Statistical Analysis Plan Amendment 4

Study ID: 217895

Official Title of the Study: A Phase 1 randomized, dose escalation study to evaluate the safety, reactogenicity and immunogenicity of an mRNA-based monovalent influenza vaccine candidate in healthy younger and older adults.

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TITLE PAGE

Protocol Title: A Phase 1 randomized, dose-escalation study to evaluate the safety, reactogenicity and immunogenicity of an mRNA-based monovalent influenza vaccine candidate in healthy younger and older adults

Study Number: 217895

Compound Number: GSK4382276A

Abbreviated Title: FLU SV MRNA-003

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

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Clintrials.gov	Not applicable

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	03 May 2022	Clinical Study Protocol (15 April 2022)	Not Applicable	Original version
SAP amendment 1	15 June 2022	Clinical Study Protocol amendment 1 (19 May 2022)	Section 1.1, 1.2 Section 4.2.1.5 Section 5	Update due to protocol amendment
SAP amendment 2	11 October 2022	Clinical Study Protocol amendment 1 (19 May 2022)	**	Clarifications were added
SAP amendment 3	25 January 2023	Clinical Study Protocol amendment 3 (12 January 2023)	Section 1.2, Section 4.1.1, 4.2.1.3, 4.2.1.4, 4.2.1.5, 4.4.1 Section 8***	Update due to protocol amendment and clarifications added
SAP amendment 4	03 May 2023	Clinical Study Protocol amendment 4 (14 February 2023)	Section 1.2, 4.1.1, 6.2.2.3	Updated due to protocol amendment. Additional clarification for control group pooling. To align the grading of solicited symptom (swelling) to study protocol.

** Section 4.1.1: reference to ULOQ was removed as quantifiable value above ULOQ will be used. Section 4.4.1, clarification was given for CCI [redacted] endpoints, Section 4.2.2, clarification that interim analysis will be based on ES was added. Section 6.2.2.4, clarification on the management of missed daily severities in ediary for duration of solicited AE derivation. Section 6.2.2.4, clarification that AE summaries will exclude ongoing solicited AE beyond the solicited period.

*** Section 4.1.1: reference to analysis based on stratum encoded in SBIR at randomization was removed. The actual value will be used for analysis. Section 4.2.1.3 was updated to clarify how AESI are identified for summaries and section 8 was removed. Section 4.2.1.4 was updated to include few additional laboratory summaries. Section 4.2.1.5: the prior for age parameter in the BLRM was updated in line with the protocol amendment 3. Section 4.4.1: CCI [redacted].

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 217895. Details of the planned analyses to support the Safety Review Team (SRT), interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoint(s) and estimand(s)
Co-primary	
To evaluate the safety and reactogenicity profile of the study interventions	Solicited events: • Percentage of participants reporting each solicited administration site and systemic events within 7 days (i.e., from Day 1 to Day 7) after study intervention administration Unsolicited adverse events (AEs): • Percentage of participants reporting unsolicited AEs within 28 days (i.e., from Day 1 to Day 28) after study intervention administration. Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI*): • Percentage of participants reporting SAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration • Percentage of participants reporting AESIs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration Safety laboratory: • Percentage of participants reporting a shift from non-clinically significant laboratory value on Day 1 (pre-dose) to clinically significant abnormal laboratory value on Day 8 (post-dose) or on Day 29 (post-dose) for hematology, clinical chemistry, coagulation and urine analysis.
To evaluate the humoral immune response induced by the study interventions	CCI [redacted] antibody titer: • Geometric mean titers (GMT) at Day 1 and Day 22 • Geometric mean increase (GMI) from Day 1 to Day 22 • CCI [redacted] from Day 1 to Day 22 • CCI [redacted] at Day 22
Secondary	
To evaluate the humoral immune response induced by the study interventions	C [redacted] antibody titer: CI • GMT at Day 62 and Day 183 • GMI from Day 1 to Day 62 • GMI from Day 1 to Day 183 • CCI [redacted] at Day 62 and Day 183
CCI [redacted]	

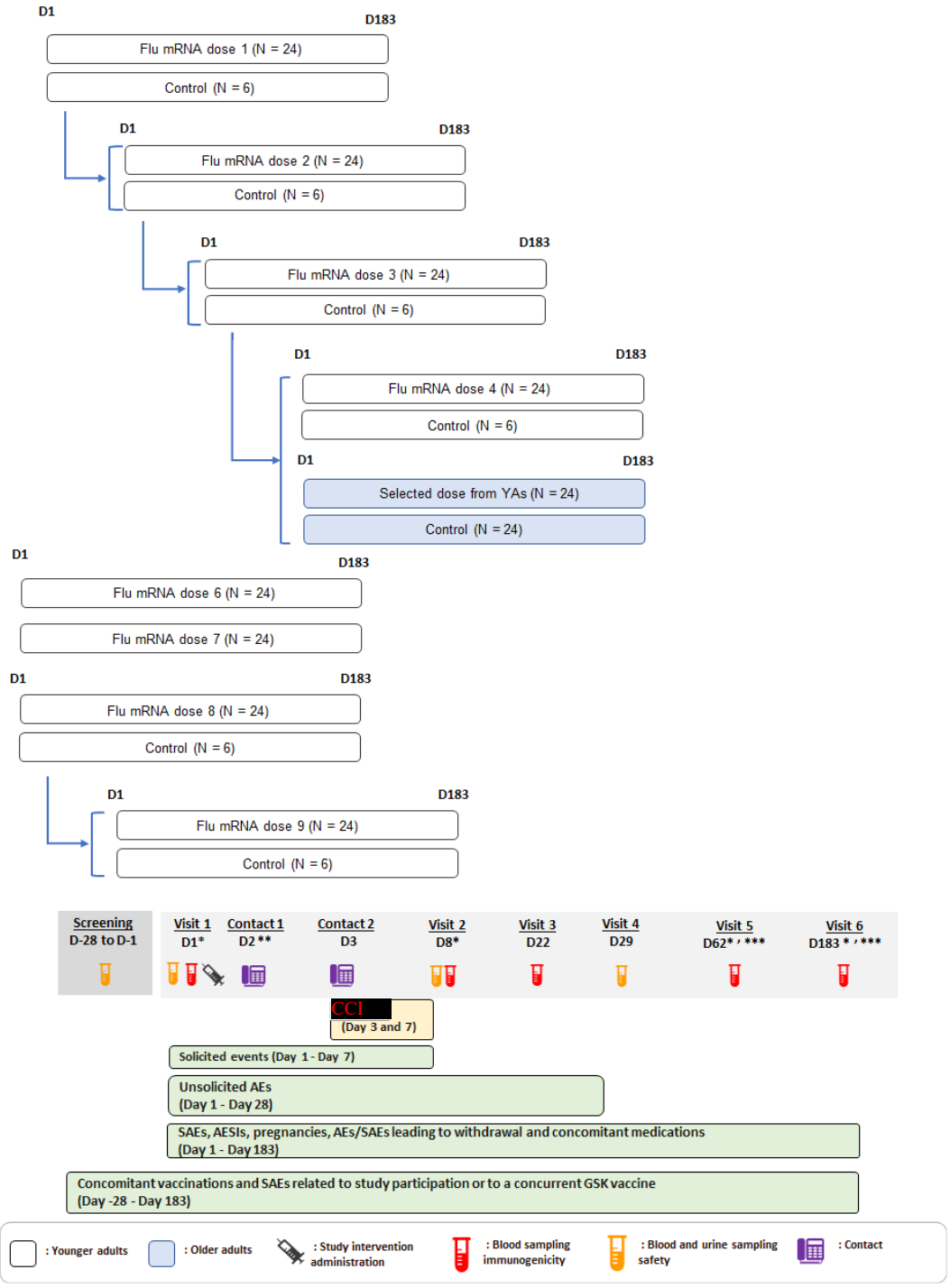
Objectives	Endpoint(s) and estimand(s)
CCI [redacted]	

CCI [redacted]

*Refer to Sections 4.2.1.1 and 4.2.1.3 for the list of solicited events and events considered as AESI, respectively.
** Note: for the CCI [redacted], and their potential intermediate dose cohorts (CCI [redacted]) no analysis for CCI [redacted] response will be performed, and humoral immune response determination will be limited to Day 1 and Day 22.

1.2. Study Design

Overview of Study Design and Key Features



AE: adverse event; SAE: serious adverse event; AESI: adverse event of special interest; D: day; CCI [redacted]; Control: Flu D-QIV (*Flu Dresden-Quadrivalent Influenza Vaccine*; GlaxoSmithKline; season 2021-2022, Northern Hemisphere [NH]). Northern Hemisphere [NH] for the CCI [redacted] dose cohorts, and season 2022-2023 NH for the CCI [redacted] dose cohorts, and their potential intermediate dose cohorts (C [redacted] CI); commercially available as α-RIX-Tetra in Belgium).

Overview of Study Design and Key Features

Doses of study intervention for YAs are coded as follows: dose 1: CCI, dose 2: CCI, dose 3: CCI, dose 4: CCI, dose 6: CCI, dose 7: CCI, dose 8: CCI, dose 9: CCI. Potential intermediate dose levels (CCI) may be evaluated with the total number of dose levels not exceeding 10 in YAs and 1 in OAs. In OAs, dose of study intervention will be selected based on safety/reactogenicity data up to dose 3 in YAs. Refer to Section 4.3 of the protocol for more information on rationale for addition of the CCI and their potential intermediate dose cohorts CCI) respectively. However, in YAs, 2 additional doses of CCI of the vaccine candidate will be tested (indicated as Flu mRNA dose 6 and 7). Refer to Section 4.3.2 of the protocol for rationale for addition of these doses.

* Blood sample for CCI will be collected from a subset of participants. CCI will be assessed in 50% of participants of each group (Flu mRNA and Control) to be enrolled at the selected sites.

** Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI dose cohort.

*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI and their potential intermediate dose cohorts (CCI). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.

Note: Each dose group consists of sentinel and non-sentinel participants, except for the CCI dose cohort.

Design Features

- First-Time-in-Human (FTiH) study with an adaptive design
- Study phase: 1
- Safety of and immune response to 1 formulation at different dose levels of study intervention will be assessed in YAs using an active controlled and dose escalation design. Unless safety concerns are identified by SRT after dosing sentinel participants, remaining participants at the current dose level will be administered the study intervention. SRT will also review data from all participants from a current dose level and advise on dosing of sentinel participants for the next dose level.
- Safety of and immune response to 1 formulation at 1 dose level of study intervention will be assessed in OAs using an active control. Unless safety concerns are identified by SRT after dosing sentinel participants, remaining participants at the current dose level will be administered the study intervention.
- For the additional CCI dose cohort, no sentinel participants will be enrolled; no dose escalation design applies; the CCI dose levels will be enrolled in parallel; no control vaccine will be used.

YA				OA			
Flu mRNA		Control		Flu mRNA		Control	
Sentinel participants N = 6/ group	Non-sentinel participants N = 18/ group	Sentinel participants N = 3/ group	Non-sentinel participants N = 3/ group	Sentinel participants N = 6/ group	Non-sentinel participants N = 18/ group	Sentinel participants N = 6/ group	Non-sentinel participants N = 18/ group

Note: No sentinel participants will be enrolled for the additional CCI dose cohort, hence all participants in that cohort will be considered as non-sentinel. No control vaccine will be used for the CCI dose cohort, where a randomization ratio of 1:1 will be applied between the CCI dose levels for a total of 48 participants.

Overview of Study Design and Key Features	
	• Staggered enrollment for CCI cohorts and their potential intermediate dose cohorts (CCI), refer to Sections 8.2.3.1 and 10 of the protocol for details. • Parallel enrollment for the CCI dose cohort. • Planned (approximate) number of participants to be enrolled is 306: • 258 YA participants (24 participants per dose level and a total number of 42 participants receiving the active control) • 48 OA participants (24 participants receiving a dose of investigational study intervention and 24 participants receiving the active control) • Due to the adaptive design, the actual number of participants enrolled might be lower than the target number or up to 336 participants in case a 10th dose level is evaluated in YAs. • Study groups: – 2 parallel groups, Flu mRNA versus Control in YAs – 2 parallel groups, Flu mRNA versus Control in OAs – For the CCI dose cohort: 2 parallel groups, Flu mRNA CCI versus Flu mRNA CCI in YAs. A CCI subset will be defined, where CCI will be assessed in 50% of participants of each group (Flu mRNA and Control) to be enrolled at the selected sites. Note: no CCI response will be assessed for the CCI and their potential intermediate dose cohorts (CCI). • Study type: primary vaccination • Level of blinding: for participants and investigators, the study will be observer-blind with regards to the study intervention, but open-label with regards to the dose level. For the sponsor, the study will be open-label. For the CCI dose cohort the study will be single-blind. • Multi-country, multi-center. However, sentinel participants will be preferably recruited at a single site. • Aspects of data collection: blood and urine samples, safety events, CCI • Intended duration of the study per participant: up to 8 months • Method of data collection: • Standardized Electronic Case Report Form (eCRF) • Solicited AEs, the occurrence of unsolicited AEs and responses to CCI will be collected using electronic Diary (eDiary) • Safety monitoring: refer to Section 8.2.3 of the protocol for the review of safety data by Safety Review Team (SRT).
Study intervention	• Study intervention: single dose intramuscular (IM) administration of different dose levels of the study intervention: – YAs: 1 formulation at 6 dose levels (CCI). Depending on the reactogenicity/safety findings after dosing with these dose levels, potential intermediate dose levels may be assessed (i.e., CCI). In any case, the total number of dose levels assessed will not exceed 10. Refer to Section 8.2.3.1 of the protocol for details on dose escalation management. – Two additional doses of CCI of the vaccine candidate will be assessed in YAs. Refer to Section 4.3.2 of the protocol for rationale for addition of these doses and CCI, and their potential intermediate dose cohorts respectively. – OAs: 1 formulation at 1 dose level (up to CCI The dose level will be selected after review by SRT of the safety/reactogenicity data obtained in YAs dose levels 1 to 3 (up to CCI

Overview of Study Design and Key Features	
	– Active control: Flu D-QIV (Flu Dresden- Quadrivalent Influenza Vaccine; GlaxoSmithKline; season 2021-2022, Northern Hemisphere [NH], commercially available as α-RIX-Tetra in Belgium) will be used as the active control for the CCI , and their potential intermediate dose cohorts in both YAs and OAs, while Flu D-QIV season 2022-2023 will be used as active control for the CCI , and their potential intermediate dose cohorts CCI). both YAs and OAs. No active control will be used for the CCI dose cohort.
Study intervention Assignment	Method of study intervention allocation: for each dose level and age group separately, randomization, using study, country, site and influenza vaccination history for the past 2 years as minimization factors for all participants • YA participants will be randomized to receive either 1 of the dose levels, or the active control • OA participants will be randomized to receive either 1 dose level or the active control. • For the CCI dose cohort, YA participants will be randomized to receive either the Flu mRNA CCI dose.
Interim Analysis	In addition to the analyses detailed below, safety analyses will be conducted to support SRT decisions as described in Section 4.5.1. Two initial interim analyses will be conducted upon availability of all primary endpoints up to Day 22 for YA participants in the CCI cohorts, respectively. An additional interim analysis will be performed upon availability of all primary endpoints up to Day 29 for all study participants. For these analyses, the GSK study team will have access to individual data while the investigator, participants and local staff will remain blinded.

2. STATISTICAL HYPOTHESES

There is no hypothesis testing in this study; where statistical methods are applied, the emphasis will be on estimation with 95% confidence intervals (CIs).

2.1. Multiplicity Adjustment

As this study is descriptive, no adjustment for type 1 error will be done.

3. ANALYSIS SETS

Analysis set	Description	Analyses Evaluated
Screened	All participants who were screened for eligibility	Screening failure
Enrolled	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study population
Exposed Set (ES)	All participants who received a study intervention. Analysis per group is based on the study intervention administered.	Safety, immunogenicity if applicable, demography
Per Protocol Set (PPS)	All eligible participants who received a dose of study intervention as per protocol, had CCI [redacted] results pre- and post-dose, without intercurrent conditions (influenza disease) that may interfere with immunogenicity and without prohibited concomitant medication/vaccination before Day 22. The analysis will be done according to the study intervention that participants received. Results from blood sample deviating from the dosing/blood draw intervals (refer to Table 2 of the protocol) as well as results obtained after intercurrent conditions (influenza disease) that may interfere with immunogenicity or after prohibited concomitant medication/vaccination during this period will be excluded from the PPS.	Immunogenicity, demography

Critical data missed or eliminated from PPS among the participants in the ES will be classified as important protocol deviation. Refer to Section 6.1.4 for details on protocol deviations.

4. STATISTICAL ANALYSES

4.1. General Considerations

All statistical analyses will be performed using SAS® software Version 9.4 or later.

Missing data will not be imputed unless mentioned otherwise (refer to Section 6.2.2).

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

Continuous data will be summarized using descriptive statistics (n, mean, standard deviation, median, interquartile range, minimum, and maximum). Categorical data will be summarized using the participant count and percentage for each category.

A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values.

The denominator for all percentages will be the number of participants with non-missing values of corresponding parameter in that study group within the analysis population of interest, unless otherwise specified.

Confidence intervals (CIs) will use 95% confidence levels.

For calculations regarding antibody levels/titers, antibody values reported as below a quantifiable threshold will be replaced by half the threshold while values above a quantifiable threshold will be assigned the value of the threshold.

Within each age group, analysis of the control group will be based on the pooled data of all participants randomized to Flu D-QIV. Note that even though in protocol amendment 4, the control was changed to FLU D-QIV 2022, the same strain of H1N1 contained in FLU D-QIV 2021 is used and so the control is considered to be the same and the participants will be continued to be pooled in the control group.

A table, figure, listing (TLF) is to be generated for any required item even where no data is available or reported. In such cases, except for table presenting percentage of participants which will show 0%, the table, figure, or listing will state: “No Data Reported”. This will confirm to the health authorities that all data for the tables, figures, listings, and narratives are accounted for.

4.1.2. Baseline Definition

Baseline will be defined as the last non-missing evaluation prior to study intervention administration, unless otherwise specified.

4.2. Primary Endpoint(s) Analyses

4.2.1. Safety Endpoints

Separate safety summaries will be produced for the different age group (YA and OA) populations.

4.2.1.1. Solicited AEs

Solicited AEs are prespecified as administration site and systemic. Solicited AEs will be collected within 7 days (Day 1 – Day 7) following the dosing using eDiary. For solicited AEs with onset within the 7-day solicitation period that continue beyond the 7-day period, the eDiary will remain open until Day 28 or until they are resolved, whichever occurs first, to allow further reporting.

The following solicited adverse events will be used to assess reactogenicity.

Solicited administration site events:

- Pain
- Redness
- Swelling

- Lymphadenopathy, defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the injection arm.

Solicited systemic events:

- Fever
- Chills
- Headache
- Fatigue
- Myalgia
- Arthralgia

Grading or actual temperature/redness and swelling will be captured in the eDiary as per a modified grading of symptoms based on the FDA toxicity grading guidance for industry [FDA, 2007] with Grades 3 and 4 combined (refer to Section 6.2.2.3). When available solicited AE information (e.g., occurrence, grading) collected by study staff when daily eDairy is missing/incorrect will be used in these summaries.

The percentage of participants reporting each individual solicited administration site event (any grade, Grade 2 or 3, Grade 3, medically attended events, ongoing after Day 7 and ongoing after Day 28) and solicited systemic event (any grade, Grade 2 or 3, Grade 3, medically attended events, events ongoing after Day 7 and events ongoing after Day 28) with onset within the 7-day follow up period (i.e., Day 1-Day 7 post-dose) will be tabulated for each group.

The duration of solicited AEs of any grade (see Section 6.2.1.9) will be summarized. The start date is the first day during the 7-day solicitation period with the symptom at grade > 0 while the stop date is the last day with the symptom at grade > 0 in or beyond the solicited period. In addition, the duration for specific grade(s) for each symptom defined as the number of days in the reporting period with grade above or equal to specific grade will be summarized.

Prolonged solicited AEs that continue beyond Day 7 or Day 28 will be identified using a flag in listing of AEs.

The number of completed eDiary days in the solicited period for a participant will be summarized by study group using frequency table.

4.2.1.2. Unsolicited AEs

An AE is any untoward medical occurrence in a participant after dosing and that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding or a serious AE), symptom, or disease temporally associated with the use of the study intervention, whether related to it or not. This definition includes exacerbations of pre-existing conditions. Stable pre-existing conditions which do not change in nature or

severity during the study are not considered AEs; however, these should be reported as part of the medical history at screening.

The verbatim reports of unsolicited AEs will be reviewed by a qualified person and the signs and symptoms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate preferred term (PT).

A study intervention causally related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". Investigators will not be required to assess the causality of solicited AEs if the onset is during the solicitation period.

The investigator will determine the causal relationship between the study intervention and the AE for all unsolicited AEs. The relationship of unsolicited AEs to the study intervention (Yes, No) will be captured in the eCRF.

The percentage of participants with any unsolicited AEs with onset within the 28-day follow up period (i.e., Day 1-Day 28 post-dose) with its exact 95% CI will be tabulated by group and by MedDRA PT and System Organ Class (SOC). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.

In the AE summaries, a participant with 2 or more AEs within the same SOC or PT level but different relationship will be counted only once in the level using the related incident.

4.2.1.3. Adverse Events of Special Interest

For adverse events of special interest (AESI) collected up to Day 183 (6 months), the following will be considered for the purpose of analyses:

- Severe hypersensitivity reactions within 24 hours after study intervention administration
- Pericarditis and myocarditis.

The summary of event characteristics will be provided for each AESI as well as any potential immune-mediated diseases (pIMDs), including number and percentage of participants with any event. In addition, summary will be provided by relationship to study intervention, maximum grade/severity, outcome, and the action taken. The worst-case approach will be applied at participant level for the maximum grade/severity, i.e., a participant will only be counted once as the worst case from all the events experienced by the participant. For action taken for an event, a participant will be counted once under each action.

The percentage of participants with at least 1 report of SAE (any, related, fatal and fatal related), and with at least 1 report of AESI respectively, classified by the MedDRA PT and SOC and reported from dosing up to study end and from Day 1 to Day 28 post-dose will be tabulated with exact 95% CI.

In the AESI/SAE summaries, a participant with 2 or more AEs within the same SOC or PT level but different relationship will be counted only once in the level using the related incident.

4.2.1.4. Laboratory Data

The following laboratory assessments will be performed:

Laboratory assessments	Parameters
Hematology	White Blood Cell (WBC) count with differential: Lymphocytes, Neutrophil, Eosinophils, Basophils, Monocytes Red Blood Cell (RBC) count Platelet count Hemoglobin Hematocrit
Clinical chemistry/Biochemistry	Creatinine, CRP, BUN, AST, ALT, cardiac troponin (Troponin I and/or Troponin T)
Coagulation	INR
Urinalysis*	Leukocytes, Blood, Proteins, Glucose, Ketones, Bilirubin, Urobilinogen, Nitrite, Specific gravity, pH

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; INR: international normalized ratio.
*Urinalysis will be done by dipstick.

Individual safety laboratory measurements for hematology, chemistry, coagulation, and urinalysis laboratory panel will be provided. All listings will include the age group, study group, participants ID, laboratory test name result, date and time of measurements, reference range, and flag for measurements that are outside the reference range.

Frequency table of normal range status (below, within, above) will be provided for each laboratory assessment/group and visit according to status at baseline.

Any clinically relevant laboratory results will be identified using a flag and these are reported as AE.

A by-participant listing will be provided for pregnancy test.

Refer to the section 4.2.1 for the analysis of participants reporting a shift from non-clinically significant laboratory value on Day 1 (pre-dose) to clinically significant abnormal laboratory value on Day 8 (post-dose) or on Day 29 (post-dose) for hematology, clinical chemistry, coagulation, and urinalysis. These events will be grouped according to MedDRA Classification.

In addition, frequency table of clinical relevance (Yes/No) will be provided for each laboratory assessment/group and visit according to status at baseline.

4.2.1.5. Analysis of Reactogenicity for Dose Escalation: Bayesian Logistic Regression Model (BLRM)

An adaptive BLRM guided by the escalation with overdose control (EWOC) principle will be used to inform the SRT on the dose escalation part of the study. The use of Bayesian response adaptive models for Phase 1 studies has been advocated by the European Medicines Agency (EMA) adopted guideline on small populations [EMA, 2006] and by Rogatko et al., 2007 [Rogatko, 2007] and is 1 of the key elements of the FDA's Critical Path Initiative.

The dose escalation will be based on a modified version of the 2-parameter BLRM described by Neuenschwander [Neuenschwander, 2008] and will account for all doses and age groups. The modification will be the addition of age-specific slope to account for a potential difference in safety profile between the 2 age groups. This approach allows the results of 1 age group to inform the decisions in the other group, which increases statistical power.

The BLRM is specified as follows:

$\text{logit}(p_i(d)) = \log(\alpha) + \beta_1 * \log(d/d^*) + \beta_2 * \text{age group}$

where

- $p_i(d)$ represents the probability of having a Grade 3 solicited event at dose d
- $\text{logit}(p) = \log(p/(1-p))$
- d^* = [redacted] is the reference dose
- α is the intercept parameter, it is equal to the odds of the probability of intolerance at d*.
- β_1 is a dose effect
- β_2 is age group effect.

The prior for α and β_1 is a mixture of 2 bivariate normal distributions:

1. 80% weight for minimally informative component: $\log(\alpha) \approx$ normal (mean= -1.516, var=1) and $\log(\beta_1) \approx$ normal (mean= -1.553, var=1), *a priori* assuming 10% and 18% Grade 3 solicited event rate at [redacted], respectively.
2. 20% weight for toxicity component: $\log(\alpha) \approx$ normal (mean= -0.708, var=1) and $\log(\beta 1) \approx$ normal (mean= -1.143, var=1), *a priori* assuming 15% and 33% Grade 3 solicited event rate at [redacted], respectively.

The age group parameter, $\beta 2$, will be assigned a half-normal prior, normal (mean = 0, var = 0.25) with $\beta 2 < 0$ to reflect a priori lower adverse reaction (AR) rate in the OA group.The variance will be set to 0.25 so that this component is minimally informative.

A zero covariance between priors is assumed.

This model was shown to be fit for purpose in the context of Phase I mRNA vaccine dose range [Walsh, 2020; Kremsner, 2021].

After at least 2 days of follow up of all sentinel participants, available safety data will be analyzed, the BLRM will be run and the posterior probability that the true Grade 3 solicited event rate in each dose level and age group lies in the following categories:

- 0% to <18%: targeted tolerance; and
- ≥18% to 100%: intolerance

will be computed.

Results will be provided to and reviewed by the SRT during scheduled meetings. The SRT will decide whether to allow the dosing of non-sentinel participants at the current dose level using the EWOC principle i.e., any dose of the study vaccine candidates that has more than a 50% chance of being in the intolerance category for an age group will not considered for the next dose administrations in that age group [Neuenschwander, 2008; Babb, 1998].

If obtaining favorable decision from SRT, non-sentinel participants at the current dose level will be dosed without restriction.

After 8 days of follow up of non-sentinel participants (Day 1 to Day 8 included), all safety data collected until this point (from both sentinel and non-sentinel participants) will be analyzed and the BLRM will be run. Note that when fitting the model after all participants in a dose level have been exposed, 0 events (#events) in the younger adults group will be replaced by 1 event; this is done to prevent results from being overinfluenced by rates of events (=0%) being on the boundary of the parameter space.

Results will be provided to and reviewed by the SRT during scheduled meetings. The SRT will decide whether to allow the initiation of dosing of new sentinel participants at the next higher (or intermediate) dose level (until the maximum dose level of [redacted] has been reached and/or a maximum of 8 dose levels have been tested in sentinel participants).

Section 10.8 of the protocol provides additional details on the model and hypothetical data scenarios.

4.2.2. Co-primary and Secondary Immunogenicity Endpoints

The analysis of immunogenicity will be performed primarily on the PPS. If 5% or more of the dosed participants with immunogenicity results are eliminated from the PPS at one timepoint, a second analysis will be performed on the ES. Immunogenicity analyses at interim will be based on the ES.

The group difference between the investigational study intervention and control group (pooled for YAs) will be assessed at each dose level separately as follows:

- At each post-dosing timepoint and in each age group separately, the 2-sided CI for group GMT ratio between Flu mRNA dose and (over) the control group (pooled across dose cohorts for YAs) will be derived from an ANCOVA model on $\log_{10}$ transformed concentration. The ANCOVA model will be based on the data from all age groups and will include group (i.e., each of the Flu mRNA doses and the (pooled) control group), country, flu vaccination history and log-transformed concentration at pre-dosing as fixed effects. The adjusted GMT and GMI in each group will be obtained from the same model with 95% CI. Missing data will not be replaced. Concentrations below the assay cut-off will be replaced by half the assay cut-off.
- For a given age group, the 2-sided 95% CI on group difference in CCI between a mRNA dose and (minus) the control group (pooled across dose cohorts for YAs) will be computed at Day 22 based on the method of Miettinen and Nurminen [Miettinen, 1985].
- The percentage of participants achieving CCI, defined as having post-dose CCI for CCI will be summarized by age group with associated exact 95% CI.

Although the ANCOVA model will be applied on the pooled data from both YA and OA groups when applicable, descriptive summaries will be produced by age and study groups.

Abbreviation/term	Definition
CCI GMI	The geometric mean of the ratios of the post-dose CCI over the Day 1 CCI
CCI	The percentage of dosed participants who have either a CCI pre-dose CCI and a post-dose CCI or a pre-dose CCI and at least a 4-fold increase in post-dose CCI.
	The percentage of dosed participants with a CCI.

GMI: geometric mean increase: CCI

The following SAS code will be used for computation of GMT ratio where AVAL and BASE are the log_{10} transformed GMC values at pre-dose and post-dose respectively, while country and vaccination history are the minimization factors at randomization:

```
PROC GLM DATA=immuno ALPHA=0.05;
    CLASS trt01a country vacchist;
    BY agecat strain;
    MODEL aval = trt01a country vacchist base;
    LSMEANS trt01a / CL;
RUN;
```

The CCI will be computed using the following SAS code where AVALC is the CCI status post-dose:

```
PROC FREQ DATA=immuno;
        BY agecat strain;
        TABLE trt01a*avalc / RISKDIFF (CL=MN) ALPHA=0.05;
RUN;
```

4.3. Secondary Endpoint(s) Analyses

The CCI titer for each strain on Day 62 and Day 183 will be assessed as follows:

- GMT at Day 62 and Day 183
- GMI from Day 1 to Day 62
- GMI from Day 1 to Day 183 and
- CCI at Day 62 and Day 183

4.3.1. Main Analytical Approach

The analyses of secondary endpoints will be performed as described in Section 4.2.2.

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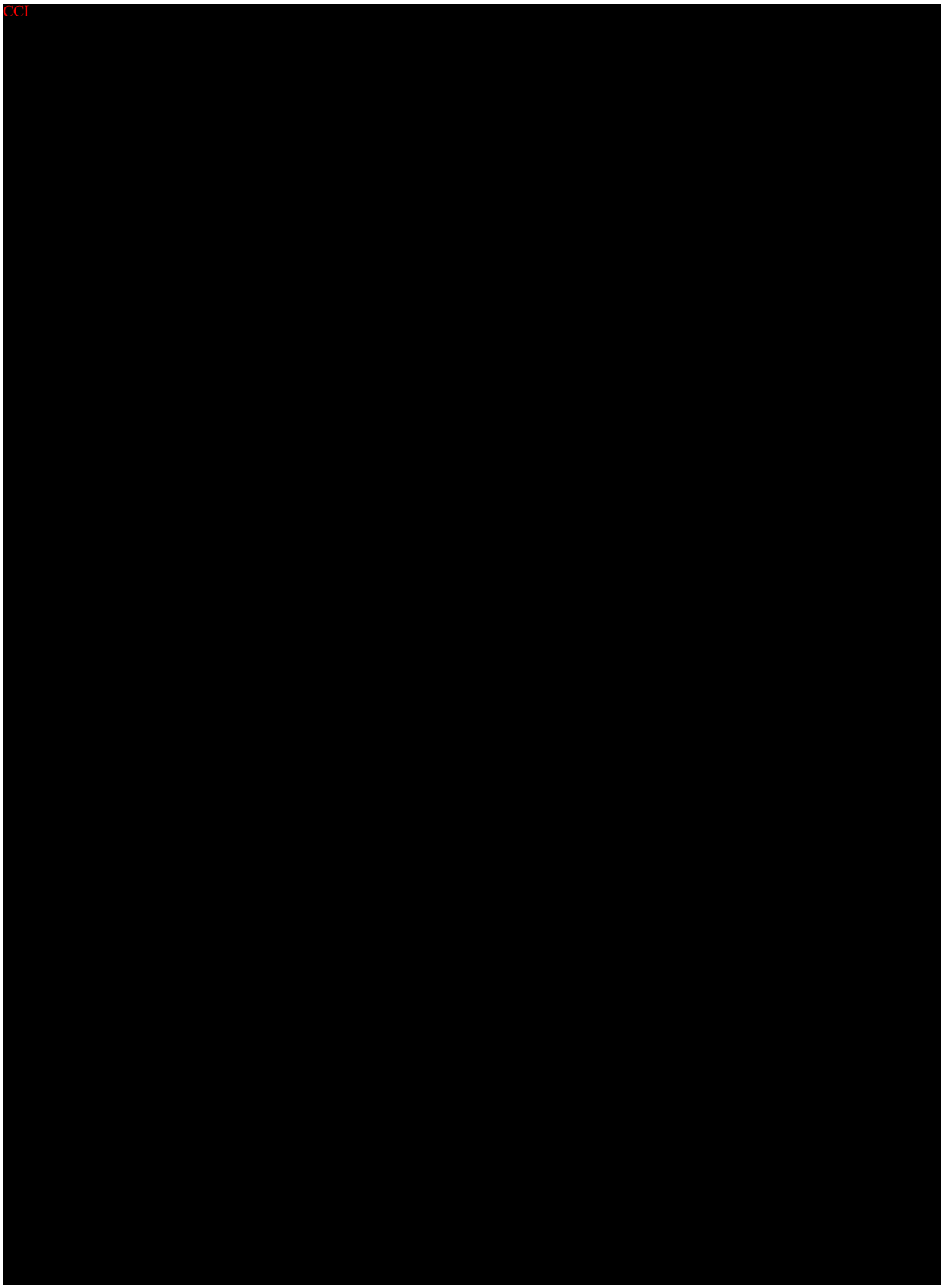

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[redacted]

4.5. Safety Analyses

Refer to Section 4.2.1.

4.5.1. Safety Review Team (SRT)

As the investigational vaccine will be administered to humans for the first time, an SRT will be appointed for the study.

The SRT will receive unblinded summaries of safety data that will be generated by the independent Data Analysis Centre (iDAC) who have access to the randomization scheme (see SRT charter for details). These unblinded summaries will include all results from the safety analysis by age and study group.

Study holding rules are presented in Table 1. If met, holding rules will trigger a hold of the study intervention administration. Holding rules 1a-1d will be monitored by the investigator on a continuous basis throughout the study and holding rules 2a-2c will be assessed during SRT safety review on unblinded data. Rule 2a relates to any Grade 3 solicited events in an investigational group, with an event onset within the 7-day (Day 1 to Day 7) post-dose period. The threshold of the holding decision is determined by a BLRM.

If a holding rule was met or safety signal observed during the SRT meeting, all dose administrations will cease immediately, but all other procedures relating to safety and immunogenicity assessments will continue. Following additional assessment by the SRT, a decision to continue, suspend or modify the conduct of the study will be taken by the committee.

In addition to the BLRM analysis, the following statistical analyses will be conducted on holding rules:

- Tabular listings for all holding rules together will be generated and include information on study group, participant number, holding rule, dose, and details including the severity grade, event outcome etc.
- Detailed listings on any event related to any holding rule will be generated for each holding rule
- Number and percentage of participants meeting each holding rule will be tabulated with exact 95% CI. This analysis will be done by group and after each dose.

Table 1 Study Holding Rules

Holding rule	Events, per dose and per individual study group	Number of participants to pause dosing in all groups, pending further evaluation by the SRT
1a	Death or any life-threatening **SAE** regardless of causality	≥ 1
1b	Any non-life-threatening **SAE** that cannot reasonably be attributed to a cause other than study intervention administration as per Investigator or Sponsor assessment	≥ 1
1c	Any **withdrawal** from the study (by investigator or participant request) due to a Grade 3 AE that cannot reasonably be attributed to a cause other than study intervention administration	≥ 1
1d	Any administration site or systemic solicited AE leading to **hospitalization**, or **necrosis** at the injection site, each with an event onset within the 7-day (Day 1-7) post-dosing period	≥ 1
2a	Any **Grade 3 solicited local or systemic AE** in an investigational vaccine group, within the 7-day (Day 1-7) post-dosing period	BLRM
2b	Any occurrence, in an investigational vaccine group, of a **Grade 3 unsolicited AE under the same High-Level Term** that cannot reasonably be attributed to a cause other than study intervention administration, within the 7-day (Day 1-7) post-dosing period	≥ 2
2c	Any **Grade 3 unsolicited** AE that can be reasonably attributed to the study intervention administration as per Investigator or Sponsor assessment, with an event onset within the 7-day (Day 1-7) post-dosing period OR Any **Grade 3** or above abnormality in pre-specified hematological or biochemical **laboratory parameters*** that are reported as AEs with onset within the 8-day (Day 1-8) post-dosing period	≥ 3

* Grading of laboratory parameters will be based on the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".

Rule 2a will be analyzed on a regular basis and reviewed during the scheduled SRT meetings to manage (i) initiation of dosing of non-sentinel participants at current dose level (ii) initiation of randomization of the sentinel participants at the next dose level in YAs (iii) initiation of randomization of the sentinel participants in OA age group (see Section 8.2.3.1 of the protocol). However, the model will only be run for planned SRT meetings in a specific age group for dose levels with at least 5 participants enrolled and followed for at least 48 hours. During these scheduled SRT meetings, the decision must be taken to allow randomization of the non-sentinel participants at the current dose level (see Section 8.2.3.1 of the protocol). The adaptive BLRM evaluates the posterior probability for the percentage of severe solicited events at the current and the next dose (Section 4.2.1.5). A greater than 50% posterior probability that the percentage is below the 18% (i.e., the maximal tolerable rate), will be favorable to progress with the current and next dose, when applicable.

4.6. Other Analyses

4.6.1. Subgroup Analyses

No subgroup analyses are planned.

4.7. Interim Analyses

In addition to the analyses detailed below, safety analyses will be conducted to support SRT decisions, as described in Section 4.5.1.

As this study is descriptive and each analysis will be completed on expected final immunogenicity data, there will be no type I error adjustment for the different analyses.

4.7.1. Sequence of analyses

Two initial interim analyses will be conducted upon availability of all primary endpoints up to Day 22 for participants in the CCI [redacted] cohorts, respectively. An interim analysis will be performed upon availability of all primary endpoints up to Day 29 for all study participants in the CCI [redacted] cohorts.

An additional interim analyses will be performed upon availability of all primary endpoints up to Day 29 for all study participants (i) all participants in the CCI [redacted] dose cohort, and (ii) all participants in the CCI [redacted], and their potential intermediate dose cohorts (CCI [redacted]).

For these analyses, the GSK unblinded statistical team will have access to individual data while the investigator, participants and local staff will remain blinded.

A final analysis including all primary and secondary endpoints obtained until the last visit (Visit 6 [Day 183]) will be performed and made available to the investigators and submitted to regulatory authorities, as appropriate.

Analysis of tertiary endpoints may be performed later and described in an annex report. Tertiary analyses deemed futile due to the other study results will not be analyzed, nor reported.

Note: If there is a delay in availability of the immunogenicity data, leading to a window between 2 analyses shorter than what is planned at the time of protocol writing, statistical analyses may be combined.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 14-FEB-2023).

5. SAMPLE SIZE DETERMINATION

5.1. Sample Size Determination for Reactogenicity and Safety

The study is designed to provide a reasonable precision for the rate of Grade 3 solicited events and to describe the safety profile of an mRNA-based monovalent seasonal influenza vaccine.

For each dose cohort, it is expected that up to 24 participants will be enrolled per age group. Assuming a maximum acceptable rate of Grade 3 solicited events of 18%, it is possible to calculate the probability of a lower true Grade 3 solicited event rate given a different number of participants with Grade 3 solicited event(s). Table 2 provides the estimate and 95% credibility interval for a given observed number of participants for a sample size of 24 participants per age group in a dose level cohort (assuming a Beta [0.5,0.5] prior distribution). For example, if 4 participants report Grade 3 solicited event(s) among 24 exposed participants, the posterior probability that the true Grade 3 solicited event rate is <18% is 54.5%.

Table 2 Posterior probability estimates of Grade 3 solicited event rate <18% for different observed numbers of participants with Grade 3 solicited event(s) and 95% credibility interval for the rate

Number of participants with Grade 3 solicited event(s)	Estimate (95% credibility interval) in %	Probability Grade 3 solicited event rate <18%
0	2 (0 - 9.8)	99.8
1	6 (0.5 - 17.9)	97.6
2	10 (1.8 - 24.1)	89.9
3	14 (3.6 - 29.7)	74.8
4	18 (5.9 - 34.9)	54.5

A further description of the BLRM, including prior, hypothetical data scenarios of number of Grade 3 solicited events that could occur in the actual study, and the decision guides are presented in Section 10.8 of the protocol.

5.2. Sample Size Determination for Immunogenicity

The primary objective is to explore how the different dose levels of mRNA-based monovalent seasonal influenza vaccine compare to standard of care control group.

The sample size is based on clinical considerations to inform dose regimen decisions for continued clinical development. With 24 participants in each dose level cohort and age group, a 10% unevaluable rate for immunogenicity results, and a standard deviation of 0.61 for log10-transformed titer, assuming that all doses will progress with enrollment, the ratio of the upper limit of a 2-sided 95% CI and the point estimate of the group GMT ratio between a mRNA dose level and the control group (pooled across dose cohorts for YAs) is 2.5.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Study Population Analyses

Unless specified otherwise, the study population analyses will be based on the enrolled set.

6.1.1. Screening Failure

A summary of the number and percentage of participants who failed screening will be provided along with the inclusion/exclusion criteria failed. This summary will be based on the screening set.

6.1.2. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for withdrawal will be summarized for the enrolled set.

6.1.3. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight, body mass index (BMI) (kg/m^2) on Day 1, race, country, and flu vaccination status in the past 2 years will be summarized with descriptive statistics. In addition, the following age categories will be summarized: 18-64 and 65-84 based on the Enrolled Analysis Set, ES and PPS.

6.1.4. Protocol Deviations

Important protocol deviations are a subset of protocol deviations (PDs) that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Important PD rules will be developed and finalized before database lock.

Important PDs include, but are not limited to, the following:

<u>All participant data is excluded from the PPS:</u>

- Study intervention not administered at all
- Invalid/missing informed consent
- Fraudulent data
- Participants got dosed but not as per protocol
- Study intervention storage temperature deviation which is not accepted by quality
- Expired study intervention administered
- Ineligible participant

Participant data collected on the day or after the event is excluded from the PPS:

- Influenza disease infection
- Administration of concomitant vaccine(s) forbidden in the protocol
- Administration of any medication forbidden by the protocol, namely administration during the study period of investigational or non-registered product (drug, vaccine or invasive medical device) other than the study intervention, of long-acting immune-modifying drugs or of immunoglobulins and/or any blood products or plasma derivatives with the exception of monoclonal antibodies specifically directed against the spike protein of SARS-CoV-2 virus, for treatment of COVID-19 disease

Participant lab data collected on the day of the event is excluded from the PPS:

- Participants did not comply with blood sample schedule (see Table 3)
- CCI [redacted] results not available pre- and post-dose
- Serological results available but results unreliable (e.g., wrong blood sample management)

The number of participants with important protocol deviations will be summarized by study group across time points and at Day 22 and Day 183. Important protocol deviations will be listed with date of occurrence, deviation description, and analysis set from which participant is excluded. Important protocol deviation summary will be based on the Enrolled Set.

The important PDs will be reported in the Clinical Study Report (CSR) for the ES while the important PDs leading to elimination from the ES will be summarized for the Enrolled Set.

Table 3 Intervals between study visits

Interval	Planned contact interval	Allowed interval range
Screening* → Visit 1	1-28 days	1 – 28 days
Visit 1 → Contact 1**	20 hours	18-24 hours
Visit 1 → Contact 2	2 days	2 days†
Visit 1 → Visit 2	7 days	6-8 days
Visit 1 → Visit 3	21 days	20-24 days
Visit 1 → Visit 4	28 days	26-35 days
Visit 1 → Visit 5***	61 days	54-68 days
Visit 1 → Visit 6***	182 days	168-196 days

* Screening visit should take place within 28 days before Visit 1, with sufficient time to receive/review the hematology, biochemistry, coagulation and urinalysis results. When applicable, a re-screening visit (including blood and urine sample collection, physical examination and re-checking of inclusion/exclusion criteria) may be scheduled at any time (but only once to assess eligibility) before Visit 1. All screening procedures need to be performed within 28 days before Visit 1. Only laboratory results from the re-screening visit, if it occurs, will be taken into consideration. The participant can only be randomized once the investigator receives the results and confirms the eligibility criteria.

** Contact 1 (Day 2) will be performed for sentinel participants only. Note that no sentinel participants are included for the CCI dose cohort.

*** Visit 5 (Day 62) and Visit 6 (Day 183) will be replaced by a contact if participant have received the standard of care vaccination against seasonal flu prior to this visit and did not report any adverse events that would require physical examination on site. Note: No blood sampling will be performed at Day 62 and Day 183 for the CCI , and their potential intermediate dose cohorts (CCI). As such, Visit 5 and Visit 6 will be replaced by a contact for all participants in these cohorts unless they reported any adverse events that would require physical examination on site.

† For non-sentinel participants, the allowed interval ranges from 1 to 3 days.

6.1.5. Concomitant Medications

Concomitant medications are defined as any medications and vaccines (other than study intervention) taken after the study intervention administration. Any medication or vaccine (other than study intervention) started prior to the study intervention administration and continued after the study intervention administration will be considered an concomitant medication.

Concomitant medications/vaccinations will be coded using both the GSK Drug and WHO Drug dictionaries and will be listed and summarized descriptively (any medication, any antipyretic, and any antipyretic taken prophylactically, respectively) by study group using the ES.

The antipyretic classification is derived from the following ATC code

ATC Code
A03D, A03DA, A03DB, A03DC, A03EA
M01, M01A, M01AA, M01AC, M01AE, M01AG, M01AB, M01AH, M01AX, M03B, M03BA, M03BB, M03BB, M03BC, M03BX
N02BG, N02AC, N02AG, N02AX, N02B, N02BA, N02BB, N02BE
R05, R05D, R05X

The percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 28-day follow up period (i.e., Day 1-Day 28 post-dose) will be summarized by group.

6.2. Appendix 2: Data Derivations Rule

6.2.1. Data derivation

6.2.1.1. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

6.2.1.2. Height

Height will be presented in centimeters. Heights reported in feet and inches will be converted as follows:

Height in centimeters = Height in inches x 2.54

6.2.1.3. Body Mass Index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

6.2.1.4. 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

6.2.1.5. 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
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

6.2.1.6. Geometric Mean Titres (GMTs) and Concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Non quantifiable antibody titres or concentrations will be converted as described in Section 6.2.1.5 for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

6.2.1.7. Onset Day

The onset day for an event (e.g., AE, concomitant medication/vaccination) is the number of days between the study dose administration 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).

6.2.1.8. Study Day

Study day will be calculated as follows:

a. Study day prior to dosing will be calculated as: date of assessment – date of the study intervention administration

b. Study day on or after the date of the dosing will be calculated as: date of assessment – date of the study intervention administration + 1

6.2.1.9. Duration of Events

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

For any grade, duration of solicited AE is defined as Start date – Stop date + 1, with Start date defined as the first day with the symptom at Grade ≥ 0 within the 7-day solicitation period and Stop date defined as the last day with the symptom (i.e., Grade > 0) in or beyond the solicited period. For solicited AE continuing beyond Day 28, stop date will be assigned the end of study.

6.2.1.10. 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 1 occurrence regardless of the number of days on which it occurs.

6.2.1.11. AESIs

GSK MedDRA queries will be used to identify AESI:

- PIMD: refer to Table 23 from the protocol
- Severe hypersensitivity (including anaphylaxis): Grade 3 unsolicited AEs under MedDRA SMQ hypersensitivity, narrow search (includes anaphylaxis), with an onset within 24 hours after dosing
- Myocarditis/Pericarditis. In addition to identification based on the medical and scientific judgement of the investigator, the following non-exhaustive list of PTs will be used: Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Autoimmune pericarditis, Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

This PIMD, Myocarditis and Pericarditis queries may be revised based on MedDRA dictionary.

AESI summaries will include AE identified by either the investigator or the MedDRA quesries.

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.
- For stop date, the maximum between the start and imputed stop date by above rule will be used instead.

The following exceptions apply:

- Adverse events start dates with missing day:
  - If the event starts in the same month as the study dose administration then the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after study dose) will be used to complete the date. If 'after study dose' is selected, the imputed start date will match the study dose given during that month. If 'before study dose' is selected, the imputed date will be one day before the study dose given during that month.
- Adverse events start dates with missing day and month:
  - If the event starts in the same year as the study doses, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after study dose) will be used to complete the date. If 'after study dose' is selected, the imputed start date will match the study dose given during that year. If 'before study dose' is selected, the imputed date will be one day before the study dose given during that year.
- Adverse events stop dates with missing day: the last day of the month or the last contact date will be used, which ever come first.
- Adverse events stop dates with missing day and month: the last day of December or the last contact date will be used, which ever come first.
- Adverse events stop dates with missing day, month, and year: the last contact date will be used.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

6.2.2.2. Laboratory Data

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

Hematology/chemistry laboratory data requiring grading as per FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials the laboratory results (see table below) may have more decimals than expected or may require conversion to the unit associated to the grade leading to more decimals than expected (e.g., Calcium results may be 7.91).

To determine the grading, the following rule will be used:

1. In case a conversion is needed, the original results will be used for the conversion without a previous rounding.
2. The result expressed in the expected unit will be rounded to the number of decimals used for the grading (e.g., 1 decimal will be used for Calcium and therefore 7.91 will be rounded to 7.9 and Grade as 2).

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Blood Urea Nitrogen (BUN) mg/dL	23 – 26	27 – 31	> 31
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	> 2.0
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5. 0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
**ULN is the upper limit of the normal range.
For CRP and Cardiac Troponin, standard grading is not available. Clinically significant abnormality will be recorded and graded as AE.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
WBC increase - cell/mm3	10,800 – 15,000	15,001 – 20,000	> 20,000
WBC decrease - cell/mm3	2,500 – 3,500	1,500 – 2,499	< 1,500
Lymphocytes decrease - cell/mm3	750 – 1,000	500 – 749	< 500
Neutrophils decrease - cell/mm3	1,500 – 2,000	1,000 – 1,499	< 1000
Eosinophils - cell/mm3	650 – 1500	1501 - 5000	> 5000
Platelets decrease - cell/mm3	125,000 – 140,000	100,000 – 124,000	<100,000
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0

WBC: white blood cells
* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
For Hematocrit, Basophil & Monocyte, standard grading is not available. Clinically significant abnormality will be recorded and graded as AE.

Coagulation	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
INR	> 1.2-1.5 x ULN >1-1.5 x baseline if on anti-coagulants	>1.5-2.5 x ULN >1.5-2.5 x baseline if on anti-coagulants	>2.5 x ULN >2.5 x baseline if on anti-coagulants

6.2.2.3. Daily Recording of Solicited Events

For studies **using electronic diaries** for the collection of solicited events, a solicited event will be considered present only when a daily recording of Grade 1 or more is present. To determine the grading, the following rule will be used:

Local reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Mild: Any pain neither interfering with nor preventing normal everyday activities.	Moderate: Painful when limb is moved and interferes with everyday activities.	Significant pain at rest. Prevents normal everyday activities.
Redness *	25 – 50 mm	51 – 100 mm	>100 mm
Swelling **	25 – 50 mm	51 – 100 mm	> 100 mm
Lymphadenopathy***	Does not interfere with activity	Interferes with normal activity	Prevents normal activity

* For redness and swelling, in addition to grading the measured administration site reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
*** Defined as localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the administration arm.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C) * (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	>38.9 >102.0
Headache	Headache that is easily tolerated	Headache that interferes with normal activity	Headache that prevents normal activity
Fatigue	Fatigue that is easily tolerated	Fatigue that interferes with normal activity	Fatigue that prevents normal activity
Myalgia	Myalgia present but does not interfere with activity	Myalgia that interferes with normal activity	Myalgia that prevents normal activity
Arthralgia	Arthralgia present but does not interfere with activity	Arthralgia that interferes with normal activity	Arthralgia that prevents normal activity
Chills	Chills present but do not interfere with activity	Chills that interfere with normal activity	Severe: chills that prevent normal activity

* Axillary temperature.

6.2.2.4. Unsolicited Adverse Events

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

For the summary of unsolicited adverse events, ongoing solicited events reported as unsolicited AEs will not be counted.

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

6.2.3. Display of Decimals

6.2.3.1. Percentages

Percentages and their corresponding confidence limits will be displayed with 1 decimal except for 100%, in which case no decimal will be displayed.

6.2.3.2. Differences in Percentages

Differences in percentages and their corresponding confidence limits will be displayed with 2 decimals.

6.2.3.3. Demographic/Baseline Characteristics Statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, BMI, pre-dose body temperature) will be presented with 1 decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height/weight variables will be displayed without decimals.

The maximum and minimum of transformed body temperatures will be displayed with 1 decimal.

6.2.3.4. Serological Summary Statistics

The number of decimals used when displaying GMT or GMC and their confidence limits is assay specific based on the magnitude of the assay result post-dose and the clinically relevant assay threshold. The same number of decimals will be used for a given assay regardless of the timepoint presented.

GMT/GMC fold increase from pre-dose follows the same principle. Namely, when the lowest clinically relevant threshold is 2-fold, 2 decimals are displayed while when the lowest clinically relevant threshold is 4-fold, 1 decimal is displayed.

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

6.2.4. Statistical Methodology

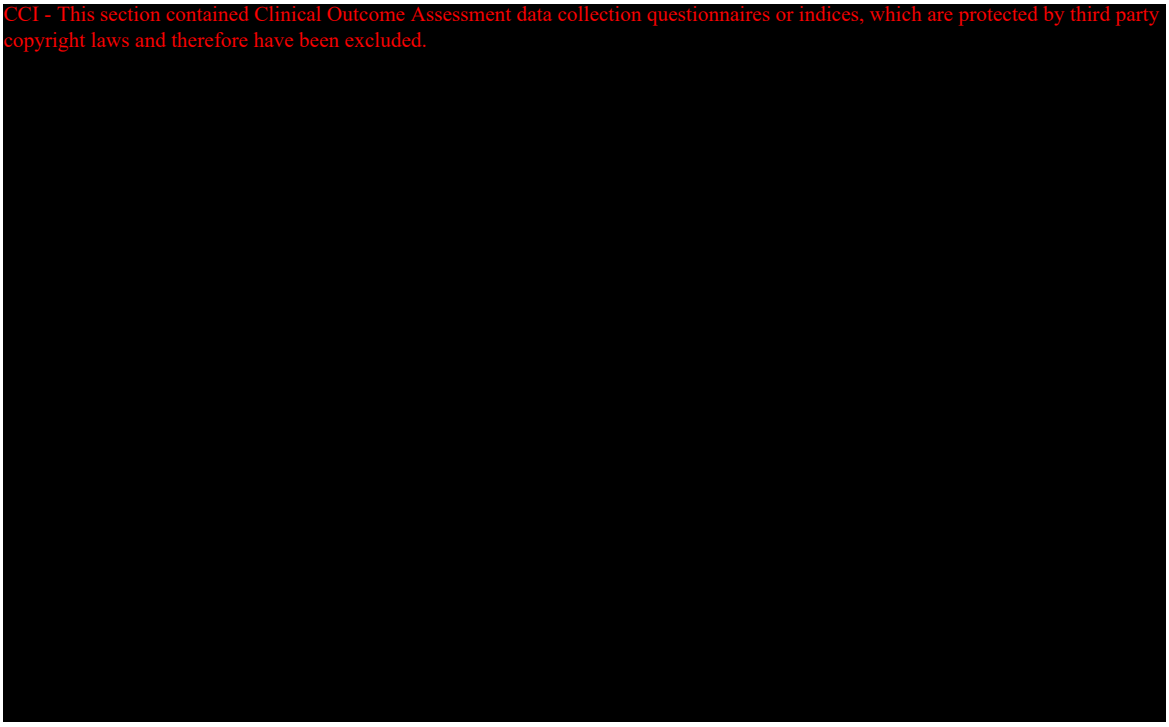
6.2.4.1. Exact Confidence Intervals around Proportions

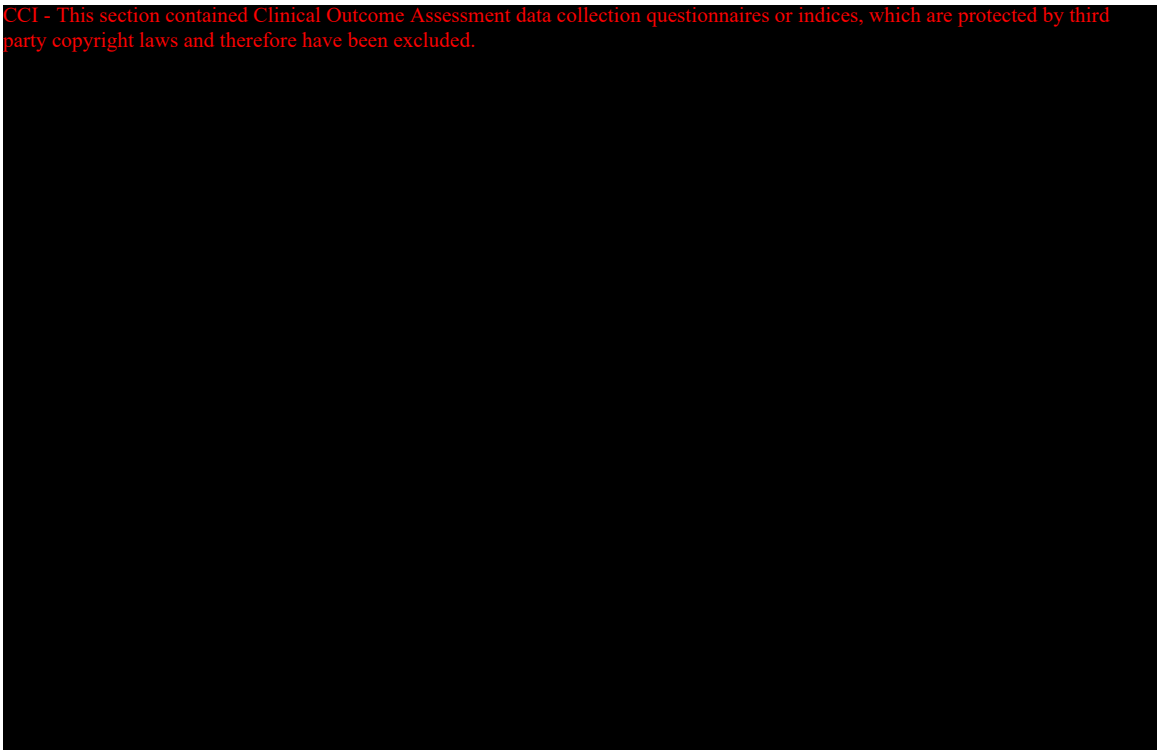
The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

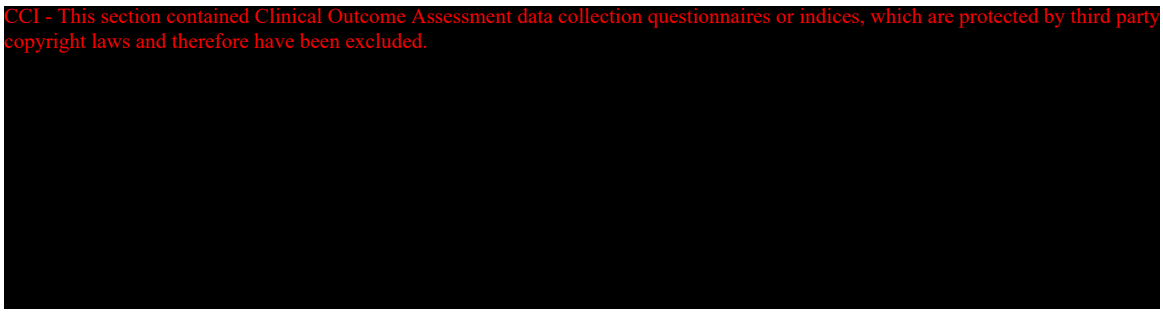
6.2.4.2. Standardized Asymptotic Confidence Intervals Around Differences in Proportions

The standardized asymptotic confidence intervals around differences in proportions are derived using the method of Miettinen and Nurminen. [Miettinen, 1985]

6.2.5. Reactogenicity Questionnaire







Instructions – General Principles of Scoring

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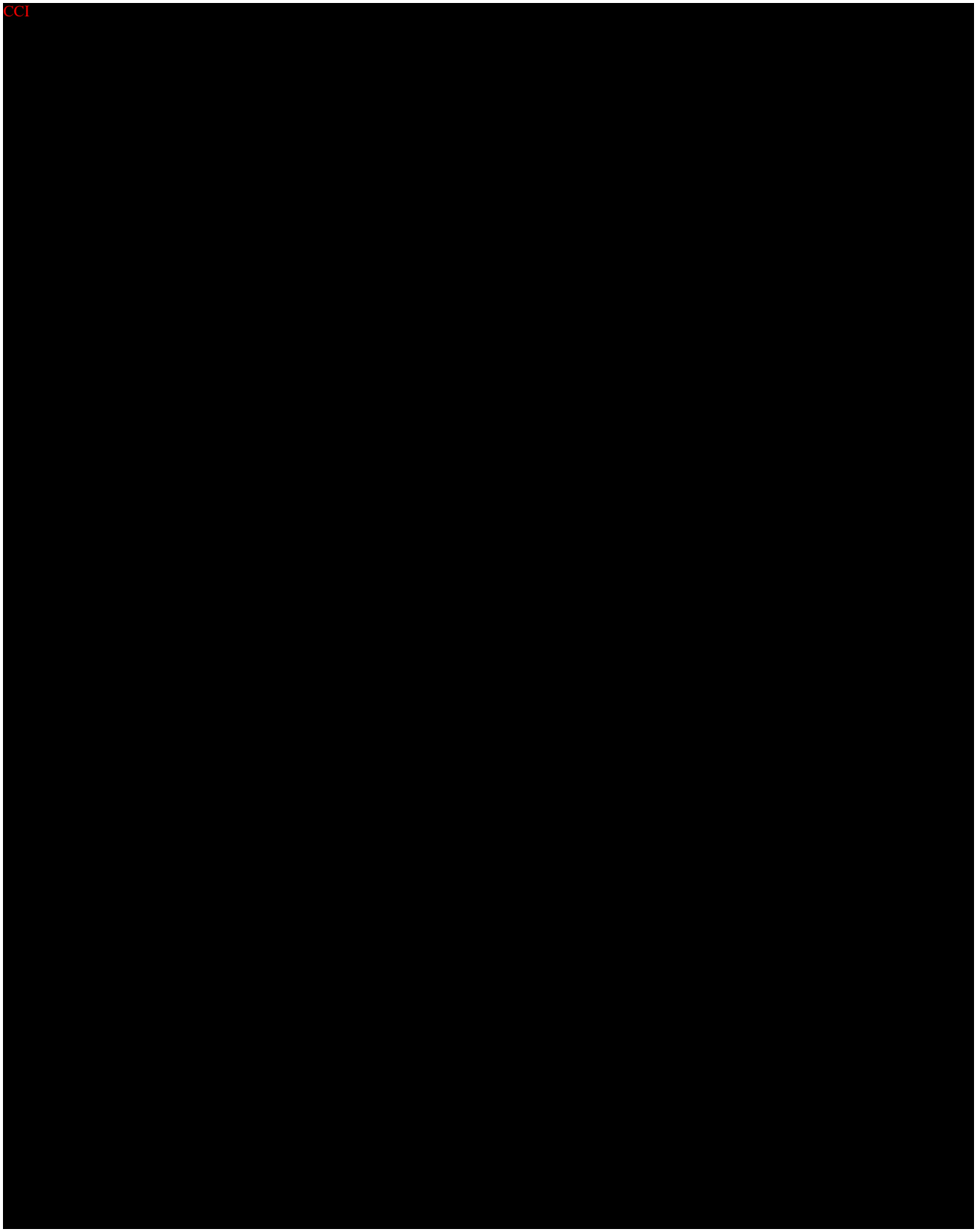

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6.2.6. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
Flu D-QIV

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