Statistical Analysis Plan

Study alias & e-track number(s): ZOSTER-063 (204928)

Detailed Title:	A phase III, open label, multicenter study to evaluate the impact of reactogenicity on Quality of Life (QoL), after intramuscular administration of GSK Biologicals' candidate Herpes Zoster subunit (HZ/su) vaccine (GSK1437173A) in adults ≥ 50 years of age
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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 SR (TFL1 for the safety analysis and TFL2 for the QoL analysis).

LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-To-Protocol
AUC	Area Under Curve
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry
Eli Type	Internal GSK database code for type of elimination code
EQ-5D	Euro-Quality of Life 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
N.A.	Not Applicable
SAE	Serious adverse event
PROC Mixed	SAS Procedure: Mixed models
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

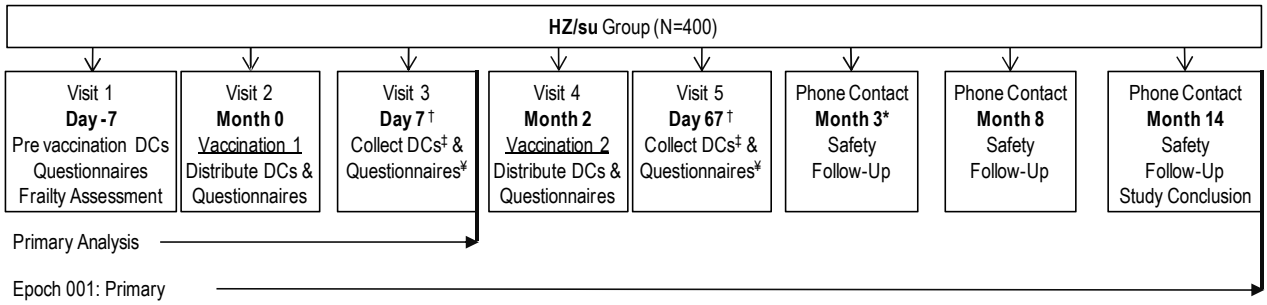
VAS	Visual Analogue Scale
YOA	Years of Age

1. DOCUMENT HISTORY

Date	Description	Protocol Version
30-MAY-2017	Version 1	Amendment 2 - 16-NOV-2016

2. STUDY DESIGN

This study is a Phase III, open lable, multi-center study with a single group.



DC = Diary Card.

† Visit 3 at Day 7 is defined as 7 days post dose 1 at Visit 2 (Month 0) and Visit 5 at Day 67 is defined as 7 days post dose 2 at Visit 4 (Month 2).

‡ Diary Cards distributed at Visit 2 and Visit 4 for solicited adverse events (Days 0–6) will be collected on Day 7 and Day 67 (Visit 3 and Visit 5), respectively.

¥ Questionnaires distributed at Visit 2 and Visit 4 will be collected on Day 7 and Day 67 (Visit 3 and Visit 5), respectively.

* The Month 3 contact will occur when the post-vaccination 2 (Days 0-29) diary cards have been received by site (returned by mail).

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

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
Age	1	50-59 YOA	50-59 year old subjects
	2	60-69 YOA	60-69 year old subjects
	3	≥ 70YOA	≥ 70 year old subjects
Frailty Index (FI)	1	Non–Frail	Subjects with frailty index <=3 are considered as Non frail
	2	Pre-Frail	Subjects with frailty index >3 and <=8 are considered as pre fail
	3	Frail	Subjects with frailty index>8 are considered as frail
Maximum Intensity / Reactogenicity Grade	1	Grade 0	Subjects with no solicited symptoms reported.
	2	Grade 1,2	Subjects with at least one grade 1 or 2 (=mild or moderate) solicited AE reported as maximum intensity.
	3	Grade 3	Subjects with at least one grade 3 (=Severe) solicited AE reported as maximum intensity.
Type of Symptom*	1	None	Subjects with no solicited symptom reported
	2	Local	Subjects with at least one solicited local symptom reported
	3	General	Subjects with at least one solicited general symptom reported
Gender	1	Male	Male Subjects
	2	Female	Female Subjects

*Note that a subject can be included in both Local or General categories

3. OBJECTIVES

3.1. Primary objective

To estimate the change in the SF-36 Physical Functioning (SF-36 PF) scale score from baseline score to the mean score over the period day 1 to day 7 following the first HZ/su vaccination in subjects ≥ 50 years of age (YOA) overall.

3.2. Secondary objectives

- To estimate the change in the SF-36 PF scale score from baseline score to the mean score over the period day 1 to day 7 following the second HZ/su vaccination in subjects ≥ 50 YOA overall.
- To estimate the change in the SF-36 PF scale score in subjects ≥ 50 YOA by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the change in SF-36 PF single item scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the mean score over the period day 1 to day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the change in SF-36 Role Physical scores in subjects ≥ 50 YOA overall, by age, gender and reactogenicity grade and type of symptom (local, systemic) from baseline score to the score on day 7 following both HZ/su vaccinations 1 and 2.
- To estimate the QALY change in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) from baseline score to the combined score on days 1 to 7 following both HZ/su vaccinations 1 and 2.
- To assess the impact of reactogenicity on the healthcare resource utilization (i.e., hospitalization, General Practitioners and specialist visits, medication intake) in subjects ≥ 50 YOA overall, by age, gender reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the work loss in subjects ≥ 50 YOA overall, by age, gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To estimate the work loss for non-dedicated caregivers (e.g., family member) of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.

- To estimate the extra work for dedicated caregivers of subjects ≥ 50 YOA overall, by gender, reactogenicity grade and type of symptom (local, systemic) following both HZ/su vaccinations 1 and 2.
- To evaluate the safety and reactogenicity following administration of the HZ/su vaccine in subjects ≥ 50 YOA.

4. ENDPOINTS

4.1. Primary endpoints

- Change in mean SF-36 PF scale score.
  - Baseline* versus mean score over the period day 1 to day 7** after first vaccination.

4.2. Secondary endpoints

- Change in mean SF-36 PF scale score.
  - Baseline* versus mean score over the period day 1 to day 7** after second vaccination.
- Change in mean SF-36 PF single item scores.
  - Baseline* versus mean score over the period day 1 to day 7** after each vaccination.
- Change in SF-36 Role Physical scores.
  - Baseline* versus score on day 7** after each vaccination.
- Change in the QALY.
  - Baseline* versus combined score over the period day 1 to day 7** after each vaccination.
- Healthcare resource utilization (i.e., hospitalization, telephone calls, medical visits and specialist visits, medication intake).
  - Days 0 to 6 after each vaccination.
- Work loss for subjects.
  - Days 0 to 6 after each vaccination.
- Work loss for the non-dedicated caregivers.
  - Days 0 to 6 after each vaccination.
- Extra work for dedicated caregivers.

  - Days 0 to 6 after each vaccination.

- Solicited local and general symptoms in subjects.
  - Occurrence, intensity and duration of solicited local symptoms within 7 days (Days 0-6**) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of solicited general symptoms within 7 days (Days 0-6**) after each vaccination.
- Unsolicited adverse events (AEs) in subjects.
  - Occurrence, intensity and relationship to vaccination during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events (SAEs).
  - Occurrence and relationship to vaccination of all SAEs from the first vaccination up to the study end.
- Occurrence of adverse events of specific interest (AESIs): potential Immune-Mediated Diseases (pIMDs).
  - Occurrence and relationship to vaccination of any pIMDs from first vaccination up to the study end.

*Note: baseline for dose 1 is defined as the mean of the assessments at day -7 and day 0; for dose 2 baseline is defined as the mean of the three assessments at day -7, day 0 and day 60 (day 0 for dose 2).

**Note: The post-vaccination completion of SF-36 and EQ-5D questionnaires brought home by the subjects will be on days 1 to day 6, with day 7 to be filled in at the site (during Visits 3 and 5); while the post-vaccination recording of solicited AEs on the diary card brought home by the subjects will be on days 0 to day 6.

5. STUDY POPULATION

5.1. Total Vaccinated cohort

The Total Vaccinated Cohort (TVC) will include all vaccinated subjects with respect to the vaccine actually administered.

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

The TVC for analysis of reactogenicity will include all subjects with at least one vaccine dose administered and documented.

5.1.1. According-to-protocol cohort for analysis of safety

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

- who met all eligibility criteria (i.e. no protocol violation linked to the inclusion/exclusion criteria, including age);
- who have received at least one dose of study vaccine;
- for whom administration site of study vaccine is known;
- who have not received other vaccine forbidden in the protocol (Section 6.5.2 in the protocol);
- Who have received the study vaccine correctly reconstituted.
- Who received the vaccine according to protocol procedures (i.e. no temperature deviation and no expired vaccine).

The list of applicable elimination codes for each cohort can be found in the study specific form FORM-BIO-CLIN-9004-05 Criteria for eliminating subjects from the analyses.

Cohort	Elimination codes	Eli Type
ATP cohort for analysis for safety	1010-1600	MA

6. STATISTICAL METHODS

6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age, gender, geographic ancestry and ethnicity) will be tabulated.

The mean age (plus range and standard deviation) of the enrolled subjects, as a whole, and stratified by age group will be calculated.

The distribution of subjects enrolled among the study sites will be tabulated as a whole.

The demographics characteristics will also be tabulated by age stratum and frailty status (sub-groups are defined in Table 1).

6.2. Analysis of Quality of Life (QoL)

The primary endpoint analysis will be based on the Total Vaccinated Cohort (TVC).

6.2.1. SF-36 and EQ-5D

The SF-36 health survey and the EQ-5D questionnaires will be completed by all subjects at each study visits (i.e., Visit 1 Day -7, Visit 2 Month 0 (before the vaccination), Visit 3 Day 7, Visit 4 Month 2 (before the vaccination) and Visit 5 Day 67). Additionally, after each vaccination, the subjects will be given the questionnaires to take home and asked to complete only questions 3a through 3j of the SF-36 questionnaires and the entire EQ-5D questionnaires, on a daily basis on Days 1 to 6 post-vaccination.

Each of the 8 components of the SF-36 Questionnaire and the EQ-5D Utility and VAS scores will be presented at each scheduled visit (Day -7, Day 0, Day 7, Day 60 and Day 67) including the derived baseline values for each dose. In addition the SF-36 physical functioning score (PF) (based on questions 3a to 3j) and the EQ-5D utility and VAS scores will be presented on days 1 to 6 following each dose. Further details of the SF-36 components and EQ-5D Utility and VAS scores can be found in section 7.1.3.

The primary endpoint variable is the SF-36 Physical Functioning (PF) scale. The analysis will be performed on the subgroups detailed in Table 1.

The 10 individual questions that form the SF-36 PF scale will be analysed on an individual basis. The three responses (Limited a lot, Limited a little, Not limited at all) to the individual questions will be assigned a score of 0, 50, or 100. In this way a baseline score and a mean score over the 7 days post each dose can be calculated for each individual question. Summary statistics of the change from baseline will be presented for each individual question.

6.2.1.1. Analysis of Compliance of SF-36 and EQ-5D

The number of questionnaires received will be tabulated by time point. Compliance with completion of SF-36 and EQ-5D questionnaires will be summarized for the questionnaires completed at each study visit (Day -7, Day 0, Day 7, Day 60 and day 67) and also for the questionnaires completed at home (Days 1 to 6 and Days 61 to 67). Compliance will be defined for each time point as follows:

% Compliance = 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 is expected

Questionnaires are expected from all subjects who received at least one dose.

6.2.1.2. Baseline Values

Baseline for dose 1 is defined as the mean of the assessments at day -7 and day 0. Dose 2 baseline is defined as the mean of the three assessments at day -7, day 0 and day 60 (day 0 for dose 2). See section 7 for further details.

6.2.2. EQ-5D Utility / Quality adjusted life years (QALY)

The calculation of the baseline and post baseline values for the analysis of QALY loss is detailed in section 7.1.3.

The 95% CI for Quality-adjusted life year (QALY) mean loss will be obtained using a multiple regression model on the change from baseline EQ-5D utility scores. The model will include age strata, gender and frailty status as the fixed effect.

The 95% CI for utility scores will be obtained pre- and post-vaccination separately assuming that utility scores were normally distributed with unknown variance.

6.2.3. Sensitivity Analysis

The complete list of adverse events observed in the study will be reviewed after database freeze and those events, not related to vaccination, which could significantly impact a subjects physical functioning, will be selected. An exploratory analysis of the primary endpoint will then be carried out excluding subjects who reported these events.

Additionally an analysis will be carried out to explore the sensitivity of the primary endpoint analysis and QALY loss to the completion of questionnaires. Only subjects with a valid assessment for at least 4 of the 7 days post each dose will be included.

6.3. Frailty Status

An assessment of frailty status will be done at Visit 1. Frailty status will be measured in relation to the accumulation of deficits using a frailty index (FI) calculated according to the model proposed by Mitnitski et al. [Mitnitski, 2001]. The different aspects of frailty composing the FI will be assessed through a series of certified tests and specific questions in the following domains:

- Cognition: a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment called the Montreal Cognitive Assessment (MoCA);
- Physical status: criteria for the definition of frailty developed by Fried et al. [Fried, 2001] to categorize the physical frailty phenotype (PFP), the physical functioning category of the SF-36 questionnaire will be used as measure of the physical activity of the subject [Ryb, 2012];
- Depression and exhaustion: a screening test for depression and depressive disorder called the Center for Epidemiologic Studies Depression Scale – Revised (CESD-R);
- Multimorbidity: occurrence of a specific age dependent list of diseases based on the published work [Mitnitski, 2001]. The 14 medical history items are : High Blood Pressure, Heart Attack, CHF, Cerebrovascular disease, Cancer, Diabetes Mellitus, Arthritis, Chronic Lung Disease, Long Term Disability or Handicap, Stomach or Intestinal Ulcers, Migraine, Cataract, Hearing Problems and Glaucoma.
- Disability: assessment of the subjects' dependence on others to perform a list of specific daily activities (based on the published work [Mitnitski, 2001; **Error! Reference source not found.**, 2008]).

The range of the index is 0 to 36. The contribution of each component is as follows:

Category	Range
Medical History	0 – 14
Disability assessment	0 – 14
CESD-R depression scale	0 – 1
SF-36 PF score	0 – 1
Cognitive assessment (MoCA)	0 – 1
Unintentional weight loss	0 – 1
Weakness (grip strength)	0 – 1
Slow walking speed	0 – 1
Self-rating of health	0 – 1
Health change in last year	0 – 1
Total	0 – 36

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

If the score is <= 3 then the subject is classified as Non-Frail. If the score is greater than 3 but less than or equal to 8 then the subject is classified as pre-frail. If the score is greater than 8 then the subject is classified as Frail.

A subject must have at least 30 non-missing components in order to be assigned a frailty index classification. However in the event that a subject with a partially completed frailty assessment has a score greater than 8 then the classification will be Frail even if the total number of completed responses is less than 30.

Further details of the Frailty index components can be found in Appendix A

6.4. Analysis of resource utilisation

An analysis of resource utilisation related to reactogenicity will be carried out. Resource use data to be collected include:

6.4.1. Medications

The specific medications taken in response to reactogenicity are detailed in the eCRF.

The percentage of subjects reporting such medication use during the solicited 7-day (Days 0-6) follow-up period after each dose will be tabulated overall and by age category. In addition a frequency table of each specific medication taken in response to reactogenicity will be presented by preferred term.

6.4.2. Medically Attended Visits

Details of reactogenicity-triggered medical attention (phone calls, visits to a general practitioner/emergency room, hospitalizations and specialists' visits) will be collected from day 0-6 post each dose and recorded in the eCRF.

The percentage of subjects reporting each medically attended visit during the solicited 7-day (Days 0-6) follow-up period after each dose will be tabulated by age category and dose (and overall) with exact 95% CI.

6.4.3. Missed time from work

Missed time from work can affect the subject and both dedicated and non-dedicated caregivers. The percentage of subjects with loss of working days will be tabulated. In addition summary statistics of the number of days lost per caregiver/subject will be presented.

6.5. Health Economic Cost Analysis

A full analysis of the costs associated with reactogenicity will be carried out at a future date. This analysis will be detailed in a separate SAP.

6.6. Analysis of safety

The primary analysis for safety will be based on the TVC. If the percentage of the vaccinated subjects excluded from the ATP cohort for safety is more than 5%, a second analysis based on the ATP cohort for safety will be performed.

Safety analyses will be performed by age stratum and frailty status (sub-groups are defined in Table 1).

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

The 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 general AE collected during the pre-vaccination period (Day -7 and Day 0 visits) will be tabulated with exact 95% CI.
- 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;

- Summary of temperature value by half degree increment taken reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall doses and subjects **with no conversion rule**.
- Summary of temperature value by half degree increment **by route temperature** taken reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall doses **with no conversion rule**.
- The number of days with each individual solicited local and general AE **during the solicited 7-day follow-up period** will be tabulated;
- The number of days with each solicited symptom local and general **during the whole post vaccination 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. The proportion of unsolicited AEs resulting in a medically attended visit (such as emergency room, out-patient visit, site investigator, etc.) will also be tabulated;
- Total number/percentages of doses followed by AEs will be tabulated;
- The percentage of subjects who started to use the medications within the 30-days post-vaccination 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;
- SAEs will be described in details;
- 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.
- pIMDs will be described in detail.

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) will be collected.

Therefore, the 15th of the month will be used to replace the missing date.

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

Note that due to incomplete date, the derived age may be incorrect by 1 month when 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.

Conversion of weight to kg : :

The following conversion rule is used, the result is rounded to 2 decimals:

- Weight in Kilogram = weight in Pounds / 2.2
- Weight in Kilogram = weight in ounces / 35.2

Conversion of height to cm : The following conversion rule is used, the result is rounded to the unit (i.e. no decimal):

- Height in Centimetres = Height in Feet * 30.48
- Height in Centimetres = Height in Inch * 2.54

7.1.2. Safety

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

Table 2 Lower level and preferred terms for solicited symptoms

Solicited symptom	Lower level term name	LLT code	Corresponding Preferred Term name
Pain	Pain	10033371	Pain
Redness	Erythema	10015150	Erythema
Swelling	Swelling	10042674	Swelling
Fatigue	Fatigue	10016256	Fatigue
Fever	Fever	10016558	Pyrexia
Gastrointestinal symptoms	Gastrointestinal disorder	10017944	Gastrointestinal disorder
Headache	Headache	10019211	Headache
Myalgia	Myalgia	10028411	Myalgia
Shivering	Shivering	10040558	Chills

Note that for all tables described in this section, the way the percentage of subjects will be derived will depend on the event analysed (see table below for details). As a result, the N value will differ from one table to another.

Table 3 Details of calculation of percentages for each category of safety analysis

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

- SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 30June is used.
- Onset day for an event (ae, medication, vaccination, …): The onset day is the number of days between the last study vaccination and the onset/start date of the event. This is 0 for an event starting on the same day as a vaccination. See SAS date derived in case the start date of the event is incomplete.
- Duration: Duration of an event is expressed in days. It is the number of days between the start and the stop dates + 1. Therefore duration is 1 day for an event starting and ending on the same day.
- Related dose: The related dose for an event (e.g., AE, medication, vaccination,…) is the study dose given before an event. In case the event takes place on a day a study dose is given, the related dose will be that of the study dose even if the event actually took place before. For instance, for a conc. medication started on the day of study dose 2 but before dose 2 administrations, the related dose will be dose 2.
- The confidence intervals will be exact 95% CIs for a proportion within a group calculated according to Clopper & al. (1934).

7.1.2.1. Grading rules

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

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

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

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

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. Such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

For the analysis, temperatures will be coded as follows:

Grade	Temperature
0	< 37.5°C
1	≥ 37.5°C - ≤ 38.0°C
2	> 38.0°C - ≤ 39.0°C
3	> 39.0°C

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

7.1.2.2. Conversion of temperature to °C

The following conversion rule is used for the conversion of temperature to °C, the result is rounded to 1 decimal:

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

7.1.3. Quality of Life data

7.1.3.1. Calculation of study day for SF-36 and EQ-5D Assessments

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.

To be considered evaluable at day 0 a questionnaire must have been filled in within 14 days of vaccination date. Questionnaires without a date of assessment were to be considered not evaluable. In case of two questionnaires with the same date of assessment the minimum value (i.e. the value which represents worst quality of life) of the two assessments will be selected as evaluable.

7.1.3.2. SF-36

The SF-36 is a multi-purpose health survey with 36 questions (refer to the website address http://www.sf-36.org/demos/SF-36.html for a sample of the questionnaire) [Ware, 2001; SF-36.org, 2014;**Error! Reference source not found.**, 2008; SF-36 sample, 2014]. The concepts underlying the construction of the SF-36™ scales and summary measures incorporates a taxonomy of three levels: (1) 36 items; (2) eight scales (see Table 4 for details); and, (3) two summary measures (Physical Component and Mental Component Scores) that aggregate scales. All but one of the 36 items (self-reported health transition) are used to score the eight SF-36™ scales. Each item is used in scoring only one scale. Scale scores will be constructed following the summated ratings and standardized SF-36™ scoring algorithms. A standardized SAS macro provided by Hays will be used to perform the scoring (http://gim.med.ucla.edu/FacultyPages/Hays/util.htm).

The SF-36 health survey questionnaires will be completed by all subjects at each study visits (i.e., Visit 1 Day -7, Visit 2 Month 0 (before the vaccination), Visit 3 Day 7, Visit 4 Month 2 (before the vaccination) and Visit 5 Day 67). Additionally, after each vaccination, the subjects will be given the SF-36 questionnaires to take home and asked to complete only questions 3a through 3j on a daily basis on Days 1 to 6 post-vaccination. Subjects will be asked to return the completed questionnaires at the next visit (Visits 3 and 5). Completed questionnaires are to be collected and the subject responses transcribed into the eCRF.

Table 4 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

7.1.3.3. EQ-5D

The EQ-5D questionnaire is a generic measure of health status that provides a simple descriptive profile and a single index value (refer to the website address http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Products/Sample_UK_English_for a sample of the questionnaire [below 1996; EQ-5D,2014; EQ-5D sample, 2014]. 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). The US TTO (Time-Trade-Off) value set will be used for the analysis.

The EQ-5D also contains a visual analogue scale (VAS). The VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The score ranges from 0 to 100, with 100 representing the best imaginable health state and 0 representing the worst imaginable health state This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The EQ-5D questionnaires will be completed by all subjects at each study visits (i.e., Visit 1 Day -7, Visit 2 Month 0 (before the vaccination), Visit 3 Day 7, Visit 4 Month 2 (before the vaccination) and Visit 5 Day 67). Additionally, after each vaccination, the subjects will be given the EQ-5D questionnaires to take home and asked to complete the entire EQ-5D questionnaire on a daily basis on Days 1 to 6 post-vaccination. Subjects will be asked to return the completed questionnaires at the next visit (Visits 3 and 5). Completed questionnaires are to be collected and the subject responses transcribed into the e-CRF.

7.1.3.4. Area Under the Curve Calculation (AUC) applied to QALY

The AUC method will be applied to the EQ-5D utility score in order to estimate the QALY loss over the 7 days (day 1 to day 7) post dose 1 and dose 2. The calculation of AUC will be based on the trapezoidal rule [Yeh, 2002]. The trapezoidal rule is a numerical integration method to be used to approximate integral or area under curve. The QALY loss will be calculated according to the following steps;

Step1

The baseline or reference value will be calculated from the assessments at day -7 and day 0 for dose 1 and the assessments at day -7, day 0 and day 60 for dose 2. For dose 1 the mean of the two assessments at day -7 and day 0 will be calculated. This value will then be assumed to have been the utility in the 7 days pre vaccination dose 1. Note that if vaccination dose 1 occurred more than 14 days after the scheduled day -7 then the EQ-5D assessment will not be used and the baseline utility score will be based on the value at day 0 only. To summarise:

Dose 1 : Baseline utility=7*mean(Day -7 utility, Day 0 utility)

Dose 2 : Baseline utility=7*mean(Day -7 utility, Day 0 utility, Day 60 Utility)

Step2

The QALY/week for the 7 days post dose is calculated for each subject using the following formula:

$$AUC_{0-7} = \sum_{k=1}^{6} (t_{k+1} - t_k) \frac{(y_k + y_{k+1})}{2}$$

Where tk is the day of assessment k relative to vaccination and Yk is the utility score on day k relative to vaccination.

Step3

The QALY Loss is then calculated as the difference between the baseline utility (from step 1) and the AUC value (from step 2).

It is anticipated that the majority of subjects will have daily assessments post dose according to the schedule (i.e. on each of the days 1 to 7) however it is expected that some subjects will be missing daily assessments post dose. In the case of missing assessments between days 1 and 7 the AUC in step 2 will be calculated regardless of the number of assessments post dose. However in the case of the last assessment falling outside of the 7 day window, (for example on day 8), an adjustment will be made before calculating the AUC.

Figure 1 represents the Utility scores for a hypothetical subject. This subject has consecutive assessments on day 5 and day 8 and no assessments on days 6 or 7. Because the AUC must be calculated over a period of 7 days, the day 8 value cannot be included in the formula. However to calculate the AUC, a derived value on day 7 is calculated based on a linear interpolation of the values on days 5 and 8. This derived value on day 7 is then included in the formula given in step 2. The dashed line in the figure represents the linear interpolation between the two assessments either side of day 7.

The calculation of the QALY loss for this hypothetical subject is explained in Table 5.

Figure 1 Hypothetical Example of utility Scores over Time

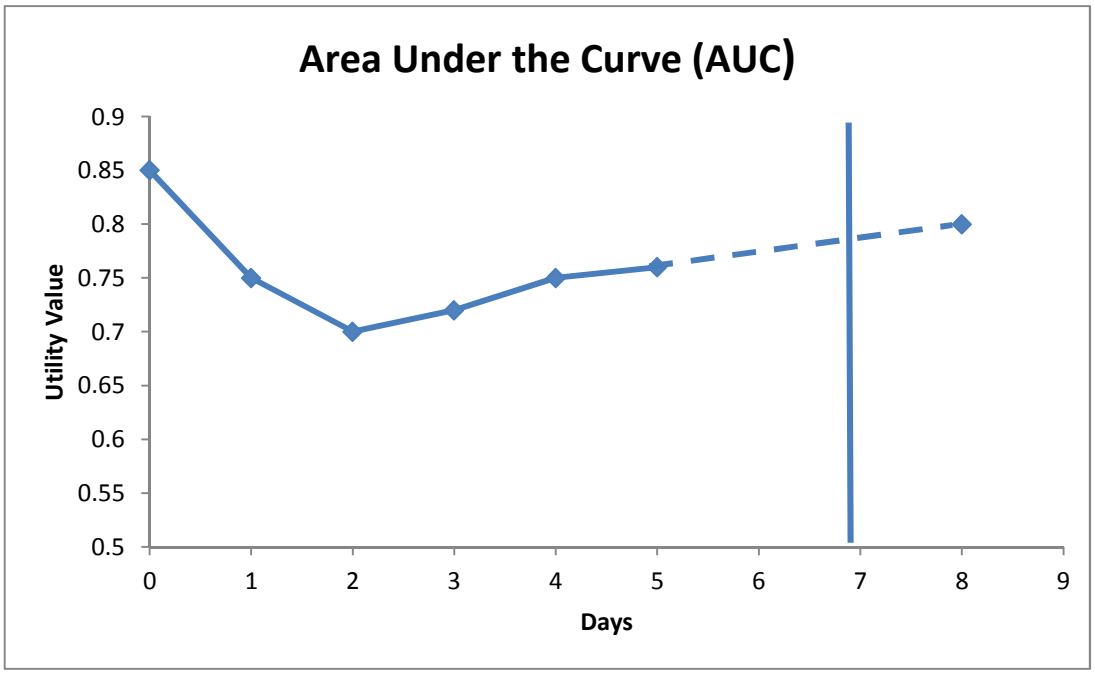


Table 5 Calculation of QALY for hypothetical Subject in figure 1

Day	Score	$t_{k+1}-t_k$	$(Y_{k+}Y_{k+1})/2$	Product
-7	0.89			
0	0.85	1	0.800	0.800
1	0.75	1	0.725	0.725
2	0.70	1	0.710	0.710
3	0.72	1	0.730	0.730
4	0.74	1	0.745	0.745
5	0.75	1	0.765	0.765
7	***0.78***	***2***		
8	0.8			
Total				4.475

Note. The value at day 7 is interpolated from the values at day 5 and day 8.

The baseline score is calculated as 7*(0.89+0.85)/2 = 6.09

The AUC between days 0 and 7 is 4.475. Hence the QALY loss / week is calculated as 1.534.

The 95% CI for the LSmeans of the QALY loss will be obtained using a multiple regression model. The model will include age strata, gender and frailty status as the fixed effect. The Following Code will implement this model in SAS:

```
ods output lsmeans=lsmeans;
proc mixed data=DATASET;
  class agecat gender frail;
  model qaly=agecat frail gender/cl;
  lsmeans frail/pdiff cl;
  lsmeans gender/pdiff cl;
  lsmeans agecat/pdiff cl;
quit;
run;
```

The 95% CI for utility scores will be obtained pre- and post-vaccination separately assuming that utility scores were normally distributed with unknown variance.

7.2. Handling of missing data

7.2.1. Demography

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

7.2.2. Reactogenicity and safety

For a given subject and a given measurement, missing or non-evaluable measurements will not be imputed. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missing value(s) being either Missing Completely At Random (MCAR) or Missing At Random (MAR) only.

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

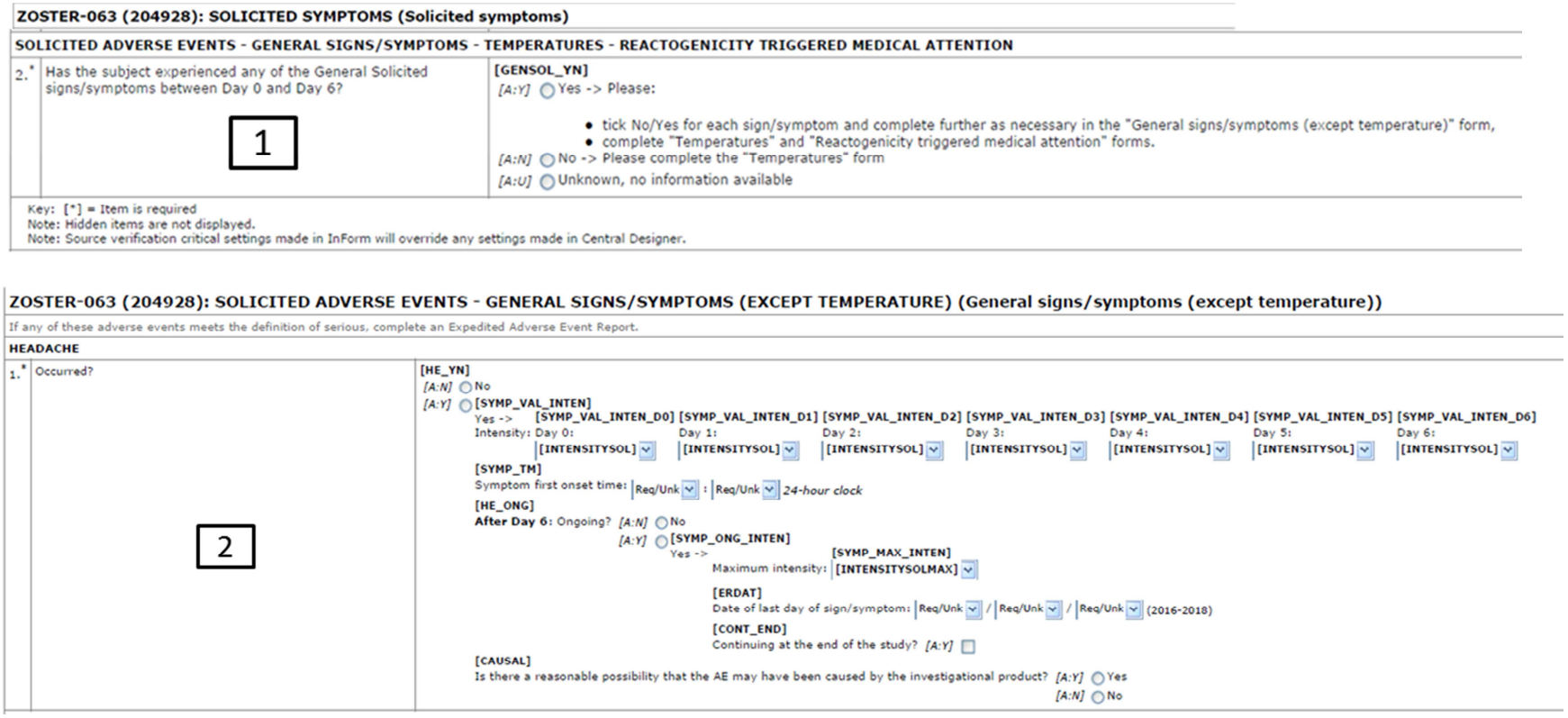
For the analysis of unsolicited symptoms/SAEs/pIMDs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

7.2.2.1. Solicited general symptoms

The analysis of solicited general symptoms will include all subjects for whom the question (1) in Figure 2 about the presence of any solicited general symptom has been answered by 'Yes' or 'No' (see the GENSOL_YN item).

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

Figure 2 Information captured in the clinical database for solicited general symptoms



ZOSTER-063 (204928): SOLICITED SYMPTOMS (Solicited symptoms)

SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS - TEMPERATURES - REACTOGENICITY TRIGGERED MEDICAL ATTENTION

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

1

[GENSOL_YN]
[A:Y] Yes -> Please:
- tick No/Yes for each sign/symptom and complete further as necessary in the "General signs/symptoms (except temperature)" form,
- complete "Temperatures" and "Reactogenicity triggered medical attention" forms.

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

Key: [*] = Item is required
Note: Hidden items are not displayed.
Note: Source verification critical settings made in InForm will override any settings made in Central Designer.

ZOSTER-063 (204928): SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (EXCEPT TEMPERATURE) (General signs/symptoms (except temperature))

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

HEADACHE

1.* Occurred?

2

[HE_YN]
[A:N] No
[A:Y] [SYMP_VAL_INTEN]
Yes -> [SYMP_VAL_INTEN_D0] [SYMP_VAL_INTEN_D1] [SYMP_VAL_INTEN_D2] [SYMP_VAL_INTEN_D3] [SYMP_VAL_INTEN_D4] [SYMP_VAL_INTEN_D5] [SYMP_VAL_INTEN_D6]
Intensity: Day 0: [INTENSITYSOL] Day 1: [INTENSITYSOL] Day 2: [INTENSITYSOL] Day 3: [INTENSITYSOL] Day 4: [INTENSITYSOL] Day 5: [INTENSITYSOL] Day 6: [INTENSITYSOL]
[SYMP_TM]
Symptom first onset time: Req/Unk : Req/Unk *24-hour clock*
[HE_ONG]
After Day 6: Ongoing? [A:N] No
[A:Y] [SYMP_ONG_INTEN]
Yes -> [SYMP_MAX_INTEN]
Maximum intensity: [INTENSITYSOLMAX]
[ERDAT]
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (2016-2018)
[CONT_END]
Continuing at the end of the study? [A:Y]
[CAUSAL]
Is there a reasonable possibility that the AE may have been caused by the investigational product? [A:Y] Yes
[A:N] No

For each solicited general symptom if the answer to (2) in Figure 2 is "No", the subject will be considered as not having that symptom after that dose.

Subjects who documented the presence of a specific symptom i.e., if the answer to (2) in Figure 2 is "Yes" (ex FA_YN=Y), the maximum intensity recording over the considered follow-up period is used for the analysis of the percentage of subjects with symptoms.

If the subject answered "Yes" to (2) in Figure 2 for a specific symptom BUT partially recorded daily measurement (e.g. intensity missing for Day 3) over the considered solicited period, s/he will be included in the summaries and classified according to their maximum observed daily recording over the solicited period.

If the subject answered "Yes" to (2) in Figure 2 for a specific symptom BUT no daily measurement is recorded, s/he will not be included and counted in the summary of subjects with symptoms above a specified threshold, however s/he will be part of the summary corresponding to the 'All' category.

7.2.2.2. Solicited general fever

Figure 3 Information captured in the clinical database for temperature record

ZOSTER-063 (204928): SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS: ONLY TEMPERATURES (Temperatures)

If there is a temperature that meets the definition of serious, complete an Expedited Adverse Event Report.

TEMPERATURES

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

1

[SYMP_VAL_TEMP]

[FE_VAL_D0]	[FE_VAL_D1]	[FE_VAL_D2]	[FE_VAL_D3]	[FE_VAL_D4]	[FE_VAL_D5]	[FE_VAL_D6]
Day 0:	Day 1:	Day 2:	Day 3:	Day 4:	Day 5:	Day 6:
[FE_VAL] xxx.x	[FE_VAL] xxx.x	[FE_VAL] xxx.x	[FE_VAL] xxx.x	[FE_VAL_D4] xxx.x	[FE_VAL_D5] xxx.x	[FE_VAL_D6] xxx.x
[FE_NT] Not taken *[A:Y]* ☐	[FE_NT] Not taken *[A:Y]* ☐	[FE_NT] Not taken *[A:Y]* ☐	[FE_NT] Not taken *[A:Y]* ☐	[FE_NT_D4] Not taken *[A:Y]* ☐	[FE_NT_D5] Not taken *[A:Y]* ☐	[FE_NT_D6] Not taken *[A:Y]* ☐

2. Primary route:
The preferred route for recording temperature in this study is oral. When there is no other alternative, the temperature may be recorded by other route.
[Primary route]

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

3. Fever first onset time:
[Fever 1st onset time]

[FEVER_TM]
Req/Unk : Req/Unk *24-hour clock*

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

2

[FE_YN]
[A:N] ○ No
[A:NT] ○ Not taken
[A:Y] ○ **[FE_ONG]**
Yes -> **After Day 6:** Temperature above or equal to threshold ? *[A:N]* ○ No
[A:Y] ○ **[SYMP_ONG_TEMP]**
[SYMP_MAX_TEMP]
Yes -> Max temperature (Farhenheit) : xxx.x
[ERDAT]
Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (2016-2018)
[CONT_END]
Continuing at the end of the study? *[A:Y]* ☐

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

For temperature

To allow the temperature recording, a separate screen had to be completed whatever the answer to question (2) in Figure 3 and even if no temperature equal or above 37.5°C has been found in the diary card.

All subjects for whom that question (2) in Figure 3 has been answered by "Yes" or "No", will be included in the summaries of temperature by **half degree (°C) cumulative increments** and classified according to their maximum temperature value observed daily recording over the solicited period. If no daily measurement is recorded for temperature, the subject will not be counted in the summary of subjects with temperature above a specific threshold. For the summary of temperature, the "all" category will not be computed. This table will be produced overall, by route with no route conversion.

For summary of fever

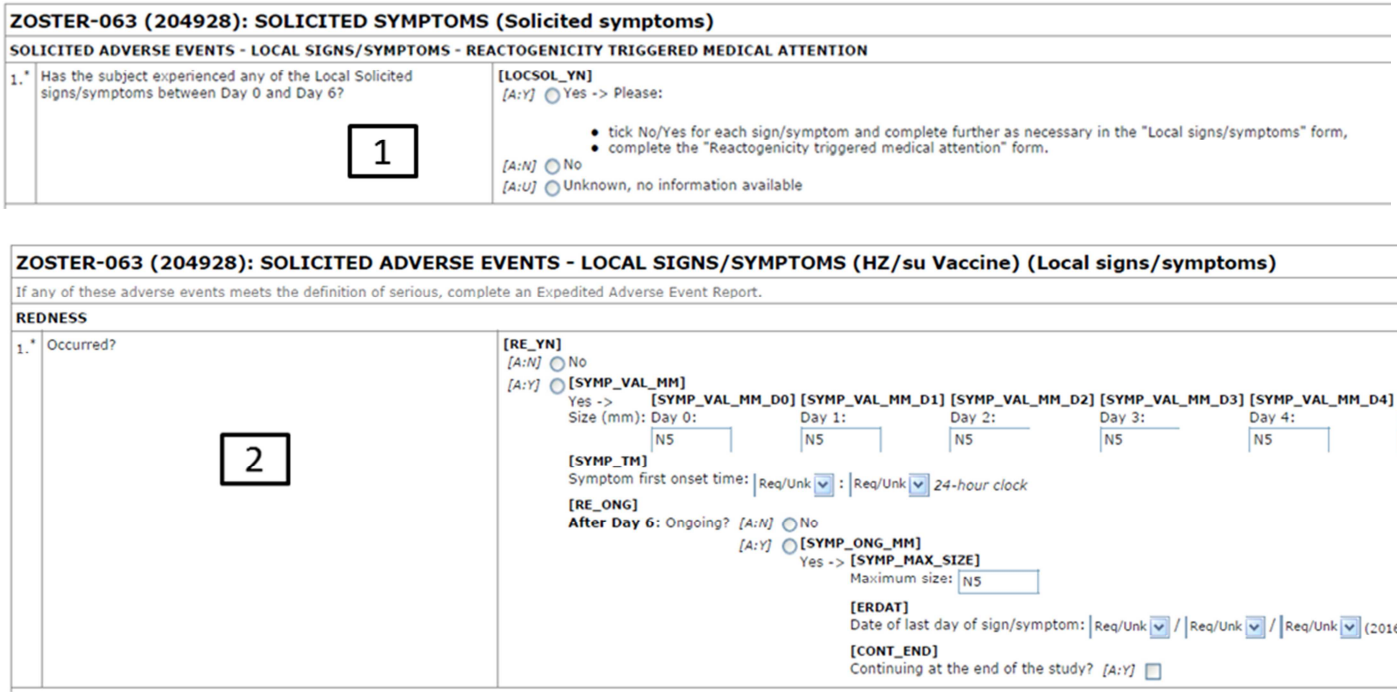
All subjects for whom that question (2) in Figure 3 has been answered by "Yes" or "No", will be included in the summaries of fever and classified according to their maximum temperature value observed daily recording over the solicited period even if partial recording. If no daily measurement is recorded for temperature, the subject will not be counted in the summary of subjects with fever and the "all" category will count the number of subject with at least one temperature measurement ≥ 37.5°C / 99.5°F for oral, axillary or tympanic route, or ≥ 38.0°C / 100.4°F for rectal route.

7.2.2.3. Solicited local symptoms

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

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

Figure 4 Information captured in the clinical database for solicited local symptoms



ZOSTER-063 (204928): SOLICITED SYMPTOMS (Solicited symptoms)

SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS - REACTOGENICITY TRIGGERED MEDICAL ATTENTION

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

1

[LOCSOL_YN]

[A:Y] ◯ Yes -> Please:

- tick No/Yes for each sign/symptom and complete further as necessary in the "Local signs/symptoms" form,
- complete the "Reactogenicity triggered medical attention" form.

[A:N] ◯ No

[A:U] ◯ Unknown, no information available

ZOSTER-063 (204928): SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS (HZ/su Vaccine) (Local signs/symptoms)

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

REDNESS

1.* Occurred?

2

[RE_YN]

[A:N] ◯ No

[A:Y] ◯ **[SYMP_VAL_MM]**

Yes -> Size (mm):

[SYMP_VAL_MM_D0] Day 0:	**[SYMP_VAL_MM_D1]** Day 1:	**[SYMP_VAL_MM_D2]** Day 2:	**[SYMP_VAL_MM_D3]** Day 3:	**[SYMP_VAL_MM_D4]** Day 4:	**[SYMP_VAL_MM_D5]** Day 5:	**[SYMP_VAL_MM_D6]** Day 6:
N5	N5	N5	N5	N5	N5	N5

[SYMP_TM]

Symptom first onset time: Req/Unk : Req/Unk *24-hour clock*

[RE_ONG]

After Day 6: Ongoing? *[A:N]* ◯ No

[A:Y] ◯ **[SYMP_ONG_MM]**

Yes -> **[SYMP_MAX_SIZE]**

Maximum size: N5

[ERDAT]

Date of last day of sign/symptom: Req/Unk / Req/Unk / Req/Unk (2016-2018)

[CONT_END]

Continuing at the end of the study? *[A:Y]* ☐

For each solicited local symptoms if the answer to (2) in Figure 4 is "No", the subject will be considered as not having that local symptom at the injection site after that dose.

Subjects who documented the presence of a specific symptom i.e. if the answer to (2) in Figure 4 is "Yes" (ex RE_YN=Y), the maximum intensity recording over the considered follow-up period is used for the analysis of the percentage of subjects with symptoms.

If the subject answered "Yes" to (2) in Figure 4 for a specific symptom BUT partially recorded daily measurement (e.g., intensity missing for Day 3) over the considered solicited period, s/he will be included in the summaries and classified according to their maximum observed daily recording over the solicited period.

If the subject answered "Yes" to (2) in Figure 4 for a specific symptom BUT no daily measurement is recorded, she/he will not be included and counted in the summary of subjects with symptoms above a specified threshold, however s/he will be part of the summary corresponding to the 'All' category.

7.2.2.4. Combined Solicited local and general symptoms

The analysis of the combined solicited general and local symptoms will include all vaccinated subjects for whom the question (1) in Figure 2 or Figure 4 about the presence of any solicited general or local symptoms has been answered by 'Yes' or 'No'.

7.2.2.5. Unsolicited symptoms

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

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

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

7.2.2.6. Concomitant medication

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

7.2.2.7. Compliance with respect to documenting safety

The number of doses injected, the number of doses not given according-to-protocol, and the number of symptom sheets (SS) transcribed for local and general symptoms, the compliance for local and general symptoms are tabulated for the Total Vaccinated cohort.

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

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

7.2.3. Quality of Life data

At dose 1, if one of the Day -7 or Day 0 pre-vaccination assessments is missing, the baseline value will simply be the non-missing assessment. At dose 2, if 2 or more of the 3 pre-vaccination assessments are missing, the baseline value will be considered missing.

7.3. 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
	QALY, including LL & UL of CI	3
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

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Two formal analyses are planned: a first analysis and an end of study analysis.

The first analysis will be performed when the reactogenicity and QoL collected from dose 1 up to Visit 3 are available (data as clean as possible). No clinical study report will be written.

The end of study analysis of QoL and safety data will be performed when all data up to the study end (Study conclusion contact) will be available. A clinical study report will be written including all available data and made available to the investigators at that time.

Description	Analysis ID	Disclosure Purpose	Reference for TFL
End of study analysis	E1_01	CTRS, Study report	All tables identified as E1_01 in TFL dated 30MAY2015
Analysis up to Visit 3 Day 7	E1_02	Internal, CTRS	All tables identified as E1_02 in TFL dated 30MAY2015, on data up to Visit 3 Day 7

8.2. Statistical considerations for interim analyses

No interim analysis is planned.

9. CHANGES FROM PLANNED ANALYSES

- pIMDs will be described in detail. Sub-groups analyses by age stratum and by frailty status have been added.

- Additional analyses of safety have been added following remarks made by CBER on the Zoster-032 study.

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Appendix A DETAILS OF COMPONENTS OF FRAILTY INDEX

Item No	Category	Response		Mapped Score as used in Frailty Index
1	Help Bathing	Yes, No		Yes=1, No=0
2	Help Dressing	Yes, No		Yes=1, No=0
3	Help getting in or out of chair	Yes, No		Yes=1, No=0
4	Help walking in or around house	Yes, No		Yes=1, No=0
5	Help eating	Yes, No		Yes=1, No=0
6	Help Grooming	Yes, No		Yes=1, No=0
7	Help using Toilet	Yes, No		Yes=1, No=0
8	Help up/down stairs	Yes, No		Yes=1, No=0
9	Help lifting	Yes, No		Yes=1, No=0
10	Help shopping	Yes, No		Yes=1, No=0
11	Help with housework	Yes, No		Yes=1, No=0
12	Help with meal preparation	Yes, No		Yes=1, No=0
13	Help taking medications	Yes, No		Yes=1, No=0
14	Help with finances	Yes, No		Yes=1, No=0
15	Cognitive score (MoCA)	Range 0 to 30	Mapped to a score between 0 and 1	If score < 6 then mapped score=1 (Severe Dementia) If 6 =< score =< 11 then mapped score=0.75 (Moderate Dementia) If 12 =< score =< 18 then mapped score=0.5 (Mild Dementia) If 19 =< score =< 25 then mapped score=0.25 (Mild Cognitive impairment) If score >= 26 then mapped score=0 (No Cognitive impairment)

Item No	Category	Response		Mapped Score as used in Frailty Index
16	Self Rating of Health	Poor, Fair, Good, Very Good, Excellent		If rating=Poor then mapped score=1 If rating=Fair then mapped score=0.75 If rating=Good then mapped score=0.5 If rating=Very Good then mapped score=0.25 If rating=Excellent then mapped score=0
17	Health Change in last year	Worse, Better/Same		If change=Worse then mapped score=1 Else mapped score=0
18	Unintentional weight loss	Yes, No		Yes=1, No=0
19	Depression score (CESD-R)	Range 0 to 60	Mapped to a score between 0 and 1	If score < 16 then mapped score=0 If 16 =< score =< 21 then mapped score=0.5 If score > 21 then mapped score=1
20	Weakness (grip strength)	Yes, No		Yes=1, No=0
21	Slow Walking Speed	Yes, No		Yes=1, No=0
22	General Medical History : High Blood pressure,	Yes, No		Yes=1, No=0
23	Heart Attack,	Yes, No		Yes=1, No=0
24	CHF,	Yes, No		Yes=1, No=0
25	Cerebrovascular Disease,	Yes, No		Yes=1, No=0
26	Cancer,	Yes, No		Yes=1, No=0
27	Diabetes Mellitus	Yes, No		Yes=1, No=0
28	Arthritis,	Yes, No		Yes=1, No=0

Item No	Category	Response		Mapped Score as used in Frailty Index
29	Chronic Lung Disease,	Yes, No		Yes=1, No=0
30	Long Term disability or Handicap	Yes, No		Yes=1, No=0
31	Stomach or Intestinal Ulcers	Yes, No		Yes=1, No=0
32	Migraine	Yes, No		Yes=1, No=0
33	Cataract	Yes, No		Yes=1, No=0
34	Hearing Problems	Yes, No		Yes=1, No=0
35	Glaucoma	Yes, No		Yes=1, No=0
36	SF-36 Physical Functioning Score	Derived score for items 3A to 3J. (Range : 0 - 100)		If derived score =0 then mapped score=0 If derived score = 50 then mapped score=0.5 If derived score =100 then mapped score=1