	Statistical Analysis Plan
Detailed Title:	A phase III, randomized, observer-blind, placebo controlled, multicenter clinical trial to assess Herpes Zoster recurrence and the reactogenicity, safety and immunogenicity of GSK Biologicals' Herpes Zoster vaccine (HZ/su) when administered intramuscularly on a 0 and 2 month schedule to adults ≥ 50 years of age with a prior episode of Herpes Zoster
eTrack study number and Abbreviated Title	204939 (ZOSTER-062)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Amendment 2: Final 06 Oct 2023

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

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LIST OF ABBREVIATIONS

CCI [redacted]

AE	Adverse event

CCI [redacted]

CI	Confidence Interval
CMI	Cell-Mediated Immunity
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
ELISA	Enzyme-linked immunosorbent assay
EoS	End of study
ES	Exposed Set
gE	VZV glycoprotein E
GMC	Geometric mean antibody concentration
GSK	GlaxoSmithKline Biologicals SA
HI	Humoral Immunogenicity
HZ	Herpes Zoster
ICF	Informed consent form

CCI [redacted]

IMC	Intercurrent Medical Condition
LL	Lower Limit of the confidence interval
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mES	Modified Exposed Set
NA	Not Applicable
PBMC	Peripheral blood mononuclear cells
PCD	Primary completion date
PD	Protocol Deviation
PHN	Postherpetic Neuralgia
pIMD	Potential Immune-Mediated Disease
PPS	Per-Protocol Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK's Internet Randomization System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables Figures and Listings
CCI [redacted]	
TOC	Table of Content
UL	Upper Limit of the confidence interval
VRR	Vaccine response rate
WBR	Web-based Randomization
YOA	Years of Age

1. DOCUMENT HISTORY

Date	Description	Protocol Version
28 AUGUST 2019	First version	Amendment 1: 18 MAR 2019
24 JANUARY 2020	Amendment 1: amendment of the SAP definition of enrolled set to better align across study documents, specifically the protocol and eCRF completion guidelines. None of these modifications are major changes to planned analysis.	Amendment 1: 18 MAR 2019
06 Oct 2023	Amendment 2: The protocol was amended to include subjects vaccinated beyond the original 2-month dose interval during the special circumstances of the COVID-19 pandemic. Per CHMP Scientific Advice received on March 24, 2022, the SAP is amended to add a sensitivity analysis for non-inferiority after removing the participants who received a second dose more than 2 months after the first dose (outside of the original scheduled window), a stratified analysis for non-inferiority by recruitment interruption, and Kaplan-Meier curves to compare the onset time of HZ recurrences. Added clarifications on how to handle extreme cases, when there are no confirmed HZ cases in one of the treatment groups. Added analysis to assess the impact of COVID-19 on safety.	Amendment 2: 14 APR 2020

2. OBJECTIVES/ENDPOINTS

2.1. Objectives

2.1.1. Primary objectives

- To compare the incidence of Herpes Zoster (HZ) recurrence in the HZ/su group to the placebo group

  A formal non-inferiority analysis with non-inferiority margin of 5 will be performed

  – *Criterion: The objective is met if the upper limit (UL) of the 95% confidence interval (CI) of the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below 5.*

2.1.2. Secondary objectives

- To evaluate the rate of HZ recurrence in HZ/su and placebo groups during the entire study period.
- To evaluate safety and reactogenicity following administration of HZ/su vaccine or placebo within 30 days after each dose.

- To evaluate safety following administration of HZ/su vaccine or placebo during the entire study period.
- To characterize anti-gE humoral immunogenicity response prior to the first vaccination (Day 1), at two months post first vaccination (Month 2) and at one month post last vaccination (Month 3) in both groups.

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2.2. Endpoints

2.2.1. Primary endpoints

- Occurrence of confirmed HZ episodes from 30 days post second vaccination until study end.

2.2.2. Secondary endpoints

- Occurrence of confirmed HZ episodes from first study vaccination until study end
- Reactogenicity and safety, in all subjects
  - Occurrence, intensity and duration of each solicited local adverse event (AE) within 7 days (Days 1-7) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of each solicited general AE within 7 days (Days 1-7) after each vaccination.
  - Occurrence, intensity and relationship to vaccination of unsolicited AEs within 30 days (Days 1-30) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
  - Occurrence and relationship to vaccination of all serious adverse events (SAEs) from dose 1 up to 30 days post last vaccination.

  - Occurrence and relationship to vaccination of any potential immune mediated diseases (pIMDs) from dose 1 up to 30 days post last vaccination.
  - Occurrence and relationship to vaccination of all SAEs within the period starting after 30 days post last vaccination until 1 year post last vaccination.
  - Occurrence and relationship to vaccination of any pIMDs within the period starting after 30 days post last vaccination until 1 year post last vaccination.
  - Occurrence of SAEs related to investigational vaccine, related to study participation or to GSK concomitant medication/vaccine during the entire study period.
- Immunogenicity, in all subjects
  - Vaccine response for Anti-gE humoral immunogenicity as determined by Enzyme-linked immunosorbent assay (ELISA) at Month 2 and Month 3.
  - Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 2 and Month 3.

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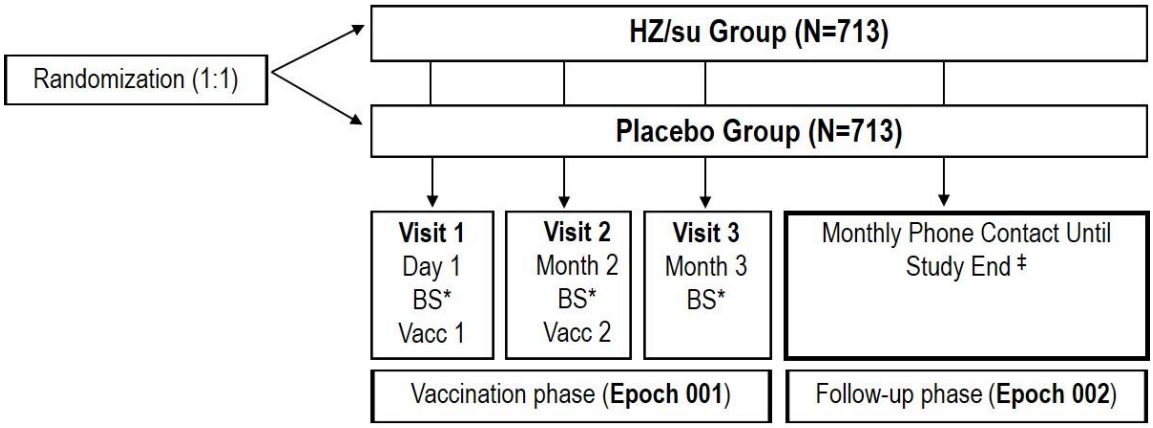
3. STUDY DESIGN

Figure 1 Overview of Study design



BS= Blood sampling; HZ= Herpes Zoster; N= number of subjects planned to be enrolled; Vacc= Vaccination
*A blood sample (approx. 5ml per visit) will be collected from all subjects at Visits 1, 2 and 3. An additional blood sample (approx. 20ml per visit) will be collected from subjects in the cell mediated immunity sub-cohort at Visits 1, 2 and 3.
‡The duration of the study will vary for each subject. Study conclusion will be scheduled based on the projected date of the last contact of the last enrolled subject, that is 26 months (790 days) from the enrolment date. The study conclusion visit/ contact for subjects with an ongoing episode of HZ will occur after a 4-week pain-free period is documented OR after Day HZ-92 follow-up has been completed.

- **Experimental design**: Phase III, observer-blind, randomized, placebo controlled, multicenter, multi-country study with two 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, 26 months (790 days) from the enrolment date. Therefore, subjects enrolled early in the trial could be followed for longer duration than the subjects who enrol later in the trial. The study conclusion visit/ contact for subjects with an ongoing episode of HZ at the time of last subject last visit (LSLV) will occur after a 4-week pain-free period is documented OR after Day HZ-92 follow-up has been completed.
  - **Epoch 001**: Starting at Visit 1 (Day 1) followed by Visit 2 at two months post first vaccination (Month 2), Visit 3 at one month post last vaccination (Month 3).
  - **Epoch-002**: Starting with 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, 26 months (790 days) from the enrolment date.
- **Primary completion Date (PCD):** The primary completion date will be when the last subject completes their study conclusion contact (within 30 days of the projected study conclusion date of the last enrolled subject, that is, 26 months [790 days] from the enrolment date.

  Refer to the protocol glossary of terms for the definition of PCD.

- **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 late enrolled subject, that is, 26 months (790 days) from the enrolment date of the last subject and **2)** the release of all polymerase chain reaction (PCR) test results for the HZ rash lesion sample.

  Refer to the protocol glossary of terms for the definition of EoS.

- **Study groups:**

Table 1 Study groups and epochs foreseen in the study

Study groups	Number of eligible subjects	Age (years)	Epochs	
			Epoch 001	Epoch 002
HZ/su	713	≥50 years	●	●
Placebo	713	≥50 years	●	●

- **Control**: placebo controlled
- **Vaccination schedule**: 0 and 2 months
- **Treatment allocation**: Eligible subjects will be randomized (1:1) to HZ/su group or placebo group. The randomization algorithm will use a stratification procedure accounting for age (50-59 years of age [YOA]; 60-69 YOA and ≥ 70 YOA) and also a stratification procedure accounting for 'time since previous HZ episode' (≤ 4 years ago, 5-9 years ago, ≥ 10 years ago). Additional minimization factors include: (female) gender, center, family (first degree blood relative) history of HZ, history of PHN 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.

Table 2 Expected enrolment based on overall age stratification

Age stratum	Sample size	Percentage of total
50-59 YOA	Min 285	Min 20
60-69 YOA	Min 285	Min 20
≥70 YOA	Min 143	Min 10
All	1426	100.0

Table 3 Expected enrolment based on time from previous HZ case

Sub-group	Sample size	Percentage of total
≤4 years ago	Min 143	Min 10
5-9 years ago	Min 143	Min 10
≥ 10 years ago	Min 143	Min 10
All	1426	100.0

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- **Blinding**:

Table 5 Blinding of study epochs

Study Epochs	Blinding
Epoch 001	observer-blind
Epoch-002	observer-blind

- **Sampling schedule**:
  - Blood samples for humoral immunity (approximately 5 mL per visit) will be collected from all subjects at Visit 1 (Day 1), Visit 2 (Month 2), and Visit 3 (Month 3).

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[redacted]

  - Clinical specimens of HZ lesions will be collected from all subjects who are clinically diagnosed with a suspected case of HZ (Section 4.1 of the protocol).
  - A urine specimen will be collected from all female subjects of child-bearing potential (see glossary of terms in protocol for definition of woman of child bearing potential) at Visit 1 (Day 1) and Visit 2 (Month 2). If a serum pregnancy test instead of a urine pregnancy test is required by country, local or ethics committee regulations, a blood sample will be collected from women of child-bearing potential at Visit 1 (Day 1) and Visit 2 (Month 2) and used for the test as per local guidance.

- **Group and sub-group information**

Table 6 Group names and description for footnote will be used in the Tables, Figures and Listings, in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote
1	HZ/su	Subjects receiving HZ/su vaccine
2	Placebo	Subjects receiving Placebo

The following sub-groups will be used in the Tables Figures and Listings (TFL), in line with the T-domains:

Table 7 Sub-group name and definitions to be used for the sub-group analysis by age stratum

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	50-59 YOA	Subjects aged 50-59 years of age
2	60-69 YOA	Subjects aged 60-69 years of age
3	≥70 YOA	Subjects aged ≥70 years of age

YOA = Years of age

Table 8 Sub-group name and definitions to be used for the sub-group analysis by time since previous HZ episode

Sub-group order in tables	Sub-group label in tables	Sub-group definition for footnote
1	Previous HZ ≤ 4 Y	Previous HZ episode was ≤ 4 years prior to enrolment
2	Previous HZ ≥ 5 - ≤ 9 Y	Previous HZ episode was 5-9 years prior to enrolment
3	Previous HZ ≥ 10 Y	Previous HZ episode was ≥ 10 years prior to enrolment

Y = Year

4. ANALYSIS SETS

4.1. Definition

4.1.1. Enrolled Set

The enrolled set will include subjects who signed the informed consent form (ICF) and were either randomized to receive treatment or have had an invasive procedure (i.e., blood draw or vaccine administration).

4.1.2. Randomized Set

The randomized set will include subjects who signed the inform consent form (ICF) and treatment is allocated for them.

4.1.3. Exposed Set

The exposed set (ES) will include all subjects with at least one study vaccine administered.

The ES for analysis of immunogenicity will include all vaccinated subjects for whom data related to immunogenicity endpoints are available. CCI [redacted]

The ES for analysis of reactogenicity (e.g., solicited AEs) will include all subjects with at least one vaccine administration documented and who have solicited safety data (i.e., symptom screen/sheet completed).

The ES for analysis of safety (e.g. SAEs) will include all subjects with at least one vaccine administered.

4.1.4. Modified Exposed Set

The modified exposed set (mES) is the primary population for HZ recurrence analysis. The mES excludes subjects from the ES who were not administered two doses of the study vaccine per protocol, or who developed a confirmed case of HZ prior to 30 days after the second vaccination.

4.1.5. Per Protocol Set for immunogenicity

The per protocol set (PPS) for immunogenicity will be defined by time-point and will include evaluable subjects from the ES:

- who meet all eligibility criteria.
- who received 2 doses of the HZ/su study vaccine or placebo according to their random assignment.
- who did not receive forbidden medications as defined in the protocol.
- who had no intercurrent medical condition (IMC) which may influence immune response.
- who complied with the vaccination schedule as specified in Table 9.
- who complied with the blood sample schedule as specified in Table 9.
- for whom data concerning immunogenicity endpoint measures are available.

The intervals allowed for the inclusion in the PPS for analysis of immunogenicity are defined as follows:

Table 9 Intervals between study visits

Interval	Optimal length of interval [1]	Allowed interval	*Allowed interval during special circumstances* [2]
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- 90 days***

[1]Whenever possible the investigator should arrange study visits according to this interval.
[2] ***Refer to protocol Section 6.7 for study procedures to be considered during special circumstances.***

Based on the availability of humoral immune response result and CCI [redacted], separate PPS will be defined for humoral sample and CCI [redacted]:

- PPS-HI - all subjects meeting the criteria described above and have humoral immune result available post vaccination

CCI [redacted]

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

More specifically,

- The analyses at the Day 1 timepoint will be based on the PPS for immunogenicity Day 1;
- The analyses at the Month 2 timepoint will be based on the PPS for immunogenicity Month 2;
- The analysis at the Month 3 timepoint will be based on the PPS for immunogenicity Month 3;

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) and code 900 (invalid ICF) will be used for identifying subjects eliminated from Enrolled Set.

4.2.2. Elimination from Randomized Set

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

4.2.3. Elimination from Exposed Set (ES)

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

4.2.4. Elimination from modified Exposed Set (mES)

Code 800 (Fraudulent data), code 900 (invalid ICF), code 1010 (vaccine number not allocated), code 1030 (Study vaccine not administered at all), code 1050 (Randomization failure), code 1070 (Vaccination not according to protocol), code 2500 (Subject who didn't receive two doses) and code 3500 (Subject having confirmed HZ episode prior to 30 days after the dose 2) will be used for identifying subjects eliminated from mES.

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

4.2.5.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions

For codes 800, 900, 1010, 1030, 1050, 1060, 2010, 2500: subjects will be eliminated from all visits.

For codes 1040, 1070, 1080, 1090, 2040, 2050, 2080, 3500: subjects will be eliminated from a specific visit (at which the condition is met) onwards.

For code 2090: subjects will be eliminated at the specific visit at which the condition is met.

Additionally, for the PPS-HI, subjects with codes 2020, 2100, 2120 will be eliminated at the specific visit at which the condition is met. CCI [redacted].

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
800	Fraudulent data	All	All
900	Invalid ICF	All	All
1010	Vaccine not allocated	All	Randomized set, ES, mES, PPS
1030	Study vaccine not administered at all	All	ES, PPS, mES

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
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 study vaccine and ending at Visit 3 (Day -30 to Month 3)	Day -30 up to Month 3	PPS
1050	Randomization failure	All	mES, PPS
1060	Randomization code was broken	Day 1 to Month 3	PPS
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 the investigator, other than side, site and route • Site or route of study vaccine administration wrong or unknown • Wrong replacement or	Day 1, Month 2	mES, PPS

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
	study vaccine administered (not compatible with the vaccine regimen associated to the treatment number) Administered study vaccine reported as being the correct one but is not compatible with the vaccine regimen associated to the treatment number		
1080	Vaccine temperature deviation	Day 1, Month 2	PPS
1090	Expired vaccine administered	Day 1, Month 2	PPS
2010	Protocol violation (inclusion/exclusion criteria)	Day 1	PPS
2020	Unknown antibody status at pre timepoint ***for anti-gE humoral result*** (baseline sampling missing or unable to test because of hemolysis, insufficient volume)	Day 1	***PPS-HI***
CCI [redacted]			
2040*	Administration of any medication forbidden by the protocol	Day 1 to Month 3	PPS

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
	Any concomitant medication or drug not foreseen by the study protocol (refer to section 7.7.2 of the protocol) administered in the period from the first dose of study vaccine and ending at Visit 3 (Day -30 to Month 3)		
2050*	Underlying medical condition forbidden by the protocol Any IMC (refer to section 7.8 of the protocol) which can affect the immune response to the study vaccine between the first dose of study vaccine and ending at Visit 3 (Day -30 to Month 3)	Day 1 to Month 3	PPS
2080	***Subjects who had planned study visits during special circumstances did not comply with vaccination schedule DOSE 1 - DOSE 2 = 49-180 days*** ***Other*** Subjects did not comply with vaccination schedule *DOSE 1 - DOSE 2 = 49-83 days*	Month 2	PPS
2090	***Subjects who had planned study visits during special circumstances did not comply with blood sample schedule***	Month 2, Month 3	PPS

Code	Condition under which the code is used	Visit (timepoints) where the code is applicable	Applicable for analysis set
	DOSE 1 - BS2 = 49-180 days for PPS at Month 2 ***DOSE2 - BS2 = 28-90 days for PPS at Month 3*** ***Other*** Subjects did not comply with blood sample schedule DOSE1 - BS2 = 49-83days for PPS at Month 2 DOSE2 - BS3 = 28-48 days for PPS at Month 3		
2100	Serological results ***of anti-gE humoral*** not available post-vaccination	Month 2, Month 3	***PPS-HI***
CCI [redacted]			
2120	Obvious incoherence or abnormality or error in ***anti-gE humoral*** data	Day 1, Month 2, Month 3	***PPS-HI***
CCI [redacted]			
2500	Subjects who did not receive two doses	Month 2	mES, PPS
3500	Subjects having confirmed HZ episode prior to 30 days after the dose 2	Day 1 to Month 3	mES, PPS
CCI [redacted]			

*Attribution of these elimination codes to subject need CSL review of individual listing
** *Attribution of code 1070 to a subject requires CSL confirmation*
PPS = PPS-HI and CCI [redacted] *(until specifically mentioned)*

5. STATISTICAL ANALYSES

5.1. Demography

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

Demographic characteristics (age at first study vaccination in years, gender and Geographic Ancestry/ethnicity), 'time since previous HZ episode', age stratum and withdrawal status will be summarized by group using descriptive statistics:

Frequency tables will be generated for categorical variable such as age stratum, 'time since previous HZ episode' and gender.

Mean, median, Standard Deviation (SD) will be provided for continuous data such as age.

The analysis will be based on ES.

5.1.2. Additional considerations

- Demographic characteristics (age at first study vaccination in years, gender, ethnicity, and race), 'time since previous HZ episode' and age stratum will also be generated on mES, PPS-HI and CCI [redacted]
- The numbers of withdrawn subjects will be tabulated according to the reason for withdrawal on ES and mES.
- Number of subjects by country and center will be presented on ES.

The following table will be generated for web disclosure:

  - Percentage of Enrolled subjects by country will be tabulated by group,
  - Percentage of Enrolled subjects in the following age strata ≤64, 65-84, ≥85 YOA will be tabulated by group.

- Summary of important protocol deviations leading to elimination will be presented from Enrolled Set.
- The number of subjects enrolled into the study as well as the number of subjects excluded from PPS analyses will be presented through tables.

5.2. Exposure

5.2.1. Analysis of exposure planned in the protocol

None

5.2.2. Additional considerations

The number of doses administered will be tabulated on ES.

5.3. Analysis of incidence rate of Herpes Zoster recurrence

5.3.1. Analysis of incidence rate of Herpes Zoster recurrence planned in protocol

The primary analysis of incidence rate of HZ recurrence will be based on the mES. The same analysis will be performed on ES to complement the mES analysis.

5.3.1.1. Within group

For each group, the number of subjects, person-time, number of confirmed HZ cases and incidence rate will be tabulated from 30 days post the last vaccination until study end and from first study vaccination until study end on ES.

5.3.1.2. Between group

A formal non-inferiority analysis with a non-inferiority margin of 5 will be performed. Non-inferiority assessment will be carried out based on the fact that the distribution of two Poisson variates conditional on their sum is binomial [Lehmann, 1959]. Let n1 and n0 be the number of HZ recurrence cases, T1 and T0 (years) be total follow up, and r1 and r0 be the incidence rate in HZ/su group and placebo group respectively. It is assumed that ni ~ Poisson(λi) (i=0,1) and $\lambda i = Ti \times ri$, and condition on n=n0+n1, n1 ~ Binomial (n, p), where $p=\lambda 1/(\lambda 1+\lambda 0)$. A 95% exact CI for p can be derived by using Clopper-Pearson approach, through which a 95% exact CI for $\pi=r1/r0$ (that is, the ratio of incidence rate of HZ recurrence (HZ/su versus placebo)) can be derived. Non-inferiority is met if the upper limit of the 95% CI for π is below 5.

In addition to performing a formal non-inferiority analysis, to further quantify the likelihood of the risk increase of HZ following *Shingrix* vaccination, a probability curve that the ratio of incidence of HZ recurrence (HZ/su versus placebo) is higher than x-fold (x varying from 1 to 5) will be estimated by Bayesian methodology. It will be assumed that the number of HZ cases in the HZ/su and in placebo groups follows Poisson distribution with rate (incidence rate) of λ_{HZ} and λ_P respectively. We further assume that λ_{HZ} and λ_P are random variables both with non-informative Gamma prior distribution: Gamma (0.001, 0.001). Based on the posterior distribution of λ_{HZ} and λ_P, the probability curve of the ratio of incidence of HZ recurrence (HZ/su versus placebo), that is, $Pr(\lambda_{HZ}/\lambda_P > x|$ data, prior), can be calculated for each given value of x.

5.3.2. Additional considerations

For analysis for non-inferiority, only the first confirmed HZ episode will be considered. The non-inferiority will be assessed by following model and fitted via the PROC GENMOD procedure according to the following code:

```
PROC GENMOD data=XXX;
    CLASS group_nb(ref="Placebo") / param=ref;
    MODEL nb_cases = group_nb / dist=poisson offset=log_T link=log type3;
```

EXACT group_nb / estimate=odds;

ODS OUTPUT ExpExactParmEst=IRR;

RUN;

where,
nb_case = number of cases
Group_nb = Group information of the subject (treatment received by subject)
Log_T = Log of the follow-up time

Note: variables names may vary as per ADAM variables however their derivations remain the same.

The estimated rate ratio and its 95% CI will be provided in the output dataset IRR.

In extreme situations, when there are no confirmed HZ cases in the HZ/su group and > 0 confirmed HZ cases in the Placebo group, the EXACT computational algorithm used in SAS will run into difficulty and cannot provide accurate results. Therefore, the rate ratio (HZ/su versus placebo) will be set to 0. When there are no confirmed HZ cases in the Placebo group and > 0 confirmed HZ cases in the HZ/su group, the rate ratio is not estimable, instead the incidence rate and 95% CI in each treatment group will be reported.

- For Bayesian analysis, the number of HZ cases in the HZ/su and in placebo groups follows Poisson distribution with rate (incidence rate) of λ_{HZ} and λ_P, respectively. We further assume that λ_{HZ} and λ_P are random variables both with non-informative Gamma prior distribution: Gamma (0.001, 0.001). The posterior distribution of λ_{HZ} and λ_P will be Gamma distribution with parameter

  $\lambda_{HZ} \sim$ Gamma $(0.001 + case_{Hz}, 0.001 + T_{Hz})$ and

  $\lambda_P \sim$ Gamma $(0.001 + case_P, 0.001 + T_P)$

  where,

  $case_{Hz} =$ number of cases in HZ/su group

  $case_p =$ number of cases in placebo group

  $T_{Hz} =$ total follow-up time in years in HZ/su group

  $T_p =$ total follow-up time in years in placebo group

To estimate the probability of incidence rate ratio, simulation program will be run to generate sample from Gamma distribution using the function above.

The probability of incidence rate ratio greater than a specified value (e.g., 1, 2, 3, 4, 5) will be plotted against incidence rate ratio in graph.

In extreme situations, when there are no confirmed HZ cases in the HZ/su group or the Placebo group, the Gamma prior distribution will be updated to Gamma (0.015, 0.015), considering the minimum acceptable alpha in SAS is 0.015.

Considering the enrolment gap due to COVID-19, if data permit, the following sensitivity analyses will be conducted to explore between group comparisons to complement the analysis of primary endpoint:

- ***A sensitivity analysis comparing HZ incidence rates between HZ/su and placebo groups on adopted mES removing the participants who received a second dose more than 2 months after the first dose (outside of the original scheduled window receiving the second dose >83 days after the first dose).***
- ***A sensitivity analysis comparing HZ incidence rates between HZ/su and placebo groups stratified by enrolment pre- and post- recruitment interruption, using March 14th 2020 (the first day of site closure) as the cut-off date.***
- ***Kaplan-Meier curves to compare the onset time of HZ recurrences since receipt of the first and second assigned dose.***
- ***Moreover, if very different distribution between the HZ/su group and placebo group is presented, the Kaplan-Meier analysis on appropriate subintervals may also be performed.***

5.4. Immunogenicity

5.4.1. Analysis of immunogenicity planned in the protocol

The primary analysis will be based on the PPS for analysis of immunogenicity. If, in any group, the percentage of vaccinated subjects with serological results excluded from the PPS for analysis of immunogenicity is 5% or more, a second analysis based on the ES will be performed to complement the PPS analysis.

5.4.1.1. Humoral immune response

5.4.1.1.1. Within group assessment

The following descriptive analyses will be performed for each group and by age stratum (50-59 YOA; 60-69 YOA and ≥70 YOA) and by 'time since previous HZ episode' (≤4 years ago, 5-9 years ago, ≥10 years ago):

- Seropositivity rate at Day 1, Month 2 and Month 3 with exact 95% CI
- GMC at Day 1, Month 2 and Month 3 with 95% CI
- VRR (vaccine response rate) at Month 2 and Month 3 with exact 95% CI.

Descriptive statistics of the fold increase over pre-vaccination for anti-gE antibody concentration at Month 2 and Month 3 (Mean, SD, Min, Q1, Median, Q3, Max).

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5.4.2. Additional considerations

None

5.5. Analysis of safety and reactogenicity

5.5.1. Analysis of safety and reactogenicity planned in the protocol

The analysis will be performed on the ES. When appropriate, tabulations will be presented overall and by time of occurrence relative to last vaccination (e.g., using windows such as Days 1-7, Days 1-30 and more than 30 days post-vaccination). Safety analyses will also be performed by age stratum (50-59 YOA; 60-69 YOA and ≥70 YOA) and by 'time since previous HZ episode' (≤4 years ago, 5-9 years ago, ≥10 years ago).

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

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

- The proportion of subjects with at least one 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 proportion of subjects reporting each individual solicited local and general AE during the solicited 7-day-follow-up period will be tabulated with exact 95% CI.
- For all solicited AEs, the same tabulation will be performed for grade 3 solicited AEs and for solicited general AEs with relationship to vaccination
- The proportion of solicited AEs resulting in a medically attended visit will be tabulated.
- Total duration of each individual solicited local and general AE will be tabulated.
- The proportion of subjects reporting temperature by half degree (°C) cumulative increments. Similar tabulations will be performed for any fever with a causal relationship to vaccination and for any fever resulting in a medically attended visit.
- The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA system organ class (SOC) and preferred term (PT) and reported up to 30 days after each vaccination will be tabulated with exact 95% CI.
- The same tabulation will be performed for grade 3 unsolicited AEs (including serious AE) and for unsolicited AEs with a relationship to vaccination. The proportion of AEs resulting in a medically attended visit will also be tabulated.
- Total number/percentages of doses (per dose and overall) followed by AEs will be tabulated.
- All pIMDs and related pIMDs occurring from first vaccination up to 30 days post last vaccination will be tabulated.
- All pIMDs and related pIMDs occurring after 30 days post last vaccination until 1 year post last vaccination will be tabulated.
- All SAEs, related SAEs occurring from first vaccination up to 30 days post last vaccination will be tabulated.
- All SAEs, related SAEs occurring after 30 days post last vaccination until one year post last vaccination will be tabulated.
- Fatal SAEs will be tabulated using date of onset of SAE in the following manner – within Day 1-Month 3 (30 days post last vaccination), Day 1 to Month 14 (one year post last vaccination) and during the entire study period. Fatal SAEs will also be tabulated using the date of death within the same time periods.
- All SAE related to investigational vaccine, related to study participation or to GSK concomitant medication/vaccine occurring during the entire study period will be tabulated.
- AEs/SAEs leading to withdrawal from the study will be tabulated.
- CCI
- [redacted]

- CCI [redacted]

5.5.2. Additional considerations

Following additional tables will be generated:

- Number and percentage of subjects with at least one report of a grade 3 non-serious unsolicited AE during the 30-day (Days 1–30) follow-up period after each vaccination classified according to the MedDRA SOC and PT will be tabulated, with exact 95% CI. The same will be generated for grade 3 non-serious unsolicited AE considered related to vaccination.
- Listing of subjects with fatal SAE during the entire study period including the associated events will be generated on Enrolled Set.
- Listing of all SAEs up to end of study will be generated on Exposed Set.
- Listing of subjects with a suspected HZ episode, PCR final result and HZAC final result from first administered dose up to end of study will be generated on Exposed Set.
- Listing of (S)AEs and solicited adverse events leading to study or treatment discontinuation up to end of study will be generated on Exposed Set.
- Duration of each individual solicited local and general AE within the solicited follow-up period will be tabulated.
- ***COVID-19 infection cases identified during the study will be assessed as follows:***
  - ***Numbers and percentage of subjects with a suspected, probable or confirmed COVID-19 infection will be summarized by group based on ES.***
  - ***Number and percentage of subjects who had a COVID-19 infection reported as an AE or SAE will be summarized by group on ES.***
- ***Number and percentage of subjects who had a COVID-19 infection leading to study or treatment discontinuation be summarized by group on ES.***

6. ANALYSIS INTERPRETATION

The primary objective of non-inferiority of the incidence of HZ recurrence in the HZ/su and placebo groups is considered met if the upper limit of the 95% CI of the ratio of the incidence of HZ recurrence (HZ/su versus placebo) is below 5.

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

The ratio of incidence of HZ recurrence (HZ/su versus Placebo) calculated using Bayesian methodology will be a descriptive analysis to provide additional information about incidence rate ratio between Hz/su and Placebo based on simulated data with assumption provided (sections 5.3.1.2 and 5.3.2) of the SAP.

7. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in the study protocol will be described and justified in the final clinical study report (CSR).

7.1. Sequence of analyses

There will be only one final analysis at the end of the study.

A CSR containing all data will be written and made available to the investigators.

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

Description	Disclosure Purpose (CTRS=public posting, SR=study report, internal)
Final analysis	CTRS, SR

7.2. Statistical considerations for interim analyses

No interim analyses are planned.

8. CHANGES FROM PLANNED ANALYSES

Following are the changes from the planned analysis described in the protocol:

- Two new cohorts – Enrolled Set and Randomized Set have been defined as required for web disclosure and SAE tables presentation on Enrolled Set.
- The PPS population has been defined separately for the humoral immune response and CCI [redacted] for each timepoint.
- Evaluation of duration of unsolicited adverse event has been removed from endpoint as it is mistakenly added.
- The grading of fever (grade 1 and grade 2) has been changed from protocol to align with other studies in Zoster project. Refer to section 9.1.4 for grading of fever.
- Timeframe of fatal SAE reporting from Month 3 to study end is changed to Day 1 to study end.
- The definition of modified Exposed Set has been modified to exclude the subjects who has not received vaccination per protocol.

- ***For the primary endpoint, added a sensitivity analysis on mES after removing the participants who received a second dose more than 2 months after the first dose (outside of the original scheduled window), added a stratified analysis by recruitment interruption, and Kaplan-Meier curves to compare the onset time of HZ recurrences if applicable.***

- ***Added analysis to assess the impact of COVID-19 on safety.***

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 Personally 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.

9.1.2. Immunogenicity

9.1.2.1. Humoral immune response

- A seronegative subject is a subject whose Ab concentration is below the cut-off value.
- A seropositive subject is a subject whose Ab concentration is greater than or equal to the cut-off value.
- The seropositivity rate is defined as the percentage of seropositive subjects.
- The VRR for anti-gE Ab concentration is defined as the percentage of subjects who have at least:
  - a 4-fold increase in the post last vaccination anti-gE Ab concentration as compared to the pre-vaccination anti-gE Ab concentration, for subjects who are seropositive at baseline, or,
  - a 4-fold increase in the post last vaccination anti-gE Ab concentration as compared to the anti-gE Ab cut-off value for seropositivity, for subjects who are seronegative at baseline.
- The GMC calculations are performed by taking the anti-log of the mean of the log base 10 concentration transformations. For descriptive statistics only, Ab concentrations below the cut-off of the assay will be given an arbitrary value equal to half the cut-off for the purpose of GMC calculation.
- To assess the VRR and the percentages of subjects with fold increase for anti-gE antibody concentration/ CD4+/CD8+ T-cells at Month 2/Month 3, subjects who are part of both PPS immunogenicity (Month 2/Month 3) and PPS immunogenicity at Day 1 will be considered.

CCI

[redacted]

9.1.3. 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 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 4.5.2.2.1 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 4.5.2.2.2 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 recurrence 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.
- A 28-day pain-free period is used to confirm cessation of HZ-associated pain
- 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 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).

9.1.4. Safety

- For the analysis of CCI /HZ related complications/solicited AEs/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 20 of the protocol.
- The maximum intensity of local injection site redness/swelling will be graded as:

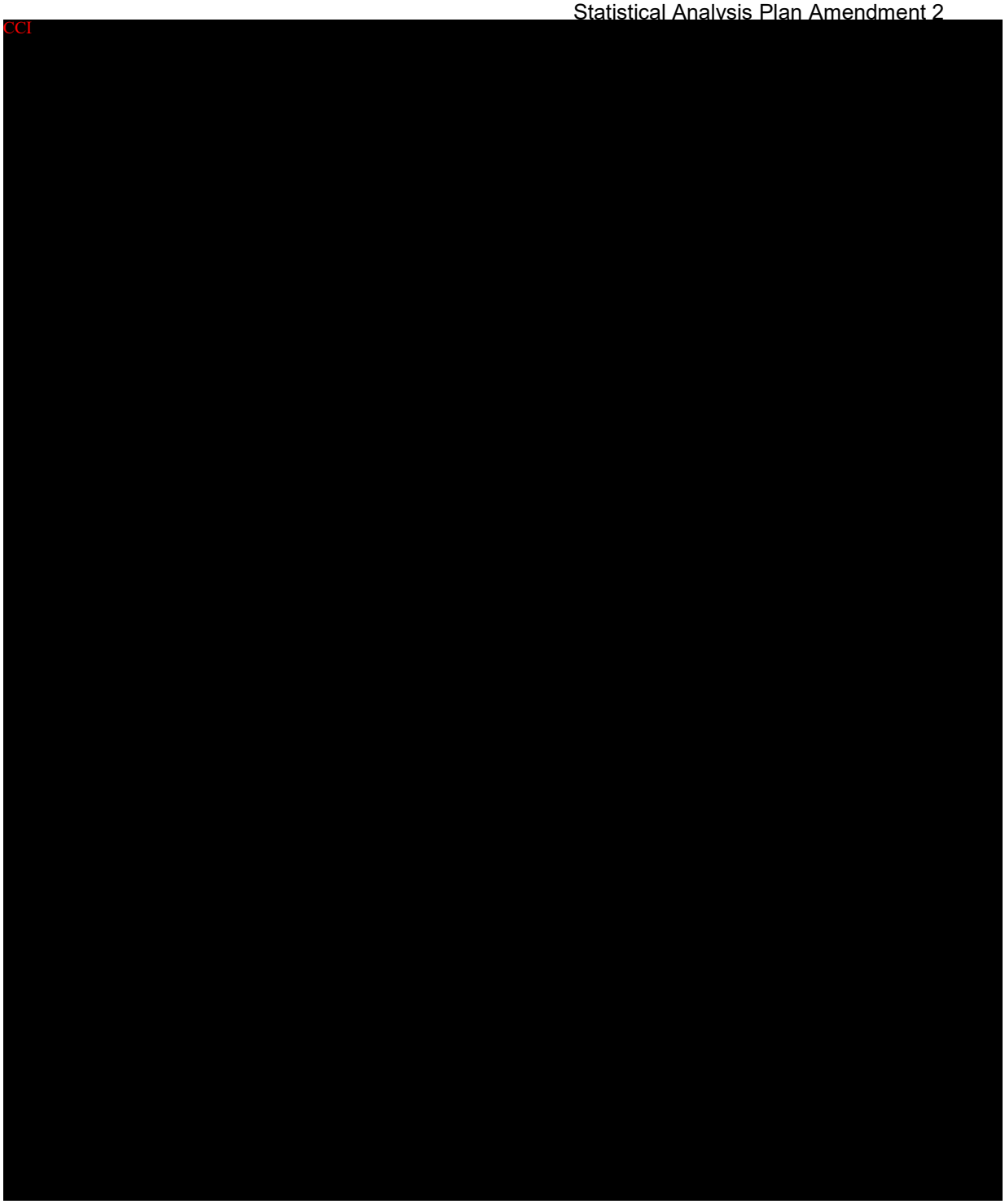
0	<20 mm diameter
1	≥20 mm to – ≤50 mm diameter
2	>50 mm to – ≤ 100 mm diameter
3	>100 mm diameter

- The fever grading to be considered for analysis will be:

0	<38.0°C
1	≥38.0°C – ≤38.5°C
2	>38.5°C – ≤ 39.0°C
3	>39.0°C

- CCI [redacted]. Severe 'worst' pain is defined as HZ-associated pain rated as 3 or greater on the "worst pain" question on the Zoster Brief Pain Inventory (ZBPI) questionnaire (see Sections 6.4.1 and 4.5.2.1 of the protocol). CCI [redacted]. The cases without severe "worst" pain (score ≥ 3) were considered as non-event case.
- CCI [redacted]

CCI



9.2. Statistical Method

9.2.1. HZ incidence

The number of HZ incidence is assumed to follow the Poisson distribution. The estimated incidence rate with 95% CI for both groups will be computed using following formula:

Incidence rate (per 1000) = Number of events*1000/Total follow-up period (in days) =n*1000/T

Exact LL of incidence rate = $\frac{X^2_{2n,\alpha/2}}{2T}$

Exact UL of incidence rate = $\frac{X^2_{2(n+1),(1-\frac{\alpha}{2})}}{2T}$

Where $X^2_{v,a}$ is the chi-square distribution quantile for upper tail probability on ν degrees of freedom, n is the number of events and T is the total follow-up time [Ulm, 1990]. Rule to derive the total follow-up period (in days) is provided in section 9.1.3 of the SAP.

9.2.2. Safety

The[redacted] and other HZ related complication is assumed to follow Poisson distribution and will be estimated for both the groups with 95% CI using the formula provided in the section 9.2.1 of the SAP.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

This section contains GSK Vaccines' 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 AE 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 vaccination. If 'after vaccination' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'before vaccination' 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:

- AE 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 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 month. If 'before vaccination' is selected, the imputed date will be one day before the first (or only) study dose given during that month.
- AE 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 paper diaries

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

Denominators for the summary of local (or general) solicited AEs will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of local (or general) AEs.

When a specific solicited AE is marked as having not occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=N for the specified post-vaccination period for the AE in question), all daily measurements will be imputed as Grade 0.

When a specific solicited AE is marked as having occurred following a specific vaccination (i.e. SDTM CE.CEOCCUR=Y for the specified post-vaccination period for the AE 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 AE summary tables.

When the occurrence of a specific solicited AE is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-vaccination period for the symptom in question) but the group of solicited AE (local or general) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all 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 AE summary tables.

The following table shows how subjects contribute to each category for a specific solicited AE over the Day X to Day Y post-vaccination period:

Solicited adverse event category	Subjects included in the calculation of the numerator
Any	All subjects 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 subjects 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 subjects 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 subjects with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

10.1.2.4. Unsolicited adverse events

Unsolicited AE summaries are including SAEs unless specified otherwise.

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

10.1.3. Data derivation

10.1.3.1. 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

10.1.3.2. 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
All other cases	missing

10.1.3.3. Geometric mean concentrations (GMCs)

Geometric Mean Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Antibody titres or concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off value is defined by the laboratory before the analysis and is described in the protocol.

10.1.3.4. Onset day

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

10.1.3.5. Duration of events

The duration of an event with a start and end date will be the number of days between the start and end dates 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 adverse event period.

10.1.3.6. Counting rules for combining solicited and unsolicited adverse events

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

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

10.1.3.7. Counting rules for occurrences of solicited adverse events

When the occurrences of solicited AEs 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. Also, in the case of co-administered study vaccines, an injection site reaction recorded for a subject following multiple vaccines will be counted as only one occurrence.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

10.1.4.3. Serological summary statistics

The number of decimals used when displaying GMC and their confidence limits is shown in the following table:

GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

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 TFL Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

11. REFERENCES

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