed HZ episode on Month 22:

- Subject's characteristics and QoL scores reported at Day 0 will be considered as **not leading** to HZ.
- Subject's characteristics and QoL scores reported at Month 14 will be considered as **leading** to HZ.

- Subject's characteristics and QoL scores reported at timepoints posterior to onset of HZ (Month 26 and Month 38) will be censored.

Further, details regarding the analysis will be provided in the statistical analysis plan.

10.7.6.4. Analysis of safety by frailty status

This analysis of the safety data from the ZOSTER-064 population will be based on the Total Vaccinated cohort for safety. Solicited, unsolicited and serious adverse events will be analysed by baseline frailty status.

Incidences of SAEs during the 30-day (Days 0 – 29) follow-up period after each vaccination, up to 8 months and during any time during the study classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated by frailty status.

10.7.7. Analysis of immunogenicity

The analysis will be based on the immunogenicity data from the ZOSTER-064 population for subjects in the adapted ATP for analysis of humoral immunogenicity, and for subjects in the TVC for analysis of CMI, respectively (Section 10.5.3).

10.7.7.1. Humoral immune response

Humoral immune response will be assessed and analysed by frailty status in the Humoral Immunogenicity subset.

Descriptive statistics:

If the data allows the following parameters will be tabulated by vaccination group and frailty status at Month 0, Month 3, Month 14, Month 26 and Month 38:

- Geometric mean concentrations (GMCs) of anti-gE/anti-VZV Ab with 95% CIs;
- Humoral seropositivity rates with exact 95% CIs;
- Vaccine response rates with 95% CIs.

10.7.7.2. Cell-mediated immune response

CMI response will only be assessed and analysed in the CMI component of the Immunogenicity subset for subjects in the ZOSTER-006 study.

Descriptive statistics:

For CMI response; provided the data allows, the following parameters will be tabulated by vaccination group and frailty status at Months 0, 3, 14, 26 and 38:

- descriptive statistics of the frequency of CD4 T cell secreting at least two different cytokines (IFN-γ, IL-2, TNF-α,CD40L) to both VZV and gE antigens;

- descriptive statistics of the frequency of CD4 T cell secreting at least IFN-γ and another cytokine (IL-2, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least IL-2 and another cytokine (IFN-γ, TNF-α,CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least TNF-α and another cytokine (IFN-γ, IL-2, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T cell secreting at least CD40L and another cytokine (IFN-γ, IL-2, TNF-α) to both VZV and gE antigens;
- proportion of responders with exact 95% CI.

10.8. Interpretation of analyses

Comparative analyses will be descriptive with the aim to characterise the difference between groups in the endpoint related to the objective. These descriptive analyses should be interpreted with caution.

10.9. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.9.1. Sequence of analyses

There will be one analysis (final analysis) after completion of the data encoding.

10.9.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP or other applicable guidelines, administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, ownership and publications must be met.

11.1. Electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor, omissions or inconsistencies detected by subsequent eCRF (specifically the QoL questionnaires) review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

Once the database is archived and the clinical study report is complete and approved by all parties, each participating investigator will be provided with a CD-ROM of the final version of the data generated at his/her investigational site.

11.2. Study monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

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

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

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

Direct access to all study-site related and source data (QoL questionnaires) is mandatory for the purpose of monitoring review. The monitor will perform eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For eCRF, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g., audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures. The source documents (QoL questionnaires) completed during ZOSTER-006 and ZOSTER-022 will be retained according to what was agreed for these studies.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility and transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available registers and publication policy

Results of research studies, utilizing data or biological samples from previous GSK clinical studies that do not evaluate GSK (or other) vaccines/products are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge.

11.6. Provision of study results to investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK Biologicals site or other mutually-agreed location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. COUNTRY SPECIFIC REQUIREMENTS

12.1. Requirements for Japan

12.1.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (Ministry of Health and Welfare [MHW] No.28 dated 27th March, 1997)" and Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices.

The statement "I acknowledge that I am responsible for the overall study conduct." on the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

Study Monitoring

Direct access to essential documents by monitors, the scope of those documents, and collection of information on safety according to the Japanese local regulation for the post-marketing clinical study will be specified separately in the written procedures for monitoring prepared for this study.

12.1.2. Study period

Study period is included in the Japanese specific exhibit document.

12.1.3. Study administrative structure

Sponsor information and List of Medical Institutions and Investigators are included in the Japanese specific exhibit document.

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APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D Protocol Administrative Change 1	
eTrack study number and Abbreviated Title	204878 (ZOSTER-064)
IND number	BB-IND-13857
Administrative change number:	Administrative change 1
Administrative change date:	27 March 2018
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

- Trademark table updated to include *Shingrix*
- Updated background text to include clinical indication
- Updated study personnel
- Additional spelling and grammar changes were made throughout for clarification.
- The Sample *EQ-5D* questionnaire in Appendix B of the protocol was missing the Visual Analogue Scale (VAS). Images of pages from a sample *EQ-5D* questionnaire, including the VAS, are now provided to replace the *EQ-5D* questionnaire text, to better represent the appearance of the *EQ-5D* questionnaire used in the study.
- To complement the images of an *EQ-5D* sample questionnaire in APPENDIX B, images of pages from a sample *SF-36* questionnaire are now provided to replace the *SF-36* questionnaire text in APPENDIX A, to better represent the appearance of the *SF-36* questionnaire used in this study.

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

Synopsis

Secondary Endpoints

- Solicited local and general symptoms from ZOSTER-006 and ***ZOSTER-022***:

Tertiary Endpoints

– Frequencies of CD4 T cells with antigen-specific Interferon gamma ***(IFN-γ)*** and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha ***(TNF-α)*** and/or CD40 Ligand (CD40L) secretion/expression to glycoprotein E (gE) and VZV as determined by intracellular cytokine staining (ICS) in a subset of subjects at Months 0, 3, 14, 26 and 38.

Trademark Section

Trademarks owned by the GlaxoSmithKline group of companies	Generic description
Shingrix	***Herpes Zoster vaccine non-live recombinant AS01$_a$ adjuvanted***

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

Secondary Endpoint (body of text)

- Solicited local and general symptoms from ZOSTER-006 and ***ZOSTER-022:***

Tertiary Endpoints (body of text)

– Frequencies of CD4 T cells with antigen-specific Interferon gamma ***(IFN-γ)*** and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha ***(TNF-α)*** and/or CD40 Ligand (CD40L) secretion/expression to glycoprotein E (gE) and VZV as determined by intracellular cytokine staining (ICS) in a subset of subjects at Months 0, 3, 14, 26 and 38.

GlaxoSmithKline Biologicals SA

Vaccines R &D
Protocol Amendment 1

eTrack study number and Abbreviated Title	204878 (ZOSTER-064)
IND number	BB-IND-13857
Amendment number:	Amendment 1
Amendment date:	17 October 2018
Co-ordinating author:	PPD, Lead Scientific Writer

Rationale/background for changes:

- This protocol is amended to include the specific requirements of the Japanese Ministry of Health and Welfare, Labour Ministerial Ordinance on the Standards for Conduct of Clinical Trials of Medicinal Products, dated 27 March 1997. (country specific).
- The list of medical conditions used to build the Frailty Index, which is based on the comorbidities terminology of Zoster 063 study, has been clarified.
- Updates to the definition of Cohorts for Analysis.
- Additional typographical changes were made throughout for clarification.

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

Title Page

Co-ordinating author(s)	• PPD, Lead Scientific Writer
	• PPD Lead Scientific Writer
Contributing authors	• PPD Clinical Research and Development Lead
	• PPD Clinical Research and Development Lead
	• PPD, Clinical Research and Development Lead
	• PPD, Study Delivery Lead
	• PPD Study Delivery Lead
	• PPD, Study Delivery Lead
	• PPD, Lead Statistician

- PPD, Study Delivery Lead
- PPD Lead Statistician
- PPD, Oversight Data Management
- PPD, Director Value Evidence
- PPD, Health Economics Biostatistician
- PPD, Global Regulatory Affairs
- PPD, Global Regulatory Affairs
- PPD Clinical and Epidemiology Project Lead (CEPL) for Zoster, Belgian US RDC

GLOSSARY OF TERMS

modified Total Vaccinated Cohort (mTVC)	~~In the~~ ***The mTVC will include only subjects from centres that participate in*** ZOSTER***-064***~~-006 and ZOSTER-022 studies, the mTVC was the primary population for efficacy analysis~~, which ~~excluded~~***will exclude*** subjects in the TVC ~~for efficacy analysis~~ who were not administered~~with~~ the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination ***(i.e. these subjects that were included in the mTVC of ZOSTER-006 and ZOSTER-022***.
Total Vaccinated cohort (TVC)	~~In the ZOSTER-006 and ZOSTER-022 studies, the TVC included all subjects who received at least one dose of study product (vaccine or placebo) and were not withdrawn due to GCP issues.~~ ***The TVC will include all subjects from centres that participate in ZOSTER-064 and all subjects who had a HZ suspected case in either the ZOSTER-006 or ZOSTER-022 studies. Subjects enrolled in ZOSTER-064 need to have been part of the TVC in ZOSTER-006 or ZOSTER-022.***

1.1.2 ZOSTER-006 and ZOSTER-022

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

8.3.2 Encoding of data in the Zoster-064 eCRF

A new eCRF database ~~study~~ (using the Inform system) will be created for ZOSTER-064.

10.5 Cohorts for Analysis

10.5.1 Total Vaccinated cohort - ZOSTER-006 and ZOSTER-022

The primary analysis of *EQ-5D* and *SF-36* questionnaires will be performed on the TVC. The TVC will include all subjects ~~analysed~~ ***from centres that participated*** in ZOSTER-064 ***and all subjects who had a HZ suspected event in either the ZOSTER-006 or ZOSTER-022 studies***.

10.5.2 ~~Modified~~ Total Vaccinated Cohort

The mTVC will ~~be the population~~ ***include only subjects*** from ***centres that participate in*** ZOSTER-064 (i.e. these subjects that were included in the mTVC of ZOSTER-006 and ZOSTER-022), which will exclude subjects in the TVC who were not administered the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination.

10.7.4 Definition of Frailty

Table 3 Detail of frailty components

Item	Scoring method based on response to question	Max Contribution to Frailty Index
Medical history	Cancer	1
	Diabetes ***Mellitus***	1
	High Blood Pressure	1
	~~Myocardial Infarction~~ ***Heart Attack***	1
	CHF	1
	Cerebrovascular ***Disease***	1
	Arthritis	1
	Chronic Lung Disease	1
	Stomach or Intestinal ~~disorders~~ ***Ulcers***	1
	Migraine	1
	Cataract	1
	Glaucoma	1
Total		**41**

If the frailty index is ***less than or equal to*** 0.08 then the subject is classified as Non-Frail. If the score is greater than 0.08 but less than **or equal to** 0.25 then the subject is classified as pre-frail. If the score is greater than ~~or equal to~~ 0.25 then the subject is classified as Frail.

10.7.7.2 Cell Mediated Response

~~If data allows,~~ CMI response will only be assessed and analysed in the CMI component of the Immunogenicity subset for subjects in the ZOSTER-006 study**.**

12. COUNTRY SPECIFIC REQUIREMENTS

12.1 Requirements for Japan

12.1.1 Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (Ministry of Health and Welfare [MHW] No.28 dated 27th March 1997)" and, Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices.

The statement "I acknowledge that I am responsible for the overall study conduct." on the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

Study Monitoring

Direct access to essential documents by monitors, the scope of those documents, and collection of information on safety according to the Japanese local regulation for the post-marketing clinical study will be specified separately in the written procedures for monitoring prepared for this study.

12.1.2 Study period

Study period is included in the Exhibit.

12.1.3 Study administrative structure

Sponsor information and List of Medical Institutions and Investigators are included in the Exhibit.

GlaxoSmithKline Biologicals SA Vaccines R &D Protocol Administrative Change 2	
eTrack study number and Abbreviated Title	204878 (ZOSTER-064)
IND number	BB-IND-13857
Administrative change number:	Administrative change 2
Administrative change date:	13 November 2018
Co-ordinating author:	PPD, Lead Scientific Writer
Rationale/background for changes: • Typographical errors corrected	

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

Synopsis

Endpoints

Secondary

- *SF-36* and *EQ-5D* scale scores:
  - At months 0, 14, 26 and 38.
- Confirmed HZ cases:
  - Incidence of HZ cases during ZOSTER-006 and ZOSTER-022 ***for subjects in the modified Total Vaccinated Cohort (mTVC).***
- Humoral Immunogenicity of the study vaccine in subset of subjects from ZOSTER-006 and ZOSTER-022.
  - Anti-gE ~~Ab~~ and ***anti-VZV Ab*** concentrations as determined by Enzyme-linked Immunosorbent Assay (ELISA), in a subset of subjects at Months 0, 3, 14, 26 and 38.

Section 4: Study Design Overview

- Type of study***: to be combined with other protocols for analysis*** ~~to be combined with other protocols for analysis to be combined with other protocols for analysis~~***:*** data to be analysed in this study have been collected in ZOSTER-006 (eTrack 110390) and ZOSTER-022 (eTrack 113077).
- Data collection***: CRF/eCRF*** ~~CRF/eCRF CRF/eCRF~~

Section 8.3.1: Check inclusion and exclusion criteria

- Check all applicable inclusion and exclusion criteria as described in Sections ~~0~~ ***6.2*** and 6.3**,** respectively, before encoding of subject data.
- Checking of the eligibility criteria will be performed centrally. Sites will receive a list of subjects for which data and QoL questionnaires should be encoded (see Section 8.1).

Section 10.5.2 *modified* Total Vaccinated Cohort

GlaxoSmithKline Biologicals SA

Vaccines R &D
Protocol Administrative Change 3

eTrack study number and Abbreviated Title	204878 (ZOSTER-064)
IND number	BB-IND-13857
Administrative change number:	Administrative Change 3
Administrative change date:	11 February 2019
Co-ordinating author:	PPD, Scientific Writer, XPE Pharma & Science for GSK Biologicals

Rationale/background for changes:

- The Japan Vaccine Company will no longer be in operation as of 01 April 2019. Therefore, the reference to "Japan Vaccine Co., Ltd." has been changed to "GSK Japan".

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

Added to authors*:*

- PPD, Scientific Writer, XPE Pharma & Science for GSK Biologicals
- PPD, Global Regulatory Affairs

On page 2 changed copyright date: © ~~2018~~ ***2019*** GSK group of companies or its licensor.

On page 7 Signature page for Japan representative**:** ***GSK Japan*** ~~JapanVaccine Co~~ representative name, function and title

Section 8.1 Subject Identification: Date of subject***'s*** consent