# Statistical Analysis Plan

**Study ID:** 214461

**Official Title of Study:** A Phase 3, Randomised, Observer-blind, Placebo-controlled, Multi-centre Study to Evaluate the Immune Response and Safety of the Herpes Zoster Subunit Vaccine When Administered Intramuscularly on a 2-dose Schedule in Adults Aged 50 Years and Older in India

**NCT ID:** NCT05219253

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# TITLE PAGE

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| **Protocol Title:** | A phase 3, randomised, observer-blind, placebo-controlled, multi-centre study to evaluate the immune response and safety of the Herpes Zoster subunit vaccine when administered intramuscularly on a 2-dose schedule in adults aged 50 years and older in India. |
| **Study Number:** | 214461 |
| **Compound Number:** | GSK1437173A |
| **Abbreviated Title:** | ZOSTER-081 |

**Sponsor Name:** GlaxoSmithKline Biologicals SA (GSK)

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| DCGI | Drug Controller General of India |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme Linked Immunosorbent Assay |
| EoS | End of Study |
| ES | Exposed Set |
| gE | VZV glycoprotein E |
| GMC | Geometric Mean Concentration |
| GSK | GlaxoSmithKline Biologicals SA |
| HZ | Herpes Zoster |
| ICF | Inform Consent Form |
| IMC | Intercurrent Medical Condition |
| LL | Lower Limit of the confidence interval |
| LSLV | Last Subject Last Visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGI | Mean Geometric Increase |
| PCD | Primary Completion Date |
| PII | Personal Identifiable Information |
| pIMD | Potential Immune-Mediated Disease |
| PPS | Per Protocol Set |
| PT | Preferred Term |

| | |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SDTM | Study Data Tabulation Model |
| SMQ | Standardized MedDRA Query |
| SOC | System Organ Class |
| VRR | Vaccine Response Rate |
| YOA | Years of Age |

## Version history

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| SAP | 25 Jan 2022 | 8 June 2021 | Not Applicable | Original version |
| SAP Amendment 1 | 29 Apr 2022 | 8 June 2021 | • New blinded early safety analyses are added into Section 4.6 Other analyses<br>• Changes to Introduction section and Section 4.8 | SAP amended to accommodate Drug Controller General of India (DCGI) requirement for early safety data |
| SAP Amendment 2 | 16 Sep 2022 | 25 May 2022 | • Analysis to be performed for Blinded early safety report has been moved from section 4.6 to section 4.7 as it is now included in the protocol amendment 1 and two new tables have been added to the report<br>• Section 6.2.2.1 a point added for date imputation<br>• Changes to section 6.2.2.3.1 to count denominator correctly for fever solicited adverse event<br>• Changes to section 6.2.3.1 for calculation of age | Based on protocol amendment 1 |

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| ***SAP Amendment 3*** | 11 Nov 2022 | ***25 May 2022*** | • ***Changes to section 4.7.1 – item 5 to remove related and grade 3 related from solicited systemic events output*** | ***As per protocol, all solicited administration site and systemic events occurring within 7 days of study intervention administration will be considered causally related to the study intervention*** |

# 1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR and in the analysis planned for the Blinded Early Safety Report for Study ZOSTER-081 (214461).

## 1.1. Objectives and Endpoints

| Objectives | Estimands/Endpoints |
|---|---|
| ***Primary*** | |
| To determine the vaccine response rate (VRR) for anti-gE humoral immune response at 1-month post-dose 2 (Month 3) of administration of HZ/su*. | Percentage of participants showing a vaccine response for anti-gE antibody concentrations at 1-month post-dose 2 (Month 3). |
| ***Secondary*** | |
| To evaluate the anti-gE humoral response at 1-month post-dose 2 (Month 3) in recipients of HZ/su compared to Placebo**. | Anti-gE antibody concentration expressed as group geometric mean concentration (GMC) ratio at 1-month post-dose 2 (Month 3). |
| To evaluate safety and reactogenicity following administration of HZ/su or placebo from first dose up to 30 days post last dose. | **Solicited AEs:** Number and percentage of participants reporting each solicited administration site AE (injection site redness, pain, swelling and pruritus) and solicited systemic AEs (fever, myalgia, fatigue, gastrointestinal [GI] symptoms, headache and shivering) within 7 days (Day 1 to Day 7) after each dose and overall.<br>**Unsolicited AEs**: Number and percentage of participants reporting unsolicited AEs within 30 days (Day 1 to Day 30) after any dose.<br>**SAEs:** Number and percentage of participants reporting SAEs from Dose 1 (Day 1) up to 30 days post last dose.<br>**pIMDs:** Number and percentage of participants reporting pIMDs from Dose 1 (Day 1) up to 30 days post last dose. |
| To evaluate safety following administration of HZ/su or placebo during the entire study period. | **SAE**- Number and percentage of participants reporting SAEs from Dose 1 (Day 1) up to study end (phone contact Month 8).<br>**pIMDs**- The number and percentage of participants reporting pIMDs from Dose 1 (Day 1) up to study end (phone contact Month 8). |
| To characterise anti-gE humoral immunogenicity response prior to the first study intervention administration (Day 1) and at 1-month post-second study intervention administration (Month 3) in both groups. | Anti-gE antibody geometric mean concentrations (GMC) and seropositivity rate at pre-study intervention administration (Day 1) and 1-month post-dose 2 (Month 3).<br>Mean geometric increase (MGI) at 1-month post- dose 2 (Month 3) compared to pre-study intervention administration (Day 1). |

*The success criteria for the primary objective and VRR definition are presented in Sections 4.2.2 and 4.2.1 respectively
**The success criteria for the secondary objective are presented in Section 4.3.3

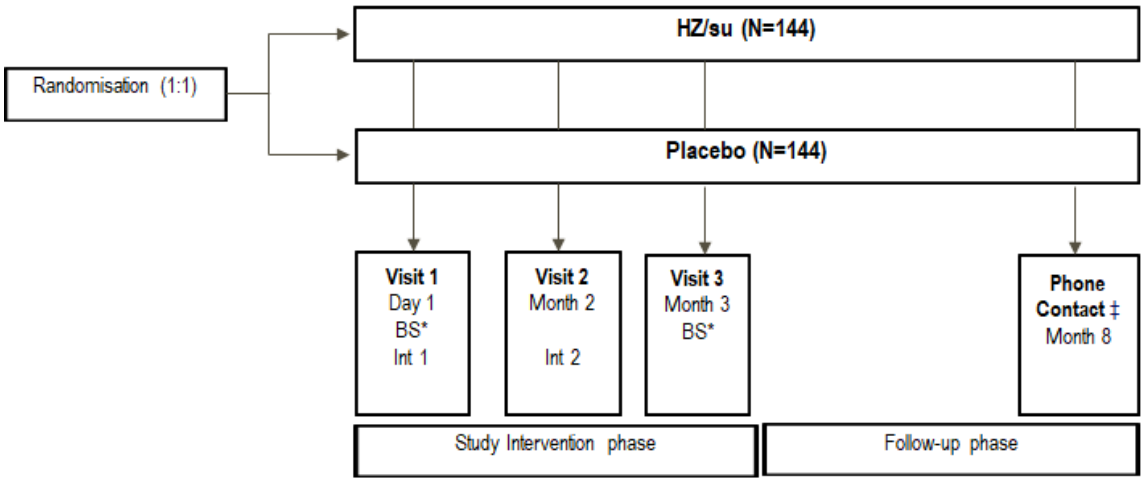
**Primary Estimand**

The primary clinical question of interest is to show that the immunogenicity for anti-gE antibody is comparable in the Indian population with respect to the vaccine response rate (VRR) 1 month post Dose 2 of *Shingrix* vaccination in eligible participants who complied with the study intervention (refer to section 3 for the definition of the per protocol set used for the primary analysis and to section 4.2.2 for the statistical method).

## 1.2. Study Design

The overview of the study design is presented in Figure 1 below.

**Figure 1 Study design overview**




*BS=Blood Sampling; Int=study intervention, N=number of participants planned to be randomised;
‡ Each participant will be followed up for 6 months post last dose/Month 8.

- **Type of study**: Self-contained.
- **Experimental design**: Phase 3, randomised, observer-blind, placebo-controlled, multi-centric, single country study with 2 parallel groups (see Figure 1).
- **Duration of the study**: Approximately 8 months for each participant.
- **Control**: Placebo-controlled
- **Blinding**: Observer-blind
- **Study intervention schedule**: 0 and 2 months (Day 1 and Month 2)
- **Biological samples**: Blood samples will be collected at Day 1 and Month 3 (1-month post-dose 2).

- **Follow-up contact**: Phone contact at Month 8 (6 months post last study intervention administration).
- **Primary completion date (PCD)**: Month 3 (1-month post-dose 2).
- **Data collection**: Standardised electronic Case Report Form (eCRF). Solicited AEs and unsolicited AEs will be collected using a Participant Diary card (paper diary card).
- **Study groups**: Refer to Table 1 for an overview of the study groups.

**Table 1 Study groups, intervention and blinding**

| Study Groups | Number of participants | Age | Study intervention | Blinding |
|---|---|---|---|---|
| | | | | Visit 1→Phone contact (Observer-blind) |
| HZ/su | 144 | ≥50 years | VZV gE<br>$AS01_B$ | X |
| Placebo | 144 | ≥50 years | Lyophilised sucrose<br>Saline (NaCl) solution for reconstitution | X |

- **Study intervention assignment**: The study will enrol approximately 288 participants who will be randomised 1:1 to the HZ/su or Placebo group of equal size to receive 2 doses of study interventions administered intramuscularly 2 months apart.
  The randomisation algorithm will use a minimisation procedure accounting for age (50- 69 YOA, ≥70 YOA). Minimisation factors will have equal weight in the minimisation algorithm.
- **End of Study (EoS):** End of Study (EoS) is achieved after Last subject* last visit (LSLV=Phone contact at Month 8) or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints (whichever is later).

  *subject=participant.

# 2. STATISTICAL HYPOTHESES

The study has one primary and one secondary immunogenicity confirmatory objective which will be assessed in a hierarchical manner. The null hypothesis related to the primary objective under consideration is that the VRR for anti-gE antibody concentration 1 month after the second HZ/su dose is <60%.

The primary objective will be met if the lower limit (LL) of the 95% Confidence Interval (CI) of the VRR for anti-gE antibody concentration 1 month after the second HZ/su dose is ≥60%.

The null hypothesis related to the secondary confirmatory objective under consideration is that the adjusted GMC ratio between the HZ/su and the Placebo group for anti-gE antibody concentration 1 month after the second study intervention dose is <3.

The secondary confirmatory objective will be met if the LL of the 95% CI of the adjusted GMC ratio between the HZ/su and the Placebo group for anti-gE antibody concentration 1 month after the second study intervention dose is ≥3.

All the safety analyses and humoral immunogenicity response under the secondary objective are descriptive.

## 2.1. Multiplicity Adjustment

The hypotheses are tested hierarchically, so no multiplicity adjustment is required.

# 3. ANALYSIS SETS

| Analysis Set | Definition/Criteria |
|---|---|
| **Enrolled Set** | Eligible participants who have signed an informed consent and were randomised or undergone an invasive procedure. |
| **Exposed Set (ES)** | All participants who received at least 1 dose of the study intervention. Analysis per group using the enrolled set is based on the administered intervention. |
| **Per Protocol Set (PPS)** | All eligible participants who received all doses as per protocol, had immunogenicity results pre- and post-dose 2, complied with allowed dosing/blood draw intervals (Table 2), without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. The analysis will be done according to the study intervention that participants received at dose 1. |

## 3.1. Intervals between study visits

The intervals allowed for the inclusion of the PPS is the 'allowed interval per protocol' as defined in Table 2 below:

**Table 2 Intervals between study visits**

| Interval | Planned visit interval | Allowed interval range | Allowed interval during special circumstances |
|---|---|---|---|
| Visit 1→Visit 2 | 60 days/2 Months | 49 days-83 days# | 49 days–180 days |
| Visit 2→Visit 3 | 30 days/1 Month | 28 days-48 days# | 28 days–60 days |
| Visit 2→Phone contact | 180 days/6 Months | 160-210 days | 160–210 days |

#Participants may not be eligible for inclusion in the PPS, if study visits occur outside the allowed interval.

## 3.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify participants to be eliminated from analysis. Details are provided below for each analysis set.

### 3.2.1. Elimination from Enrolled Set

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

### 3.2.2. Elimination from Exposed Set (ES)

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

### 3.2.3. Elimination from Per-protocol analysis Set (PPS)

#### 3.2.3.1. Excluded participants

A participant 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 intervention not administered at all | Visit 1 |
| 1040* | Administration of concomitant vaccine(s) forbidden in the protocol<br>*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)* | Visit 1 to Visit 3 |
| 1050 | Randomisation failure | All |
| 1060 | Randomisation code was broken | Visit 1 to Visit 3 |
| 1070** | Study intervention not according to protocol: -<br>• Participants got vaccinated with the correct study intervention but containing a lower volume<br>• Administration not according to protocol for reason specified by investigator other than route, side and site.<br>• Site and route of study intervention is wrong or unknown | Visit 1, Visit 2 |

| Code | Condition under which the code is used | Visit (timepoints) where the code is applicable |
|---|---|---|
| | • Wrong replacement or study intervention administered (not compatible with the vaccine regimen associated to the treatment number) | |
| 1080 | Temperature deviated study intervention administered | Visit 1, Visit 2 |
| 1090 | Expired study intervention 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 5.2.1 and 5.2.2 of the protocol) in the period from the first dose of study intervention and ending at Visit 3 (Day 1 to Month 3) | Visit 1 to Visit 3 |
| 2050* | Underlying medical condition forbidden by the protocol<br>Any intercurrent medical condition (IMC) (refer to section 9.3.1 of the protocol) which can affect the immune response to the study intervention during the study up to 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 |
| 2080 | Participant did not comply with study intervention schedule<br>*DOSE 1 – DOSE 2 = 49-83 days* | Visit 2 |
| 2090 | Participant did not comply with blood sample schedule<br>*DOSE2-blood sample (BS)2 = 28-48 days* | Visit 3 |
| 2100 | Serological results not available post-vaccination<br>*Check for humoral result for PPS* | Visit 3 |
| 2120 | Obvious incoherence or abnormality or error in data<br>*Check for humoral result for PPS* | Visit 3 |
| 2500 | Participant who didn't receive two doses | Visit 2 |

*Attribution of these elimination codes to participants need CRDL review of individual listing
**Attribution of these elimination codes will be evaluated on case-by-case basis and requires CRDL confirmation

# 4. STATISTICAL ANALYSES

## 4.1. General Considerations

### 4.1.1. General Methodology

95% confidence levels will be used unless otherwise specified.

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

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

### 4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value.

Unless otherwise stated, if baseline data is missing, no derivation will be performed, and baseline will be set to missing.

## 4.2. Primary Endpoints Analyses

The primary immunogenicity analysis will be performed on the PPS and if more than 5% participants are eliminated from the PPS then a complementary analysis will be performed on ES.

### 4.2.1. Definition of endpoints

The VRR is defined as the percentage of participants who has at least:

- a 4-fold increase in the post last vaccination anti-gE antibody concentration as compared to the pre-vaccination anti-gE antibody concentration for participants who are seropositive at baseline.

  OR

- a 4-fold increase in the post last vaccination anti-gE antibody concentration as compared to the anti-gE antibody cut-off value (97 mIU/ml) for seropositivity for participants who are seronegative at baseline.

Two-sided 95% CIs for VRR will be computed by Clopper-Pearson method [Clopper, 1934].

### 4.2.2. Main analytical approach

The point estimate and the 95% CI for VRR on anti-gE antibody concentration as assessed by ELISA will be calculated in all participants at 1-month post-dose 2 (Month 3).

As stated in Section 2 the objective is met if the LL of the 95% CI of the VRR for anti-gE antibody concentration 1 month after the second HZ/su dose is at least 60%.

## 4.3. Secondary Endpoints Analyses

### 4.3.1. Key/Confirmatory secondary endpoints

#### 4.3.1.1. Confirmatory secondary immunogenicity endpoints

The secondary confirmatory immunogenicity analysis will be performed on the PPS and if more than 5% participants are eliminated from the PPS then a complementary analysis will be performed on ES.

#### 4.3.1.2. Definition of endpoints

The geometric mean concentration (GMC) calculations are performed by taking the anti-log of the mean of the log base 10 concentration transformations. For descriptive statistics only, antibody concentrations below the cut-off of the assay will be imputed with a value equal to half the cut-off for the purpose of GMC calculation.

#### 4.3.1.3. Main analytical approach

For the secondary confirmatory group comparison, the GMC ratio with nominal 95% CI will also be provided. This will be obtained using an analysis of variance (ANOVA) model on log-transformed concentrations adjusted for age-strata (50-69 YOA and ≥ 70 YOA) and baseline titres as continuous covariate and will use Satterthwaite method for adjusting the degree of freedom for unequal variance.

For this analysis, the following SAS code using the proc mixed procedure will be used to do the model fitting:

```
PROC MIXED DATA=sero;
CLASS grp_labl agecat;/*age-minimization factor*/
MODEL log_val=grp_labl agecat base/DDFM=satterth;
REPEATES/GROUP=grp_labl;
LSMEANS grp_labl /AT MEANS CL DIFF ALPHA=0.05 COV;
ODS OUTPUT LSMEANS=m_lsml;
ODS OUTPUT DIFFS=m_difl;
RUN;
```

The group GMC ratio will be based on a back transformation of group contrast in an ANCOVA model applied to the logarithm-transformed concentrations.

### 4.3.2. Key secondary immunogenicity endpoint

Descriptive statistics of immune response with respect to anti-gE assessed by ELISA at each timepoint and by study group will be presented:

- Number and percentage of participants with anti-gE assessed by ELISA above seropositivity cut-off will be tabulated with 95% CI.
- GMCs will be tabulated with 95% CI.
- Geometric mean of ratios of antibody concentrations at 1- month post-dose 2 timepoint over pre-study intervention administration (MGI) will be tabulated with 95% CI.

### 4.3.3. Key secondary safety endpoints

The analyses for safety will be descriptive and based on the ES. The analyses will be performed by study group.

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

- Solicited administration site AEs and solicited systemic AEs
  - Number and percentage of participants reporting each solicited administration site AE (any grade, grade 3, resulting in a medically-attended visit) during the 7-day follow-up period after each dose and overall per participant and per dose will be tabulated with exact 95% CIs.
  - Number and percentage of participants reporting each solicited systemic AE (any grade, grade 3, resulting in a medically-attended visit) during the 7-day follow-up period after each dose and overall per participant and per dose will be tabulated with exact 95% CIs.
- Unsolicited AEs: Number and percentage of participants reporting unsolicited AE (any grade, grade 3, any related, grade 3 related, resulting in a medically-attended visit) within 30 days after any dose coded by the Medical Dictionary for Regulatory Activities (MedDRA) by primary system organ class (SOC) and preferred term (PT) with exact 95% CIs will be tabulated.
- SAEs and pIMDs: Number and percentage of participants reporting SAEs (any and related), fatal SAEs (any and related) and pIMDs (any and related) from Dose 1 (Day 1) up to 30 days post last dose and from Dose 1 (Day 1) up to study end coded by the MedDRA primary SOC and PT with exact 95% CIs will be tabulated.
- 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 from first study intervention up to study end.
- Listing of pregnancy during the entire study period will be generated.

### 4.3.4. Supportive secondary endpoints

Not applicable

## 4.4. Tertiary/Exploratory Endpoints Analyses

Not Applicable.

## 4.5. Other Safety Analyses

Below are the other safety analyses planned for the final analysis and based on the ES. These analyses will be performed by study group.

- The percentage of participants with at least 1 administrative site adverse event (solicited only), with at least one systemic AE (solicited only) and with any AE (solicited only), all with onset during the solicited 7-day follow-up period, will be tabulated with exact 95% CI after each vaccine dose and overall. The same tabulations will be done for grade 3 solicited AEs.
- In the solicited systemic adverse event table, fever will be reported per 0.5°C cumulative increments.
- Duration of each solicited administrative site and systemic AE during the solicited follow-up period will be presented. Total duration of each individual solicited administrative site and systemic AE will be tabulated.
- Duration of each grade 3 solicited administrative site and systemic AE during the solicited follow-up period will be presented. Total duration of each individual solicited grade 3 administrative site and systemic AE will be tabulated.

### 4.5.1. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The overall incidence of AEs and SAEs of COVID-19, COVID-19 AEs leading to study intervention discontinuation, COVID-19 AEs leading to study withdrawal, and severe COVID-19 AEs will be summarized. The incidence of these events at individual PT level can be obtained from the standard AE/SAE summaries.

COVID-19 assessments (confirmed, probable and suspected diagnosis) for participants with COVID-19 AEs will be summarized.

The number and percentages of participants with concomitant vaccination (COVID-19) before and during the study will be tabulated with exact 95% CI.

Summaries of the number of participants who had a COVID-19 diagnosis test performed and the number of participants with positive, negative, or indeterminate results will be presented.

Additional tables may be planned as required.

## 4.6. Other Analyses

Not applicable.

## 4.7. Interim Analyses

No interim analysis is planned for this study. An EoS analysis with all data including the safety data obtained until study end (6 months post-dose 2) will be performed. A Clinical Study Report (CSR) containing all available data will be written and made available to the investigators. Individual listings will only be provided at this stage.

### 4.7.1. Blinded Early Safety Report

To fulfil the post-approval commitment to the Indian regulatory authority, a blinded early safety assessment report after completion of 30 days safety follow-up post HZ/su dose 2 (i.e., Visit 3, Month 3) for the initial 200 randomised participants will be provided and the following analyses will be performed. The analyses performed will be descriptive in nature.

1. Table on summary of participants withdrawn up to the snapshot date with reasons for withdrawal on the Exposed Set
2. Summary of demography and baseline characteristics on the Exposed Set
3. Table showing the exposure to study intervention on the Enrolled Set
4. Number and percentage of participants with any, grade 3, or medically attended solicited administration site events, per dose, in the Exposed Set.
5. ***Number and percentage of participants with any, grade 3, or medically attended solicited systemic events, per dose, in the Exposed Set***
6. Number and percentage of participants with any, grade 3, related, or grade 3 related unsolicited adverse events with onset within 30 days following any dose in the Exposed Set
7. Number and percentage of participants with serious adverse events from first dose up to 30 days post last dose in the Exposed Set
8. Number and percentage of participants with serious adverse events from first dose up to snapshot day in the Exposed Set
9. Number and percentage of participants with pIMDs from first dose up to 30 days post last dose in the Exposed Set
10. Number and percentage of participants with pIMDs from first dose up to snapshot day in the Exposed Set
11. Listing of SAEs from first dose up to snapshot day.
12. Listing of pIMDs from first dose up to snapshot day.

All the data derivation rules for demography and safety analyses of Appendix 2 will be applicable for the above demography and safety analyses.

## 4.8. Changes to Protocol Defined Analyses

Not applicable.

# 5. SAMPLE SIZE DETERMINATION

Approximately 288 (144 participants per study group) eligible participants will be randomised to achieve 200 (100 participants per study group) evaluable participants for the evaluation of the primary objective assuming that approximately 30% of the enrolled participants will not be evaluable. Participants who withdraw from the study will not be replaced.

Considering a 95% VRR in the HZ/su group, the study has at least 99% power to meet the primary objective under the hypothesis given below:-

- Null hypothesis: The VRR for anti-gE ELISA at 1 month after second HZ/su dose in participants from India is less than 60%.
- Alternative hypothesis: The VRR for anti-gE ELISA at 1 month after second HZ/su dose in participants from India is at least 60%.

Power to show the LL of the 95% CI for VRR at one month after second HZ/su dose.

| Endpoint | NI criteria | N1:N2 (evaluable) | Reference** | Power* |
|---|---|---|---|---|
| Vaccine response rate – anti-gE ELISA | LL of 95% CI for VRR ≥60% | 100:100 | 95% | ≥99% |

*Power computed using PASS 2019 software, Non-Inferiority Test for one proportion, 1-sided alpha=2.5%;
**References used for the sample size calculation: ZOSTER-006 study.

Considering the adjusted GMC ratio of 44.31 between HZ/su and Placebo group and SD of 0.30 and 0.46 for HZ/su and Placebo group, respectively, the study has at least 99% power to meet the secondary confirmatory objective under below hypothesis.

- Null hypothesis: The adjusted GMC ratio for anti-gE ELISA at 1 month after second study intervention dose in participants from India is less than 3.
- Alternative hypothesis: The adjusted GMC ratio for anti-gE ELISA at 1 month after second study intervention dose in participants from India is greater than or equal to 3.

Power to show the LL of the 95% CI for adjusted GMC ratio at one month after second dose.

| Endpoint | Criteria for evaluation | N1:N2 (evaluable) | Reference** | Power* |
|---|---|---|---|---|
| Adjusted GMC ratio | LL of 95% CI for adjusted GMC ratio ≥3 | 100:100 | Adjusted GMC ratio – 44.31<br>SD for HZ/su group – 0.30<br>SD for Placebo group – 0.46 | ≥ 99% |

*Power computed using PASS 2019 software, Two-Sample T-Tests for Superiority by a Margin Allowing Unequal Variance,
1-sided alpha=2.5%;
**References used for the sample size calculation: ZOSTER-006 study.

# 6. SUPPORTING DOCUMENTATION

## 6.1. Appendix 1 Study Population Analyses

### 6.1.1. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who withdrew from the study will be provided. Reasons for study withdrawal will be summarized. For those who neither completed nor withdrawn, they will be categorized as on study intervention or in follow up. This analysis will be based on the ES.

The number of participants enrolled into the study as well as the number of participants excluded from the PPS analyses will be presented through 2 consort tables:

- Consort table 1: Showing the participants disposition from ***participants with ICF signed to*** Enrolled Set ***and from Enrolled Set*** to ES.
- Consort table 2: Showing the participants disposition for ES to PPS.

### 6.1.2. Demographic and Baseline Characteristics

Demographic and other baseline characteristics will be described for the ES and the PPS

Demographic characteristics (age at first vaccination with study intervention in years, age category [50-69, ≥70 YOA], sex, race and ethnicity) will be summarized 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.

Number of participants by center will be presented on ES. Percentage of Enrolled participants by age categories (18-64,65-84, ≥85) YOA will be tabulated by group for the purpose of web disclosure.

### 6.1.3. Protocol Deviations

The number of participants enrolled into the study as well as the number of participants excluded from the per protocol set (PPS) analyses will be tabulated for the total population.

The number of participants enrolled into the study as well as the number of participants excluded from the ES will be tabulated for the total population. This will be based on all enrolled participants.

Important protocol deviations will be summarized. Protocol deviations which result in exclusion from an analysis set will also be summarized. Data will be reviewed prior to unblinding and freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset.

### 6.1.4. Prior and Concomitant Medications

No table is planned for the prior medications taken by participants.

The proportion of participants with concomitant medications (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) will be tabulated, within 30 days post each vaccination (i.e., on the day of vaccination and 29 subsequent days) with study intervention and overall, with exact 95% CI.

### 6.1.5. Prior and Concomitant Vaccinations

No table is planned for the prior vaccinations taken by participants.

The proportion of participants with concomitant vaccinations will be tabulated, within 30 days post each vaccination (i.e., on the day of vaccination and 29 subsequent days) with study intervention and overall, with exact 95% CI.

### 6.1.6. Study Intervention Compliance

The number of doses administered will be tabulated.

The number and percentage of participants who returned the diary cards and those who returned the diary cards with documentation of the presence or absence of AEs will be tabulated on the Exposed Set.

Summary of time interval between Visit 1 or 2 and Visit 2 and Visit 3 will be tabulated for the Exposed Set.

### 6.1.7. Additional Analyses Due to the COVID-19 Pandemic

Depending on how the COVID-19 pandemic evolves, the SAP may be amended to reflect the additional analyses corresponding to COVID-19.

## 6.2. Appendix 2 Data Derivations Rule

This section contains standard rules for data display and derivation for clinical and epidemiological studies.

### 6.2.1. Attributing events to vaccine doses

The dose relative to an event is the most recent study intervention dose given to a participant 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 case report form (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.

### 6.2.2. Handling of missing data

#### 6.2.2.1. Dates

When partially completed dates (i.e. dates missing a day and/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:

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

- Adverse event start dates with missing day:
  - If the month is not the same as the study intervention dose, then the imputed start date will be the 1st of the month
  - If the event starts in the same month as at least one of the study interventions, the flag indicating if the event occurred before or after study intervention (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the study intervention dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the study intervention dose given during that month.
  - If we cannot impute the missing parts of the date using the rule under above categories, then we need to apply Version 15 rule - 15 for the missing day and 30JUN for missing month and day.

- Adverse event start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.
  - If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first study intervention dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first study intervention dose given during that year.
  - If we cannot impute the missing parts of the date using the rule under above categories, then we need to apply Version 15 rule - 15 for the missing day and 30JUN for missing month and day.
- Adverse event end dates with missing day: the imputed end date will be the last day of the month (30 or 31) or the study conclusion date whichever comes first.
- Adverse event end dates with missing day and month: the imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.

All incomplete concomitant medication/vaccination start/end date will follow the rules above.

#### 6.2.2.2. Laboratory data

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

#### 6.2.2.3. Daily recording of solicited events

##### *6.2.2.3.1. Studies with paper diaries*

For studies using paper diaries which have questions in the eCRF 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 to one occurrence of the specific administration site (or systemic) events. If there is 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, then that participant 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 event over the Day X to Day Y post-dose period:

| Solicited 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, grade 2, or grade 3 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 |
| At least grade 1 | All participants with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y |
| At least grade 2 | All participants with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y |
| At least grade 3 | All participants with at least one occurrence of the adverse event at grade 3 between Day X and Day Y |

## 6.2.3. Data derivation

### 6.2.3.1. 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 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 June 30th of the year.

### 6.2.3.2. 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

### 6.2.3.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

| IS.ISORRES | Derived value |
|---|---|
| "value" and value is < cut-off | cut-off/2 |
| "value" and value is >= cut-off | Value |

#### 6.2.3.4. Geometric mean concentrations (GMCs)

Geometric Mean Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log concentration transformations. Non quantifiable antibody concentrations will be converted as described in section 6.2.3.3 for the purpose of GMC calculation. Cut-off values are defined by the laboratory before the analysis.

#### 6.2.3.5. Onset day

The onset day for an event (e.g. AE, concomitant 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 study dose).

#### 6.2.3.6. 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 3 March 2018 and ends on 12 March 2018 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.

#### 6.2.3.7. 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.

Solicited events will be coded by MedDRA as per the following codes:

| Solicited event | Lower level term code | Corresponding Lower level term decode |
|---|---|---|
| Pain | 10022086 | Injection site pain |
| Erythema | 10015150 | Injection site erythema |
| Swelling | 10053425 | Injection site swelling |
| Pruritus | 10022093 | Injection site pruritus |
| Fever | 10016558 | Pyrexia |

| Solicited event | Lower level term code | Corresponding Lower level term decode |
|---|---|---|
| Headache | 10019211 | Headache |
| Fatigue | 10016256 | Fatigue |
| Myalgia | 10028411 | Myalgia |
| Shivering | 10040558 | Shivering |
| GI symptom | 10017944 | Gastrointestinal disorder |

The latest available MedDRA version will be used for coding

### 6.2.3.8. 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.

### Table 3 Intensity scales for solicited events

| Adults (≥50 years) | | |
|---|---|---|
| **Event** | **Intensity grade** | **Parameter** |
| Pain at administration site | 0 | None |
| | 1 | Mild: Any pain neither interfering with nor preventing normal everyday activities. |
| | 2 | Moderate: Painful when limb is moved and interferes with everyday activities. |
| | 3 | Severe: Significant pain at rest. Prevents normal everyday activities. |
| Redness at administration site | | Greatest surface diameter in mm |
| Swelling at administration site | | Greatest surface diameter in mm |
| Pruritis at administration site | 0 | None |
| | 1 | Mild: Itchy sensation that neither interferes with nor preventing normal everyday activities. |
| | 2 | Moderate: Itchy sensation that interferes with normal everyday activities. |
| | 3 | Severe: Itchy sensation that prevents normal everyday activities. |
| Temperature* | | Temperature in °C/°F (with 1 decimal) |
| Headache | 0 | None |
| | 1 | Mild: Headache that is easily tolerated |
| | 2 | Moderate: Headache that interferes with normal activity |
| | 3 | Severe: Headache that prevents normal activity |
| Fatigue | 0 | None |
| | 1 | Mild: Fatigue that is easily tolerated |
| | 2 | Moderate: Fatigue that interferes with normal activity |
| | 3 | Severe: Fatigue that prevents normal activity |
| Gastrointestinal symptoms | 0 | None |
| | 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 |

| Adults (≥50 years) | | |
|---|---|---|
| **Event** | **Intensity grade** | **Parameter** |
| 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 |
| Shivering | 0 | None |
| | 1 | Shivering that is easily tolerated |
| | 2 | Shivering that interferes with normal activity |
| | 3 | Shivering that prevents normal activity |

* Fever is defined as temperature ≥38.0°C/100.4°F regardless of the location of measurement. The preferred route for measuring temperature is oral.

The maximum intensity of injection administration site redness/swelling and fever will be scored at GSK as follows:

| Intensity grade | Redness/swelling | Fever |
|---|---|---|
| 0: | ≤20 mm | <38.0°C (100.4°F) |
| 1: | >20-≤50 mm | ≥38.0°C (100.4°F)- ≤38.5°C (101.3°F) |
| 2: | >50-≤100 mm | >38.5°C (101.3°F)- ≤39.0°C (102.2°F) |
| 3: | >100 mm | >39.0°C (102.2°F) |

#### 6.2.3.9. Counting rules for occurrence of unsolicited adverse events

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

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the Adverse Events (AE) domain, but they do not contribute to the summaries of unsolicited adverse events.

Missing severity, 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.

### 6.2.4. Display of decimals

#### 6.2.4.1. Percentages

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

#### 6.2.4.2. 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.

#### 6.2.4.3. Serological summary statistics

For anti-gE ELISA, geometric mean concentrations (GMC) and their confidence limits will be presented with one decimal, as well as GMC fold increase from pre-dose.

GMC group ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

# 7. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.