Statistical Analysis Plan	
Detailed Title:	A phase IIIb, open-label, multi-country, multi-centre, long-term follow-up study (ZOE-LTFU) of studies 110390 and 113077 (ZOSTER-006/022) to assess the prophylactic efficacy, safety, and immunogenicity persistence of GSK Biologicals' Herpes Zoster subunit (HZ/su) vaccine and assessment of 1 or 2 additional doses on a 0 or 0, 2-month schedule in two subgroups of older adults.
eTrack study number and Abbreviated Title	201190 (ZOSTER-049 EXT:006-022)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 10 February 2017 Amendment 1 Final: 23 September 2019 Amendment 2 Final: 18 March 2021 ***Amendment 3 Final: 20 Sep 2023***

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3 June 2019)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

The complete statistical analysis plan and results presentation is divided into 2 parts: the first part detailing the analyses to be performed (known as SAP, current document) and a second part, annex (-es) (called OPS) describing the flow and format of tables, figures and listings to be annexed to the study report (SR).

LIST OF ABBREVIATIONS

Ab	Antibody
AE	Adverse event
$AS01_B$	MPL, QS21, liposome-based Adjuvant System (50 µg MPL and 50 µg QS21)
ATP	According-To-Protocol
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medical Products for Human use
CI	Confidence Interval
CMI	Cell-Mediated Immunogenicity
CRF	Case Report Form
CSL	Clinical Science Lead
CTRS	Clinical Trial Registry
EL.U/ml	ELISA unit per milliliter
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
CCI [redacted]	
gE	VZV Glycoprotein E
GMC	Geometric mean antibody concentration
GSK	GlaxoSmithKline
HI	Humoral Immunogenicity
HZ	Herpes Zoster
IMC	Intercurrent medical condition
IU/ml	International units per milliliter
LL	Lower Limit of the confidence interval
LTFU	Long-Term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean Geometric Increase
mTVC	Modified Total Vaccinated Cohort
N.A.	Not Applicable

OPS	Output and Programming Specification
PHN	Postherpetic Neuralgia
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals' Internet Randomization System
SD	Standard Deviation
SR	Study Report
SU	Subunit
SYN	Synopsis
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval
VE	Vaccine efficacy
VRR	Vaccine Response Rate

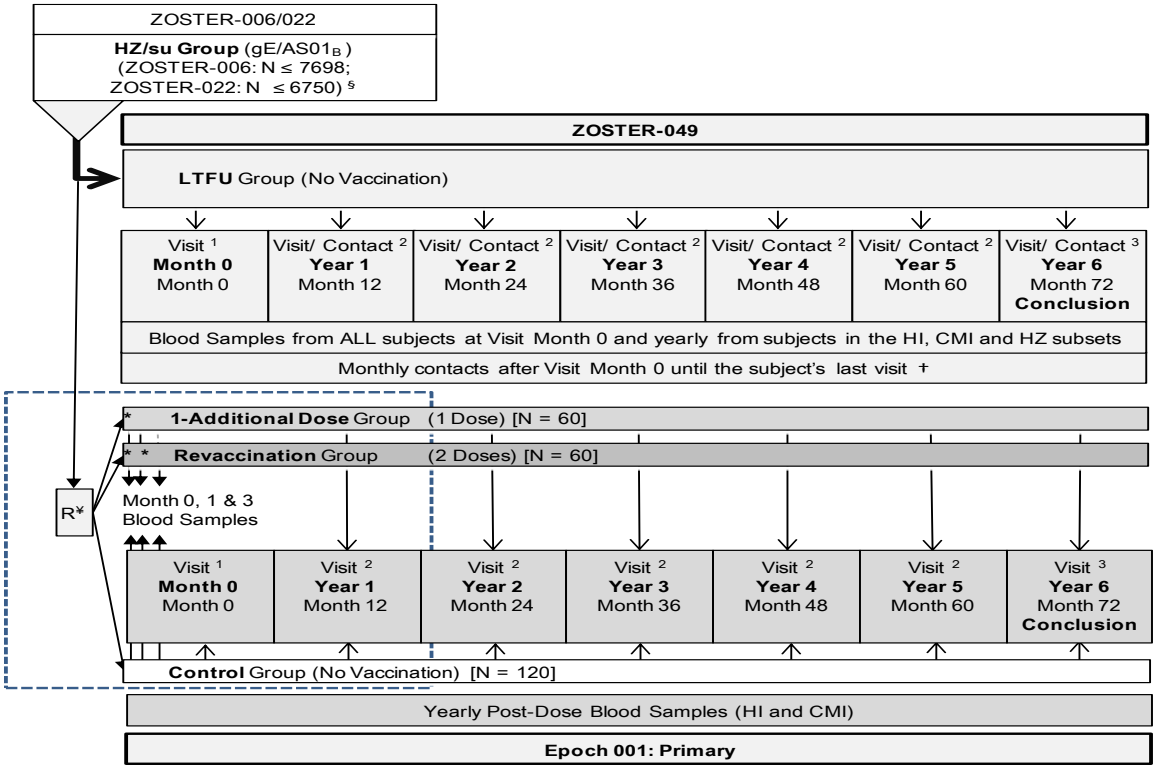
1. DOCUMENT HISTORY

Date	Description of SAP version	Protocol Version
10 FEB 2017	Initial Version	Amendment 2: 19 JAN 2017
23 SEP 2019	Amendment 1 – Following are the changes from initial version: • Addition of VE against HZ related complication under secondary objective/endpoint • Addition of tertiary objective and related analysis • Analysis of efficacy section was updated to mention that VE for PHN and HZ complication will be performed if enough numbers of cases are there to have robust analysis • Additional consideration for safety has been added	Protocol Administrative Change 2: 11 FEB 2019
18 MAR 2021	Amendment 2 - Following are the changes from Amendment 1: • Elimination section was updated to include the carry forward elimination from primary studies • In the derived and transformed section for demography, the calculation for age was updated and interval between the end of the primary studies Z-006/022 and start time for Z-049 has been added. • In the analysis of persistence for LTFU group, the calculation for time frame for 1st visit in Z-049 study has been updated • Editorial changes in the naming of the cohorts.	Amendment 5: 11MAY2020
20 Sep 2023	***Amendment 3 – Following are the changes from Amendment 2 primarily per comments/requests from regulatory agencies: FDA, EMA and Swissmedic.*** • ***Addition of sub-group analysis for vaccine efficacy, immunogenicity persistence, and safety*** • ***Addition of VE sensitivity analysis, VE descriptive analysis and additional computational rule for VE when 0 confirmed case in either HZ/su or Placebo group*** • ***Additional age sub-group analysis planned for the VE*** • ***Specification of elimination has been added as Appendix to the SAP***	Amendment 5: 11MAY2020

Date	Description of SAP version	Protocol Version
	• ***Update in the analysis of safety section to include the specific timeframe of analysis of AEs, non-serious AEs, sub-group analysis*** • ***Update in the persistence modelling for the Immunogenicity on the cohort*** • ***Sensitivity reactogenicity analysis planned in case >1% of subjects documented the presence of a solicited symptom after one dose without having recorded any daily measurement during the 7-day follow-up period following vaccination has been removed***	

2. STUDY DESIGN

Figure 1 Study design overview



§ N = Maximum number of subjects expected for ZOSTER-049 based on the number of subjects in the ZOSTER-006/022 studies.

Note: The interval between the end of ZOSTER-006/022 studies and start of study ZOSTER-049 is depicted by the gray inverted triangle. There is to be a database freeze and unblinding of subjects at the end of the ZOSTER-006/022 studies and before ZOSTER-049 begins. The interval between the end of the ZOSTER-006/022 studies and start of study the ZOSTER-049 will vary per subject and is dependent on receipt of approval or implementing the study in the different participating countries/centres.

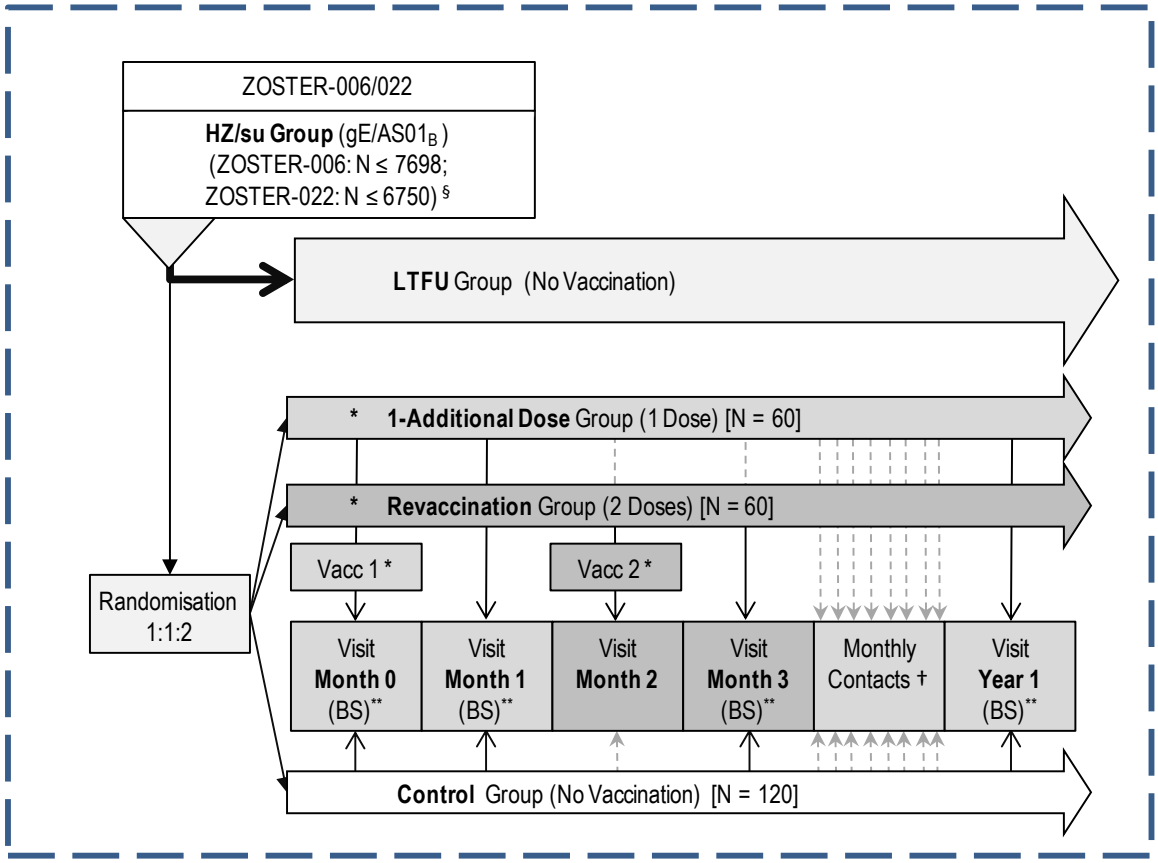
Note: In case of suspected HZ, there are additional visits and phone contacts for follow-up of the HZ episode

[1] A new reference timepoint Visit Month 0 is set for the first visit in ZOSTER-049.

[2] From Visit Month 0 onwards, yearly visits/contacts occur at Months 12, 24, 36, 48, 60 and 72.

[3] Study conclusion takes place at the last yearly visit/ contact.
† Monthly phone contacts will be done to assess HZ cases and safety follow up for all study groups and will NOT occur when subjects have a scheduled visit.
¥ R= Randomisation 1:1:2.
See Figure 2 for study activities up to Year 1 for the 1-Additional Dose, Revaccination and Control groups.

Figure 2 Detailed overview of the 1-Additional Dose, Revaccination and Control groups (Year 1 only)



§ N = Maximum number of subjects expected for ZOSTER-049 based on the number of subjects in the ZOSTER-006/022 studies.
* The two groups (1-Additional Dose and Revaccination, only) will have a HZ/su vaccination (Vacc 1) at Visit Month 0 and the Revaccination group will have a second dose (Vacc 2) at Visit Month 2.
** Blood sampling (BS) as in the Sampling schedule (See protocol)
Refer to Figure 1 for study activities beyond Year 1.
† Monthly phone contacts will be done to assess HZ cases and safety follow up for all study groups and will NOT occur when subjects have a scheduled visit.

- Experimental design: Phase IIIb, open-label, multi-centre, multi-country study with 4 groups.
- Duration of the study: Each subject will be followed for approximately 6 years.
- Epoch 001: LTFU of studies ZOSTER-006/022 starting at Visit Month 0 and ending at Visit Year 6 (Month 72) and assessment of 1 or 2 additional doses in two groups of subjects.
- Study groups: The study will be comprised of four study groups as follows:

LTFU Group: Subjects from this group [N ≤ 14,000] will be followed for vaccine efficacy (VE) and safety. In addition, immunogenicity will be followed in subjects that were part of the immunogenicity subset (HI) in the ZOSTER-006/022 studies and Cell-Mediated Immunity (CMI) subset from the ZOSTER-006 study;

1-Additional Dose Group: Subjects from this group [N = 60] will receive 1 additional dose of the HZ/su vaccine, at the time of enrolment, to assess the immunogenicity, reactogenicity and safety of 1 additional dose;

Revaccination Group: Subjects from this group [N = 60] will be revaccinated with 2 additional doses of the HZ/su vaccine, on a 0, 2-month schedule from the time of enrolment, to assess the immunogenicity, reactogenicity and safety of 2 additional doses;

Control Group: Subjects from this group [N = 120] will not be vaccinated but will serve as a control to assess immunogenicity and safety compared to the two vaccinated groups 1-Additional Dose and Revaccination. This Control group will also be used to evaluate the VE, safety and immunogenicity.

Subjects (N, to be determined) who developed HZ during the ZOSTER-006/022 studies (confirmed HZ) and/or during the interval between the end of the ZOSTER-006/022 studies and beginning of the ZOSTER-049 study, and/or during the ZOSTER-049 study (suspected HZ) will be part of the **HZ subset**.

Subjects from the 1-Additional Dose and Revaccination groups who will develop HZ cases during the ZOSTER-049 study will follow the sampling schedule as per their original group and will not be part of the HZ subset.

Note: Subjects from the immunogenicity subset of studies ZOSTER-006/022 are not allocated to the 1-Additional Dose, Revaccination and Control groups. Subjects in these three groups will be enrolled amongst subjects who received 2 doses of the HZ/su vaccine and were part of the ATP cohort for analysis of efficacy in the previous studies ZOSTER-006/022. In order not to confound immune responses, subjects who developed HZ prior to enrolment in the ZOSTER-049 study (confirmed HZ during the ZOSTER-006/022 studies or suspected HZ during the interval between the end of the ZOSTER-006/022 studies and beginning of the ZOSTER-049 study), will not be enrolled in the 1-Additional Dose, Revaccination and Control groups.

- Control: historical control.
- Vaccination schedule: Two groups of subjects (1-Additional Dose and Revaccination) will receive 1 or 2 additional doses of HZ/su vaccine at Month 0 or Months 0 and 2, respectively.
- Treatment allocation: Randomized to treatment schedule accounting for age at primary vaccination in studies ZOSTER-006/022 (50-59, 60-69 and ≥ 70 YOA) and countries for the three groups 1-Additional Dose, Revaccination and Control.
- Blinding: Open-label.
- Sampling schedule:

  All subjects (N ≤ 14,448) entering the study will have a HI blood sample (approximately 5 mL) at Visit Month 0.

  For subjects in the LTFU group, who do not belong to any subset, these samples will be stored and tested for HI only if the subject develops HZ during the ZOSTER-049 study or if there are other reasons requiring the HI testing of these samples.

  LTFU Group (HI subset): Subjects (N ≤ 1,729) who were in the immunogenicity subset during studies ZOSTER-006/022 and continue participation in this study. Blood samples (approximately 5 mL) will be collected and tested from Visit Month 0 to Visit Year 6, on a yearly basis, to assess HI responses.

  LTFU Group (CMI subset): Subjects (N ≤ 234) who were in the CMI subset during study ZOSTER-006 and continue participation in this study. Blood samples (approximately 20 mL) will be collected and tested from Visit Month 0 to Visit Year 6 on a yearly basis to assess CMI responses.

  HZ subset: Subjects (N to be determined) who developed confirmed HZ during ZOSTER-006 or ZOSTER-022, or who develop HZ during the interval between the end of the ZOSTER-006/022 and the beginning of ZOSTER-049, or who develop suspected HZ during ZOSTER-049 will be part of the HZ subset. Blood sampling for subjects in the HZ subset is described below.

  Subjects who develop HZ at any time after enrolment in ZOSTER-006 or ZOSTER-022 and who are already part of the HI subset in ZOSTER-006 or ZOSTER-022 will provide blood samples to assess HI responses (approximately 5 mL) from Visit Month 0 to Visit Year 6 irrespective of when the HZ episode occurs. If these subjects are part of the ZOSTER-006 CMI subset, then they will also continue to provide blood to assess CMI responses (approximately 20 mL).

  Subjects who develop HZ at any time after enrolment in ZOSTER-006 or ZOSTER-022 and who were NOT part of the HI or CMI subsets in these studies, will provide blood samples to assess HI responses (approximately 5 mL) beginning at the annual visit in the ZOSTER-049 study subsequent to the occurrence of the HZ episode. The blood sample taken upon enrolment at Visit Month 0 will be tested and included in the analyses for these subjects.

1-Additional Dose Group: Subjects (N = 60) to be administered HZ/su vaccine on a 1-dose schedule at Visit Month 0. Blood samples (approximately 5 and 20 mL) will be collected at Visit Month 0, Visit Month 1, and from Visit Year 1 to Visit Year 6 on a yearly basis to assess HI and CMI responses.

Revaccination Group: Subjects (N = 60) to be administered HZ/su vaccine on a 2-dose schedule at Visit Month 0 and Visit Month 2. Blood samples (approximately 5 and 20 mL) will be collected at Visit Month 0, Visit Month 1, Visit Month 3 and from Visit Year 1 to Visit Year 6 on a yearly basis to assess HI and CMI responses.

Control Group: Subjects (N = 120) in the non-vaccinated control group. Blood samples (approximately 5 and 20 mL) will be collected at Visit Month 0, Visit Month 1, Visit Month 3 and from Visit Year 1 to Visit Year 6 on a yearly basis to assess HI and CMI responses.

Specimens of HZ lesions will be collected from subjects clinically diagnosed as having a suspected case of HZ.

- Type of study: extension of other protocols, i.e., 110390 (ZOSTER-006) and 113077 (ZOSTER-022).
- Data collection: Electronic Case Report Form (eCRF).

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables	Pooled definition for footnote
1	LTFU Group	***LTFU Group = subjects who were enrolled in the Long-Term Follow-up group***	LTFU_Contr	LTFU and Control group
2	1_Add dose Group	***1_Add dose group = 1-Additional Dose Group, subjects who received one additional dose of HZ/su***		
3	Revacc Group	***Revacc Group = Revaccination Group, subjects who received two additional doses of HZ/su***		
4	Control Group	***Control group = Control group, subjects did not receive any additional HZ/su***	LTFU_Contr	LTFU and Control group

The following sub-groups have been defined to be used for the statistical analyses:

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Age Group – Age strata 1 (for efficacy in LTFU and Control group)		
1	50-59 YOA	50-59 YOA at primary vaccination
2	60-69 YOA	60-69 YOA at primary vaccination
3	***70-79 YOA***	***70-79 YOA*** at primary vaccination
4	***≥ 80 YOA***	***≥ 80 YOA*** at primary vaccination
5	***≥ 60 YOA***	***≥ 60 YOA*** at primary vaccination
6	≥ 70 YOA	≥ 70 YOA at primary vaccination
Age Group – Age strata 2 (only for immunogenicity and safety analysis in LTFU group)		
1	***50-59 YOA***	***50-59 YOA*** at primary vaccination
2	***60-69 YOA***	***60-69 YOA*** at primary vaccination
3	***≥70 YOA***	***≥70 YOA*** at primary vaccination
4	***≥60 YOA****	***≥60 YOA*** at primary vaccination
Gender		
1	Female	Female
2	Male	Male
Ethnicity		
1	American Hispanic or Latino	American Hispanic or Latino
2	Not American Hispanic or Latino	Not American Hispanic or Latino
Race		
1	African Heritage/African American	African Heritage/African American
2	Asian	Asian-Central/South Asian Heritage, Asian-East Asian Heritage, Asian- Japanese Heritage and Asian – South East Asian Heritage
3	White	White – Arabic/North African heritage and White – Caucasian / European Heritage
4	Other	American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander and other

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Region		
1	***North America***	***Canada, United States***
2	***Australasia***	***Australia, Hong Kong, Japan, Korea Republic of, Taiwan***
3	***Europe***	***Czechia, Estonia, Finland, France, Germany, Italy, Spain, Sweden, United Kingdom***
4	***Latin America***	***Brazil, Mexico***

* Age stratum ≥60 YOA is not used for safety analysis in LTFU

3. OBJECTIVES

The statistical analyses to be performed for the study objectives described in Sections 3.1 and 3.2 will be descriptive. No success criteria have been defined.

3.1. Primary objective

- To assess the VE in the prevention of HZ over the total duration of the ZOSTER-049 study as measured by the reduction in HZ risk in subjects ≥ 50 YOA overall at the time of first vaccination in the ZOSTER-006/022 studies.

Refer to Section 4.1 for the definition of the primary endpoint.

3.2. Secondary objectives

- To assess the VE in the prevention of HZ over the total duration of the ZOSTER-049 study as measured by the reduction in HZ risk in subjects within each of the age ranges* at the time of first vaccination in the ZOSTER-006/022 studies;
- To assess the VE in the prevention of HZ from one month post dose 2 in the ZOSTER-006/022 studies until the end of the ZOSTER-049 study as measured by the reduction in HZ risk in subjects ≥ 50 YOA overall and within each of the specified age ranges* at the time of first vaccination in the ZOSTER-006/022 studies;
- To assess the VE in the prevention of HZ over each year of follow-up from one month post dose 2 in the ZOSTER-006/022 studies as measured by the reduction in HZ risk in subjects ≥ 50 YOA overall and within each of the specified age ranges* at the time of first vaccination in the ZOSTER-006/022 studies;
- To assess the VE over the total duration of the ZOSTER-049 study in prevention of PHN in subjects ≥ 50 YOA overall and within each of the specified age ranges* at the time of first vaccination in the ZOSTER-006/022 studies;

- To assess the VE in the prevention of PHN from one month post dose 2 in the ZOSTER-006/022 studies until the end of the ZOSTER-049 study in subjects ≥ 50 YOA and within each of the specified age ranges* at the time of first vaccination in the ZOSTER-006/022 studies;
- To assess the VE over the total duration of the ZOSTER-049 study in prevention of HZ related complications (other than PHN) in subjects ≥ 50 YOA overall and within each of the specified age ranges* at the time of first vaccination in the ZOSTER-006/022 studies;
- To assess the VE in the prevention of HZ related complications (other than PHN) from one month post dose 2 in the ZOSTER-006/022 studies until the end of the ZOSTER-049 study in subjects ≥ 50 YOA overall and within each of the specified age ranges* at the time of first vaccination in the ZOSTER-006/022 studies;
- To assess persistence of humoral immune responses at Year 5, 6, 7, 8, 9 and 10 and beyond after the primary vaccination in the ZOSTER-006/022 studies in the HI subset in subjects ≥ 50 YOA overall and within each of the specified age ranges* at the time of first vaccination, in the ZOSTER-006/022 studies;
- To assess persistence of vaccine induced cell-mediated immune responses at Year 5, 6, 7, 8, 9 and 10 and beyond after the primary vaccination in the ZOSTER-006/022 studies **in the CMI subset** in subjects ≥ 50 YOA overall and within each of the specified age ranges* at the time of first vaccination, in the ZOSTER-006 study;
- To assess humoral immune responses at Year 5, 6, 7, 8, 9 and 10 and beyond after the primary vaccination in the ZOSTER-006/022 studies in subjects ≥ 50 YOA at the time of first vaccination, in the ZOSTER-006/022 studies, who had a confirmed HZ episode previously for the timepoint considered;
- To assess vaccine induced cell-mediated immune responses at Year 5, 6, 7, 8, 9 and 10 and beyond after the primary vaccination in the ZOSTER-006/022 studies **in the CMI subset** in subjects ≥ 50 YOA at the time of first vaccination, in the ZOSTER-006 study, who had a confirmed HZ episode previously for the timepoint considered;
- To assess humoral immune responses one month after the first additional HZ/su vaccine dose (1-Additional Dose and Revaccination groups) and at the same timepoint in the Control group;
- To assess vaccine induced cell-mediated immune responses one month after the first additional HZ/su vaccine dose (1-Additional Dose and Revaccination groups) and at the same timepoint in the Control group;
- To assess humoral immune responses one month after the second additional HZ/su vaccine doses (Revaccination group and at the same timepoint in the Control group);
- To assess vaccine induced cell-mediated immune responses one month after the second additional HZ/su vaccine doses (Revaccination group and at the same timepoint in the Control group);
- To assess persistence of humoral immune responses at Year 1, 2, 3, 4, 5 and 6 timepoints of this study in subjects from the 1-Additional Dose, Revaccination and Control groups;

- To assess persistence of vaccine induced cell-mediated immune responses at Year 1, 2, 3, 4, 5 and 6 timepoints of this study in subjects from the 1-Additional Dose, Revaccination and Control groups;
- To assess vaccine safety and reactogenicity in the 1-Additional Dose and Revaccination groups;
- To assess vaccine safety in the LTFU and Control groups.

3.3. Tertiary objectives (Amended 23 September 2019)

CCI

[redacted]

4. ENDPOINTS

4.1. Primary endpoint

- Confirmed HZ cases (LTFU and Control groups);
  - Confirmed HZ cases during the ZOSTER-049 study.

4.2. Secondary endpoints

- Confirmed HZ cases;
  - Confirmed HZ cases since one month post dose 2 in the previous ZOSTER-006/022 studies;
- PHN cases;
  - PHN cases during the ZOSTER-049 study and since one month post dose 2 in the previous ZOSTER-006/022 studies;

- HZ related complications (other than PHN);
  - HZ related complications (other than PHN) during the ZOSTER-049 study and since one month post dose 2 in the previous ZOSTER-006/022 studies;
- Anti-gE humoral immunogenicity at Months 0, 12, 24, 36, 48, 60 and 72 (LTFU HI subset, 1-Additional Dose, Revaccination and Control groups), at Month 1 (1-Additional Dose, Revaccination and Control groups), and at Month 3 (Revaccination and Control groups);
  - Anti-gE Ab concentrations as determined by ELISA;
- CMI in terms of frequencies of antigen-specific CD4+ T cells at Months 0, 12, 24, 36, 48, 60 and 72 (LTFU CMI subset, 1-Additional Dose, Revaccination and Control groups), at Month 1 (1-Additional Dose, Revaccination and Control groups), and at Month 3 (Revaccination and Control groups);
  - Frequencies of CD4+ T cells with antigen-specific Interferon gamma (IFN-γ) and/or Interleukin-2 (IL-2) and/or Tumour Necrosis Factor alpha (TNF-α) and/or CD40 Ligand (CD40L) secretion/expression to gE as determined by ICS;
- Solicited local and general symptoms in subjects administered with 1 or 2 additional doses of HZ/su vaccine (1-Additional Dose and Revaccination groups);
  - Occurrence, intensity and duration of each solicited local symptom within 7 days (Days 0 - 6) after each vaccination;
  - Occurrence, intensity, duration and relationship to vaccination of each solicited general symptom within 7 days (Days 0 - 6) after each vaccination;
- Unsolicited AEs in subjects administered with 1 or 2 additional doses of HZ/su vaccine (1-Additional Dose and Revaccination groups);
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 - 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification;
- Serious AEs;
  - Occurrence and relationship to vaccination of all SAEs;
    - from Visit Month 0 until 12 months: for Control and 1-Additional Dose groups;
    - from Visit Month 0 until 12 months after last HZ/su vaccination: for the Revaccination group;
  - Occurrence of SAEs related to investigational vaccine, related to study participation or to GSK concomitant medication/vaccine during the entire study period in all subjects;

- Occurrence of AEs of specific interest: Potential immune-mediated diseases (pIMDs) (1-Additional Dose, Revaccination and Control groups);
  - Occurrence and relationship to vaccination of all pIMDs;
    - from Visit Month 0 until 12 months: for Control and 1-Additional Dose groups;
    - from Visit Month 0 until 12 months after last HZ/su vaccination: for the Revaccination group.

4.3. Tertiary endpoints

CCI

[redacted]

5. STUDY POPULATION

5.1. Total Vaccinated cohort

The Total Vaccinated cohort (TVC) will include all subjects from the ZOSTER-006/022 studies who are enrolled in the ZOSTER-049.

The TVC for efficacy will include all subjects in the LTFU and control groups for whom data related to efficacy endpoints are available.

The TVC for the groups 1-Additional Dose and Revaccination will include all vaccinated subjects from the ZOSTER-006/022 studies who received at least one additional dose of HZ/su vaccine in the ZOSTER-049 study.

The TVC for the Control group will include vaccinated subjects from the ZOSTER-006/022 studies who are enrolled and randomized in Control group of ZOSTER-049.

The TVC for immunogenicity and humoral/CMI persistence will include subjects for whom data related to immunogenicity and humoral/CMI persistence endpoints are available.

The TVC for analysis of safety will include:

- For 1-Additional Dose and Revaccination groups only, the TVC for the analysis of solicited symptoms will include all subjects who received at least 1 dose of the study treatment in ZOSTER-049 and who have documented solicited symptoms (i.e., diary card for solicited AEs completed and returned).
- For 1-Additional Dose and Revaccination groups, the TVC for the analysis of any other AEs other than solicited symptom will include all subjects who received at least 1 dose of the study treatment in ZOSTER-049.
- For Control and LTFU groups, the TVC for the analysis of any AEs will include all subjects who came for Month 0 visit.

5.2. Modified Total Vaccinated cohort – (LTFU and Control group)

The mTVC will be the primary population for efficacy analysis, which excludes subjects in the TVC for efficacy analysis who were not administered with the second vaccination during the ZOSTER-006/022 study, or who developed a confirmed case of HZ prior to 1 month after the second vaccination in the ZOSTER-006/022 primary study.

5.3. According to Protocol Cohort for efficacy – (LTFU and Control groups)

The According to Protocol (ATP) cohort for efficacy will include all evaluable subjects:

- Who meet all eligibility criteria;
- Who have received 2 doses of the HZ/su study vaccine according to their random assignment in the primary ZOSTER-006/022 studies;
- For whom administration site of study vaccine is known and correct from ZOSTER-006/022;
- Who have not received a vaccine not specified or forbidden in the protocol;
- Complying with the procedures defined in the protocol;
- Who did not receive a medication/ product leading to elimination from the ATP analysis;
- Who did not present with an IMC leading to exclusion from an ATP analysis;
- Who complied with the vaccination schedule, i.e., 49-83 days between the first and the second dose in ZOSTER-006/022;
- Who did not develop a confirmed case of HZ prior to 1 month (30 days) after the second vaccination, during the ZOSTER-006/022 studies.

5.4. According to Protocol Cohort for immunogenicity – (1-Additional Dose, Revaccination and Control groups)

The ATP cohort for immunogenicity will include all subjects from the TVC:

- Who meet all eligibility criteria;
- Who have received 1 dose (1-Additional Dose group) or 2 doses (Revaccination group) of study vaccine(s) according to their random assignment;
- For whom administration site of study vaccine is known and correct;
- Who have not received a vaccine not specified or forbidden in the protocol;
- Who complied with the procedures defined in the protocol;
- Who did not receive a medication/ product leading to exclusion from an ATP analysis;
- Who did not present with an IMC leading to exclusion from an ATP analysis;
- Who complied with the vaccination schedule, i.e., 49-83 days between the first and the second dose for the Revaccination group;
- Who complied with the Month 1 blood sample schedule, i.e., 28-48 days from Month 0 to Month 1 for the 1-Additional Dose group and Control group;
- Who complied with the post-Dose 2 blood sample schedule, i.e., 28-48 days post-Dose 2 for the Revaccination group;
- Who had immunogenicity results available post-dose 1 for the 1-Additional Dose group, post dose 2 for the Revaccination group and at Month 1 and Month 3 for the Control group;
- Who had no episode of HZ prior to study start;
- Who received 2 doses of HZ/su vaccine in the primary ZOSTER-006/022 studies.

Please note – To avoid long title for the OPS based on this cohort, the cohort name to be used in the OPS is 'ATP cohort for humoral immunogenicity – Randomized groups' and ATP cohort for CMI immunogenicity – Randomized groups' for humoral and CMI analysis, respectively.

5.5. According to Protocol Cohort for persistence of immunogenicity – (LTFU group)

The ATP cohort for persistence of immunogenicity (humoral/CMI) for ***LTFU group*** will include all evaluable subjects, i.e., those who were included in the ATP cohort for immunogenicity (humoral/CMI) in the primary ZOSTER-006/022 studies, or were excluded from this cohort solely because they had no blood samples taken, or because of incompliance with blood sample schedule, and:

- Who did not receive a concomitant medication/product leading to elimination from the ATP analysis for immunogenicity up to the timepoint considered (***section 7.6.2 of the protocol***)
- Who did not present with an IMC leading to elimination from the ATP analysis for immunogenicity (including HZ infection) up to the timepoint considered (***section 7.7 of the protocol***)
- For whom persistence immunogenicity results are available for the considered time point in ZOSTER-049 study.

Please note – "ATP cohort for humoral persistence – LTFU" and "ATP cohort for CMI persistence - LTFU" are used in OPS to differentiate humoral and CMI results and avoid long titles for tables based on this cohort.

5.6. According to Protocol Cohort for persistence of immunogenicity – (1-Additional Dose, Revaccination and Control groups)

The ATP cohort for persistence of immunogenicity will include all evaluable subjects i.e., those who were included in the ATP cohort for immunogenicity **–** ***Randomized group*** in the ZOSTER-049 study, or were excluded from this cohort solely because they had no blood samples taken or because of incompliance with blood sample schedule, and:

- Who did not receive a concomitant medication/product leading to elimination from the ATP analysis for immunogenicity up to the timepoint considered ***(section 7.6.2 of the protocol)***
- Who did not present with an IMC leading to elimination from the ATP analysis for immunogenicity (including HZ infection) up to the timepoint considered (***section 7.7 of the protocol***)
- For whom persistence immunogenicity results are available for the timepoint considered.

Please note – To avoid long title for the OPS based on this cohort, the cohort name to be used in the OPS is 'ATP cohort for immunogenicity persistence – Randomized groups'.

For the immunogenicity/persistence tables where different timepoints are presented, the concept of "Adapted ATP/TVC cohort" will be used to denote that for each timepoint, the corresponding ATP/TVC cohort for immunogenicity has been used.

5.7. Elimination from study cohorts

The elimination code and elimination type applicable for cohorts are mentioned below:

Cohort	Elimination codes	Eli Type
TVC – Randomized groups	***900, 1030***	***M3***
TVC for humoral persistence – LTFU	***900, 2130, 3615, 3616, 2110***	***F0 - F6 T1 - T9***
TVC for CMI persistence – LTFU	***900, 2130, 3615, 4130, 2111***	***F0 - F6 T1 - T9***
TVC for immunogenicity persistence – Randomized groups	***900, 1030***	***L1 - L6***
HZ subset for HI	***900, 901, 2110 for HI***	***HS1-HS6***
HZ subset for CMI	***900, 901, 2111 for CMI***	***HS1-HS6***
TVC Efficacy – LTFU and Control group	***900, 901***	***EF***
mTVC – LTFU and Control group	***900, 901, 1071, 1501, 2501, 3501***	***E2, E4, EF***
ATP cohort for efficacy - LTFU and Control group	***900, 901, 1040, 1041, 1051, 1061, 1071, 1081, 1091, 1501, 1600, 1601, 2040, 2041, 2050, 2051, 2070, 2071, 2081, 2501, 3501***	***EF***
ATP cohort for immunogenicity - Randomized groups*	***900, 1030, 1040, 1050, 1070, 1080, 1090, 1600, 2040, 2050, 2060, 2070, 2080, 2090, 2100, 2500***	***M3***
ATP cohort for immunogenicity persistence - Randomized groups*	***900, 1030, 1040, 1050, 1070, 1080, 1090, 1600, 2040, 2050, 2060, 2070, 2080, 2100, 2500***	***L1 – L6***
ATP cohort for humoral persistence – LTFU	***900, 901, 1040, 1041, 1051, 1061, 1071, 1081, 1091, 1501, 1600, 1601, 2040, 2041, 2050, 2051, 2060, 2061, 2070, 2071, 2081, 2100, 2130, 2501, 3615, 3616, 2110***	F0 - F6 T1 - T9
ATP cohort for CMI persistence – LTFU	***900, 901, 1040, 1041, 1051, 1061, 1071, 1081, 1091, 1501, 1600, 1601, 2040, 2041, 2050, 2051, 2060, 2061, 2070, 2071, 2081, 2100, 2130, 2501, 3615, 3616, 4130, 2111***	F0 - F6 T1 - T9

In OPS, to reduce the number of tables, "Adapted ATP cohort for immunogenicity - Randomized groups" is used in tables that include both immunogenicity and persistence of immunogenicity results, i.e., Month 0, 1, 3 and each year follow-up in ZOSTER-049.

The specification of each elimination code is presented in the Sections 11, 12, 13, 14, 15, and 16 of the SAP.

6. STATISTICAL METHODS

6.1. Analysis of demographics (for each of the four groups of the study)

6.1.1. Analysis of demographics planned in the protocol.

Except when specified otherwise, summary by age strata (***50-59, 60-69, and ≥70 YOA***) will be set up as per the age at the first vaccination in the ZOSTER-006/022 studies.

Demographic characteristics (age at first vaccination in the ZOSTER-006/022 studies, ***age at enrolment in ZOSTER-049***, gender, race, region, and ethnicity), cohort description and withdrawal status will be summarized.

For LTFU group, mean age at first vaccination in the ZOSTER-006/022 and mean ***age at enrolment in ZOSTER-049*** studies (plus range and standard deviation) of the enrolled subjects, as a whole, and stratified by ***age strata*** (***50-59, 60-69 ≥70 and ≥60 YOA at primary vaccination***) will be calculated on TVC, ATP cohort for humoral persistence – LTFU, ATP cohort for CMI persistence – LTFU at baseline.

In addition, for the 1-Additional Dose, Revaccination and Control groups***, mean age at first vaccination in the ZOSTER-006/022 and*** mean age at Month 0 in the ZOSTER-049 (plus range and standard deviation) of the enrolled subjects ***on TVC - Randomized groups***, and ***ATP cohort for immunogenicity – Randomized groups*** as a whole will be calculated.

The distribution of subjects enrolled among the study sites ***from different countries*** will be tabulated.

Descriptive statistics of interval (in years) between the end of study efficacy cut-off date (21 April 2015) of ZOSTER-006/022 and the first visit of the LTFU and control group will be calculated overall and by age strata (***50-59, 60-69, 70-79, ≥80 YOA at primary vaccination) on mTVC - LTFU and Control group***.

Descriptive statistics of interval (in years) between the second dose of HZ/su vaccine in ZOSTER-006/022 and the first dose in the Revaccination group and the 1-Additional Dose group and the first visit for the control group will be calculated overall ***on TVC – Randomised groups***.

Descriptive statistics of interval (in years) between the second dose of HZ/su vaccine in ZOSTER-006/022 and the first visit for the control group ***and LTFU*** will be calculated overall and by age strata (***50-59, 60-69, 70-79, ≥80 YOA at primary vaccination) on mTVC -LTFU and Control group***.

Descriptive statistics of interval (in years) between the second dose of HZ/su vaccine in ZOSTER- 006/022 and Year 6 visit for the LTFU and Control will be calculated overall and by age strata (50-59, 60-69, 70-79, ≥80 YOA at primary vaccination) on mTVC - LTFU and Control group.

Frequency and percentage will be generated for categorical variables such as gender, race, region, and ethnicity.

6.1.2. Additional consideration

Following CHMP recommendation, in order to evaluate the comparability of demographic characteristics between subjects enrolled in ZOSTER-049 and subjects enrolled in ZOSTER-006/022 studies, demographic characteristics of age, gender, race, region and ethnicity will also be summarized for subjects enrolled in ZOSTER-049, and subjects receiving at least one dose of HZ/su vaccine in ZOSTER-006/022 studies. In addition, selected medical conditions present at enrolment of ZOSTER-049 will be summarized.

Summary of demography will also be performed by age-strata (50-59, 60-69, 70-79, ≥80, ≥60, ≥70 YOA at primary vaccination), gender, region, race and ethnicity on mTVC -LTFU and Control group.

6.2. Analysis of efficacy (LTFU and Control group)

6.2.1. Analysis of efficacy planned in the protocol (LTFU and Control group)

The efficacy analyses are summarized by age strata and overall as presented in the Table 1. The calculations involving ZOSTER-049 only will consider data collected only in the present study follow-up. The calculations involving ZOSTER-006/022 and ZOSTER-049 will combine results from the studies as described below.

Table 1 Efficacy analyses per study periods and age-strata

Analysis	Study period	≥ 50 YOA	≥ 60 YOA	≥ 70 YOA	50-59 YOA	60-69 YOA	70-79 YOA	≥ 80 YOA	Objective
A	Z-049 duration overall	X	X	X	X	X	X	X	Primary and Secondary
B	Z-006/Z022 * + Z049 duration overall	X	X	X	X	X	X	X	Secondary
C	Z-006/022 + Z-049 duration yearly**	X	X	X	X	X	X	X	Secondary and CCI

YOA = Year of age
* from one month post dose 2 in the ZOSTER-006/022 studies
** yearly follow-up will be computed from one month post dose 2 in the ZOSTER-006/022 studies. Note that results from the pooled ZOSTER-006/022 studies will be presented for each year after vaccination with methods used in these studies.

The primary analysis of efficacy will be performed on the mTVC, the analysis will be also performed on the TVC for efficacy and the ATP for efficacy to complement the mTVC analysis.

The ***VE analysis for HZ*** on TVC, mTVC and ATP cohort for efficacy over the study duration of present study ZOSTER-049 will be performed over the follow-up time calculated from enrolment in the present study to the time of first confirmed HZ case for a subject with a confirmed HZ case, and to the date of last contact for subjects without the occurrence of confirmed HZ case.

The ***VE analysis for HZ*** on mTVC and ATP cohort for efficacy over the duration starting from ZOSTER-006/ -022 study will be performed over the follow-up time calculated from one month post Dose 2 to the time of first confirmed HZ case for a subject with a confirmed HZ case, and to the date of last contact for subjects without the occurrence of confirmed HZ case.

The ***VE analysis for HZ*** on the TVC will be performed over the complete follow-up period and will include confirmed HZ cases from Dose 1 administered in the ZOSTER-006/022 studies for vaccine efficacy evaluation. The end of the follow-up period will be calculated according to the same principle as will be done for the mTVC and ATP analyses for efficacy, i.e., up to the confirmed HZ case for a subject with a confirmed HZ case, or up to the date of last contact for subjects without a confirmed HZ case.

In the VE analysis for PHN and HZ related complication (other than PHN), the follow-up time will be calculated in the similar way as in VE analysis for HZ.

All above analyses will be performed overall and by age strata. The age strata for VE are defined as: ***50-59, 60-69, 70-79, ≥80, ≥60, ≥70 YOA*** at primary vaccination in ZOSTER-006/022 studies.

The primary analysis (A) will assess the VE during this study and will use the historical control estimates adjusted for region and age categories at randomization/vaccination during the ZOSTER-006/022 studies. Vaccine effects will be estimated by calculating the VE and estimating 95% CIs based on the variance of the observed population in this study and treating the historical control as constant, similarly, as described in [Morrison, 2015]. The secondary analysis C in Table 1 will assess the VE over each year of follow-up, similarly to what is planned in analysis A.

See Section 7.3 for more details on the vaccine efficacy methodology.

The purpose of these analyses will be descriptive and therefore the CIs will not be adjusted for multiple testing.

6.2.2. Additional Consideration

In addition to the above mentioned analysis, following additional, sensitivity and sub-group analysis will be performed:-

- ***Frequency of confirmed HZ episodes in ZOSTER-049 on mTVC – LTFU and Control group.***
- ***Distribution of confirmed HZ episodes amongst suspected HZ episodes in ZOSTER-049 on mTVC – LTFU and Control group.***
- ***Distribution of HZAC final decision for each PCR testing results in ZOSTER-049***
- ***Summary of the number of HZ lesion samples not taken on suspected cases in relation to Covid-19 pandemic impact in ZOSTER-049***
- ***Cumulative incidence curve for first or only episode of HZ since one month post dose 2 in ZOSTER-006/022 studies***
- ***Forrest plot: Vaccine efficacy: First or only episode of HZ during ZOSTER-049 study by age strata and overall using Poisson regression method***

- ***Forrest plot: Vaccine efficacy: First or only episode of HZ since one month post dose 2 in ZOSTER-006/022 studies by age strata and overall using Poisson regression method***
- ***Listing of subjects with severe 'worst pain' cases in ZOSTER-049, listing of subjects with confirmed HZ-related complications in ZOSTER-049 (other than PHN), listing of subjects with confirmed HZ related hospitalizations in ZOSTER-049 and listing of subjects with use of pain medications associated with confirmed HZ cases in ZOSTER-049 will be generated on TVC- LTFU and Control group.***

6.2.2.1. Summary of Covid-19 pandemic impact on suspected sample lesion testing

Summary of the number of HZ lesion samples not taken on suspected cases in relation to Covid-19 pandemic impact in ZOSTER-049 will be presented.

6.2.2.2. Sensitivity analysis including suspected HZ cases captured in the gap between primary studies and ZOSTER-049 study.

In the current calculation of VE for study ZOSTER-049, the suspected HZ cases during the time between the last visit of studies ZOSTER-006/022 and initiation of study ZOSTER-049 (the "gap period") is not considered as confirmed cases. Per CHMP recommendation, a sensitivity analysis on the primary VE analysis during the entire follow-up period since ZOSTER-006/022 is planned to include potentially confirmed HZ cases during this gap period (Analysis B on mTVC-pooled ZOSTER-006/022 and mTVC-LTFU and Control group).

It is known that there are some self-reported suspected cases of HZ during the gap period, but these cases were not able to be confirmed as per the study protocol requirements, hence the true number of confirmed cases is unknown. The planned sensitivity analysis will assume different, yet conservatively high positive rates on the self-reported suspected cases to adequately assess the impact due to potentially confirmed cases. Please refer to Section 7.3.5 for more details

6.2.2.3. Sensitivity analysis considering subjects aging when enrolled into ZOSTER-049 from ZOSTER-006/-022

Since all subjects enrolled in ZOSTER-049 study had aged for ~5 years compared to when they were enrolled in ZOSTER-006/022 studies, a sensitivity analysis on VE (analysis A, B and C on mTVC - LTFU and Control group only.) is planned to consider the aging factor on ZOSTER-049 subjects when utilizing the historical control to estimate the incident rate on the hypothetical control in ZOSTER-049 study. Please refer to Section 7.3.6 for more details

6.2.2.4. Additional VE sub-group analysis

As per CBER's recommendation, vaccine efficacy for first or only episode of confirmed HZ episode of the ZOSTER-049 study using Poisson method on modified Total Vaccinated Cohort will also be presented by gender, race, region and ethnicity.

Vaccine efficacy for first or only episode of confirmed HZ episode from one month post dose 2 in the ZOSTER-006/022 studies using Poisson method on modified Total Vaccinated Cohort will also be presented by gender, race, region and ethnicity.

6.3. Analysis of immunogenicity

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

All analyses will be presented overall and by age strata. The main age strata for reporting purposes are 50-59, 60-69 and ≥ 70 YOA. Additional analysis will be presented in ≥ 60 YOA.

6.3.1. Assessment for 1-Additional Dose, Revaccination and Control groups

6.3.1.1. Humoral immune response

Descriptive analysis – within group:

The following parameters will be tabulated by vaccine group at each time point when a blood sample result is available:

- Seropositivity rate with exact 95% CI;
- GMC with 95% CI;
- The MGI Post Month 1 and Post Month 3 current study over pre-vaccination in the primary studies with 95% CI;
- The MGI Post Month 3 primary vaccination over the Post Month 1 and Post Month 3 current study with 95% CI;
- The MGI Post Month 1 and Post Month 3 current study over Visit Month 0, in the current study with 95% CI;
- The MGI Post Month 3 over Post Month 1 current study for the Revaccination and Control groups with 95% CI;
- VRR [post additional dose groups over pre-vaccination in the primary studies] with exact 95% CI;
- The distribution of Ab titres will be tabulated and also presented using reverse cumulative curves.

Exploratory assessment – between group:

- CCI [redacted]

6.3.1.2. Persistence analysis – Randomized groups

Persistence data will be analysed from the Visit Year 1 to the Visit Year 6 timepoint after vaccination.

For each year X (X varying from year 1 to year 6): The analysis of Ab persistence will be based on the ATP cohort for persistence at year X –adapted for each timepoint. If the percentage of subjects, excluded from the ATP cohort for the Year X follow-up serological results, is higher than 5% for any group, a second analysis based on the TVC – ***Randomized groups*** at Year X will be performed to complement the ATP analysis.

The following parameters will be tabulated by group at each timepoint when a blood sample result is available (including Month 0, Month 1 and Month 3):

- Seropositivity rate with exact 95% CI;
- GMC with 95% CI;
- The MGI Post Month 3 primary vaccination over the Post year x for the 1-Additional Dose or Revaccination group with 95% CI;
- The MGI Post year x for the 1-Additional Dose or Revaccination group over Visit Month 0, in the current study with 95% CI;
- The MGI Post year x over pre-vaccination in the primary ZOSTER-006/022 studies with 95% CI;
- VRR [post year x (1-Additional Dose or Revaccination group) over pre-vaccination in the primary ZOSTER-006/022 studies] with exact 95% CI;
- The distribution of Ab titres will be tabulated, and also presented using reverse cumulative curves.

6.3.1.3. Cell-mediated immune response

Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of the following parameters will be tabulated by group at all timepoints:

- Descriptive statistics of the frequency of CD4+ T-cells secreting at least two activation markers (from among IFN-γ, IL-2, TNF-α, CD40L) for gE-specific stimulation.
- CCI [redacted]

CCI [redacted]

6.3.2. Analysis on subjects with confirmed HZ cases

The following analysis will be also performed at each time point when a blood sample result is available on subjects who had a confirmed HZ case:

For HI

- Seropositivity rate with exact 95% CI;
- GMC with 95% CI.
- For CMI
  - ***Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of the frequency of CD4+ T-cells secreting at least two activation markers (from among IFN-γ, IL-2, TNF-α, CD40L) for gE-specific stimulation will be presented***

6.3.3. Analysis of persistence (immune subset of LTFU group)

Since the interval between the end of ZOSTER-006/022 studies and the start of this study will vary per subject and is dependent on receipt of approval or implementing the study in the different participating countries, some results from the first blood sample may correspond to year 5, year 6 or year 7 post vaccination. To be able to complement the modelling prediction by descriptive data analysis, yearly timeframes will be defined around the anniversary date post vaccination. The details of the set up for these intervals is described below.

The timeframe of first visit of ZOSTER-049 study in LTFU group will be computed between the date of the first visit of ZOSTER-049 study and the second dose administration date of previous ZOSTER-006/022 studies.

Time frame of first visit= (date of the first visit of ZOSTER-049 - date of vaccination dose 2 in ZOSTER-006/022+1) /365.25.

The result of the first visit will be assigned to each yearly timeframe derived as follow

Timeframe of first visit	*Allowed interval for computed time of first visit*	*Lower bound of timeframe of first visit*	*Upper bound of timeframe of first visit*
4	*[3.5, 4.5)*	*[3.5*	*4.5[*
5	*[4.5, 5.5)*	*[4.5*	*5.5[*
6	*[5.5, 6.5)*	*[5.5*	*6.5[*

Yearly timeframe for the persistent analysis in LTFU will be calculated by adding 1 year to the timeframe of first visit for each subsequent visit.

Example

	Dose 2 – previous studies	*Month 0- current study BS*	*Time since vacc 2*	*Assigned time frame for the Month 0 blood sample*	*Assigned time frame for the year 1 blood sample*	*Assigned time frame for the year 2 blood sample*	*Assigned time frame for the year 3 blood sample*
pid 1	*1-nov-11*	*2-feb-16*	*4,260273973*	*4*	*5*	*6*	*7*
pid 2	*1-nov-11*	*5-jul-16*	*4,682191781*	*5*	*6*	*7*	*8*

6.3.3.1. Humoral immune response

For the yearly prediction of the GMCs (year 5 to year 10 and beyond): the analysis of Ab persistence will be based on the ATP cohort for persistence adapted for each year. ***The methodology of modelling prediction is mentioned in Section 7.4.3.***

In order to assess the persistence at Year 5, 6, 7, 8, 9 and 10 and beyond after the primary vaccination in the ZOSTER-006/022 studies, a longitudinal analysis will be performed and will include all results from ZOSTER-006/022 studies and all results from this ZOSTER-049 study.

The following parameters will be tabulated by vaccine group for all timeframes:

- Seropositivity rate with exact 95% CI;
- GMC with 95% CI;
- Vaccine response rate with exact 95% CI;
- MGI from baseline with 95% CI for anti-gE;
- The distribution of Ab titres will be tabulated and also presented using reverse cumulative curves.

Note that the baseline that will be used for the computation of MGI and VRR will be the concentration obtained at pre-vaccination in the primary studies.

6.3.3.2. Cell-mediated immune response

For the yearly prediction of the GMCs (year 5 to year 10 and beyond): the analysis of CMI persistence will be based on the ATP cohort for persistence adapted for each year. ***The methodology of modelling prediction is mentioned in Section 7.4.3.***

In order to assess the persistence at Year 5, 6, 7, 8, 9 and 10 and beyond after the primary vaccination in the ZOSTER-006/022, a longitudinal analysis will be performed and will include all results from ZOSTER-006/022 studies and all results from this ZOSTER-049 study.

The following parameters on the frequency of CD4+ T-cells secreting at least two activation markers (from among IFN-γ, IL-2, TNF-α, CD40L) for gE-specific stimulation will be tabulated by group for all timeframes.

- Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max)
- Vaccine response rate with exact 95% CI.

Note that the baseline that will be used for the computation of VRR will be the concentration obtained at pre-vaccination in the primary studies.

6.3.3.3. Additional consideration

Following analysis will be performed by age strata (50-59, 60-69, ≥70 and ≥60 YOA at primary vaccination), gender, race, ethnicity and region for HI:-

- ***Seropositivity rate and GMC with exact 95% CI;***
- ***VRR over pre-vaccination in the primary ZOSTER-006/022 studies with exact 95% CI;***
- ***MGI from baseline with 95% CI***

Following analysis will be performed by age strata (50-59, 60-69, ≥70and ≥60 YOA at primary vaccination), gender, race, ethnicity and region for CMI:-

- ***Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max) of the frequency of CD4+ T-cells secreting at least two activation markers (from among IFN-γ, IL-2, TNF-α, CD40L) for gE-specific stimulation will be presented***
- ***CMI Vaccine response rate with exact 95% CI.***

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

The analysis will be performed on the TVC.

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

- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AEs during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall (1-Additional Dose and Revaccination groups). The same tabulation will be performed for grade 3 solicited adverse events;
- 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 (1-Additional Dose and Revaccination groups). For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs, grade 3 related, ***medically attended*** and for solicited general AEs ***with causal*** relationship to vaccination (1-Additional Dose and Revaccination groups);

- The percentage of subjects reporting temperature by half degree (°C) cumulative increments. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for any fever resulting in a medically attended visit (1-Additional Dose and Revaccination groups);
- The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination will be tabulated with exact 95% CI (1-Additional Dose and Revaccination groups). ***The same tabulation will be performed for grade 3 unsolicited AEs, for unsolicited AEs with a relationship to vaccination and grade 3 unsolicited AEs related to vaccination;***
- The percentage of unsolicited AEs resulting in a medically attended visit will also be tabulated (***Control,*** 1-Additional Dose and Revaccination groups). ***The table for medically attended unsolicited adverse events will be presented within 30 days post each vaccination for 1-Additional Dose and Revaccination group and within 30 days post Month 0 and Month 2 visit for Control group. The medically attended unsolicited adverse events will also be presented from first vaccination up to 6 months post last vaccination for 1-Additional Dose and Revaccination group and within 6 months of Month 0 visit for Control group.***
- Total number/percentages of doses (per dose and overall) followed by ***unsolicited*** Aes will be tabulated (1-Additional Dose and Revaccination groups);
- Number of subjects with pIMDs and SAEs will be tabulated (1-Additional Dose, Revaccination and Control groups). ***The table will be presented within 30 days post each vaccination for 1-Additional Dose and Revaccination group and within 30 days post Month 0 and Month 2 visit for Control group. The pIMDs and SAEs will also be presented from first vaccination up to 12 months post last vaccination for 1-Additional Dose and Revaccination group and within 12 months of Month 0 visit for Control group; The same will be presented for pIMD and SAEs causally related to vaccination for 1-Additional and Revaccination groups.***
- ***Number and percentage of subjects with SAEs reported related to investigational vaccine, related to study participation or concurrent GSK medication/vaccine will be presented till end of the study for all groups.***
- ***Listing of SAEs from first vaccination up to 12 months post last vaccination for 1-Additional dose and Revaccination group and within 12 months of Month 0 visit for Control group***
- ***Listing of*** all SAEs and all pIMDs ***(all groups) collected in the Expediated AE form***
- ***Listing of*** SAEs related to study participation or to GSK concomitant medication/vaccine (all groups);
- ***Listing of*** Adverse events (AEs)/SAEs leading to withdrawal from the study (all groups);
- ***Listing of*** HZ complications (all groups).

6.4.2. Additional considerations

Following analyses will be performed:

- ***As part of safety endpoint assessment:***
  - ***The percentage of subjects with at least one local (solicited and unsolicited) AE, with at least one general (solicited and unsolicited) AE and with any (solicited and unsolicited) AEs during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall (1-Additional Dose and Revaccination groups). The same tabulation will be performed for grade 3 solicited adverse events;***
- ***Duration of each separate solicited local and general AE during the solicited follow-up period will be presented. Total duration of each individual (any and grade 3) solicited local and general AE will be tabulated. Tabulations will be provided on duration of solicited symptoms ongoing beyond the 7-day (Days 0-6) post vaccination period***
- ***Number and percentage of subjects with fatal SAEs, classified by MedDRA Primary System Organ Class and Preferred Term will be presented with exact 95% CI in two ways:-***
  - ***With respect to onset of fatal SAE:- With onset of fatal SAE within 30 days post each vaccination for 1-Additional Dose and Revaccination group and within 30 days post Month 0 and Month 2 visit for Control group; with onset of fatal SAE within 12 months post last vaccination for 1-Additional Dose and Revaccination group and within 12 months post Month 0 visit for Control group; with onset of fatal SAE from study start up to study end for all groups group collected in Expediated AE report as per protocol.***
  - ***With respect to date of death:- Who died within 30 days post each vaccination for 1-Additional Dose and Revaccination group and within 30 days post Month 0 and Month 2 visit for Control group; with death within 12 months post last vaccination for 1-Additional Dose and Revaccination group and within 12 months post Month 0 visit for Control group; with death from study start to study end for all groups collected in Expediated AE report as per protocol.***

  Please note – before protocol amendment 2, the fatal SAEs were collected in the Expediated AE report and after protocol amendment 2 only the related fatal SAE were reported in Expediated AE report.
- ***Listing of subjects who died (related and not related to vaccination before Protocol Amendment 2) and their fatal SAEs collected in Expediated AE report.***
- ***Listing of subjects who died (not related to vaccination) collected in the study continuation form after protocol amendment 2.***
- ***Listing of intercurrent medical condition for all groups***
- ***As per recommendation from CBER, following 2 tables will be generated for 1-Additional dose and Revaccination group:***

  - subjects with Grade 3 non-serious unsolicited AEs up to 30 days post each vaccination (day 0-29)
  - subjects with Grade 3 non-serious unsolicited AEs with causal relationship to vaccination up to 30 days post each vaccination (day 0-29)

- ***As per recommendation from CBER, the following analysis will be performed by age strata 2, gender, race, ethnicity and region:-***
  - ***Percentage of SAEs reported related to investigational vaccine, related to study participation or concurrent GSK medication/vaccine, during the entire study period for the LTFU group.***

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Date derivation

- SAS date derived from a character date: If day is missing, 15 is used. If day and month are missing, 30 June is used.
- Onset day for an event (ae, medication, vaccination, …): The onset day is the number of days between the last study vaccination and the onset/start date of the event. This is 0 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.
- Duration: The duration of an event is expressed in days. It is the number of days between the start and the stop dates + 1. Therefore, duration is 1 day for an event starting and ending on the same day.

7.1.2. Dose number

- The study dose number is defined in reference to the number of study visits at which vaccination occurred. More specifically dose 1 refers to all vaccines administered at the first vaccination visit while dose 2 corresponds to all vaccinations administered at the second vaccination visit even if this is the first time a product is administered to the subject.
- Relative dose: the relative dose for an event (AE, medication, vaccination) is the most recent study dose given before an event. In case the event takes place on the day a study dose is given, the relative dose will be that of the study dose, even if the event actually took place before vaccination. For instance, if an adverse event begins on the day of the study vaccination but prior to administration of the vaccine, it will be assigned to this dose. In case a study dose is not administered, and an event occurs after the subsequent study dose (e.g., 2nd study dose), the relative dose of the event will be study dose associated to the subsequent study dose (e.g., dose 2).
- The number of doses for a product is the number of times the product was administered to a subject.
- The incidence per dose is the number of vaccination visits at which an event was reported among all vaccination visits.

7.2. Demography

For a given subject and a given demographic variable, missing measurement will *not be replaced* except for age.

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.

Note that due to incomplete date, the derived age may be incorrect by 1 month when day is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used at enrolment.

Also note that due to some countries' restrictions regarding collecting the full date of birth at the start of ZOSTER-049 study, in some subjects the date of birth information collected in ZOSTER-049 study was less complete than the date of birth collected in ZOSTER-006/022 (e.g., only the year of birth was collected for ZOSTER-049 study). Consequently, the calculation of age would be different for some subjects when using the date of birth info collected in ZOSTER-049 vs. in ZOSTER-006/022. To be consistent with the analyses already done in previous ZOSTER-006/022 studies, the calculated age as on 1st vaccination from ZOSTER-006/022 study will be used. For calculation of age as on enrolment day/additional dose in ZOSTER-049 study, the age difference between the first vaccination in ZOSTER-006/022 and enrolment day/additional dose should be calculated and added to the age calculated as on the 1st vaccination in ZOSTER-006/022 studies.

Interval (in years) between the end of study efficacy cut-off date (21 April 2015) of ZOSTER-006/022 and the first and last visit of the LTFU and control group will be calculated by dividing the number of months between the two dates by 12. The same method is used to calculate the interval (in years) between the second dose of ZOSTER-006/022 and the first dose in the revaccination group and the 1-additional group and the first visit for the control group.

7.3. Method for Vaccine Efficacy

7.3.1. Efficacy data

There is no concurrent placebo/control group in this study, therefore efficacy estimates derived from ZOSTER-049 are not equivalent to vaccine efficacy estimated in well-controlled randomized studies. Any comparison with ZOSTER-006/022 estimates should be considered with caution.

An "event" in the efficacy analysis is defined as an endpoint of interest. This could be HZ confirmed case, PHN or HZ related complications (other than PHN). The incidence rate of an "event" is determined with reference to the first "event" observed in the subject, should several "events" occur in the same subject.

The follow-up time already observed for each subject at inclusion in ZOSTER-049, and at the time of discharge will be calculated and accounted in the assessment of HZ rate estimates of the HZ/su vaccine group.

The follow-up time for each subject **will start:**

If the follow-up period to be considered is the duration over ZOSTER-049 study

- ***The date of the first visit in the study ZOSTER-049 study***

If the follow-up period to be considered is from the primary study ZOSTER-006/022 study

- ***at the day after first vaccination (Month 0) if analyses are done on the Total Vaccinated Cohort for efficacy, or***
- ***at 30 days after second vaccination (Month 3) if analyses are done on the mTVC or ATP cohort for efficacy.***

The follow-up time for each subject **will end:**

- at the time of the event; or,
- ***at the time of receiving any vaccination for shingles which is not assigned as per protocol (for mTVC only); or,***
- at the latest visit for which data is available for subjects in case of no event. Practically, this will be set at the minimum date between the following dates
  - Date of withdrawal
  - Date of death ***collected on the conclusion page for the subject who died***
  - Date of study conclusion
  - Cut of date for interim reporting for Y2, Y4

Start date of confirmed HZ case will be the earliest of the start date of the rash or start date of the pain to assess the onset of HZ, whichever comes first.

Consideration on subjects who had HZ/PHN/HZ related complication (other than PHN) cases in ZOSTER-006/022 studies and were enrolled into ZOSTER-049 study:

- ***For the VE analysis in the prevention of HZ/PHN/HZ related complication (other than PHN) over the total duration of the ZOSTER-049 study, these subjects with previous confirmed cases will be excluded from ZOSTER-049 data.***

- ***For the VE analysis in the prevention of HZ/PHN/HZ related complication (other than PHN) from one month post dose 2 in the ZOSTER-006/022 studies until the end of the ZOSTER-049 study, the first confirmed case will be considered, and the corresponding follow-up times will be censored to the time at 1st confirmed episode.***

As there is no elimination code in primary studies ZOSTER-006/022 which eliminate subject with confirmed HZ episode, it will not be identified by elimination but rather by creating flag based on the w_algo dataset generated during primary analysis. The follow-up time will be calculated in days as Date of end of follow-up period – Date of vaccination +1 and expressed in person-years at risk (number of days/365.25).

For the clinical endpoint linked to a **confirmation of HZ**, since there is no possibility to confirm a suspected HZ case during the gap, the follow-up time for subjects who came back to ZOSTER-049 will be computed minus the gap between the end of study efficacy cut-off date (21 April 2015) of ZOSTER-006/022 and the first visit for each subject ***in ZOSTER-049***.

7.3.2. Sensitivity analysis Bayesian method

Bayesian method may be used to reflect the sample distribution of the HZ cases in the control group, should a placebo arm be available in ZOSTER-049. The method will provide posterior predictive credible interval around the expected HZ incidence rate for the placebo historical controls and will be used to provide uncertainty estimates around the vaccine efficacy. The Poisson-regression model and other details of the methodology will be identical to the method described above. Non-informative (Jeffrey's) prior will be used in order to provide means and variance estimates very close to the frequentist estimates.

7.3.3. Method for determining Historical Control Reference Group for Planned Analysis

The proposed model is specified prior to performing any interim analysis and is based on analysis performed on previous studies ZOSTER-006/022.

Since there is no concurrent placebo group in ZOSTER-049, incidence rates estimations on the hypothetical Control group in ZOSTER-049 study are done by utilizing Poisson regression model using data from the Placebo group in ZOSTER-006/022 study to obtain the coefficients for region and by age strata (based on age on primary vaccination). The resulting estimated incidence rate adjusted for region and by age strata are then multiplied by the actual follow-up (FU) time observed in the ZOSTER-049 study (all vaccinated subjects) to obtain the estimated number of HZ cases on the hypothetical Control group. The same incidence rate estimates by region and by age strata will be used in both yearly and overall VE calculation.

The statistical methodology used to estimate the incidence rate on the hypothetical ZOSTER-049 control from the historical control reference group is described below. The calculation of the vaccine efficacy is based on the methodologies used in the Merck paper (Morrison) and will be done stepwise as described below:

1. Poisson regression models are used to estimate the incidence rate for HZ for the ZOSTER-049 study hypothetical placebo group based on historical controls from ZOSTER-006/022 study:

A Poisson regression model based on placebo's HZ rates in ZOSTER-006/022 studies is developed for estimating the regression coefficient in each age strata (age at first vaccination in ZOSTER-006/022 studies): ***50-59, 60-69, 70-79, ≥80, ≥ 60, ≥ 70 YOA***.

$$\text{Ln}(r\_Hz_{\text{placebo in zoster-006/022}}) = \alpha + \beta_{\text{Australasia}} * \text{Region}_{\text{Australasia}} + \beta_{\text{Europe}} * \text{Region}_{\text{Europe}} + \beta_{\text{North America}} * \text{Region}_{\text{North America}} \beta_{\text{Latin America}} * \text{Region}_{\text{Latin America}}$$

Where

- $\text{Exp}(\alpha)$ = mean HZ rate across all regions
- $\text{Region}_{\text{Australasia}}$, $\text{Region}_{\text{Europe}}$, $\text{Region}_{\text{North America}}$, $\text{Region}_{\text{Latin America}}$ are indicator variable(1/0)
- $\beta_{\text{Australasia}}$, β_{Europe}, $\beta_{\text{North America}}$, $\beta_{\text{Latin America}}$: estimated region-specific Poisson regression coefficients for HZ rate.

To note - North America is used as reference group

2. Determine the Age adjusted historical control rate:

Using the coefficients from the Poisson regression in (1), the age-specific HZ incidence rates for an age stratum for Placebo group will be calculated as:

$$\text{Age specific } r\_HZ_{\text{historical control reference group}} = \exp(\alpha + \beta_{\text{Australasia}} * \text{Region}\_\text{Australasia} + \beta_{\text{Europe}} * \text{Region}\_\text{Europe} + \beta_{\text{Latin America}} * \text{Region}\_\text{Latin America})$$

Once the age-specific incidence rates are calculated for the historical control data from the ZOSTER-006 and ZOSTER-022, the results will be used to calculate age-specific controls rates on the hypothetical control group for the ZOSTER-049 interim and final analyses.

3. Determine the number of HZ cases for the age adjusted historical controls:

For each scheduled analysis, the age-specific follow-up time observed in ZOSTER-049 will be used as the follow-up time on the corresponding age-specific hypothetical control on ZOSTER-049. The total number of subject-years of HZ surveillance (F_{Age}) for each age-strata will be then multiplied by the age-specific incidence rate that was estimated from step 2, to obtain the expected number of evaluable cases of HZ (n_{Age}) for a specific age strata in the hypothetical control in ZOSTER-049:

$$n_{Age\_} = F_{Age} * \exp(\alpha + \beta_{\text{Australasia}} * \text{Region}_{\text{Australasia}} + \beta_{\text{Europe}} * \text{Region}\_\text{Europe} + \beta_{\text{Latin America}} * \text{Region}\_\text{Latin America})$$

Once the expected number of cases for the hypothetical controls are determined for each age strata, expected HZ incidence rate for the hypothetical controls will be calculated by summing the numbers of expected evaluable cases of HZ for each age strata, and dividing by the total number of subject-years of HZ surveillance among all subjects during the ZOSTER-049 study.

For the overall calculation of VE starting from the ZOSTER-006/022 study, the observed incidence rate for Placebo during ZOSTER-006/022 and the predicted incidence rate during ZOSTER-049 will be used in the calculation.

In the situation that there are very few subjects during the last year of follow-up with limited total follow-up time, data from both year 11 and year 12 will be pooled in the VE analysis.

For the sensitivity analysis considering subjects aging when enrolled into ZOSTER-049 from ZOSTER-006/022. The same step 1,2 and 3 will be used to calculate the incidence rates on ZOSTER-049 historical control using data from ZOSTER-006/022 control. The only difference is that estimated incidence rates will be applied to the age-specific group based on the approximate age in years when the subjects were enrolled in the beginning of study ZOSTER-049 to estimate the HZ cases in the hypothetical control.

For the VE analysis for PHN or HZ related complication (other than PHN) the same poison regression models detailed in step 1, 2 and 3 will be used to generate the hypothetical controls for the incidence of PHN or HZ related complication (other than PHN) in study ZOSTER-049.

7.3.4. Method for computing VE and the associated CIs

Once estimated data for the hypothetical control are generated as per steps listed in Section 7.3.2, following similar approach in ZOSTER-006/022, Poisson regression model will be used to estimate VEs and the associated CIs for all the planned VE analysis. Region will be included as a fixed effect and analysis will be performed on the following age strata ((***50-59, 60-69, 70-79, ≥80, ≥60, ≥70 YOA s***eparately and overall.

In the situation that there is no case in HZ/su group and >0 cases in Placebo group, VE and UL of VE will be set to be 100%. In the situation that there is >0 cases in HZ/su group and 0 case in Placebo group, VE and CI of VE will be set as "not available" ("-" or "U").

7.3.5. Calculation details for sensitivity analysis including suspected HZ cases captured in the gap between primary and ZOSTER-049 study

The following positive rates of confirmed cases out of the suspected cased are assumed in this sensitivity analysis: 30%, 40% and 50%. The selection of those positive rates considers the true positive rate from clinically evaluated suspected cases on the HZ/su cohorts from study ZOSTER-006, ZOSTER-022 and ZOSTER-049, which are 13%, 35% and 39% respectively. Please note that the actual positive rate based on self-

reported suspected cases is expected to be lower than what is based on clinically evaluated suspected cases. Therefore, these selected positive rates are conservatively high and would be able to adequately assess the possible influence on VE.

The following simulation considering 30% confirmation rate is planned to account for the uncertainties around which suspected subjects could have been positive and what is their respective follow-up times:

1. ***Assume p=30%, the number of confirmed cases is denoted as n which equals N*30%, where N is the total # of subjects who self-reported HZ case during the gap period.***
2. ***Randomly draw n subjects from N. For each drawn subject, their follow-up time is simulated from a uniform distribution (0, GT] where GT is the actual time that subject had during the gap period.***
3. ***Update the follow-up time for each of the n subjects with the simulated follow-up time***
4. ***Data from those n subjects are excluded from ZOSTER-049 data.***
5. ***Following the same steps in VE analysis B to calculate VE with the updated total number of confirmed cases and updated total follow-up time. Obtain the results for each round of simulation***
6. ***Repeat step 2-5 for 100 times.***
7. ***Calculate and present mean, min, max, Q1 and Q3 of VEs obtained by the 100 simulations***

Repeat Step 1 through 7 to derive the VE results using other two assumed p=40% and 50%.

7.3.6. Calculation details for sensitivity analysis considering subjects aging when enrolled into ZOSTER-049 from ZOSTER-006/-022

Please see below for the illustration on the implementation steps to perform this VE sensitivity analysis by age strata:

ZOSTER-006/022 control		*ZOSTER-049 hypothetical control (estimated HZ cases to be used in 049 VE analysis)*				
Age group	*IR estimate*	*Age group*	*N (ZOSTER -049)*	*FU Time (FT) (ZOSTER-049)*	*IR estimate Based on ZOSTER-006/022 control*	*HZ case*
50-54 YOA (at primary vaccination)	*IR1*	*50-54 YOA (at Z-049 enrollment)*	*NA*	*NA*	*NA*	*NA*

ZOSTER-006/022 control		*ZOSTER-049 hypothetical control (estimated HZ cases to be used in 049 VE analysis)*				
55-59 YOA (at primary vaccination)	*IR2*	*55-59 YOA (at Z-049 enrollment)*	*N1*	*FT_1*	*IR2*	*n1=FT1*IR 2*
60-64 YOA (at primary vaccination)	*IR3*	*60-64 YOA (at Z-049 enrollment)*	*N2*	*FT_2*	*IR3*	*n2=FT2*IR 3*
65-69 YOA (at primary vaccination)	*IR4*	*65-69 YOA (at Z-049 enrollment)*	*N3*	*FT_3*	*IR4*	*n3=FT3*IR 4*
70-74 YOA (at primary vaccination)	*IR5*	*70-74 YOA (at Z-049 enrollment)*	*N4*	*FT_4*	*IR5*	*n4=FT4*IR 5*
75-79 YOA (at primary vaccination)	*IR6*	*75-79 YOA (at Z-049 enrollment)*	*N5*	*FT_5*	*IR6*	*n5=FT5*IR 6*
80-84 YOA (at primary vaccination)	*IR7*	*80-84 YOA (at primary vaccination)*	*N6*	*FT_6*	*IR7*	*n6=FT6*IR 7*
>=85 YOA (at primary vaccination)	*IR8*	*>=85 YOA (at Z-049 Enrollment)*	*N7*	*FT_7*	*IR8*	*n7=FT7*IR 8*

The resulting HZ cases for age strata defined by subjects' age at first vaccination in ZOSTER-006/022 studies are then calculated in the following way which are to be used in the VE sensitivity analysis by strata following the same methodology used in VE Analysis A, B and C:

HZ cases for 50-59 YOA: n1+n2

HZ cases for 60-69 YOA: n3+n4

HZ cases for 70-79 YOA: n5+n6

HZ cases for >=80 YOA: n7

Since all subjects in ZOSTER-049 study were >= 55 YOA at their enrollment, for the overall VE sensitivity analysis, subjects who were 50-54 YOA at primary vaccination were excluded from the ZOSTER-006/022 Placebo group when building the

hypothetical control. The estimated IR are then multiplied by the total follow-up time observed in ZOSTER-049 study to obtain the estimated HZ cases, which will be subsequently used to calculate overall VE following the same methodology used in VE Analysis A, B and C.

7.4. Immunogenicity

For the analysis of immunogenicity, 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.

7.4.1. Humoral immune response

A seronegative subject is a subject whose Ab concentration is below the cut-off value.

A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.

The seropositivity rate is defined as the percentage of seropositive subjects.

The Vaccine Response Rate (VRR) for anti-gE is defined as the percentage of subjects who have at least:

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

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

The Mean Geometric Increase (MGI) is defined as the geometric mean of the within subject ratios of two different timepoints.

- The assay cut-off is the value under which there is no quantifiable result available. For an assay with a specific ‘cut_off’, numerical immuno result is derived from a character field (rawres):
  - If rawres is ‘NEG’ or ‘-’ or ‘(-)’, numeric result= cutt_off/2,
  - if rawres is ‘POS’ or ‘+’ or ‘(+)’, numeric result = cut_off,
  - if rawres is ‘< value’ and value<=cut_off, numeric result =cut_off/2,
  - if rawres is ‘< value’ and value>cut_off, numeric result =value,
  - if rawres is ‘> value’ and value<cut_off, numeric result =cut_off/2,
  - if rawres is ‘> value’ and value>=cut_off, numeric result =value,

- if rawres is '<= value' or '>= value' and value<cut_off, numeric result =cut_off/2,
- if rawres is '<= value' or '>= value' and value>=cut_off, numeric result =value,
- if rawres is a value < cut_off, numeric result = cut_off/2,
- if rawres is a value >= cut_off, numeric result = rawres,
- if rawres is a value >= cut_off, numeric result = rawres,
- else numeric result is left blank.

- All CI computed will be two-sided 95% CI.

7.4.2. CMI response

- For the descriptive analyses, the frequency of CD4[2+] T-cells upon in vitro stimulation with the gE-antigen (induction condition) is calculated by dividing the number of activated CD4[2+] T-cells (numerator) over the total number of CD4 T-cells involved (denominator). The same calculation will be performed for the frequency computation for any kinds of cells and for each individual activation marker as appropriate.

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}}$$

$n_{Induction}^{2+} = \text{number of CD4 T} - \text{cells secreting at least 2 activation markers after induction with the antigen}$

$N^{CD4} = \text{Total number of CD4 T} - \text{cells involved in the assay (induction)}$

- The frequency of gE-specific CD4 T-cells for each individual subject is calculated as the difference between the frequency of CD4[2+] T-cells, upon in vitro stimulation with the gE antigen (induction condition) minus the frequency of CD4[2+] T-cells upon in vitro stimulation in medium only (background condition). The differences less or equal to one are imputed to one gE-specific CD4[2+] T-cell per 10^6 $CD4^+$ T-cells. The same calculation will be performed for the frequency computation for any kind of cells and for each individual activation marker as appropriate.

$$Freq_{Specific}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} - \frac{n_{Background}^{2+}}{N_{Background}^{CD4}} \qquad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} > 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$$Freq_{Specific}^{CD4[2+]} = 1 \qquad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} \le 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$n_{Induction}^{2+} = \text{number of CD4 T - cells secreting at least 2 activation markers after induction with the gE - antigen}$

$n_{Background}^{2+} = \text{number of CD4 T - cells secreting at least 2 activation markers in the medium conditions}$

$N^{CD4} = \text{Total number of CD4 T - cells involved in the assay (induction of background)}$

- The GM frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations.
- The CMI vaccine response to gE will be based on the gE-specific data. The VRR is defined as the percentage of subjects who have at least:

- a 2-fold increase as compared to the threshold 320 polypositive CD4+ T cells/10E6 CD4+ T cells, for subjects with pre-vaccination T-cell frequencies below the threshold 320 polypositive CD4+ T cells/10E6 CD4+ T cells;
- a 2-fold increase as compared to pre-vaccination T-cell frequencies, for subjects with pre-vaccination above the threshold 320 polypositive CD4+ T cells/10E6 CD4+ T cells.

7.4.3. Prediction modelling for humoral *and cellular immune* response

Descriptive long-term analysis of other ZOSTER studies indicated that both cellular and humoral gE-specific immune responses were highest at Month 3 and then declined until they began to plateau by Month 12 [Chlibek, 2016].

A mixed effect model for repeated measurements will be used to model over time the log10-transformation concentration of gE ELISA and the frequency of CD4 T-cells producing at least 2 immunological activation markers following stimulation with gE.

The covariates will include the log-transformed pre-vaccination response and the time (or the log-transformed of the time if needed) elapsed (measured in months) following the last vaccination. CCI [redacted] The model will contain a random intercept effect and, if data allows, the random slope effect. Indeed, the model allows for random individual deviations from the overall mean response (random intercept) and, if necessary, according to Schwarz' Bayesian Information Criterion (SBIC) and Akaike's information Criterion (AIC) goodness-of-fit statistics, for a random individual deviation from the immunogenicity endpoints decay over time (random coefficient [slope]).

Since the focus here is on long-term persistence rather than antibody rise induced by vaccination, and because it has proved difficult to apply modelling to the first rapid decay phase, the model will use data starting from 1 month post dose 2. Sensitivity analysis will use data starting from 1 year post dose 2. The model will include assay results from a time point provided that these were part of the ATP cohort for that time point (adapted ATP). ***The model is also going to be used to predict the antibody up to 15 years post vaccinations.*** Given the nonlinear nature of antibody decay, three mixed-effects models will be explored to model over time the immunogenicity endpoint: wo exponential models proposed by [Fraser, 2007] and the piecewise model proposed by [David, 2009]

The first model used by Fraser is the conventional power-law model that include the rate of immunogenicity endpoint decay to estimate the persistence of antibody levels over time after vaccination

The second model is the extension of the first model called modified power-law model and takes into account both antibody persistence over time and immune memory which would be involved in a long-term antibody plateau.

A third model, the piece-wise model fits the data based on two or three different non-overlapping intervals corresponding to the observed decay of vaccine-induced antibodies.

Using the model selection criteria of AIC, results from the best model selected out of those 3 mentioned above will be summarized.

The selection of the break points will be made using Akaike's information criterion and will depend on the data. CCI [redacted]

7.5. Safety and reactogenicity

7.5.1. Counting rule

The way the percentage of subjects will be derived will depend on the event analysed (see the following table for details). As a result, the denominator (N) will differ from one table to another.

Event	N used for deriving %	Terminology used in the tables for N
Concomitant medication	All vaccinated subjects	Number of subjects with at least one administered dose
Solicited general symptom	All vaccinated subjects with at least one solicited general symptom documented as either present or absent	For each dose and overall/subject: N= number of subjects with at least one documented dose For overall/dose: N= number of documented doses
Solicited local symptom	All vaccinated subjects with at least one solicited local symptom documented as either present or absent	For each dose and overall/subject: N= number of subjects with at least one documented dose For overall/dose: N= number of documented doses
Unsolicited symptom from day 0 to day 29	All vaccinated subjects	Number of subjects with at least one administered dose
SAE/ Related SAE	All vaccinated subjects	Number of subjects with at least one administered dose

Documented dose= symptom screen completed

7.5.2. Grading rule

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

0 : < 20 mm diameter

1 : ≥ 20 mm to ≤ 50 mm diameter

2 : > 50 mm to ≤ 100 mm diameter

3 : > 100 mm diameter

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

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

0	:	< 37.5°C
1	:	≥37.5°C – ≤ 38.0°C
2	:	>38.0- ≤ 39.0°C
3	:	> 39.0°C

Note that Fever is defined as temperature ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route.

7.5.3. Conversion of temperature to °C

The following conversion rule is used for the conversion of temperature to °C

Temperature in °Celsius = ((Temperature in °Fahrenheit -32) *5)/9

The result is rounded to 1 decimal digit.

7.6. Handling missing data for Reactogenicity and safety

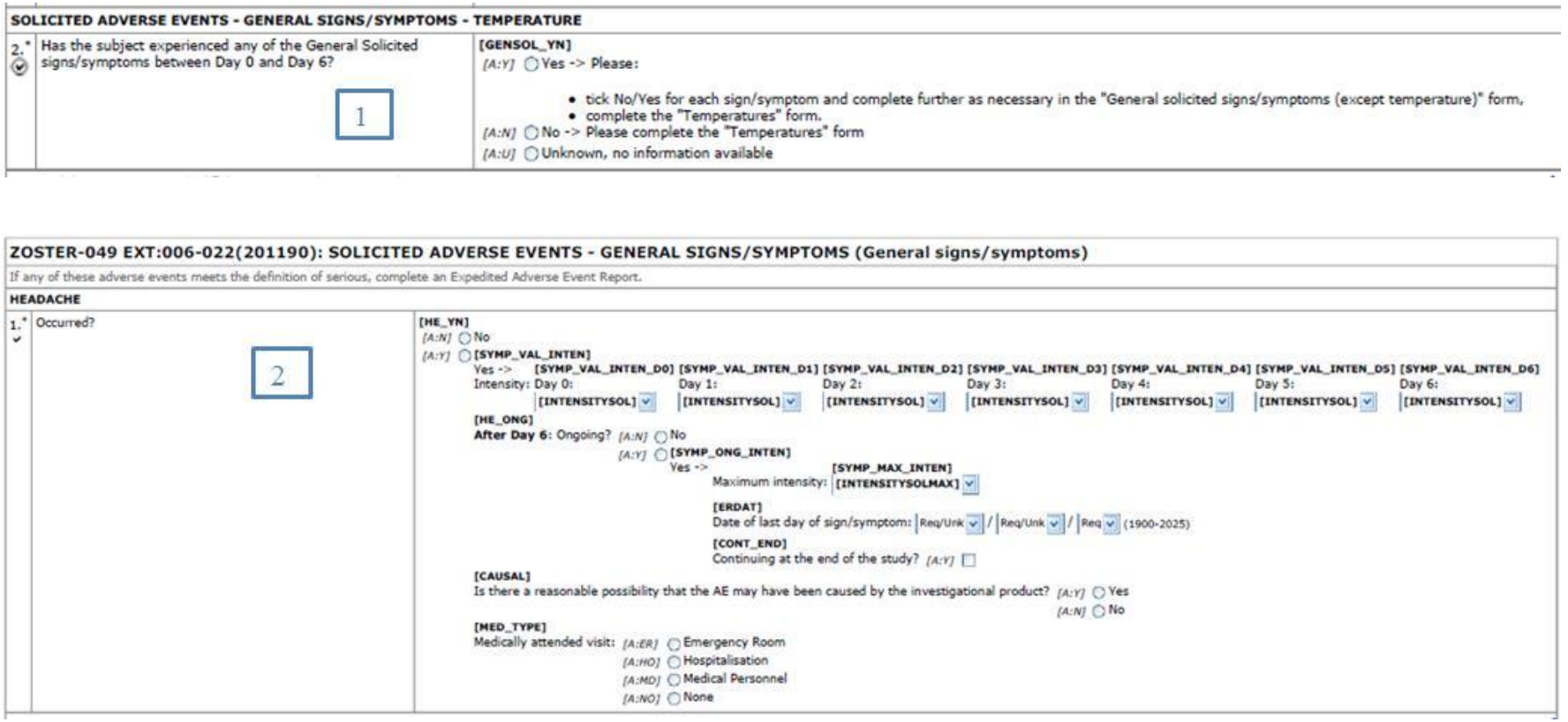
All efforts will be made during the study database cleaning, through queries to the investigators, to keep the number of missing recordings as small as possible.

7.6.1. Solicited general symptoms

For a given subject and the analysis of solicited symptoms within 7 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of the solicited symptoms based on the Total Vaccinated Cohort will include only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed). This means that the analysis of solicited general symptoms will include all subjects for whom the question (1) in Figure 3 about the presence of any solicited general symptom has been answered by 'Yes' or 'No' (see the GENSOL_YN item).

The next sections describe how each subject contributes to the analyses, depending on the endpoints.

Figure 3 Information captured in the clinical database for solicited general symptoms



SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS - TEMPERATURE

2.* Has the subject experienced any of the General Solicited signs/symptoms between Day 0 and Day 6?

1

[GENSOL_YN]
[A:Y] ◯ Yes -> Please:

- tick No/Yes for each sign/symptom and complete further as necessary in the "General solicited signs/symptoms (except temperature)" form,
- complete the "Temperatures" form.

[A:N] ◯ No -> Please complete the "Temperatures" form
[A:U] ◯ Unknown, no information available

ZOSTER-049 EXT:006-022(201190): SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (General signs/symptoms)

If any of these adverse events meets the definition of serious, complete an Expedited Adverse Event Report.

HEADACHE

1.* Occurred?

2

[HE_YN]
[A:N] ◯ No
[A:Y] ◯ [SYMP_VAL_INTEN]
Yes -> [SYMP_VAL_INTEN_D0] [SYMP_VAL_INTEN_D1] [SYMP_VAL_INTEN_D2] [SYMP_VAL_INTEN_D3] [SYMP_VAL_INTEN_D4] [SYMP_VAL_INTEN_D5] [SYMP_VAL_INTEN_D6]
Intensity: Day 0: [INTENSITYSOL] Day 1: [INTENSITYSOL] Day 2: [INTENSITYSOL] Day 3: [INTENSITYSOL] Day 4: [INTENSITYSOL] Day 5: [INTENSITYSOL] Day 6: [INTENSITYSOL]
[HE_ONG]
After Day 6: Ongoing? [A:N] ◯ No
[A:Y] ◯ [SYMP_ONG_INTEN]
Yes ->
[SYMP_MAX_INTEN]
Maximum intensity: [INTENSITYSOLMAX]
[ERDAT]
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req (1900-2025)
[CONT_END]
Continuing at the end of the study? [A:Y] ☐
[CAUSAL]
Is there a reasonable possibility that the AE may have been caused by the investigational product? [A:Y] ◯ Yes
[A:N] ◯ No
[MED_TYPE]
Medically attended visit: [A:ER] ◯ Emergency Room
[A:HO] ◯ Hospitalisation
[A:MD] ◯ Medical Personnel
[A:NO] ◯ None

The following rules will be used in the analysis of each solicited general symptom:

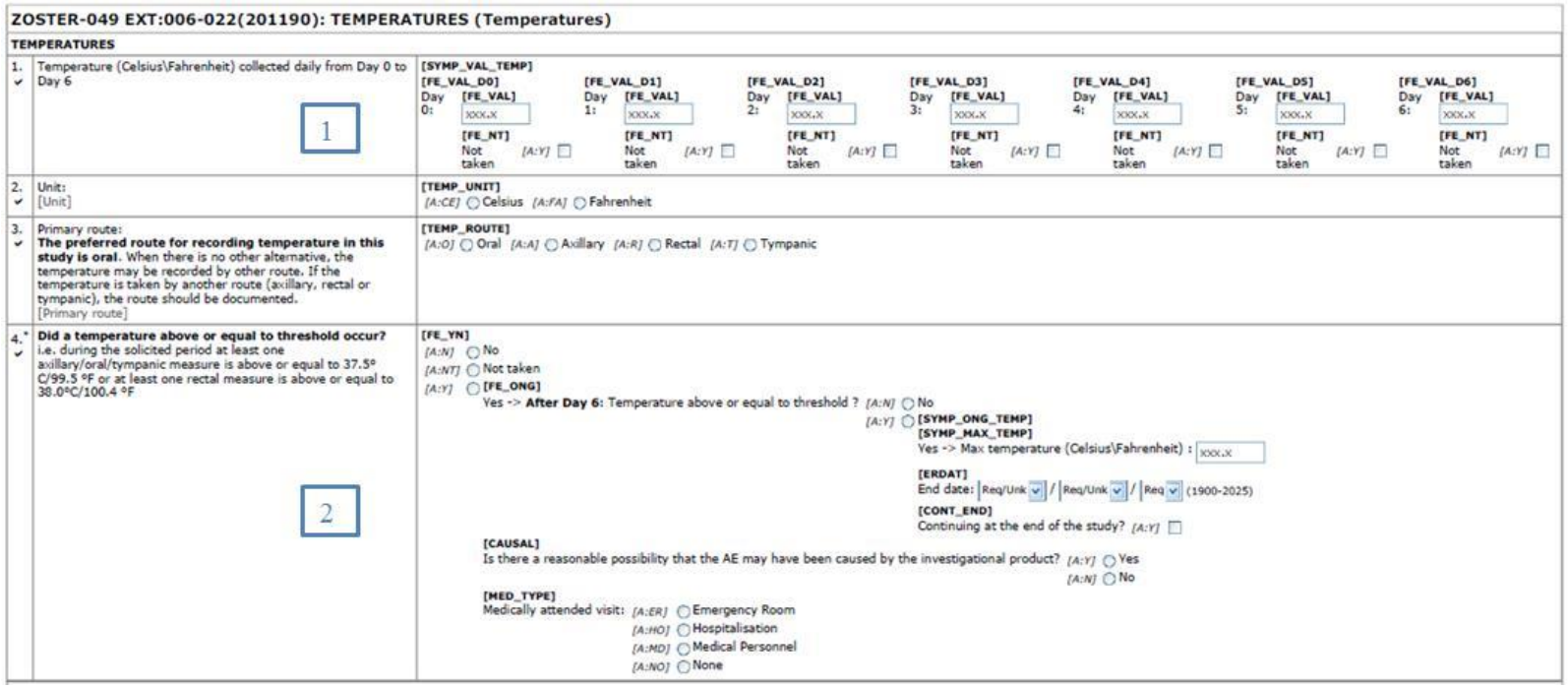
- Subjects who documented the absence of a specific solicited symptom after one dose (i.e. if the answer to question (2) in Figure 3 is "No" ex HE_YN=N)) will be considered not having that symptom after that dose.
- Subjects who documented the presence of a specific solicited symptom after one dose (i.e. if the answer to question (2) in Figure 3 is "Yes"(ex HE_YN=Y)) without having recorded any daily measurement will not be counted in the summary of subjects with symptoms above a specified threshold, however they will be part of the summary corresponding to the 'All' category.).
- Subjects who documented the presence of a specific solicited symptom (i.e. if the answer to question (2) in Figure 3 is "Yes" ex HE_YN=Y)) and fully or partially recorded daily measurement over the solicited period will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Doses without symptom screen documented will be excluded.

For summary of temperature

To allow the temperature recording, a separate screen has had to been completed whatever the answer to question (2) in Figure 4 and even if no temperature equal or above 37.5°C has been found in the diary card.

All subjects for whom that question (2) in Figure 4 has been answered by "Yes" or "No", will be included in the summaries of temperature by **half degree (°C) cumulative increments** and classified according to their maximum temperature value observed daily recording over the solicited period. If no daily measurement is recorded for temperature, the subject will not be counted in the summary of subjects with temperature above a specific threshold. For the summary of temperature, the "all" category will not be computed. This table will be produced overall, and by route with no route conversion

Figure 4 Information captured in the clinical database for temperature record



ZOSTER-049 EXT:006-022(201190): TEMPERATURES (Temperatures)

TEMPERATURES

1. ✔ Temperature (Celsius\Fahrenheit) collected daily from Day 0 to Day 6

1

[SYMP_VAL_TEMP]

[FE_VAL_D0]	[FE_VAL_D1]	[FE_VAL_D2]	[FE_VAL_D3]	[FE_VAL_D4]	[FE_VAL_D5]	[FE_VAL_D6]
Day 0: [FE_VAL] xxx.x	Day 1: [FE_VAL] xxx.x	Day 2: [FE_VAL] xxx.x	Day 3: [FE_VAL] xxx.x	Day 4: [FE_VAL] xxx.x	Day 5: [FE_VAL] xxx.x	Day 6: [FE_VAL] xxx.x
[FE_NT] Not taken [A:Y] ☐	[FE_NT] Not taken [A:Y] ☐	[FE_NT] Not taken [A:Y] ☐	[FE_NT] Not taken [A:Y] ☐	[FE_NT] Not taken [A:Y] ☐	[FE_NT] Not taken [A:Y] ☐	[FE_NT] Not taken [A:Y] ☐

2. ✔ Unit: [Unit]

[TEMP_UNIT]
[A:CE] ◯ Celsius [A:FA] ◯ Fahrenheit

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

[TEMP_ROUTE]
[A:O] ◯ Oral [A:A] ◯ Axillary [A:R] ◯ Rectal [A:T] ◯ Tympanic

4.* ✔ **Did a temperature above or equal to threshold occur?**
i.e. during the solicited period at least one axillary/oral/tympanic measure is above or equal to 37.5° C/99.5 °F or at least one rectal measure is above or equal to 38.0°C/100.4 °F

2

[FE_YN]
[A:N] ◯ No
[A:NT] ◯ Not taken
[A:Y] ◯ **[FE_ONG]**
Yes -> **After Day 6:** Temperature above or equal to threshold ? [A:N] ◯ No
[A:Y] ◯ **[SYMP_ONG_TEMP]**
[SYMP_MAX_TEMP]
Yes -> Max temperature (Celsius\Fahrenheit) : xxx.x
[ERDAT]
End date: Req/Unk / Req/Unk / Req (1900-2025)
[CONT_END]
Continuing at the end of the study? [A:Y] ☐

[CAUSAL]
Is there a reasonable possibility that the AE may have been caused by the investigational product? [A:Y] ◯ Yes
[A:N] ◯ No

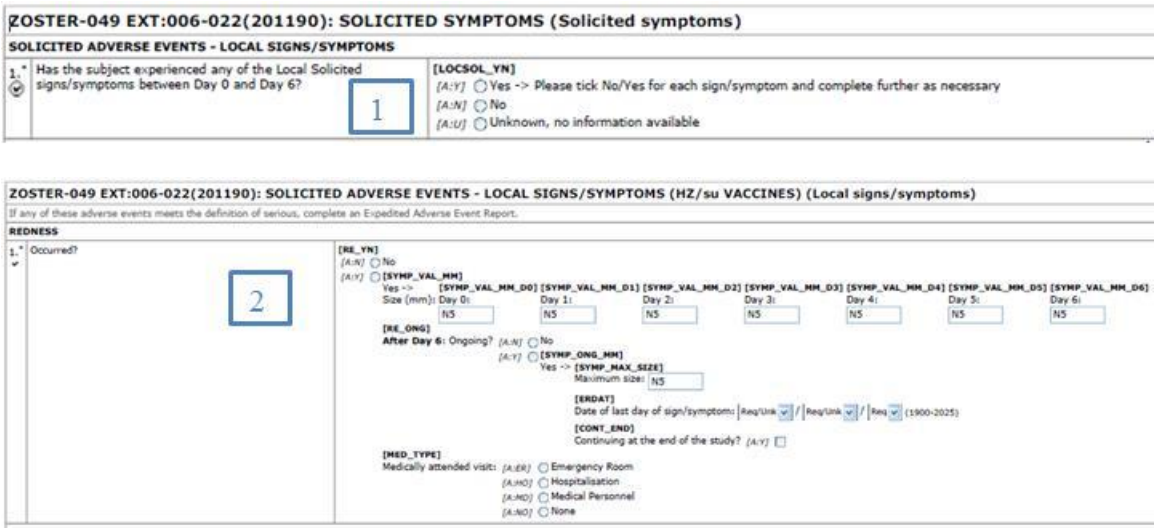
[MED_TYPE]
Medically attended visit: [A:ER] ◯ Emergency Room
[A:HO] ◯ Hospitalisation
[A:MD] ◯ Medical Personnel
[A:NO] ◯ None

7.6.2. Solicited local symptoms

The analysis of solicited local symptoms will include all subjects for whom the question (1) in Figure 4 about the presence of a solicited local symptoms has been answered by 'Yes' or 'No'(see LOCSOL_YN item).

The next sections describe how each subject contributes to the analyses, depending on the endpoints.

Figure 5 Information captured in the clinical database for solicited local symptoms



The following rules will be used in the analysis of each solicited local symptom:

- Subjects who documented the absence of a specific solicited symptom after one dose (i.e. if the answer to question (2) in Figure 5 is "No" (ex RE_YN=N)) will be considered not having that symptom at the injection site after that dose.
- Subjects who documented the presence of a specific solicited symptom after one dose (i.e. if the answer to question (2) in Figure 5 is "Yes" (ex RE_YN=Y)) without having recorded any daily measurement will not be counted in the summary of subjects with symptoms above a specified threshold, however they will be part of the summary corresponding to the 'All' category.).
- Subjects who documented the presence of a specific solicited symptom (i.e. if the answer to question (2) in Figure 5 is "Yes" (ex RE_YN=Y)) and fully or partially recorded daily measurement over the solicited period (e.g., intensity missing for Day 3) will be included in the summaries at that dose and classified according to their maximum observed daily recording over the solicited period.
- Doses without symptom screen documented will be excluded.

7.6.3. Combined Solicited local and general symptoms

The analysis of the combined solicited general and local symptoms will include all vaccinated subjects for whom the question (1) in Figure 3 or Figure 5 about the presence of any solicited general or local symptoms has been answered by 'Yes' or 'No'.

7.6.4. Unsolicited symptoms

All vaccinated subjects will be considered for the analysis of unsolicited symptoms.

The analysis of unsolicited adverse events, including serious adverse events, consists of evaluating the percentage of subjects with at least 1 report of an unsolicited adverse event classified by the Medical Dictionary for Regulatory Activities (MedDRA).

Subjects who missed reporting unsolicited symptoms will be treated as subjects without unsolicited symptoms.

7.6.5. Combined unsolicited symptoms with Solicited local and general symptoms

The analysis of the combined unsolicited symptoms with solicited general and local symptoms will include all vaccinated subjects.

- For analysis as per MedDRA classification that combines solicited and unsolicited symptoms, the following lower-level term will be used for the solicited symptoms:

Solicited Symptom Code	Value	Source Verbatim Text	LLT Name	LLT Code	PT Name	PT Code
FA	FA	FATIGUE	Fatigue	10016256	Fatigue	10016256
GI	GI	GASTROINTESTINAL	Gastrointestinal disorder	10017944	Gastrointestinal disorder	10017944
HE	HE	HEADACHE	Headache	10019211	Headache	10019211
MY	MY	MYALGIA	Myalgia	10028411	Myalgia	10028411
PA	PA	PAIN	Pain	10033371	Pain	10033371
RE	RE	REDNESS	Erythema	10015150	Erythema	10015150
SH	SH	SHIVERING	Shivering	10040558	Chills	10008531
SW	SW	SWELLING	Swelling	10042674	Swelling	10042674
TE	TE	TEMPERATURE/ fever	Fever	10016558	Pyrexia	10037660

7.7. Concomitant medication

All vaccinated subjects will be considered for the analysis of concomitant medication use. Subjects who did not report the use of a concomitant medication will be considered as subjects without medication. Subjects will be counted in the summary who **started** a concomitant medication during the mentioned period and took at least one dose.

7.8. Compliance with respect to documenting safety

The number of doses injected, the number of doses not given according-to-protocol, and the number of symptom screen transcribed for local and general symptoms, the compliance for local and general symptoms are tabulated for the TVC.

Compliance (%) is defined as the number of general (local) symptom screens completed divided by the number of doses administered for a specified vaccination (dose) and group.

The number of doses not given according-to-protocol, are the doses injected at the wrong site and/or side, or injected using the wrong route as defined in the study protocol for each study vaccine. This number is issued from the following question in the vaccine administration screen of the CRF: “Has the study vaccine been administered according-to-protocol?” Study vaccine dose not administered according to protocol can lead to elimination from the ATP cohort, depending to the ATP cohort definition in the protocol.

7.9. Number of decimals:

The following decimal description from the decision rules will be used for the demography, immunogenicity and safety/reactogenicity.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2
Immunogenicity	GMC including LL & UL	1
Immunogenicity	Ratio of GMC	2
Reactogenicity	Mean, Min, Q1, Median, Q3, Max for duration	1
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2

7.10. Methodology for computing CI

Unless otherwise mentioned, the confidence intervals will be 2 sided 95% CI and calculated according to the following methods:

7.10.1. Binomial Data

The exact 95% CIs for a proportion within a group will be calculated according to [Clopper, 1934].

7.10.2. Continuous Data

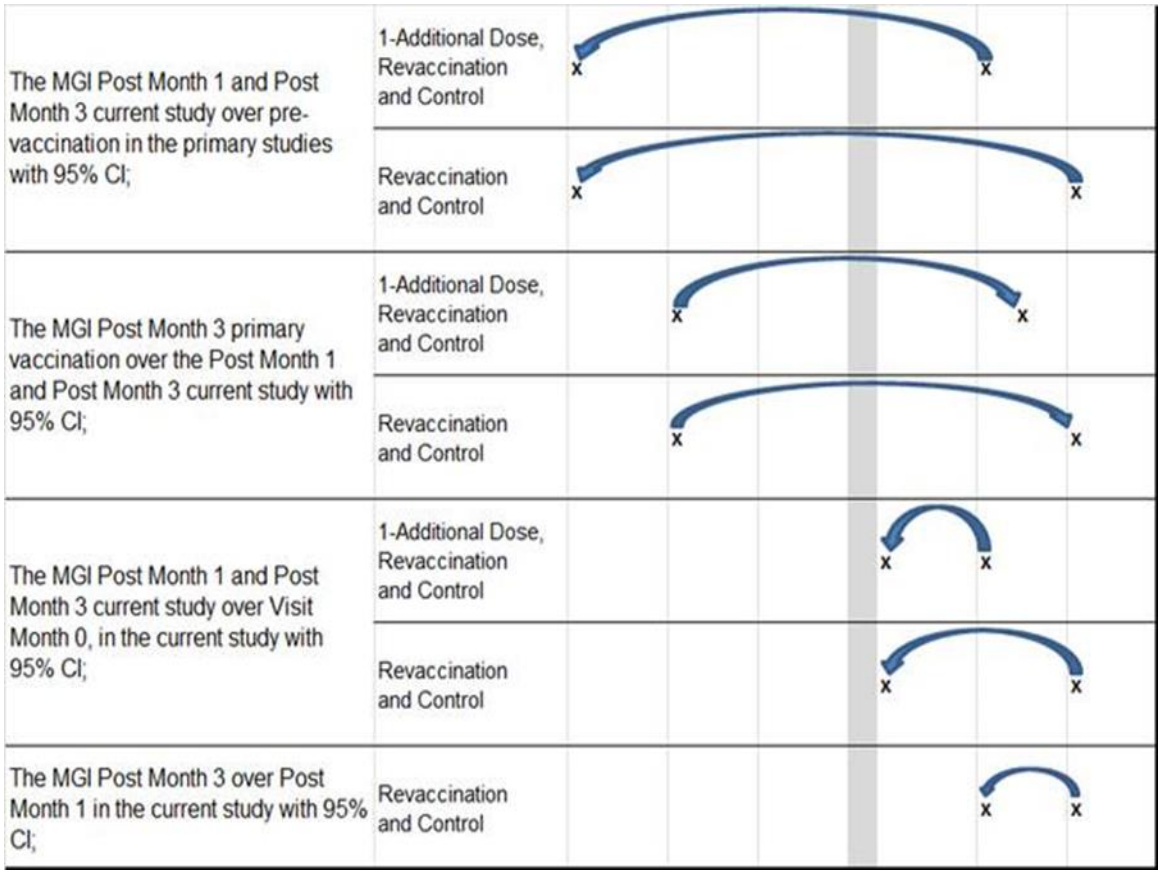
The CI for GMCs will be obtained within each group separately. The 95% CI for geometric mean concentrations GMCs analyses will be obtained. The 95% CI for the mean of log-transformed concentration will be first obtained assuming that log-

transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed concentration.

The 95% CI for each group ratio [vaccinated groups (1-Additional Dose or Revaccination group) over Control] will be computed using an Analysis of Covariance (ANCOVA) model on the logarithm-transformed concentrations/titres. The ANCOVA model will include the vaccine group as fixed effect, the age category effect, the pre-vaccination at Visit Month 0 of this current study log-transformed concentration as the regressor. The GMC ratio and their 95% CI will be derived by exponential-transformation of the corresponding group contrast in the model

The MGI is defined as the geometric mean of the within subject ratios between 2 different timepoint. The 95% CI for geometric mean (GM) of the individual ratio of a timepoint 2 over a timepoint 1 were obtained by computing the 95% CI for the mean of differences between log-transformed result at timepoint 2 and the log-transformed result at timepoint 1. The 95% CI for the GM of the individual ratios were then obtained by exponential-transformation of the 95% CI for the mean of differences of log-transformed titres.

The following figures summarise all the MGI computation planned to be done for 1-Additional Dose, Revaccination group and the Control group



8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

The analysis will be performed in the following steps:

1. The Month 3 analysis is on:

- immunogenicity and safety (SAEs and pIMDs) data in (1-Additional dose, Revaccination and Control groups), and;
- reactogenicity data (1-Additional Dose and Revaccination groups), will be performed when all those data up to Visit Month 3 are available and as clean as possible. Because the analysis is purely descriptive, no adjustment on type I error is foreseen. No clinical study report is planned to be written at this time and at this point no individual data listings will be provided. At this point, the GSK central clinical team will have access to the lab data and the treatment assignment from SBIR.

2. Two intermediate analyses to assess the VE at Year 2 and Year 4 (LTFU and Control groups):

- An assessment of the VE and immunogenicity will be performed when the last subjects have completed their Year 2 visit/contact and when efficacy data (on confirmed HZ cases) for the LTFU and Control groups, immunogenicity data in LTFU group as well as related SAEs for all groups up to Year 2 are available and as clean as possible. Because the analysis is purely descriptive, no adjustment on type I error is foreseen. A clinical study report is planned to be written at this time but no individual data listings will be provided. This study report will also include Month 3 analysis result.
- An assessment of the VE and immunogenicity will be performed when the last subjects have completed their Year 4 visit/contact and when efficacy data (on confirmed HZ cases) ***for LTFU and Control groups, immunogenicity data for LTFU group as well as related SAEs for all groups up to Year 4*** are available and as clean as possible. Because the analysis is purely descriptive, no adjustment on type I error is foreseen. A clinical study report is planned to be written at this time but no individual data listings will be provided.

3. End of study analysis:

- The end of study analysis will be performed at the end of study. End of study analysis will include all the objectives. Individual data listings will be generated at this stage. An integrated end-of-study report will be written.

Description	Analysis ID	Disclosure Purpose	Reference for TFL
End of study	E1_01	Study report	***All tables from EOS OPS***
Month 3 analysis	E1_03	Internal	Only data (immunogenicity, reactogenicity, safety) up to visit Month 3 visit for randomized groups
Vaccine Efficacy year 2	E1_04	Study report	Efficacy data and related SAE up to visit year 2 visit/contact for LTFU and control groups, Immunogenicity data for LTFU and safety data for all groups
Vaccine Efficacy year 4	E1_05	Study report	Efficacy data and related SAE up to visit year 4 visit/contact for LTFU and control groups, Immunogenicity data for LTFU and safety data for all groups

8.2. Statistical considerations for interim analyses

Long term efficacy part:

All the analyses will be descriptive with the aim to characterise the long-term efficacy.

Additional dose and revaccination part:

All the analyses will be descriptive with the aim to characterise the effect of 1 and 2 additional doses of HZ/su vaccine.

9. CHANGES FROM PLANNED ANALYSES

- CCI [redacted]

10. REFERENCES

Chlibek et al . Long-term immunogenicity and safety of an investigational herpes zoster subunit vaccine in older adults. Vaccine 34 (2016) 863-868.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934;26:404-413

David, M., Van Herck, K., Hardt, K., Tibaldi, F., Dubin, G., Descamps, D., Van Damme, P. (2009). Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: Modeling of sustained antibody responses. Gynecologic Oncology 115:S1–S6.

Fraser C., Tomassini J.E., Xi L., Golm G., Watson M., Giuliano A.G., Barr E., Ault K.A. Modeling the long-term antibody response of a human papillomavirus (HPV) virus-like particle (VLP) type 16 prophylactic vaccine. Vaccine 25 (2007) 4324–4333

Morrison VA et al. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis. 2015 Mar 15;60(6):900-9

11. APPENDIX 1: ELIMINATION TYPE FOR THE STUDY

The following is the detail of the elimination type applicable for the study:-

Eli_type	***Description of eli_type***
F0	***Persistence analysis at M0 LTFU***
F1	***Persistence year 1 (Month 12) after start of Zoster 049 (Month 0) LTFU group***
F2	***Persistence year 2 (Month 24) after start of Zoster 049 (Month 0) LTFU group***
F3	***Persistence year 3 (Month 36) after start of Zoster 049 (Month 0) LTFU group***
F4	***Persistence year 4 (Month 48) after start of Zoster 049 (Month 0) LTFU group***
F5	***Persistence year 5 (Month 60) after start of Zoster 049 (Month 0) LTFU group***
F6	***Persistence year 6 (Month 72) after start of Zoster 049 (Month 0) LTFU group***
T1	***Persistence year 4 after dose 2 vaccination in Zoster 006/022 LTFU group***
T2	***Persistence year 5 after dose 2 vaccination in Zoster 006/022 LTFU group***
T3	***Persistence year 6 after dose 2 vaccination in Zoster 006/022 LTFU group***
T4	***Persistence year 7 after dose 2 vaccination in Zoster 006/022 LTFU group***
T5	***Persistence year 8 after dose 2 vaccination in Zoster 006/022 LTFU group***
T6	***Persistence year 9 after dose 2 vaccination in Zoster 006/022 LTFU group***
T7	***Persistence year 10 after dose 2 vaccination in Zoster 006/022 LTFU group***

Eli_type	*Description of eli_type*
T8	*Persistence year 11 after dose 2 vaccination in Zoster 006/022 LTFU group*
T9	*Persistence year 12 after dose 2 vaccination in Zoster 006/022 LTFU group*
M3	*Immunogenicity analysis at Month 3 for the randomized group*
E2	*Efficacy analysis – Interim year 2 - LTFU and Control group*
E4	*Efficacy analysis – Interim year 4 – LTFU and Control group*
EF	*Efficacy analysis – Final – LTFU and Control group*
L1	*Persistence year 1 Revaccination, 1-additionnal dose and control group*
L2	*Persistence year 2 Revaccination, 1-additionnal dose and control group*
L3	*Persistence year 3 Revaccination, 1-additionnal dose and control group*
L4	*Persistence year 4 Revaccination, 1-additionnal dose and control group*
L5	*Persistence year 5 Revaccination, 1-additionnal dose and control group*
L6	*Persistence year 6 Revaccination, 1-additionnal dose and control group*
HS0	*Persistence analysis at M0 – HZ subset*
HS1	*Persistence year 1 (Month 12) after start of Zoster 049 (Month 0) – HZ subset*
HS2	*Persistence year 2 (Month 24) after start of Zoster 049 (Month 0) HZ subset*
HS3	*Persistence year 3 (Month 36) after start of Zoster 049 (Month 0) HZ subset*
HS4	*Persistence year 4 (Month 48) after start of Zoster 049 (Month 0) HZ subset*
HS5	*Persistence year 5 (Month 60) after start of Zoster 049 (Month 0) HZ subset*
HS6	*Persistence year 6 (Month 72) after start of Zoster 049 (Month 0) HZ subset*

12. APPENDIX 2: ELIMINATION DETAIL FOR MODIFIED TOTAL VACCINATED COHORT

Following is the elimination code applicable for modified Total Vaccinated Cohort for LTFU and Control groups:-

Elimcode	*Description*	*Eli_Type*
901	*Subjects excluded from all stat analyses (please comment here below)* *Subjects receiving a code 901 should not receive any other elimination codes.* *Comment – Subjects who received code 900 in ZOSTER-006/022 studies*	*EF*
900	*Subjects excluded from all stat analyses (please comment here below)* *Subjects receiving a code 900 should not receive any other elimination codes.* *Comment - During the duration of ZOSTER 049 only*	*EF*

Elimcode	*Description*	*Eli_Type*
1071	• ***Incomplete vaccination course before treatment withdrawal*** • ***site or route of study vaccine administration wrong or unknown.*** • ***Administration not according to protocol for reason specified by the investigator, other than side, site and route.*** • ***Wrong side is allowed.*** ***Comment – Subjects assigned code 1070 in ZOSTER-006/022 studies***	***EF***
1501	***Other, specify: Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number).*** ***Comment – Subjects assigned 1500 in ZOSTER 006/022 studies***	***EF***
2501	***Other, specify: Subjects not received two doses*** ***Comment – Subjects assigned 2500 in ZOSTER 006/022 studies***	***EF***
3501	***Subjects having an episode of HZ prior than 30 days after the dose 2 in Zoster 006/022*** ***Comment – Subjects assigned 3500 in ZOSTER- 006/022 studies***	***EF***

13. APPENDIX 3: ELIMINATION DETAIL FOR ATP COHORT FOR EFFICACY

Following is the elimination code applicable for ATP cohort for efficacy for LTFU and Control groups:-

Elimcode	*Description*	*Eli_Type*
901	***Subjects excluded from all stat analyses (please comment here below)*** ***Subjects receiving a code 901 should not receive any other elimination codes.*** ***Comment – Subjects who received code 900 in ZOSTER-006/022 studies***	***EF***
900	***Subjects excluded from all stat analyses (please comment here below)*** ***Subjects receiving a code 900 should not receive any other elimination codes.*** ***Comment - During the duration of ZOSTER 049 only***	***EF***
1041	***Administration of concomitant vaccine(s) forbidden in the protocol (see also eligibility criteria)*** ***Comment – Subjects assigned code 1040 in ZOSTER 006/022 studies***	***EF***
*1040**	***Administration of concomitant vaccine(s) forbidden in the protocol (see also eligibility criteria) during Zoster 049 study - Including any zoster vaccine*** ***Comment - During the duration of ZOSTER 049 only***	***EF***
1051	***Randomization failure (subject not randomized in the correct group)*** ***Comment – Subjects assigned code 1050 in ZOSTER 006/022 studies***	***EF***
1061	***Randomization code broken at the investigator site OR at GSK Safety department*** ***Comment – Subjects assigned code 1060 in Zoster 006/022 studies***	***EF***

Elimcode	*Description*	*Eli_Type*
1071	• *Incomplete vaccination course before treatment withdrawal* • *site or route of study vaccine administration wrong or unknown.* • *Administration not according to protocol for reason specified by the investigator, other than side, site and route.* • *Wrong side is allowed.* *Comment – Subjects assigned code 1070 in ZOSTER 006/022 studies*	*EF*
1081	*Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by Status QA GMP NON Use* *Comment – Subjects assigned 1080 in ZOSTER 006/022 studies*	*EF*
1091	*Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration* *Comment – Subjects assigned 1090 in ZOSTER 006/022 studies*	*EF*
1501	*Other, specify: Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number).* *Comment – Subjects assigned 1500 in ZOSTER 006/022 studies*	*EF*
1601	*Other, specify: = code 1600 (Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.)* *Comment – Subjects assigned 1600 in ZOSTER 006/022 studies*	*EF*
1600	*Other, (Protocol violation linked to the inclusion/exclusion criteria including age during Zoster 049 study)* *Comment - During the duration of ZOSTER 049 only*	*EF*
2041	*Administration of any medication forbidden by the protocol* *Comment – Subjects assigned 2040 in ZOSTER 006/022 studies*	*EF*
*2040**	*Administration of any medication forbidden by the protocol during the Zoster 049 study* *Comment - During the duration of ZOSTER 049 only*	*EF*
2051	*Underlying medical condition forbidden by the protocol* *Comment – Subjects assigned 2050 in ZOSTER 006/022 studies*	*EF*
*2050**	*Underlying medical condition forbidden by the protocol during Zoster 049 study* *Comment - During the duration of ZOSTER 049 only*	*EF*
2071	*Concomitant infection not related to the vaccine which may influence immune response (e.g. Hepatitis infection in a lyme study)* *Comment – Subjects assigned 2070 in ZOSTER 006/022 studies*	*EF*
*2070**	*Concomitant infection not related to the vaccine which may influence immune response (e.g. Hepatitis infection in a lyme study)* *Comment - During the duration of ZOSTER 049 only*	*EF*
2081	*Vaccination done but: non-compliance with vaccination schedules (dates of vaccination not corresponding to protocol intervals or unknown vaccination dates)* *Comment – Subjects assigned 2080 in ZOSTER 006/022 studies*	*EF*

Elimcode	*Description*	*Eli_Type*
2501	***Other, specify: Subjects not received two doses*** ***Comment – Subjects assigned 2500 in ZOSTER 006/022 studies***	***EF***
3501	***Subjects having an episode of HZ prior than 30 days after the dose 2 in Zoster 006/022*** ***Comment – Subjects assigned 3500 in ZOSTER 006/022 studies***	***EF***

based on CSL review of the listing

14. APPENDIX 4: ELIMINATION DETAIL FOR ATP COHORT FOR HUMORAL/CMI PERSISTENCE – LTFU GROUP

Following is the elimination code applicable for ATP cohort for humoral/CMI persistence for LTFU group:

Elimcode	*Description*	*Eli_Type*
901	***Subjects excluded from all stat analyses (please comment here below)*** ***Subjects receiving a code 901 should not receive any other elimination codes.*** ***Comment – Subjects who received code 900 in ZOSTER-006/022 studies***	***Apply to all F0 – F6, T1-T9***
900	***Subjects excluded from all stat analyses (please comment here below)*** ***Subjects receiving a code 900 should not receive any other elimination codes*** ***Comment - During the duration of ZOSTER 049 only***	***Apply to all F0 – F6, T1-T9***
1041	***Administration of concomitant vaccine(s) forbidden in the protocol (see also eligibility criteria)*** ***Comment – Subjects assigned code 1040 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
*1040**	***Administration of concomitant vaccine(s) forbidden in the protocol (see also eligibility criteria) during Zoster 049 study - Including any zoster vaccine*** ***Comment - During the duration of ZOSTER 049 only***	***Apply to associated visit, and subsequent visit***
1051	***Randomisation failure (subject not randomized in the correct group)*** ***Comment – Subjects assigned 1050 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
1061	***Randomisation code broken at the investigator site OR at GSK Safety department*** ***Comment – Subjects assigned 1060 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***

Elimcode	*Description*	*Eli_Type*
1071	• ***Incomplete vaccination course before treatment withdrawal*** • ***site or route of study vaccine administration wrong or unknown.*** • ***Administration not according to protocol for reason specified by the investigator, other than side, site and route.*** • ***Wrong side is allowed.*** ***Comment – Subjects assigned 1070 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
1081	***Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by Status QA GMP NON Use*** ***Comment – Subjects assigned 1080 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
1091	***Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration*** ***Comment – Subjects assigned 1090 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
1501	***Other, specify: Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number).*** ***Comment – Subjects assigned 1500 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
1601	***Other, specify: = code 1600 (Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.)*** ***Comment – Subjects assigned 1600 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
1600	***Other, specify: = code 2010 (Protocol violation linked to the inclusion/exclusion criteria including age during Zoster 049 study)*** ***Comment - During the duration of ZOSTER 049 only***	***Apply to all F0 – F6, T1-T9***
2041	***Administration of any medication forbidden by the protocol*** ***Comment – Subjects assigned code 2040 from ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
*2040**	***Administration of any medication forbidden by the protocol during the Zoster 049 study*** ***Comment - During the duration of ZOSTER 049 only***	***Apply to associated visit, and subsequent visit***
2051	***Underlying medical condition forbidden by the protocol*** ***Comment – Subjects assigned 2050 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***

Elimcode	*Description*	*Eli_Type*
*2050**	***Underlying medical condition forbidden by the protocol during Zoster 049 study*** ***Comment - During the duration of ZOSTER 049 only***	***Apply to associated visit, and subsequent visit***
2061	***Concomitant infection related to the vaccine which may influence immune response*** ***Comment – Subjects having confirmed HZ episode in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
*2060**	***Concomitant infection related to the vaccine which may influence immune response*** ***Comment - During the duration of ZOSTER 049 only***	***Apply to associate visit, and subsequent visit***
2071	***Concomitant infection not related to the vaccine which may influence immune response (e.g. Hepatitis infection in a lyme study)*** ***Comment – Subjects assigned 2070 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
*2070**	***Concomitant infection not related to the vaccine which may influence immune response*** ***Comment - During the duration of ZOSTER 049 only***	***Apply to associate visit, and subsequent visit***
2081	***Vaccination done but: non-compliance with vaccination schedules (dates of vaccination not corresponding to protocol intervals or unknown vaccination dates)*** ***Comment – Subjects assigned 2080 in ZOSTER 006/022 studies***	***Apply to all F0 – F6, T1-T9***
2100	***Serological results not available for antigens POST vaccination (including lost samples, blood sample not done, unable to test, absence of parallelism) during Zoster-049 study*** ***elimination code if ALL (anti-gE and CD4[2+] frequencies) are missing <u>BY Yearly visit</u>***	***Apply only to associated visit***
*2110^*	***Serological HI sample with ICF issue*** ***Comment – Applicable only for the HI sample from the immune subset***	***Apply only to associated visit***
*2111^*	***Serological CMI sample with ICF issue*** ***Comment – Applicable only for the CMI sample from the CMI subset***	***Apply only to associated visit***
2130	***Subjects not belonged to the Immunogenicity subset***	***Apply to all F0 – F6, T1-T9***

Elimcode	*Description*	*Eli_Type*
2501	***Other, specify: Subjects not received two doses*** ***Comment – Subjects assigned 2500 in Zoster 006/022 studies***	***Apply to all F0 – F6, T1-T9***
3615	***Subject not enrolled in Zoster-049 at time of persistent year x after dose 2 vaccination of Zoster 006/022***	***Apply only to associated visit, T1 – T9 only***
3616	***Subjects who completed their end of study visit prior to year x post dose 2 vaccination of Zoster 006/022***	***Apply only to associated visit, T1 – T9 only***
4130	***Subjects not belonged to the CMI sub-cohort***	***Apply to all F0 – F6, T1-T9***

based on CSL review of the listing
^ This code has been added to eliminate the subject who has not signed the ICF Addendum 2 and Ethics committee of the respective country has not allowed to use the lab samples and which entry date of the lab samples results is after the withdrawal date of the subject.

15. APPENDIX 5: ELIMINATION DETAIL FOR ATP COHORT FOR IMMUNOGENICITY – RANDOMIZED GROUPS

All the elimination code need to assigned only on the subject randomized in the ZOSTER-049 study and from this study only (not from Zoster-006/022). Following are the elimination code applicable for ATP cohort for immunogenicity for 1-Additional Dose, Revaccination and Control groups:-

Elimcode	*Description*	*Eli_Type*
900	***Subjects excluded from all stat analyses (please comment here below)*** ***Subjects receiving a code 900 should not receive any other elimination codes.***	***M3***
1030	***Study vaccine dose not administered AT ALL but subject number allocated*** ***Subjects receiving a code 1030 should not receive any other elimination codes.***	***M3***
1040	***Administration of concomitant vaccine(s) forbidden in the protocol (see also eligibility criteria) – Including any zoster vaccine*** ***Time frame: - Up to Month 1 visit for 1-Additional group and Up to Month 3 for Revaccination and Control group***	***M3***
1050	***Randomisation failure (subject not randomized in the correct group)***	***M3***

Elimcode	*Description*	*Eli_Type*
*1070**	***Use strikethrough / Modify as applicable:*** • ***Incomplete vaccination course before treatment withdrawal:*** • ***site or route of study vaccine administration wrong or unknown.*** • ***Administration not according to protocol for reason specified by the investigator, other than side, site and route.*** • ***Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number*** ***Wrong side is allowed.***	***M3***
1080	***Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by Status QA GMP NON Use***	***M3***
1090	***Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration***	***M3***
1600	***Other, specify: = code 2010 (Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.)***	***M3***
*2040**	***Administration of any medication forbidden by the protocol*** ***Time frame: - Up to Month 1 visit for 1-Additional group and Up to Month 3 for Revaccination and Control group***	***M3***
*2050**	***Underlying medical condition forbidden by the protocol*** ***Time frame: - Up to Month 1 visit for 1-Additional group and Up to Month 3 for Revaccination and Control group***	***M3***
*2060**	***Concomitant infection related to the vaccine which may influence immune response*** ***Time frame: - Up to Month 1 visit for 1-Additional group and Up to Month 3 for Revaccination and Control group***	***M3***
*2070**	***Concomitant infection not related to the vaccine which may influence immune response (e.g. Hepatitis infection in a lyme study)*** ***Time frame: - Up to Month 1 visit for 1-Additional group and Up to Month 3 for Revaccination and Control group***	***M3***
2080	***Vaccination done but: non-compliance with vaccination schedules (dates of vaccination not corresponding to protocol intervals or unknown vaccination dates)*** ***Comment – Revaccination group – VAC1- VAC2 = 49-83 days***	***M3***

Elimcode	*Description*	*Eli_Type*
2090	***Blood sample taken but: non-compliance with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS/vaccination dates)*** ***Comment – 1_Additional dose – VAC1 – SER2 = 28-48 days; Control – VIS1 – SER2 = 28-48 days; Revaccination – VAC2 – SER 3 = 28-48 days***	*M3*
2100	***Serological results not available for antigens POST vaccination (including lost samples, blood sample not done, unable to test, absence of parallelism) during Zoster-049 study*** ***Comment – Elimination code if ALL (anti-gE and CD4[2+] frequencies) are missing at 1 month post 1 dose in 1-Additional group and post 2 doses in Revaccination group and Month 3 for Control group.***	*M3*
2500	***Other, specify: Subjects not received two doses (applicable for the Revaccination group only)***	*M3*

based on CSL review of the listing

16. APPENDIX 6: ELIMINATION DETAIL FOR ATP COHORT FOR IMMUNOGENICITY PERSISTENCE – RANDOMIZED GROUPS

All the elimination codes will be assigned only on the subject randomized in the Zoster-049 study and from this study only (not from Zoster-006/022). Following are the elimination code applicable for ATP cohort for immunogenicity persistence for 1-Additional Dose, Revaccination and Control groups:-

Elimcode	*Description*	*Eli_Type*
900	***Subjects excluded from all stat analyses (please comment here below)*** ***Subjects receiving a code 900 should not receive any other elimination codes.***	*Applied to L1 to L6*
1030	***Study vaccine dose not administered AT ALL but subject number allocated*** ***Subjects receiving a code 1030 should not receive any other elimination codes.***	*Applied to L1 to L6*
1040	***Administration of concomitant vaccine(s) forbidden in the protocol (see also eligibility criteria) – Including any zoster vaccine*** ***To check from the Month 0 to blood sample timepoint of the persistence***	*Apply to associate visit, and subsequent visit*
1050	***Randomisation failure (subject not randomized in the correct group)***	*Applied to L1 to L6*
*1070**	***Use strikethrough / Modify as applicable:*** • ***Incomplete vaccination course before treatment withdrawal:***	*Applied to L1 to L6*

Elimcode	*Description*	*Eli_Type*
	• *site or route of study vaccine administration wrong or unknown.* • *Administration not according to protocol for reason specified by the investigator, other than side, site and route.* • *Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number* ***Wrong side is allowed.***	
1080	*Vaccine has been administered (effective treatment number) despite a temperature deviation qualified by Status QA GMP NON Use*	*Applied to L1 to L6*
1090	*Vaccine has been administered (effective treatment number) out of the expiration date at the time of administration*	*Applied to L1 to L6*
1600	*Other, specify: = code 2010 (Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.)*	*Applied to L1 to L6*
*2040**	*Administration of any medication forbidden by the protocol*	*Apply to associated visit, and subsequent visit*
*2050**	*Underlying medical condition forbidden by the protocol*	*Apply to associated visit, and subsequent visit*
*2060**	*Concomitant infection related to the vaccine which may influence immune response*	*Apply to associated visit, and subsequent visit*
*2070**	*Concomitant infection not related to the vaccine which may influence immune response (e.g. Hepatitis infection in a lyme study)*	*Apply to associated visit, and subsequent visit*
2080	*Vaccination done but: non-compliance with vaccination schedules (dates of vaccination not corresponding to protocol intervals or unknown vaccination dates)* *Revaccination group – VAC1- VAC2 = 49-83 days*	*Applied to L1 to L6*

Elimcode	*Description*	*Eli_Type*
2100	***Serological results not available for antigens POST vaccination (including lost samples, blood sample not done, unable to test, absence of parallelism) during Zoster-049 study*** ***elimination code if ALL (anti-gE and CD4[2+] frequencies) are missing BY Yearly visit***	***Apply only to associated visit***
2500	***Other, specify: Subjects not received two doses (only applicable for the Revaccination group)***	***Applied to L1 to L6***

based on CSL review of the listing