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

Primary Study vaccine	• GlaxoSmithKline (GSK) Biologicals' lyophilized formulation of the Herpes Zoster (HZ) subunit (HZ/su) vaccine (GSK1437173A)
Other Study vaccine	Licensed pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed), *Prevenar13*™.
eTrack study number and Abbreviated Title	204487 (ZOSTER-059 PRI)
Investigational New Drug (IND) number	BB-IND-13857
EudraCT number	2017-001220-22
Date of protocol	Final Version 2: 26 September 2017
Date of protocol amendment	Amendment 1 Final: 30 October 2017 Amendment 2 Final: 30 January 2018
Title	Immunogenicity and safety study of GSK Biologicals' Herpes Zoster vaccine GSK1437173A when co-administered with *Prevenar13* in adults aged 50 years and older.
Detailed Title	A Phase IIIB, randomized, open-label, multicenter clinical trial to assess the immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A when co-administered with *Prevenar13* in adults aged 50 years and older.
Co-ordinating author	PPD, Scientific Writer, contractor for GSK Biologicals
Contributing authors **(Amended 30 January 2018)**	• PPD, ***Clinical and Epidemiology Scientist*** • PPD, Clinical and Epidemiology Project Lead • PPD, ***Clinical and Epidemiology Project Leader*** • PPD, Project Statistician • PPD, Lead Statistician

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Contributing authors (Contd.) **(Amended 30 January 2018)**	• PPD, Study Delivery Lead • PPD ***, Study Delivery Lead, Synteract Inc. for GSK Biologicals*** • PPD, Study Delivery Associate • PPD, Clinical Trial Supply Manager • PPD, Clinical Safety representative • PPD ***, Clinical Safety representative*** • PPD, Study Data Manager (Tata Consultancy Services for GSK Biologicals) • PPD ***Study Data Manager (Tata Consultancy Services for GSK Biologicals)*** • PPD, Oversight Data Manager • PPD, Global Regulatory Affairs • PPD ***, Global Regulatory Affairs*** • PPD, United States Regulatory Affairs • PPD, Global Patents • PPD, Global Medical Affairs • PPD, Clinical Readout Team Lead • PPD, Laboratory Study Manager

GSK Biologicals' Protocol DS v 15.0

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	204487 (ZOSTER-059 PRI)
IND number	BB-IND-13857
EudraCT number	2017-001220-22
Date of protocol amendment	Amendment 2 Final: 30 January 2018
Detailed Title	A Phase IIIB, randomized, open-label, multicenter clinical trial to assess the immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A when co-administered with *Prevenar13* in adults aged 50 years and older.
Sponsor signatory (Amended 30 January 2018)	***Anne Schuind*** ***Clinical and Epidemiology Project Leader, Zoster Program, US Research and Development Center (RDC)***
Signature	
Date	

Protocol Amendment 2 Rationale

Amendment number:	Amendment 2

Rationale/background for changes:

Major change:

- This amendment is in response to the Center for Biologics Evaluation and Research (CBER) comments on Protocol Amendment 1, received on 09-January-2018, requesting clarification on 1. the adjustment for baseline titers in the computation of the Multiplex Opsonophagocytosis Assay (MOPA) Geometric Mean Titers (GMT) ratios (Section 10.7.2) and 2. time points for primary evaluations on co-primary immunogenicity objectives (Section 10.10.1).

Other changes:

- The tradename for pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed) in Canada has been corrected to *Prevnar13* from *Prevenar13*.
- The laboratory to be used for MOPA testing has been selected and is presented in Appendix B.
- A typographical error in the estimated number of subjects in each age strata and study group has been corrected. Table 4 reflects the correct number of subjects for age stratification.

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' study vaccine(s) 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(s) 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	204487 (ZOSTER-059 PRI)
IND number	BB-IND-13857
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Investigator name	_____
Signature	_____
Date	_____
Leiter der klinischen Prüfung name, function and title	_____
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 IIIB, randomized, open-label, multicenter clinical trial to assess the immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A when co-administered with *Prevenar13* in adults aged 50 years and older.
Indication	Prevention of Herpes Zoster (HZ) and related complications in adults ≥50 years of age (YOA) and immunocompromized (IC) adults ≥18 YOA.
Rationale for the study and study design	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. Herpes zoster (HZ; shingles) occurs when VZV reactivates from latency and typically manifests as a localized, dermatomal rash. The typical HZ rash usually lasts 2 to 4 weeks and is typically 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. The objective of the current phase III study is to assess immunogenicity, reactogenicity and safety of GSK Biologicals' HZ vaccine when its first dose is co-administered with a pneumococcal polysaccharide conjugate vaccine (*Prevenar13*) in adults aged ≥50 YOA, as compared to the control group where the two HZ/su doses are administered subsequent to *Prevenar13*. The two parallel arms study design was selected to allow an assessment of the immunogenicity, reactogenicity and safety of HZ/su and *Prevenar13* vaccines when they are co-administered and when administered separately in a staggered schedule (*Prevenar13* followed by HZ/su).
Objectives	**Co-Primary** • To determine the vaccine response rate (VRR) to HZ/su (based on humoral immune response) one month after the second vaccine dose, when the first dose of HZ/su is co-administered with *Prevenar13* (Co-Ad group).*

Criterion to be used:

The objective is met if the lower limit (LL) of the 95% CI of the VRR for anti-gE antibody concentrations in the Co-Ad group one month after the second vaccine dose is ≥60%.

* The VRR for anti-gE 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.

If the above objective is met in the Co-Ad group, then the following objective will be evaluated:

- To demonstrate non-inferiority of the humoral immune response to two doses of HZ/su at one month after the last vaccine dose, when the first dose of HZ/su is co-administered with *Prevenar13* (Co-Ad group) compared to when two doses of HZ/su are administered subsequent to *Prevenar13* (Control Group).

  Criterion for non-inferiority:

  One month after the last vaccine dose in each study group, the upper limit (UL) of the 95% confidence interval (CI) for the anti-gE antibodies Geometric Mean Concentration (GMC) ratio between the Control group and the Co-Ad group is <1.5.

If the above non-inferiority objective is met, then the following objective will be evaluated:

- To demonstrate non-inferiority of the humoral immune response to *Prevenar13* at one month after the vaccine dose, when *Prevenar13 is* co-administered with the first HZ/su dose (Co-Ad group) compared to when *Prevenar13* is administered separately from HZ/su (Control group), for the 13 serotypes included in *Prevenar13* analyzed sequentially.

  Criterion for non-inferiority:

  One month after the Prevenar13 vaccine dose in each study group, the UL of the 95% CI for each individual pneumococcal conjugate serotype Geometric Mean Titer (GMT) ratio of the Control group over the Co-Ad group is <2.

For the co-primary objectives, fixed sequence testing which allows for full alpha propagation in pre-ordered hypotheses families will be used.

Secondary

- To evaluate the safety and reactogenicity following administration of HZ/su and *Prevenar13* vaccines, up to one month post last vaccination and during the whole follow-up period, in the Control group and the Co-Ad group.

Study design

- **Experimental design**: Phase IIIB, open-label, randomized, controlled, multi-centric, and multi-country, with two parallel groups.
- **Duration of the study**: The intended duration of the study per subject is approximately 14 months for subjects from the Co-Ad group and approximately 16 months for subjects from the Control group.
  - Epoch 001: Primary starting at Visit Day 1 and ending with the phone contact at Month 16.
- **Primary completion date (PCD)**: Visit Month 5.
- **End of Study (EoS)**: Last testing results released of samples collected at Visit Month 3 (Co-Ad group) or at Visit Month 5 (Control group).
- **Study groups**:

Synopsis Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age	Epochs
			Epoch 001
Co-Ad	456	≥ 50 years	x
Control	456	≥ 50 years	x

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		Co-Ad	Control
HZ/su	VZV gE	X	x
	AS01B	x	x
Prevenar13	*Prevenar 13*	x	x

- **Control**: active control.
- **Vaccination schedule(s):**

  Co-Ad Group:

  – at Visit Day 1: first dose of HZ/su and one dose of *Prevenar13*,

  – at Visit Month 2: second dose of HZ/su.

  Control Group:

  – at Visit Day 1: one dose of Prevenar13,

  – at Visit Month 2: first dose of HZ/su,

  – at Visit Month 4: second dose of HZ/su.

- **Treatment allocation**: Subjects to be randomized in a 1:1 ratio at Visit Day 1 to either Co-Ad or Control group. Subjects in each group will be stratified by age with the following approximate distribution (not less than 25% in each age strata):

  – 171 subjects in the 50-59 YOA stratum,

  – 171 subjects in the 60-69 YOA stratum, and

  – 114 subjects in the ≥ 70 YOA stratum.

- **Blinding**: open-label

Synopsis Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- **Sampling schedule**: Blood samples (approximately 8 mL) will be collected for each group, as described below.

  For Co-Ad group:

  – at Visit Day 1 to assess baseline antibody concentrations/titers with respect to Prevenar13 and HZ/su vaccine antigens, prior to vaccination,

  – at Visit Month 1 to assess humoral immune response with respect to Prevenar13 vaccine antigens, 1 month post-vaccination,

  – at Visit Month 3 to assess humoral immune response with respect to the HZ/su vaccine antigen, 1 month post-second vaccination dose.

For Control group:

- at Visit Day 1 to assess baseline antibody concentrations/titers with respect to Prevenar13 vaccine antigens, prior to vaccination,
- at Visit Month 1 to assess humoral immune response with respect to Prevenar13 vaccine antigens, at 1 month post-vaccination,
- at Visit Month 2 to assess baseline antibody concentrations/titers with respect to the HZ/su vaccine antigen, prior to first vaccination dose,
- at Visit Month 5 to assess humoral immune response with respect to the HZ/su vaccine antigen, at 1 month post-second vaccination dose.

For both groups:

- A urine specimen will be collected from all female subjects of childbearing potential at Visit Day 1 and Visit Month 2 for Co-Ad group, and at Visit Day 1, Visit Month 2 and Visit Month 4 for the Control group. If a serum pregnancy test instead of a urine pregnancy test is required by country, local or ethics committee regulations, a blood sample will be collected from women of childbearing potential at these visits and will be used for the test as per local guidance.

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

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

Safety monitoring: An internal GSK Safety Review Team (SRT) part of the HZ/su vaccine project will oversee the safety of the study subjects on a regular basis. Serious Adverse Events (SAEs) and Adverse Events (AEs) including pIMDs will be reviewed by the SRT at regular intervals together with data from other ongoing HZ/su vaccine studies. Any potential safety concern related to conduct of the study will be escalated to higher internal decision boards as per internal GSK process.

Number of subjects Target enrollment will be approximately 912 eligible subjects, to obtain 820 evaluable subjects (410 in each study group).

Endpoints

Primary

- HZ/su immunogenicity:
  - Vaccine response for anti-gE humoral immunogenicity, as determined by ELISA, in subjects from the Co-Ad group at one month post-dose 2, at Visit Month 3.
  - Anti-gE antibody concentrations as determined by ELISA at one month post-dose 2, at Visit Month 3 for the Co-Ad group and Visit Month 5 for the Control group.
- Pneumococcal vaccine immunogenicity:
  - Anti-pneumococcal antibody titers for the 13 following serotypes as determined by MOPA at one month post-dose at Visit Month 1: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

Secondary

- Occurrence of solicited local and general symptoms:
  - Occurrence, duration and intensity of each solicited local symptom within 7 days (Days 1 - 7) after each vaccination.
  - Occurrence, duration, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 1 to 7) after each vaccination.
- Occurrence of unsolicited AEs:
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs within 30 days (Days 1 to 30) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs:
  - Occurrence and relationship to vaccination of all SAEs from first vaccination at Day 1 up to 30 days post last vaccination.
  - Occurrence and relationship to vaccination of all SAEs during the period starting after 30 days post last vaccination up to study end.
- Occurrence of pIMDs:
  - Occurrence and relationship to vaccination of any pIMDs from first vaccination at Day 1 up to 30 days post last vaccination.
  - Occurrence of any pIMDs during the period starting after 30 days post last vaccination up to study end.

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LIST OF ABBREVIATIONS

AE:	Adverse event
ANCOVA:	Analysis of Covariance
AS01$_B$:	MPL, QS21, liposome based Adjuvant System (50 μg MPL and 50 μg QS21)
BS:	Blood Sample
CBER:	***Center for Biologics Evaluation and Research***
	(Amended 30 January 2018)
CDC:	Centers for Disease Control and Prevention
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
Co-Ad:	Co-administration
CRO:	***Contract Research Organization***
	(Amended 30 January 2018)
CSF:	Cerebrospinal fluid
eCRF:	Electronic Case Report Form
EGA:	Estimated Gestational Age
ELISA:	Enzyme-linked Immunosorbent Assay
EMA:	European Medicines Agency
EoS:	End of Study
eTDF:	Electronic Temperature excursion Decision Form
FDA:	Food and Drug Administration, United States
FU:	Follow up
GCP:	Good Clinical Practice
gE:	VZV glycoprotein E
GMC/GMT:	Geometric Mean Concentration/Titers
GSK:	GlaxoSmithKline
HIV:	Human Immunodeficiency Virus
HZ:	Herpes Zoster
HZ/su:	Herpes Zoster subunit vaccine (50 μg gE/AS01$_B$)
IB:	Investigator's Brochure
ICF:	Informed Consent Form

ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IDMC:	Independent Data Monitoring Committee
IgG:	Immunoglobulin G
IM:	Intramuscular
IND:	Investigational New Drug
IRB:	Institutional Review Board
LL:	Lower Limit
LMP:	Last Menstrual Period
LSLV:	Last Subject Last Visit
MACDP:	Metropolitan Atlanta Congenital Defects Program
MATEX:	MATerial EXcellence
MedDRA:	Medical Dictionary for Regulatory Activities
MOPA:	Multiplex Opsonophagocytosis Assay
MPL:	3-O-desacyl-4'-monophosphoryl lipid A
PCD:	Primary Completion Date
PHN:	Postherpetic Neuraligia
pIMD:	Potential Immune-Mediated Disease
PPC:	Per-protocol cohort
Pre-Vacc:	Pre-vaccination
QS21:	*Quillaja saponaria* Molina, fraction 21 (purified saponin extract from the South American tree)
SAE:	Serious Adverse Event
SAS:	Statistical Analysis System
SBIR:	Randomization System on Internet
SD:	Standard Deviation
SDV:	Source Document Verification
SmPC:	Summary of Product Characteristics
SPM:	Study Procedures Manual
SRT:	Safety Review Team
TVC:	Total Vaccinated Cohort
UL:	Upper Limit

VRR: Vaccine Response Rate

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,
- Combined estrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- Contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, 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.
End of Study: **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV.
Epoch:	An epoch is a set of consecutive timepoints or a single timepoint from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, 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 per-protocol analysis (see Sections 6.7.2 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.

Intercurrent medical condition:	An intercurrent medical condition is defined as a condition that has the capability of confounding the immune response to the study vaccine or its interpretation.
Investigational vaccine: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Legally acceptable representative: **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
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.

Pharmacogenomics:	The International Conference on Harmonization (ICH) E15 Guidance for Industry defines pharmacogenomics as Study of variation of DNA and RNA characteristics as related to drug or treatment response. Pharmacogenetics, which is a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (pharmacokinetics, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research are not pharmacogenomics.
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International 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.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.

Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/ product /placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Sub-cohort:	A group of subjects for whom specific study procedures are planned as compared to other subjects or a group of subjects who share a common characteristic (e.g. ages, vaccination schedule,…) at the time of enrolment.
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) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

TRADEMARKS

The following trademarks are used in the present protocol.

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

Trademarks of the GSK group of companies		Generic description
Shingrix		Zoster Vaccine Recombinant, Adjuvanted

Trademarks not owned by the GSK group of companies		Generic description
Prevenar13 (Trade name for Germany and Estonia)/ **Prevnar13** Trade name for ***Canada and*** United States)* Wyeth Pharmaceuticals Inc./Pfizer Inc.		Pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed)
Pneumovax 23 (Trade name for Canada, Colombia, Germany and United States)/ **Pneumo 23** (Trade name for Estonia) Merck & Co., Inc.		Pneumococcal polysaccharide conjugate vaccine (23-valent adsorbed)

* For clarity and consistency, the pneumococcal vaccine has been written as *Prevenar13* throughout the document

(Amended 30 January 2018)

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. Herpes zoster (HZ; shingles) occurs when VZV reactivates from latency and typically manifests as a localized, dermatomal rash.

The typical HZ rash usually lasts 2 to 4 weeks and is typically 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 [Dworkin, 2007; National Network for Immunization Information (NNii), 2008].

About half of all HZ cases occur in individuals over the age of 60, and individuals who reach 85 YOA have a 50% chance of having HZ during their lifetime [Oxman, 2005, Chua, 2010]. The risk of developing PHN varied from 5% to more than 30% depending on the study design and age distribution [Kawai, 2014]. Since the loss of VZV-specific T-cell responses as a result of aging is associated with a heightened susceptibility to HZ, vaccination is considered as a means to reduce the risk of HZ in older adults [Oxman, 2005; Sperber, 1992].

GlaxoSmithKline (GSK) Biologicals' vaccine (*Shingrix*) for the prevention of HZ is a recombinant subunit (su) vaccine consisting of VZV glycoprotein E (gE) as antigen and an adjuvant system $AS01_B$. It has been evaluated in several studies in healthy adults and shown to elicit strong cellular and humoral immune responses. The safety and reactogenicity profile of the study vaccine was also acceptable. Based on phase II data from the antigen dose-ranging study ZOSTER-003 [Chlibek, 2014], and the adjuvant dose comparison study ZOSTER-010 [Chlibek, 2013], a gE antigen dose of 50 µg and the adjuvant system $AS01_B$ were selected for the final vaccine formulation. Henceforth in the document, the final vaccine formulation will be referred to as HZ/su.

Two large pivotal phase III trials, ZOSTER-006 (also referred to as ZOE-50) in subjects ≥50 YOA and ZOSTER-022 (also referred to as ZOE-70) in subjects ≥70 YOA, evaluated the vaccine efficacy and safety of HZ/su. These placebo-controlled trials enrolled more than 30,000 subjects who received either HZ/su or placebo on a 0, 2-month schedule. The final analysis of the ZOSTER-006 primary efficacy objective demonstrated that the vaccine is highly efficacious in adults ≥50 YOA, with 97.2% (95% confidence interval [CI] of 93.7 - 99.0) overall efficacy against HZ. In addition, vaccine efficacy against HZ was between 96.6% and 97.9% for all pre-specified age groups (50-59, 60-69 and ≥70 YOA) [Lal, 2015]. The results from ZOSTER-022 demonstrated that the first primary objective has been successfully met, with 89.8% (95% CI of 84.3-93.7) efficacy against HZ in subjects ≥70 YOA, and are therefore consistent with the results of ZOSTER-006. In addition, the co-primary objective of a pre-specified pooled analysis of ZOSTER-006 and ZOSTER-022 demonstrated that HZ/su has a vaccine efficacy against HZ of 91.3% (with 95% CI of 86.8-94.5) and effectively prevents PHN in subjects ≥70

YOA (efficacy of 88.8% with 95% CI of 68.7-97.1). No safety concerns have been raised [Cunningham, 2016].

The immunogenicity, reactogenicity, and safety of HZ/su when co-administered with a 23-valent pneumococcal polysaccharide conjugate vaccine (*Pneumovax 23* [trade name for Canada, Germany and United States]/*Pneumo 23* [trade name for Estonia], Merck& Co., Inc) have been assessed in a phase III study in subjects ≥50 YOA (ZOSTER-035). The immunogenicity co-primary objectives have been met.

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

1.2. Rationale for the study and study design

The objective of the current phase III study is to assess immunogenicity, reactogenicity and safety of GSK Biologicals' HZ vaccine when its first dose is co-administered with a pneumococcal polysaccharide conjugate vaccine (*Prevenar13*) in adults aged ≥50 YOA, as compared to the control group where the two HZ/su doses are administered subsequent to *Prevenar13*.

The two parallel arms study design was selected to allow an assessment of the immunogenicity, reactogenicity and safety of HZ/su and *Prevenar13* vaccines when they are co-administered and when administered separately in a staggered schedule (*Prevenar13* followed by HZ/su).

1.3. Benefit : Risk Assessment

Please refer to the current IB for the summary of potential risks and benefits of GSK Biologicals' study HZ vaccine (HZ/su).

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of *Prevenar13.*

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

1.3.1. Risk Assessment

Important Potential Risk	Data/Rationale for Risk	Mitigation Strategy
Study vaccine: HZ/su		
Hypersensitivity reactions (including anaphylaxis).	No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.	Administration of the study vaccination is to be preceded by a review of the subjects' medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.
Theoretical risk of acquiring a vaccine induced autoimmune disease after vaccination.	No confirmed signals related to this potential risk have been identified during the clinical program. Available clinical data do not highlight any concern.	Close monitoring of potential Immune-Mediated Diseases (pIMDs) as per study protocol. The potential risk of events of possible autoimmune etiology to occur is mentioned in the Informed Consent Form (ICF). In addition, the ICF advises subjects to contact the study doctor or the study staff immediately, should they get any symptoms that they feel may be serious.
Study Procedures		
Risk from blood sampling.	Blood sampling associated risk of discomfort, syncope, dizziness, infection at the site after or during venipuncture.	Blood samples will be obtained by a trained professional and medical assistance will be available. The potential risk of feeling faint, or experiencing mild local pain, bruising, irritation or redness at the site where blood was taken, is mentioned in the ICF. The amount of blood to be taken for sampling will not be harmful to the subject's health.

1.3.2. Benefit Assessment

Benefits include:

- Receiving HZ/su during the study may reduce the risk of HZ occurrence and HZ-related complications.
- Receiving *Prevenar13* during the study may prevent occurrence of pneumococcal pneumonia and invasive disease caused by 13 *Streptococcus pneumoniae* strains (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).
- Medical evaluations/assessments associated with study procedures (e.g. physical examination).

1.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to subjects participating in this study, the potential or recognized risks identified in association with the study HZ vaccine (HZ/su) and study procedures are justified by the potential benefits (prevention of HZ and related complications) that may be afforded to the subjects receiving HZ/su.

Please refer to the approved product label/package insert for the summary of potential risks and benefits of *Prevenar13*.

2. OBJECTIVES

2.1. Co-Primary objectives

- To determine the vaccine response rate (VRR) to HZ/su (based on humoral immune response) one month after the second vaccine dose, when the first dose of HZ/su is co-administered with *Prevenar13* (Co-Ad group).

  Criterion to be used:

  The objective is met if the lower limit (LL) of the 95% CI of the VRR for anti-gE antibody concentrations in the Co-Ad group one month after the second vaccine dose is ≥60%.

If the above objective is met in the Co-Ad group, then the following objective will be evaluated:

- To demonstrate non-inferiority of the humoral immune response to two doses of HZ/su at one month after the last vaccine dose, when the first dose of HZ/su is co-administered with *Prevenar13* (Co-Ad group) compared to when two doses of HZ/su are administered subsequent to *Prevenar13* (Control Group).

Criterion for non-inferiority:

One month after the last vaccine dose in each study group, the upper limit (UL) of the 95% confidence interval (CI) for the anti-gE antibodies Geometric Mean Concentration (GMC) ratio between the Control group and the Co-Ad group is <1.5.

If the above non-inferiority objective is met, then the following objective will be evaluated:

- To demonstrate non-inferiority of the humoral immune response to *Prevenar13* at one month after the vaccine dose, when *Prevenar13 is* co-administered with the first HZ/su dose (Co-Ad group) compared to when *Prevenar13* is administered separately from HZ/su (Control group), for the 13 serotypes included in *Prevenar13* analyzed sequentially.

  Criterion for non-inferiority:

  One month after the Prevenar13 vaccine dose in each study group, the UL of the 95% CI for each individual pneumococcal conjugate serotype Geometric Mean Titer (GMT) ratio of the Control group over the Co-Ad group is <2.

For the co-primary objectives, fixed sequence testing which allows for full alpha propagation in pre-ordered hypotheses families will be used (see section 10.7.2).

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

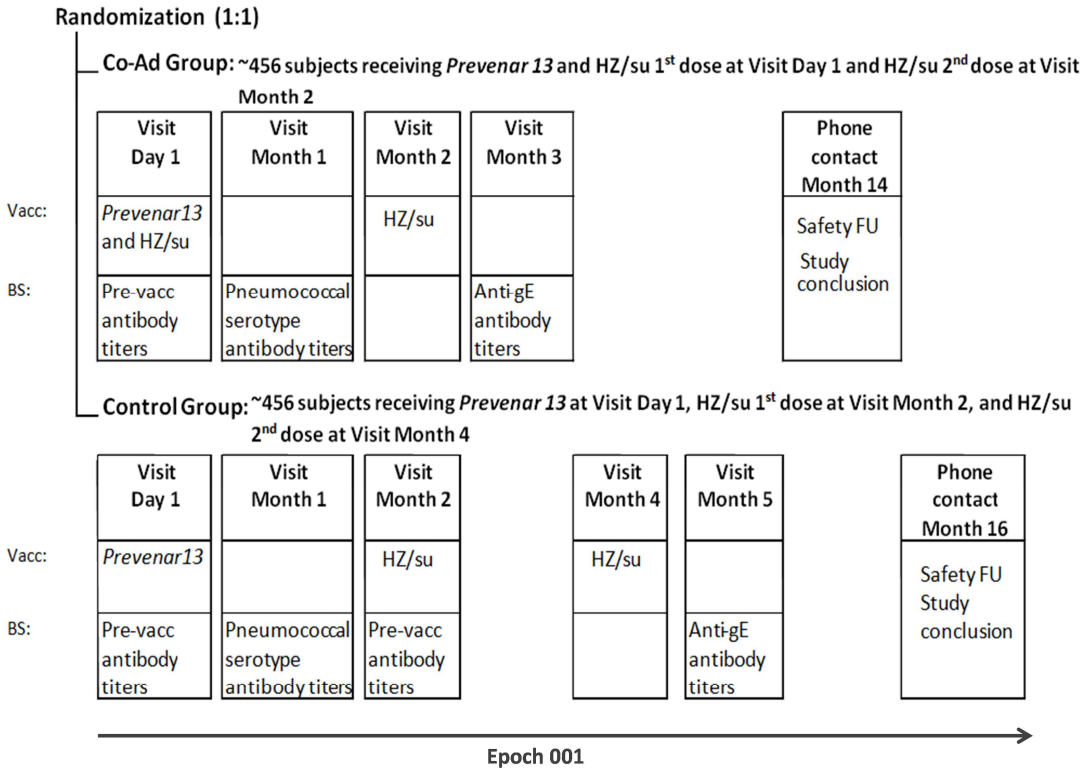
2.2. Secondary objective

- To evaluate the safety and reactogenicity following administration of HZ/su and *Prevenar13 vaccines*, up to one month post last vaccination and during the whole follow-up period, in the Control group and the Co-Ad group.

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

3. STUDY DESIGN OVERVIEW

Figure 1 Overview of Study Design



Vacc: vaccination; BS: blood sample; Pre-Vacc: pre-vaccination; FU: follow-up

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.6), are essential and required for study conduct.

- **Experimental design**: Phase IIIB, open-label, randomized, controlled, multi-centric, and multi-country, with two parallel groups.
- **Duration of the study**: The intended duration of the study per subject is approximately 14 months for subjects from the Co-Ad group and approximately 16 months for subjects from the Control group.

Epoch 001: Primary starting at Visit Day 1 and ending with the phone contact at Month 16.

- **Primary completion date (PCD)**: Visit Month 5.

Refer to glossary of terms for the definition of PCD.

- **End of Study (EoS)**: Last testing results released of samples collected at Visit Month 3 (Co-Ad group) or at Visit Month 5 (Control group).

Refer to glossary of terms for the definition of EoS.

- **Study groups**:

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of subjects	Age	Epochs
			Epoch 001
Co-Ad	456	≥ 50 years	x
Control	456	≥ 50 years	x

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine/Product name	Study Groups	
		Co-Ad	Control
HZ/su	VZV gE	x	x
	AS01B	x	x
Prevenar13	*Prevenar 13*	x	x

- **Control**: active control.
- **Vaccination schedule(s):**

Co-Ad Group:

- at Visit Day 1: first dose of HZ/su and one dose of Prevenar13,
- at Visit Month 2: second dose of HZ/su.

Control Group:

- at Visit Day 1: one dose of Prevenar13,
- at Visit Month 2: first dose of HZ/su,
- at Visit Month 4: second dose of HZ/su.

- **Treatment allocation**: Subjects to be randomized in a 1:1 ratio at Visit Day 1 to either Co-Ad or Control group. Subjects in each group will be stratified by age with the following approximate distribution (not less than 25% in each age strata):
  - 171 subjects in the 50-59 YOA stratum,
  - 171 subjects in the 60-69 YOA stratum, and
  - 114 subjects in the ≥ 70 YOA stratum.
- **Blinding**: open-label.

Table 3 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	open

- **Sampling schedule**: Blood samples (approximately 8 mL) will be collected for each group, as described below.

  For Co-Ad group:

  – at Visit Day 1 to assess baseline antibody concentrations/titers with respect to Prevenar13 and HZ/su vaccine antigens, prior to vaccination,

  – at Visit Month 1 to assess humoral immune response with respect to Prevenar13 vaccine antigens, 1 month post-vaccination,

  – at Visit Month 3 to assess humoral immune response with respect to the HZ/su vaccine antigen, 1 month post-second vaccination dose.

  For Control group:

  – at Visit Day 1 to assess baseline antibody concentrations/titers with respect to Prevenar13 vaccine antigens, prior to vaccination,

  – at Visit Month 1 to assess humoral immune response with respect to Prevenar13 vaccine antigens, at 1 month post-vaccination,

  – at Visit Month 2 to assess baseline antibody concentrations/titers with respect to the HZ/su vaccine antigen, prior to first vaccination dose,

  – at Visit Month 5 to assess humoral immune response with respect to the HZ/su vaccine antigen, at 1 month post-second vaccination dose.

  For both groups:

  – A urine specimen will be collected from all female subjects of childbearing potential at Visit Day 1 and Visit Month 2 for Co-Ad group, and at Visit Day 1, Visit Month 2 and Visit Month 4 for the Control group. If a serum pregnancy test instead of a urine pregnancy test is required by country, local or ethics committee regulations, a blood sample will be collected from women of childbearing potential at these visits and will be used for the test as per local guidance.

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

- **Type of study**: self-contained.
- **Data collection**: Electronic Case Report Form (eCRF).
- **Safety monitoring**: An internal GSK Safety Review Team (SRT) part of the HZ/su vaccine project will oversee the safety of the study subjects on a regular basis. Serious Adverse Events (SAEs) and Adverse Events (AEs) including pIMDs will be reviewed by the SRT at regular intervals together with data from other ongoing HZ/su vaccine studies. Any potential safety concern related to conduct of the study will be escalated to higher internal decision boards as per internal GSK process.

4. STUDY COHORT

4.1. Number of subjects/centres

Target enrollment will be approximately 912 eligible subjects, to obtain 820 evaluable subjects (410 in each study group). Detailed description of the criteria used in the estimation of sample size can be found in Section 10.3.

Within each study group, subjects will be stratified by age at the time of recruitment (not less than 25% in each age strata), as described in Table 4.

Table 4 Age Stratification

(Amended 30 January 2018)

Group	Description	Estimated number of subjects
Co-Ad	Subjects 50 to 59 YOA	***171***
	Subjects 60 to 69 YOA	***171***
	Subjects ≥70 YOA	***114***
Control	Subjects 50 to 59 YOA	***171***
	Subjects 60 to 69 YOA	***171***
	Subjects ≥70 YOA	***114***

YOA: years of age.

Overview of the recruitment plan

- This study is planned to be conducted at sites in multiple countries.
- The recruitment rate will be monitored using a study-specific central Randomization System on Internet (SBIR).
- The randomization algorithm will use a stratification procedure accounting for the three age strata (50-59 YOA, 60-69 YOA and ≥70 YOA).

4.2. Inclusion criteria for enrolment

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

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- Written informed consent obtained from the subject prior to performance of any study specific procedure.

- A male or female, aged ≥50 YOA at the time of the first vaccination with the study vaccine(s).
- Female subjects of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral 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, regulatory acceptability of the study 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:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the period starting 30 days before the first dose of study vaccines (Day -30 to Day 1), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular (IM) injection unsafe.
- Use or anticipated use of immunosuppressants or other immune-modifying drugs during the period starting six months prior to study start and during the whole study period. This includes chronic administration of corticosteroids (>14 consecutive days of prednisone at a dose of ≥20 mg/day [or equivalent]), long-acting immune modifying agents (e.g., infliximab) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders). Inhaled, topical and intra-articular corticosteroids are allowed.
- Administration or planned administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose and ending 30 days after the last dose of study vaccine administration. This includes any type of vaccine such as (but not limited to) live, inactivated and subunit vaccines (e.g., inactivated and subunit influenza 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 and/or planned administration of an HZ or VZV vaccine (including an investigational or non-registered vaccine) other than the study vaccine during the study period.
- History of HZ.
- History of documented pneumococcal infection within 5 previous years.
- Prior receipt of any pneumococcal vaccine or planned use during the study period, other than the study vaccines.
- 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 vaccines.
- Acute disease and/or fever at the time of enrollment.
  - Fever is defined as temperature ≥ 38.0°C/100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first dose of study vaccine or planned administration during the study period.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions before 2 months after the last dose of study vaccine.
- Any person with cerebrospinal fluid (CSF) leaks, cochlear implants, chronic renal failure, nephrotic syndrome and functional or anatomic asplenia.
- Any medical condition that in the judgment of the investigator would prevent the subject from participating in the study.

5. CONDUCT OF THE STUDY

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

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

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

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

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

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

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

Freely given and written or witnessed/ thumb printed 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

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.

5.2.2. Randomization of treatment

The treatment allocation will be performed using SBIR. The treatment numbers will be allocated by dose. The allocation ratio will be 1:1 between each study group.

5.2.2.1. Randomization of supplies

The randomization of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks 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-randomization 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 912 eligible subjects who will be randomly assigned to two study groups in a 1:1 ratio (approximately 456 in each study group).

The enrolment will be performed to ensure distribution of the population across the three age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA). Therefore the expected distribution of subjects is as shown in Table 5.

Age will be calculated as the number of years between the date of birth and the date of first vaccination. To ensure that the collection of date of birth will not jeopardise the privacy of Personally Identifiable Information (PII), only a partial date of birth* (MMYYYY) will be collected. Therefore, the 15th of the month will be used to replace the missing date.

In case the month is missing, the date will be replaced by the June 30th of the year.

* In Germany, as per local regulations, only the year of birth will be collected.

Table 5 Number of subjects required for enrolment

Age Stratum	Vaccine	N
50-59 YOA	HZ/su	342
	Prevenar13	
60-69 YOA	HZ/su	342
	Prevenar13	
≥ 70 YOA	HZ/su	228
	Prevenar13	

N = number of subjects to be enrolled

Allocation of the subject to a study group at the investigator site will be performed using SBIR. Within each age strata (50-59 YOA, 60-69 YOA and ≥ 70 YOA), the randomization algorithm will use a minimisation procedure accounting for centre.

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, 60-69 YOA and ≥ 70 YOA) at the time of enrolment in the study and the subject identification number, the randomization system will determine the study group and will provide the treatment number(s) 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.

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 study group.

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.

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

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). A diagnosis of suspected HZ will be based upon investigator judgment. 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 is an intercurrent medical condition (see Section 6.8) which should be reported until study end. All other intercurrent medical conditions should be reported until Month 3 for subjects from the Co-Ad group and Month 5 for subjects from the Control group.

The standard reporting period as specified in Section 8.4.1 for Adverse Event (AE)/Serious Adverse Event (SAE) should be used for HZ complications.

At Visit Day 1, all subjects will be informed of the signs and symptoms of typical HZ.

5.6. Outline of study procedures

The lists of study procedures are presented in Table 6 and Table 7 for Co-Ad and Control groups, respectively.

Table 6 List of study procedures for Co-Ad Group

Epoch	Epoch 001				
Type of contact	Visit	Visit	Visit	Visit	Phone contact
Timepoint (s)	Day 1	Month 1	Month 2	Month 3	Month 14
Sampling timepoint(s)	Pre-vacc	*Prevenar13* Post-vacc		HZ/su Post-vacc 2	
Informed consent	●				
Inclusion/exclusion criteria	●				
Collect and record demographic data	●				
General Medical history	●				
Vaccination history	●				
General physical examination (history directed)	O				
Pregnancy test [1]	●		●		
Check contraindications and warnings and precautions	●		●		
Pre-vaccination body temperature [2]	●		●		
Randomization	O				
Study group and treatment number allocation	O				
Recording of administered treatment number	●		●		
Blood sampling for antibody determination (~8 mL) in all subjects	●	●		●	
HZ/su administration	●		● [3]		
Prevenar13 vaccine administration	●				
Post-vaccination observation (30 minutes minimum)	O		O		
Training on self-reporting by subjects [4]	O	O	O	O	
Training on completion of diary cards	O		O		

Epoch	Epoch 001				
Type of contact	**Visit**	**Visit**	**Visit**	**Visit**	**Phone contact**
Timepoint (s)	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 14**
Sampling timepoint(s)	**Pre-vacc**	***Prevenar13* Post-vacc**		**HZ/su Post-vacc 2**	
Distribution of diary cards for solicited AEs, unsolicited AEs and concomitant medication/vaccination to subjects	O		O		
Daily recording of solicited AEs by subjects (Days 1-7 after each vaccination) [5]	O		O		
Daily recording of unsolicited AEs and concomitant medication/vaccination by subjects (Days 1-30 after each vaccination)	O		O		
Return of diary cards for solicited AEs, unsolicited AEs and concomitant medication/vaccination		O		O	
Transcription of diary cards for solicited AEs, unsolicited AEs and concomitant medication/vaccination by study staff/investigator		●		●	
Recording of serious adverse event [6]	●	●	●	●	●
Recording of pIMDs	●	●	●	●	●
Recording of pregnancy	●	●	●	●	●
Recording of intercurrent medical conditions other than HZ [7]	●	●	●	●	
Recording of HZ (intercurrent medical condition) [8]	●	●	●	●	●
Recording of concomitant medication/vaccination [9]	●	●	●	●	●
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 up to Month 3 for Co-Ad group.

Pre-vacc: pre-vaccination, post-vac: post-vaccination. AE: adverse event; HZ: Herpes Zoster.

● 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.

[1]. For women of childbearing potential. If a serum pregnancy test instead of a urine pregnancy test is required by country, local or ethics committee regulations, a blood sample will be collected from women of childbearing potential.

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

[3]. Any subject with a suspected HZ episode anytime following the first HZ/su dose should not receive the second HZ/su dose or any subject with an event of HZ between Visit Day 1 and any dose of HZ/su vaccine should not receive the upcoming dose(s) of the HZ/su vaccine.

[4]. Subjects will be instructed to contact their study site immediately if they manifest any symptoms they perceive as serious and, in case of pregnancy for women of childbearing potential.

[5]. The preferred route for the daily recording of temperature is oral. When there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.

[6]. All serious adverse events (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.

[7]. According to Section 6.8

[8]. At Visit Day 1, all subjects will be informed of the signs and symptoms of typical HZ.

[9]. According to Section 6.7.1

Table 7 List of study procedures for Control Group

Epoch	Epoch 001					
Type of contact	**Visit**	**Visit**	**Visit**	**Visit**	**Visit**	**Phone contact**
Timepoint (s)	**Day 1**	**Month 1**	**Month 2**	**Month 4**	**Month 5**	**Month 16**
Sampling timepoint(s)	**Pre-vacc**	***Prevenar13* Post-vacc**	**Pre-vacc**		**HZ/su Post-vacc 2**	
Informed consent	●					
Inclusion/exclusion criteria	●					
Collect and record demographic data	●					
General medical history	●					
Vaccination history	●					
General physical examination (history directed)	O					
Pregnancy test [1]	●		●	●		
Check contraindications and warnings and precautions	●		●	●		
Pre-vaccination body temperature [2]	●		●	●		
Randomization	O					
Study group and treatment number allocation	O					
Recording of administered treatment number	●		●	●		
Blood sampling for antibody determination (~8 mL) in all subjects	●	●	●		●	
HZ/su administration			● [3]	● [3]		
Prevenar13 vaccine administration	●					
Post-vaccination observation (30 minutes minimum)	O		O	O		
Training on self-reporting by subjects [4]	O	O	O	O	O	
Training on completion of diary cards	O		O	O		
Distribution of diary cards for solicited AEs, unsolicited AEs and concomitant medication/vaccination to subjects	O		O	O		
Daily recording of solicited AEs by subjects (Days 1-7 after each vaccination) [5]	O		O	O		
Daily recording of unsolicited AEs and concomitant medication/vaccination by subjects (Days 1-30 after each vaccination)	O		O	O		
Return of diary cards for solicited AEs, unsolicited AEs and concomitant medication/vaccination		O		O	O	
Transcription of diary cards for solicited AEs, unsolicited AEs and concomitant medication/vaccination by study staff/investigator		●		●	●	
Recording of serious adverse event [6]	●	●	●	●	●	●
Recording of pIMDs	●	●	●	●	●	●
Recording of pregnancy	●	●	●	●	●	●
Recording of intercurrent medical conditions other than HZ [7]	●	●	●	●	●	
Recording of HZ (intercurrent medical condition) [8]	●	●	●	●	●	●
Recording of concomitant medication/vaccination [9]	●	●	●	●	●	●
Study conclusion						●

Note: The double-line border following Month 5 indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Month 5 for Control group.

Pre-vacc: pre-vaccination, post-vac: post - vaccination; AE: adverse event; HZ: Herpes Zoster.

● 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.

[1]. For women of childbearing potential. If a serum pregnancy test instead of a urine pregnancy test is required by country, local or ethics committee regulations, a blood sample will be collected from women of childbearing potential.

[2]. Pre-vaccination temperatures should always be recorded orally at study sites. In rare situations when there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.
[3]. Any subject with a suspected HZ episode anytime following the first HZ/su dose should not receive the second HZ/su dose or any subject with an event of HZ between Visit Day 1 and any dose of HZ/su vaccine should not receive the upcoming dose(s) of the HZ/su vaccine.
[4]. Subjects will be instructed to contact their study site immediately if they manifest any symptoms they perceive as serious and, in case of pregnancy for women of childbearing potential.
[5]. The preferred route for the daily recording of temperature is oral. When there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.
[6]. All serious adverse events (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.
[7]. According to Section 6.8.
[8]. At Visit Day 1, all subjects will be informed of the signs and symptoms of typical HZ.
[9]. According to Section 6.7.1

Whenever possible the investigator should arrange study visits within the intervals provided in Table 8 and Table 9 for Co-Ad and Control groups, respectively.

Table 8 Intervals between study visits/contact for Co-Ad group

Interval	Optimal length of interval[1]	Allowed interval
Visit Day 1 → Visit Month 1	1 month	30 - 42 days [1]
Visit Day 1 →Visit Month 2	2 months	49 - 83 days [1]
Visit Month 2 →Visit Month 3	1 month	30 - 48 days [1]
Visit Month 2 →Phone contact Month 14	12 months	335 - 395 days

[1]Subjects may not be eligible for inclusion in the :Per-protocol cohort (PPC) for analysis of immunogenicity if they make the study visit outside this interval.

Table 9 Intervals between study visits/contact for Control group

Interval	Optimal length of interval1	Allowed interval
Visit Day 1 → Visit Month 1	1 month	30 - 42 days [1]
Visit Day 1 → Visit Month 2	2 months	60 - 83 days [1]
Visit Month 2 →Visit Month 4	2 months	49 - 83 days [1]
Visit Month 4 →Visit Month 5	1 month	30 - 48 days [1]
Visit Month 4 →Phone contact Month 16	12 months	335 - 395 days

[1]Subjects may not be eligible for inclusion in the PPC for analysis of immunogenicity if they make the study visit outside this interval.

5.7. Detailed description of study procedures

5.7.1. Informed consent

The signed/witnessed/thumb printed 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*, sex, race and ethnicity in the subject's eCRF.

* In Germany, as per local regulations, only the year of birth will be collected.

5.7.4. General medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF.

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.

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 urine/blood pregnancy test prior to any study vaccine administration. Generally, 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(s) may only be administered if the pregnancy test is negative.

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

5.7.7. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.7.8. Assess pre-vaccination body temperature

The body temperature of each subjects needs to be measured prior to any study vaccine(s) administration. The preferred location for measuring temperature in this study will be the oral cavity. If the subject has fever [fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 8 and Table 9).

In rare situations when there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.

5.7.9. Study group and treatment number allocation

Study group and 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 Investigator Lab Manual 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 at least approximately 8 mL of whole blood (to provide at least 2.8 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 Investigator Lab Manual for more details on sample storage conditions.

5.7.11. Study Vaccine(s) administration

- After completing all prerequisite procedures prior to vaccination, the dose(s) of vaccine(s) will be administered IM in the deltoid(s) of the arms according to the administration schedule (refer to Section 6.3 for detailed description of the vaccine(s) administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine(s) administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 8 and Table 9).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine(s), with appropriate medical treatment readily available in case of anaphylaxis.
- Any subjects with an event of HZ between Visit Day 1 and any dose of HZ/su vaccine should not receive the upcoming dose(s) of the HZ/su vaccine.

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 6.7.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.8.

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 and how to report 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 be instructed to measure and record the oral body temperature, and any solicited local/general AEs (i.e. on the day of vaccination and during the next 6 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 29 days occurring after vaccination. 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 Visit Month 1 and Visit Month 3 in Co-Ad group and at Visit Month 1, Visit Month 4 and Visit Month 5 in Control group).
- Any unreturned diary cards will be sought from the subject through telephone call(s) or any other convenient method.
- The investigator will transcribe the collected information into the eCRF in English.

5.7.14. Study conclusion

The investigator will:

- collect and record SAEs, pIMDs, any pregnancy cases, HZ occurences and concomitant medication/ vaccination taken,
- 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 Investigator Lab Manual 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).

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in the respective countries and will only be performed once an independent Ethics Committee or Review Board has approved this research.

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

If additional testing is performed, the marker priority ranking given in Section 5.8.4 may be changed.

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 per-protocol analysis (See Section 10.4 for the definition of cohorts 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 Investigator Lab Manual.

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 10.

Table 10 Biological samples

Sample type	Quantity	Unit	Timepoint Co-Ad group	Timepoint Control group
Whole blood	Approximately 8	mL	Visit Day 1 Visit Month 1 Visit Month 3	Visit Day 1 Visit Month 1 Visit Month 2 Visit Month 5

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.

Serological assays for the determination of anti-gE antibodies will be performed by enzyme-linked immunosorbent assay (ELISA) at a GSK Biologicals' laboratory. Serological assays for the determination of pneumococcal serotype antibodies will be performed by multiplex opsonophagocytosis assay (MOPA) at a laboratory designated by GSK Biologicals using standardized and validated procedures (refer to Table 11).

(Amended 30 January 2018)

Table 11 Humoral Immunity (Antibody determination)

System	Component	Method	Unit	Cut-off	Laboratory
Serum	Varicella Zoster Virus Glycoprotein E Ab IgG	ELISA	mIU/mL	97	GSK Biologicals*
Serum	*Streptococcus pneumoniae* Serotype 01/37 Brugmann Hospital Ab	MOPA	1/dilution	14	University of Alabama at Birmingham**
	Streptococcus pneumoniae Serotype 03/1 Statens Serum Institut Ab			10	
	Streptococcus pneumoniae Serotype 04/2656 Brugmann Hospital Ab			41	
	Streptococcus pneumoniae Serotype 05 Ambrose- Statens Serum Institut Ab			11	
	Streptococcus pneumoniae Serotype 06A Centers for Disease Control Ab			15	
	Streptococcus pneumoniae Serotype 06B/DS2212/94 Centers for Disease Control Ab			29	
	Streptococcus pneumoniae Serotype 07F/46 Brugmann Hospital Ab			28	
	Streptococcus pneumoniae Serotype 09V/112 161/95 Statens Serum Institut Ab			14	
	Streptococcus pneumoniae Serotype 14/58 Brugmann Hospital Ab			14	
	Streptococcus pneumoniae Serotype 18C/4593/40 Statens Serum Institut Ab			26	
	Streptococcus pneumoniae Serotype 19A/DB18 Kansanterveyslaitos Folkhalsoinstitutet Ab			13	
	Streptococcus pneumoniae Serotype 19F/2737 Brugmann Hospital Ab			15	
	Streptococcus pneumoniae Serotype 23F Mac-Statens Serum Institut Ab			22	

[2]GSK Biologicals laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium.

**Pathology Department of Professor, Moon H. Nahm, M.D, WHO Pneumococcal Serology Reference Laboratory, The University of Alabama at Birmingham, Bevill Building, Room 614 (BBRB 614), 845 19th Street South, Birmingham AL, 35294

MOPA: multiplex opsonophagocytosis assay; ELISA: enzyme-linked immunosorbent assay; Ab: antibody; IgG: immunoglobulin G; *S pneumoniae: Streptococcus pneumoniae.*

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

The GSK Biologicals'/ ***contract research organizations' (CRO)*** clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals'/ ***CROs'*** clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department. ***Clinical laboratories contracted by GSK also conform to Good Laboratory Practice guidelines and operate in compliance with regulatory standards.***

(Amended 30 January 2018)

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 12 and Table 13 for Co-Ad and Control groups, respectively.

Table 12 Immunological read-outs for Co-Ad group

Blood sampling timepoint		No. subjects	Component
Type of contact and timepoint	Sampling timepoint		
Visit Day 1 [1]	*Prevenar13* pre-vaccination	456	*S pneumoniae* 01 Ab
			S pneumoniae 03 Ab
			S pneumoniae 04 Ab
			S pneumoniae 05 Ab
			S pneumoniae 06A Ab
			S pneumoniae 06B Ab
			S pneumoniae 07F Ab
			S pneumoniae 09V Ab
			S pneumoniae 14 Ab
			S pneumoniae 18C Ab
			S pneumoniae 19A Ab
			S pneumoniae 19F Ab
			S pneumoniae 23F Ab
	HZ/su pre-vaccination	456	VZV Glycoprotein E Ab IgG
Visit Month 1	*Prevenar13* post-vaccination	456	*S pneumoniae* 01 Ab
			S pneumoniae 03 Ab
			S pneumoniae 04 Ab
			S pneumoniae 05 Ab
			S pneumoniae 06A Ab
			S pneumoniae 06B Ab
			S pneumoniae 07F Ab
			S pneumoniae 09V Ab
			S pneumoniae 14 Ab
			S pneumoniae 18C Ab
			S pneumoniae 19A Ab
			S pneumoniae 19F Ab
			S pneumoniae 23F Ab
Visit Month 3	HZ/su post-vaccination	456	VZV Glycoprotein E Ab IgG

Ab: antibody; IgG: immunoglobulin G; *S pneumoniae: Streptococcus pneumoniae;* VZV: Varicella Zoster Virus.
[1] In case of inadequate samples from Visit Day 1, anti-gE testing (ELISA) will be prioritized over testing for pneumococcal serotype antibodies (MOPA).

Table 13 Immunological read-outs for Control group

Blood sampling timepoint		No. subjects	Component
Type of contact and timepoint	**Sampling timepoint**		
Visit Day 1	*Prevenar13* pre-vaccination	456	*S pneumoniae* 01 Ab
			S pneumoniae 03 Ab
			S pneumoniae 04 Ab
			S pneumoniae 05 Ab
			S pneumoniae 06A Ab
			S pneumoniae 06B Ab
			S pneumoniae 07F Ab
			S pneumoniae 09V Ab
			S pneumoniae 14 Ab
			S pneumoniae 18C Ab
			S pneumoniae 19A Ab
			S pneumoniae 19F Ab
			S pneumoniae 23F Ab
Visit Month 1	*Prevenar13* post-vaccination	456	*S pneumoniae* 01 Ab
			S pneumoniae 03 Ab
			S pneumoniae 04 Ab
			S pneumoniae 05 Ab
			S pneumoniae 06A Ab
			S pneumoniae 06B Ab
			S pneumoniae 07F Ab
			S pneumoniae 09V Ab
			S pneumoniae 14 Ab
			S pneumoniae 18C Ab
			S pneumoniae 19A Ab
			S pneumoniae 19F Ab
			S pneumoniae 23F Ab
Visit Month 2	HZ/su pre-vacc	456	VZV Glycoprotein E Ab IgG
Visit Month 5	HZ/su post-vacc	456	VZV Glycoprotein E Ab IgG

Ab: antibody; IgG: immunoglobulin G; *S pneumoniae: Streptococcus pneumoniae;* VZV:Varicella Zoster Virus

5.8.5. Immunological correlates of protection

No generally accepted immunological correlate of protection against HZ has been demonstrated so far for the gE antigen used in the HZ/su study vaccine.

No correlate of protection for pneumococcal conjugate vaccines for use in adults has been established.

The investigator is encouraged to share the immunological assay results for non-responders with the study subjects.

For the subjects identified as non-responders, it remains the responsibility of the investigator in charge of the subject's clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

6. STUDY VACCINES AND ADMINISTRATION

6.1. Description of study vaccines

The study vaccine to be used has been developed and manufactured by GSK Biologicals. The *Prevenar13* vaccine is marketed by Pfizer Inc..

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

The vaccines are labelled and packed according to applicable regulatory requirements.

Commercial vaccine(s) are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

The characteristics of the study vaccines are presented in Table 14.

Table 14 Study vaccines

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered	No. 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
	$AS01_B$	MPL=50µg; QS21=50µg; Liposomes per 0.5 mL of reconstituted vaccine	Liquid in a monodose vial		
Prevenar13	Prevenar13	13 pneumococcal 13 polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), conjugated to cross-reactive material 197 carrier protein and adsorbed on aluminum phosphate (PS1=2.2µg CRM197; PS3=2.2µg CRM197; PS4=2.2µg CRM197; PS5=2.2µg CRM197; PS6A=2.2µg CRM197; PS6B=4.4µg CRM197; PS7F=2.2µg CRM197; PS9V=2.2µg CRM197; PS14=2.2µg CRM197; PS18C=2.2µg CRM197; PS19A=2.2µg CRM197; PS19F=2.2µg CRM197; PS23F=2.2µg CRM197; $AlPO_4$=125µg Al3+)	Homogenous white suspension after shaking (in pre-filled syringe)	0.5 mL	1

HZ/su = Herpes Zoster subunit vaccine; VZV = Varicella Zoster Virus; gE = recombinant purified envelope glycoprotein E; µg = microgram; mL = milliliter; $AS01_B$ = Adjuvant System $AS01_B$; MPL: 3-O-desacyl-4'-monophosphoryl lipid A.
*QS21: Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation).

6.2. Storage and handling of study vaccine(s)

The study vaccine(s) 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 SPM for more details on storage of the study vaccine(s).

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

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

Refer to the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine(s).

6.3. Dosage and administration of study vaccines

For HZ/su:

After reconstitution, the vaccine should be used promptly; if this is not possible, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

For Prevenar13:

Prevenar13 is a commercially available vaccine and should be administered in accordance with the instructions provided in the manufacturer's product label/packaging insert.

Both vaccines will be administered as indicated in Table 15 and Table 16. The vaccines should be administered by IM injection into the deltoid muscle of different arms, using a standard aseptic technique. For subjects in the Co-Ad group at Visit Day 1, the HZ/su and *Prevenar13* vaccinations must be administered in different arms.

Table 15 Dosage and administration for the Co-Ad group

Type of contact and timepoint	Treatment name	Volume to be administered	Route	Site	
				Location	Laterality
Visit Day 1	HZ/su	0.5 ml	IM	Deltoid	Non-dominant
	Prevenar13	0.5 ml	IM	Deltoid	Dominant
Visit Month 2	HZ/su	0.5 ml	IM	Deltoid	Non-dominant [1]

IM: Intramuscular.
[1] In rare situations when there is no alternative, the injection may be given in the other arm.

Table 16 Dosage and administration for the Control group

Type of contact and timepoint	Treatment name	Volume to be administered	Route	Site	
				Location	Laterality[1]
Visit Day 1	*Prevenar13*	0.5 ml	IM	Deltoid	Dominant
Visit Month 2	HZ/su	0.5 ml	IM	Deltoid	Non-dominant
Visit Month 4	HZ/su	0.5 ml	IM	Deltoid	Non-dominant

IM: Intramuscular.
[1] In rare situations when there is no alternative, the injection may be given in the other arm

6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 30% 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 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(s).
- Pregnancy.
- If the subject experiences an SAE judged to be vaccine-related by the investigator.
- The occurrence of a new potential immune-mediated diseases (pIMDs) or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine(s)/product(s).

  Refer to Section 8.1.5.1 for the definition of pIMDs.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.

- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- If the subject experiences an event of HZ between the first and the second dose of HZ/su or between Visit Day 1 and any dose of HZ/su vaccine (Refer Section 5.5 and 6.8).

The following events constitute contraindications to administration of HZ/su study 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, or withdrawn at the discretion of the investigator (Time windows between visits are given in Table 8 and Table 9).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 38.0°C / 100.4°F. The preferred location for measuring 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.

6.6. Warnings and precautions

Refer to the approved product label/package insert of *Prevenar13*.

6.7. Concomitant medications/products and concomitant vaccinations

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

6.7.1. Recording of concomitant medications/products and concomitant vaccinations

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

- All concomitant medications/products, except vitamins and dietary supplements, administered during 30 days following each dose of study vaccine (Day 1 to Day 30).
- Relevant medications/products administered during the period.
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ending 30 days after the last dose, and any concomitant vaccination against HZ or pneumococcal vaccine (other than the study vaccines) during the study period.
- 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 ≥ 38.0°C/100.4°F regardless the location of measurement]. The preferred location for measuring temperature in this study will be the oral cavity.

- Any concomitant medications/products/vaccines listed in Section 6.7.2.
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered during the study period for the treatment of a SAE /pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.
- Any concomitant medication administered for the treatment of confirmed or suspected HZ or any HZ-related complications (including pain) at any time during the study period.

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

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis. See Section 10.4 for cohorts 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. >14 days in total) up to the last blood sampling. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period up to the last blood sampling (e.g. infliximab).
- A vaccine not foreseen by the study protocol administered during the period starting 30 days before and ending 30 days after the last dose of study vaccine administration.
  In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.
- Immunoglobulins and/or any blood products administered during the study period up to the last blood sampling.
- Receipt of a vaccine against HZ or VZV or pneumococcal vaccine other than the study vaccine during the study period.

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

At each study visit subsequent to the first vaccination/the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition (IMC). If it is the case, the condition(s) must be recorded in the eCRF. An IMC is defined as a condition that has the capability of confounding the immune response to the study vaccine or its interpretation. Subjects may be eliminated from the Per-protocol cohort for immunogenicity if, during the study, they incur an IMC.

Examples of IMCs include cases of HZ or a confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, HIV infection).

All IMCs including HZ will be recorded until Visit Month 3 for subjects in the Co-Ad group and Visit Month 5 for subjects in the Control group. All IMCs will be recorded in AE/SAE screens as appropriate**.**

Occurrences of HZ from Visit Month 3 (Co-Ad group) and Visit Month 5 (Control group) are to be reported till study end (phone contact at Month 14 for the Co-Ad group and Month 16 for the Control group) but will not be considered as IMCs.

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 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 study vaccine(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s) administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

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

Examples of an AE DO NOT include:

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

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

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

c. Requires hospitalization or prolongation of existing hospitalization,

   Note: In general, hospitalization signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have

been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, OR

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

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

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

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

Table 17 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 18 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

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

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

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 19.

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 19 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, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)

Vasculitides	Blood disorders	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 aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

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

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

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

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

8.2.1. Pregnancy

Female subjects who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine(s) 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 study vaccine(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 approximately 12 months following administration of the last dose of study vaccine for each subject. See Section 8.4 for instructions on reporting of SAEs.

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

SAEs that are related to the study vaccine(s) will be collected and recorded from the time of the first receipt of study vaccine(s) until the subject is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent 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 approximately 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 approximately 12 months following administration of the last dose of study vaccine. See section 8.4 for instructions on reporting of pIMDs.

Intercurrent medical conditions other than HZ (see Section 6.8) will be recorded from Day 1 until Month 3 for subjects from the Co-Ad group and Month 5 for subjects from the Control group. Intercurrent medical conditions will be recorded in AE/SAE screens as appropriate.

The occurrence of HZ will constitute an AE/SAE as appropriate. The reporting period for cases of HZ will be from Day 1 to study end.

An overview of the protocol-required reporting periods for AEs, SAEs, pIMDs, pregnancies, and intercurrent medical conditions (including HZ) is given in Table 20.

Table 20 Reporting periods for collecting safety information

Event / Time of reporting	Visit: Day1 pre-vacc[1]	Visit: Day1 post-vacc	Visit: 7 days post-vacc	Visit: 30 days post-vacc		Visit: Month 2	Visit: 7 days post-vacc	Visit: 30 days post-vacc		Visit: Month 4[2]	Visit: 7 days post-vacc	Visit: 30 days post-vacc		Study Conclusion Month 14 (Co-Ad group) /Month 16 (Control group)
Solicited local and general AEs														
Unsolicited AEs														
SAEs[3]														
Pregnancies														
pIMDs														
HZ (see Section 6.8)[4]														
IMCs (see Section 6.8)[4]														

Pre-vacc: pre-vaccination; post-vacc: post-vaccination; AE: adverse event; SAE: serious adverse event; pIMDs: potential Immune Mediated Diseases; HZ: Herpes Zoster; IMC: intercurrent medical condition.

[1] Includes the period on Visit Day 1 from the time the subject consents to participate in the study till administration of study vaccine.

[2] Only for subjects from Control Group.

[3] All 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 study vaccine.

[4] All IMCs (including HZ) should be reported from Visit Day 1 until Visit Month 3 for subjects from the Co-Ad group and Visit Month 5 for subjects from the Control group. From Visit Month 3 (Co-Ad group) and Visit Month 5 (Control group), HZ cases will be collected till the end of the study but not considered as IMCs.

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 20. 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 study vaccine(s), 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(s) or since the previous visit?*'

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

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

8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

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

Table 21 Intensity scales for solicited symptoms in adults

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 ≥ 38.0°C / 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity. When there is no other alternative, the temperature may be recorded by other route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented.

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

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

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

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

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (such an AE would, for example, prevent attendance at work/school 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 study vaccine(s) and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the AE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine(s) will be considered and investigated. The investigator will also consult the IB and/or and/or SmPC and/or Prescribing Information for marketed products to determine his/her assessment.

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

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

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

YES	:	There is a reasonable possibility that the study vaccine(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(s), 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 hospitalization, or an otherwise unscheduled visit to or from nurses practitioners, health care workers or 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 22, 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 22, 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 22, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 22 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

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

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

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

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

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

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

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

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

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

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

8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

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

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

8.4.5. Reporting of pIMDs to GSK Biologicals

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

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

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

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

When additional SAE, pregnancy, or pIMD information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 22.

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 study vaccine(s) 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 22).

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

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

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

The investigator will follow subjects:

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

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

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible

the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.5.2. Follow-up of pregnancies

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

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

8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE / pIMDs should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.7).

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.

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.
- Unsolicited non-serious adverse event.
- Solicited 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 has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF .

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

9.2.2. Subject withdrawal from study vaccine(s)

A 'withdrawal' from the study vaccine(s) refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the study vaccine(s) 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 study vaccine(s) will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment 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.
- Unsolicited non-serious adverse event.
- Solicited adverse event
- Not willing to be vaccinated
- Other (specify).

9.3. Extension study

During the study conclusion visit/contact, the investigator will ask each subject if he/she is interested in participating in a long-term study. If a subject is not interested in participating in the long-term study the reason for refusal will be documented in the subject's eCRF.

10. STATISTICAL METHODS

10.1. Primary endpoints

- HZ/su immunogenicity:
  - Vaccine response for anti-gE humoral immunogenicity, as determined by ELISA, in subjects from the Co-Ad group at one month post-dose 2, at Visit Month 3.
  - Anti-gE antibody concentrations as determined by ELISA at one month post-dose 2, at Visit Month 3 for the Co-Ad group and Visit Month 5 for the Control group.
- Pneumococcal vaccine immunogenicity:
  - Anti-pneumococcal antibody titers for the 13 following serotypes as determined by MOPA at one month post-dose at Visit Month 1: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

The criteria used to define the VRR is given in Section 10.7.1.

10.2. Secondary endpoints

- Occurrence of solicited local and general symptoms:
  - Occurrence, duration and intensity of each solicited local symptom within 7 days (Days 1 - 7) after each vaccination,
  - Occurrence, duration, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 1 to 7) after each vaccination.
- Occurrence of unsolicited AEs:
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs within 30 days (Days 1 to 30) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of SAEs:
  - Occurrence and relationship to vaccination of all SAEs from first vaccination at Day 1 up to 30 days post last vaccination.
  - Occurrence and relationship to vaccination of all SAEs during the period starting after 30 days post last vaccination up to study end.
- Occurrence of pIMDs:
  - Occurrence and relationship to vaccination of any pIMDs from first vaccination at Day 1 up to 30 days post last vaccination.
  - Occurrence of any pIMDs during the period starting after 30 days post last vaccination up to study end.

10.3. Determination of sample size

Assumptions used for the sample-size calculations come from data available from study Zoster-010 (112077) and the *Prevenar13* assessment report [EMA, 2011] which provides a summary of the data used by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to extend the indication of *Prevenar13* to include adults aged ≥50 YOA.

The evaluation of the VRR following administration of two doses of HZ/su will be one of the co-primary objectives. The objective will be met if the LL of the 95% CI of VRR is equal to or more than 60% (criterion used in other studies in the HZ/su vaccine program). In the absence of correlate of protection or threshold level, this criterion ensures that an acceptable percentage of subjects meet GSK definition of responder (a 4-fold increase in anibody concentration/titer). Based on ZOSTER-010 (112077) study results, the vaccine response assumed in healthy adults (≥50 years of age) is 95%.

The humoral immune responses to the 13 serotypes of *Prevenar13* one month post-dose and to HZ/su (anti-gE) one month post-dose 2 will be the two other co-primary objectives and will be compared to demonstrate non-inferiority of the Co-Ad to the Control groups.

Non-inferiority with respect to the antibody responses to gE will be demonstrated if the ULs of the 95% CIs of the GMC ratios (Control group divided by Co-Ad group) are below the pre-defined clinical limit of 1.5 (based on variability of the assays used in the HZ/su vaccine program), one month post-dose 2 (Visit Month 3 for the Co-Ad group and Visit Month 5 for the Control group).

Non-inferiority with respect to the immune responses to the 13 vaccine pneumococcal serotypes will be demonstrated if the UL of the 95% CI of the MOPA GMTs ratios (Control group divided by Co-Ad group) is below the pre-defined clinical limit of 2 (based on variability of the assays used) for each of 13 pneumococcal vaccine serotypes, one month post-dose (Month 1).

No adjustment is needed for the type I error due to multiple comparison since fixed sequence test which allows full alpha propagation in pre-ordered family of hypotheses will be used.

The global power to meet all co-primary objectives with 410 evaluable subjects in Co-Ad and Control groups is approximately 91% (Table 23). Assuming that about 10% of the subjects enrolled are non-evaluable (e.g. due to dropout, bad sample), approximately 912 subjects will need to be enrolled (456 subjects in each treatment group).

Table 23 Power to demonstrate VRR objective and non-inferiority of the immunogenicity of HZ/su and *Prevenar13* co-administered compared to Control group

Family 1: HZ/su: VVR*(1-sided test with alpha = 2.5%)				
Endpoint	Threshold	VR assumed	Total β	Power
VRR in Co-Ad group	0.60	95%	0.001%	99.99%
***Family 2: HZ/su*: non-inferiority* (1-sided test with alpha = 2.5%) N=410**				
Endpoint	Standard deviation	δ	Total β	Power
Anti-gE GMC ratio	0.35	1.5	0.001 %	99.99 %
***Family 3: Prevenar13*: Non-inferiority* (1-sided test with alpha = 2.5%) N=410**				
Endpoint (13 vaccine pneumococcal serotypes)	Standard deviation	δ	Total β	Power
3 GMT ratio	0.660	2	0.001%	99.99%
19A GMT ratio	0.644	2	0.001%	99.99%
1 GMT ratio	0.798	2	0.029%	99.97%
18C GMT ratio	0.891	2	0.203%	99.80%
4 GMT ratio	0.906	2	0.260%	99.74%
6A GMT ratio	0.919	2	0.320%	99.68%
5 GMT ratio	0.931	2	0.383%	99.62%
19F GMT ratio	0.971	2	0.664%	99.33%
6B GMT ratio	0.995	2	0.891%	99.11%
7F GMT ratio	1.014	2	1.107%	98.89%
9V GMT ratio	1.021	2	1.194%	98.81%
14 GMT ratio	1.045	2	1.530%	98.47%
23F GMT ratio	1.094	2	2.398%	97.60%
Global β to show non-inferiority			~9%	
Global power				**~91%**

VRR: vaccine response rate; gE: Varicella Zoster Virus glycoprotein E; GMT: geometric mean titer; GMC: geometric mean concentration.

* Pass 12, alpha = 2.5%, for VRR: Exact test, for non-inferiority one-sided equivalence of means.

For gE: non-inferiority limit = 0.176 (=log10(1.5)), power under equal GMC

For each pneumococcal serotype: non-inferiority limit = 0.301 (=log10(2)), variability for each of the 13 vaccine pneumococcal serotype taken from the EMA assessment report for *Prevenar13* and multiplied by 1.1, power under equal GMT.

10.4. Cohorts for Analyses

10.4.1. Total vaccinated cohort

The Total vaccinated cohort (TVC) will include all subjects with at least one vaccine administration documented:

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

The TVC analysis will be performed per treatment actually administered (at Dose 1).

10.4.2. Per-protocol cohort for analysis of immunogenicity

The Per-protocol cohort for analysis of immunogenicity will include all evaluable subjects:

- who meet all eligibility criteria,
- who comply with the procedures and intervals allowed for the analysis,
- who do not meet any of the criteria for elimination during the study,
- for whom data concerning immunogenicity endpoint measures are available.

10.5. Derived and transformed data

- Immunogenicity

The cut-off value is defined by the laboratory before the analysis and is described in Section 5.8.3.

10.5.1. Handling of missing data

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

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

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

10.6. Analysis of demographics

Demographic characteristics (age, sex, race and ethnicity) will be tabulated per treatment group.

The mean age (plus range and standard deviation [SD]) of the enrolled subjects, as a whole, and per treatment group will be calculated. The distribution of subjects enrolled among the study sites will be tabulated as a whole and per treatment group.

The same tabulations might be performed by age category if deemed necessary.

10.7. Analysis of immunogenicity

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

10.7.1. Humoral immune response

- A seronegative subject is a subject whose antibodies concentration/titer is below the cut-off value (cut-off value is defined by the laboratory prior to the analysis).
- A seropositive subject is a subject whose antibodies concentration/titer is greater than or equal to the assay cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.
- The VRR for anti-gE 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 GMC/GMT calculations are performed by taking the anti-log of the mean of the log concentration transformations. Antibody 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/GMT calculation.

10.7.2. Statistical considerations for confirmatory objectives

All analyses will be performed overall and by age stratum, if the number of subjects enrolled is sufficient in each stratum.

For the multiplicity adjustment, all hypotheses will be ranked into three families and one subfamily according to the power of test (Table 23). Fixed sequence testing which allows for full alpha propagation in pre-ordered hypotheses families will be applied in the following manner:

Family 1:

In the Co-Ad group, for anti-gE, at one month post-dose 2:

- The VRR and 95% CI will be computed.

The objective is met if the LL of the 95% CI is ≥60%.

Family 2:

For anti-gE, at one month post-dose 2:

- The 95% CI of the group GMCs ratio will be computed using an analysis of covariance (ANCOVA) model on the log10 transformation of the concentrations. The pre-vaccination log-transformed antibody concentrations will be included as continuous covariate and the ANCOVA model will include the vaccine group and age strata as fixed effects.

In terms of concentrations, the Co-Ad group will be considered non-inferior to the Control group if the UL of the 95% CI for the GMC ratio of the Control group to the Co-Ad group is <1.5.

Family 3:

For each vaccine pneumococcal serotype (according to the order in Table 23), one month post-dose:

- The 95% CI of the group MOPA GMT ratios will be computed using an AN***C***OVA model on the log10 transformation of the titers. ***The pre-vaccination log-transformed antibody titers will be included as a continuous covariate.*** The AN***C***OVA model will include the vaccine group and age strata as fixed effects. **(Amended 30 January 2018)**

In terms of MOPA GMTs, the Co-Ad group will be considered non-inferior to the Control group if the UL of the 95% CI for the MOPA GMTs ratio of the Control group to the Co-Ad group is <2 for each of the 13 vaccine serotypes.

10.8. Analysis of safety

The analysis for safety will be based on the TVC; all safety analyses may also be performed by age strata (50-59, 60-69 and ≥70 YOA).

When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g. using windows such as Days 1 to 7, Days 1 to 30 and more than 30 days post-vaccination).

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

- The number and percentage of subjects with at least one local solicited AE, with at least one general solicited AE, and with any solicited AE during the 7-day follow-up period with exact 95% CIs after each vaccine dose and overall by vaccination group will be provided;
- 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;

- Number of days with each individual solicited local and general AE during the solicited 7-day follow-up period;
- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA preferred term 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 will be tabulated;
- SAEs, including fatalities and withdrawal due to AE(s) will be described in detail.

10.9. Interpretation of analyses

All co-primary objectives will be evaluated using a one-sided Type I error of 2.5% (as already justified by fixed sequential testing procedure, no alpha adjustment needed). The trial will be considered conclusive if all co-primary objectives 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 analysis will be performed in the following steps:

1. ***Analysis of the co-primary immunogenicity objectives will be performed at the end of the active phase on data as clean as possible. A confirmatory re-analysis will be done at the end of the study using the final database. In addition, analyses of secondary objectives will also be performed at the end of the active phase.*** **(Amended 30 January 2018)**..
2. Analyses on safety data will be performed when all data up to study end (i.e., phone contact at Month 14 for Co-Ad group and phone contact at Month 16 for Control group) will be available and cleaned. **(Amended 30 January 2018)**

An integrated clinical study report containing all data will be written and made available to the investigators.

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, public disclosure requirements and publications must be fulfilled.

11.1. electronic Case Report Form instructions

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

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

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction 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 other items, 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 an eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF entries by comparing them with the source data that will be made available by the investigator for this purpose.

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

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. 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 25 years after completion of the study report.

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

11.4. Quality assurance

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

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

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

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

As per EU regulation, summaries of the results of GSK interventional studies (phase I-IV) in adult population conducted in at least one EU member state will be posted on publicly available EMA registers within 12 months of EoS (as defined in the protocol) in the concerned EU member state. However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results one year in the concerned EU member state, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

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

11.6. Provision of study results to investigators

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

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

11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

12. COUNTRY SPECIFIC REQUIREMENTS

12.1. Germany

Explanatory statement concerning Gender Distribution (Article 7, paragraph 2 (12) of the German GCP ORDER)

EudraCT Number: 2017-001220-22

Study Identifier: 204487 (ZOSTER-059 PRI)

Compound Number: GSK1437173A

Title of Study: A Phase IIIB, randomized, open-label, multicenter clinical trial to assess the immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A when co-administered with *Prevenar13*™ in adults aged 50 years and older.

There is no intention to conduct specific analyses investigating the relationship between gender of subjects and the immunogenicity and safety of GSK Biologicals' lyophilized formulation of the Herpes Zoster (HZ) subunit (HZ/su) vaccine (GSK1437173A). The ratio of male to female subjects recruited into study Zoster-059 PRI is expected to be in line with the demographics of the population aged 50 years and older in the Member State.

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APPENDIX A LABORATORY ASSAYS

Specific antibody measurements:

Anti-gE ELISA: Anti-gE antibody concentrations will be measured using an anti-gE ELISA. Diluted blood serum samples of study subjects will be added to microtiter wells pre-coated with gE antigen. Secondary peroxidase-conjugated anti-human Abs will be added, which bind to the primary human anti-gE Abs. After incubation of the microtiter wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE antibody concentrations are calculated from a standard curve. The assay cut-off is 97 mIU/mL.

(Amended 30 January 2018)

Pneumococcal serotype antibodies OPA: Opsonophagocytic activity for antibodies against each of the pneumococcal serotype will be measured by an opsonophagocytosis mulitplex killing-assay (MOPA) using the HL 60 cell line as the phagocytic effector cell [Romero-Steiner, 1997]. The results will be presented as the dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions.

APPENDIX B CLINICAL LABORATORIES

Table 24 GSK Biologicals' laboratories

(Amended 30 January 2018)

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Rue de l'Institut, 89 - B-1330 Rixensart – Belgium

Table 25 Outsourced laboratories

Laboratory	Address
University of Alabama at Birmingham	Pathology Department of Professor, Moon H. Nahm, M.D, WHO Pneumococcal Serology Reference Laboratory, The University of Alabama at Birmingham, Bevill Building, Room 614 (BBRB 614), 845 19th Street South, Birmingham AL, 35294
Q^2 Solutions Clinical Trials (US)	27027 Tourney Road, Suite 2E Valencia, CA 91355 USA
Q^2 Solutions Clinical Trials (UK)	Unit B1, Parkway West Industrial Estate Cranford Lane – Heston, Middlesex TW5 9QA UK

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Vaccine Value & Health Science (VVHS) **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	204487 (ZOSTER-059 PRI)
EudraCT number	2017-001220-22
Amendment number:	Amendment 1
Amendment date:	30 October 2017
Co-ordinating author:	PPD, Scientific Writer, contractor for GSK Biologicals

Rationale/background for changes:

- Following the initial approval of the GlaxoSmithKline (GSK) Biologicals' HZ/su vaccine, this protocol was amended to indicate that the Trademark is *Shingrix*. In addition, the term "candidate" vaccine has been replaced by "study" vaccine throughout the protocol in Sections 1.1, 1.3, 5.8.5 and 6.1; and the term "investigational" vaccine has been replaced by "study" vaccine in Sections 1.3.1 and 1.3.3.

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

TRADEMARKS:

Trademarks of the GSK group of companies		Generic description
Shingrix		***Zoster Vaccine Recombinant, Adjuvanted***

Section 1.1 1.1 Background:

GlaxoSmithKline (GSK) Biologicals' ~~candidate~~***study***vaccine ***(Shingrix)*** for the prevention of HZ is a recombinant subunit (su) vaccine consisting of VZV glycoprotein E (gE) as antigen and an adjuvant system $AS01_B$. It has been evaluated in several studies in healthy adults and shown to elicit strong cellular and humoral immune responses. The safety and reactogenicity profile of the ~~candidate~~***study*** vaccine was also acceptable.

Please refer to the current Investigator Brochure (IB) for information regarding the pre-clinical and clinical studies of GSK Biologicals' ~~candidate~~***study*** HZ/su vaccine.

Section 1.3 Benefit : Risk Assessment:

Please refer to the current IB for the summary of potential risks and benefits of GSK Biologicals' ~~candidates~~***study*** HZ vaccine (HZ/su).

Section 1.3.1 Risk Assessment:

Important Potential Risk	Data/Rationale for Risk	Mitigation Strategy
~~Investigational~~***Study*** vaccine: HZ/su		

Section 1.3.3 Overall Benefit: Risk Conclusion:

Considering the measures taken to minimize risk to subjects participating in this study, the potential or recognized risks identified in association with the ~~investigationals~~***study*** HZ vaccine (HZ/su) and study procedures are justified by the potential benefits (prevention of HZ and related complications) that may be afforded to the subjects receiving HZ/su.

Section 5.8.5 Immunological correlates of protection:

No generally accepted immunological correlate of protection against HZ has been demonstrated so far for the gE antigen used in the HZ/su ~~candidates~~***study*** vaccine

Section 6.1 Description of study vaccines:

The ~~candidates~~***study*** vaccine to be used has been developed and manufactured by GSK Biologicals. The *Prevenar13* vaccine is marketed by Pfizer Inc.

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

GlaxoSmithKline Biologicals

Vaccine Value & Health Science (VVHS)

Protocol Amendment 2

eTrack study number and Abbreviated Title	204487 (ZOSTER-059 PRI)
EudraCT number	2017-001220-22
Amendment number:	Amendment 2
Amendment date:	30 January 2018
Co-ordinating author:	PPD, Scientific Writer, contractor for GSK Biologicals
Contributing authors	• PPD, ***Clinical and Epidemiology Scientist*** ~~G Clinical Research and Development Lead, Business & Decision Life Sciences for GSK Biologicals~~ • PPD, ***Clinical and Epidemiology Project Leader*** • PPD, ***Study Delivery Lead, Synteract Inc. for GSK Biologicals*** • PPD, ***Global Regulatory Affairs*** • PPD, ***Clinical Safety representative*** • PPD ***Study Data Manager (Tata Consultancy Services for GSK Biologicals)***

Rationale/background for changes:

Major change

- This amendment is in response to the Center for Biologics Evaluation and Research (CBER) comments on Protocol Amendment 1, received on 09-January-2018, requesting clarification on 1. the adjustment for baseline titers in the computation of the Multiplex Opsonophagocytosis Assay (MOPA) Geometric Mean Titers (GMT) ratios (Section 10.7.2) and 2. time points for primary evaluations on co-primary immunogenicity objectives (Section 10.10.1).

Other changes

- The tradename for pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed) in Canada has been corrected to *Prevnar13* from *Prevenar13*.
- The laboratory to be used for MOPA testing has been selected and is presented in Appendix B.
- A typographical error in the estimated number of subjects in each age strata and study group has been corrected. Table 4 reflects the correct number of subjects for age stratification.

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

Protocol Amendment 2 Sponsor Signatory Approval

Sponsor signatory	PPD ~~Clinical and Epidemiology Project Leader (CEPL), Zoster Program, Beligian Research and Development Center (RDC)~~ PPD ***Clinical and Epidemiology Project Leader, Zoster Program, US Research and Development Center (RDC)***

List of abbreviations:

CBER:	***Center for Biologics Evaluation and Research***
CRO:	***Contract Research Organization***

Trademarks

Trademarks not owned by the GSK group of companies		Generic description
Prevenar13 (Trade name for ~~Canada,~~ Germany and Estonia)/ **Prevnar13** Trade name for ***Canada and*** United States)* Wyeth Pharmaceuticals Inc./Pfizer Inc.		Pneumococcal polysaccharide conjugate vaccine (13-valent adsorbed)

Section 4.1 Number of subjects/centers

Table 4 Age Stratification

Group	Description	Estimated number of subjects
Co-Ad	Subjects 50 to 59 YOA	~~342~~ ***171***
	Subjects 60 to 69 YOA	~~342~~ ***171***
	Subjects ≥70 YOA	~~228~~ ***114***
Control	Subjects 50 to 59 YOA	~~342~~ ***171***
	Subjects 60 to 69 YOA	~~342~~ ***171***
	Subjects ≥70 YOA	~~228~~ ***114***

YOA: years of age.

Section 5.8.3 Laboratory assays

Serological assays for the determination of pneumococcal serotype antibodies will be performed by multiplex opsonophagocytosis assay (MOPA) at ~~a GSK Biologicals' laboratory~~ or in a laboratory designated by GSK Biologicals using standardized and validated procedures (refer to Table 11).

The GSK Biologicals'***/ contract research organizations' (CRO)*** clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals'***/ CROs'*** clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department. ***Clinical laboratories contracted by GSK also conform to Good Laboratory Practice guidelines and operate in compliance with regulatory standards.***

Section 10.7.2 Statistical considerations for confirmatory objectives

Family 3:

The 95% CI of the group MOPA GMT ratios will be computed using an ~~analysis of variance (~~AN***C***OVA~~)~~ model on the log10 transformation of the ~~concentrations/~~ titers. ***The pre-vaccination log-transformed antibody titers will be included as a continuous covariate.*** The AN***C***OVA model will include the vaccine group and age strata as fixed effects.

Section 10.10.1 Sequence of analyses

The analysis will be performed in the following steps:

~~*1.* Analyses after end of active phase at Visit Month 3 for Co-Ad group and Visit Month 5 for Control group will be performed on data as clean as possible, in order to explore the demography as well as reactogenicity and safety. Analysis on the humoral response may also be performed at this point in time if the data is available.. These data will also be available for the purpose of public data disclosure~~.
Analysis of the co-primary immunogenicity objectives will be performed at the end of the active phase on data as clean as possible. A confirmatory re-analysis will be done at the end of the study using the final database. In addition, analyses of secondary objectives will also be performed at the end of the active phase.

2. Analyses on ~~immunogenicity and~~ safety data will be performed when all data up to study end (i.e., phone contact at Month 14 for Co-Ad group and phone contact at Month 16 for Control group) will be available and cleaned. ~~After the study completion, results from both analyses will be presented in a single study report.~~

APPENDIX A LABORATORY ASSAYS

Specific antibody measurements:

Anti-gE ELISA: Anti-gE antibody concentrations will be measured using an anti-gE ELISA. Diluted blood serum samples of study subjects will be added to microtiter wells pre-coated with gE antigen. Secondary peroxidase-conjugated anti-human Abs will be added, which bind to the primary human anti-gE Abs. After incubation of the microtiter wells with a chromogen substrate solution, the enzymatic reaction will be stopped. Optical densities will be recorded and anti-gE antibody concentrations are calculated from a standard curve. The assay 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.~~

APPENDIX B CLINICAL LABORATORIES

Table 24 GSK Biologicals' laboratories

Laboratory	Address
GSK Biological's Clinical Laboratory Sciences, Rixensart	Rue de l'Institut, 89 - B-1330 Rixensart – Belgium
~~GSK Biological's Clinical Laboratory Sciences, Wavre Nord Noir Epine~~	~~Avenue Fleming, 20 - B-1300 Wavre - Belgium~~