



Clinical Study Protocol

Sponsor:

GlaxoSmithKline Biologicals

Rue de l'Institut 89, 1330 Rixensart, Belgium

Primary Study vaccine (and number)	GlaxoSmithKline (GSK) Biologicals' lyophilized formulation of the Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A)
eTrack study number and Abbreviated Title	204928 (ZOSTER-063)
Investigational New Drug (IND) number	BB-IND 13857
Date of protocol	Final Version 1: 22 June 2016
Date of protocol amendment	Amendment 1 Final: 22 August 2016 Amendment 2 Final: 16 November 2016
Title	Study to evaluate the impact of reactogenicity on Quality of Life (QoL), after administration of GSK Biologicals' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults \geq 50 years of age.
Detailed Title	A phase III, open label, multicenter study to evaluate the impact of reactogenicity on Quality of Life (QoL), after intramuscular administration of GSK Biologicals' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults \geq 50 years of age.
Co-ordinating author	<ul style="list-style-type: none"> PPD <i>Scientific Writer (Amended 16 November 2016)</i>
Contributing authors (Amended 16 November 2016)	<ul style="list-style-type: none"> PPD <i>Clinical Research and Development Lead</i> PPD <i>Clinical Research and Development Lead</i> PPD <i>Clinical Research and Development Lead</i> PPD <i>Project Statistician</i> PPD <i>Project Statistician</i> PPD <i>Health Economics</i>

eTrack study number and Abbreviated Title	204928 (ZOSTER-063)
Investigational New Drug (IND) number	BB-IND 13857
Detailed Title	A phase III, open label, multicenter study to evaluate the impact of reactogenicity on Quality of Life (QoL), after intramuscular administration of GSK Biologicals' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults \geq 50 years of age.
Contributing authors (continued) (Amended 16 November 2016)	<ul style="list-style-type: none">• PPD [REDACTED], Study Delivery Lead• PPD [REDACTED], Study Delivery Lead• PPD [REDACTED], Study Delivery Lead, Contractor for GSK Biologicals• PPD [REDACTED], Study Delivery Manager, SynteractHCR, Contractor for GSK Biologicals• PPD [REDACTED], Vaccine Supply Coordinator• PPD [REDACTED], Safety representative• PPD [REDACTED], <i>Oversight</i> Data Manager, Keyrus Biopharma, Contractor for GSK Biologicals• PPD [REDACTED], US Regulatory Affairs• PPD [REDACTED], Global Regulatory Affairs• PPD [REDACTED], US Medical Affairs• PPD [REDACTED], Global Medical Affairs• PPD [REDACTED], Global Patent• PPD [REDACTED], Global Vaccine Clinical Laboratories Clinical readout Team Lead• PPD [REDACTED], Lead Statistician• PPD [REDACTED], Clinical and Epidemiology Project Leader (CEPL), Belgian RDC

GSK Biologicals' Protocol DS v 14.1.1

Copyright 2016 the GlaxoSmithKline group of companies. All rights reserved. Unauthorised copying or use of this information is prohibited.

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title 204928 (ZOSTER-063)

IND number BB-IND 13857

Date of protocol amendment Amendment 2 Final: 16 November 2016

Detailed Title A phase III, open label, multicenter study to evaluate the impact of reactogenicity on Quality of Life (QoL), after intramuscular administration of GSK Biologicals' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults \geq 50 years of age.

Sponsor signatory Lidia Oostvogels, MD
Director, Clinical and Epidemiology Project Leader,
Zoster Program, Belgian RDC

Signature

Date

For internal use only

-----Checksum-----!Ver.!Created On - -
67d8391faef64e9d05fd1c8f3a9b938732fdd18a 2.0 11/25/2016 3:45:45 PM - -

Protocol Amendment 2 Rationale

Amendment number:	Amendment 2
Rationale/background for changes:	
<ul style="list-style-type: none">• 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 that will be used in this 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 that will be used in this study.• The term VAS has been added to the List of Abbreviations and Section 10.6.2.4 since it has now been included in the EQ-5D questionnaire used in this study.• References to hypertext links for examples of the SF-36 and EQ-5D questionnaires in Sections 10.6.2.3 and 10.6.2.4, respectively as well as in the Reference Section have been deleted, since images of pages for these questionnaires are provided as examples in APPENDIX A and B.• Typographic errors were corrected and other minor modifications were made throughout for clarification.	

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational vaccine and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally acceptable representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

CONFIDENTIAL

204928 (ZOSTER-063)
Protocol Amendment 2 Final

eTrack study number and Abbreviated Title 204928 (ZOSTER-063)

IND number BB-IND 13857

Date of protocol amendment Amendment 2 Final: 16 November 2016

Detailed Title A phase III, open label, multicenter study to evaluate the impact of reactogenicity on Quality of Life (QoL), after intramuscular administration of GSK Biologicals' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults \geq 50 years of age.

Investigator name

Signature

Date

For internal use only

-----Checksum-----!Ver.!Created On - -
67d8391faef64e9d05fd1c8f3a9b938732fdd18a 2.0 11/25/2016 3:45:45 PM - -

Sponsor Information

1. Sponsor

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

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

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

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section [8.4.2](#).

SYNOPSIS

Detailed Title	A phase III, open label, multicenter study to evaluate the impact of reactogenicity on Quality of Life (QoL), after intramuscular administration of GSK Biologicals' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults \geq 50 years of age.
Indication	Prevention of Herpes Zoster (HZ) and related complications in adults aged 50 years and older and in immunocompromised (IC) adults aged 18 years and older.
Rationale for the study and study design	<ul style="list-style-type: none">Rationale for the study <p>Varicella-Zoster Virus (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 to reduce risk of HZ has been examined in both older and immunocompromised persons.</p> <p>HZ is characterized by rash, and pain/or pruritus. The typical HZ rash, vesicles in a localized, dermatomal band on one side of the body, lasts 2 to 4 weeks and is often accompanied by severe pain that is described as burning, shooting, or stabbing. In some patients, even lightly touching 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 postherpetic neuralgia (PHN). Notably, PHN can last for months or even years.</p> <p>Half of all HZ cases occur in individuals \geq 60 years of age (YOA). Individuals who reach 85 years old have a 50% chance of having HZ during their lifetime. The risk for PHN is also highest in older people with HZ, occurring in 18-50% of those \geq 70 YOA. Since the loss of VZV-specific T-cell responses as a result of aging leads to heightened susceptibility to HZ, vaccination is considered as a means to reduce the risk of HZ in older adults.</p> <p>Associated with HZ and its complications is a substantial negative impact on patients' Quality of Life (QoL) and their ability to engage in Activities of Daily Living (ADL). In addition to the morbidity encountered by the individual with HZ, including productivity loss, it can also have significant consequences for the caregivers of patients, including partners and relatives of people with HZ. Acute HZ and HZ-</p>

related complications such as PHN have a considerable economic cost to healthcare systems caring for HZ and PHN patients. These healthcare costs will most likely increase due to the aging population, where age-related diseases such as HZ are becoming a growing economic burden in the developing world.

A live attenuated VZV vaccine, *Zostavax* (Merck & Co), is licensed in the United States (US) to prevent HZ in persons ≥ 50 YOA. Live attenuated vaccine is contraindicated in immunosuppressed or immunodeficient individuals.

GlaxoSmithKline (GSK) Biologicals' HZ candidate vaccine is an adjuvanted recombinant VZV envelope glycoprotein E (gE) subunit vaccine, hereafter referred to as HZ/su. The antigen component of the study vaccine is a truncated form of gE. The adjuvant is AS01_B, which consists of liposomes in combination with 50 μ g 3-O-desetyl-4'-Monophosphoryl Lipid A (MPL) and 50 μ g *Quillaja saponaria*, Molina, fraction 21 (purified natural saponin molecule extracted from the South American tree, *Quillaja saponaria*) (QS21) per 0.5 mL dose.

The GSK Biologicals' HZ/su candidate vaccine has been evaluated in several studies in healthy and immunocompromised adults. In these studies it elicited strong cellular and humoral immune responses. Furthermore, the safety and reactogenicity profile of the candidate vaccine was acceptable.

Two large pivotal phase III trials ZOE-50 (ZOSTER-006) and ZOE-70 (ZOSTER-022) that enrolled subjects ≥ 50 and ≥ 70 YOA, respectively, evaluated the vaccine efficacy, immunogenicity and safety of GSK Biologicals' HZ/su vaccine. These randomized trials together enrolled more than 30,000 subjects who either received the HZ/su vaccine or placebo on a 0, 2-month schedule.

The final analysis of the ZOSTER-006 primary efficacy objective (Q4 2014) demonstrated that the vaccine is highly efficacious in adults ≥ 50 YOA, with efficacy against HZ of 97.2% (95% confidence interval (CI) of 93.7-99.0). In addition, efficacy against HZ was between 96.6% and 97.9% for all pre-specified age groups (50-59, 60-69 and ≥ 70 YOA). The results from ZOSTER-022 indicated that the primary objectives were also successfully met, demonstrating 89.8% (95% CI of 84.2-93.7) efficacy against HZ in subjects ≥ 70 YOA and are therefore consistent with the results of

ZOSTER-006. In addition, the first primary objective of pre-specified pooled analysis of ZOSTER-006 and ZOSTER-022 demonstrated that HZ/su effectively prevents PHN. HZ/su was demonstrated to be 88.8% (95% CI of 68.7-97.1) efficacious in preventing PHN in people \geq 70 YOA. No safety concerns have been raised.

In the pooled analysis of the ZOSTER-006 and ZOSTER-022 studies the most common side effects were at the site of injection, including pain, redness, and swelling. Up to 70% of people who received the HZ/su vaccine had pain at the injection site. These symptoms were usually mild and resolved within about 3 days on average. The incidence of grade 3 solicited local pain, was about 4%, with an average duration of less than 2 days. Grade 3 reactogenicity is defined as preventing ADL. Other side effects seen in more than 10% of people who received the vaccine included myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms such as nausea, vomiting, diarrhoea and/or abdominal pain. The incidence of myalgia and fatigue was about 33% (overall/dose) and had an average duration of 2.5 days. The incidence of grade 3 solicited general symptoms was 3% or less (overall/dose) with average durations of less than 2 days.

While grade 3 reactogenicity is defined as preventing ADL, there is no clear understanding on how this impacts the daily Physical Functioning (PF) of an individual. As such this study is designed to quantify the impact of reactogenicity in terms of PF (e.g., walking carrying groceries, climbing stairs, etc.). The Quality-adjusted life year (QALY) loss associated with a HZ case that did not lead to PHN has been estimated to be approximately 3.65 days. For HZ cases that led to PHN, it was between 38.69 and 56.94 days, resulting in QALY losses of 0.106–0.156 depending on age for non-vaccinees. This QALY loss can be avoided by preventing HZ and PHN through vaccination. However reductions in QALY loss by preventing HZ and PHN through HZ/su administration could be partially offset by the QALY loss related to reactogenicity that is associated with vaccination.

- Rationale for the study design

The impact on QoL or QALY loss due to the reactogenicity will be compared to the impact on QoL or QALY loss due to HZ and its complications, notably PHN. This important information will be used to better assess the public health impact of HZ/su. For this purpose, SF-36 and EQ-5D questionnaires – the same questionnaires used in the

ZOSTER-006 and ZOSTER-022 studies to measure the impact of HZ and PHN on QoL – will be collected during this study.

The study will estimate any changes in QoL or QALY loss within the same subjects between before and after HZ/su vaccination, and therefore a placebo control will not be included.

Objectives**Primary**

- To estimate the change in the SF-36 Physical Functioning (SF-36 PF) scale score from baseline score to the mean score over the period day 1 to day 7 following the first HZ/su vaccination in subjects ≥ 50 years of age (YOA) overall.

Secondary

- To estimate the change in the SF-36 PF scale score from baseline score to the mean score over the period day 1 to day 7 following the second HZ/su vaccination in subjects ≥ 50 YOA overall.
- To estimate the change in the SF-36 PF scale score in subjects ≥ 50 YOA by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the change in SF-36 PF single item scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the change in SF-36 Role Physical scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the QALY change in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To assess the impact of reactogenicity on the healthcare resource utilization (i.e., hospitalization, General

Practitioners and specialist visits, medication intake) in subjects ≥ 50 YOA overall, by age, gender reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.

- To estimate the work loss in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the work loss for non-dedicated caregivers (e.g., family member) of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the extra work for dedicated caregivers of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To evaluate the safety and reactogenicity following administration of the HZ/su vaccine in subjects ≥ 50 YOA.

Study design

- Experimental design: Phase III, open label, multi-center study with a single group.
- Duration of the study: Approximately 14 months.
 - Epoch 001: Primary starting at Visit 1 (Day -7) and ending at the Study conclusion contact (Month 14).
- Primary completion Date (PCD): Visit 3.
- End of Study (EoS): Last data released for all subjects from the Month 14 phone contact.
- Study groups:

Synopsis Table 1 Study group and epoch foreseen in the study

Study groups	Number of subjects	Age (Minimum)	Epochs
			Epoch 001
HZ/su	400	≥ 50 years	x

Synopsis Table 2 Study group and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Group
		HZ/su
HZ/su	VZV gE	x
	AS01B	x

- Control: Pre-vaccination baseline control.

- Vaccination schedule: Months 0 and 2.
- Treatment allocation:
Eligible subjects will be enrolled into the single study group.
- Blinding:

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule:
 - A urine specimen will be collected from all female subjects of child-bearing potential at Visit 2 and Visit 4. If a serum pregnancy test instead of a urine pregnancy test is required by local or ethics committee regulations, a blood sample will be collected from women of child-bearing potential at Visit 2 and Visit 4 and used for the test as per local guidance.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects Target enrolment is 400 eligible subjects.

Endpoints

Primary

- Change in mean SF-36 PF scale score.
 - Baseline* versus mean score over the period day 1 to day 7** after first vaccination.

Secondary

- Change in mean SF-36 PF scale score.
 - Baseline* versus mean score over the period day 1 to day 7** after second vaccination.
- Change in mean SF-36 PF single item scores.
 - Baseline* versus mean score over the period day 1 to day 7** after each vaccination.
- Change in SF-36 Role Physical scores.
 - Baseline* versus score on day 7** after each vaccination.
- Change in the QALY.

- Baseline* versus combined score over the period day 1 to day 7** assessment after each vaccination.
- Healthcare resource utilization (i.e., hospitalization, telephone calls, medical visits and specialist visits, medication intake).
 - Days 0 to 6 after each vaccination.
- Work loss for subjects.
 - Days 0 to 6 after each vaccination.
- Work loss for the non-dedicated caregivers.
 - Days 0 to 6 after each vaccination.
- Extra work for dedicated caregivers.
 - Days 0 to 6 after each vaccination.
- Solicited local and general symptoms in subjects.
 - Occurrence, intensity and duration of solicited local symptoms within 7 days (Days 0-6**) after each vaccination.
 - Occurrence, intensity, duration and relationship to vaccination of solicited general symptoms within 7 days (Days 0-6**) after each vaccination.
- Unsolicited adverse events (AEs) in subjects.
 - Occurrence, intensity and relationship to vaccination during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events (SAEs).
 - Occurrence and relationship to vaccination of all SAEs from the first vaccination up to the study end.
- Occurrence of adverse events of specific interest (AESIs): potential Immune-Mediated Diseases (pIMDs).
 - Occurrence and relationship to vaccination of any pIMDs from first vaccination up to the study end.

*Note: baseline for dose 1 is defined as the mean of the assessments at day -7 and day 0; for dose 2 baseline is defined as the mean of the three assessments at day -7, day 0 and day 60 (day 0 for dose 2). Further details on baseline calculation will be given in the Statistical Analysis Plan (SAP).

**Note: The post-vaccination completion of SF-36 and EQ-5D questionnaires brought home by the subjects will be on days 1

to day 6, with day 7 to be filled in at the site (during Visits 3 and 5); while the post-vaccination recording of solicited AEs on the diary card brought home by the subjects will be on days 0 to day 6.

TABLE OF CONTENTS

	PAGE
SPONSOR INFORMATION	7
SYNOPSIS.....	8
LIST OF ABBREVIATIONS	22
GLOSSARY OF TERMS	25
TRADEMARKS	29
1. INTRODUCTION.....	30
1.1. Background	30
1.2. Rationale for the study and study design	31
1.2.1. Rationale for the study	31
1.2.2. Rationale for the study design.....	32
1.3. Benefit : Risk Assessment	33
1.3.1. Risk Assessment	33
1.3.2. Benefit Assessment	34
1.3.3. Overall Benefit:Risk Conclusion.....	34
2. OBJECTIVES.....	34
2.1. Primary objective	34
2.2. Secondary objectives	34
3. STUDY DESIGN OVERVIEW	36
4. STUDY COHORT.....	38
4.1. Number of subjects/ centers	38
4.2. Inclusion criteria for enrolment	38
4.3. Exclusion criteria for enrolment	39
5. CONDUCT OF THE STUDY	40
5.1. Regulatory and ethical considerations, including the informed consent process.....	40
5.2. Subject identification and randomization of treatment	41
5.2.1. Subject identification.....	41
5.2.2. Randomization of treatment.....	41
5.2.2.1. Randomization of supplies.....	41
5.2.2.2. Treatment allocation to the subject	41
5.2.2.2.1. Study group and treatment number allocation	41
5.2.2.2.2. Treatment number allocation for subsequent doses	42
5.3. General study aspects	42
5.3.1. Data collection	43
5.3.1.1. Questionnaires and Diary cards.....	43
5.4. Outline of study procedures	44
5.5. Detailed description of study procedures	47

5.5.1.	Procedures during Visit 1	47
5.5.1.1.	Informed consent	47
5.5.1.2.	Check inclusion and exclusion criteria	47
5.5.1.3.	Training on the completion of SF-36 and EQ-5D questionnaires	47
5.5.1.4.	Distribution and completion of SF-36 and EQ-5D questionnaires	48
5.5.1.5.	Physical examination and assessment of frailty status	48
5.5.1.6.	Record demographic data	48
5.5.1.7.	Medical history	48
5.5.1.8.	Distribution, training, completion and collection of pre-vaccination diary card	48
5.5.1.9.	Review and transcribe pre-vaccination diary cards	49
5.5.2.	Procedures during Visit 2	49
5.5.2.1.	Re-check inclusion and exclusion criteria	49
5.5.2.2.	Distribution, completion and collection of second pre-vaccination diary card	49
5.5.2.3.	Review and transcribe pre-vaccination diary cards	49
5.5.2.4.	Distribution and completion of SF-36 and EQ-5D questionnaires at Visit 2	49
5.5.2.5.	Check contraindications	50
5.5.2.6.	Pregnancy test	50
5.5.2.7.	Assess pre-vaccination body temperature	50
5.5.2.8.	Study vaccine administration	50
5.5.2.9.	Check and record concomitant medication/vaccination	51
5.5.2.10.	Recording of AEs, SAEs, pregnancies and pIMDs	51
5.5.2.11.	Distribution and completion of SF-36 and EQ-5D questionnaires post-vaccination	51
5.5.3.	Study conclusion	52
6.	STUDY VACCINE AND ADMINISTRATION	52
6.1.	Description of study vaccine	52
6.2.	Storage and handling of study vaccine	52
6.3.	Dosage and administration of study vaccine	53
6.4.	Contraindications to subsequent vaccination	53
6.5.	Concomitant medications/products and concomitant vaccinations	54
6.5.1.	Recording of concomitant medications/products and concomitant vaccinations	54
6.5.2.	Concomitant vaccines that may lead to the elimination of a subject from ATP analyses	55
7.	HEALTH ECONOMICS	56
8.	SAFETY	56
8.1.	Safety definitions	56
8.1.1.	Definition of an adverse event	56
8.1.2.	Definition of a serious adverse event	57

8.1.3.	Solicited adverse events	58
8.1.3.1.	Solicited local (injection-site) adverse events.....	58
8.1.3.2.	Solicited general adverse events	59
8.1.4.	Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events	59
8.1.5.	Adverse events of specific interest.....	59
8.1.5.1.	Potential immune-mediated diseases	59
8.2.	Events or outcomes not qualifying as adverse events or serious adverse events	61
8.2.1.	Pregnancy	61
8.3.	Detecting and recording adverse events, serious adverse events and pregnancies	62
8.3.1.	Time period for detecting and recording adverse events, serious adverse events and pregnancies	62
8.3.2.	Post-Study adverse events and serious adverse events	64
8.3.3.	Evaluation of adverse events and serious adverse events	64
8.3.3.1.	Active questioning to detect adverse events and serious adverse events	64
8.3.3.2.	Assessment of adverse events	65
8.3.3.2.1.	Assessment of intensity	65
8.3.3.2.2.	Assessment of causality	66
8.3.3.3.	Assessment of outcomes.....	67
8.3.3.4.	Medically attended visits.....	68
8.4.	Reporting of serious adverse events, pregnancies, and other events	68
8.4.1.	Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals.....	68
8.4.2.	Contact information for reporting serious adverse events, pregnancies and pIMDs	69
8.4.3.	Completion and transmission of SAE reports to GSK Biologicals	69
8.4.3.1.	Back-up system in case the electronic reporting system does not work.....	69
8.4.4.	Completion and transmission of pregnancy reports to GSK Biologicals	70
8.4.5.	Reporting of pIMDs to GSK Biologicals.....	70
8.4.6.	Updating of SAE, pregnancy, and pIMD information after removal of write access to the subject's eCRF.....	70
8.4.7.	Regulatory reporting requirements for serious adverse events	70
8.5.	Follow-up of adverse events, serious adverse events, and pregnancies	71
8.5.1.	Follow-up of adverse events and serious adverse events	71
8.5.1.1.	Follow-up during the study.....	71
8.5.1.2.	Follow-up after the subject is discharged from the study.....	71
8.5.2.	Follow-up of pregnancies	72
8.6.	Treatment of adverse events	72
8.7.	Subject card.....	72
9.	SUBJECT COMPLETION AND WITHDRAWAL	72
9.1.	Subject completion	72

9.2. Subject withdrawal	72
9.2.1. Subject withdrawal from the study	72
9.2.2. Subject withdrawal from investigational vaccine	73
10. STATISTICAL METHODS	74
10.1. Primary endpoint	74
10.2. Secondary endpoints	74
10.3. Determination of sample size	75
10.4. Cohorts for Analyses	76
10.4.1. Total vaccinated cohort	76
10.4.2. According-to-protocol cohort for analysis of safety	76
10.5. Derived and transformed data	76
10.6. Statistical analyses	76
10.6.1. Analysis of demographics/baseline characteristics	76
10.6.2. Quality of life	77
10.6.2.1. Analysis of QALY (Utility)	77
10.6.2.2. Assessment of frailty status	77
10.6.2.3. SF-36 health survey	78
10.6.2.4. EQ-5D questionnaire	78
10.6.3. Analysis of safety	79
10.7. Interpretation of analyses	80
10.8. Conduct of analyses	80
10.8.1. Sequence of analyses	80
10.8.2. Statistical considerations for interim analyses	80
11. ADMINISTRATIVE MATTERS	80
11.1. electronic Case Report Form instructions	80
11.2. Study Monitoring by GSK Biologicals	81
11.3. Record retention	81
11.4. Quality assurance	82
11.5. Posting of information on publicly available clinical trial registers and publication policy	82
11.6. Provision of study results to investigators	83
12. COUNTRY SPECIFIC REQUIREMENTS	83
13. REFERENCES (Amended 16 NOVEMBER 2016)	83

LIST OF TABLES

	PAGE
Table 1	37
Table 2	37
Table 3	37
Table 4	42
Table 5	44
Table 6	47
Table 7	52
Table 8	53
Table 9	58
Table 10	59
Table 11	60
Table 12	63
Table 13	65
Table 14	68
Table 15	78

LIST OF APPENDICES

	PAGE
APPENDIX A SF-36 (Version 2.0 SAMPLE) (Amended 16 November 2016)	85
APPENDIX B EQ-5D (English Version US SAMPLE) (Amended 16 November 2016).....	91
APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL.....	94

LIST OF ABBREVIATIONS

ADL:	Activities of Daily Living
AE:	Adverse Event
AESI:	Adverse Event of Specific Interest
ANCA:	Anti-Neutrophil Cytoplasmic Antibodies
AS01_B:	MPL, QS21, liposome based Adjuvant System (50 µg MPL and 50 µg QS21)
ATP:	According-To-Protocol
BMI:	Body Mass Index
CDC:	Centers for Disease Control
CESD-R:	Center for Epidemiologic Studies Depression Scale – Revised
CI:	Confidence Interval
CREST:	Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia (syndrome)
D:	Dominant
DC:	Diary Card
eCRF:	electronic Case Report Form
EDD:	Estimated Date of Delivery
EGA:	Estimated Gestational Age
EoS:	End of Study
EQ-5D:	EuroQol five dimension health questionnaire
eTDF:	Electronic Temperature excursion Decision Form
FDA:	Food and Drug Administration, United States of America
FI:	Frailty Index
GCP:	Good Clinical Practice
gE:	VZV envelope glycoprotein E

GSK:	GlaxoSmithKline
HCP:	Health Care Provider
HZ:	Herpes Zoster
HZ/su:	Herpes Zoster subunit vaccine
IB:	Investigator Brochure
IC:	Immunocompromised
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IM:	Intramuscular
IMP:	Investigational Medicinal Product
IND:	Investigational New Drug
IRB:	Institutional Review Board
LL:	Lower Limit
LMP:	Last Menstrual Period
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MATEX:	MAterial EXcellence
MedDRA:	Medical Dictionary for Regulatory Activities
 mL:	Milliliter
MoCa:	Montreal Cognitive Assessment
MPL:	3- <i>O</i> -desacyl-4'-Monophosphoryl Lipid A
N-D:	Non-dominant
PCD:	Primary Completion Date
PF:	Physical Functioning

PFP:	Physical Frailty Phenotype
PHN:	Postherpetic Neuralgia
pIMD:	Potential Immune-Mediated Disease
PT:	Preferred Terms
QALY:	Quality-adjusted life year
QoL:	Quality of Life
QS21:	<i>Quillaja saponaria</i> Molina, fraction 21 (Antigenics, Delaware, USA)
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SAS:	Statistical Analysis System
SBIR:	Randomization System on Internet
SDV:	Source Document Verification
SF-36:	A Short Form 36-item health survey
SPM:	Study Procedures Manual
TVc:	Total Vaccinated cohort
UL:	Upper Limit
US:	United States (of America)
VAS:	<i>Visual Analogue Scale (Amended 16 November 2016)</i>
VZV:	Varicella-Zoster Virus
YOA:	Years of age

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- oral contraceptives, either combined or progestogen alone,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- estrogenic vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,

The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.

- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository),
- male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, when this is their preferred and usual lifestyle.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of

efficacy), abuse or misuse.

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Dedicated Caregiver	A caregiver that may be a member of an organization, or working independently as a volunteer caregiver, or may be an employed professional.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV).
(Synonym of End of Trial)	For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.
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 to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
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 according-to-protocol (ATP) analysis (see Sections 6.5.2 and 10.4 for details on criteria for evaluability).

Frailty:	Frailty is a term used in geriatric medicine to identify older adults who are at increased risk of poor clinical outcomes, such as incident disability, cognitive decline, falls, hospitalization, institutionalization, or increased mortality. Frailty represents a reduction in resistance to stressors leading to increased clinical vulnerability and adverse health outcomes.
Investigational vaccine: (Synonym of Investigational Medicinal Product)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g., > 45 years.
Non-Dedicated Caregiver	A caregiver that is not a member of an organization or employed through a professional agency, has no formal training; for example, they may be a family member or friend.
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 the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference 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.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.

Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
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, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomization or 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.

TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Zostavax [®] (Merck & Co., Inc.)	Herpes zoster vaccine consisting of high-titre live attenuated Varicella-zoster virus (Oka strain)
QS-21: <i>Quillaja saponaria</i> Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)	Triterpene glycoside immune enhancer

1. INTRODUCTION

1.1. Background

Varicella-Zoster Virus (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 to reduce risk of HZ has been examined in both older and immunocompromised persons.

HZ is characterized by rash, and pain/or pruritus. The typical HZ rash, vesicles in a localized, dermatomal band on one side of the body, lasts 2 to 4 weeks and is often accompanied by severe pain that is described as burning, shooting, or stabbing. In some patients, even lightly touching 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 postherpetic neuralgia (PHN). Notably, PHN can last for months or even years.

Half of all HZ cases occur in individuals \geq 60 years of age (YOA). Individuals who reach 85 years old have a 50% chance of having HZ during their lifetime [Oxman, 2005]. The risk for PHN is also highest in older people with HZ, occurring in 18-50% of those \geq 70 YOA [Oxman, 2005; Scott, 2006; Dworkin, 2007]. Since the loss of VZV-specific T-cell responses as a result of aging leads to heightened susceptibility to HZ, vaccination is considered as a means to reduce the risk of HZ in older adults [Oxman, 2005; Sperber, 1992].

Associated with HZ and its complications is a substantial negative impact on patients' Quality of Life (QoL) and their ability to engage in Activities of Daily Living (ADL). In addition to the morbidity encountered by the individual with HZ, including productivity loss, it can also have significant consequences for the caregiver(s) of patients including partners and relatives of people with HZ [Gater, 2015]. Acute HZ and HZ-related complications such as PHN have a considerable economic cost to healthcare systems caring for HZ and PHN patients. These healthcare costs will most likely increase due to the aging population, where age-related diseases such as HZ are becoming a growing economic burden in the developing world [Szucs, 2013].

A live attenuated VZV vaccine, *Zostavax* (Merck & Co), is licensed in the United States (US) to prevent HZ in persons \geq 50 YOA [*Zostavax* Prescribing Information, 2011]. Live attenuated vaccine is contraindicated in immunosuppressed or immunodeficient individuals [Kroger, 2011].

GlaxoSmithKline (GSK) Biologicals' HZ candidate vaccine is an adjuvanted recombinant VZV envelope glycoprotein E (gE) subunit vaccine, hereafter referred to as HZ/su. The antigen component of the study vaccine is a truncated form of gE. The adjuvant is AS01_B, which consists of liposomes in combination with 50 μ g 3-O-desyl-4'-Monophosphoryl Lipid A (MPL) and 50 μ g *Quillaja saponaria*, Molina, fraction 21

(purified natural saponin molecule extracted from the South American tree, *Quillaja saponaria*) (QS21) per 0.5 mL dose.

The GSK Biologicals' HZ/su candidate vaccine has been evaluated in several studies in healthy and immunocompromised adults. In these studies it elicited strong cellular and humoral immune responses. Furthermore, the safety and reactogenicity profile of the candidate vaccine was acceptable.

Two large pivotal phase III trials ZOE-50 (ZOSTER-006) and ZOE-70 (ZOSTER-022) that enrolled subjects ≥ 50 and ≥ 70 YOA, respectively, evaluated the vaccine efficacy, immunogenicity and safety of GSK Biologicals' HZ/su vaccine. These randomized trials together enrolled more than 30,000 subjects who either received the HZ/su vaccine or placebo on a 0, 2-month schedule.

The final analysis of the ZOSTER-006 primary efficacy objective (Q4 2014) demonstrated that the vaccine is highly efficacious in adults ≥ 50 YOA, with efficacy against HZ of 97.2% (95% confidence interval (CI) of 93.7-99.0). In addition, efficacy against HZ was between 96.6% and 97.9% for all pre-specified age groups (50-59, 60-69 and ≥ 70 YOA) [Lal, 2015]. The results from ZOSTER-022 indicated that the primary objectives have also been successfully met, demonstrating 89.8% (95% CI of 84.2-93.7) efficacy against HZ in subjects ≥ 70 YOA and are therefore consistent with the results of ZOSTER-006. In addition, the first primary objective of pre-specified pooled analysis of ZOSTER-006 and ZOSTER-022 demonstrated that HZ/su effectively prevents PHN. HZ/su was demonstrated to be 88.8% (95% CI of 68.7-97.1) efficacious in preventing PHN in people ≥ 70 YOA. No safety concerns have been raised.

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

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

Nearly 22,900 subjects received the active HZ/su study vaccine in clinical trials worldwide, most of whom (95%) were ≥ 50 YOA. Due to the high efficacy of the vaccine, most HZ and PHN cases were prevented, thus avoiding any negative impact on QoL in those subjects. No imbalance between the vaccine and the placebo arms were found in terms of SAEs, potential Immune-Mediated Diseases (pIMDs) or death during the entire duration of the studies. The vaccine was generally well tolerated. However, the vaccine was more reactogenic than placebo (saline solution).

In the pooled analysis of the ZOSTER-006 and ZOSTER-022 studies the most common side effects were at the site of injection, including pain, redness, and swelling. Up to 70% of people who received the HZ/su vaccine had pain at the injection site. These symptoms were usually mild and resolved within about 3 days on average. The incidence of grade 3 solicited local pain, was about 4%, with an average duration of less than 2 days. Grade 3 reactogenicity is defined as preventing ADL. Other side effects seen in more than 10% of people who received the vaccine included myalgia, fatigue, headache, shivering, fever

and gastrointestinal symptoms such as nausea, vomiting, diarrhoea and/or abdominal pain. The incidence of myalgia and fatigue was about 33% (overall/dose) and had an average duration of 2.5 days. The incidence of grade 3 solicited general symptoms was 3% or less (overall/dose) with average durations of less than 2 days. The reactogenicity is likely to be secondary to the enhanced innate immune responses elicited at the site of injection and therefore is expected [Didierlaurent, 2014]. This is consistently observed in studies evaluating AS01 – (and other) adjuvanted vaccines, in which higher reactogenicity is observed with adjuvanted versus non-adjuvanted vaccines [Stassijns, 2016].

While grade 3 reactogenicity is defined as preventing ADL, there is no clear understanding available on how this translates to impact on the daily Physical Functioning (PF) of an individual. As such this study is designed to quantify the impact of reactogenicity in terms of PF (e.g., walking, carrying groceries, climbing stairs, etc.). In addition, the Quality-adjusted life year (QALY) loss associated for both *Zostavax*-vaccinated and non-vaccinated subjects with a HZ case that did not lead to PHN, has been estimated to be approximately 0.01 (i.e., 3.65 days) [Pellissier, 2007]. For HZ cases that led to PHN, it was between 38.69 and 56.94 days, resulting in QALY losses of 0.106–0.156 depending on age for non-vaccinated subjects, [Pellissier, 2007]. Similar results were observed in the ZOSTER-006 and ZOSTER-022 studies with the HZ/su vaccine. As such, QALY loss can be avoided by preventing HZ and PHN, through HZ/su vaccination. However reductions in QALY loss by preventing HZ and PHN through HZ/su administration could be partially offset by the QALY loss related to reactogenicity that is associated with vaccination.

In assessing the impact on QoL, the QALY loss due to adverse events is an important parameter to include when calculating the cost/effectiveness of HZ/su compared to no vaccination. These data will be included in models which analyze net QALY loss avoided by preventing HZ and PHN by vaccinating with HZ/su. Furthermore, only limited data are available to assess the impact of the reactogenicity on the Quality of Life (QoL) and PF of individuals exposed to the HZ/su vaccine or vaccination in general. These data are important to both Health Care Providers (HCPs) and policy makers. Additional characterization of the reactogenicity will allow vaccinators to better inform vaccinees before the administration of the vaccine. Therefore, this study will be conducted to enhance our understanding of HZ/su vaccine reactogenicity, and to provide more complete information to vaccinators and persons who will receive the vaccine.

1.2.2. Rationale for the study design

The impact on QoL and QALY loss due to the reactogenicity will be compared to the impact on QoL or QALY loss due to HZ and its complications, notably PHN. This information will be used to better assess the public health impact of HZ/su. For this purpose, SF-36 [APPENDIX A] and EQ-5D [APPENDIX B] questionnaires – the same questionnaires used in the ZOSTER-006 and ZOSTER-022 studies to measure the impact of HZ and PHN on QoL – will be collected during this study.

The study will estimate changes in QoL or QALY loss within the same subjects between before and after HZ/su vaccination, and therefore a placebo control will not be included. (Amended 16 November 2016)

Subjects in the general population (especially older adults), are on average unable to achieve perfect QoL scores, because many subjects may be somewhat limited in “climbing several flights of stairs” or “bending, kneeling, or stooping”. To estimate the impact of reactogenicity on an individual’s SF-36 PF and QoL, we will compare two periods, i.e., pre-vaccination and post-vaccination. The difference is considered to be the effect of vaccination and reactogenicity on the SF-36 PF and QoL. To characterize the study population and determine if frailty may influence reactogenicity and consequently the impact on QoL scores, the subjects’ frailty status will be assessed at inclusion (see Section 10.6.2.2).

In addition to the SF-36 and EQ-5D questionnaires, a more complete characterization of the reactogenicity of the vaccine will be achieved by including a detailed collection of the use of healthcare resources and the occurrence of symptoms through diary card data collection (see Section 5.3.1.1). Impact on days of work loss, both for the subject or for a caregiver, as applicable, will be assessed.

1.3. Benefit : Risk Assessment

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

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

1.3.1. Risk Assessment

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational HZ/su vaccine		
Theoretical risk of acquiring a vaccine induced autoimmune disease after vaccination.	No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.	Close monitoring of pIMDs as per study protocol. The potential risk of events of possible autoimmune etiology occurring is mentioned in the ICF. In addition, the ICF advises subjects to contact the study doctor or the study staff immediately, should they develop any symptoms that they feel maybe serious.

1.3.2. Benefit Assessment

Benefits include:

- Receiving the HZ/su study vaccine that may provide the prevention of HZ.
- Medical evaluations/assessments associated with study procedures [e.g., physical examination].

1.3.3. Overall Benefit:Risk Conclusion

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

2. OBJECTIVES

2.1. Primary objective

- To estimate the change in the SF-36 Physical Functioning (SF-36 PF) scale score from baseline score to the mean score over the period day 1 to day 7 following the first HZ/su vaccination in subjects ≥ 50 years of age (YOA) overall.

Refer to Section 10.1 for the definition of the primary endpoint.

2.2. Secondary objectives

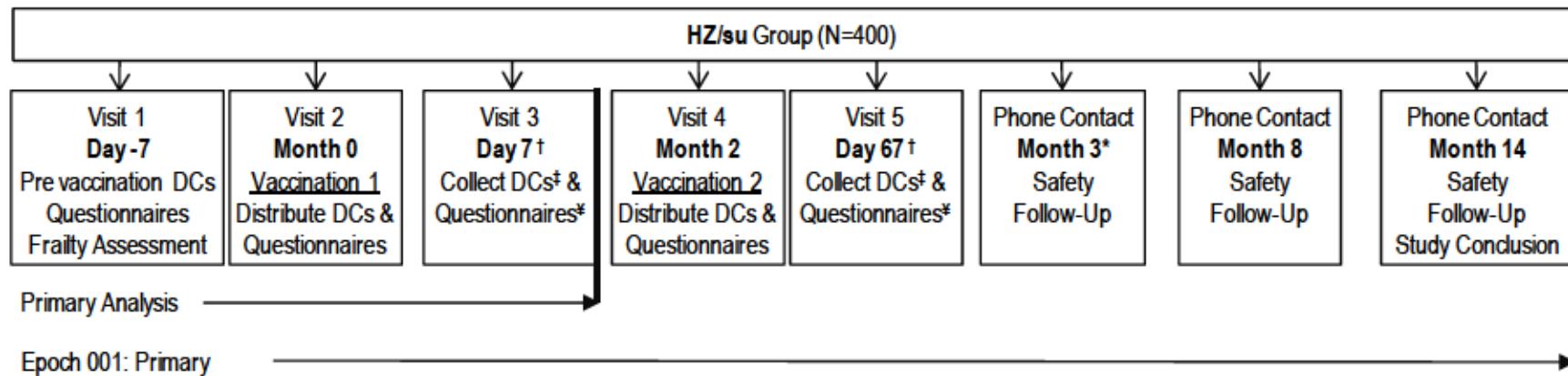
- To estimate the change in the SF-36 PF scale score from baseline score to the mean score over the period day 1 to day 7 following the second HZ/su vaccination in subjects ≥ 50 YOA overall.
- To estimate the change in the SF-36 PF scale score in subjects ≥ 50 YOA by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the change in SF-36 PF single item scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the change in SF-36 Role Physical scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the score on day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the QALY change in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) from baseline score to the combined score on days 1 to 7 following both HZ/su vaccinations 1 and 2.
- To assess the impact of reactogenicity on the healthcare resource utilization (i.e., hospitalization, General Practitioners and specialist visits, medication intake) in

subjects ≥ 50 YOA overall, by age, gender reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.

- To estimate the work loss in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the work loss for non-dedicated caregivers (e.g., family member) of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the extra work for dedicated caregivers of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To evaluate the safety and reactogenicity following administration of the HZ/su vaccine in subjects ≥ 50 YOA.

Refer to Section 10.2 for the definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW



DC = Diary Card.

† Visit 3 at Day 7 is defined as 7 days post dose 1 at Visit 2 (Month 0) and Visit 5 at Day 67 is defined as 7 days post dose 2 at Visit 4 (Month 2) (Refer to [Table 6](#) for visit intervals).

‡ Diary Cards distributed at Visit 2 and Visit 4 for solicited adverse events (Days 0–6) will be collected on Day 7 and Day 67 (Visit 3 and Visit 5), respectively (Refer to [Table 5](#)).

* Questionnaires distributed at Visit 2 and Visit 4 will be collected on Day 7 and Day 67 (Visit 3 and Visit 5), respectively (Refer to [Table 5](#) and Section 5.5.2.11).

* The Month 3 contact will occur when the post-vaccination 2 (Days 0-29) diary cards have been received by site (returned by mail).

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.4), are essential and required for study conduct.

- Experimental design: Phase III, open label, multi-center study with a single group.
- Duration of the study: Approximately 14 months.
Epoch 001: Primary starting at Visit 1 (Day -7) and ending at the Study conclusion contact (Month 14).
- Primary completion Date (PCD): Visit 3.
Refer to the [glossary of terms](#) for the definition of PCD.
- End of Study (EoS): Last data released for all subjects from the Month 14 phone contact.
Refer to the [glossary of terms](#) for the definition of EoS.
- Study group:

Table 1 Study group and epoch foreseen in the study

Study group	Number of subjects	Age (Minimum)	Epochs
			Epoch 001
HZ/su	400	≥ 50 years	x

Table 2 Study group and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Group
		HZ/su
HZ/su	VZV gE	x
	AS01B	x

- Control: Pre-vaccination baseline control.
- Vaccination schedule: Months 0 and 2.
- Treatment allocation: Eligible subjects will be enrolled into the single study group.
- Blinding:

Table 3 Blinding of study epochs

Study Epoch	Blinding
Epoch 001	open

- Sampling schedule:
 - A urine specimen will be collected from all female subjects of child-bearing potential at Visit 2 and Visit 4. If a serum pregnancy test instead of a urine pregnancy test is required by local or ethics committee regulations, a blood

sample will be collected from women of child-bearing potential at Visit 2 and Visit 4 and used for the test as per local guidance.

Note: the result of the urine/serum pregnancy test must be obtained before vaccination.

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

4. STUDY COHORT

4.1. Number of subjects/ centers

Target enrolment is 400 eligible subjects. Refer to Sections 4.2 and 4.3 for eligibility criteria. Refer to Section 10.3 for a description of the criteria used in the estimation of sample size.

Overview of the recruitment plan:

Enrolment target numbers per study center will be assigned at the study start and may be adjusted during the study. The recruitment rate will be monitored using a study-specific central randomization system on the Internet (SBIR).

Transfer of supplies will be tracked by the central randomization system. Monitoring visit frequency will be adapted to the pace of enrolment. Vaccine doses will be distributed to each study site respecting the block size.

4.2. Inclusion criteria for enrolment

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

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the questionnaires and diary cards).
- Written informed consent obtained from the subject prior to performance of any study specific procedure.
- A male or female aged ≥ 50 YOA at the time of consent.
- Female subjects of non-childbearing potential may be enrolled in the study.
 - For this study population, non-childbearing potential is defined as current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the [glossary of terms](#) for the definition of menopause.

- Female subjects of childbearing potential may be enrolled in the study, if the subject:
 - has practiced adequate contraception for 30 days prior to vaccination, and
 - has a negative pregnancy test on the day of vaccination, and
 - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

Please refer to the [glossary of terms](#) for the definition of adequate contraception.

4.3. **Exclusion criteria for enrolment**

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

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

- Any condition which, in the judgment of the investigator, would make intramuscular (IM) injection unsafe.
- Use or planned use of any investigational or non-registered product (drug or vaccine) other than the study vaccine or current participation or planned concurrent participation in another clinical study, in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device) during the period starting 30 days before the first dose of study vaccine and the study end.
- Use or anticipated use of immunosuppressants or other immune-modifying drugs during the period starting 180 days prior to study start and during the whole study period. This includes chronic administration of corticosteroids (> 14 consecutive days of prednisone at a dose of \geq 20 mg/day [or equivalent]), long-acting immune-modifying agents (e.g., infliximab) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders). Inhaled, topical and intra-articular corticosteroids are allowed.
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, human immunodeficiency virus [HIV] infection) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders).
- Administration of immunoglobulins and/or any blood products in the period starting 90 days preceding the first dose of study vaccine or planned administration during the study period.
- Administration or planned administration of a live vaccine in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose of study vaccine, or, administration or planned administration of a non-replicating vaccine* in the period starting 15 days prior to and ending 14 days after either dose of study vaccine.

*E.g., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines for seasonal or pandemic flu, without adjuvant, and pneumococcal conjugate vaccines.

- Previous or planned administration of a vaccine against HZ (including an investigational or non-registered vaccine) other than the study vaccine, during the entire study period.
- History of HZ.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- Pregnant or lactating female.
- Significant underlying illness requiring medications that might confound the evaluation of general/ local AEs, or in the opinion of the investigator, would be expected to prevent completion of the study.
- Any other condition that, in the opinion of the investigator, might interfere with the evaluations required by the study.

5. CONDUCT OF THE STUDY

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

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

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

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

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

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

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

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

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

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

5.2. Subject identification and randomization of treatment

5.2.1. Subject identification

Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study center. Age group will be used as a stratification factor to ensure recruitment of the pre-specified number of subjects in each age group (refer to [Table 4](#)).

5.2.2. Randomization of treatment

Even though there will be no randomization of treatment, SBIR will be used for treatment number allocation and for enrolment tracking purposes.

5.2.2.1. Randomization of supplies

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

5.2.2.2. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

5.2.2.2.1. Study group and treatment number allocation

The target will be to enrol approximately 400 eligible subjects aged ≥ 50 years.

The enrolment will be performed to ensure equal distribution of the population across the three age strata (50-59 YOA versus 60-69 YOA versus ≥ 70 YOA). Therefore the expected distribution of subjects is as shown in [Table 4](#).

Table 4 Number of subjects required for enrolment

Age strata	Sample size
50-59 YOA	≈ 134
60-69 YOA	≈ 133
≥ 70 YOA	≈ 133
All	≈ 400

The subject will be entered into the applicable age stratum (50-59 YOA versus 60-69 YOA versus ≥ 70 YOA) in SBIR at the investigator site.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the study staff in charge of the vaccine administration will access SBIR. Upon providing the age (50-59 YOA versus 60-69 YOA versus ≥ 70 YOA) and the subject identification number, the randomization system will provide the treatment number to be used for the first dose.

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

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

Note that as soon as the target number of subjects in a specific age group has been reached, the enrolment will be frozen for this age group.

5.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number.

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

5.3. 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.

5.3.1. Data collection

5.3.1.1. Questionnaires and Diary cards

The questionnaires (SF-36 [[APPENDIX A](#)] and EQ-5D [[APPENDIX B](#)]) and diary cards, that will be distributed and explained by the investigator or his/her delegate, are to be completed by the subject/ subject's caregiver. Any supplied questionnaires and diary cards should be preferably completed by the subject themselves.

Following vaccination, 7-day and 30-day diary cards will be dispensed to be completed by the subjects/ subjects' caregiver. The 7-day diary cards will be completed for solicited AEs (from Day 0 to Day 6 after each vaccination) and the 30-day diary cards will be completed for unsolicited AEs (from Day 0 to Day 29 after each vaccination) and any concomitant medication and vaccination taken from Day 0 to Day 29 after each vaccination (see [Table 5](#) and [Table 12](#)). These diary cards will allow a detailed characterization of the vaccine reactogenicity through a detailed collection of the occurrence of symptoms and any use of healthcare resources. Please refer to the SPM for more information on diary card and questionnaire data collection.

The questionnaires will be filled in by the subject/subjects caregiver on site at each visit. In addition, the subject/subjects caregiver will be required to complete the SF-36 PF component of the SF-36 questionnaire (i.e., items 3a to 3j, see [Table 15](#)) and the EQ-5D questionnaire at home on days 1 to 6 following each vaccination.

When the completed questionnaires and diary cards are returned to the study staff, the study staff will ask *the subject* (at the time of return or at subsequent contact) if he/she received any assistance in completing questionnaires or diary cards. If the subject had assistance completing the questionnaires and/or diary card (e.g., by a caregiver), it should be noted in the eCRF. *When questionnaires or pre-vaccination diary cards are completed at the study site, study staff can assist in reading the questions (verbatim).*
(Amended 16 November 2016)

Also, when the completed diary cards are returned to the study staff the study staff will review it together with the subject. **(Amended 16 November 2016)**

5.4. Outline of study procedures

Table 5 summarizes the list of procedures to be followed during the study.

Table 5 List of study procedures

Epoch	Primary							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	M3 Contact	M8 Contact	M14 Contact
Type of contact	Day -7	Month 0	Day 7 ¹	Month 2	Day 67 ¹	Month 3 ²	Month 8	Month 14
Timepoint(s)								
Informed consent (see Section 5.5.1.1)	•							
Check inclusion / exclusion criteria (see Sections 5.5.1.2 and 5.5.2.1)	•	0						
Training on completion of SF-36 and EQ-5D questionnaires (see Section 5.5.1.3)	0	0	0	0	0			
On site completion of SF-36 and EQ-5D questionnaires by the subject	0	0	0	0	0			
Transcription of SF-36 and EQ-5D questionnaires by investigator/ designee	•	•	•	•	•			
Physical examination including height and weight (see Section 5.5.1.5) (Amended 16 November 2016)	•							
Assessment of frailty status by means of a specific tool ³	•							
Record demographic data including subject's working status and if they have a caregiver (see Section 5.5.1.6)	•							
Medical history and record medications taken by the subject (see Section 5.5.1.7)	•							
Training of subjects on the completion of pre-vaccination diary cards (see Sections 5.5.1.8 and 5.5.2.2)	0							
On site completion of pre-vaccination diary cards by the subject (see Sections 5.5.1.9 and 5.5.2.2)	0	0						
Review and transcription of pre-vaccination diary cards (see Section 5.5.2.3)	•	•						
Check contraindications ⁴ (see Section 5.5.2.5)		•		•				
Pregnancy test ⁵		•		•				
Pre-vaccination body temperature (oral route preferred) ⁶ (see Section 5.5.2.7)		•		•				
Assignment/recording of treatment number		•		•				
Vaccination (see Section 5.5.2.8)		•		•				
Training on completion of diary cards		0		0				
Distribution of diary cards		0		0				
Distribution of post-vaccination daily SF-36 and EQ-5D questionnaires (see Section 5.5.2.11)		0		0				
Daily post-vaccination completion of SF-36 and EQ-5D questionnaires by subject		0		0				

CONFIDENTIAL

204928 (ZOSTER-063)
Protocol Amendment 2 Final

Epoch	Primary							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	M3 Contact	M8 Contact	M14 Contact
Type of contact	Day -7	Month 0	Day 7 ¹	Month 2	Day 67 ¹	Month 3 ²	Month 8	Month 14
Daily post-vaccination recording of solicited AEs (Days 0-6) by subjects on diary card	0		0					
Daily post-vaccination recording of unsolicited AEs and concomitant medication/vaccination (Days 0-29) by subjects on diary card	0	0	0	0	0			
Return of daily SF-36 and EQ-5D questionnaires (see Sections 5.5.1.4, 5.5.2.4 and 5.5.2.11)			0		0			
Transcription of daily SF-36 and EQ-5D questionnaires by investigator/ designee (see Section 5.5.2.11)			•		•			
Return of diary cards			0	0	0	0 ⁷		
Review and transcription of solicited adverse events within 7 days (Days 0-6) post-vaccination, from diary cards by investigator/site staff			•		•			
Review and transcription of non-serious adverse events within 30 days (Days 0-29) post-vaccination, from diary cards by investigator/ site staff				•		•		
Record any concomitant medication/vaccination (Refer to Section 6.5)	•	•	•	•	•	•	•	•
Recording of serious adverse events (SAEs) by investigator (Refer to Table 12) ⁸	•	•	•	•	•	•	•	•
Recording of potential immune-mediated diseases (pIMDs) (Refer to Section 8.1.5 and Table 11)	•	•	•	•	•	•	•	•
Recording of pregnancies (Refer to Section 8.2.1 and Table 12)		•	•	•	•	•	•	•
Investigator sign off for the analysis (Amended 16 November 2016)			•					•
Study Conclusion								•

Note: The double-line border following Visit 3 Day 7 indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to Visit 3 (see Section 10.8.1).

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

0 is used to indicate a study procedure that does not require documentation in the individual eCRF. However, items with this designation should be noted in the subject's source documentation.

¹ Visit 3 at Day 7 is defined as 7 days post dose 1 at Visit 2 (Month 0) and Visit 5 at Day 67 is defined as 7 days post dose 2 at Visit 4 (Month 2) (Refer to Table 6 for visit intervals).

² The Month 3 contact will occur when the post-vaccination 2 (Days 0-29) diary cards have been received by site (returned by mail) and will allow the site staff to review and verify the post-vaccination 2 (Days 0-29) diary cards by discussing them with the subject/ subject's caregiver.

³ An assessment of frailty status defined through a Frailty Index (FI) described as accumulation of deficits, including but not limited to a series of certified tests, will be performed at inclusion and data recorded in the eCRF (see Section 10.6.2.2).

⁴ Any subject with a clinically diagnosed HZ episode between Visit 1 and Visit 4 should not receive the subsequent dose(s).

⁵ Only for women of child-bearing potential. A serum pregnancy test instead of a urine pregnancy test should only be considered if required by local or ethics committee regulations (see Section 5.5.2.6).

CONFIDENTIAL

204928 (ZOSTER-063)
Protocol Amendment 2 Final

⁶ Pre-vaccination temperatures should always be recorded orally at study sites. In rare situations when there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.

⁷ The post-vaccination 2 diary cards for daily recording of unsolicited AEs and concomitant medication/vaccination (Days 0-29) by subjects will be returned by mail.

⁸ SAEs related to study participation or GSK concurrent medication/vaccine are to be recorded from the time the subject consents to participate in the study.

Time intervals between study visits/contact related to study procedures performed in subjects participating in the study are presented in [Table 6](#).

Table 6 Intervals between study visits

Interval	Optimal length of interval ¹	Allowed interval (range in days)
Visit 1 (Day -7) → Visit 2 (Month 0)	7 days	7 – 10 ²
Visit 2 (Month 0) → Visit 3 (Day 7) ³	7 days	7 – 10
Visit 2 (Month 0) → Visit 4 (Month 2)	60 days	49 – 83
Visit 4 (Month 2) → Visit 5 (Day 67) ³	7 days	7 – 10
Visit 4 (Month 2) → M3 Contact (Month 3)	35 days ⁴	30 – 60
Visit 4 (Month 2) → M8 Contact (Month 8)	150 days	120 – 180
Visit 4 (Month 2) → Study conclusion M14 Contact (Month 14)	365 days	335 – 395

¹ Whenever possible the investigator should arrange study visits within this interval.

² This interval can be extended up to 14 days if subject is not able to be vaccinated at Visit 2 and needs to be rescheduled.

³ Visit 3 at Day 7 is defined as 7 days post dose 1 at Visit 2 (Month 0) and Visit 5 at Day 67 is defined as 7 days post dose 2 at Visit 4 (Month 2).

⁴ The Month 3 contact will occur when the post-vaccination 2 (Days 0-29) diary cards have been received by site (returned by mail).

5.5. Detailed description of study procedures

5.5.1. Procedures during Visit 1

Note that Visit 1 will take place at least 7 days before the first vaccination Visit (Visit 2) (see [Table 6](#) for visit intervals).

5.5.1.1. Informed consent

The signed/witnessed informed consent of the subject must be obtained before study participation. Refer to Section [5.1](#) for the requirements on how to obtain informed consent.

5.5.1.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections [4.2](#) and [4.3](#) before enrolment.

5.5.1.3. Training on the completion of SF-36 and EQ-5D questionnaires

Subjects/ subjects' caregiver(s) will be trained on completing the SF-36 and EQ-5D questionnaires at Visits 1, 2, 3, 4 and 5 (see Sections [10.6.2.3](#) and [10.6.2.4](#) for information on the SF-36 and EQ-5D questionnaires, respectively).

5.5.1.4. Distribution and completion of SF-36 and EQ-5D questionnaires

Subjects /subjects' caregiver(s) will complete the SF-36 and EQ-5D questionnaires (see Sections 10.6.2.3 and 10.6.2.4). The SF-36 and EQ-5D questionnaires will be distributed to subjects at the Pre-Vaccination Visit 1. Subjects will be asked to complete both SF-36 and EQ-5D questionnaires on Day -7 (Visit 1). Completed questionnaires will be collected at Visit 1 and subject responses transcribed into the eCRF.

5.5.1.5. Physical examination and assessment of frailty status

Perform a physical examination of the subject at Visit 1 including weight and height (body mass index [BMI] will be calculated). The physical examination can be performed per the site's medical judgment and standard of care. Collected information needs to be recorded in the eCRF. (Amended 16 November 2016)

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

An assessment of frailty status defined through a Frailty Index (FI) described as accumulation of deficits, including but not limited to a series of certified tests will be done at Visit 1 and data recorded in the eCRF (see Section 10.6.2.2, *and refer to the SPM for details on the assessment of frailty status*). (Amended 16 November 2016)

5.5.1.6. Record demographic data

Record demographic data such as date of birth, gender, geographic ancestry and ethnicity*. Working status of the subject, if the subject has a caregiver (as well as the working status of the caregiver if applicable) will also be included in the subject's eCRF.

*Since differences in the safety and efficacy of certain medical products have been observed in racially and ethnically distinct subgroups of the US population, ethnicity will be collected.

5.5.1.7. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first visit in the eCRF. Medications taken by the subject must also be recorded.

5.5.1.8. Distribution, training, completion and collection of pre-vaccination diary card

A pre-vaccination diary card will be dispensed to each subject prior to the first study vaccination and subjects/ subjects' caregiver will be informed how to complete this card by the site staff. This pre- vaccination diary card will only query general symptoms and

should be completed by the subject /subjects' caregiver(s) and collected by the site staff at Visit 1.

5.5.1.9. Review and transcribe pre-vaccination diary cards

The investigator/study staff will ensure that subject has completed the Visit 1 pre-vaccination diary card. The investigator or designee will transcribe the information that the subject documented on the diary card into the eCRF.

5.5.2. Procedures during Visit 2

Note that the first vaccination at Visit 2 will take place at least 7 days after the first visit (Visit 1) (see [Table 6](#) for visit intervals).

5.5.2.1. Re-check inclusion and exclusion criteria

Inclusion and exclusion criteria are re-checked at Visit 2 for any changes compared to Visit 1. In case the subject is no longer eligible at Visit 2, the subject will be withdrawn from the study and the reason for this will be recorded in the eCRF. 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 6](#) for visit intervals).

5.5.2.2. Distribution, completion and collection of second pre-vaccination diary card

A second pre-vaccination diary card will be dispensed to each subject at Visit 2. The card will only query general symptoms and should be completed by the subject /subjects' caregiver(s) and collected by the site staff prior to the first study vaccination.

5.5.2.3. Review and transcribe pre-vaccination diary cards

The investigator/study staff will ensure that subject has completed the (Visit 2) pre-vaccination diary cards prior to Vaccination 1. The investigator or designee will transcribe the information that the subject documented on the diary card prior to the visit into the eCRF.

5.5.2.4. Distribution and completion of SF-36 and EQ-5D questionnaires at Visit 2

The SF-36 and EQ-5D questionnaires will be distributed to subjects again at Visit 2. Subjects will be asked to complete the entire SF-36 and EQ-5D questionnaires on site just before vaccination at Visit 2. Completed questionnaires will then be collected and subject responses will be transcribed into the e-CRF. The same procedure for questionnaires will be followed at Visit 4 (see Section [5.5.2.11](#)).

5.5.2.5. Check contraindications

Contraindications must be checked at the beginning of each vaccination visit. Refer to Section [6.4](#) for more details.

5.5.2.6. Pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test* prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative. Note: The urine pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

*A urine pregnancy test is sufficient. A serum pregnancy test, instead of a urine pregnancy test, should only be considered if required by local or ethics committee regulations.

5.5.2.7. Assess pre-vaccination body temperature

The body temperature of all subjects needs to be measured prior to any study vaccine administration. Pre-vaccination temperatures should always be recorded orally. In rare situations when there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented and justified. If the subject has a fever (fever is defined as temperature $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ by oral route, axillary or tympanic setting, or $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ on rectal setting) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see [Table 6](#) for visit intervals).

5.5.2.8. Study vaccine administration

- After completing all prerequisite procedures prior to vaccination, one dose(s) of HZ/su study vaccine will be administered IM in the deltoid of the non-dominant arm (refer to Section [6.3](#) for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to [Table 6](#) for visit intervals). In that case, all activities that need to be performed on the day of vaccination (e.g., pregnancy test, questionnaires completion, ...) will also have to be postponed until vaccination day.
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine(s), with appropriate medical treatment readily available in case of anaphylaxis.
- Any subjects with an event of HZ between Visit 1 (Day -7) and any dose of HZ/su vaccine should not receive the upcoming dose(s) of the HZ/su vaccine.

5.5.2.9. Check and record concomitant medication/vaccination

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section [6.5](#).

5.5.2.10. Recording of AEs, SAEs, pregnancies and pIMDs

- Refer to Section [8.3](#) for procedures for the investigator to record AEs, SAEs, pregnancies and pIMDs. Refer to Section [8.4](#) for guidelines and how to report SAE, pregnancy and pIMD reports to GSK Biologicals.
- The subjects/subjects' caregiver(s) will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to the subject/subject's caregiver(s) see Section [5.3.1.1](#)). The subject/subject's caregiver(s) will record body (oral route preferred) temperature and any solicited local/general AEs (i.e., on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e., on the day of vaccination and during the next 29 days occurring after vaccination). If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented with an explanation for why it was different from the oral route. The subject/subject's caregiver(s) will be instructed to return the completed diary cards.
- The subject/subject's caregiver(s) will be instructed to return the completed diary card to the investigator at the next study visit. The post-vaccination 2 diary cards for daily recording of unsolicited AEs and concomitant medication/vaccination (Days 0-29) by subjects will be returned by mail.
- Collection and verification of completed diary cards will occur during discussion with the subject/ subject's caregiver(s) at the visit following each vaccination visit (except for the post-vaccination 2 diary cards for daily recording of unsolicited AEs and concomitant medication/vaccination (Days 0-29) which will be returned by mail and discussed during the Month 3 phone contact).
- Any unreturned diary cards will be sought from the subject/subject's caregiver(s) through telephone call(s) or any other convenient procedure. The investigator and/or delegate will transcribe the collected information into the eCRF.

5.5.2.11. Distribution and completion of SF-36 and EQ-5D questionnaires post-vaccination

The SF-36 PF component of the SF-36 questionnaire (only questions 3a through 3j, see [Table 15](#)) and EQ-5D daily questionnaires will be distributed to the subjects to take home following both vaccinations at Visit 2 and Visit 4. These questionnaires will need to be completed on a daily basis (Days 1 to 6) and must be returned at the next visits (Visit 3 and Visit 5). Additionally, during Visits 3 and 5, subjects will be asked to once again fill in the entire SF-36 and EQ-5D questionnaires on site. Completed questionnaires, collected at Visits 3 and Visit 5, will be transcribed into the eCRF (see Sections [10.6.2.3](#) and [10.6.2.4](#)).

5.5.3. Study conclusion

The investigator will:

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

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

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

The Quality Control Standards and Requirements for the candidate 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.

The characteristics of the study vaccine are detailed in [Table 7](#).

Table 7 Study vaccine

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	Number of doses
HZ/su	VZV gE	gE=50µg	Lyophilized pellet in a vial	0.5 mL	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes	Liquid in a mono-dose vial		

HZ/su = Herpes Zoster subunit vaccine; VZV = Varicella Zoster Virus; gE = recombinant purified envelope glycoprotein E; µg = microgram; mL = milliliter; AS01_B = Adjuvant System AS01_B; MPL = 3-O-desacyl-4'-monophosphoryl lipid A; QS21 = *Quillaja saponaria* Molina, fraction 21 (purified saponin extract from the South American tree).

6.2. 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 authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must

be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

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

6.3. Dosage and administration of study vaccine

After removal of the vaccine components from the temperature monitored refrigerator, the vaccine should be reconstituted and administered within 6 hours, and should be kept at room temperature (between 2°C/36°F and 30°C/86°F).

Vaccine will be administered as indicated in [Table 8](#).

Table 8 Dosage and administration

Type of contact and timepoint	Study group	Treatment name	Volume to be administered	Route ¹	Site ²	Side ³
Visit 2 (Month 0)						
Visit 4 (Month 2)	HZ/su	HZ/su	0.5 mL	IM	D	N-D

¹ Intramuscular (IM)

² Deltoid (D)

³ Non-dominant (N-D)

mL = millilitre; HZ/su = Herpes Zoster subunit vaccine.

The reconstituted vaccine (0.5 mL) should be administered by IM injection into the deltoid (D) muscle of the non-dominant (N-D) arm using a standard aseptic technique. In rare situations when there is no alternative, the injection may be given in the dominant arm.

6.4. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of HZ/su vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see [Section 8.5](#)).

- Anaphylaxis following the administration of vaccine.
- Pregnancy (see [Section 8.2.1](#)).

- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- If the subject experiences an SAE judged to be vaccine-related by the investigator/ delegate.
- If the subject experiences an event of HZ before administration of the first dose of the vaccine or between the first and the second dose of vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgment prior to administering the next dose of the vaccine. Refer to Section 8.1.5.1 for the definition of pIMDs.

The following events constitute contraindications to administration of HZ/su vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.4), or the subject may be withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever at the time of vaccination.
 - Fever is defined as temperature $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ for oral, axillary or tympanic setting, or $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ for rectal route. The preferred route for recording temperature in this study will be oral.
 - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever can be administered all vaccines/products.

6.5. Concomitant medications/products and concomitant vaccinations

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

6.5.1. Recording of concomitant medications/products and concomitant vaccinations

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

- All concomitant medications/products, except vitamins and dietary supplements, administered starting 7 days before the first dose and during the period 30 days (Day 0 to Day 29) following each dose of study vaccine.
- Any concomitant vaccination administered in the period starting 30 days before enrolment and ending at one month post dose 2.

- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).
E.g., an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ for oral route, axillary or tympanic setting, or $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ on rectal setting. The preferred route for recording temperature in this study will be oral].
- Any investigational or non-registered product (drug or vaccine) other than the study vaccine.
- Any concomitant medications/products/vaccines listed in Section 6.5.2.
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered during the study period for the treatment of a SAE /pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

6.5.2. Concomitant vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.4 for cohorts to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine used during the study period.
- Administration of a live vaccine in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose of study vaccine, or, administration of a non-replicating vaccine* within 15 days prior to or within 14 days after either dose of study vaccine. *E.g., inactivated and subunit vaccines, including inactivated and subunit influenza vaccines for seasonal or pandemic flu, without adjuvant, and pneumococcal conjugate vaccines.
- 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 Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Receipt of a vaccine against HZ other than the study vaccine from enrolment to 1 month post-dose 2.

7. HEALTH ECONOMICS

Direct medical and indirect cost (the number of days of work loss) data related to the reactogenicity will be estimated based on the corresponding information recorded in the CRF. Resource use data to be collected include:

- Direct medical costs:
 - Medication, i.e., the change in medication pre-vaccination and post-vaccination will be analysed to identify which medication is associated with reactogenicity.
 - Medically Attended Visits (i.e., hospitalization, General Practitioners and specialist visits).
 - Telephone contacts for healthcare reasons will be recorded in the diary cards and then transcribed into the eCRF.
- Indirect costs:
 - Missed time from work (subject and caregiver). The percentage of subjects with loss of working days will be tabulated.
 - An approximated monthly salary (for full-time and self-employed workers) or average daily wage (for part-time workers) will be estimated based on subject's type of work, hours worked, age, etc., collected on Day -7 (Visit 1).

Further details of cost analysis will be detailed in a Health Economics analysis plan.

8. SAFETY

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

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

8.1. Safety definitions

8.1.1. Definition of an adverse event

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

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine(s)/product(s) 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 investigational vaccine(s)/product(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- 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).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

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

8.1.2. Definition of a serious adverse event

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

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 jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

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

8.1.3. **Solicited adverse events**

8.1.3.1. **Solicited local (injection-site) adverse events**

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

Table 9 Solicited local adverse events

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

8.1.3.2. Solicited general adverse events

The following general AEs will be solicited:

Table 10 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

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

Note: Temperature (oral) will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

The time of first onset of the solicited local and general AEs needs to be recorded in the diary cards and eCRF.

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

In absence of diagnosis, abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments 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 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.

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

8.1.5. Adverse events of specific interest**8.1.5.1. Potential immune-mediated diseases**

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in [Table 11](#).

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 11 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
<ul style="list-style-type: none"> • Cranial nerve disorders, including paralyses/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 • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy 	<ul style="list-style-type: none"> • Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome • Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder 	<ul style="list-style-type: none"> • Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphea)
Vasculitides	Blood disorders	Others
<ul style="list-style-type: none"> • Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis. 	<ul style="list-style-type: none"> • Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia 	<ul style="list-style-type: none"> • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

Liver disorders	Gastrointestinal disorders	Endocrine disorders
<ul style="list-style-type: none"> Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis Autoimmune cholangitis 	<ul style="list-style-type: none"> Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis Celiac disease Autoimmune pancreatitis 	<ul style="list-style-type: none"> Autoimmune thyroiditis (including Hashimoto thyroiditis) Grave's or Basedow's disease Diabetes mellitus type I Addison's disease Polyglandular autoimmune syndrome Autoimmune hypophysitis

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

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

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

8.2.1. Pregnancy

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

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

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

The following should always be considered as SAE and will be reported as described in Sections 8.4.1 and 8.4.3:

- Spontaneous pregnancy loss, including:
 - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
 - ectopic and molar pregnancy
 - stillbirth (intrauterine death of foetus after 22 weeks of gestation).
- Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognized that national regulations might be different.
- Any early neonatal death (i.e., death of a live born infant occurring within the first 7 days of life).

- Any congenital anomaly or birth defect (as per [CDC MACDP 2007] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the investigational vaccine will be reported to GSK Biologicals as described in Section 8.4.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

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

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

All AEs starting 30 days following administration of each dose of study vaccine 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 and will end approximately 12 months following administration of the last dose of study vaccine for each subject. See Section 8.4 for instructions on reporting of SAEs.

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

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 the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine. See Section 8.4 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end 12 months following administration of the last dose of study vaccine. See Section 8.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in [Table 12](#).

Table 12 Reporting periods for collecting safety information

Timepoint	Visit 1 Day -7	Visit 2 Month 0	Visit 3 Day 7	Month 1	Visit 4 Month 2	Visit 5 Day 67	Contact Month 3		Contact Month 8		Contact Month 14
Timing of reporting / Study activity	Day -7 Pre-Vacc.	Day 0 Dose 1	Day 6 post-Dose 1	Day 29 post-Dose 1	Day 60 Dose 2	Day 6 post-Dose 2	Day 29 post-Dose 2		Safety Follow-Up		Study Conclusion
Solicited general AEs (see Sections 5.3.1.1 and 5.5.1.8) (Amended 16 November 2016)											
Solicited local AEs											
Unsolicited AEs ^a											
AEs/SAEs leading to withdrawal from the study											
SAEs											
SAEs related to the investigational vaccine											
SAEs related to study participation or concurrent GSK medication/vaccine ^b											
Pregnancies											
pIMDs (see Section 8.1.5.1 and Table 11)											

Vacc. = Vaccination; AE = Adverse Event; SAE = Serious Adverse Event; GSK = GlaxoSmithKline; pIMDs = potential Immune Mediated Diseases.

^a The post-vaccination 2 diary cards for daily recording of unsolicited AEs and concomitant medication/vaccination (Days 0-29) by subjects will be returned by mail.

^b The reporting period of these events starts from the time the subject consents to participate in the study.

8.3.2. Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in [Table 12](#). Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.3. Evaluation of adverse events and serious adverse events

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

As a consistent method of collecting AEs, the subject should be asked a non-leading question such as:

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

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

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

8.3.3.2. Assessment of adverse events**8.3.3.2.1. Assessment of intensity**

The intensity of the following solicited AEs will be assessed as described in [Table 13](#).

Table 13 Intensity scales for solicited symptoms in adults

Adverse Event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever*		Record temperature in °C/F
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, diarrhoea 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 interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Shivering	0	None
	1	Shivering that is easily tolerated
	2	Shivering that interferes with normal activity
	3	Shivering that prevents normal activity

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

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF and the time when the temperature was recorded.

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

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

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

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

- 1 (mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- 2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.
- 3 (severe) = An AE which prevents normal, everyday activities. 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 one of the pre-defined outcomes as described in Section 8.1.2.

8.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccine/product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. 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 investigational vaccine/product 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 Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the *Expedited Adverse Events Report* to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and

update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

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 investigational vaccine/product?

YES : There is a reasonable possibility that the vaccine(s) contributed to the AE.

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

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine **ALL** possible contributing factors for each SAE.

Possible contributing factors include:

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

8.3.3.3. Assessment of outcomes

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

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.

- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

8.3.3.4. Medically attended visits

The subjects will be asked if they received medical attention defined as hospitalization, an emergency room visit or a visit to medical personnel (medical doctor) for any reason, other than routine health care visits, from the first vaccination until Month 14, and this information will be recorded in the eCRF.

In addition, for solicited AEs specific information on reactogenicity-triggered medical attention (phone calls, visits to a general practitioner/emergency room, hospitalizations and specialists' visits) will be collected from day 0-6 and recorded in the eCRF.

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

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

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in [Table 14](#), once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in [Table 14](#), once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in [Table 14](#), once the investigator determines that the event meets the protocol definition of a pIMD.

Table 14 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.

** Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.

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

8.4.2. Contact information for reporting serious adverse events, pregnancies and pIMDs

Study Contact for Reporting SAEs, pregnancies and pIMDs
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs, pregnancies and pIMDs
24/24 hour and 7/7 day availability:
GSK Biologicals Clinical Safety & Pharmacovigilance
US sites only:
Fax: PPD

SAEs = Serious Adverse Events; pIMDs = potential Immune Mediated Diseases.

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

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

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

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

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

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

8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

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

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

8.4.5. Reporting of pIMDs to GSK Biologicals

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report **WITHIN 24 HOURS** after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD and whether it is serious or non-serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated **WITHIN 24 HOURS**.

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

Refer to Section [8.4.3.1](#) for back-up system in case the electronic reporting system does not work.

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

When additional SAE, pregnancy, or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the [Sponsor Information](#)) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in [Table 14](#).

8.4.7. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section [8.4.1](#). GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the

safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

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

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

8.5.1.1. Follow-up during the study

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to [Table 14](#)).

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

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.

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

The investigator will follow subjects:

- with SAEs, pIMDs (serious or non-serious), or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, 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 Biologicals using a paper/ electronic Expedited Adverse Events Report and/or pregnancy report as applicable.

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

8.5.2. Follow-up of pregnancies

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

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

8.6. 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 an AE should be recorded in the subject's eCRF (refer to Section 6.5).

8.7. Subject card

Study subjects / subjects' caregiver(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 caregiver(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 / subjects' caregiver(s) must be instructed to keep subject cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

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

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

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

All data collected until the date of 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.

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

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she/the subject's caregiver(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's caregiver(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 8.5.1.2).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational 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 investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

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

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

10. STATISTICAL METHODS

10.1. Primary endpoint

- Change in mean SF-36 PF scale score.
 - Baseline* versus mean score over the period day 1 to day 7** after first vaccination.

10.2. Secondary endpoints

- Change in mean SF-36 PF scale score. (Amended 16 November 2016)
 - Baseline* versus mean score over the period day 1 to day 7** after second vaccination.
- Change in mean SF-36 PF single item scores.
 - Baseline* versus mean score over the period day 1 to day 7** after each vaccination.
- Change in SF-36 Role Physical scores.
 - Baseline* versus score on day 7** after each vaccination.
- Change in the QALY.
 - Baseline* versus combined score over the period day 1 to day 7** after each vaccination.
- Healthcare resource utilization (i.e., hospitalization, telephone calls, medical visits and specialist visits, medication intake).
 - Days 0 to 6 after each vaccination.
- Work loss for subjects.
 - Days 0 to 6 after each vaccination.
- Work loss for the non-dedicated caregivers.
 - Days 0 to 6 after each vaccination.
- Extra work for dedicated caregivers.

- Days 0 to 6 after each vaccination.
- Solicited local and general symptoms in subjects.
 - Occurrence, intensity and duration of solicited local symptoms within 7 days (Days 0-6**) after each vaccination.
 - Occurrence, intensity, duration and relationship to vaccination of solicited general symptoms within 7 days (Days 0-6**) after each vaccination.
- Unsolicited adverse events (AEs) in subjects.
 - Occurrence, intensity and relationship to vaccination during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events (SAEs).
 - Occurrence and relationship to vaccination of all SAEs from the first vaccination up to the study end.
- Occurrence of adverse events of specific interest (AESIs): potential Immune-Mediated Diseases (pIMDs).
 - Occurrence and relationship to vaccination of any pIMDs from first vaccination up to the study end.

*Note: baseline for dose 1 is defined as the mean of the assessments at day -7 and day 0; for dose 2 baseline is defined as the mean of the three assessments at day -7, day 0 and day 60 (day 0 for dose 2). Further details on baseline calculation will be given in the Statistical Analysis Plan (SAP).

**Note: The post-vaccination completion of SF-36 and EQ-5D questionnaires brought home by the subjects will be on days 1 to day 6, with day 7 to be filled in at the site (during Visits 3 and 5); while the post-vaccination recording of solicited AEs on the diary card brought home by the subjects will be on days 0 to day 6.

10.3. Determination of sample size

To estimate the overall change in PF scores in HZ/su vaccinated subjects, the loss in PF scores due to the reactogenicity from the HZ/su vaccination will be evaluated by the difference in PF scale scores in subjects before and after HZ/su vaccination.

The PF score will be estimated as the change in mean PF score between baseline and mean score over the period day 1 to day 7 after first vaccination.

In the older adult population from ZOSTER-006 and based on the assessment of PF at Month 0, 14, 26 and 38, the baseline mean PF score and the standard deviation are estimated as 81.8 and 18.45, respectively. This study is designed to provide an estimate of precision around the mean change in PF scores. Assuming a standard deviation of 21.2 for the change in PF scores this allows us to generate an estimate of the mean with a precision of 2.2 with a sample size of 360 subjects. Assuming a non-evaluable proportion of approximately 10% of subjects a total of 400 subjects need to be enrolled in the study.

10.4. Cohorts for Analyses

10.4.1. Total vaccinated cohort

The total vaccinated cohort (TVC) will include all vaccinated subjects with respect to the vaccine actually administered.

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

The TVC for analysis of reactogenicity will include all subjects with at least one vaccine dose administered and documented (with the 7 day diary card available).

10.4.2. According-to-protocol cohort for analysis of safety

The ATP cohort for analysis of safety will include all subjects:

- who have received at least one dose of study vaccine;
- for whom administration site of study vaccine is known;
- who have not received other vaccine forbidden in the protocol (Section 6.5.2);
- Who have received the study vaccine correctly reconstituted.

10.5. Derived and transformed data

The calculation of the QALY will be based on the EQ-5D questionnaire. The EQ-5D is a generic measure of health status that provides a simple description profile based on the following 5 items: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

For each day, the combination of the scores recorded in each of these 5 items, will be transformed in a single index value.

The QALY/week is calculated for each subject using the following formula:

$$AUC_{0-6} = \sum_{(0 \text{ to } 6)} (t_{k+1} - t_k) * (Y_k + Y_{k+1}) / 2$$

where Y_k is the score at day k and t is time at day k.

10.6. Statistical analyses

10.6.1. Analysis of demographics/baseline characteristics

- Demographic characteristics (age, gender, geographic ancestry and ethnicity) will be tabulated.
- The mean age (plus range and standard deviation) of the enrolled subjects, as a whole, and stratified by age group will be calculated.

- The distribution of subjects enrolled among the study sites will be tabulated as a whole.

10.6.2. Quality of life

The analysis of QoL will be based on the TVc. An analysis of the impact on reactogenicity and QoL of frailty status will be performed if data allows (see Section 10.6.2.2). Details of this sub-analysis will be elaborated upon in the SAP.

10.6.2.1. Analysis of QALY (Utility)

The 95% CI for QALY mean loss will be obtained using a multiple regression model on the change from baseline utility scores. The model will include age strata, gender and frailty status as the fixed effect.

The 95% CI for utility scores will be obtained pre- and post-vaccination separately assuming that utility scores were normally distributed with unknown variance.

10.6.2.2. Assessment of frailty status

An assessment of frailty status will be done at Visit 1. Frailty status will be measured in relation to the accumulation of deficits using an FI calculated according to the model proposed by Mitnitski et al. [Mitnitski, 2001]. The different aspects of frailty composing the FI will be assessed through a series of certified tests and specific questions in the following domains:

- Cognition: a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment called the Montreal Cognitive Assessment (MoCa);
- Physical status: criteria for the definition of frailty developed by Fried et al. [Fried, 2001] to categorize the physical frailty phenotype (PFP), the physical functioning category of the SF-36 questionnaire will be used as measure of the physical activity of the subject [Ryb, 2012];
- Depression and exhaustion: a screening test for depression and depressive disorder called the Center for Epidemiologic Studies Depression Scale – Revised (CESD-R);
- Multimorbidity: occurrence of a specific age dependent list of diseases based on the published work [Mitnitski, 2001];
- Disability: assessment of the subjects' dependence on others to perform a list of specific daily activities (based on the published work [Mitnitski, 2001; Searle, 2008]).

In the unlikely event that any of the above mentioned tests for cognition, physical status or depression are unable to be implemented in the protocol, a suitable replacement will be substituted as an alternative.

10.6.2.3. SF-36 health survey

The SF-36® is a multi-purpose health survey with 36 questions (refer to [APPENDIX A](#) [Ware, 2001] that will be used to evaluate PF using questions 3a through 3j. (Amended 16 November 2016) The concepts underlying the construction of the SF-36 scales and summary measures incorporates a taxonomy of three levels: (1) 36 items; (2) eight scales (see [Table 15](#) for details); and, (3) two summary measures (Physical Component and Mental Component Scores) that aggregate scales. All but one of the 36 items (self-reported health transition) are used to score the eight SF-36 scales. Each item is used in scoring only one scale. Scale scores will be constructed following the summated ratings and standardized SF-36 scoring algorithms.

Table 15 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

The SF-36 health survey questionnaires will be completed by all subjects at each study visits (i.e., Visit 1 Day -7, Visit 2 Month 0 (before the vaccination), Visit 3 Day 7, Visit 4 Month 2 (before the vaccination) and Visit 5 Day 67). Additionally, after each vaccination, the subjects will be given the SF-36 questionnaires to take home and asked to complete only questions 3a through 3j on a daily basis on Days 1 to 6. Subjects will be asked to return the completed questionnaires at the next visit (Visits 3 and 5). Completed questionnaires are to be collected and the subject responses transcribed into the e-CRF.

10.6.2.4. 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 (refer to [APPENDIX B](#) [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 using country specific value sets). Note, higher scores represent a better QoL, *and refer to Section 10.5 for how the calculation of the QALY will be based on the EQ-5D questionnaire. The EQ-5D also includes a Visual Analogue Scale (VAS) ranging from 0 to 100, with 100 representing the best imaginable health state and 0 representing the*

worst imaginable health state. Further details will be provided in the SAP. (Amended 16 November 2016)

The EQ-5D questionnaires will be completed by all subjects at each study visits (i.e., Visit 1 Day -7, Visit 2 Month 0 (before the vaccination), Visit 3 Day 7, Visit 4 Month 2 (before the vaccination) and Visit 5 Day 67). Additionally, after each vaccination, the subjects will be given the EQ-5D questionnaires to take home and asked to complete the entire EQ-5D questionnaire on a daily basis on Days 1 to 6. Subjects will be asked to return the completed questionnaires at the next visit (Visits 3 and 5). Completed questionnaires are to be collected and the subject responses transcribed into the e-CRF. (Amended 16 November 2016)

10.6.3. Analysis of safety

The primary analysis for safety will be based on the TVc. If the percentage of the vaccinated subjects excluded from the ATP cohort for safety is more than 5%, a second analysis based on the ATP cohort for safety will be performed.

The following analyses will be performed for safety endpoints:

- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3;
- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any AE during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3;
- The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day-follow-up period will be tabulated with exact 95% CI. For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination;
- The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination. The proportion of unsolicited AEs resulting in a medically attended visit (such as emergency room, out-patient visit, site investigator, etc.) will also be tabulated;
- The percentage of subjects who started to use the medications within the 30-days post-vaccination will be tabulated.
- The percentage of subjects with at least one report of serious adverse event classified by the MedDRA Preferred Terms and reported during the whole post-vaccination follow up period will be tabulated with exact 95% CI;
- SAEs will be described in details;

- The proportion of subjects with at least one report of pIMDs classified by the MedDRA Preferred Terms and reported during the whole post-vaccination period will be tabulated with exact 95% CI.
- pIMDs will be described in detail.

10.7. Interpretation of analyses

There is no pre-defined success criterion for the primary objective assessment. The analyses remain descriptive.

10.8. 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.

10.8.1. Sequence of analyses

Two formal analyses are planned: a first analysis and an end of study analysis.

The first analysis will be performed when the reactogenicity and QoL collected from dose 1 up to Visit 3 are available.

The end of study analysis of QoL and safety data will be performed when all data up to the study end (Study conclusion contact) will be available.

10.8.2. Statistical considerations for interim analyses

No interim analysis is planned.

11. ADMINISTRATIVE MATTERS

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

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 at the study site, omissions or inconsistencies detected by subsequent eCRF 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.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

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 is mandatory for the purpose of monitoring review. The monitor will perform a 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 freezes 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, any institutional requirements, applicable laws or regulations, or GSK standards/procedures.

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

11.4. Quality assurance

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

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

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

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

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

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 site or other mutually-agreeable location.

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

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

13. REFERENCES (Amended 16 NOVEMBER 2016)

Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP) guidelines. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; 2007.

<http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf>. Website accessed 19 October 2015.

Didierlaurent AM, Collignon C, Bourguignon P, et al. Enhancement of adaptive immunity by the human vaccine adjuvant AS01 depends on activated dendritic cells. *J Immunol*. 2014; 193(4): 1920-30.

Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007; 44 Suppl 1:S1-26.

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005) 'adopted at Community level in May 2006';

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf. Accessed 24 October 2016.

FDA, U.S. Department of Health and Human Services, Center for Biologics Evaluation and Research. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Version of September 2007.

Fried LP, Tangen CM, Walston J, et al., (Cardiovascular Health Study Collaborative Research Group). Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001; 56(3): M146-56.

Gater A, Uhart M, McCool R, Préaud E. The humanistic, economic and societal burden of herpes zoster in Europe: a critical review. *BMC Public Health*. 2015; 15: 193.

Kind P. The EuroQL instrument: An index of health-related quality of life. in: Spilker B, editor. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Second Edition. Philadelphia: Lippincott-Raven Publishers; 1996.

Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011; 60: 1-61.

Lal H, Cunningham AL, Godeaux O et al. Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults. *N Engl J Med*. 2015; DOI: 10.1056/NEJMoa1501184.

Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Sci World J*. 2001; 1: 323-36.

Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005; 352:2271-84.

Pellissier JM, Brisson M, Levin MJ. Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *Vaccine*. 2007; 25(49): 8326-37.

Ryb GE, Dischinger PC, Burch CA, et al. Frailty and injury causation. *Ann Adv Automot Med*. 2012; 56: 175-81.

Scott F, Johnson R, Leedham-Green M, et al. The burden of herpes zoster: A prospective population based study. *Vaccine*. 2006; 24: 1308-14.

Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008; 8: 24-33.

Sperber SJ, Smith BV, Hayden FG. Serologic response and reactogenicity to booster immunization of healthy seropositive adults with live or inactivated varicella vaccine. *Antiviral Res*. 1992; 17: 21-22.

Stassijns J, Bollaerts K, Baay M, Verstraeten T. A systematic review and meta-analysis on the safety of newly adjuvanted vaccines among children. *Vaccine*. 2016; 34(6): 714-22.

Szucs TD, Pfeil AM. A systematic review of the cost effectiveness of herpes zoster vaccination. *Pharmacoeconomics*. 2013 (2): 125-36.

Ware JE, Kosinski M, Interpreting SF-36 summary health measures: a response. *Qual Life Res*, 2001; 1-(5): 405-13.

Zostavax [shingles (herpes zoster) vaccine (live)] Prescribing Information. June 2011.

**APPENDIX A SF-36 (Version 2.0 SAMPLE) (Amended 16
November 2016)**

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

- a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3
- b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3
- c. Lifting or carrying groceries 1 2 3
- d. Climbing several flights of stairs 1 2 3
- e. Climbing one flight of stairs 1 2 3
- f. Bending, kneeling, or stooping 1 2 3
- g. Walking more than a mile 1 2 3
- h. Walking several hundred yards 1 2 3
- i. Walking one hundred yards 1 2 3
- j. Bathing or dressing yourself 1 2 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities..... 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5
- d. Had difficulty performing the work or other activities (for example, it took extra effort) 1..... 2..... 3..... 4..... 5

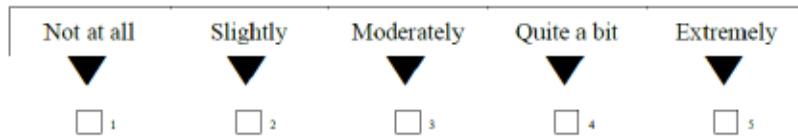
5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities..... 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Did work or other activities less carefully than usual..... 1..... 2..... 3..... 4..... 5

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

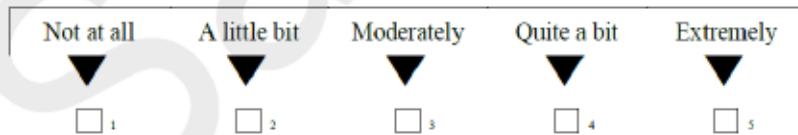
6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much bodily pain have you had during the past week?



8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?



SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

11. How TRUE or FALSE is each of the following statements for you?

Definitely true	Mostly true	Don't know	Mostly false	Definitely false
▼	▼	▼	▼	▼

- a I seem to get sick a little easier than other people 1 2 3 4 5
- b I am as healthy as anybody I know 1 2 3 4 5
- c I expect my health to get worse 1 2 3 4 5
- d My health is excellent 1 2 3 4 5

Thank you for completing these questions!

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

**APPENDIX B EQ-5D (English Version US SAMPLE) (Amended
16 November 2016)**



Health Questionnaire

English version for the USA

USA (English) © 1998 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about

I have some problems in walking about

I am confined to bed

Self-Care

I have no problems with self-care

I have some problems washing or dressing myself

I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities

I have some problems with performing my usual activities

I am unable to perform my usual activities

Pain / Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety / Depression

I am not anxious or depressed

I am moderately anxious or depressed

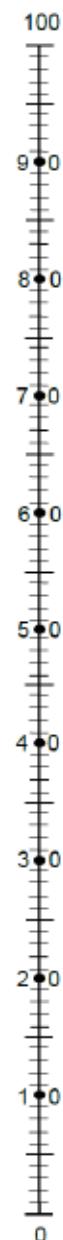
I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Best imaginable health state



Worst imaginable health state

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals	
Vaccine Value & Health Science (VVHS)	
Protocol Amendment 1	
eTrack study number and Abbreviated Title	204928 (ZOSTER-063)
IND number:	BB-IND 13857
Amendment number:	Amendment 1
Amendment date:	22 August 2016
Co-ordinating author:	PPD [REDACTED], Scientific writer, XPE Pharma & Science, Contractor for GSK Biologicals
Rationale/background for changes:	
<ul style="list-style-type: none"> • In response to CBER feedback, the objectives and endpoints were edited to clarify the time points for the measurement of the SF-36 Physical Functioning (SF-36 PF) and SF-36 Physical Role scores in the Synopsis and Sections 2.1, 2.2, 10.1 10.2 and 10.2. • The objectives and endpoints were edited to remove the unit of hours for the estimated work loss for subjects and non-dedicated caregivers and extra work for dedicated caregivers in the Synopsis and Sections 2.1, 2.2, 10.1 and 10.2. • The abbreviations for the questionnaires “EQ-5D” and “SF-36” were added to the List of Abbreviations and the term “Frailty” was defined in the Glossary of Terms. • Clarification about the filling out the questionnaires was added to Sections 5.3.1.1, 5.5.2.4 and 5.5.2.11 as well as indicating that the physical examination at Visit 1 can be performed according to local practice in Section 5.5.1.5. • The back-up study contact Fax number for reporting SAEs, pregnancies and pIMDs in the US was added to Section 8.4.2. • Additional edits were made to clarify how the PF score will be estimated in Section 10.3 and that the SF-36 questionnaire will be used for the measurement of Physical Functioning in Section 10.6.2.3. • In response to CBER feedback, clarification was made to indicate that the analysis of Quality of Life (QoL) data will be based on the Total Vaccinated Cohort (TVC) in Sections 10.4.1 and 10.6.2. • The timeframe for question 2 has been reduced from “one year ago” to “one week ago” and the timeframe for questions 4 - 10 has been reduced from “the past 4 weeks” to “the past week” in the sample SF-36 questionnaire (Appendix A). 	

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

SYNOPSIS

Rationale for the study and study design	<ul style="list-style-type: none">Rationale for the study <p>Other side effects seen in more than 10% of people who got received the vaccine included myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms such as nausea, vomiting, diarrhoea and/or abdominal pain.</p>
Objectives	<p>Primary</p> <ul style="list-style-type: none">To estimate the change in the <i>SF-36</i> Physical Functioning (<i>SF-36</i> PF) scale scores from baseline score to the <i>mean score over the period day 1 to day 7</i> following the first HZ/su vaccination in subjects ≥ 50 years of age (YOA) overall. <p>Secondary</p> <ul style="list-style-type: none">To estimate the change in the <i>SF-36</i> PF scale scores from baseline score to the <i>mean score over the period day 1 to day 7</i> following the second HZ/su vaccination in subjects ≥ 50 YOA overall.To estimate the change in the <i>SF-36</i> PF scale scores in subjects ≥ 50 YOA by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the <i>mean score over the period day 1 to day 7</i> following both HZ/su vaccinations 1 and 2.To estimate the change in <i>SF-36</i> PF-single item scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the <i>mean score over the period day 1 to day 7</i> following both HZ/su vaccinations 1 and 2.To estimate the change in <i>SF-36</i> Role Physical scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the <i>mean score over the period day 1 to day 7</i> following both HZ/su vaccinations 1 and 2.To estimate the QALY change in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) from baseline score to the <i>mean score over the period day 1 to day 7</i> following both HZ/su vaccinations 1 and 2.To estimate the work loss (hours) in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su

vaccinations 1 and 2.

- To estimate the work loss (~~hours~~) for non-dedicated caregivers (e.g., family member) of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the ~~hours~~ of extra work for dedicated caregivers of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.

Endpoints**Primary**

- Change in mean *SF-36* PF scale scores.
 - Baseline* versus *mean score over the period* days 1 to *day 7* after first vaccination.

Secondary

- Change in mean *SF-36* PF scale scores.
 - Baseline* versus *mean score over the period* days 1 to *day 7* after second vaccination.
- Change in mean *SF-36* PF single item scores.
 - Baseline* versus *mean score over the period* days 1 to *day 7* after each vaccination.
- Change in *SF-36* Role Physical scores.
 - Baseline* versus ~~days 1 and~~ *score on day 7* after each vaccination.
- Change in the QALY.
 - Baseline* versus *combined score over the period* days 1 to *day 7 assessment* after each vaccination.
- ~~Hours of~~ Work loss for subjects.
 - Days 0 to 6 after each vaccination.
- ~~Hours of~~ Work loss for the non-dedicated caregivers.
 - Days 0 to 6 after each vaccination.
- ~~Hours of~~ Extra work for dedicated caregivers.
 - Days 0 to 6 after each vaccination.

*Note: baseline for dose 1 is defined as the mean of the assessments at day -7 and day 0; for dose 2 baseline is defined as the mean of the three assessments at day -7, day

~~0 and day 60 (day 0 for will be defined for dose 1 and dose 2).~~ Further details on baseline calculation will be given in the Statistical Analysis Plan (SAP).

****Note: The post-vaccination completion of SF-36 and EQ-5D questionnaires brought home by the subjects will be on days 1 to day 6, with day 7 to be filled in at the site (during Visits 3 and 5); while the post-vaccination recording of solicited AEs on the diary card brought home by the subjects will be on days 0 to day 6.**

LIST OF ABBREVIATIONS

EQ-5D: *EuroQol five dimension health questionnaire*

SF-36: *A Short Form 36-item health survey*

GLOSSARY OF TERMS

Frailty: *Frailty is a term used in Geriatric Medicine to identify older adults who are at increased risk of poor clinical outcomes, such as incident disability, cognitive decline, falls, hospitalization, institutionalization, or increased mortality. Frailty represents a reduction in resistance to stressors leading to increased clinical vulnerability and adverse health outcomes.*

Section 1.2.1. Rationale for the study

Other side effects seen in more than 10% of people who ~~got received~~ the vaccine included myalgia, fatigue, headache, shivering, fever and gastrointestinal symptoms such as nausea, vomiting, diarrhoea and/or abdominal pain.

Section 1.2.2. Rationale for the study design

Subjects in the general population (especially older adults), are on average unable to achieve perfect QoL scores, because many subjects may be somewhat limited in “climbing several flights of stairs” or “bending, kneeling, or stooping”. To estimate the impact of reactogenicity on an individual’s **SF-36** PF and QoL, we will compare two periods, i.e., pre-vaccination and post-vaccination. The difference is considered to be the effect of vaccination and reactogenicity on the **SF-36** PF and QoL.

Section 2.1. Primary objective

- To estimate the change in the *SF-36* Physical Functioning (*SF-36* PF) scale scores from baseline score to the *mean score over the period day 1 to day 7* following the first HZ/su vaccination in subjects ≥ 50 years of age (YOA) overall.

Section 2.2. Secondary objectives

- To estimate the change in the *SF-36* PF scale scores from baseline score to the *mean score over the period day 1 to day 7* following the second HZ/su vaccination in subjects ≥ 50 YOA overall.
- To estimate the change in *the SF-36* PF scale scores in subjects ≥ 50 YOA by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the *mean score over the period day 1 to day 7* following both HZ/su vaccinations 1 and 2.
- To estimate the change in *SF-36* PF single item scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the *mean score over the period day 1 to day 7* following both HZ/su vaccinations 1 and 2.
- To estimate the change in *SF-36* Role Physical scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the *score on day 7* following both HZ/su vaccinations 1 and 2.
- To estimate the QALY change in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) from baseline score to the *combined score on days 1 to 7* following both HZ/su vaccinations 1 and 2.
- To estimate the work loss (~~hours~~) in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the work loss (~~hours~~) for non-dedicated caregivers (e.g., family member) of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the ~~hours of~~ extra work for dedicated caregivers of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.

Section 5.3.1.1. Questionnaires and Diary cards

Following vaccination, 7-day and 30-day diary cards will be dispensed to be completed by the subjects/ subjects' caregiver.

The questionnaires will be filled in by the subject/subjects caregiver on site at each visit. In addition, the subject/subjects caregiver will be required to complete the SF-36

PF component of the SF-36 questionnaire (i.e., items 3a to 3j, see Table 15) and the EQ-5D questionnaire at home on days 1 to 6 following each vaccination.

Section 5.5.1.5. Physical examination and assessment of frailty status

Perform a physical examination of the subject at Visit 1 including weight and height (body mass index [BMI] will be calculated). *The physical examination can be performed per the site's medical judgment and standard of care (refer to the SPM for details of the physical examination).*

Section 5.5.2.4. Distribution and completion of SF-36 and EQ-5D questionnaires at Visit 2

The SF-36 and EQ-5D questionnaires will be distributed to subjects again at Visit 2. Subjects will be asked to complete the entire SF-36 and EQ-5D questionnaires *on site* just before vaccination at Visit 2. Completed questionnaires will *then* be collected at ~~Visit 2~~, and subject responses *will be* transcribed into the e-CRF.

Section 5.5.2.11. Distribution and completion of SF-36 and EQ-5D questionnaires post-vaccination

The SF-36 *PF component of the SF-36 questionnaire (only questions 3a through 3j, see Table 15)* and EQ-5D daily questionnaires will be distributed to the subjects to take home following both vaccinations at Visit 2 and Visit 4.

Section 6.1. Description of study vaccine

Table 7 Study vaccine

HZ/su = Herpes Zoster subunit vaccine; VZV = Varicella Zoster Virus; gE = recombinant purified envelope Glycoprotein E; μ g = microgram; mL = milliliter; AS01a = Adjuvant System AS01a; MPL = 3-O-desacyl-4'-monophosphoryl lipid A; QS21 = *Quillaja saponaria* Molina, fraction 21 (purified saponin extract from the South American tree).

Section 8.4.2. Contact information for reporting serious adverse events, pregnancies and pIMDs

Back-up Study Contact for Reporting SAEs, pregnancies and pIMDs
24/24 hour and 7/7 day availability:
GSK Biologicals Clinical Safety & Pharmacovigilance
<i>US sites only:</i> Fax: PPD

Section 10.1. Primary endpoint

- Change in mean *SF-36* PF scale scores.
 - Baseline* versus mean score over the period days 1 to day 7 after first vaccination.

Section 10.2. Secondary endpoints

- Change in mean *SF-36* PF scale scores.
 - Baseline* versus *mean score over the period days 1 to day 7* after second vaccination.
- Change in mean *SF-36* PF single item scores.
 - Baseline* versus *mean score over the period days 1 to day 7* after each vaccination.
- Change in *SF-36* Role Physical scores.
 - Baseline* versus ~~days 1 and~~ score on day 7 after each vaccination.
- Change in the QALY.
 - Baseline* versus *combined score over the period days 1 to day 7 assessment* after each vaccination.
- ~~Hours of work~~ loss for subjects.
 - Days 0 to 6 after each vaccination.
- ~~Hours of work~~ loss for the non-dedicated caregivers.
 - Days 0 to 6 after each vaccination.
- ~~Hours of extra work~~ for dedicated caregivers.
 - Days 0 to 6 after each vaccination.

*Note: baseline for dose 1 is defined as the mean of the assessments at day -7 and day 0; for dose 2 baseline is defined as the mean of the three assessments at day -7,

~~day 0 and day 60 (day 0 for will be defined for dose 1 and dose 2). Further details on baseline calculation will be given in the Statistical Analysis Plan (SAP).~~

***Note: The post-vaccination completion of SF-36 and EQ-5D questionnaires brought home by the subjects will be on days 1 to day 6, with day 7 to be filled in at the site (during Visits 3 and 5); while the post-vaccination recording of solicited AEs on the diary card brought home by the subjects will be on days 0 to day 6.*

Section 10.3. Determination of sample size

The PF score will be estimated as the change in mean PF score between baseline and *mean score over the period days 1 to day 7 after first vaccination.*

Section 10.4.1. Total vaccinated cohort

~~The TVc for analysis of QoL will include all subjects with at least one vaccine dose administered and with QoL data collected at pre- and post-vaccination.~~

Section 10.6.2.1. Quality of life

The analysis of QoL will be based on the TVc ~~for analysis of QoL~~.

Section 10.6.2.3. SF-36 health survey

The SF-36® is a multi-purpose health survey with 36 questions (refer to APPENDIX A or the website address <http://www.sf-36.org/demos/SF-36.html> for a sample of the questionnaire) [Ware, 2001; SF-36.org, 2014; SF-36 sample, 2014] *that will be used to evaluate PF using questions 3a through 3j.*

APPENDIX A SF-36 (Version 2.0 SAMPLE)

2. Compared to one ~~year~~~~week~~ ago, how would you rate your health in general now?

Much better now than one year week ago	Somewhat better now than one year week ago	About the same as one year week ago	Somewhat worse now than one year week ago	Much worse now than one year week ago
--	--	---	---	---

4. During the past 4-weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

5. During the past 4-weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
6. During the past 4-weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
7. How much bodily pain have you had during the past 4-weeks?
8. During the past 4-weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
9. These questions are about how you feel and how things have been with you during the past 4-weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4-weeks...

10. During the past 4-weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

GlaxoSmithKline Biologicals**Vaccine Value & Health Science (VVHS)
Protocol Amendment 2****eTrack study number and Abbreviated Title** 204928 (ZOSTER-063)**IND number:** BB-IND 13857**Amendment number:** Amendment 2**Amendment date:** 16 November 2016**Co-ordinating author:** PPD, Scientific Writer**Rationale/background for changes:**

- 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 that will be used in this 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 that will be used in this study.
- The term VAS has been added to the List of Abbreviations and Section 10.6.2.4 since it has now been included in the EQ-5D questionnaire used in this study.
- References to hypertext links for examples of the SF-36 and EQ-5D questionnaires in Sections 10.6.2.3 and 10.6.2.4, respectively as well as in the Reference Section have been deleted, since images of pages for these questionnaires are provided as examples in APPENDIX A and B.
- Typographic errors were corrected and other minor modifications were made throughout for clarification.

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

Cover page

Co-ordinating author	• PPD, <i>Scientific Writer, XPE Pharma & Science, Contractor for GSK Biologicals</i>
Contributing authors	<ul style="list-style-type: none"> • PPD, <i>Clinical Research and Development Lead</i> • PPD, <i>Project Statistician</i> • PPD, <i>Project Oversight Data Manager, Keyrus Biopharma, Contractor for GSK</i>

LIST OF ABBREVIATIONS

VAS: *Visual Analogue Scale*

Section 1.2.2. Rationale for the study design

The study will estimate ~~any~~ changes in QoL or QALY loss within the same subjects between before and after HZ/su vaccination, and therefore a placebo control will not be included.

Section 5.3.1.1. Questionnaires and Diary cards

When the completed questionnaires and diary cards are returned to the study staff, the study staff will ~~review it together with the subject and ask him/her~~ *the subject* (at the time of return or at subsequent contact) if he/she received any assistance in completing questionnaires or diary cards. If the subject had assistance completing the questionnaires and/or diary card (e.g., by a caregiver), it should be noted in the eCRF. ~~In case~~ *When* questionnaires *or pre-vaccination diary cards* are completed at the study site, study staff can assist in reading the questions (verbatim).

Also, when the completed diary cards are returned to the study staff the study staff will review it together with the subject.

Section 5.4. Outline of study procedures**Table 5 List of study procedures**

Epoch	Primary							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	M3 Contact	M8 Contact	M14 Contact
Type of contact	Day -7	Month 0	Day 7 ¹	Month 2	Day 67 ¹	Month 3 ²	Month 8	Month 14
Timepoint(s)								
Physical examination including height and weight (see Section 5.5.1.5)	•	□						
Investigator sign off for the analysis			•					

Section 5.5.1.5. Physical examination and assessment of frailty status

Perform a physical examination of the subject at Visit 1 including weight and height (body mass index [BMI] will be calculated). The physical examination can be performed per the site's medical judgment and standard of care (~~refer to the SPM for details of the physical examination~~). Collected information needs to be recorded in the eCRF.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

An assessment of frailty status defined through a Frailty Index (FI) described as accumulation of deficits, including but not limited to a series of certified tests will be done at Visit 1 and data recorded in the eCRF (see Section 10.6.2.2, *and refer to the SPM for details on the assessment of frailty status*).

Section 8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

Table 12 Reporting periods for collecting safety information

Timepoint	Visit 1 Day -7	Visit 2 Month 0	Visit 3 Day 7	Month 1		Visit 4 Month 2	Visit 5 Day 67	Contact Month 3		Contact Month 8		Contact Month 14
Timing of reporting / Study activity	Day -7	Day 0	Day 6	Day 29		Day 60	Day 6	Day 29		Safety		Study
	Pre-Vacc.	Dose 1	post-Dose 1	post-Dose 1		Dose 2	post-Dose 2	post-Dose 2		Follow-Up		Conclusion
Solicited general AEs (see Sections 5.3.1.1 and 5.5.1.8)												

Section 10.2. Secondary endpoints

- Change in mean SF-36 PF scale scores.

Section 10.6.2.3 SF-36 health survey

The SF-36® is a multi-purpose health survey with 36 questions (refer to APPENDIX A or the website address <http://www.sf-36.org/demos/SF-36.html> for a sample of the questionnaire) [Ware, 2001; SF-36.org, 2014; SF-36 sample, 2014] that will be used to evaluate PF using questions 3a through 3j.

Section 10.6.2.4. 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 (refer to APPENDIX B or the website address http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Products/Sample_UK_English_for_a_sample_of_the_questionnaire [Kind, 1996; EQ-5D, 2014; EQ-5D sample, 2014]). 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 using country specific value sets). ~~A full list of value sets is available on the designer's website [EQ-5D, 2014]. Note, higher scores represent a better QoL, and refer to Section 10.5 for how the calculation of the QALY will be based on the EQ-5D questionnaire. The EQ-5D also includes a Visual Analogue Scale (VAS) ranging from 0 to 100, with 100 representing the best imaginable health state and 0 representing the worst imaginable health state. Further details will be provided in the SAP.~~

The EQ-5D questionnaires will be completed by all subjects at each study visits (i.e., Visit 1 Day -7, Visit 2 Month 0 (before the vaccination), Visit 3 Day 7, Visit 4 Month 2 (before the vaccination) and Visit 5 Day 67). Additionally, after each vaccination, the subjects will be given the EQ-5D questionnaires to take home and asked to complete the entire EQ-5D questionnaires on a daily basis on Days 1 to 6.

REFERENCES

EMA Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Doc. Ref. EMEA/CHMP/313666/2005) 'adopted at Community level in May 2006);
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf. Accessed 24 October 2016.

~~EQ 5D: <http://www.euroqol.org/> Accessed 9 October 2014.~~

~~EQ 5D sample:~~

~~http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Products/Sample_UK_English_EQ_5D_3L_Paper_Self_complete_v1.0_ID_23963.pdf Accessed 9 October 2014.~~

~~SF 36.org: A community for measuring health outcomes using SF tools. <http://www.sf36.org/tools/sf36.shtml> Accessed 9 October 2014.~~

~~SF 36 sample: http://www.sf36.org/demos/SF_36.html Accessed 9 October 2014.~~

APPENDIX A SF-36 (Version 2.0 SAMPLE)

~~SF 36v2™ Health Survey Scoring Demonstration~~

~~This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities.~~

~~Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.~~

~~4. In general, would you say your health is:~~

~~Excellent Very good Good Fair Poor~~

~~2. Compared to one week ago, how would you rate your health in general now?~~

~~Much better now than one week ago Somewhat better now than one week ago About the same as one week ago Somewhat worse now than one week ago Much worse now than one week ago~~

~~3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?~~

~~Yes, Yes, No, not~~

- a ~~Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports~~
- b ~~Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf~~
- c ~~Lifting or carrying groceries~~
- d ~~Climbing several flights of stairs~~
- e ~~Climbing one flight of stairs~~
- f ~~Bending, kneeling, or stooping~~
- g ~~Walking more than a mile~~
- h ~~Walking several hundred yards~~
- i ~~Walking one hundred yards~~
- j ~~Bathing or dressing yourself~~

4. ~~During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?~~

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
--	-----------------------	------------------------	------------------------	----------------------------	------------------------

- a ~~Cut down on the amount of time you spent on work or other activities~~
- b ~~Accomplished less than you would like~~
- c ~~Were limited in the kind of work or other activities~~
- d ~~Had difficulty performing the work or other activities (for example, it took extra effort)~~

5. ~~During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional~~

problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities					
b Accomplished less than you would like					
c Did work or activities less carefully than usual					
<hr/>					
d During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?					
Not at all	Slightly	Moderately	Quite a bit	Extremely	

7. ~~How much bodily pain have you had during the past week?~~

None	Very mild	Mild	Moderate	Severe	Very severe
<hr/>					
d During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?					
Not at all	A little bit	Moderately	Quite a bit	Extremely	

9. ~~These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling.~~

~~How much of the time during the past week...~~

All of the time	Most of the time	Some of the time	A little of the time	None of the time
-----------------------	------------------------	------------------------	----------------------------	------------------------

- a ~~Did you feel full of life?~~
- b ~~Have you been very nervous?~~
- c ~~Have you felt so down in the dumps that nothing could cheer you up?~~
- d ~~Have you felt calm and peaceful?~~
- e ~~Did you have a lot of energy?~~
- f ~~Have you felt downhearted and depressed?~~
- g ~~Did you feel worn out?~~
- h ~~Have you been happy?~~
- i ~~Did you feel tired?~~

10. ~~During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?~~

All of the time	Most of the time	Some of the time	A little of the time	None of the time
-----------------------	------------------------	------------------------	----------------------------	------------------------

11. ~~How TRUE or FALSE is each of the following statements for you?~~

Definitely true	Mostly true	Don't know	Mostly false	Definitely false
--------------------	----------------	---------------	-----------------	---------------------

- A ~~I seem to get sick a little easier than other people~~
- B ~~I am as healthy as anybody I know~~
- C ~~I expect my health to get worse~~
- D ~~My health is excellent~~

~~Thank you for completing these questions!~~

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
				

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
				

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

- a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3
- b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf..... 1 2 3
- c. Lifting or carrying groceries 1 2 3
- d. Climbing several flights of stairs..... 1 2 3
- e. Climbing one flight of stairs 1 2 3
- f. Bending, kneeling, or stooping..... 1 2 3
- g. Walking more than a mile..... 1 2 3
- h. Walking several hundred yards 1 2 3
- i. Walking one hundred yards 1 2 3
- j. Bathing or dressing yourself 1 2 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities..... 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5
- d. Had difficulty performing the work or other activities (for example, it took extra effort) 1..... 2..... 3..... 4..... 5

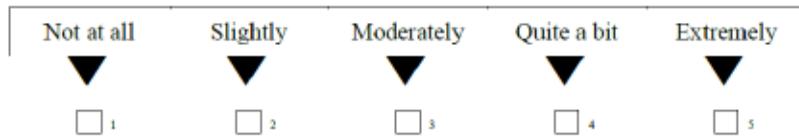
5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼

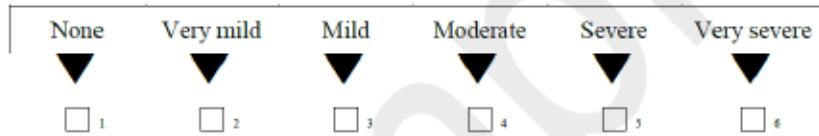
- a. Cut down on the amount of time you spent on work or other activities..... 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Did work or other activities less carefully than usual..... 1..... 2..... 3..... 4..... 5

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

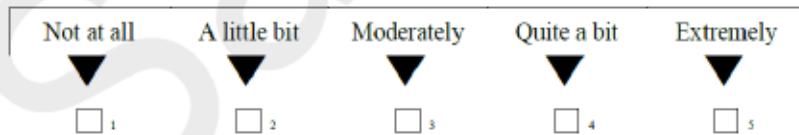
6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much bodily pain have you had during the past week?



8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?



SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

11. How TRUE or FALSE is each of the following statements for you?

Definitely true	Mostly true	Don't know	Mostly false	Definitely false
▼	▼	▼	▼	▼

- a I seem to get sick a little easier than other people 1 2 3 4 5
- b I am as healthy as anybody I know 1 2 3 4 5
- c I expect my health to get worse 1 2 3 4 5
- d My health is excellent 1 2 3 4 5

Thank you for completing these questions!

SF-36v2® Health Survey © 1992, 1996, 2000 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2® Health Survey Acute, United States (English))

APPENDIX B EQ-5D (English Version US SAMPLE)

~~By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.~~

Mobility

~~I have no problems in walking about~~

~~I have some problems in walking about~~

~~I am confined to bed~~

Self Care

~~I have no problems with self care~~

~~I have some problems washing or dressing myself~~

~~I am unable to wash or dress myself~~

Usual Activities (e.g., work, study, housework, family or leisure activities)

~~I have no problems with performing my usual activities~~

~~I have some problems with performing my usual activities~~

~~I am unable to perform my usual activities~~

Pain/Discomfort

~~I have no pain or discomfort~~

~~I have moderate pain or discomfort~~

~~I have extreme pain or discomfort~~

Anxiety/Depression

~~I am not anxious or depressed~~

~~I am moderately anxious or depressed~~

~~I am extremely anxious or depressed~~

~~© 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group~~



Health Questionnaire

English version for the USA

USA (English) © 1998 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about

I have some problems in walking about

I am confined to bed

Self-Care

I have no problems with self-care

I have some problems washing or dressing myself

I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities

I have some problems with performing my usual activities

I am unable to perform my usual activities

Pain / Discomfort

I have no pain or discomfort

I have moderate pain or discomfort

I have extreme pain or discomfort

Anxiety / Depression

I am not anxious or depressed

I am moderately anxious or depressed

I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Best imaginable health state

100

9•0

8•0

7•0

6•0

5•0

4•0

3•0

2•0

1•0

Worst imaginable health state

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title 204928 (ZOSTER-063)

IND number BB-IND 13857

Date of protocol amendment Amendment 2 Final: 16 November 2016

Detailed Title A phase III, open label, multicenter study to evaluate the impact of reactogenicity on Quality of Life (QoL), after intramuscular administration of GSK Biologics' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults \geq 50 years of age.

Sponsor signatory Lidia Oostvogels, MD
Director, Clinical and Epidemiology Project Leader,
Zoster Program, Belgian RDC

PPD

Signature**Date**

28 Nov 2016

For internal use only

-----Checksum-----!Vcr.!Created On - -
67d8391faef64e9d05fd1c8f3a9b938732fdd18a 2.0 11/25/2016 3:45:45 PM - -
