GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Observational study to assess frailty of subjects during ZOSTER-006 and ZOSTER-022 and HZ efficacy, immunogenicity and safety of HZ/su by frailty status
eTrack study number and Abbreviated Title	204878 (ZOSTER-064)
Scope:	All data pertaining to the above study. All analyses for the primary, secondary and tertiary objectives of the study.
Date of Statistical Analysis Plan	Amendment 1: 18 June 2019

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

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATP	According-To-Protocol
AUC	Area Under Curve
CI	Confidence Interval
CMI	Cellular-Mediated Immunogenicity
CRF	Case Report Form
CTRS	Clinical Trial Registry
Eli Type	Internal GSK database code for type of elimination code
EQ-5D	Euro-QoL 5 Dimension
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
LSMEANS	Least Squares Means
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mTVC	Modified Total Vaccinated Cohort
PBMC	Peripheral Blood Mononuclear Cell Processing
pIMD	potential Immune Mediated Diseases
PROC Phreg	SAS Procedure: Proportional Hazards Regression
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SE	Standard Error

SF-36	Short Form – 36
TTO	Time Trade Off
TVC	Total Vaccinated Cohort
VAS	Visual Analogue Scale
YOA	Years of Age
ZBPI	Zoster Brief Pain Inventory

1. DOCUMENT HISTORY

Date	Description	Protocol Version
27 NOV 2018	Final	Amendment 1: 17 OCT 2018
18 JUN 2019	Amendment 1	Administrative Change 3: 11 FEB 2019

2. STUDY DESIGN

This is a retrospective, observational study, in which pooled data from the ZOSTER-006 and ZOSTER-022 will be analysed. As a consequence no new subjects will be enrolled in this study and no new ICF will be required from study subjects.

In ZOSTER-006 and ZOSTER-022, encoding of Quality of Life (QoL) questionnaires (*SF-36*, *EQ-5D*) was only performed for subjects who developed a suspected Herpes Zoster (HZ) episode during the study. This was done to assess the QoL of subjects who developed suspected cases of HZ between the vaccine group and the placebo group. The remaining study subjects who did not develop suspected cases of HZ completed the questionnaires; however, these questionnaires were never encoded or analysed as part of ZOSTER-006 and ZOSTER-022. The remaining questionnaires will be encoded in ZOSTER-064. These questionnaires will be used, in association with already encoded medical history from each subject, to derive a frailty index and thus assign each subject to a baseline frailty status (non-frail, pre-frail, frail, missing). This will allow efficacy, safety and immunogenicity data to be re-analysed according to frailty status.

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

Group order in tables	Group label in tables	Group definition for footnote
PPD	HZ/su	Herpes Zoster subunit vaccine
	Placebo	Placebo

The following sub-groups will be used for the statistical analysis:

Table 1 Details of subgroups

Sub-group category	Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Frailty Status	PPD	Non–Frail	Subjects with frailty index score ≤0.08
		Pre-Frail	Subjects with frailty index score >0.08 and ≤0.25
		Frail	Subjects with frailty index score >0.25
		Unknown	Subjects who were not assigned a Frailty Status
Gender		Male	Male Subjects
		Female	Female Subjects

Table 2 Details of age and region subgroups

Analysis by age group

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups 1 label in tables	Pooled Groups 2 label in tables
PPD	50-59YOA	50-59 years old subjects	50-59YOA	< 70YOA
	60-69YOA	60-69 years old subjects	60-69YOA	< 70YOA
	70-79YOA	70-79 years old subjects	70-79YOA	≥ 70YOA
	80-89YOA	80-89 years old subjects	≥ 80YOA	≥ 70YOA
	≥ 90YOA	≥ 90 years old subjects	≥ 80YOA	≥ 70YOA

Analysis by country/region

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups label in tables
PPD	PPD	Czechia	Europe
		Estonia	Europe
		Finland	Europe
		France	Europe
		Germany	Europe
		Italy	Europe
		Spain	Europe
		Sweden	Europe
		United Kingdom	Europe
		Australia	Australasia
		Hong Kong	Australasia
		Japan	Australasia
		South Korea	Australasia
		Taiwan	Australasia
		Brazil	Latin America
		Mexico	Latin America
		United States	North America
		Canada	North America

3. OBJECTIVES

3.1. Primary objective

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

3.2. Secondary objectives

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

Tertiary

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

4. ENDPOINTS

4.1. Primary endpoint

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

4.2. Secondary endpoints

- *SF-36* and *EQ-5D* scale scores.
  - At months 0, 14, 26 and 38.
- Confirmed HZ cases.
  - Incidence of HZ cases during ZOSTER-006 and ZOSTER-022 for subjects in the modified Total Vaccinated Cohort (mTVC).
- HZ Burden of Illness.
  - HZ Burden of Illness score for subjects in both ZOSTER-006 and ZOSTER-022 as calculated from the Zoster Brief Pain Inventory (ZBPI)

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

4.3. Tertiary endpoints

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

5. STUDY POPULATION

5.1. Total Vaccinated cohort

The TVC will include all subjects in the TVC in ZOSTER-006 or ZOSTER-022 who were enrolled at centres participating in ZOSTER-064. All subjects in the TVC in ZOSTER-006 or ZOSTER-022 who were enrolled at centres not participating in ZOSTER-064 will be excluded from the TVC.

5.2. Total Vaccinated cohort - diary card subset

The TVC diary card subset for analysis of reactogenicity will include all subjects in the TVC who were also included in the diary card subset in either the ZOSTER-006 or ZOSTER-022 studies.

5.3. Modified Total Vaccinated cohort

The mTVC will include all subjects in the mTVC in ZOSTER-006 or ZOSTER-022 who were enrolled at centres participating in ZOSTER-064.

5.4. According-To-Protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will consist of all subjects in the ATP cohort for analysis of immunogenicity in ZOSTER-006 or ZOSTER-022 who were enrolled at centres participating in ZOSTER-064.

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

More specifically,

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

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

Similarly, for the analysis of cell mediated immunogenicity, ATP cohort is further defined as ATP cohort for immunogenicity – CMI.

6. STATISTICAL METHODS

6.1. Analysis of demographics

Centres that participated in ZOSTER-064 along with their corresponding centre numbers in ZOSTER-006 or ZOSTER-022 will be presented. The distribution of subjects across the study centres will be tabulated by vaccination group and country.

Demographic characteristics (age at first vaccination, gender, race, geographic ancestry and ethnicity) of each study cohort will be tabulated by vaccination group for each of the cohorts defined above. Demographic characteristics will also be tabulated by vaccination group and frailty status.

The mean age (including range and standard deviation) of subjects will be calculated overall, by vaccination group and by frailty status.

The distribution of subjects included in the study across sites will be tabulated overall and per vaccine group.

Frequency tables will be generated for categorical variables such as gender.

Mean, median and standard deviation will be provided for continuous data such as age.

No inferential analyses of demographic data or baseline characteristics are planned.

6.2. Primary Objective

6.2.1. Analysis of Frailty Status

The primary analysis will be based on the TVC.

The number of subjects in each frailty category will be presented by age group, gender and country.

Demographic characteristics will be presented by frailty status.

Details of the assignment of subjects to frailty categories are presented in section 7.1.

6.3. Secondary Objectives

6.3.1. SF-36 and EQ-5D

The quality of life questionnaires to be analysed in this study are the SF-36 and EQ-5D. The SF-36 health survey and the EQ-5D questionnaires were to be completed by all subjects at Months 0, 14, 26 and 38 in ZOSTER-006 and ZOSTER-022.

Basic summary statistics (N, Mean, Standard Deviation) of each of the 8 components of the SF-36 Questionnaire (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health) and the EQ-5D Utility and visual analogue scale (VAS) scores will be presented at each scheduled timepoint by country and age group.

In addition, a more detailed statistical analysis, including the median, quartiles and minimum and maximum values, of the 10 components will be presented by timepoint, age-category and gender and will be presented in a separate annex.

The EQ-5D utility will be based on country specific Time Trade-off (TTO) values for the analysis by country. The UK TTO will be used for countries for which there is no specific TTO.

Presenting the data by country will allow for comparison with normative values for those questionnaires in the general population of the countries participating in the study

This analysis will be based on the TVC.

6.3.1.1. Analysis of Completion of SF-36 and EQ-5D

Compliance with completion of both SF-36 and EQ-5D questionnaires will be summarised by country at each time point (Months 0, 14, 26 and 38) and overall. This compliance will be presented for the TVC and will include in the calculation both newly encoded and previously encoded questionnaires.

% Completion will be defined for each time point as follows:

% Completion = 100 x N1 / N2

Where:

N1 = number of subjects with a completed SF-36/EQ-5D questionnaire.

N2 = number of subjects for whom a questionnaire was expected.

6.3.2. Vaccine efficacy by frailty status

The vaccine efficacy (VE) of the combined ZOSTER-006 and ZOSTER-022 studies will be based on the mTVC and will be classified by frailty status.

The VE will be estimated separately for each frailty category.

Further details of the model used to calculate the VE is contained in the statistical analysis plans (SAPs) for the ZOSTER-006 and ZOSTER-022 studies.

6.3.3. HZ Burden of illness by frailty status

The pooled HZ burden of illness (BOI) scores from the ZOSTER-006 and ZOSTER-022 studies will be presented by frailty category.

The number of subjects with a confirmed HZ episode, the mean BOI scores and the total follow-up time will be presented by Frailty category and vaccination group. The burden of illness vaccine efficacy and 95% confidence intervals (CIs) will be presented by frailty category. This analysis will be carried out for subjects in the mTVC.

6.3.4. Predictive factors for subjects developing HZ

A Cox regression model allowing for time-dependent covariates will be fitted to identify which factors are predictive of developing HZ. The model will include time to HZ as the outcome variable, the demographic variables age and gender and the time dependent *SF-36* variables and *EQ-5D* variables as potential predictors. This analysis will be performed for subjects in the Placebo group in the TVC.

Subjects who did not develop HZ will be censored at the time of their last study visit. The regression model will be used for both minimally adjusted analyses and multivariate analyses. All factors will initially be examined in an age- and gender-adjusted model with further adjustment for the original study (ZOSTER-006 or ZOSTER-022). Factors will be included in the multivariate model if they are associated ($P < 0.05$ using a two-sided Wald test) with HZ in the minimally adjusted model. The multivariate model will also include age, gender and original study. A step-down (backward) variable selection procedure will be used to fit the final multivariate model. This model will be fitted using the PHREG procedure of the *SAS/STAT* package.

The parameter estimates and standard error of each SF-36 and EQ-5D parameter from the minimally adjusted model will be presented. The final multivariate model will also be presented.

The analysis will be performed with the event defined as a HZ confirmed case. Three separate analyses will be performed examining the impact of excluding suspected but not confirmed cases.

The first analysis will exclude subjects who had a suspected case that was later proven not to be a HZ episode.

The second analysis will include all subjects. Those subjects who had a suspected case that was later proven not to be a HZ episode will be censored at their latest available assessment and will be considered not to have had the event.

The third analysis will also include all subjects. The definition of event will be changed to having a suspected case of HZ.

The distribution of confirmed cases of HZ amongst suspected cases will be presented by age group for subjects in the placebo group in the TVC.

Details of the process behind the inclusion of time dependent covariates are included in section 7.4

6.3.5. Analysis of safety by frailty status

The safety analysis will be based on the TVC. The analysis of Reactogenicity will be based on the TVC diary card subset.

All safety analyses will be categorised by frailty status.

The following analyses will be performed for safety endpoints:

- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3; related and grade 3 related AEs;
- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any AE during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3, related and grade 3 related AEs;
- The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day-follow-up period will be tabulated with exact 95% CI. For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination;
- Summary of temperature value by half degree increment reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall doses and subjects. The same tabulation for fever with relationship to vaccination will be done;
- The number of days with each individual solicited local and general AE during **the solicited** 7-day follow-up period will be tabulated;
- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE reported during the solicited 7-day follow-up period and **lasting beyond this period** will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3;

- The percentage of subjects with each individual solicited local and general symptoms **ongoing beyond the 7-day follow-up period** will be tabulated. The same tabulation will be performed for grade 3;
- The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.
- Total number/percentages of doses followed by AEs will be tabulated;
- The percentage of subjects with at least one report of serious adverse event classified by the MedDRA Preferred Terms and reported during the whole post-vaccination follow up period will be tabulated with exact 95% CI;
- The proportion of subjects with at least one report of pIMDs classified by the MedDRA Preferred Terms and reported during the whole post-vaccination period (from dose 1 up to study end) will be tabulated with exact 95% CI.

6.3.6. Analysis of immunogenicity by Frailty status

The analysis of immunogenicity will be categorised by vaccination group and frailty status. The primary analysis will be based on the ATP cohort for analysis of immunogenicity.

6.3.6.1. Humoral immune response

Humoral immune response will be assessed and analysed in the ATP cohort for analysis of immunogenicity – Humoral.

Descriptive statistics

For the humoral immune response, at each timepoint that a blood sample is available (Months 0, 3, 14, 26 and 38), the following parameters (with 95% CIs) will be tabulated by vaccination group and frailty status:

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

Inferential Analyses

No inferential analysis will be carried out on the humoral immune response data.

6.3.6.2. Cell-mediated immune response

Cell-mediated immune response will be assessed and analysed in the ATP cohort for analysis of immunogenicity – CMI.

The CMI analyses was performed for ZOSTER-006 only in the Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that had access to a PBMC processing facility within the acceptable time window from sample collection to PBMC processing. The CMI subset contained approximately 350 subjects. We are expecting some attrition of data, i.e. some centres who took part in the ZOSTER-006 may not take part in the ZOSTER-064. In addition, we are expecting that approximately 5% of subjects will be classified as frail. As a consequence, the analysis of CMI by frailty status will only be carried out if we have a minimum of 20 CMI subjects classified as frail.

Descriptive statistics

For CMI response, the following parameters (for gE and VZV specific CD4[2+] frequency and CD4[+2] T-cell following induction with gE and VZV) will be tabulated by vaccination group, overall and by frailty status at Months 0, 3, 14, 26 and 38:

- descriptive statistics of the frequency of CD4 T-cell secreting at least two different cytokines (IFN-γ, IL-2, TNF-α, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least IFN-γ and another cytokine (IL-2, TNF-α, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least IL-2 and another cytokine (IFN-γ, TNF-α, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least TNF-α and another cytokine (IFN-γ, IL-2, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least CD40L and another cytokine (IFN-γ, IL-2, TNF-α) to both VZV and gE antigens;
- Vaccine response rate with exact 95% CI at Months 3, 14, 26 and 38 (only in the gE-specific CD4[2+] T-cell frequency at Months 3, 14, 26 and 38)

Inferential Analyses

No inferential analysis will be carried out on the CMI data.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Demography

Age at vaccination

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) was 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 month is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age group used for randomization.

7.1.2. Efficacy data

Details of derived and transformed efficacy data including the methodology behind the VE is contained in the SAPs for the ZOSTER-006 and ZOSTER-022 studies.

7.1.3. Safety

Details of derived and transformed safety data is contained in the SAPs for the ZOSTER-006 and ZOSTER-022 studies.

7.1.4. Immunogenicity

7.1.4.1. Humoral immune response

Full details of the methods used in the humoral immune response analyses are contained in the ZOSTER-006 and ZOSTER-022 SAPs (Demog, Safety, Immuno).

7.1.4.2. Cellular-mediated immune (CMI) response

Full details of the methods used in the CMI analysis including calculation of the frequency of antigen-specific (gE or VZV) CD4[2+] T-cells for each individual subject and the definition of CMI vaccine response to gE and VZV are contained in the ZOSTER-006 SAP (Demog, Safety, Immuno).

7.2. Quality of Life data

7.2.1. SF-36 and EQ-5D

Details of the derivation of the 8 scales generated from the SF-36 and the derivation of the utility score from the EQ-5D are contained in the QoL SAPs for the ZOSTER-006 and ZOSTER-022 studies.

7.2.2. HZ Burden of illness

The HZ BOI scores are based on the ZBPI questionnaire already encoded in the ZOSTER-006 and ZOSTER-022 studies.

Full details of the ZBPI questionnaire and the methodology behind the calculation of the HZ BOI scores are contained in the QoL SAPs for the ZOSTER-006 and ZOSTER-022 studies.

7.3. Frailty Index

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

The total frailty score will be between 0 and 41. The subject's pre-vaccination questionnaires will contribute a max score of 29 and the medical history will contribute a max score of 12. Table 3 details the components of the SF-36 and EQ-5D questionnaires that contribute to the calculation of the frailty index.

Table 3 Detail of SF-36 and EQ-5D components of frailty Index

Item	Scoring method based on response to question	Max Contribution to Frailty Index
SF-36 Q1	Poor=1, Fair=0.5 Good=0, Very good=0 Excellent=0	1
SF-36 Q11A-11D	**Q11A, Q11C** Definitely true=1 Mostly true=0.5 Don't know=0 Mostly false=0 Definitely false=0 **Q11B, Q11D** Definitely true=0 Mostly true=0 Don't know=0 Mostly false=0.5 Definitely false=1	4
SF-36 Q3I - Q3J	Limited a lot=1 Limited a little=0.5 Not limited at all=0	10
SF-36 Q9A - Q9I	**Q9A, Q9D, Q9E, Q9H** : All of the Time=0 Most of the time=0 Some of the time=0 A little of the time=0.5 None of the time=1 **Q9B, Q9C, Q9F, Q9G, Q9I** : All of the Time=1 Most of the time=0.5 Some of the time=0 A little of the time=0 None of the time=0	9
SF-36 Q2 Compared to one week before, how did the subject rate his / her health in general?	Much worse=1, Somewhat worse=0.5, Same=0 Somewhat better=0 Better=0	1
EQ-5D Mobility	No Problems=0 Some Problems=0.5 Confined to bed=1	1
EQ-5D Anxiety	No Anxiety=0 Moderate Anxiety=0.5 Extreme Anxiety=1	1
EQ-5D Self care	No Problems=0 Some Problems=0.5 Inability to wash or dress himself /herself=1	1
EQ-5D Usual activities	No Problems=0 Some Problems=0.5 Inability to perform usual activities=1	1
Total		**29**

The medical history is divided into 12 selected categories; each category contributing a score of 0 or 1. The coded combined ZOSTER-006 and ZOSTER-022 medical history database will be searched and events that fall into any one of the 12 categories will be selected Table 4 details the MedDRA terms that will be used to search the database. If a subject had any one of the listed events in a category they would be assigned a max score of 1 for that category and a max score of 12 overall.

The frailty index is then calculated by combining the accumulation of deficits into a score from 0 to 1: frailty index = (accumulation of deficits) / (41 – nmissQoL) where nmissQoL is the number of missing components of the 29 items from the SF-36 and EQ-5D questionnaires. If a subject has more than 10 missing QoL components the frailty index will not be calculated.

Each subject will then be assigned to one of three categories, Non-Frail, Pre-Frail and Frail based on the frailty index.

- If the frailty index is **less than or equal to** 0.08 then the subject is classified as Non-Frail. If the score is greater than 0.08 **but less than or equal to** 0.25 then the subject is classified as pre-frail. If the score is **greater than** 0.25 then the subject is classified as Frail. Subjects without a frailty index score will be classified as missing.

Table 4 Detail of Medical history search items

Category	*MedDRA version 18 Search Terms*
Cancer	Malignancy related conditions (SMQ)
	Malignant tumours (SMQ)
Diabetes Mellitus	Diabetes mellitus (incl subtypes) (HLT)
	Diabetic complications (HLGT)
High Blood Pressure,	Hypertension (SMQ)
Heart Attack	Ischaemic heart disease (SMQ)
CHF	Cardiac failure (SMQ)
Cerebrovascular Disease	Central nervous system vascular disorders (SMQ)
Arthritis	Arthritis (SMQ)
Chronic Lung Disease	Asthma/bronchospasm (SMQ)
	Interstitial lung disease (SMQ)
	Pulmonary hypertension (SMQ)
	Chronic Obstructive Pulmonary Disease (PT) / Infective exacerbation of chronic obstructive airways disease (PT)
	Bronchiectasis (PT) /Infective exacerbation of bronchiectasis (PT)
	Cystic fibrosis (PT)/ Cysitic fibrosis lung (PT) / Infective pulmonary exacerbation of cystic fibrosis (PT)
	Chronic respiratory disease (PT)
	Chronic respiratory failure (PT)
Stomach or Intestinal Ulcers	Gastrointestinal ulceration (SMQ)
Migraine	Migraine headaches (HLT)
	Migraine prophylaxis (PT)
Cataract	Cataract Conditions (HLT)
	Cataract operation (PT)
	Cataract diabetic (PT)
	Cataract operation complication (PT)
Glaucoma	Glaucoma (SMQ)

- SMQ: Standardised MedDRA queries. HLGT: High Level Group Term. HLT: High Level Term. PT: Preferred Term

7.4. Predictive factors for individuals developing HZ

Only subjects in the placebo group will be included in the analysis of potential predictive factors. A Cox regression model allowing for time-dependent covariates will be fitted to identify which factors are predictive of developing HZ. The model will include time to HZ as the outcome variable, the demographic variables age and gender and the *SF-36* variables and *EQ-5D* variables as potential predictors.

Each EQ-5D and SF-36 assessment at a scheduled time point will be re-classified into time points based on the date of assessment relative to date of vaccination:

Studyday=date of assessment – date of vaccination.

The study day will be time component used in the model.

Since there are a maximum of four SF-36 and EQ-5D assessment times we define the variables T_0, T_1,T_2,T_3 as the study day relative to vaccination (day 0) of the QoL assessment and QoL_0 QoL_1, QoL_2, QoL_3 as the values of the QoL assessment at each timepoint. The value of the time-dependent variable QoLt is equal to QoL_0 if $0 < t \leq T_1$, QoL_1 if $T_1 < t \leq T_2$, QoL_2 if $T_2 < t \leq T_3$, with QoLt = QoL_3 if $t > T_3$.

The above model is implemented in SAS as follows:

```
ODS output ParameterEstimates=PE1;
PROC PHREG DATA=tsurv;
 CLASS study gender;
 MODEL fu_time*hz_conf(0)=age study gender PFT;
 PFT=PF0;
 IF fu_time > time1 and time1 ne . then PFT=PF1;
 IF fu_time > time2 and time2 ne . then PFT=PF2;
 IF fu_time > time3 and time3 ne . then PFT=PF3;
RUN;
```

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

Example: To illustrate the method the following hypothetical 3 subjects are examined:

Table 5 Data from hypothetical subjects to illustrate time dependent covariates

Subject	QoL0	T0	QoL1	T1	QoL2	T2	QoL3	T3	Censored /day	Event/ day
PPD	80	0	75	425	65	790	24	1050	Yes/1090	No
	90	0	65	420	50	800	45	1050	No	Yes/480
	98	0	43	435	45	790	45	1060	No	Yes/900

Table 6 Resolution of hypothetical subject PP

Subject	Event	Time Interval	QoL
PPD	0	(0, 425]	80
	0	(425, 790]	75
	0	(790, 1050]	65
	0	(1050, 1090]	24

Subject PP will be censored at day 1090.

Table 7 Resolution of hypothetical subject PP

Subject	Event	Time Interval	QoL
PPD	0	(0, 420]	90
	1	(420, 480]	65

Subject PP had the HZ episode on day 480. The QoL assessment on day 420 is considered as leading to the HZ episode. The subsequent QoL assessments will not be included in the analysis.

Table 8 Resolution of hypothetical subject PP

Subject	Event	Time Interval	QoL
PPD	0	(0, 435]	98
	0	(435, 790]	43
	1	(790, 900]	45

Subject PP had the HZ episode on day 900. The QoL assessment on day 790 is considered as leading to the HZ episode. The subsequent QoL assessment at day 1060 will not be included in the analysis.

7.5. Handling of missing data

7.5.1. Demography

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

7.5.2. Quality of Life data

If any item of the SF-36 or EQ-5D is missing it will not be imputed.

7.6. Number of Decimals

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

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2
QoL	SF-36 Components, including LL & UL of CI	2
	EQ-5D Utility Scores, including LL & UL of CI	3
	EQ-5D VAS Scores, including LL & UL of CI	1
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
Efficacy	VE, including LL & UL of CI	2
	IR	2
	T, T/N	1
	p-value	4

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose	Reference for TFL
End of study analysis	E1_01	CTRS, Study report	All tables identified as TFL

8.2. Statistical considerations for interim analyses

No interim analysis is planned.

9. CHANGES FROM PLANNED ANALYSES

- In the protocol the following secondary objective was intended for baseline only:
  - To present the distribution of *SF-36* and *EQ-5D* scores in subjects included in ZOSTER-006 and ZOSTER-022 at baseline by country to allow comparison with normative values for those questionnaires in the general population of the countries participating in the study.
  - In order to align with the corresponding endpoint, the analysis will be performed at baseline, Months 14, 26 and 38 by country and gender
- The definition of the TVC, mTVC and ATP cohorts have been clarified. In order to minimize bias it was decided that only subjects belonging to centres that participate in ZOSTER-064 will be included. Subjects with data already encoded as part of the ZOSTER-006 or ZOSTER-022 studies will be excluded if the centre to which they belong did not take part in the ZOSTER-064.
- SAEs and pIMDs will not be described in detail as no new safety data was collected in ZOSTER-064 and all SAEs and pIMDs were described in detail in the ZOSTER-006 and ZOSTER-022 CSRs
- Due to the large number of QoL tables generated as a result of the planned analysis by various categories, the key summary tables will be presented as post-text tables in the CSR and more detailed tables will be presented separately in an Annex

10. REFERENCES

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

Statistical Analysis Plan

Study alias & e-track number(s): ZOSTER-064 (204878)

Detailed Title:	Observational study to assess frailty of subjects during ZOSTER-006 and ZOSTER-022 and HZ efficacy, immunogenicity and safety of HZ/su by frailty status
SAP version:	Final
SAP date:	27-NOV-2018
Scope:	All data pertaining to the above study.
Co-ordinating author:	PPD (Value Evidence)
Other author(s):	PPD (Clinical STAT)
Reviewers:	PPD (Lead stat analyst) PPD (CRDL) PPD (CEPL)
Approved by:	PPD (Director, Value Evidence) PPD (Lead Statistician), PPD (Lead Sc writer), PPD (CRDL)

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LIST OF TABLES

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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 TFL) describing the flow and format of tables, figures and listings to be annexed to the CSR.

LIST OF ABBREVIATIONS

AE	Adverse Event
ATP	According-To-Protocol
AUC	Area Under Curve
CI	Confidence Interval
CMI	Cellular-Mediated Immunogenicity
CRF	Case Report Form
CTRS	Clinical Trial Registry
Eli Type	Internal GSK database code for type of elimination code
EQ-5D	Euro-QoL 5 Dimension
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
LSMEANS	Least Squares Means
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mTVC	Modified Total Vaccinated Cohort
SAE	Serious Adverse Event
PBMC	Peripheral Blood Mononuclear Cell Processing
pIMD	potential Immune Mediated Diseases
PROC Phreg	SAS Procedure: Proportional Hazards Regression
QOL	Quality of Life
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomization System
SD	Standard Deviation
SE	Standard Error

SF-36	Short Form – 36
TTO	Time Trade Off
TVC	Total Vaccinated Cohort
VAS	Visual Analogue Scale
YOA	Years of Age
ZBPI	Zoster Brief Pain Inventory

1. DOCUMENT HISTORY

Date	Description	Protocol Version
27-NOV-2018	Final	Amendment 1 17-OCT-2018

2. STUDY DESIGN

This is a retrospective, observational study, in which pooled data from the ZOSTER-006 and ZOSTER-022 will be analysed. As a consequence no new subjects will be enrolled in this study and no new ICF will be required from study subjects. In ZOSTER-006 and ZOSTER-022, encoding of QoL questionnaires (*SF-36*, *EQ-5D*) was only performed for subjects who developed a suspected HZ episode during the study. This was done to assess the QoL of subjects who developed suspected cases of HZ between the vaccine group and the placebo group. The remaining study subjects who did not develop suspected cases of HZ completed the questionnaires; however, these questionnaires were never encoded or analysed as part of ZOSTER-006 and ZOSTER-022. The remaining questionnaires will be encoded in ZOSTER 064. These questionnaires will be used, in association with already encoded medical history from each subject, to derive a frailty index and thus assign each subject to a baseline frailty status (non-frail, pre-frail, frail, missing). This will allow efficacy, safety and immunogenicity data to be re-analysed according to frailty status.

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

Group order in tables	Group label in tables	Group definition for footnote
1	HZ/su	Herpes Zoster subunit vaccine
2	Placebo	Placebo

The following sub-groups will be used for the statistical analysis:

Table 1 Details of subgroups

Sub-group category	Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
Frailty Status	PPD	PPD	Subjects with frailty index ≤0.08 are considered as Non frail
			Subjects with frailty index >0.08 and ≤0.25 are considered as pre fail
			Subjects with frailty index>0.25 are considered as frail
			Subjects who were not assigned a Frailty category
Gender			Male Subjects
			Female Subjects

Table 2 Details of age and region subgroups

Analysis by age group

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups 1 label in tables	Pooled Groups 2 label in tables
PPD	PPD	50-59 years old subjects	50-59YOA	< 70YOA
		60-69 years old subjects	60-69YOA	< 70YOA
		70-79 years old subjects	70-79YOA	≥ 70YOA
		80-89 years old subjects	≥ 80YOA	≥ 70YOA
		≥ 90 years old subjects	≥ 80YOA	≥ 70YOA

Analysis by country/region

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote	Pooled Groups label in tables
PPD	PPD	Czechia	Europe
		Estonia	Europe
		Finland	Europe
		France	Europe
		Germany	Europe
		Italy	Europe
		Spain	Europe
		Sweden	Europe
		United Kingdom	Europe
		Australia	Australasia
		Hong Kong	Australasia
		Japan	Australasia
		South Korea	Australasia
		Taiwan	Australasia
		Brazil	Latin America
		Mexico	Latin America
		United States	North America
		Canada	North America

3. OBJECTIVES

3.1. Primary objective

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

3.2. Secondary objectives

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

Tertiary

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

4. ENDPOINTS

4.1. Primary endpoint

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

4.2. Secondary endpoints

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

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

4.3. Tertiary endpoints

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

5. STUDY POPULATION

5.1. Total Vaccinated cohort - ZOSTER-006 and ZOSTER-022

This cohort corresponds to the 29305 subjects of the total vaccinated cohort (TVC) in either the ZOSTER-006 or ZOSTER-022 studies.

5.2. Total Vaccinated cohort - ZOSTER-064

The TVC for ZOSTER-064 will include subjects in the TVC - ZOSTER-006 and ZOSTER-022 but excludes those subjects from centres that did not participate in the ZOSTER-064. All subjects who had a HZ suspected case in either the ZOSTER-006 or ZOSTER-022 studies are included in this cohort as their QoL data has already been entered in the database as part of these studies.

5.3. Total Vaccinated cohort - diary card subset

The TVC diary card subset for analysis of reactogenicity will include all subjects in the TVC ZOSTER-064 who were also included in the diary card subset in either the ZOSTER-006 or ZOSTER-022 studies.

5.4. Modified Total Vaccinated cohort - ZOSTER-006 and ZOSTER-022

This cohort corresponds to the mTVC of the ZOSTER-006 and ZOSTER-022 studies. The difference from the TVC ZOSTER-006 and ZOSTER-022 is that subjects who were not administered the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination are excluded.

5.5. Modified Total Vaccinated cohort - ZOSTER-064

The mTVC for ZOSTER-064 will include subjects in the mTVC in the ZOSTER-006 and ZOSTER-022 studies but excludes all subjects from centres that did not participate in the ZOSTER-064. In contrast to the definition of total vaccinated cohort ZOSTER-064 subjects who had a suspected case of HZ in either the ZOSTER-006 or ZOSTER-022 studies, will be removed from the cohort if they belong to a centre not participating in ZOSTER-064.

5.6. According-To-Protocol cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will consist of all subjects in the ATP cohort for analysis of immunogenicity in either the ZOSTER-006 or ZOSTER-022 studies who are also part of the TVC-ZOSTER-064 as described above.

The adapted ATP cohort for immunogenicity will similarly consist of all subjects in this cohort in either the ZOSTER 006 or ZOSTER 022 studies who are also part of the TVC-ZOSTER-064.

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

Similarly, for the analysis of cell mediated immunogenicity, ATP cohort is further defined as ATP cohort for immunogenicity – CMI.

6. STATISTICAL METHODS

6.1. Analysis of demographics/baseline characteristics

The distribution of subjects across the study sites and country will be tabulated. The number of subjects with data encoded and the number of subjects who were expected to have data encoded will be tabulated by center. The resulting percentage will provide an encoding compliance rate. This analysis will be performed on the TVC ZOSTER-006 and ZOSTER-022.

Demographic characteristics (age at first vaccination, gender, race, geographic ancestry and ethnicity) of each study cohort will be tabulated overall.

The mean age (including range and standard deviation) of subjects will be calculated overall, by vaccination group and by frailty status.

The distribution of subjects included in the study across sites will be tabulated overall and per vaccine group.

Frequency tables will be generated for categorical variables such as gender.

Mean, median and standard deviation will be provided for continuous data such as age.

No inferential analyses of demographic data or baseline characteristics are planned.

6.2. Primary Objective

6.2.1. Analysis of Frailty Status

The primary analysis will be based on the TVC – ZOSTER-064.

The number of subjects in each frailty category will be presented by pooled age categories 1 and 2 as detailed in Table 2. The number of subjects in each frailty category will also be presented by country.

Demographic characteristics will be presented by frailty status.

Details of the assignment of subjects to frailty categories are presented in section 7.1.

6.3. Secondary Objectives

6.3.1. SF-36 and EQ-5D

The quality of life questionnaires to be analysed in this study are the SF-36 and EQ-5D. The SF-36 health survey and the EQ-5D questionnaires were to be completed by all subjects at Months 0, 14, 26 and 38.

Summary statistics of each of the 8 components of the SF-36 Questionnaire (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health) and the EQ-5D Utility and VAS scores will be presented at each scheduled visit by country, gender, age group and overall. The EQ-5D utility will be based on country specific Time Trade-off (TTO) values for the analysis by country. The UK TTO will be used for countries for which there is no specific TTO.

Presenting the data by country will allow for comparison with normative values for those questionnaires in the general population of the countries participating in the study

This analysis will be based on the TVC ZOSTER-064.

6.3.1.1. Analysis of Completion of SF-36 and EQ-5D

The number of questionnaires encoded and evaluable will be tabulated by center and country and overall. A questionnaire will be considered evaluable if it has a full completion date.

% Completion will be defined for each time point as follows:

% Completion = 100 x N1 / N2

Where:

N1 = number of subjects with a completed and newly encoded SF-36/EQ-5D questionnaire.

N2 = number of subjects for whom a questionnaire was expected, i.e. every subject in the TVC ZOSTER-006 and ZOSTER-022 with the exception the subjects who had a suspected HZ episode in either the ZOSTER-006 or ZOSTER-022

Compliance with completion of QoL questionnaires will also be summarized by country at each time point (Months 0, 14, 26 and 38). This compliance will be presented for the TVC ZOSTER-064 and will include in the calculation both newly encoded and previously encoded questionnaires.

6.3.2. Vaccine efficacy by frailty status

The vaccine efficacy (VE) of the combined ZOSTER-006 and ZOSTER-022 studies will be based on the mTVC ZOSTER-064 and will be stratified by frailty status.

The overall VE estimate will be obtained from the model that is stratified by the 3 frailty strata. The VE will also be estimated separately for each individual frailty strata, with the same model being run using only the data pertaining to the strata under consideration.

Further details of the model used to calculate the VE is contained in the statistical analysis plans (SAPs) for the ZOSTER-006 and ZOSTER-022 studies.

6.3.3. HZ Burden of illness by frailty status

The pooled HZ burden of illness scores from the ZOSTER-006 and ZOSTER-022 studies will be presented by frailty category.

The number of subjects with a confirmed zoster episode, the mean burden of illness scores and the total follow-up time will be presented by Frailty category and vaccination group. The burden of illness vaccine efficacy and 95% confidence intervals will be presented by frailty category. This analysis will be carried out for subjects in the mTVC – ZOSTER 064.

6.3.4. Predictive factors for subjects developing HZ

A Cox regression model allowing for time-dependent covariates will be fitted to identify which factors are predictive of developing HZ. The model will include time to HZ as the outcome variable, the demographic variables age and gender and the time dependent *SF-36* variables and *EQ-5D* variables as potential predictors. This analysis will be performed for subjects in the Placebo group in the mTVC- ZOSTER 064.

In addition, all subjects from centres who had a poor compliance in encoding data from the ZOSTER-006 and ZOSTER-022 studies will not be included. If a centre encoded less than 50 % of the available data then all subjects, including those who had a HZ suspected case in either the ZOSTER-006 or ZOSTER-022, belonging to that centre will be removed from the mTVC for the purposes of this analysis.

Subjects who did not develop HZ will be censored at the time of their last study visit. The regression model will be used for both minimally adjusted analyses and multivariate analyses. All factors will initially be examined in an age- and gender-adjusted model with stratification for the clinical trial. Factors will be included in the multivariate model if they are associated ($P < 0.05$ using a two-sided Wald test) with HZ in the minimally adjusted model. The multivariate model will also include age and gender with stratification for the clinical trial (i.e. ZOSTER-006 and ZOSTER-022). A step-down (backward) variable selection procedure will be used to fit the final multivariate model. This model will be fitted using the PHREG procedure of the *SAS/STAT* package.

The parameter estimates and standard error of each SF-36 and EQ-5D parameter from the minimally adjusted model will be presented. The final multivariate model will also be presented.

The analysis will be performed with the event defined as a HZ confirmed case. Three separate analyses will be performed examining the impact of excluding suspected but not confirmed cases.

The first analysis will exclude subjects who had a suspected case that was later proven not to be a HZ episode.

The second analysis will include all subjects. Those subjects who had a suspected case that was later proven not to be a HZ episode will be censored at their latest available assessment and will be considered not to have had the event.

The third analysis will also include all subjects. The definition of event will be changed to having a suspected case of HZ.

Details of the process behind the inclusion of time dependent covariates are included in section 7.4

6.3.5. Analysis of safety by frailty status

The safety analysis will be based on the TVC – ZOSTER-064. The analysis of Reactogenicity will be based on the TVC – ZOSTER 064 diary card subset.

All safety analyses will be categorised by frailty status.

The following analyses will be performed for safety endpoints:

- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3; related and grade 3 related AEs;
- The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any AE during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3, related and grade 3 related AEs;
- The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day-follow-up period will be tabulated with exact 95% CI. For all solicited symptoms, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination;
- Summary of temperature value by half degree increment reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall doses and subjects. The same tabulation for fever with relationship to vaccination will be done;
- The number of days with each individual solicited local and general AE during **the solicited** 7-day follow-up period will be tabulated;

- The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE reported during the solicited 7-day follow-up period and **lasting beyond this period** will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulation will be performed for grade 3;
- The percentage of subjects with each individual solicited local and general symptoms **ongoing beyond the 7-day follow-up period** will be tabulated. The same tabulation will be performed for grade 3;
- The percentage of subjects with at least one report of unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.
- Total number/percentages of doses followed by AEs will be tabulated;
- SAEs will be described in detail;
- The percentage of subjects with at least one report of serious adverse event classified by the MedDRA Preferred Terms and reported during the whole post-vaccination follow up period will be tabulated with exact 95% CI;
- pIMDs will be described in detail.
- The proportion of subjects with at least one report of pIMDs classified by the MedDRA Preferred Terms and reported during the whole post-vaccination period (from dose 1 up to study end) will be tabulated with exact 95% CI.

6.3.6. Analysis of immunogenicity by Frailty status

The analysis of immunogenicity will be categorised by vaccination group and frailty status. The primary analysis will be based on the ATP cohort for analysis of immunogenicity – ZOSTER064.

6.3.6.1. Cell-mediated immune response

Cell-mediated immune response will be assessed and analysed in the ATP cohort for analysis of immunogenicity – CMI.

The CMI analyses was performed for ZOSTER-006 only in the Immunogenicity subset in three countries (Czech Republic, Japan and United States) at designated sites that had access to a PBMC processing facility within the acceptable time window from sample collection to PBMC processing. The CMI subset contained approximately 350 subjects. We are expecting some attrition of data, i.e. some centres who took part in the ZOSTER-006 may not take part in the ZOSTER-064. In addition, we are expecting that approximately 5% of subjects will be classified as frail. As a consequence, the analysis of CMI by frailty status will only be carried out if we have a minimum of 20 CMI subjects classified as frail.

6.3.6.2. Descriptive statistics

For CMI response, the following parameters (for gE and VZV specific CD4[2+] frequency and CD4[+2] T-cell following induction with gE and VZV) will be tabulated by vaccination group, overall and by frailty status at Months 0, 3, 14, 26 and 38:

- descriptive statistics of the frequency of CD4 T-cell secreting at least two different cytokines (IFN-γ, IL-2, TNF-α, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least IFN-γ and another cytokine (IL-2, TNF-α, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least IL-2 and another cytokine (IFN-γ, TNF-α, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least TNF-α and another cytokine (IFN-γ, IL-2, CD40L) to both VZV and gE antigens;
- descriptive statistics of the frequency of CD4 T-cell secreting at least CD40L and another cytokine (IFN-γ, IL-2, TNF-α) to both VZV and gE antigens;
- Vaccine response rate with exact 95% CI at Months 3, 14, 26 and 38 (only in the gE-specific CD4[2+] T-cell frequency at Months 3, 14, 26 and 38)

6.3.6.3. Inferential Analyses

No inferential analysis will be carried out on the CMI data.

6.3.6.4. Humoral immune response

Humoral immune response will be assessed and analysed in the ATP cohort for analysis of immunogenicity – Humoral.

6.3.6.5. Descriptive statistics

For the humoral immune response, at each timepoint that a blood sample is available (Months 0, 3, 14, 26 and 38), the following parameters (with 95% CIs) will be tabulated by vaccination group and frailty status:

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

6.3.6.6. Inferential Analyses

No inferential analysis will be carried out on the humoral immune response data.

7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

7.1.1. Demography

Age at vaccination

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) was 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 month is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

7.1.2. Efficacy data

Details of derived and transformed efficacy data including the methodology behind the VE is contained in the SAPs for the ZOSTER-006 and ZOSTER-022 studies.

7.1.3. Safety

Details of derived and transformed safety data is contained in the SAPs for the ZOSTER-006 and ZOSTER-022 studies.

7.1.4. Immunogenicity

7.1.4.1. Humoral immune response

Full details of the methods used in the humoral immune response analyses are contained in the ZOSTER-006 and ZOSTER-022 SAPs (Demog, Safety, Immuno)

7.1.4.2. Cellular-mediated immune (CMI) response

Full details of the methods used in the CMI analysis including calculation of the frequency of antigen-specific (gE or VZV) CD4[2+] T cells for each individual subject and the definition of CMI vaccine response to gE and VZV are contained in the ZOSTER-006 SAP (Demog, Safety, Immuno)

7.2. Quality of Life data

7.2.1. SF-36 and EQ-5D

Details of the derivation of the 8 scales generated from the SF-36 and the derivation of the utility score from the EQ-5D are contained in the quality of life (QoL) SAPs for the ZOSTER-006 and ZOSTER-022 studies.

7.2.2. HZ Burden of illness

The HZ burden of illness scores are based on the ZBPI questionnaire already encoded in the ZOSTER-006 and ZOSTER-022 studies.

Full details of the ZBPI questionnaire and the methodology behind the calculation of the HZ burden of illness scores are contained in the statistical analysis plans (QoL) for the ZOSTER-006 and ZOSTER-022 studies.

7.3. Frailty Index

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

The total frailty score will be between 0 and 41. The subject's pre-vaccination questionnaires will contribute a max score of 29 and the medical history will contribute a max score of 12. Table 3 details the components of the SF-36 and EQ-5D questionnaires that contribute to the calculation of the frailty index.

Table 3 Detail of SF-36 and EQ-5D components of frailty Index

Item	Scoring method based on response to question	Max Contribution to Frailty Index
SF-36 Q1	Poor=1, Fair=0.5 Good=0, Very good=0 Excellent=0	1
SF-36 Q11A-11D	**Q11A, Q11C** Definitely true=1 Mostly true=0.5 Don't know=0 Mostly false=0 Definitely false=0 **Q11B, Q11D** Definitely true=0 Mostly true=0 Don't know=0 Mostly false=0.5 Definitely false=1	4
SF-36 Q3I - Q3J	Limited a lot=1 Limited a little=0.5 Not limited at all=0	10
SF-36 Q9A - Q9I	**Q9A, Q9D, Q9E, Q9H** : All of the Time=0 Most of the time=0 Some of the time=0 A little of the time=0.5 None of the time=1 **Q9B, Q9C, Q9F, Q9G, Q9I** : All of the Time=1 Most of the time=0.5 Some of the time=0 A little of the time=0 None of the time=0	9
SF-36 Q2 Compared to one week before, how did the subject rate his / her health in general?	Much worse=1, Somewhat worse=0.5, Same=0 Somewhat better=0 Better=0	1
EQ-5D Mobility	No Problems=0 Some Problems=0.5 Confined to bed=1	1
EQ-5D Anxiety	No Anxiety=0 Moderate Anxiety=0.5 Extreme Anxiety=1	1
EQ-5D Self care	No Problems=0 Some Problems=0.5 Inability to wash or dress himself /herself=1	1

Item	Scoring method based on response to question	Max Contribution to Frailty Index
EQ-5D Usual activities	No Problems=0 Some Problems=0.5 Inability to perform usual activities=1	1
Total		**29**

The medical history is divided into 12 categories; each category contributing a score of 0 or 1. The coded combined ZOSTER-006 and ZOSTER-022 medical history database will be searched and events that fall into any one of the 12 categories will be selected Table 4 details the MedDRA terms that will be used to search the database. If a subject had any one of the listed events in a category they would be assigned a max score of 1 for that category and a max score of 12 overall.

The frailty index is then calculated by combining the accumulation of deficits into a score from 0 to 1: frailty index = (accumulation of deficits) / (41 – nmissQoL) where nmissQoL is the number of missing components of the 29 items from the SF-36 and EQ-5D questionnaires. If a subject has more than 10 missing QoL components the frailty index will not be calculated.

Each subject will then be assigned to one of three categories, Non-Frail, Pre-Frail and Frail based on the frailty index.

- If the frailty index is **less than or equal to** 0.08 then the subject is classified as Non-Frail. If the score is greater than 0.08 **but less than or equal to** 0.25 then the subject is classified as pre-frail. If the score is **greater than** 0.25 then the subject is classified as Frail. Subjects without a frailty index score will be classified as missing.

Table 4 Detail of Medical history search items

Category	*MedDRA version 18 Search Terms*
Cancer	Malignancy related conditions (SMQ)
	Malignant tumours (SMQ)
Diabetes Mellitus	Diabetes mellitus (incl subtypes) (HLT)
	Diabetic complications (HLGT)
High Blood Pressure,	Hypertension (SMQ)
Heart Attack	Ischaemic heart disease (SMQ)
CHF	Cardiac failure (SMQ)
Cerebrovascular Disease	Central nervous system vascular disorders (SMQ)
Arthritis	Arthritis (SMQ)
Chronic Lung Disease	Asthma/bronchospasm (SMQ)
	Interstitial lung disease (SMQ)
	Pulmonary hypertension (SMQ)
	Chronic Obstructive Pulmonary Disease (PT) / Infective exacerbation of chronic obstructive airways disease (PT)
	Bronchiectasis (PT) /Infective exacerbation of bronchiectasis (PT)
	Cystic fibrosis (PT)/ Cysitic fibrosis lung (PT) / Infective pulmonary exacerbation of cystic fibrosis (PT)
	Chronic respiratory disease (PT)
	Chronic respiratory failure (PT)
Stomach or Intestinal Ulcers	Gastrointestinal ulceration (SMQ)
Migraine	Migraine headaches (HLT)
	Migraine prophylaxis (PT)
Cataract	Cataract Conditions (HLT)
	Cataract operation (PT)
	Cataract diabetic (PT)
	Cataract operation complication (PT)
Glaucoma	Glaucoma (SMQ)

- SMQ: Standardised MedDRA queries. HLGT: High Level Group Term. HLT: High Level Term. PT: Preferred Term

7.4. Predictive factors for individuals developing HZ

Only subjects in the placebo group will be included in the analysis of potential predictive factors. A Cox regression model allowing for time-dependent covariates will be fitted to identify which factors are predictive of developing HZ. The model will include time to HZ as the outcome variable, the demographic variables age and gender and the *SF-36* variables and *EQ-5D* variables as potential predictors.

Each EQ-5D and SF-36 assessment at a scheduled time point will be re-classified into time points based on the date of assessment relative to date of vaccination:

Studyday=date of assessment – date of vaccination.

The study day will be time component used in the model.

Since there are a maximum of four SF-36 and EQ-5D assessment times we define the variables T_0, T_1,T_2,T_3 as the study day relative to vaccination (day 0) of the QoL assessment and QoL_0 QoL_1, QoL_2, QoL_3 as the values of the QoL assessment at each timepoint. The value of the time-dependent variable QoLt is equal to QoL_0 if $0 < t \leq T_1$, QoL_1 if $T_1 < t \leq T_2$, QoL_2 if $T_2 < t \leq T_3$, with $QoLt = QoL_3$ if $t > T_3$.

The above model is implemented in SAS as follows:

```
ODS output ParameterEstimates=PE1;
PROC PHREG DATA=tsurv;
 CLASS study gender;
 MODEL fu_time*hz_conf(0)=age study gender PFT;
 PFT=PF0;
 IF fu_time > time1 and time1 ne . then PFT=PF1;
 IF fu_time > time2 and time2 ne . then PFT=PF2;
 IF fu_time > time3 and time3 ne . then PFT=PF3;
RUN;
```

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

Example: To illustrate the method the following hypothetical 3 subjects are examined:

Table 5 Data from hypothetical subjects to illustrate time dependent covariates

Subject	QoL0	T0	QoL1	T1	QoL2	T2	QoL3	T3	Censored /day	Event/ day
PPD	80	0	75	425	65	790	24	1050	Yes/1090	No
	90	0	65	420	50	800	45	1050	No	Yes/480
	98	0	43	435	45	790	45	1060	No	Yes/900

Table 6 Resolution of hypothetical subject 1

Subject	Event	Time Interval	QoL
PPD	0	(0, 425]	80
	0	(425, 790]	75
	0	(790, 1050]	65
	0	(1050, 1090]	24

- Subject PP will be censored at day 1090.

Table 7 Resolution of hypothetical subject 1

Subject	Event	Time Interval	QoL
PP	0	(0, 420]	90
PP	1	(420, 480]	65

Subject PP had the HZ episode on day 480. The QoL assessment on day 420 is considered as leading to the HZ episode. The subsequent QoL assessments will not be included in the analysis.

Table 8 Resolution of hypothetical subject 3

Subject	Event	Time Interval	QoL
PPD	0	(0, 435]	98
	0	(435, 790]	43
	1	(790, 900]	45

Subject PP had the HZ episode on day 900. The QoL assessment on day 790 is considered as leading to the HZ episode. The subsequent QoL assessment at day 1060 will not be included in the analysis.

7.5. Handling of missing data

7.5.1. Demography

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

7.5.2. Quality of Life data

If any item of the SF-36 or EQ-5D is missing it will not be imputed.

7.6. Number of Decimals

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

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2
QoL	SF-36 Components, including LL & UL of CI	2
	EQ-5D Utility Scores, including LL & UL of CI	3
	EQ-5D VAS Scores, including LL & UL of CI	1
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
Efficacy	VE, including LL & UL of CI	2
	IR	2
	T, T/N	1
	p-value	4

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose	Reference for TFL
End of study analysis	E1_01	CTRS, Study report	All tables identified as TFL

8.2. Statistical considerations for interim analyses

No interim analysis is planned.

9. CHANGES FROM PLANNED ANALYSES

In the protocol the following secondary objective was intended for baseline only:

- To present the distribution of *SF-36* and *EQ-5D* scores in subjects included in ZOSTER-006 and ZOSTER-022 at baseline by country to allow comparison with normative values for those questionnaires in the general population of the countries participating in the study.
- In order to align with the corresponding endpoint, the analysis will be performed at baseline, months 14, 26 and 38 by country

10. REFERENCES

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