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 (HZ) vaccine (GSK 1437173A).
eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
Investigational New Drug (IND) number	BB-IND 13857
EudraCT number	2012-003643-30
Date of protocol	Final: 29 August 2012
Date of protocol amendment/ administrative change	Administrative change 1 Final: 12 February 2013 Amendment 1 Final: 23 April 2013 Amendment 2 Final: 20 February 2014
Title	Immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults with a prior episode of herpes zoster.
Detailed Title	A phase III, non-randomized, open-label, multicentre clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of herpes zoster.

eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
IND number	BB-IND 13857
EudraCT number	2012-003643-30
Detailed Title	A phase III, non-randomized, open-label, multicentre clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of herpes zoster.
Co-ordinating author	[redacted], Scientific Writer
Contributing authors	• [redacted], Director, Clinical Development Manager, Global Vaccine Development • [redacted], Director, Global Clinical Development, Global Vaccine Development • [redacted], Lead Clinical Development Manager, Director, Global Vaccine Development • [redacted], Project Statistician • [redacted], Global Study Manager • [redacted], Global Study Manager • [redacted], Global Vaccine Clinical Laboratories Project Manager • [redacted], ***Director, Project Manager (Amended: 20 February 2014)*** • [redacted], Manager, Global Regulatory Affairs • [redacted], Director, US Regulatory Affairs • [redacted], Manager, US Regulatory Affairs • [redacted], Clinical Safety Physician • [redacted], Study Data Manager • [redacted], Study Data Manager • [redacted], Project Data Manager • [redacted], ***Study Delivery Lead (Amended: 20 February 2014)***

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
IND number	BB-IND 13857
EudraCT number	2012-003643-30
Date of protocol amendment	Amendment 2 Final: 20 February 2014
Detailed Title	A phase III, non-randomized, open-label, multicentre clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of herpes zoster.
Sponsor signatory	[redacted], Lead Clinical Development Manager, Director, Global Vaccine Development
Signature	_____
Date	_____

Protocol Amendment 2 Rationale

Amendment number: Amendment 2
Rationale/background for changes: • The cut-off of the gE-specific ELISA assay has been changed from 18 to 97 mIU/mL. Background signal has been measured with the anti-gE ELISA on samples from Varicella Zoster Virus (VZV) naïve paediatric subjects. This observation of background signal on VZV naïve samples was not part of the original validation of the assay and establishment of the assay cut-off. Background signal measured with the anti-gE ELISA has no impact on Zoster project clinical conclusions as the vast majority of the samples (at all timepoints) have high titers well above the unspecific response level measured on VZV naïve samples from Measles, Mumps, Rubella and Varicella (MMRV) studies and Zoster vaccine responses are very robust. However this finding triggered re-evaluation of the assay cut-off. Based on complementary validation experiments performed in line with Clinical and Laboratory Standards Institute (CLSI) guidelines and taking into account internal company guidelines the technical and seropositivity cut-off has been set at 97 mIU/mL. (Section 5.8.3, Table 9, and Appendix A).

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.

eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
IND number	BB-IND 13857
EudraCT number	2012-003643-30
Date of protocol amendment	Amendment 2 Final: 20 February 2014
Detailed Title	A phase III, non-randomized, open-label, multicentre clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of herpes zoster.
Investigator name	_____
Signature	_____
Date	_____

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, non-randomized, open-label, multicentre clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of herpes zoster.

Indication

Prevention of Herpes Zoster (HZ) and related complications in adults ≥ 50 years of age and immunocompromised adults ≥ 18 years of age.

Rationale for the study and study design

- **Rationale for the study**

GSK Biologicals' candidate vaccine for the prevention of HZ is a recombinant subunit (su) vaccine consisting of VZV glycoprotein E (gE) antigen and an adjuvant system ($AS01_B$). Different gE antigen doses (25, 50 or 100 µg) combined with the AS01 Adjuvant System have been evaluated in completed studies in over a thousand adults and will be administered to approximately 15,000 subjects in ongoing trials not yet analyzed. In the analyzed studies it was shown to elicit strong cellular and humoral immune responses. Furthermore, the safety and reactogenicity profile of this candidate vaccine was acceptable. Based on phase II data from the antigen dose-ranging study, ZOSTER-003, and the adjuvant dose comparison study, ZOSTER-010, a gE antigen dose of 50 µg and the Adjuvant System $AS01_B$ were selected as the final vaccine formulation (henceforth, the final vaccine formulation of GSK Biologicals' candidate HZ vaccine will be referred to as HZ/su).

No information is currently available on the immune response conferred by HZ/su and the safety of HZ/su in subjects with a previous episode of HZ. Study ZOSTER-033 will therefore be conducted to evaluate the immunogenicity and safety (primary objectives) of GSK Biologicals' HZ/su vaccine in subjects ≥ 50 years of age (YOA), who previously have had HZ.

- **Rationale for the study design**

Study ZOSTER-033 will be an open and single arm study to collect immunogenicity and reactogenicity/safety data in subjects ≥ 50 years of age who previously have had HZ. These data will be compared with the ones from subjects without HZ in other HZ/su trials.

Objectives

Co-Primary

- To evaluate anti-gE vaccine response rate one month following a two-dose administration with HZ/su vaccine in all study subjects ≥50 YOA with a previous episode of HZ.

  Criteria to be used:

  – *The objective is met if the lower limit of the 95% CI of the vaccine response rate for anti-gE ELISA antibody concentrations one month after the second dose is at least 60%.*

- To evaluate the safety and reactogenicity following administration of HZ/su vaccine from the first vaccination up to 30 days post last vaccination in all study subjects ≥50 YOA with a previous episode of HZ.

Secondary

- To characterize anti-gE humoral immunogenicity response prior to first vaccination (Month 0) and at one month post last vaccination (Month 3) within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.
- To evaluate safety following administration of HZ/su vaccine, from 30 days post last vaccination until study end, in all study subjects ≥50 YOA with a previous episode of HZ.

Study design

- Experimental design: Phase III, non-randomized, open-label, multi-centre study with a single group.
- Duration of the study: Approximately 14 months. Each subject will be followed for approximately 12 months after the second vaccine dose for safety follow-up.
  - Epoch 001: Primary starting at Visit 1, Month 0 and ending at final safety follow up contact (i.e. 12 months following Dose 2).
  - Study group:

Synopsis Table 1 Study group and epoch foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
HZ Group	96	≥ 50 YOA	x

Synopsis Table 2 Study group and treatment foreseen in the study

Treatment name	Product name	Study Group
		HZ Group
HZ/su	VZV gE	x
	$AS01_B$	

HZ/su = Herpes Zoster subunit vaccine; VZV = Varicella Zoster Virus; gE = recombinant purified Glycoprotein E; $AS01_B$ = Adjuvant System $AS01_B$

- Control: historical control (results of this study will be compared with the ones of other HZ/su trials which include subjects without a history of HZ).
- Vaccination schedules: 0, 2 months
- Treatment allocation: Non-randomized. Subjects will be stratified by age: 50-59 YOA; 60-69 YOA and ≥ 70 YOA.
- Blinding: open-label

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule: Blood samples for humoral immunity (approximately 8 mL per visit) will be collected from all subjects at Visits 1 and 3.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

Number of subjects Target enrolment will be approximately 96 eligible subjects to provide 84 subjects evaluable for immunogenicity.

Subjects will be stratified according to age.

Endpoints **Primary**

- Anti-gE humoral immunogenicity.
  - Vaccine response for anti-gE humoral immunogenicity, as determined by enzyme-linked immunosorbent assay (ELISA), at Month 3.
- Occurrence of solicited local and general symptoms.
  - Occurrence, intensity and duration of each solicited local symptom within 7 days (Days 0-6) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of each solicited general symptom within 7

days (Day 0-6) after each vaccination.

- Occurrence of unsolicited adverse events.
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of Serious Adverse Events (SAEs).
  - Occurrence and relationship to vaccination of all SAEs from first vaccination up to 30 days post last vaccination.
- Occurrence of AEs of specific interest.
  - Occurrence of any potential Immune Mediated Diseases (pIMDs) from first vaccination up to 30 days post last vaccination.

Secondary

- Anti-gE humoral immunogenicity in each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.
  - Anti-gE antibody concentrations, as determined by ELISA, at Month 0 and Month 3.
- Occurrence of SAEs.
  - Occurrence and relationship to vaccination of all SAEs during the period starting after 30 days post last vaccination until study end.
  - Occurrence of SAEs considered by the investigator to be related to vaccination during the period starting after 30 days post last vaccination until study end.
- Occurrence of AEs of specific interest.
  - Occurrence of any pIMDs during the period starting after 30 days post last vaccination until study end.

TABLE OF CONTENTS

PAGE

SPONSOR INFORMATION 7

SYNOPSIS 8

LIST OF ABBREVIATIONS 18

GLOSSARY OF TERMS 20

TRADEMARKS 24

1. INTRODUCTION 25
   - 1.1. Background 25
   - 1.2. Rationale for the study and study design 25
     - 1.2.1. Rationale for the study 25
     - 1.2.2. Rationale for the study design 26

2. OBJECTIVES 26
   - 2.1. Co-Primary objectives 26
   - 2.2. Secondary objective 26

3. STUDY DESIGN OVERVIEW 27

4. STUDY COHORT 28
   - 4.1. Number of subjects/centres 28
   - 4.2. Inclusion criteria for enrolment 28
   - 4.3. Exclusion criteria for enrolment 29

5. CONDUCT OF THE STUDY 31
   - 5.1. Regulatory and ethical considerations, including the informed consent process 31
   - 5.2. Subject identification and randomization of treatment 31
     - 5.2.1. Subject identification 31
     - 5.2.2. Randomization of treatment 32
       - 5.2.2.1. Randomization of supplies 32
       - 5.2.2.2. Treatment allocation to the subject 32
         - 5.2.2.2.1. Study group and treatment number allocation 32
         - 5.2.2.2.2. Treatment number allocation for subsequent doses 33
   - 5.3. Method of blinding 33
   - 5.4. General study aspects 33
   - 5.5. Suspected HZ cases 33
   - 5.6. Outline of study procedures 34
   - 5.7. Detailed description of study procedures 36
     - 5.7.1. Informed consent 36
     - 5.7.2. Check inclusion and exclusion criteria 36
     - 5.7.3. Collect demographic data 36
     - 5.7.4. Medical history including previous HZ history 36

5.7.5. History directed physical examination 36
5.7.6. Pregnancy test 36
5.7.7. Check contraindications to vaccination 36
5.7.8. Assess pre-vaccination body temperature 37
5.7.9. Treatment number allocation 37
5.7.10. Sampling 37
5.7.10.1. Blood sampling for immune response assessments 37
5.7.11. Study Vaccine administration 37
5.7.12. Check and record concomitant medication/vaccination and intercurrent medical conditions 37
5.7.12.1. Follow up of events of HZ 38
5.7.13. Recording of AEs, SAEs, pregnancies and pIMDs 38
5.7.14. Study conclusion 38
5.8. Biological sample handling and analysis 38
5.8.1. Use of specified study materials 39
5.8.2. Biological samples 39
5.8.3. Laboratory assays 40
5.8.4. Biological samples evaluation 40
5.8.4.1. Immunological read-outs 40
5.8.5. Immunological correlates of protection 40

6. STUDY VACCINE AND ADMINISTRATION 41
6.1. Description of study vaccine 41
6.2. Storage and handling of study vaccines 41
6.3. Dosage and administration of study vaccine 42
6.4. Replacement of unusable vaccine doses 42
6.5. Contraindications to subsequent vaccination 42
6.6. Concomitant medication/product and concomitant vaccination 43
6.6.1. Recording of concomitant medications/products and concomitant vaccination 43
6.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses 44
6.7. Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses 44

7. HEALTH ECONOMICS 45

8. SAFETY 45
8.1. Safety definitions 45
8.1.1. Definition of an adverse event 45
8.1.2. Definition of a serious adverse event 46
8.1.3. Solicited adverse events 47
8.1.3.1. Solicited local (injection-site) adverse events 47
8.1.3.2. Solicited general adverse events 47
8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events 47
8.1.5. Adverse events of specific interest 48
8.1.5.1. Potential immune-mediated diseases 48
8.2. Events or outcomes not qualifying as adverse events or serious adverse events 50

8.2.1. Pregnancy 50
8.3. Detecting and recording adverse events, serious adverse events and pregnancies 51
8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies 51
8.3.2. Post-Study adverse events and serious adverse events 54
8.3.3. Evaluation of adverse events and serious adverse events 54
8.3.3.1. Active questioning to detect adverse events and serious adverse events 54
8.3.3.2. Assessment of adverse events 54
8.3.3.2.1. Assessment of intensity 54
8.3.3.2.2. Assessment of causality 56
8.3.3.3. Assessment of outcomes 57
8.3.3.4. Medically attended visits 58
8.4. Reporting of serious adverse events, pregnancies, and other events 58
8.4.1. Prompt reporting of serious adverse events, pregnancies, and other events to GSK Biologicals 58
8.4.2. Contact information for reporting serious adverse events and other events to GSK Biologicals 58
8.4.3. Completion and transmission of SAE reports to GSK Biologicals 58
8.4.3.1. Back-up system in case the electronic SAE reporting system does not work 59
8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals 59
8.4.5. Reporting of pIMDs to GSK Biologicals 59
8.4.6. Updating of SAE, pregnancy, and pIMD information after freezing of the subject's eCRF 60
8.4.7. Regulatory reporting requirements for serious adverse events 60
8.5. Follow-up of adverse events, serious adverse events, and pregnancies 60
8.5.1. Follow-up of adverse events and serious adverse events 60
8.5.1.1. Follow-up during the study 60
8.5.1.2. Follow-up after the subject is discharged from the study 61
8.5.2. Follow-up of pregnancies 61
8.6. Treatment of adverse events 61
8.7. Subject card 61

9. SUBJECT COMPLETION AND WITHDRAWAL 62
9.1. Subject completion 62
9.2. Subject withdrawal 62
9.2.1. Subject withdrawal from the study 62
9.2.2. Subject withdrawal from investigational vaccine 63

10. STATISTICAL METHODS 63
10.1. Primary endpoints 63
10.2. Secondary endpoint 64
10.3. Determination of sample size 64
10.3.1. Assumptions and software 64
10.4. Study cohorts/ data sets to be analysed 65

10.4.1. Total vaccinated cohort 65
10.4.2. According To Protocol cohort for analysis of safety *(Amended: 20 February 2014)* 65
10.4.3. According To Protocol cohort for analysis of immunogenicity 66
10.5. Derived and transformed data 66
10.5.1. Handling of missing data 66
10.5.2. Humoral immune response 66
10.6. Analysis of demographics 67
10.7. Analysis of immunogenicity 67
10.8. Analysis of safety 67
10.9. Interpretation of analyses 68
10.10. Conduct of analyses 68
10.10.1. Sequence of analyses 68
10.10.2. Statistical considerations for interim analyses 69

11. ADMINISTRATIVE MATTERS 69
11.1. Remote Data Entry instructions 69
11.2. Study Monitoring by GSK Biologicals 69
11.3. Record retention 70
11.4. Quality assurance 70
11.5. Posting of information on publicly available clinical trial registers and publication policy 71
11.6. Provision of study results to investigators 71

12. COUNTRY SPECIFIC REQUIREMENTS 71

13. REFERENCES 71

LIST OF TABLES

PAGE

Table 1 Study group and epoch foreseen in the study 27

Table 2 Study group and treatment foreseen in the study 27

Table 3 Blinding of study epoch 28

Table 4 Age stratification 28

Table 5 Number of subjects required for enrolment 32

Table 6 List of study procedures 34

Table 7 Intervals between study visits 35

Table 8 Biological samples 39

Table 9 Humoral Immunity (Antibody determination) *(Amended: 20 February 2014)* 40

Table 10 Immunological read-outs 40

Table 11 Study vaccine/product 41

Table 12 Dosage and administration 42

Table 13 Solicited local adverse events 47

Table 14 Solicited general adverse events 47

Table 15 List of potential immune-mediated diseases 49

Table 16 Reporting periods for adverse events, serious adverse events, intercurrent medical conditions and pregnancies 52

Table 17 Intensity scales for solicited symptoms in adults 55

Table 18 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals 58

Table 19 Power calculations for a one-sided binomial test for Relevant Superiority 65

Table 20 GSK Biologicals' laboratories 74

LIST OF APPENDICES

PAGE

APPENDIX A LABORATORY ASSAYS 73

APPENDIX B CLINICAL LABORATORIES 74

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL 75

LIST OF ABBREVIATIONS

Ab	Antibody
AE:	Adverse Event
$AS01_B$	Adjuvant System $AS01_B$
ATP:	According-To-Protocol
CDC:	Centers for Disease Control
CI	Confidence Interval
D	Deltoid
eCRF:	electronic Case Report Form
EDD	Estimated date of delivery
ELISA	Enzyme Linked Immunosorbent Assay
eTDF:	Electronic Temperature excursion Decision Form
EGA	Estimated gestational age
FDA:	Food and Drug Administration, United States of America
GCP:	Good Clinical Practice
GMC:	Geometric Mean (antibody) Concentration
gE	VZV glycoprotein E
GSK:	GlaxoSmithKline
GVCL	Global Vaccines Clinical Laboratories
HZ	Herpes Zoster
HZ/su	Herpes Zoster subunit vaccine
IB:	Investigator Brochure
ICF:	Informed Consent Form
IAF:	Informed Assent Form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IMP:	Investigational Medicinal Product
IM	Intramuscular

IND:	Investigational New Drug
IRB:	Institutional Review Board
LMP	Last menstrual period
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MedDRA:	Medical Dictionary for Regulatory Activities
MPL	3-O-desacyl-4'-monophosphoryl lipid A
N-D	Non-dominant
PHN	Postherpetic Neuralgia
PI	Product Information
pIMD:	Potential Immune-Mediated Disease
QS21	*Quillaja saponaria* Molina, fraction 21 (purified saponin extract from the South American tree)
RDE:	Remote Data Entry
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SFU	Safety follow-up
SPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
su	subunit
TVC	Total Vaccinated cohort
Vacc	Vaccination
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 sterilisation 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.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
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 6.6.2 and 10.4 for details on criteria for evaluability).
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine/product: **(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 authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
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.
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 Harmonisation (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. Note: Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomisation:	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(s)/product(s) 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 randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation 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 will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Zostavax® (Merck & Co.)	Live attenuated VZV vaccine

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 and typically manifests as a localized, dermatomal rash.

The typical HZ rash usually lasts about 2 to 4 weeks and is usually accompanied by pain and pruritus. The most common complication of HZ is postherpetic neuralgia (PHN), defined as pain that persists after the resolution of the HZ rash. Declining VZV-specific immune responses with older age are a clear risk factor for developing shingles and PHN [Nii, 2008; Dworkin, 2007].

Zostavax (Merck), a live attenuated VZV vaccine for the prevention of HZ, was shown to be immunogenic and have an acceptable safety profile when administered to persons with a prior history of HZ [Mills, 2010]. Based on these and other data, *Zostavax* has been approved by the Food and Drug Administration (FDA) for adults 50 years and older and recommended in the US for the prevention of HZ in adults older than 60 years of age regardless of the HZ history [CDC, 2011; Guenther, 2011].

Please refer to the current Investigator Brochure for information regarding the pre-clinical and clinical studies, the epidemiological information and the potential risks and benefits of HZ/su vaccine.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

GSK Biologicals' candidate vaccine for the prevention of HZ is a recombinant subunit (su) vaccine consisting of VZV glycoprotein E (gE) antigen and an adjuvant system ($AS01_B$). Different gE antigen doses (25, 50 or 100 μg) combined with the AS01 Adjuvant System have been evaluated in completed studies in over a thousand adults and administered to approximately 15000 subjects in ongoing trials not yet analyzed. In the analyzed studies it was shown to elicit strong cellular and humoral immune responses. Furthermore, the safety and reactogenicity profile of this candidate vaccine was acceptable. Based on phase II data from the antigen dose-ranging study, ZOSTER-003, and the adjuvant dose comparison study, ZOSTER-010, a gE antigen dose of 50 μg and the Adjuvant System $AS01_B$ were selected as the final vaccine formulation (henceforth, the final vaccine formulation of GSK Biologicals' candidate HZ vaccine will be referred to as HZ/su).

No information is currently available on the immune response conferred by HZ/su and the safety of HZ/su in subjects with a previous episode of HZ. Study ZOSTER-033 will therefore be conducted to evaluate the immunogenicity and safety (primary objectives) of GSK Biologicals' HZ/su vaccine in subjects ≥ 50 years of age (YOA), who previously have had HZ.

1.2.2. Rationale for the study design

Study ZOSTER-033 will be an open and single arm study to collect immunogenicity and reactogenicity/safety data in subjects ≥ 50 years of age who previously have had HZ. These data will be compared with the ones from subjects without HZ in other HZ/su trials.

2. OBJECTIVES

2.1. Co-Primary objectives

- To evaluate anti-gE vaccine response rate one month following a two-dose administration with HZ/su vaccine in all study subjects ≥50 YOA with a previous episode of HZ.

  Criteria to be used:

  – *The objective is met if the lower limit of the 95% CI of the vaccine response rate for anti-gE ELISA antibody concentrations one month after the second dose is at least 60%.*

- To evaluate the safety and reactogenicity following administration of HZ/su vaccine from the first vaccination up to 30 days post last vaccination in all study subjects ≥50 YOA with a previous episode of HZ.

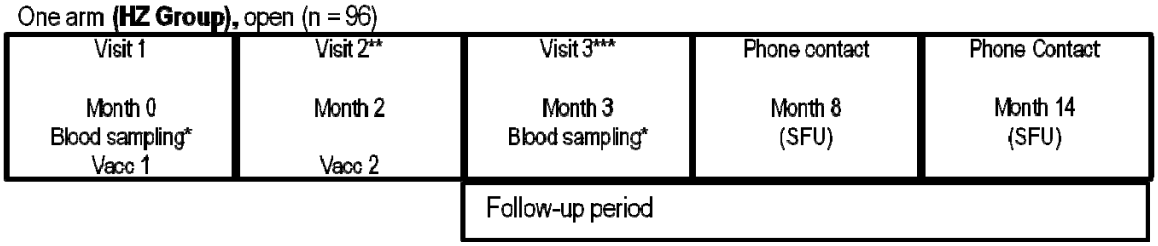
Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objective

- To characterize anti-gE humoral immunogenicity response prior to first vaccination (Month 0) and at one month post last vaccination (Month 3) within each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.
- To evaluate safety following administration of HZ/su vaccine, from 30 days post last vaccination until study end, in all study subjects ≥50 YOA with a previous episode of HZ.

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

3. STUDY DESIGN OVERVIEW



n = number of subjects
Vacc = vaccination
SFU = Safety follow-up
* Blood samples (approximately 8 mL) will be collected from all subjects at Visits 1 and 3 to assess humoral immune responses by a gE ELISA.
** The second dose of study vaccine will be administered 2 months after the first dose.
*** Visit 3 occurs approximately one month after the second vaccination.

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 5.6), are essential and required for study conduct.

- Experimental design: Phase III, non-randomised, open-label, multi-centre study with a single group.
- Duration of the study: Approximately 14 months. Each subject will be followed for approximately 12 months after the second vaccine dose for safety follow-up.
  - **Epoch 001:** Primary starting at Visit 1, Month 0 and ending at final safety follow up contact (i.e. 12 months following Dose 2).
- Study groups:

Table 1 Study group and epoch foreseen in the study

Study groups	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
HZ Group	96	≥ 50 YOA	x

Table 2 Study group and treatment foreseen in the study

Treatment name	Product name	Study Group
		HZGroup
HZ/su	VZV gE	x
	$AS01_B$	

HZ/su = Herpes Zoster subunit vaccine; VZV = Varicella Zoster Virus; gE = recombinant purified Glycoprotein E; $AS01_B$ = Adjuvant System $AS01_B$

- Control: historical control (results of this study will be compared with the ones of other HZ/su trials which include subjects without a history of HZ).
- Vaccination schedules: 0, 2 months

- Treatment allocation: Non-randomized. Subjects will be stratified by age: 50-59 YOA; 60-69 YOA and ≥ 70 YOA.
- Blinding: open-label (Table 3)

Table 3 Blinding of study epoch

Study Epochs	Blinding
Epoch 001	open

- Sampling schedule: Blood samples for humoral immunity (approximately 8 mL per visit) will be collected from all subjects at Visits 1 and 3.
- Type of study: self-contained.
- Data collection: Electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centres

Target enrolment will be approximately 96 eligible subjects to provide 84 subjects evaluable for immunogenicity.

Subjects will be stratified according to age. The details are given in the table below.

Table 4 Age stratification

Age strata	Sample size	Percentage of total
50-59 YOA	32	33
60-69 YOA	32	33
≥ 70 YOA	32	33
All	96	

Overview of the recruitment plan

- The study is planned to be conducted at multiple sites.
- The study duration per subject will be approximately 14 months.
- Enrolment is expected to be completed within a period of approximately 4 months.

The recruitment rate will be monitored using a study-specific central Randomization System on Internet (SBIR).

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 with a physician-documented history of HZ (documented physician clinical judgment is enough).
- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female aged 50 years or older at the time of the first vaccination.
- Written informed consent obtained from the subject.
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the glossary of terms for the definition of menarche and 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:

- Active Herpes Zoster infection (a case is considered no more active when all lesions have at least turned to crusts).
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine/product within 30 days preceding the first dose of study vaccine/product, or planned use during the study period.
- Chronic administration (defined as > 14 consecutive days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, a prednisone dose of <20 mg/day, or equivalent, is allowed. Inhaled, topical and intra-articular corticosteroids are allowed.
- Administration of long-acting immune-modifying drugs (e.g. infliximab) within six months prior to the first vaccine dose or expected administration at any time 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* within 8 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 and pneumococcal conjugate vaccines.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination against VZV or HZ and/or planned administration during the study of an HZ vaccine (including an investigational or non-registered vaccine) other than the study vaccine;
- 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).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine/product.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 37.5°C /99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C /100.4°F on rectal route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.
- Any condition which, in the judgment of the investigator, would make intramuscular injection unsafe.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions before Month 4 (i.e. 2 months after the last dose of study vaccine).

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 informed consent must be obtained from each subject 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 centre. Age group will be used as stratification factor to ensure a correct distribution of age (refer to Table 5).

5.2.2. Randomization of treatment

Not applicable as this is a non-randomized study.

5.2.2.1. Randomization of supplies

The randomisation 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 will be shipped to the study centres /warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

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 96 eligible subjects aged ≥ 50 years and with a previous history of Herpes Zoster.

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 5.

Table 5 Number of subjects required for enrolment

Age strata	Sample size
50-59 YOA	32
60-69 YOA	32
≥ 70 YOA	32
All	96

Allocation of the subject to an age strata at the investigator site will be performed using a randomisation system on internet (SBIR). Within each age stratum (50-59 YOA versus 60-69 YOA versus ≥ 70 YOA), the randomisation algorithm will use a minimisation procedure accounting for centre and age. Minimisation factors will have equal weight in the minimisation algorithm.

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 randomisation 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 32 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 consistent with the allocated age strata.

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

5.3. Method of blinding

This study is an open-label study as all subjects are administered the same vaccine.

5.4. 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.

5.5. Suspected HZ cases

Suspected HZ is defined as a new rash characteristic of HZ (i.e., unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations). Complications of HZ include, but are not limited to, PHN, HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, and visceral disease.

The occurrence of HZ and/or HZ complications will constitute an AE/SAE as appropriate. The occurrence of HZ is an intercurrent medical condition (see Section 6.7).

The reporting period for cases of HZ will be from Month 0 to study end. The occurrence of HZ is an intercurrent medical condition (see Section 6.7) which should be reported until study end rather than Month 3. All other intercurrent medical conditions should be reported until Month 3. The standard reporting period as specified in Section 8.3.1 for AE/SAE should be used for HZ complications.

At Visit 1, all subjects will be educated to recognize the signs and symptoms of typical HZ.

5.6. Outline of study procedures

The list of study procedures is presented in Table 6.

Table 6 List of study procedures

Epoch	***Epoch 001***				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**M8 Phone Contact**	***M14 Phone Contact***
Time points	**Month 0***	**Month 2****	**Month 3**	**Month 8**	***Month 14***
Sampling time points	**Pre-Vacc**		**Post-Vacc**		
Informed consent	●				
Check inclusion and exclusion criteria	●				
Collect demographic data	●				
Medical history including previous HZ history	●				
Check contraindications	●	●			
History directed physical examination	O				
Pregnancy test, if applicable [a]	●	●			
Pre-vaccination body temperature	●	●			
Blood sampling (approximately 8 mL) from all subjects	●		●		
Assignment/recording of treatment number	●	●			
Vaccination	●	● [b]			
Educate subjects to recognize signs and symptoms of typical HZ	***O***				
Dispensing diary cards to subjects	O	O			
Daily post-vaccination recording of solicited adverse events (Days 0–6) by subjects on diary card	O	O			
Recording of non-serious AEs (Days 0-29) after each vaccination by subjects on diary card	O	O			
Record any concomitant medication/vaccination (Days 0-29) after each vaccination by subjects on diary card	***O***	O	O		
Return of diary cards		O	O		
Diary card transcription by investigator		●	●		
Recording of non-serious adverse events within 30 days (Days 0-29) post-vaccination, by investigator	●	●	●		
Reporting of HZ (intercurrent medical conditions [IMC]) [c]	● [d]	●	●	●	●

Epoch	***Epoch 001***				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**M8 Phone Contact**	***M14 Phone Contact***
Time points	**Month 0***	**Month 2****	**Month 3**	**Month 8**	***Month 14***
Sampling time points	**Pre-Vacc**		**Post-Vacc**		
Reporting of IMCs, excluding HZ [c]	●[d]	●	●		
Recording of serious adverse events (SAEs), by investigator	●	●	●	●	●
Recording of pregnancies	● [d]	●	●	●	●
Recording of potential immune-mediated diseases (pIMDs)	● [d]	●	●	●	●
Study analysis			O		***O***
Study Conclusion					●

NOTE: The double-line border following Month 3 indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained after completion of Visit 3.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
* Day of first vaccination.
** The second dose of study vaccine will be administered 2 months after the first dose.
[a] Only for women of child-bearing potential. Refer to Section 5.7.6 for details.
[b] Any subject with a clinically diagnosed HZ episode between Visit 1 and Visit 2 should **not** receive the second dose.
[c] According to Section 6.7.
[d] Study procedure to be assessed only after administration of vaccine after Visit 1.

Table 7 Intervals between study visits

Interval between visits	**Optimal length of interval[1]**	**Allowed interval[2] (range in days)**
Visit 1 → Visit 2	2 months	49 - 83
Visit 2 → Visit 3	1 month	30 - 48
Visit 2 → Phone contact at Month 8	6 months	180 -240*
Visit 2 → Phone contact at Month 14	12 months	335 - 395 *

[1]. Whenever possible the investigator should arrange study visits within this interval.
[2]. Subjects will not be eligible for inclusion in one or more cohorts if they make the study visit outside this interval. Refer to Section 10.4 for the definition of the cohorts for analysis
* Intervals pertaining to phone contacts are only indicative and will not determine a subject's eligibility for inclusion for ATP analysis

5.7. Detailed description of study procedures

5.7.1. Informed consent

The signed 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.

5.7.2. Check inclusion and exclusion criteria

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.7.3. Collect demographic data

Record demographic data such as date of birth, gender and geographic ancestry in the subject's eCRF.

5.7.4. Medical history including previous HZ 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 study vaccination in the eCRF.

The physician who was in charge of the past HZ episode should be contacted and a copy of the patient file documenting the HZ episode should be obtained.

5.7.5. History directed physical examination

Perform a history directed physical examination. If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled. Collected information needs to be recorded in the eCRF.

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

5.7.6. Pregnancy test

Female subjects of childbearing potential are to have a pregnancy test prior to any study vaccine administration. A urine pregnancy test is sufficient. A serum pregnancy test, instead of a urine pregnancy test, should only be considered if required by country, local or ethics committee regulations. The results of the applicable test will be recorded in the eCRF. The study vaccine may only be administered if the pregnancy test is negative. Note: The pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

5.7.7. Check contraindications to vaccination

Contraindications to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 for more details.

5.7.8. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral. If the subject has fever [fever is defined as temperature ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 7).

5.7.9. Treatment number allocation

Treatment number allocation will be performed as described in Section 5.2.2. The number of each administered treatment must be recorded in the eCRF.

5.7.10. Sampling

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

5.7.10.1. Blood sampling for immune response assessments

Blood samples will be taken during certain study visits as specified in Section 5.6 List of Study Procedures.

- A volume of approximately 8 mL of whole blood (to provide approximately 2.5 mL of serum) should be drawn from all subjects for each analysis of humoral immune response at each pre-defined timepoint. After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.7.11. Study Vaccine administration

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (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 7).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.
- Any subject with an event of HZ between Visit 1 and Visit 2 should not receive the second dose.

5.7.12. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.6.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.7.

5.7.12.1. Follow up of events of HZ

- The occurrence of HZ will constitute an AE/SAE as appropriate. The occurrence of HZ is an intercurrent medical condition (see Section 6.7) which should be reported until study end rather than Month 3. All other intercurrent medical conditions should be reported until Month 3.

5.7.13. 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 on how to submit SAE, pregnancy and pIMD reports to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- At each vaccination visit, diary cards will be provided to the subject. The subject will record body (oral) 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 30 days occurring after vaccination. The subject will be instructed to return the completed diary card to the investigator at the next study visit.
- Collect and verify completed diary cards during discussion with the subject at the visit following each vaccination visit.
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.

5.7.14. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness;
- complete the Study Conclusion screen in the eCRF.

5.8. Biological sample handling and analysis

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

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

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

- Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccine and its constituents or the disease under study.
- Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccine or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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

Any sample testing will be done in line with the consent of the individual subject.

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

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

5.8.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of study cohorts/ data sets to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator's site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.8.2. Biological samples

The different biological samples collected in the study, the quantity needed, the unit and the time points are described in Table 8.

Table 8 Biological samples

Sample type	Quantity	Unit	Time point
Blood	Approximately 8	ml	Visit 1 Visit 3

5.8.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

Details about the laboratory assays that will be performed are presented below in Table 9.

Table 9 Humoral Immunity (Antibody determination) *(Amended: 20 February 2014)*

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory*
SER	Varicella Zoster Virus.Glycoprotein E Ab.IgG	ELI	NA	mIU/ml	97	GSK Biologicals**

*Refer to APPENDIX B for the laboratory addresses.
**GSK Biologicals laboratory refers to the Global Vaccines Clinical Laboratories (GVCL) in Rixensart, Belgium; Wavre, Belgium.

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

5.8.4. Biological samples evaluation

5.8.4.1. Immunological read-outs

The plan for immunogenicity testing on samples obtained is shown in Table 10.

Table 10 Immunological read-outs

Blood sampling time point		No. subjects	Component	Components priority rank
Type of contact and time point	Sampling time point			
Visit 1 (Month 0)	Pre-Vacc	All	Ab gE ELISA	1
Visit 3 (Month 3)	Post-Vacc	All	Ab gE ELISA	1

5.8.5. Immunological correlates of protection

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

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 description of the study vaccine is presented in Table 11.

Table 11 Study vaccine/product

Treatment name	Product name	Formulation	Presentation	Volume to be administered	Number of doses
HZ/su	VZV gE	gE=50µg per 0.5 mL of reconstituted vaccine	Lyophilized pellet in a monodose vial	0.5 ml	2
	AS01B	MPL=50µg; QS21=50µg; Liposomes per 0.5 mL of reconstituted vaccine	Liquid in a monodose vial		2

gE: recombinant purified Glycoprotein E; $AS01_B$: Adjuvant System $AS01_B$; VZV: Varicella Zoster Virus; MPL: 3-O-ml 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 vaccines

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

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 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 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 vaccines.

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 and 30°C).

Vaccine will be administered as indicated in Table 12.

The reconstituted vaccine (0.5 mL) should be administered by IM injection into the deltoid muscle of the non-dominant arm using a standard aseptic technique. In rare situations, the injection may be given in the dominant arm.

Table 12 Dosage and administration

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

[1]Intramuscular (IM); [2]Deltoid (D); [3] Non-dominant (N-D)

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 15% additional vaccine doses will be supplied to replace those that are unusable.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the 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).
- If the subject experiences an SAE judged to be vaccine-related by the investigator/ delegate.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.

The following events constitute contraindications to administration of the 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 5.6), 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 ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered all vaccines/products.
- Any condition which, in the judgment of the investigator, would make intramuscular injection unsafe.

Refer to Section 5.7.11 for instruction that any subject with an event of HZ between Visit 1 and Visit 2 should not receive the second dose.

6.6. Concomitant medication/product and concomitant vaccination

At each study visit/contact, the investigator should question the subject about any medication/product taken and vaccination received by the subject.

6.6.1. Recording of concomitant medications/products and concomitant vaccination

The following concomitant medications/products/vaccines must be recorded in the eCRF or SAE report if administered during the indicated recording period:

- All concomitant medications/products, except vitamins and dietary supplements, administered 30 days following each dose of study vaccine.
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ending at the last blood sampling (Visit 3/Month 3).
- 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 ≥ 37.5°C/99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C/100.4°F for rectal route].
- Any concomitant medications/products/vaccines listed in Section 6.6.2.
- Any concomitant medication/product/vaccine relevant to a SAE* or administered at any time during the study period for the treatment of a SAE*.

  * SAEs that are required to be reported per protocol.

6.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

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

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 consecutive days) during the study period. For corticosteroids, a prednisone dose of <20 mg/day, or equivalent, is allowed. Inhaled, topical and intra-articular corticosteroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (e.g. infliximab).
- 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 8 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 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 SPC or PI and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Receipt of a vaccine against VZV or HZ other than the study vaccine during the study period.
- Immunoglobulins and/or any blood products administered during the study period.

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

At each study visit subsequent to the first vaccination visit until Month 3, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition which could influence the subject's immune response to the study vaccine. If it is the case, the condition(s) must be recorded in the eCRF. Intercurrent medical conditions will be recorded in AE/SAE screens as appropriate.

The occurrence of HZ is an intercurrent medical condition which should be reported until study end rather than Month 3. All other intercurrent medical conditions should be reported until Month 3.

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of confounding their immune response to the study vaccine or its interpretation (e.g., cases of HZ up to and including the last immunogenicity assessment at Month 3).

7. HEALTH ECONOMICS

Not applicable.

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 adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject 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 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 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 serious adverse event 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 hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation 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 hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation 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 hospitalisation 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 hospitalisation.

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 13 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 14 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

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

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.

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

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

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 15.

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 15 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• 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, myeloradiculomyelitis • 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	• Systemic lupus erythematosus • Scleroderma, including diffuse systemic form and CREST syndrome • Systemic sclerosis • Dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, • Juvenile chronic arthritis, (including Still's disease) • Polymyalgia rheumatic • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Cutaneous lupus erythematosus • Alopecia areata • Lichen planus • Sweet's syndrome • Morphoea

Liver disorders	Gastrointestinal disorders	Metabolic diseases
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Crohn's disease • Ulcerative colitis • Ulcerative proctitis • Celiac disease	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease

Vasculitides	Others
• 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.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Uveitis • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

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 an 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] 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(s)/product(s) 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 within 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 at Month 14 (study end), i.e. at least 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 at Month 14 (study end), i.e. at least 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 at Month 14 (study end), i.e. at least 12 months following administration of the last dose of study vaccine. See Section 8.4 for instructions on reporting of pIMDs.

Intercurrent medical conditions (see Section 6.7) will be recorded until from Month 0 until Month 3. Intercurrent medical conditions will be recorded in AE/SAE screens as appropriate.

The occurrence of HZ will constitute an AE/SAE as appropriate. The occurrence of HZ is an intercurrent medical condition which should be reported until study end rather than Month 3. All other intercurrent medical conditions should be reported until Month 3.

An overview of the protocol-required reporting periods for AEs, SAEs, and pregnancies is given in Table 16.

Table 16 Reporting periods for adverse events, serious adverse events, intercurrent medical conditions and pregnancies

Study activity	Dose 1 (Visit 1)	7 days Post Dose 1	30 days Post Dose 1		Dose 2 (Visit 2)	7 days Post Dose 2	30 days Post Dose 2		Phone contact Month 8	Phone contact Month 14 Study Conclusion
	Month 0				Month 2		Month 3		Month 8	Month 14
Timing of reporting	Day 0	Day 6	Day 29		Day 0	Day 6	Day 29			
Solicited AEs										
Unsolicited AEs										
AEs/SAEs leading to withdrawal from the study										
All SAEs [a]										
Potential immune-mediated diseases (pIMDs)										
Pregnancies										
Herpes Zoster (HZ) episodes *(see Section 6.7)*										
Intercurrent medical conditions (IMCs) excluding HZ *(see Section 6.7)*										

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

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

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 16. 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/product, 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 on the 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:

Table 17 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	Gastrointestinal symptoms 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

*Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route. The preferred route for recording temperature in this study will be oral.

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

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

Temperature (measured by oral, axillary or tympanic route) will be scored at GSK Biologicals as follows:

0	:	< 37.5°C
1	:	37.5°C to 38.0°C
2	:	38.1°C to 39.0°C
3	:	> 39.0°

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 (In adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

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

For each solicited and unsolicited symptom the subject experiences, the subject will be asked if he/she received medical attention defined as hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the 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 18, 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 18, 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 18, once the investigator becomes aware of the pIMD.

Table 18 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 SAE report	24 hours*	electronic SAE report
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report
pIMDs	24 hours**	electronic SAE report	24 hours*	electronic SAE report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed after the diagnosis is established and known to the investigator

8.4.2. Contact information for reporting serious adverse events and other events to GSK Biologicals

Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: GSK Biologicals Clinical Safety & Pharmacovigilance Fax: + [redacted] or + [redacted]

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 SAE report

WITHIN 24 HOURS. The SAE 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.

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

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the electronic SAE 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 onset of a new pIMD or exacerbation of a pre-existing pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic SAE report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. A field on the SAE report allows to specify that the event is a pIMD and whether it is serious or non serious. The SAE 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.

Refer to Section 8.4.3.1 for back-up system in case the electronic SAE reporting system does not work.

8.4.6. Updating of SAE, pregnancy, and pIMD information after freezing of the subject's eCRF

When additional SAE, pregnancy, or pIMD information is received after freezing of the subject's eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) within the designated reporting time frames specified in Table 18.

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/product 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 18).

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 SAE 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 SAE 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 6.6).

8.7. Subject card

Study subjects 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. 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 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 returns for the concluding visit/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 did not come back for the concluding visit/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, 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 parent(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the CRF.

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 screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject himself/herself, 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 endpoints

- Anti-gE humoral immunogenicity.
  - Vaccine response for anti-gE humoral immunogenicity, as determined by enzyme-linked immunosorbent assay (ELISA), at Month 3.
- Occurrence of solicited local and general symptoms.
  - Occurrence, intensity and duration of each solicited local symptom within 7 days (Days 0-6) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of each solicited general symptom within 7 days (Day 0-6) after each vaccination.
- Occurrence of unsolicited adverse events.
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of Serious Adverse Events (SAEs).
  - Occurrence and relationship to vaccination of all SAEs from first vaccination up to 30 days post last vaccination.

- Occurrence of AEs of specific interest.
  - Occurrence of any potential Immune Mediated Diseases (pIMDs) from first vaccination up to 30 days post last vaccination.

10.2. Secondary endpoint

- Anti-gE humoral immunogenicity in each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.
  - Anti-gE antibody concentrations, as determined by ELISA, at Month 0 and Month 3.
- Occurrence of SAEs.
  - Occurrence and relationship to vaccination of all SAEs during the period starting after 30 days post last vaccination until study end.
  - Occurrence of SAEs considered by the investigator to be related to vaccination during the period starting after 30 days post last vaccination until study end.
- Occurrence of AEs of specific interest.
  - Occurrence of any pIMDs during the period starting after 30 days post last vaccination until study end.

10.3. Determination of sample size

A sample size of 84 evaluable subjects is needed to demonstrate the primary objectives of this study. Assuming 10% non-evaluable subjects, approximately 96 subjects will be enrolled:

- 84 subjects will be necessary to rule out the null hypothesis that the lower limit (LL) of the vaccine response of the treatment group is inferior to 60% with at least 97% power.

10.3.1. Assumptions and software

The following assumptions are made:

- Type I error: 0.025 (One-sided).
- No information is currently available on the immune response conferred by HZ/su vaccine in subjects with a previous episode of HZ therefore, we assume a conservative vaccine response rate of 80%.
- Null-hypothesis: The LL of the vaccine response of the treatment group is lower than 60%.
- Alternative hypothesis: The LL of the vaccine response of the treatment group is at least 60%.
- Criteria for superiority based on vaccine response rate evaluated at one month post Dose 2, the Lower Limit of the 95% CI of the LL is at least 60%.

- Sample size calculations were done using Pass 2005 (Power Analysis of One Proportion).

Table 19 shows an overview of the different assumptions and power calculations when 96 subjects are enrolled.

Table 19 Power calculations for a one-sided binomial test for Relevant Superiority

Power	N evaluable	Vaccine response		Significance level	
		Lower limit	Assumed	Alpha 1-Sided	Beta
0.8124	84	0.6	0.75	0.025	0.1876
0.9786	84	0.6	0.80	0.025	0.0214

10.4. Study cohorts/ data sets to be analysed

Three cohorts are defined for the purpose of the analysis:

- Total Vaccinated cohort (TVC)
- According To Protocol (ATP) cohort for analysis of safety
- ATP cohort for analysis of immunogenicity

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 immunogenicity will include vaccinated subjects for whom data related to immunogenicity endpoints are available.
- The TVC for analysis of safety will include all subjects with at least one vaccine administered.
- The TVC for analysis of reactogenicity will include all subjects with at least one vaccine administration documented.

10.4.2. According To Protocol cohort for analysis of safety *(Amended: 20 February 2014)*

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

- who have received at least one dose of study vaccine according to their random assignment;
- for whom administration site of study vaccine is known***/correct***;
- who have not received other vaccine forbidden in the protocol.

10.4.3. According To Protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort for safety analysis:

- Who meet all eligibility criteria (refer to Sections 4.2 and 4.3).
- Who comply with the procedures and intervals defined in the protocol for the active phase (till Month 3) (refer to Table 7).
- Who do not meet any of the criteria for elimination from an ATP analysis during the active phase (till Month 3) as listed in Section 6.6.2,
- Who did not receive a product leading to elimination from an ATP analysis during the active phase (till Month 3) as listed in Section 6.6.2,
- Who did not present with a medical condition leading to elimination from an ATP analysis during the active phase (till Month 3) as listed Section 6.7,
- For whom data concerning immunogenicity endpoint measures are available during the active phase (till Month 3).

10.5. Derived and transformed data

10.5.1. Handling of missing data

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, a subject will be excluded from an analysis if all measurements are missing or non-evaluable.

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

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

10.5.2. Humoral immune response

- A seropositive subject is a subject whose anti-gE Ab concentration is greater than or equal to the cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.
- The VZV gE-specific humoral immune response is defined as the percentage of subjects who have at least:
  - a 4-fold increase in the anti-gE antibodies concentration as compared to the pre-vaccination anti-gE antibodies concentration, for subjects who are seropositive at baseline, or,

  - a 4-fold increase in the anti-gE antibodies concentration as compared to the anti-gE antibodies cut-off value for seropositivity, for subjects who are seronegative at baseline.

- The GMCs calculations are performed by taking the anti-log of the mean of the log concentration transformations. For descriptive statistics only, Ab concentrations below the cut-off of the assay will be given an arbitrary value equal to half the cut-off for the purpose of GMC calculation.

10.6. Analysis of demographics

Demographic characteristics (age at first study vaccination in weeks or years and gender), vaccination history, cohort description, withdrawal status will be summarised by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as centre.
- Mean, median, standard deviation will be provided for continuous data such as age.

10.7. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for analysis of immunogenicity. If, in any vaccine group, the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity is 5% or more, a second analysis based on the TVC will be performed to complement the ATP analysis.

Inferential analysis:

- The gE vaccine response rate (with exact 95% CI) will be calculated:

  The primary objective is met if the 95% lower limit of the gE vaccine response rate is at least 60%.

Descriptive analysis:

At each time point when a blood sample result is available:

- Seropositivity rates for anti-gE (with exact 95% CI) will be calculated;
- GMCs with 95% CI will be tabulated for anti-gE.
- The distribution of antibody concentrations for anti-gE will be displayed using reverse cumulative distribution curves.
- Depending on the distribution of time from the last HZ episode to enrolment in this study, a stratified exploratory analysis of immunogenicity may be conducted. Details will be provided in the SAP.

10.8. Analysis of safety

The primary analysis for safety will be based on the TVC. A second analysis based on this ATP cohort will be performed to complement the TVC analysis.

When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g., using windows such as Days 0 – 6, Days 0 – 29 and more than 30 days post-vaccination).

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

- The percentage of subjects with at least one local ***solicited*** AE (solicited and unsolicited), 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% Confidence Intervals (CI) after each vaccine dose and overall; ***(Amended: 20 February 2014)***
- 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 proportion of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (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 AEs resulting in a medically attended visit will also be tabulated;
- Total number/percentages of doses (per dose and overall) followed by AEs will be tabulated;
- Number of subjects with pIMDs as listed in Section 8.1.5.1 will be tabulated;
- SAEs and withdrawal due to AE(s) will be described in detail.
- Depending on the distribution of time from the last HZ episode to enrolment in this study, a stratified exploratory analysis of safety may be conducted. Details will be provided in the SAP.

10.9. Interpretation of analyses

With respect to primary and secondary objectives, the interpretation must be done according to a hierarchical procedure. More specifically, the first secondary objective will be assessed if the primary objective(s) has/have been reached and will be considered as reached if all its associated criteria are met.

10.10. 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.

10.10.1. Sequence of analyses

The main analysis of immunogenicity, reactogenicity and safety data will be performed when all data up to and including Month 3 will be available. A study report will be written.

At the end of the study (Month 14 i.e. 12 months after Dose 2), an additional analysis will assess the safety follow-up (secondary safety endpoints). An annex report will be written.

10.10.2. Statistical considerations for interim analyses

No interim analyses are 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. Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, 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 RDE review and a Source Document

Verification (SDV). By SDV we understand verifying RDE 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 RDE. 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 RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

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

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

11.3. Record retention

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

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

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

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject's last visit.

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

Centers for disease control and prevention (CDC). General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 2011;60(2):1-61.

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;
http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf

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

Guenther LC; Lynde CW. A refresher on herpes zoster, current status on vaccination, and the role of the dermatologist. *J Cutan Med Surg* 2011;15(4):185-91.

Mills R, Tyring SK, Levin MJ et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects with a history of herpes zoster. *Vaccine* 2010;28:4204–09.

National Network for Immunization Information (Nii). Herpes Zoster. Updated: April 2008. http://www.immunizationinfo.org/vaccines/shingles-herpes-zoster. Accessed on 19 June 2012.

APPENDIX A LABORATORY ASSAYS

Specific Ab (anti-gE) measurements:

Anti-gE ELISA: Anti-gE Ab concentrations will be measured using an anti-gE ELISA. Diluted blood serum samples of study subjects will be added to microtitre wells pre-coated with gE antigen. Secondary peroxidase-conjugated anti-human Abs will be added, which bind to the primary human anti-gE Abs. After incubation of the microtitre wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE Ab concentrations are calculated from a standard curve. The assay cut-off is ***97*** mIU/mL. The assay will be performed on human serum at GSK Biologicals' laboratory or another laboratory designated by GSK Biologicals. ***(Amended: 20 February 2014)***

APPENDIX B CLINICAL LABORATORIES

Table 20 GSK Biologicals' laboratories

Laboratory	Address
GSK Biologicals Global Vaccine Clinical Laboratory, Rixensart	Biospecimen Reception - B7/44 Rue de l'Institut, 89 - B-1330 Rixensart - Belgium
GSK Biologicals Global Vaccine Clinical Laboratory, North America- Laval	Biospecimen Reception - Clinical Serology 525 Cartier blvd West - Laval - Quebec - Canada - H7V 3S8
GSK Biologicals Global Vaccine Clinical Laboratory, Wavre-Nord Noir Epine	Avenue Fleming, 20 - B-1300 Wavre - Belgium

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
EudraCT number	2012-003643-30
Administrative change number:	Administrative change 1
Administrative change date:	12 February 2013
Co-ordinating author:	[redacted]reira, Scientific Writer
Rationale/background for changes: The IND number has been included in the protocol as the protocol will be submitted to the FDA. Additionally, a typo with regard to asset number in the title and study visit for vaccination in the dosage and administration table have been corrected.	

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

In the cover page, protocol administrative change 1 sponsor signatory approval and protocol administrative change 1 investigator agreement, IND number has been added:

Investigational New Drug (IND) number	***BB-IND 13857***

In the title of the study, a typo in the asset number has been corrected:

Title	Immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults with a prior episode of herpes zoster.

In Section 6.3 Dosage and administration of study vaccine, a typo has been corrected in the table (Table 12):

Table 12 Dosage and administration

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

[1]Intramuscular (IM); [2]Deltoid (D); [3] Non-dominant (N-D)

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 1

eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
EudraCT number	2012-003643-30
Amendment number:	Amendment 1
Amendment date:	23 April 2013
Co-ordinating author:	[redacted], Scientific Writer

Rationale/background for changes:

- In response to a request from US FDA/CBER, a second phone contact was added at Month 14 in order to extend the safety follow-up period to one year after the last vaccination. All references to study duration have been edited accordingly (Synopsis, Sections 3, 4.1, 5.6, 8.3.1 and 10.10.1).
- In response to a suggestion from US FDA/CBER, a stratified exploratory analysis may be added for evaluation of immunogenicity and safety, depending on the distribution of time from last HZ episode to enrolment (Sections 10.7 and 10.8).
- The volume of the blood sample for immunogenicity testing was clarified and is now consistently stated throughout the protocol as "approximately 8 mL" (Synopsis, Sections 3 and 5.7.10.1).
- For sites required to test serum for pre-vaccination pregnancy status, due to country, local or ethics committee regulations, this option has been added. (Note that a urine pregnancy test is still sufficient per protocol). (Section 5.7.6).
- An additional exclusion criterion and corresponding contra-indication to subsequent vaccination has been added: "Any condition which, in the judgment of the investigator would make intramuscular injection unsafe." This criterion is now added to all GSK Biologicals vaccine study protocols which include intramuscular route of administration (Sections 4.3 and 6.5).
- In Tables 6 and 16 (List of study procedures and Reporting periods for AEs, SAEs and pregnancies), the recording of intercurrent medical conditions (IMCs) is now split into two rows (one for recording herpes zoster (HZ) and another for recording all other IMCs). The intent was to clarify the different reporting periods for these events (Sections 5.6 and 8.3.1).

- In Table 6 (List of study procedures) the activity "Educate subjects to recognize the signs and symptoms of typical HZ" was added for clarification. It was therefore removed from footnote "c".
- The study group name was not consistently stated throughout the protocol. Now, "HZ Group" appears at each reference to group name (Synopsis and Sections 3 and 6.3).
- The definition of immunological correlate of protection has been edited to "[t]he defined immune response....." to indicate that a future established correlate of protection may not necessarily be a humoral antibody response (Glossary).
- Due to personnel changes for some of the central study team functions, additional contributing authors have been added to the cover page.
- Minor typographical and formatting errors have been corrected.

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

Cover page

Contributing authors

- [redacted], ~~Lead~~***Project*** ~~s~~***S***tatistician
- [redacted]***, Global Study Manager***
- [redacted], ~~Expert Scientist~~***Manager,*** ~~Clinical~~***Global*** Regulatory Affairs
- [redacted]***, US Regulatory Affairs***
- [redacted], Clinical Safety ~~Representative~~***Physician***
- [redacted]***, Study Data Manager***
- [redacted], Project Data ***M***anager

Synopsis

Study design

- Duration of the study: Approximately ~~8~~ ***14*** months. Each subject will be followed for approximately ~~six~~ ***12*** months after the second vaccine dose for safety follow-up.
  - Epoch 001: Primary starting at Visit 1, Month 0 and ending at ***final*** safety follow up contact (i.e. ~~six~~ ***12*** months following Dose 2).

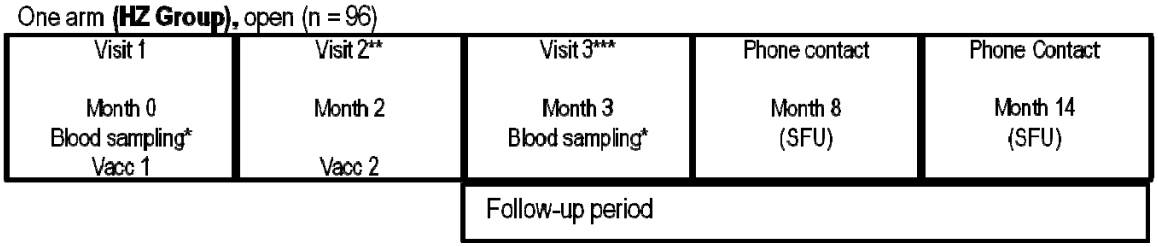
Synopsis Table 2 Study group and treatment foreseen in the study

Treatment name	Product name	Study Group
		HZ~~/su~~ *Group*
HZ/su	VZV gE	x
	$AS01_B$	

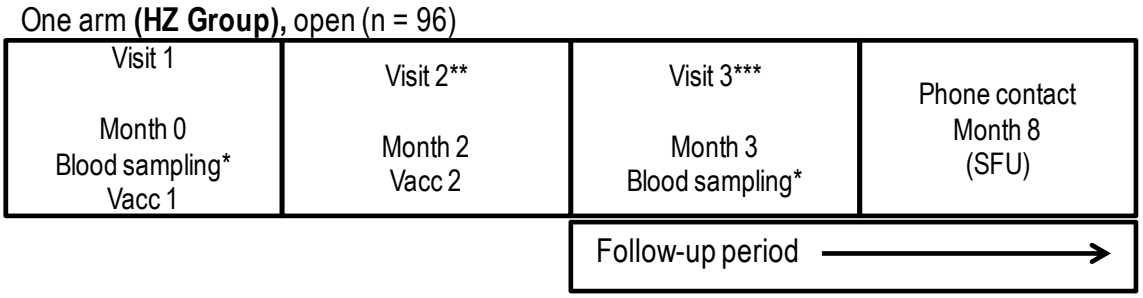
Glossary

Immunological correlate of protection:	The defined ~~humoral antibody~~ ***immune*** response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.

Section 3 - Study design overview



PREVIOUS FIGURE



n = number of subjects
Vacc = vaccination
SFU = Safety follow-up
* Blood samples (***approximately*** 8 mL) will be collected from all subjects at Visit***s*** 1 and 3 ***to*** assess humoral immune responses by a gE ELISA.

- Duration of the study: Approximately ~~8~~ ***14*** months. Each subject will be followed for approximately ~~six~~ ***12*** months after the second vaccine dose for safety follow-up.
  - **Epoch 001:** Primary starting at Visit 1, Month 0 and ending at ***final*** safety follow up contact (i.e. ~~six~~ ***12*** months following Dose 2).

Table 2 Study group and treatment foreseen in the study

Treatment name	Product name	Study Group
		HZ~~/su~~ *Group*
HZ/su	VZV gE	x
	$AS01_B$	

Section 4.1 - Number of subjects/centres

- The study duration per subject will be approximately ~~8~~ ***14*** months.

Section 4.3 - Exclusion criteria for enrolment

- ***Any condition which, in the judgment of the investigator, would make intramuscular injection unsafe.***

Section 5.6 - Outline of study procedures

Table 6 List of study procedures

Epoch	***Epoch 001***				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**M8 Phone Contact**	***M14 Phone Contact***
Time points	**Month 0***	**Month 2****	**Month 3**	**Month 8**	***Month 14***
Sampling time points	**Pre-Vacc**		**Post-Vacc**		
Informed consent	●				
Check inclusion and exclusion criteria	●				
Collect demographic data	●				
Medical history including previous HZ history	●				
Check contraindications	●	●			
History directed physical examination	O				
Pregnancy test, if applicable [a]	●	●			
Pre-vaccination body temperature	●	●			
Blood sampling (***approximately*** 8 mL) from all subjects	●		●		
Assignment/recording of treatment number	●	●			
Vaccination	●	● [b]			
Educate subjects to recognize signs and symptoms of typical HZ	***O***				
Dispensing diary cards to subjects	O	O			
Daily post-vaccination recording of solicited adverse events (Days 0–6) by subjects on diary card	O	O			
Recording of non-serious AEs (Days 0-29) after each vaccination by subjects on diary card	O	O			
Record any concomitant medication/vaccination (Days 0-29) after each vaccination by subjects on diary card	***O***	O	O		
Return of diary cards		O	O		
Diary card transcription by investigator		●	●		
Recording of non-serious adverse events within 30 days (Days 0-29) post-vaccination, by investigator	●	●	●		
~~Record any~~ ***Reporting of HZ (*** intercurrent medical conditions ***[IMC])*** ~~including HZ by investigator~~ [c]	● [d]	●	●	●	●
Reporting of IMCs, excluding HZ [c]	●[d]	●	●		
Recording of serious adverse events (SAEs), by investigator	●	●	●	●	●

Epoch	***Epoch 001***				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**M8 Phone Contact**	***M14 Phone Contact***
Time points	**Month 0***	**Month 2****	**Month 3**	**Month 8**	***Month 14***
Sampling time points	**Pre-Vacc**		**Post-Vacc**		
Recording of pregnancies	● [d]	●	●	~~○~~ ●	●
Recording of potential immune-mediated diseases (pIMDs)	● [d]	●	●	●	●
Study analysis			○	~~○~~	***○***
Study Conclusion					●

NOTE: The double-line border following Month 3 indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained after completion of Visit 3.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
* Day of first vaccination.
** The second dose of study vaccine will be administered 2 months after the first dose.
[a] Only for women of child-bearing potential. ***Refer to Section 5.7.6 for details.***
[b] Any subject with a clinically diagnosed HZ episode between Visit 1 and Visit 2 should **not** receive the second dose.
[c] ~~Refer~~ ***According*** to Section 6.7 . ~~for details regarding intercurrent medical conditions. The occurrence of HZ is an intercurrent medical condition which should be reported until study end rather than Month 3. All other intercurrent medical conditions should be reported until Month 3. At Visit 1, all subjects will be educated to recognize the signs and symptoms of typical HZ~~

Table 7 Intervals between study visits

Interval between visits	**Optimal length of interval[1]**	**Allowed interval[2] (range in days)**
Visit 1 → Visit 2	2 months	49 - 83
Visit 2 → Visit 3	1 month	30 - 48
Visit 2 → Phone contact at Month 8	6 months	180 -240*
Visit 2 → Phone contact at Month 14	***12 months***	***335 - 395 ****

[1]. Whenever possible the investigator should arrange study visits within this interval.
[2]. Subjects will not be eligible for inclusion in one or more cohorts if they make the study visit outside this interval. Refer to Section 10.4 for the definition of the cohorts for analysis
* Interval***s*** pertaining to phone contact***s*** ~~is~~ ***are*** only indicative and will not determine a subject's eligibility for inclusion for ATP analysis.

Section 5.7.6 -~~Urine~~ p*P*regnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. ***A urine pregnancy test is sufficient. A serum pregnancy test, instead of a urine pregnancy test, should only be considered if required by country, local or ethics committee regulations. The results of the applicable test will be recorded in the eCRF.*** 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.

Section 5.7.10.1 - Blood sampling for immune response assessments

A volume of ~~at least~~ ***approximately*** 8 mL of whole blood (to provide approximately 2.5 mL of serum) should be drawn from all subjects for each analysis of humoral immune response at each pre-defined timepoint.

Section 6.3 - Dosage and administration of study vaccine

Table 12 Dosage and administration

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

Section 6.5 - Contraindications to subsequent vaccination

- ***Any condition which, in the judgment of the investigator, would make intramuscular injection unsafe.***

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

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at Month ~~8~~***14*** (study end), i.e. at least ~~6~~***12*** months following administration of the last dose of study vaccine for each subject. See Section 8.4 for instructions on reporting of SAEs.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end at Month ~~8~~***14*** (study end), i.e. at least ~~6~~***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 at Month ~~8~~***14*** (study end), i.e. ***at least*** ~~6~~***12*** months following administration of the last dose of study vaccine. See section 8.4 for instructions on reporting of pIMDs.

Table 16 Reporting periods for adverse events, serious adverse events, intercurrent medical conditions and pregnancies

Study activity	Dose 1 (Visit 1)	7 days Post Dose 1	30 days Post Dose 1		Dose 2 (Visit 2)	7 days Post Dose 2	30 days Post Dose 2		Phone contact Month 8 ~~Study Conclusion~~	*Phone contact Month 14 Study Conclusion*
	Month 0				Month 2		Month 3		Month 8	*Month 14*
Timing of reporting	Day 0	Day 6	Day 29		Day 0	Day 6	Day 29			
~~Reporting of~~ Solicited AEs										
~~Reporting of~~ *U*nsolicited AEs										
AEs/SAEs leading to withdrawal from the study										
All SAEs [a]										
~~Reporting of~~ p*Potential immune-mediated diseases* (pIMDs)										
~~Reporting of~~ p*P*regnancies										
Herpes Zoster (HZ) episodes (see Section 6.7)										
~~Recording of~~ i*I*ntercurrent medical conditions *(IMCs)* ~~in~~*ex*cluding HZ [b] *(see Section 6.7)*										

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

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

~~[b] Intercurrent medical conditions will be recorded in AE/SAE screens as appropriate. The occurrence of HZ is an intercurrent medical condition which should be reported until study end rather than Month 3. All other intercurrent medical conditions should be reported until Month 3.~~

Section 10.7 - Analysis of immunogenicity

- ***Depending on the distribution of time from the last HZ episode to enrolment in this study, a stratified exploratory analysis of immunogenicity may be conducted. Details will be provided in the SAP.***

Section 10.8 - Analysis of safety

Depending on the distribution of time from the last HZ episode to enrolment in this study, a stratified exploratory analysis of safety may be conducted. Details will be provided in the SAP.

Section 10.10.1 - Sequence of analysis

At the end of the study (Month ~~8~~***14*** i.e. ~~6~~***12*** months after Dose 2), an additional analysis will assess the safety follow-up (secondary safety endpoints). An annex report will be written.

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 2

eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
EudraCT number	2012-003643-30
Amendment number:	Amendment 2
Amendment date:	20 February 2014
Co-ordinating author:	[redacted], Scientific Writer, XPE Pharma & Science for GSK Biologicals

Rationale/background for changes:

- The cut-off of the gE-specific ELISA assay has been changed from 18 to 97 mIU/mL. Background signal has been measured with the anti-gE ELISA on samples from Varicella Zoster Virus (VZV) naïve paediatric subjects. This observation of background signal on VZV naïve samples was not part of the original validation of the assay and establishment of the assay cut-off. Background signal measured with the anti-gE ELISA has no impact on Zoster project clinical conclusions as the vast majority of the samples (at all timepoints) have high titers well above the unspecific response level measured on VZV naïve samples from Measles, Mumps, Rubella and Varicella (MMRV) studies and Zoster vaccine responses are very robust. However this finding triggered re-evaluation of the assay cut-off. Based on complementary validation experiments performed in line with Clinical and Laboratory Standards Institute (CLSI) guidelines and taking into account internal company guidelines the technical and seropositivity cut-off has been set at 97 mIU/mL. (Section 5.8.3, Table 9, and Appendix A).

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

Cover page

Co-ordinating author	• [redacted]***, Scientific Writer, XPE Pharma & Science for GSK Biologicals***
Contributing authors	• [redacted]***, Director, Project Manager***
	• [redacted]***, Study Delivery Lead***

Section 5.8.3. Laboratory assay

Table 9 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit	Cut-off	Laboratory*
SER	Varicella Zoster Virus.Glycoprotein E Ab.IgG	ELI	NA	mIU/ml	~~18~~***97***	GSK Biologicals**

*Refer to APPENDIX B for the laboratory addresses.
**GSK Biologicals laboratory refers to the Global Vaccines Clinical Laboratories (GVCL) in Rixensart, Belgium; Wavre, Belgium.

Section 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 according to their random assignment;
- ~~with sufficient data to perform an analysis of safety (at least one dose with safety follow-up);~~
- for whom administration site of study vaccine is known***/correct***;
- who have not received other ~~medication/~~vaccine forbidden in the protocol.

Section 10.8. Analysis of safety

- The percentage of subjects with at least one local ***solicited*** AE ~~(solicited and unsolicited)~~, with at least one general ***solicited AE*** ~~adverse event (solicited and unsolicited)~~ and with any ***solicited*** AE during the solicited 7-day follow-up period will be tabulated with exact 95% Confidence Intervals (CI) after each vaccine dose and overall;

APPENDIX A LABORATORY ASSAYS

Specific Ab (anti-gE) measurements:

Anti-gE ELISA: Anti-gE Ab concentrations will be measured using an anti-gE ELISA.Diluted blood serum samples of study subjects will be added to microtitre wells pre-coated with gE antigen. Secondary peroxidase-conjugated anti-human Abs will be added, which bind to the primary human anti-gE Abs. After incubation of the microtitre wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE Ab concentrations are calculated from a standard curve. The assay cut-off is ~~18~~***97*** mIU/mL. The assay will be performed on human serum at GSK Biologicals' laboratory or another laboratory designated by GSK Biologicals.

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	116796 (ZOSTER-033)
IND number	BB-IND 13857
EudraCT number	2012-003643-30
Date of protocol amendment	Amendment 2 Final: 20 February 2014
Detailed Title	A phase III, non-randomized, open-label, multicentre clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥50 years of age with a prior episode of herpes zoster.
Sponsor signatory	[redacted] Lead Clinical Development Manager, Director, Global Vaccine Development
Signature	[redacted]
Date	3-19-2014

For internal use only

- ----------Checksum----------!Ver.!Created On - -
79f8b9c37181037efe7e3f31dba5530bb058e2eb 2.0 3/7/2014 9:27:49 PM - -
---------- -