Statistical Analysis Plan Amendment 1

Study ID: 212884

Official Title of Study: A phase IV, randomized, observer-blind, placebo-controlled, multi-center study to assess the prophylactic efficacy against Herpes Zoster, immunogenicity and safety of Shingrix when administered intramuscularly on a 2-dose schedule in Chinese adults aged 50 years and older

NCT number: NCT04869982

Date of Document: 10 May 2023

Statistical Analysis Plan	
Title:	A phase IV, randomized, observer-blind, placebo-controlled, multi-center study to assess the prophylactic efficacy against Herpes Zoster, immunogenicity and safety of *Shingrix* when administered intramuscularly on a 2-dose schedule in Chinese adults aged 50 years and older
eTrack study number and Abbreviated Title	212884 (ZOSTER-076)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 08 February 2021 **Amendment 1 Final: 10 May 2023**

APP 9000058193 Statistical Analysis Plan Template V5 (Effective date: 1July2020)

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List of abbreviations

AE	Adverse event
AAC	***All Analyses Complete***
CI	Confidence Interval
CCI	[redacted]
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EoS	End of Study
ES	Exposed Set
gE	VZV glycoprotein E
GM	Geometric Mean
GSK	GlaxoSmithKline Biologicals SA
HZ	Herpes Zoster
HZAC	HZ Ascertainment Committee
ICF	Inform Consent Form
ICS	Intracellular staining
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
mES	Modified Exposed Set
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
RAPIDO DV	***Reporting & Analysis Plan Improving Design and Delivery of Outputs Data Viewer***
RR	Relative Risk
RZV	Recombinant Zoster Vaccine
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biological's Internet Randomisation System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
VE	Vaccine Efficacy
YOA	Years of Age

1. DOCUMENT HISTORY

Date	Description	Protocol Version
08 FEB 2021	***Initial*** Version	Amendment 2 Final: 23 NOV 2020
10 May 2023	***Amendment 1: Following are the changes from SAP from 08 FEB 2021:-*** • ***Added RAPIDO DV*** • ***Added analysis of deviation from protocol-defined age and visit interval on ES.*** • ***Updated model of vaccine efficacy: added by agecat statement and removed agecat from model.*** • ***Substituted kaplan meier curves by cumulative incidence curves.*** • ***Calculation and derivation rule for some solicited adverse event grade 4 and duration has been added*** • ***Related grade 1 and related grade 2 have been added to GSK and Chinese scale analyses.*** • ***Substituted 'grade 3' by at 'least grade 3' in solicited local and solicited general summaries based on GSK scale. Also, added the categories that will be displayed for fever in solicited general summaries*** • ***Update of grade 3 definition for redness and swelling based on Chinese scale*** • ***Update of the Preferred Terms used to determine grade 4 for Redness and Swelling.*** • ***Update in handling of missing data in section 10.1.2.3.2*** • ***Analysis for secondary safety endpoint related to 'SAE due to study participation and GSK concomitant medication/vaccination' has been added.*** • ***Analysis of concomitant medication related to confirmed HZ episode has been added*** • ***Covid-19 related analyses have been added*** • ***Minor edits in text for clarification.*** • ***Added site specific Covid-19 pandemic measure periods***	***Amendment 2 Final: 23 NOV 2020***

2. OBJECTIVES/ENDPOINTS

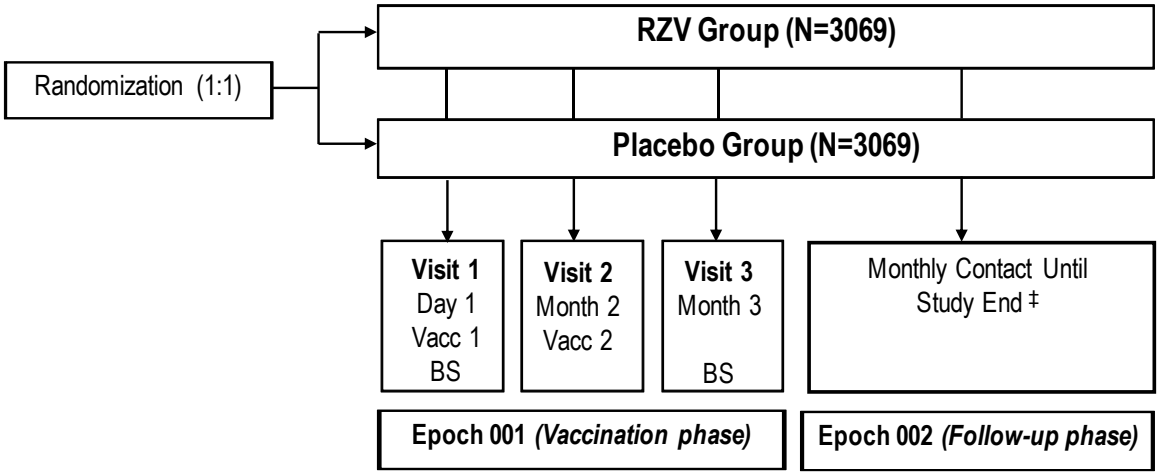
Below are the study objectives and endpoints:-

Objectives	Endpoints
Primary	
To evaluate vaccine efficacy (VE) in the prevention of HZ compared to placebo in Chinese adults ≥ 50 YOA, as measured by the reduction in herpes zoster (HZ) risk. ***Criterion:*** *The objective is met if the lower limit (LL) of the 2-sided 95% confidence interval (CI) of VE is above 25%.*	Confirmed HZ cases in the modified Exposed Set (mES).
Secondary	
To evaluate VE in the prevention of HZ compared to placebo in subjects within each of the following age ranges: 50-69 years of age (YOA) and ³ 70 YOA, as measured by the reduction in HZ risk	Confirmed HZ cases within each of the following age ranges: 50-69 YOA and ³ 70 YOA in the mES.
To evaluate vaccine reactogenicity and safety	Solicited local and general adverse events (AEs) • Occurrence, intensity and resulting in medically attended visit of each solicited local AE within 7 days (Days 1 – 7) after each vaccination • Occurrence, intensity and resulting in medically attended visit and relationship to vaccination of each solicited general AE within 7 days (Days 1 – 7) after each vaccination. Unsolicited AEs • Occurrence, intensity, resulting in a medically-attended visit, and relationship to vaccination of unsolicited AEs (including cellulitis) within 30 days (Days 1 – 30) post-vaccination period, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification. Serious Adverse Events (SAEs) • Occurrence and relationship to vaccination of SAEs from Day 1 up to 30 days post last vaccination.

Objectives	Endpoints
	• Occurrence and relationship to vaccination of SAEs from Day 1 up to 12 months post last vaccination. • Occurrence of SAEs related to study vaccine, from Day 1 up to end of study. • Occurrence of SAEs related to study participation or to GlaxoSmithKline concomitant medication/vaccine, from Day 1 up to end of study. • Occurrence and relationship to vaccination of fatal SAEs from Day 1 up to 30 days post last vaccination. • Occurrence and relationship to vaccination of fatal SAEs from Day 1 up to 12 months post last vaccination. • Occurrence of related-fatal SAEs from Day 1 up to end of study. potential Immune-Mediated Diseases (pIMDs) • Occurrence and relationship to vaccination of pIMDs from Day 1 up to 30 days post last vaccination. • Occurrence and relationship to vaccination of pIMDs from Day 1 up to 12 months post last vaccination. • Occurrence of related serious pIMDs after 12 months post last vaccination up to study end.
Exploratory	
CCI [redacted]	

3. STUDY DESIGN

Figure 1 Study design overview



CCI ; N= number of subjects planned to be enrolled; Vacc= Vaccination
RZV= Recombinant Zoster Vaccine
CCI
‡ All subjects will be followed-up until last enrolled subject has completed 1 year of follow-up post last vaccination. In case criteria for vaccine efficacy analyses are not met during this period, the follow-up will be extended.

- **Experimental design**: Phase IV, randomized, observer-blind, placebo-controlled, multi-centric, single-country study with 2 parallel groups.
- **Duration of the study:** The duration of the study will vary for each subject. The duration of the study will be up to the study conclusion contact that occurs within 30 days of the projected study conclusion date of the last enrolled subject, that is, 14 months (approximately 430 days) from the enrolment date. Therefore, subjects enrolled early in the trial will be followed for longer duration than the subjects who enrol later in the trial. In case criteria for VE analyses are not met during this period, the follow-up will be extended.

  The study conclusion visit/ contact for subjects with an ongoing episode of HZ at the time of last subject last contact will occur at Visit HZ-5 (Day HZ-29).

  – **Epoch 001 (Vaccination phase)**: Starting at Visit 1 (Day 1) until Visit 3 (Month 3) at one month post last vaccination.

  – **Epoch 002 (Follow-up phase):** Starting with the first monthly contact after Visit 3 (Month 3) and ending at the monthly contact that occurs within 30 days of the projected study conclusion date of the last enrolled subject, that is, 14 months (approximately 430 days) from the enrolment date of the last enrolled subject.
- **Primary completion Date (PCD):** The primary completion date will be when the last subject completes his/her study conclusion contact (within 30 days of the projected study conclusion date of the last enrolled subject, that is, 14 months (approximately 430 days) from the enrolment date. In case criteria for VE analyses are not met during this period, the follow-up will be extended.

- **End of Study (EoS):** 1) After all the subjects complete their study conclusion contact, occurring within 30 days of the projected study conclusion date of the last enrolled subject, that is, 14 months (approximately 430 days) from the enrolment date of the last subject; In case criteria for VE analyses are not met during this period, the follow-up will be extended and 2) the release of all polymerase chain reaction (PCR) test results for the HZ rash lesion samples. Refer to section 7.1 for more detail.
- **Control**: placebo controlled
- **Vaccination schedule**: 0 and 2 months
- **Treatment allocation:** Eligible subjects will be randomized (1:1) to RZV group or Placebo group. The randomization algorithm will use a stratification procedure accounting for age (50-69 YOA and≥ 70 YOA).
- **Sampling schedule:**
  - CCI [redacted]
  - Clinical specimens of HZ lesions will be collected from all subjects who are clinically diagnosed with a suspected case of HZ (Section 8.3.2 of the protocol).
  - A urine specimen will be collected from all female subjects of child-bearing potential (see glossary of terms in the protocol definition of woman of child bearing potential) at Visit 1 (Day 1) and Visit 2 (Month 2).
- **Study group and treatment number allocation:** The target will be to enrol approximately 6138 eligible subjects who will be randomly assigned to 2 study groups in a (1:1) ratio (approximately 3069 subjects in each group).

The enrolment will be performed to ensure distribution of the population across the 2 age strata (50-69 YOA and ≥70 YOA). Approximately 75-80% and 20-25% subject should be enrolled in 50-69 YOA and ≥70 YOA, respectively. The expected distribution of subjects within these 2 age strata is as shown in Table 1.

To ensure that the collection of date of birth will not jeopardize the privacy of Personally Identifiable Information (PII), only year of birth (YYYY) will be collected.

Table 1 Number of subjects required for enrolment

Age Stratum	Vaccine	Targeted number (%) of subjects
50-69 YOA	RZV	4604-4910 (75-80%)
	Placebo	
≥ 70 YOA	RZV	1228-1534 (20-25%)
	Placebo	

Allocation of the subject to a study group at the investigator site will be performed using a randomization system on internet (SBIR). Within each age stratum, the randomization algorithm will use a minimization procedure accounting for center, gender, age (50-59, 60-69, 70-79 and ≥80 YOA) and a combined minimization factor to reflect the presence of any of the following conditions: type 2 diabetes mellitus, asthma, chronic obstructive pulmonary disease, chronic kidney disease and depression. Minimization factors will have equal weight in the minimization algorithm.

- **Allocation of subjects to assay subsets -** CCI [redacted]

CCI [redacted]

4. ANALYSIS SETS

4.1. Definition

4.1.1. Enrolled Set

The enrolled set will include all eligible subjects who have signed an informed consent and were randomized or undergone an invasive procedure.

4.1.2. Exposed Set

Exposed Set (ES) will include all subjects who receive at least 1 dose of the study treatment. The allocation in a group is done in function of the administered treatment.

The ES for the analysis of solicited AEs will include all participants who received at least 1 dose of the study treatment and who have documented solicited AEs (i.e. diary card for solicited AEs completed and returned).

The ES for the analysis of any other AEs other than solicited AEs will include all participants who received at least 1 dose of the study treatment.

CCI [redacted]

4.1.3. Modified Exposed Set

The modified Exposed Set (mES) excludes subjects from the ES who were not administered 2 doses of the study treatment per protocol, or who developed a confirmed case of HZ prior to 30 days after the second vaccination (Refer to section 4.2.3 for more detail on the criteria).

4.1.4. Per Protocol Set

All subjects who received at least 1 dose of the study treatment to which they are randomised and have post-vaccination data minus subjects with protocol deviations that lead to exclusion. The Per Protocol Set (PPS) (in vaccinated subjects) will include all evaluable vaccinated subjects:

- CCI [redacted];
- who have received 2 doses of study vaccine;
- for whom the study vaccine has been administered as per protocol;
- who have not received medication/vaccine forbidden in the protocol (refer to Section 4.2.4 for details on the criteria);
- who meet all eligibility criteria (refer to Sections 6.1 and 6.2 of the protocol);
- who comply with the procedures and intervals defined in the protocol;
- who do not meet any of the criteria for elimination during the study (refer to Section 4.2.4 for details on the criteria);
- for whom data concerning immunogenicity endpoint measures are available.

The intervals allowed for the inclusion in the PPS is the 'allowed interval per protocol' as defined in following table:

Table 2 Intervals between study visits *applicable for PPS*

Interval	*Optimal length of interval*	*Allowed interval per protocol*
Visit 1→Visit 2	*60 days (2 months)*	*49 days - 83 days*
Visit 2→Visit 3	*30 days (1 month)*	*28 days - 48 days*

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Detail is provided below for each set.

4.2.1. Elimination from Enrolled Set

Code 800 (fraudulent data), 900 (invalid ICF) and 1010 (treatment number not allocated) will be used for identifying subjects eliminated from Enrolled Set.

4.2.2. Elimination from Exposed Set (ES)

Code 1030 (Study treatment not administered at all), 800 (fraudulent data), ***900 (invalid ICF)*** and 1010 (treatment number not allocated) will be used for identifying subjects eliminated from ES.

4.2.3. Elimination from modified Exposed Set (mES)

Code 1030 (Study treatment not administered at all), 800 (fraudulent data), ***900 (invalid ICF),*** 1010 (treatment number not allocated), 1070 (treatment not administered according to protocol), 2500 (Subject who didn't receive two doses) and 3500 (Subject having confirmed HZ episode prior to 30 days after the dose 2) will be used for identifying subjects eliminated from mES.

Please note that impact of COVID-19 on the modified Exposed Set for vaccine efficacy analysis will be determined on a case-by-case basis.

4.2.3.1. Excluded subjects

A subject will be excluded from the mES analysis under the following conditions. Please note that impact of COVID 19 on the mES will be determined on a case-by-case basis.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
800	Fraudulent data	All
900	Invalid ICF	Visit 1
1010	Treatment number not allocated	Visit 1
1030	Study vaccine not administered at all	Visit 1
1070**	Vaccination not according to protocol: • Subjects got vaccinated with the correct vaccine but containing a lower volume • Administration not according to protocol for reason specified by investigator other than route, side and site. • Site and route of vaccination is wrong or unknown • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number)	Visit 1, Visit 2
2500	Subjects who didn't receive two doses	Visit 2
3500	Subjects having confirmed HZ episode prior to 30 days after the dose 2	Visit 1 to Visit 3

** Attribution of these elimination codes will be evaluated on case-by-case basis and requires CRDL confirmation

4.2.4. Elimination from Per-protocol analysis Set (PPS)

4.2.4.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions. Please note that impact of COVID 19 on the per protocol set will be determined on a case-by-case basis.

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
800	Fraudulent data	All
900	Invalid ICF	Visit 1
1010	Treatment number not allocated	Visit 1
1030	Study vaccine not administered at all	Visit 1
1040*	Administration of concomitant vaccine(s) forbidden in the protocol *Any concomitant vaccination not foreseen by the study protocol administered in the period starting 30 days before the first dose of the study vaccine and ending at Visit 3 (Day -30 to Month 3)*	***- 30 days to Visit 1 through Visit 3***
1050	Randomisation failure	All
1060	Randomisation code was broken	Visit 1 to Visit 3
1070**	Vaccination not according to protocol: • Subjects got vaccinated with the correct vaccine but containing a lower volume • Administration not according to protocol for reason specified by investigator other than route, side and site. • Site and route of vaccination is wrong or unknown • Wrong replacement or study vaccine administered (not compatible with the vaccine regimen associated to the treatment number)	Visit 1, Visit 2
1080	Vaccine temperature deviation	Visit 1, Visit 2
1090	Expired vaccine administered	Visit 1, Visit 2
2010	Protocol violation (inclusion/exclusion criteria)	Visit 1
2040*	Administration of any medication forbidden by the protocol (refer to Section 7.5.2 of the protocol) administered in the period from the first dose of study vaccine and ending at Visit 3 (Day 1 to Month 3)	Visit 1 to Visit 3

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable
2050*	Underlying medical condition forbidden by the protocol Any intercurrent medical condition (IMC) (refer to section 7.6 of the protocol) which can affect the immune response to the study vaccine and ending at Visit 3 (Day 1 to Month 3)	Visit 1 to Visit 3
2060*	Concomitant infection related to the vaccine which may influence immune response	Visit 1 to Visit 3
2070*	Concomitant infection not related to the vaccine which may influence immune response	Visit 1 to Visit 3
2080	Subjects did not comply with vaccination schedule *DOSE 1 – DOSE 2 = 49-83 days*	Visit 2
2090	Subjects did not comply with blood sample schedule *DOSE2 - blood sample (BS)2 = 28-48 days*	Visit 3
2100	Serological results not available post-vaccination CCI [redacted]	Visit 3
2120	Obvious incoherence or abnormality or error in data CCI [redacted]	Visit 3
2500	Subjects who didn't receive two doses	Visit 2
3500	Subjects having confirmed HZ episode prior to 30 days after the dose 2	Visit 1 to Visit 3
2130	CCI [redacted]	[redacted]

*Attribution of these elimination codes to subject need CRDL review of individual listing
** Attribution of these elimination codes will be evaluated on case-by-case basis and requires CRDL confirmation
#CCI [redacted]

4.2.5. Elimination from unsolicited and solicited safety set

Unsolicited and solicited safety set is not applicable for the study.

5. STATISTICAL ANALYSES

The standard data derivation rules and stat methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9 of the SAP.

Analysis on Covid-19 cases has been added in the analysis of safety section of the SAP.

5.1. General Considerations

Note: Subject-level data will be available interactively via RAPIDO DV after AAC.

5.2. Subjects Disposition

Number of enrolled and vaccinated (at least 1 vaccination) subjects, included in each group or in total for a given age category or for all age categories will be described.

5.3. Demography

5.3.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic and other baseline characteristics will be described by assigned group and for the total for ES and mES and the [redacted].

Demographic characteristics (age at first study vaccination in years, gender, race and ethnicity) will be summarized overall and by study groups using descriptive statistics:

- Frequency tables will be generated for categorical variables such as center.
- Mean, standard deviation, median, minimum and maximum will be provided for continuous data such as age.

Cohort description and withdrawal status will be summarized by group and overall. All important protocol deviations leading to elimination will be presented.

All the above analyses will be performed by age strata (50-69 YOA and ≥ 70 YOA) on ES and mES.

5.3.2. Additional considerations

Following additional tables will also be generated:

- Number of subjects by centers will be presented on ES.
- ***Deviation from protocol-defined age and visit interval on ES.***
- The following table will be generated for web disclosure:
  - Percentage of enrolled subjects by age categories (18-64, 65-84, ≥85) YOA will be tabulated by group.
- Summary of important protocol deviations leading to elimination from any analysis will be presented for the Enrolled Set overall and by age strata.
- The number of subjects enrolled into the study as well as the number of subjects excluded from ***mES and*** PPS analyses will be presented through 3 consort tables, overall and by age strata only for Consort table 1 and 2:
  - Consort table 1 - Showing the subjects disposition from Enrolled Set to ES
  - Consort table 2 – Showing the subjects disposition from ES to mES
  - Consort table 3 - Showing the subjects disposition from ES to PPS

5.4. Exposure

5.4.1. Analysis of exposure planned in the protocol

None

5.4.2. Additional considerations

The number of doses administered will be tabulated. The number of doses administered will be tabulated by age stratum.

5.5. Efficacy/Effectiveness

The primary analysis of efficacy will be based on the mES. A secondary analysis based on the ES will performed to complement the mES analysis.

5.5.1. Analysis of efficacy planned in the protocol

5.5.1.1. Primary Objective

The primary inferential analysis of efficacy on the mES will be based on the occurrence of the primary endpoint anytime from 30 days after the administration of the second dose of the study vaccine up to study end. All subjects from the mES will contribute to the comparison.

It will consider the exact inference on the relative risk (RR) adjusted for age strata conditionally to the total number of HZ cases observed and time at risk. This method computes an exact CI around the rate ratio (ratio of the event rates in the RZV group versus control group) and takes into account, the sum of the time at risk of the subjects within each group.

Incidence rate and VE with 95% CI will be calculated using Poisson method. The VE will be defined as 1 minus the RR. RR is defined as the ratio of the incidence rates of the RZV group over the placebo group [VE= (1 – RR) x 100]

The VE of RZV against HZ will be demonstrated if the LL of the two-sided 95% CI of VE is above 25%. All p-values reported will be related to the null hypothesis test VE = 0.

The calculation of the time at risk and other statistical method detail are provided in Section 9.2.1.

5.5.1.2. Secondary Objective

The number of confirmed HZ cases, follow-up days, associated rate, VE with 95% CI will be presented by each age category, descriptively, as for the primary endpoint.

5.5.2. Additional considerations

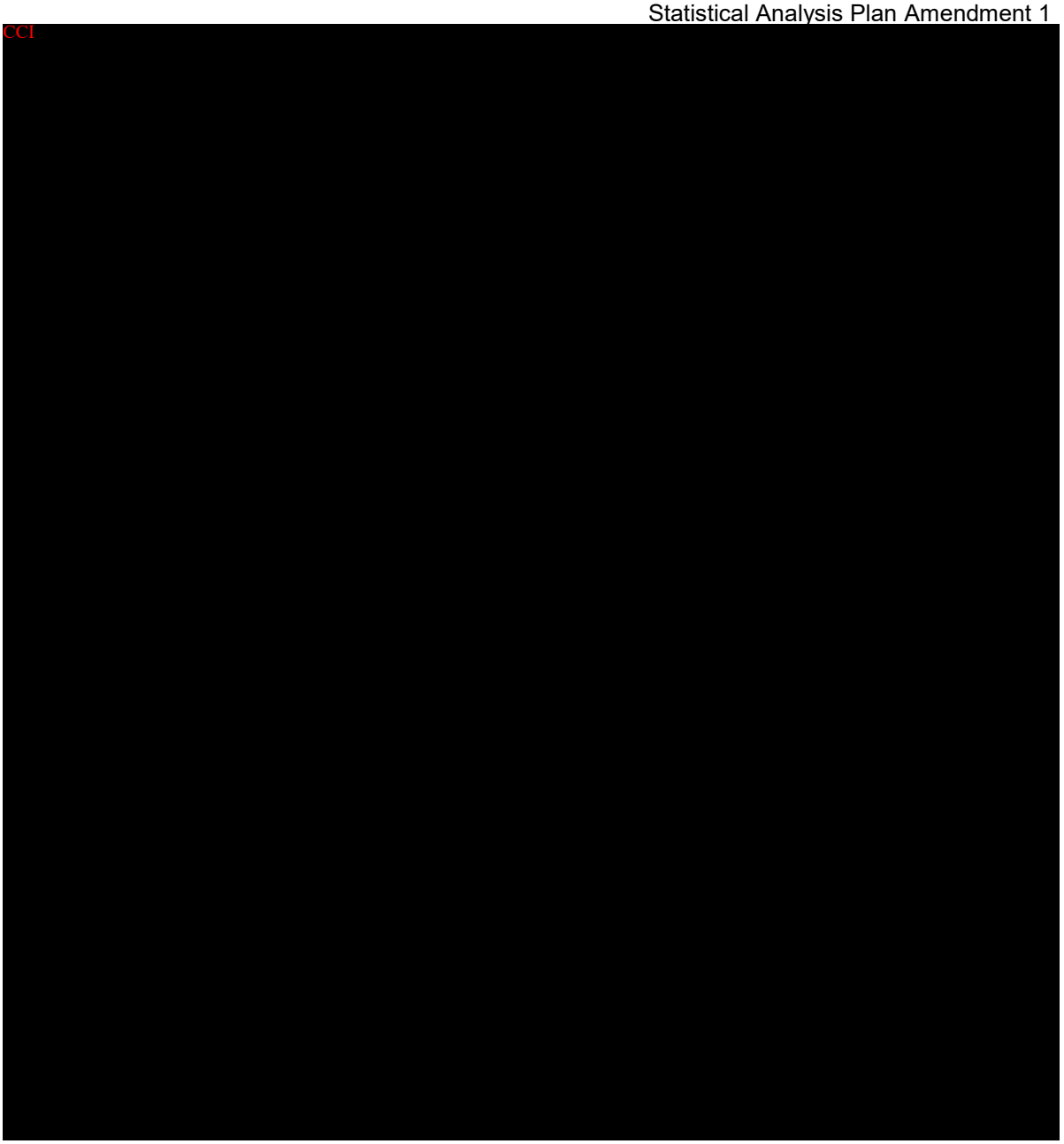
Following descriptive table and figure will be generated by study groups on mES and ES:

- For each study group, the number of subjects at risk, person-year, number and incidence of confirmed HZ will be tabulated overall.
- Forest plot for vaccine efficacy against HZ by age strata and overall during the entire study period
- ***Cumulative incidence curve for HZ for each study group.***
- Number and percentage of episodes of all confirmed HZ episodes during the entire study period.
- Number and percentage of confirmed HZ episodes out of all the suspected cases reported.
- Number and percentage of suspected cases for which at least one PCR sample was collected on ES only.
- Distribution of suspected HZ cases using the HZ classification tools (PCR testing & HZ Ascertainment Committee (HZAC))
- The vaccine efficacy will be assessed by Poisson method for primary objective and fitted via the PROC GENMOD procedure according to the following code

```
PROC GENMOD DATA=pois_ve EXACTONLY;
BY AGECAT;
STRATA AGECAT;
CLASS AGECAT/PARAM=ref;
MODEL nb_cases = group_nb/DIST=poisson OFFSET = Log_T LINK=log;
EXACT group_nb /ESTIMATE OUTDIST=dist ALPHA=0.05;
ODS OUTPUT ExactParmEst=estimate ExactTests=ExactTest;
RUN;
```

Where,
nb_case = number of cases
agecat = Age strata categories (50-69 and >=70 YOA)
group_nb = Group information of the subject (treatment received by subject)
Log_T = Log of the follow-up time

```
DATA VE ;
SET ESTIMATE;
FORMAT VE best12. ll best12. ul best12.;
VE = ( 1 - exp (estimate)) * 100;
ll = ( 1 - exp (UPPERCL)) * 100;
ul = ( 1 - exp (LOWERCL)) * 100;
RUN;
```

CCI


5.6.2. Additional considerations

None

5.7. Analysis of safety and reactogenicity

5.7.1. Analysis of safety and reactogenicity planned in the protocol

The primary analysis of safety will be performed on the ES. All analyses will also be performed by age strata (50-69 YOA and ≥70 YOA). Following analysis is planned to be performed:

The percentage of subjects with at least 1 local AE (solicited and unsolicited), with at least 1 general AE (solicited and unsolicited) and with any AE (solicited and unsolicited) during the solicited follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall. The percentage of doses followed by at least 1 local AE (solicited and unsolicited), by at least 1 general AE (solicited and unsolicited) and by any AE will be tabulated, with exact 95% CI. The percentage of subjects with at least 1 local AE (solicited only), with at least one general AE (solicited only) and with any AE (solicited only) during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall.

The percentage of subjects reporting each solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE will be tabulated, with exact 95% CI. Fever will be reported ***with any (>=38.0), >=38.0 - <=38.5, >38.5 - <=39.0 and >39.0 in GSK scale. In Chinese scale, it will be reported with any (>=37.3), 37.3 - <38.0, 38.0 - <38.5, 38.5 - <39.5 and >=39.5****. T*he same tabulation will be performed for fever with causal relationship to the study vaccine.

In the table presented based on the GSK scale, for all other solicited AEs, the same table will have grade 1, grade 2 and ***at least*** grade 3 AEs and for any and ***at least*** grade 3 general AEs with relationship to the study vaccine. ***Related grade 1 and related grade 2 will also be displayed.***

In the table presented based on the Chinese scale, for all other solicited AEs, the same table will have grade 1, grade 2, grade 3 and grade 4 applicable for table with Chinese intensity scale) AEs and for any, grade 3 and grade 4 general AEs with relationship to the study vaccine. Related grade 1 and related grade 2 will also be displayed.

The proportion of solicited AEs resulting in a medically attended visit will be tabulated.

The percentage of subjects with at least 1 report of unsolicited AE (including cellulitis) classified by MedDRA primary system organ class (SOC) and preferred terms (PT) will be reported within 30 days (Days 1-30) post each vaccination with exact 95% CI. The same tabulation will be performed for grade 3 unsolicited AEs, for unsolicited AEs with a relationship to vaccination, grade 3 unsolicited AEs with a relationship to vaccination.

Number and percentage of any, grade 3, related, grade 3 related and medically attended unsolicited AEs reported within 30 days (Days 1-30) post ***any*** vaccination according to MedDRA primary system organ class and preferred terms will be presented.

Number and percentage of SAEs from first vaccination up to 12 months post last vaccination will be presented with 95% CI. The same tabulation will also be done for the interval- starting from first vaccination up to 30 days post last vaccination.

Number and percentage of SAEs causally related to vaccination for the interval- starting from first vaccination up to 30 days post last vaccination and from first vaccination up to 12 months post last vaccination and from study start up to study end will be presented with 95% CI.

Number and percentage of subjects experiencing fatal SAEs, classified by MedDRA Primary System Organ Class and Preferred Term will be tabulated using date of onset of SAE for the time periods –from first vaccination up to 30 days post last vaccination and first vaccination up to 12 months post last will be presented with 95% CI.

Number and percentage of fatal SAEs causally related to vaccination for the interval-starting from first vaccination up to 30 days post last vaccination and from first vaccination up to 12 months post last vaccination and from study start up to study end will be presented with 95% CI.

Number and percentage of pIMDs from first vaccination up to 12 months post last vaccination will be presented with 95% CI. The same tabulation will also be done for the interval – starting from first vaccination up to 30 days post last vaccination.

Number and percentage of pIMDs causally related to vaccination from first vaccination up to 12 months post last vaccination will be presented with 95% CI. The same tabulation will also be done for the interval – starting from first vaccination up to 30 days post last vaccination. Number and percentage of serious pIMDs causally related to vaccination from 12 months post last vaccination up to study end and will be presented with 95% CI.

The proportion of subjects with concomitant medication will be tabulated, within 30 days post each vaccination and overall only, with exact 95% CI.

Listing of fatal SAEs, SAEs, pIMDs and withdrawals (from the study or from vaccination) due to AEs, SAEs, solicited and unsolicited AEs will be generated.

Listing of pregnancy during the entire study period will be generated.

Listing for all the suspected HZ episodes will be generated.

5.7.2. Additional considerations

The table on solicited local and general AEs will be presented separately according to GSK grading and grading scale provided by Chinese authorities.

Duration of each solicited local and general AE during the solicited follow-up period will be presented. Total duration of each individual solicited local and general AE will be tabulated.

Duration of each grade 3 solicited local and general AE during the solicited follow-up period will be presented in the table by GSK grading. Duration of each grade 3 and above solicited local and general AE during the solicited follow-up period will be presented in the table by Chinese authority grading.

Listing of complication related to confirmed HZ episode will be presented.

Number and percentage of subjects experiencing fatal SAEs, classified by MedDRA Primary System Organ Class and Preferred Term will be tabulated using date of onset of SAE from study start up to study end will be presented with 95% CI for web disclosure.

The table for web disclosure related to ***solicited adverse events*** endpoint will be based on both GSK and Chinese intensity scale.

Summary of subjects with serious adverse events related to study participation and not by the study vaccines or to GlaxoSmithKline concomitant medication/vaccine during the entire study period based on ES.

Following listings of concomitant medications related to confirmed HZ episode will be presented based on Exposed Set:

- ***Pain rescue medication to control HZ pain***
- ***Antiviral treatment for HZ***
- ***Other therapy for HZ***

Additional analyses/considerations due to COVID-19 pandemic on ES:

- ***Summary of COVID-19 Assessment.***
- ***Incidence of COVID-19 as an AE and SAE. A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 cases reported as AEs.***
- ***A column to identify COVID-19 AEs/SAEs will be added to listing of (S)AEs and solicited adverse events leading to study or treatment discontinuation from first vaccination up to study end.***

6. ANALYSIS INTERPRETATION

The primary objective of VE in the prevention of HZ compared to placebo in Chinese adults≥ 50 YOA, as measured by the reduction in HZ risk is considered met if the LL of the 2-sided 95% CI of VE is above 25%.

For all secondary objectives, analyses will be descriptive with the aim to characterize the differences in reactogenicity, safety and immunogenicity between groups.

7. INTERIM ANALYSES

7.1. Sequence of analyses

The analysis of all primary and secondary endpoints will be performed when all data up to study conclusion are available. A clinical study report (CSR) will be written at this stage and individual listings will be included.

One final analysis is planned and will be triggered when the following will take place:

- When at least 27 confirmed cases of HZ have accrued in the primary cohort for efficacy (cut-off date for primary efficacy analysis); AND
- When all subjects have completed at least 12 months safety follow-up post last vaccination.

Data contributing to the analysis of the primary efficacy objective (confirmed HZ cases) will be collected until the cut-off date. After the cut-off date, case confirmation of any new suspected HZ will not be performed. Once the study reaches the cut-off date, the conclusion contact for a subject will be planned based on the status of the safety follow-up:

- **Cut-off date reached before the completion of safety follow-up** – Continue the monthly safety follow-up after the cut-off date until all subjects have completed 12 months of follow-up post last dose.
- **Cut-off date reached after the completion of safety follow-up** – Continue the monthly contacts after the completion of the 12 months safety follow-up period until at least 27 confirmed HZ cases have accrued (cut-off date).

When the trigger for primary efficacy analysis is reached, subjects with an ongoing HZ episode will be followed until Day HZ-29.

The conclusion contact of the last subject will be the study end.

If the data for exploratory endpoints become available at a later stage, (an) additional analysis/ analyses will be performed. These analyses will be documented in the annex study report.

Description	Disclosure Purpose (CTRS=public posting, SR=Study report, internal)
Final	Public disclosure, Study report

7.2. Statistical considerations for interim analyses

No interim analysis will be performed.

8. CHANGES TO THE PROTOCOL DEFINED STATISTICAL ANALYSIS

Following is the change from protocol defined statistical analysis:-

- Fatal SAEs will not be tabulated using the date of death within the same time periods.
- CCI [redacted]
- ***Grade 3 for redness/swelling will be defined as redness/swelling with diameter >=100 mm in Chinese scale***
- ***Preferred Terms to identify Grade 4 for swelling and redness have been added***
- ***The analysis on at least 1 local AE (solicited and unsolicited; solicited only) with at least 1 general AE (solicited and unsolicited; solicited only) and with any AE (solicited and unsolicited; solicited only) during the solicited follow-up period with causal relationship with vaccine and AE rated as at least grade 3 according to GSK and Chinese scale will not be performed.***

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

The following sections describe additional derivation rules and statistical methods which are not presented in section 10.1.

9.1. Data derivation

9.1.1. Demography

For computation of age, following rule need to be considered:

- 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 Personal Identifiable Information (PII), only a partial date of birth (YYYY) will be collected. As the date and month will be missing, the date will be replaced by the June 30th of the year.

9.2. Statistical Method

9.2.1. HZ incidence

- For the primary analysis of HZ incidence, first confirmed HZ episode will be considered.
- The HZ onset date is the earlier of the following two events: 1) the HZ rash start date; or 2) the date on which pain/itching or abnormal sensation at the site of a subsequent HZ rash is first noted.
- A suspected case of HZ can be confirmed by GSK in two ways:
  - **By PCR**: Rash lesion samples will be collected from subjects clinically diagnosed as having a suspected case of HZ. The samples will be transferred to GSK or a validated laboratory designated by GSK Biologicals and analyzed using standardized and validated procedures for laboratory diagnosis of HZ by PCR (see Section 12.2 of the protocol).
  - **By the HZ Ascertainment Committee (HZAC):** All suspected HZ cases will be referred to the HZAC. The HZAC will classify all referred cases as either "HZ" or "not HZ" or "not able to decide" (see Section 12.2 of the protocol). The HZAC classification will serve as the final case definition only when the case cannot be confirmed or excluded by PCR. Therefore, definitive PCR results, when available, will determine the final HZ case assignment. In such cases, the HZAC classification will not contribute to HZ case determination decision
- For a given subject and for HZ episode, missing or non-evaluable measurements will not to be imputed for the primary analysis. The missing endpoint and censoring are considered to occur independently, and the pattern being either Missing Completely At Random (MCAR) or Missing At Random (MAR) only.
- For HZ analysis, due to the algorithm used and taking into account both laboratory and HZAC results, no imputation and no sensitivity analysis for missing data will be performed.
- The "follow-up time at risk" for confirmed HZ is expressed in days and is computed according to the following rules:
  - The start date of the follow-up time (start) will be computed as follows:
    - From the dose 1 administration date for the analysis on the ES;
    - From 30 days post-dose 2 date for the analysis on the mES.
  - The end date of the follow-up time (stop) will be computed as follows:
    - Date of the last visit/contact for subjects who did not have an event;
    - Last contact date for subjects dropped out of the study, if not preceded by an event;

  - Date of the event
  - Date of HZ and/or VZV vaccination outside the study, if not preceded by an event

- The follow-up time at risk is computed using the following formula:
  - **stop – start +1**.

The **time at risk** will be expressed in Person-Year and derived from the follow up time (follow up time in days/365.25).

CCI

[redacted]

9.2.3. Safety

- For the analysis of HZ related complications/unsolicited AEs/SAEs/pIMDs/ concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.
- AEs that need to be reported as pIMDs are listed in Table 23 of the protocol. ***The table presenting pIMDs, will also include the AEs considered as pIMDs as per MedDRA dictionary.***
- Assessment of intensity for solicited local and general AEs will be done separately as per GSK scale and Chinese scale. From an analysis perspective, the intensity of nausea, vomiting and diarrhoea will be presented separately as per the guidelines of Chinese authorities. In addition, as per GSK standard grading, the solicited general AEs of nausea, vomiting, diarrhoea and/or abdominal pain will be presented collectively as "gastrointestinal symptoms".

  For analysis as per GSK standard grading, the maximum intensity of any one of these solicited general AEs (i.e. nausea, vomiting and diarrhoea ***and abdominal pain***) reported by a subject will be attributed as maximum intensity of "gastrointestinal symptoms" for that subject. Maximum of grade 3 and 4 will be considered as grade 3 ***for all applicable solicited symptoms (not only gastrointestinal symptoms) in GSK standard grading table.***

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

Table 3 Intensity scales for solicited symptoms in adults

Adults		
Adverse Event	**Intensity grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Do not influence or do slightly influence limb activities.
	2	Moderate Influence limb activities.
	3	Severe: Influence daily life.
	4	Lose the basic selfcare ability, or hospitalization
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C (with 1 decimal)
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
	4	Refractory; require emergency presentation or hospitalization
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
	4	Emergency presentation or hospitalization
Gastrointestinal symptom (Diarrhea)	0	Normal
	1	Slight or transient, 3-4 times/day, stool with abnormal properties, or slight diarrhea persisting for not more than 1 week

Adults		
Adverse Event	**Intensity grade**	**Parameter**
	2	Moderate or persistent, 5-7 times/days, stool with abnormal properties, or diarrhea >1 week
	3	>7 times/day, stool with abnormal properties, or bloody diarrhea, orthostatic hypotension, electrolyte imbalance, and requiring intravenous fluid >2 L
	4	Hypotensive shock, requiring hospitalization for treatment
Gastrointestinal symptom (Nausea)	0	Normal
	1	Transient (<24 h) or intermittent, while food intake basically normal
	2	Persistent nausea, leading to decreased food intake (24-48 h)
	3	Persistent nausea, leading to little food intake (>48 h) or require intravenous fluid infusion
	4	Life-threatening (such as hypotensive shock)
Gastrointestinal symptom (Vomiting)	0	Normal
	1	1-2 times/24 h and do not influence activities
	2	3-5 times/24 h or activities restricted
	3	>6 times within 24 h or require intravenous fluid infusion
	4	Due to hypotension, require hospitalization or nutrition by other routes
Gastrointestinal symptom (Abdominal pain)	0	Normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Myalgia	0	None
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity

* For this study, fever is defined as temperature ≥ 37.3°C as per guidelines from the Chinese authorities for axillary measurement. The preferred location for measuring temperature in this study will be the axilla.

The maximum intensity of local injection site redness/swelling will be scored at GSK using GSK's standard grading scale (based on the US Food and Drug Administration (FDA) guidelines [FDA, 2007]) and the guidelines of grading standards for AEs set by the Chinese authorities as follows.

Grade	GSK standard grading scale	Grading scale defined by Chinese authorities
0	< 20 mm diameter	Absent
1	≥ 20 mm to ≤50 mm diameter	25 mm to <50 mm
2	> 50 mm to ≤100 mm diameter	50 mm to <100 mm
3	> 100 mm diameter	>=100 mm
4	Not defined	Abscess, exfoliative dermatitis, and dermis or deep tissue necrosis*

The solicited symptom diary card doesn't allow to choose grade 4 swelling or redness. Per team agreement, the grade 4 of swelling and redness will be identified when the below Preferred Terms (from MedDRA version 25.0) are reported as unsolicited adverse events within or ongoing 7 days post each dose:

- ***Dermatitis exfoliative***
- ***Necrosis***

- ***Skin necrosis***
- ***Soft tissue necrosis***
- ***Abscess***
- ***Abscess sterile***
- ***Abscess limb***
- ***Abscess soft tissue***

Fever will be graded as:

Grade	GSK standard grading scale	Grading scale defined by Chinese authorities (for axillary measurement)
0	<38.0°C	<37.3°C
1	≥38.0°C –≤38.5°C	37.3°C – <38°C
2	>38.5°C –≤39.0°C	38.0°C -<38.5°C
3	>39.0°C	38.5°C - <39.5°C
4	Not defined	≥ 39.5°C

The preferred location for measuring temperature in this study will be the axilla. If temperature is measured by other routes (such as oral or rectal), fever grading as per GSK scale will remain the same irrespective of route of measurement. For the grading scale as per Chinese authorities, the following conversion will be used:

- Axillary temperature = Oral temperature minus 0.2°C;
- Axillary temperature = Rectal temperature minus 0.5°C.
- ***Axillary temperature = Tympanic membrane temperature***

- ***For the duration of solicited adverse event within the solicited symptom follow-up or total duration, the unknown or missing end date will not be imputed.***
- The definition of HZ related complication is described in section 12.5.2 of the protocol and is presented below:-

Post-herpetic neuralgia	PHN is defined by the presence of HZ-associated severe pain persisting or appearing more than 90 days after onset of the HZ rash.
Disseminated disease	Defined as ≥ 6 HZ lesions clearly outside the primary dermatome as per the investigator's judgment.
Ophthalmic disease	Defined as HZ affecting any eye structure as per the investigator's judgment.

Neurologic disease	Defined as cranial or peripheral nerve palsies, myelitis, meningoencephalitis, stroke, etc. that is temporally associated with an episode of HZ and, in the opinion of the investigator, is caused directly by VZV infection arising from the HZ episode.
Visceral disease	Defined as an abnormality of one or more internal organs (e.g., hepatitis, pneumonitis, gastroenteritis, etc.) that is temporally associated with an episode of HZ and, in the opinion of the investigator, is caused directly by VZV infection arising from the HZ episode
HZ vasculitis	Vasculopathy or vasculitis (based on clinical, laboratory or radiologic findings) that is temporally associated with an episode of HZ and, in the opinion of the investigator, is caused directly by the VZV infection arising from the HZ episode.
Stroke	A diagnosis of stroke requires that criteria 1, 2 and 3 are fulfilled or criteria 1 and 4 and in the opinion of the investigator is temporally associated with an episode of HZ Criterion 1: Rapid onset of localizing neurological deficit and/or change in level of consciousness; Criterion 2: Localizing neurological deficit or change in level of consciousness that lasts greater than 24 hours; Criterion 3: No other cerebral process, peripheral lesion, or other disorder is the cause of the localizing neurological deficit or change in level of consciousness; Criterion 4: Computerized Tomography (CT) scan or Magnetic Resonance Imaging (MRI) scan evidence of an acute thrombotic or hemorrhagic lesion

- ***A specific COVID-19 eCRF page is used to collect any event related to COVID-19 pandemic. Input from local regulatory, local medical affairs and sites was provided to define pandemic measures periods at each site. Start date of pandemic measure period will be considered first day of month and end date of pandemic measure period will be considered as last day of month.***

Location	*Center*	*First subject first visit date at Center*	*Start date of pandemic measure period*	*End date of pandemic measure period*	*Reason/s for pandemic measure period*
			Mar21	*May21*	***Strong recommendation of mass vaccination of Covid-19 vaccines to wide population.*** ***Isolated cases in country lack of resources that delay the Study start***
			Mar22	*Jun22*	***Covid-19 outbreak in Shanghai*** ***High business, public life and health impact*** ***Widespread disease in region and community*** ***Citywide static management*** ***lack of resources that lead to miss of month phone contact***
			Oct22	*Nov22*	***Province/Partial control to prevent Covid-19*** ***Isolated cases in country*** ***Lack of resources that impact data entry***
	248981	*14-May-21*	*Nov22*	*Jan23*	***High business public life and health impact*** ***Widespread disease in country*** ***Sustained community spread in geographic area local to GSK community*** ***Public health service capacity exceeded*** ***lack of resources that impact data entry***
Shanghai	*248302*	*21-Jul-21*	*Mar21*	*May21*	***Strong recommendation of mass vaccination of Covid-19 vaccines to wide population.*** ***Isolated cases in country lack of resources that delay the Study start***

Location	*Center*	*First subject first visit date at Center*	*Start date of pandemic measure period*	*End date of pandemic measure period*	*Reason/s for pandemic measure period*
			Mar22	*Jun22*	*Covid-19 outbreak in Shanghai* *High business, public life and health impact* *Widespread disease in region and community* *Citywide static management* *Lack of resources that impact data entry*
			Oct22	*Nov22*	*Province/Partial control to prevent Covid-19* *Isolated cases in country* *Lack of resources that impact data entry*
			Nov22	*Jan23*	*High business public life and health impact* *Widespread disease in country* *Sustained community spread in geographic area local to GSK community* *Public health service capacity exceeded* *lack of resources that impact data entry*
			Mar21	*May21*	*Strong recommendation of mass vaccination of Covid-19 vaccines to wide population.* *Isolated cases in country* *lack of resources that delay the Study start*
	248303	*15-Jul-21*	*Mar22*	*Jun22*	*Covid-19 outbreak in Shanghai* *High business, public life and health impact* *Widespread disease in region and community* *Citywide static management* *Lack of resources that impact data entry*

Location	*Center*	*First subject first visit date at Center*	*Start date of pandemic measure period*	*End date of pandemic measure period*	*Reason/s for pandemic measure period*
			Oct22	*Nov22*	*Province/Partial control to prevent Covid-19* *Isolated cases in country* *Lack of resources that impact data entry*
			Nov22	*Jan23*	*High business public life and health impact* *Widespread disease in country* *Sustained community spread in geographic area local to GSK community* *Public health service capacity exceeded* *lack of resources that impact data entry*
			Mar21	*May21*	*Strong recommendation of mass vaccination of Covid-19 vaccines to wide population.* *Isolated cases in country* *lack of resources that delay the Study start*
			Mar22	*Jun22*	*Covid-19 outbreak in Shanghai* *High business, public life and health impact* *Widespread disease in region and community* *Citywide static management* *Lack of resources that impact data entry*
	247421	*06-Jun-21*	*Oct22*	*Nov22*	*Province/Partial control to prevent Covid-19* *Isolated cases in country* *Lack of resources that impact data entry*

Location	*Center*	*First subject first visit date at Center*	*Start date of pandemic measure period*	*End date of pandemic measure period*	*Reason/s for pandemic measure period*
			Nov22	*Jan23*	***High business public life and health impact Widespread disease in country Sustained community spread in geographic area local to GSK community Public health service capacity exceeded lack of resources that impact data entry***
			Mar21	*Jul21*	***Strong recommendation of mass vaccination of Covid-19 vaccines to wide population. Isolated cases in country lack of resources that delay the Study start***
			Jul21	*Aug21*	***Covid19 outbreak in Nanjing city and Jiangsu province Province/Partial control to prevent Covid-19 Lack of resources that delay the study start***
			Mar22	*Jun22*	***Covid-19 outbreak in Shanghai Province/Partial control to prevent Covid-19 Lack of resources that delay the data entry***
			Oct22	*Nov22*	***Province/Partial control to prevent Covid-19 Isolated cases in country Lack of resources that delay the data entry***
Lianshui	*247564*	*11-Sep-21*	*Nov22*	*Jan23*	***High business public life and health impact Widespread disease in country Sustained community spread in geographic area***

Location	*Center*	*First subject first visit date at Center*	*Start date of pandemic measure period*	*End date of pandemic measure period*	*Reason/s for pandemic measure period*
					local to GSK community Public health service capacity exceeded lack of resources that impact data entry
			Mar21	***Jul21***	***Strong recommendation of mass vaccination of Covid-19 vaccines to wide population. Isolated cases in country lack of resources that delay the Study start***
			Jul21	***Aug21***	***Covid19 outbreak in Nanjing city and Jiangsu province Province/Partial control to prevent Covid-19 Lack of resources that delay the study start***
			Mar22	***Jun22***	***Covid-19 outbreak in Shanghai Province/Partial control to prevent Covid-19 Lack of resources that impact the data entry***
			Jul22	***Aug22***	***Covid-19 epidemic in Ganyu citywide static management Partial control and travel restrictions to prevent and control Covid-19 lack of resources that impact the data entry***
Ganyu	***248595***	***15-Sep-21***	***Oct22***	***Nov22***	***Province/Partial control to prevent Covid-19 Isolated cases in country Lack of resources that impact the data entry***

Location	*Center*	*First subject first visit date at Center*	*Start date of pandemic measure period*	*End date of pandemic measure period*	*Reason/s for pandemic measure period*
			Nov22	*Jan23*	***High business public life and health impact*** ***Widespread disease in country*** ***Sustained community spread in geographic area local to GSK community*** ***Public health service capacity exceeded*** ***lack of resources that impact data entry***

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains standard rules for data display and derivation for clinical and epidemiological studies. These rules will be applied along with those detailed in section 9 (additional study-specific rules).

10.1.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the CRF using the contents of the flag indicating if the event occurred before or after study dose. If 'after study dose' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before study dose' is selected, the relative dose for the event will be the dose prior to this one.

10.1.2. Handling of missing data

10.1.2.1. Dates

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

- Adverse event start dates with missing day: If the event starts in the same month as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after study dose) will be used to complete the date. If 'after study dose' is selected, the imputed start date will match the first (or only) study dose given during that month. If 'before study dose' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- Adverse event start dates with missing day and month: If the event starts in the same year as at least one of the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first (or only) study dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that year.
- All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited adverse events

10.1.2.3.1. Studies with electronic diaries

Not applicable for the study

10.1.2.3.2. Studies with paper diaries

For studies using paper diaries which have questions in the CRF indicating the presence or absence of solicited events, the following rules are applicable.

- ***Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of participants who respond "Yes" or "No" to at least one occurrence of the specific administration site (or systemic) solicited event. If there are at least 1 non-missing value of temperature from day 1 to day 7 post vaccination, that occurrence will be counted as well in the denominator of systemic solicited events.***
- When a specific solicited event is marked as having not occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.

- ***For fever, if there are missing values and/or non-missing values of temperature from day 1 to day 7 post vaccination which are not qualifying fever definition per protocol for GSK intensity and Chinese intensity tables, then that subject would not be considered for 'Any' rows of the solicited event summary tables.***
- When a specific solicited event is marked as having occurred following a specific study dose (i.e. SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.
- The following table shows how participants contribute to each category for a specific solicited adverse event over the Day X to Day Y post-dose period:

Solicited adverse event category	**Participants included in the calculation of the numerator**
Any	All participants with at least one occurrence of the adverse event at grade 1, 2, or 3 for table by GSK intensity scale and at grade 1, 2, 3 or 4 for table by Chinese intensity scale between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
Grade 1	***All participants with at least one occurrence of the adverse event at grade 1 between Day X and Day Y***
Grade 2	***All participants with at least one occurrence of the adverse event at grade 2 between Day X and Day Y***
At least grade 3	All participants with at least ***grade 3 or grade 4***
Grade 4*	All participants with at least one occurrence of the adverse event at grade 4 between Day X and Day Y

*this is specific to the study as grade 4 has also been defined for some solicited adverse event collected in the study as per Chinese regulation.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

Missing severity will follow the next imputation rules:

- ***If serious adverse event = 'Y' then severity = 'Severe'***
- ***If serious adverse event = 'N' and action taken with study vaccine(s) as a result of the event = 'Dose not changed' and subject did not withdraw from the study due to this event, then severity = 'Mild'***
- ***If previous two rules were not applicable, then severity = 'Moderate'***

10.1.3. Data derivation

10.1.3.1. Age at first dose in years

When age at first dose is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of first dose. For example:

DOB = 10SEP1983, Date of first dose = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of first dose = 10SEP2018 -> Age = 35 years

10.1.3.2. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

10.1.3.3. Onset day

The onset day for an event (e.g. AE, medication, vaccination) is the number of days between the last study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after first dose).

10.1.3.4. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e. an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

The duration of solicited events will be calculated as the sum of the individual days with the adverse event reported at grade 1 or higher during the solicited event period.

If symptom is ongoing and the end date of event is partially or fully missing, end date will not be imputed for the calculation of duration.

10.1.3.5. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited adverse events, all serious adverse events will be considered systemic events since the administration site flag is not included in the expedited adverse event CRF pages. Unsolicited adverse events with missing administration site flag will also be considered systemic.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.6. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed.

10.1.4.2. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics will be presented with one decimal.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.2. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL for final analysis with their associated lay-out is developed as a separate document.

11. REFERENCES

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