	This should help confirm previously hypothesized predictive factors such as age, stress or functional status, and also to assess other potential risk factors such as frailty, fatigue or emotional and mental health.
Study design	• A multi-country, observational, retrospective study. • Study population: All subjects enrolled in ZOSTER-006 and ZOSTER-022. • Type of study: Data to be analysed in this study have been collected in the ZOSTER-006 (eTrack 110390) and ZOSTER-022 (eTrack 113077) and will be combined for assessment of primary, secondary and tertiary objectives. • Data collection: QoL questionnaires and the year of birth of subjects enrolled in ZOSTER-006 and ZOSTER-022. – QoL questionnaires: The *SF-36* is a multi-purpose health survey with 36 questions. The *EQ-5D* is a questionnaire with 5 questions designed as a generic measure of health status that provides a simple descriptive profile and a single index value. The *EQ-5D* defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. • Method: Frailty scores for study subjects in ZOSTER-006 and ZOSTER-022 will be calculated by incorporating the subject's medical history and items from the *SF-36* and *EQ-5D* questionnaires.
Discussion of study design	This is a retrospective, observational study of subjects previously enrolled in ZOSTER-006 and ZOSTER-022, therefore no new subjects will be enrolled in this study and no new ICF will be required from study subjects.
Number of subjects	Approximately 30,000 subjects who were enrolled in ZOSTER-006 and ZOSTER-022
Endpoints	**Primary** • 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.

GLOSSARY OF TERMS

According to Protocol (ATP)	In ZOSTER-006 and ZOSTER-022, the ATP cohort included all evaluable subjects meeting all eligibility criteria, complying with the procedures and intervals allowed for the analysis, with no elimination criteria during the study.
Case-control study:	A form of epidemiological study where the study population is selected on the basis of whether the subjects do (cases) or do not (controls) have the particular outcome (disease) under study. The groups are then compared with respect to exposure/ characteristic of interest.
Coded:	Data from which personal identifier information has been removed and replaced by a key. These data are not anonymised since a decode listing exists and it is therefore possible to identify the patient under certain circumstances by an authorised or legally appointed third party data custodian, or by the original holder of the data.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive timepoints or a single timepoint from a single protocol. Self-contained means that data collected for all subjects at all-timepoints within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
modified Total Vaccinated cohort (mTVC)	The mTVC will include only subjects from centres that participate in ZOSTER-064, which will exclude subjects in the TVC who were not administered the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination (i.e. these subjects that were included in the mTVC of ZOSTER-006 and ZOSTER-022.

4. STUDY DESIGN OVERVIEW

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 8), are essential and required for study conduct.

- Type of design: Observational, retrospective study.
- Study population: Adults aged ≥50 years of age who participated in either ZOSTER-006 or ZOSTER-022.
- Type of study*:* to be combined with other protocols for analysis*:* data to be analysed in this study have been collected in ZOSTER-006 (eTrack 110390) and ZOSTER-022 (eTrack 113077).
- Data collection*:* CRF/eCRF
- Duration of the study: The time between the first and the last information to be encoded will be approximately 8 months.

4.1. Discussion of study design

This is a retrospective, observational study, therefore no new subjects will be enrolled in this study and no new ICF will be required from study subjects (see Section 7.2). 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 purpose of ZOSTER-064 is to allow for the encoding of the remaining questionnaires to assess the baseline frailty of all the subjects in ZOSTER-006 and ZOSTER-022.

5. HZ CASE DEFINITION

Classification as a HZ confirmed case was done during ZOSTER-006 and ZOSTER-022, after confirmation of all suspected HZ cases by either of the two following ways:

- Polymerase Chain Reaction (PCR):

  Rash lesion samples were collected from subjects clinically diagnosed as having a suspected case of HZ. The samples were transferred to GSK Biologicals or a validated laboratory designated by GSK Biologicals using standardised and validated procedures for laboratory diagnosis of HZ by PCR. For more information, please refer to Appendix B of the ZOSTER-006 protocol.

- The HZ Ascertainment Committee:

All suspected HZ cases were referred to the HZ Adjudication Committee (HZAC). The HZAC classified all referred cases as either "HZ", "not HZ", or "not able to decide". However, the HZAC classification was to serve as the final case definition only when the case could not be confirmed or excluded by PCR, e.g., when all samples from a given subject were inadequate (as when both VZV and β-actin PCR results were negative), or when no samples were available for a given subject. If the case could not be confirmed or excluded by PCR and the HZAC final outcome was 'not able to decide', the overall final outcome was "No possible classification"; for analysis the categories "not HZ" and "No possible classification" were considered as "not HZ".

6. STUDY POPULATION

6.1. Number of subjects/ centres

Approximately 30,000 subjects enrolled in ZOSTER-006 and ZOSTER-022

There will be no new subjects enrolled in the ZOSTER-064 study. The protocol is developed to allow for the encoding into the eCRF of all QoL questionnaires of subjects enrolled in ZOSTER-006 and ZOSTER-022 and analysing frailty status.

6.2. Inclusion criteria for the study

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- All subjects enrolled in ZOSTER-006 and ZOSTER-022 (See Section 7.2 and 8.3.1)

6.2.1. Inclusion criteria for the study data encoding

- All subjects enrolled in ZOSTER-006 and ZOSTER-022 (See Section 7.2 and 8.3.1)
- Subjects who died or were lost to follow-up during ZOSTER-006 and ZOSTER-022 will be considered for enrolment in ZOSTER-064 and their data/questionnaires up to that point will be used.

See Section 8.1 for site specific subject lists.

- HZ Burden of Illness
  - HZ Burden of Illness score for subjects in both the ZOSTER-006 and -022 studies as calculated from the 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.

10.3. 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 (ICS) in a subset of subjects at Months 0, 3, 14, 26 and 38.

10.4. Determination of sample size

Approximately 30,000 subjects were enrolled in ZOSTER-006 and ZOSTER-022. Out of these, approximately 1000 subjects will have developed suspected HZ cases over the course of the studies and their QoL questionnaires were encoded in the eCRF for ZOSTER-006 and ZOSTER-022, according to the protocols of those studies, respectively. Therefore approximately 29,000 subjects whose QoL questionnaires were completed and collected but not encoded in the earlier studies, will be encoded in the ZOSTER-064 study. Data encoded as part of the 064 study will be combined with data from the ZOSTER-006 and ZOSTER-022 studies to ensure that subjects data are available for analysis, as appropriate taking into account inclusion/exclusion criteria (see section 6) and cohorts for analysis (see section 10.5).

10.4.1. Number of subjects in the CMI subset

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. As a consequence, analysis of CMI by frailty status is expected to be limited.

10.4.2. Number of subjects in the Humoral subset

The analysis of humoral immunogenicity was performed in both the ZOSTER-006 and ZOSTER-022 studies. The Humoral subset contained approximately 2800 subjects in total between ZOSTER-006 and ZOSTER-022.

10.5. Cohorts for Analysis

10.5.1. Total Vaccinated cohort

The primary analysis of EQ-5D and SF-36 questionnaires will be performed on the TVC. The TVC will include all subjects from centres that participated in ZOSTER-064 and all subjects who had a HZ suspected event in either the ZOSTER-006 or ZOSTER-022 studies.

Subjects enrolled in ZOSTER-064 need to have been part of the TVC in ZOSTER-006 or ZOSTER-022. Refer to the glossary of terms for the definition of TVC.

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

Table 2 Construction of the eight scales generated from the *SF-36*

Scale	Items	Response Categories Per Item
Physical Functioning (PF)	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	3
Role Physical (RP)	4a, 4b, 4c, 4d	5
Bodily Pain (BP)	7*, 8*	6, 5
General Health (GH)	1*, 11a, 11b*, 11c, 11d*	5
Vitality (VT)	9a*, 9e*, 9g, 9i	5
Social functioning (SF)	6*, 10	5
Role Emotional (RE)	5a, 5b, 5c	5
Mental Health (MH)	9b, 9c, 9d*, 9f, 9h*	5

* Item Reversed

10.7.3. *EQ-5D* questionnaire

The *EQ-5D* questionnaire is a generic measure of health status that provides a simple descriptive profile and a single index value [Kind, 1996]. The *EQ-5D* defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 items are combined to generate health profiles, i.e. a respondent who responds 1 (no problem\no symptom) to all 5 items has a profile "11111" and similarly a subject who responds with the highest level of difficulty or symptom to all items has a profile "33333". These profiles are subsequently converted to a continuous single index utility score using a one to one matching, e.g. "11111"=1.00, "22222"=0.52 and "33333"= -0.59, using value sets (i.e. matching profiles to single index utility scores). As suggested by the developers, for international studies, the United Kingdom Time-Trade-Off (TTO) value set is to be used for the main analysis. Note: higher scores represent a better QoL. See APPENDIX B for a sample of *EQ-5D* questionnaire.

10.7.4. Definition of Frailty

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 FI will be assessed through the medical history and *SF-36* and *EQ-5D* questionnaires recorded pre-vaccination dose 1. The frailty index will be a score between 0 and 41 as detailed in Table 3.

Table 3 Detail of frailty components

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	4

Item	Scoring method based on response to question	Max Contribution to Frailty Index
	Q11B, Q11D Definitely true=0 Mostly true=0 Don't know=0 Mostly false=0.5 Definitely false=1	
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
Medical history	Cancer	1
	Diabetes Mellitus	1
	High Blood Pressure	1
	Heart Attack	1
	Congestive Heart Failure	1
	Cerebrovascular Disease	1
	Arthritis	1
	Chronic Lung Disease	1
	Stomach or Intestinal Ulcers	1
	Migraine	1
	Cataract	1
	Glaucoma	1
Total		**41**

10.7.6.2.2. Vaccine efficacy against HZ BOI by frailty status

Vaccine efficacy against HZ BOI will be analysed by frailty status (non-frail, pre-frail, frail) for subjects in the modified Total Vaccinated cohort.

10.7.6.3. Predictive factors for individuals developing HZ

Only subjects in the placebo vaccination group will be included in the analysis of potential predictive factors. A Cox proportional hazards 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 and as potential predictors: demographic and clinical characteristics, *SF-36* variables and *EQ-5D* variables. Subjects who did not develop HZ will be censored at the time of their last study visit. The proportional hazards regression model will be used for both minimally adjusted analyses and multivariate analyses. All factors will initially be examined in an age- and sex-adjusted model with stratification for the clinical trial (i.e. ZOSTER-006 and ZOSTER-022). Factors will be included in the multivariate model if they are associated ($P < 0.05$ using a two-sided 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.

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

In the analysis, the impact of excluding "suspected but not confirmed cases" of HZ will be explored. Three analyses will be performed whereby it will be assumed that "suspected but not confirmed cases" are (1) "Not in at risk group" (2) "In at risk group" and event=0, (3) "In at risk group" and event=1.

Due to the multiple measurements of the *EQ-5D* and *SF-36* over time, repartition in the HZ positive or HZ negative will be dynamic. Subjects who did not develop a confirmed HZ before one-timepoint (Day 0, Month 14, Month 26 and Month 38) will be considered HZ negative at that timepoint, and the characteristics and QoL scores reported for this subject at the previous timepoint will be considered as **not leading** to HZ.

Subjects who developed a confirmed HZ during the interval between two timepoints will be considered HZ+ at the later timepoint. Characteristics and QoL scores reported for this subject at the last timepoint before onset of HZ will be considered **leading** to HZ**.**

Example: A subject developed a confirmed HZ episode on Month 22:

- Subject's characteristics and QoL scores reported at Day 0 will be considered as **not leading** to HZ.
- Subject's characteristics and QoL scores reported at Month 14 will be considered as **leading** to HZ.

Secondary

- 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.

Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Quality of Life (QoL)	Quality of life is measured, using two questionnaires (*EQ-5D* and *SF-36*) that were completed by the subject. *EQ-5D* and *SF-36* provide multi-dimensional evaluation of the health status.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Total Vaccinated cohort (TVC)	The TVC will include all subjects from centres that participate in ZOSTER-064 and all subjects who had a HZ suspected case in either the ZOSTER-006 or ZOSTER-022 studies. Subjects enrolled in ZOSTER-064 need to have been part of the TVC in ZOSTER-006 or ZOSTER-022.

6.3. Exclusion criteria for the study

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- Subjects who were excluded from all analyses from ZOSTER-006 and ZOSTER-022. This will include any subject eliminated following deviations from GCP compliance.

6.3.1. Exclusion criteria for data encoding

- Subjects who developed a suspected HZ case during ZOSTER-006 and ZOSTER-022 (since their QoL questionnaires were encoded in the eCRF for ZOSTER-006 and ZOSTER-022).

7. CONDUCT OF THE STUDY

7.1. Regulatory and ethical considerations

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

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

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

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

7.2. Informed consent

ZOSTER-064 is a study related to ZOSTER-006 and ZOSTER-022 that allows for encoding and analysis of questionnaires already completed by the subjects who were part of those earlier studies. Not all of the previously completed questionnaires have been encoded and analysed yet. As such, ZOSTER-064 will provide an opportunity to assess the frailty index of all subjects enrolled in ZOSTER-006 and ZOSTER-022.

Every subject considered for inclusion in this study has previously signed an ICF from the investigational sites of ZOSTER-006 or ZOSTER-022. The ICF signed by the patients in ZOSTER-006 and ZOSTER-022 allows for the use of all collected information in new studies. In these ICFs, it was specified that:

10.5.2. *modified* Total Vaccinated Cohort

The mTVC will include only subjects from centres that participate in ZOSTER-064 (i.e. these subjects that were included in the mTVC of ZOSTER-006 and ZOSTER-022), which will exclude subjects in the TVC who were not administered the second vaccination or who developed a confirmed case of HZ prior to 1 month after the second vaccination.

10.5.3. According to Protocol cohort for analysis of immunogenicity

The analysis of the immunogenicity data from the ZOSTER-064 (i.e. combined immunogenicity data from ZOSTER-006 and ZOSTER-022) will be performed on the ATP cohort for analysis of immunogenicity

In ZOSTER-006 and ZOSTER-022, the ATP cohort for analysis of immunogenicity included all evaluable subjects from the ATP cohort for analysis of safety (i.e., those meeting all eligibility criteria, complying with the procedures and intervals allowed for the analysis, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available.

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

More specifically,

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

The goal was to include all evaluable subjects in the statistical analysis at a specific timepoint, i.e., by including all the subjects not impacted by the elimination code for a specific Adapted ATP cohort for immunogenicity. For the criterion impacted only a specified timepoint (specified blood sampling interval), the subject was excluded from the analysis at that timepoint. For the criteria impacting a specified timepoint and the subsequent ones (e.g., medication forbidden by the protocol), the subject was excluded from the analyses performed at that timepoint onwards. For the criteria impacting all timepoints (e.g., not received two doses), the subject was excluded from the analyses at all-timepoints.

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

The medical history is divided into 12 categories; each category will contribute a score of 0 or 1 to the frailty index. The coded medical history database will be searched and subjects with the relevant preferred terms will be assigned to 1 or more of the above categories. A frailty index will be defined by combining all 41 items into a score from 0 to 1 whereby: frailty index = (accumulation of deficits) / (number of items).

Each subject will then be assigned to one of three categories, Non-Frail, Pre-Frail and Frail.

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.

Further details of the calculation of the frailty index will be provided in the statistical analysis plan (SAP).

10.7.5. HZ burden-of-illness score

For each confirmed case of HZ in ZOSTER-006 and ZOSTER-022, responses to the "worst pain" question in the ZBPI were used to calculate a "HZ burden-of-illness" score, defined as the area under the curve (AUC) of HZ-associated pain plotted against time during the 182-day period after the onset of the case. Subjects who developed HZ presented "burden-of-illness" scores ranging from 0 up to, theoretically, 1820. A score of 0 is recorded for subjects in whom HZ did not develop during the study period.

10.7.6. Analysis of Frailty

10.7.6.1. Analysis of primary objective

The number and percentage of subjects in each of the frailty status categories (non-frail, pre-frail and frail) pre-vaccination dose 1 will be presented by vaccination group, overall by age and the following age strata: 50-59, 60-69, 70-79 and ≥ 80 YOA.

10.7.6.2. Analysis of secondary objectives

Descriptive statistics of the 8 derived scales of the *SF-36* and the *EQ-5D* Utility is presented at vaccination day 0 and post-vaccination months 14, 26 and 38.

The analyses will also be presented by country to allow comparison with normative values for those questionnaires in the general population of the countries participating in the study.

10.7.6.2.1. Vaccine efficacy against HZ by frailty status

The primary efficacy endpoint in ZOSTER-006 and ZOSTER-022, vaccine efficacy against HZ, will be summarised by baseline frailty status (non-frail, pre-frail, frail) for subjects in the modified Total Vaccinated cohort.

- Subject's characteristics and QoL scores reported at timepoints posterior to onset of HZ (Month 26 and Month 38) will be censored.

Further, details regarding the analysis will be provided in the statistical analysis plan.

10.7.6.4. Analysis of safety by frailty status

This analysis of the safety data from the ZOSTER-064 population will be based on the Total Vaccinated cohort for safety. Solicited, unsolicited and serious adverse events will be analysed by baseline frailty status.

Incidences of SAEs during the 30-day (Days 0 – 29) follow-up period after each vaccination, up to 8 months and during any time during the study classified according to the MedDRA System Organ Class and Preferred Terms will be tabulated by frailty status.

10.7.7. Analysis of immunogenicity

The analysis will be based on the immunogenicity data from the ZOSTER-064 population for subjects in the adapted ATP for analysis of humoral immunogenicity, and for subjects in the TVC for analysis of CMI, respectively (Section 10.5.3).

10.7.7.1. Humoral immune response

Humoral immune response will be assessed and analysed by frailty status in the Humoral Immunogenicity subset.

Descriptive statistics:

If the data allows the following parameters will be tabulated by vaccination group and frailty status at Month 0, Month 3, Month 14, Month 26 and Month 38:

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

10.7.7.2. Cell-mediated immune response

CMI response will only be assessed and analysed in the CMI component of the Immunogenicity subset for subjects in the ZOSTER-006 study.

Descriptive statistics:

For CMI response; provided the data allows, the following parameters will be tabulated by vaccination group and 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;