Statistical Analysis Plan Amendment 4

Study ID: 217884

Official Title of Study: A Phase 1/2, randomized, dose-finding/dose confirmation study to evaluate the reactogenicity, safety and immunogenicity of mRNA-based multivalent seasonal influenza vaccine candidates administered in healthy younger and older adults

NCT number: NCT05823974

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TITLE PAGE

Protocol Title: A Phase 1/2, randomized, dose-finding/dose confirmation study to evaluate the reactogenicity, safety and immunogenicity of mRNA-based multivalent seasonal influenza vaccine candidates administered in healthy younger and older adults

Study Number: 217884

Compound Number: GSK4382276A

Abbreviated Title: FLU SV MRNA-002

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s) Not Applicable

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Clintrials.gov	NCT05823974

Statistical Analysis Plan (SAP) Template v3.0 14 September 2022

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	01 March 2023	Clinical Study Protocol (02 February 2023)	Not Applicable	Original version
SAP Amendment 1	13 April 2023	Clinical Study Protocol amendment 1 (07 April 2023)	Sections 1.1, 1.2, 4.5.1 Sections 4.2.1.5, 4.8, 6.2.2.2*	Update due to protocol amendment
SAP Amendment 2	20 June 2023	NA	Sections 6.2.2.3, 4.8, 4.4, 6.2.1.10 1.1**	
SAP Amendment 3	27 July 2023	NA	Section 3, 4.2.2, 4.4***	
SAP Amendment 4	30 Jan 2024	Clinical Study Protocol amendment 2 (28 Aug 2023)	Section 1.2, 3, 4.2.1.5, 4.5.1, 4.7, 5.2 Section 1.1.1, 4.1, 4.2.1.1, 4.2.2, 4.8, 6.1.3, 6.1.4****	Update due to protocol amendment

* Section 4.2.1.5: The BLRM was updated to account for the CCI [redacted] components of the mRNA vaccine compositions; Section 4.8: Updated to indicate the deviation from

protocol due to the change to the BLRM and CCI testing; Section 6.2.2.2: Conversion factors added to Table 7 and Table 8.

** Section 6.2.2.3: To align the grading of solicited symptom (swelling) to study protocol; Section 4.8: Updated to indicate the deviation from protocol limiting CCI testing to some groups; Section 4.4: Updated to reflect the addition of neutralization titers assessments using MN assay for H3N2 in Phase 1; Section 6.1.1.10: Updated to provide further clarification on occurrence count; Section 1.1 and 4.4: Correction of immunogenicity readouts by removing 'antibody'.

*** Section 3: Clarification of criterion on availability of immunogenicity result for PPS; Section 4.2.2: Addition of LLOQs for assays used in the study; Section 4.4: The addition of LLP for Elispot assay and additional clarification on how values below LLP are used.

****Section 1.1.1: Addition of estimands table; Section 4.1: Updated to reflect the analysis of participants randomized in the wrong age stratum; Section 4.2.1.1: Clarification of the summarization of solicited AEs and addition of summary by category; Section 4.2.2: Added assays and cut-offs for Phase 2; Section 5.2: updated to reflect the actual unevaluable rate and half-width used in Phase 2 sample size computation; Section 4.8: updated to reflect changes in Section 5.2; Section 6.1.4: Age category added to reflect Phase 2 design; Section 6.1.4: updated to reflect protocol amendment and an additional protocol deviation leading to exclusion from PPS.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 217884. Details of the planned analyses to support the Joint Safety Review Team (SRT), internal Safety Review Committee (iSRC) and internal Data Review Committee (iDRC), interim analysis, as well as the final analyses, are provided.

1.1. Objectives, Estimands and Endpoints

Table 1 Objectives and endpoints

Objectives	Endpoints (population summary)
Co-primary	
To evaluate the safety and reactogenicity profile of the investigational study intervention	Solicited events*: • Occurrence of solicited administration site and systemic events within 7 days (i.e., from Day 1 to Day 7 included) of study intervention administration (percentage of participants). Unsolicited AEs*: • Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28 included) after study intervention administration (percentage of participants). SAEs*, AESI* and MAEs: • Occurrence of SAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants) • Occurrence of AESIs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants) • Occurrence of MAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants). For participants in Phase 1: Safety laboratory: • Shift from a non-clinically significant laboratory value on Day 1 (pre-dose) to a clinically significant abnormal laboratory value on Day 8 (post-dose) and/or Day 29 (post-dose) for hematology and clinical chemistry (percentage of participants).
To evaluate the humoral immune response induced by the investigational study intervention	• CCI [redacted] at Day 29 (GMT) • Fold increase in CCI [redacted] from Day 1 to Day 29 (GMI) • CCI [redacted] from Day 1 to Day 29 (SCR)

Objectives	Endpoints (population summary)
	• CCI at Day 1 and Day 29 (SPR) • CCI (CCI at Day 29 (GMT) • Fold increase in CCI from Day 1 to Day 29 (GMI) • CCI from Day 1 to Day 29 (SCR†)
Secondary	
To evaluate the humoral immune response induced by the investigational study intervention	• CCI at Day 92 and Day 183 (GMT) • Fold increase in CCI from Day 1 to Day 92 (GMI) • Fold increase in CCI from Day 1 to Day 183 (GMI) • CCI at Day 183 (SPR†) • CCI at Day 92 and Day 183 (GMT) • Fold increase in CCI from Day 1 to Day 92 (GMI) • Fold increase in CCI from Day 1 to Day 183 (GMI)
Tertiary	
CCI	

Objectives	Endpoints (population summary)
CCI [redacted]	[redacted]

Endpoints are designed for all the participants, unless indicated otherwise in the table.

AE: adverse event; SAE: serious adverse event; AESI: adverse events of special interest; MAE: medically attended event; SCR: seroconversion rate; SPR: seroprotection rate; CCI [redacted]

* Refer to Section 8.4.1 of the protocol for the list of safety events and timeframe for collection.

† Refer to Section 9.3.2 of the protocol for definition of SCR and SPR.

1.1.1. Estimands

Table 2 Estimands

Ref #	Population	Objectives	Variable (Endpoint)	Intercurrent event (ICE)[2]		Population level summary
				Description	Handling strategy	
Primary						
1	Healthy younger (18-64 YOA) and older adults (65-85 YOA)	To evaluate the safety and reactogenicity profile of the investigational study intervention	Solicited events: • Occurrence of solicited administration site and systemic events within 7 days (i.e., from Day 1 to Day 7 included) of study intervention administration (percentage of participants). Unsolicited AEs: • Occurrence of unsolicited AEs within 28 days (i.e., from Day 1 to Day 28 included) after study intervention administration (percentage of participants). SAEs*, AESI* and MAEs: • Occurrence of SAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants) • Occurrence of AESIs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants)	Not applicable	Treatment policy: all data collected will be included in summaries.	Proportion of participants who report each of the endpoint. No treatment comparison is planned.

Ref #	Population	Objectives	Variable (Endpoint)	Intercurrent event (ICE)[2]		Population level summary
				Description	Handling strategy	
			• Occurrence of MAEs within 6 months (i.e., from Day 1 to Day 183) after study intervention administration (percentage of participants). For participants in Phase 1: Safety laboratory: • Shift from a non-clinically significant laboratory value on Day 1 (pre-dose) to a clinically significant abnormal laboratory value on Day 8 (post-dose) and/or Day 29 (post-dose) for hematology and clinical chemistry (percentage of participants).			
2	Refer to 1	To evaluate the humoral immune response induced by the investigational study intervention	• CCI [redacted] at Day 29 (GMT) • Fold increase in CCI [redacted] from Day 1 to Day 29 (GMI) • CCI [redacted] from Day 1 to Day 29 (SCR) • CCI [redacted] at Day 1 and Day 29 (SPR) • CCI [redacted] at Day 29 (GMT) • Fold increase in CCI [redacted] from Day 1 to Day 29 (GMI) • CCI [redacted] from Day 1 to Day 29 (SCR†)	a. Vaccination administration errors. b. Taken prohibited medication or vaccination prior to Day 29 blood draw. c. Medical condition forbidden by protocol (i.e., either a confirmed immunodeficiency condition, new malignancy, or development of confirmed influenza disease) prior to	Hypothetical strategy: data from participant after ICE will be excluded from the analysis.	• Between-group geometric mean titer (GMT) ratio (Flu mRNA candidate over Comparator) with 95% confidence interval (CI) • Within-group geometric mean increase (GMI) with 95% CI • Between-group difference in seroconversion rate (SCR[3]) (Flu mRNA candidate minus Comparator) with 95% CI • Between-group difference in seroprotection rate (SPR[3]) (Flu mRNA candidate

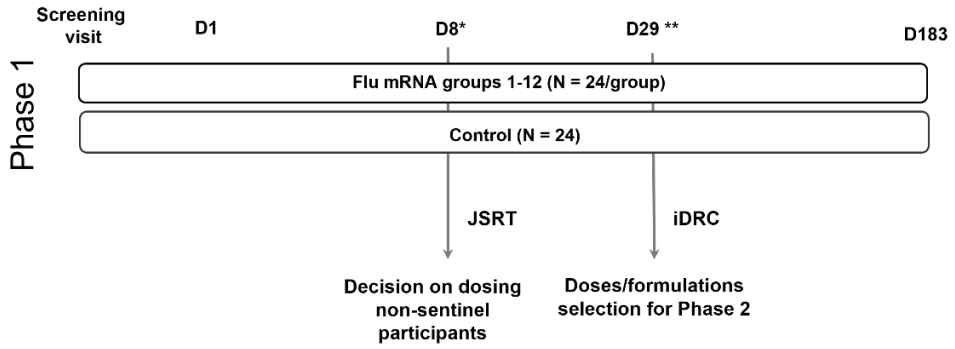
Ref #	Population	Objectives	Variable (Endpoint)	Intercurrent event (ICE)[2]		Population level summary
				Description	Handling strategy	
				Day 29 blood draw. d. Blood sample collected for Day 29 out of window		minus Comparator) with 95% CI
	Secondary					
2	Refer to 1	To evaluate the humoral immune response induced by the investigational study intervention	• CCI at Day 92 and Day 183 (GMT) • Fold increase in CCI CCI from Day 1 to Day 92 (GMI) • Fold increase in CCI CCI from Day 1 to Day 183 (GMI) • CCI at Day 183 (SPR†) • CCI at Day 92 and Day 183 (GMT) • Fold increase in CCI CCI from Day 1 to Day 92 (GMI) Fold increase in CCI from Day 1 to Day 183 (GMI)	Refer to 2	Refer to 2	Refer to 2

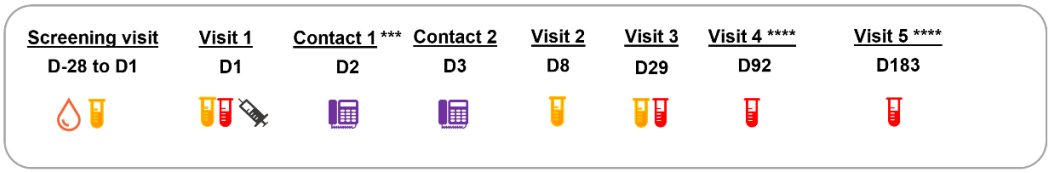
Endpoints are designed for all the participants, unless indicated otherwise in the table.
AE: adverse event; AESI: adverse event of special interest; CI: confidence interval; GMI: mean geometric increase; GMT: geometric mean titer; CCI ; ICE: intercurrent event; MAE: medically attended event; CCI CCI , SAE: serious adverse event; SCR: seroconversion rate; SPR: seroprotection rate; YOA: years of age.
Study discontinuation, blood sample taken out of window and missing result at pre- or post-dose are not considered intercurrent events and will be handled as missing data. More details will be provided in the statistical analysis plan (SAP).
Refer to Section 3 for more information on intercurrent events.
Refer to Section 4.2.2 for definition of SCR and SPR.

1.2. Study Design

Overview of Study Design and Key Features

Phase 1

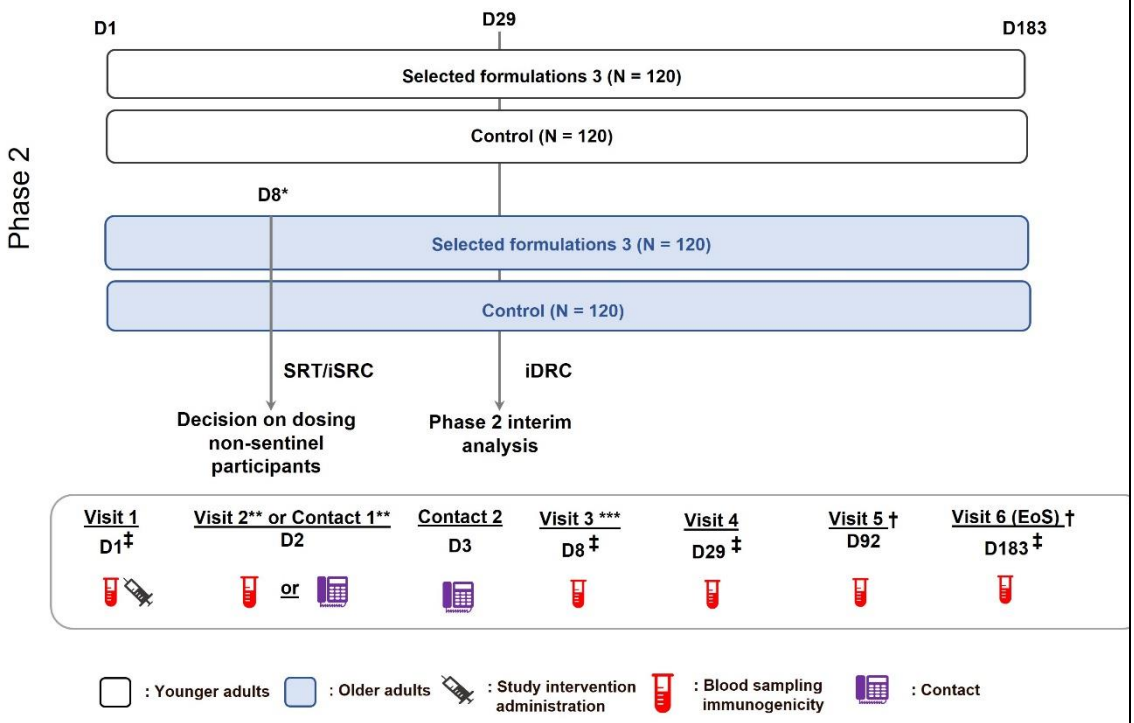




D: day; SRT: joint safety review team; iDRC: internal data review committee; N: number of participants
Control: licensed influenza vaccine. Refer to Section 4.1 of the protocol for more information.
* Safety review of 7-days post-dosing (Day 8) data of sentinel participants by SRT. Refer to Section 8.3.7.1 of the protocol for details.
** Selection of doses/formulations for Phase 2 by the iDRC. Refer to Section 4.3 of the protocol for more information.
*** Contact 1 will only be applicable for the first 5 participants per group. Remaining Phase 1 participants will not have any contact at Day 2.
**** Visit 4 and 5 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.

Overview of Study Design and Key Features

Phase 2



D: day; EoS: end of study; ***SRT:*** safety review team; iSRC: internal safety review committee; N: number of participants. Control: licensed influenza vaccine. Refer to Section 4.1 of the protocol for more information.
* Safety review of 7-days post-dosing (Day 8) data of sentinel OA participants by ***SRT***/iSRC. Refer to Section 8.3.7.1 of the protocol for details.
** Contact 1 will only be applicable for the first 5 participants in OA groups. Visit 2 (Day 2) will only be applicable for participants in the CCI [redacted] subset in Phase 2. Remaining Phase 2 participants will not have any contact or visit at Day 2.
*** Visit 3 (Day 8) will be replaced by a Contact for all non-subset participants in Phase 2.
† Visit 5 and 6 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 prior to this visit and did not report any adverse events that would require physical examination on site.
‡ Additional blood samples will be collected for a subset of participants in Phase 2.

Design Features	• Multi-country, multi-center. • Self-contained. • Intended duration of the study per participant: Up to 7 months for participants enrolled in Phase 1 (screening period included) and 6 months for participants enrolled in Phase 2 of the study. • Aspects of data collection: blood samples, safety events, CCI [redacted] • Method of data collection: – Standardized electronic Case Report Form (eCRF) – Solicited AEs, the occurrence of unsolicited AEs and responses to CCI [redacted] will be collected using an electronic Diary (eDiary); participants, with support from the site, may install the eDiary application on their own personal, handheld device (e.g.,

Overview of Study Design and Key Features	
	mobile phone, tablet) or the site may provide a device that is pre-programmed with the eDiary. • Safety monitoring: the review of safety data will be performed by an internal Joint Safety Review Team (SRT) and internal Safety Review Committee (iSRC). Refer to Section 8.3.7.1 of the protocol for more information on safety monitoring strategy applicable to this study and Section 10.1.6 of the protocol for SRT and iSRC composition and role. • Dose selection for Phase 2: refer to Section 4.3.2 of the protocol for detailed information on dose selection by an internal Data Review Committee (iDRC) and Section 10.1.6 of the protocol for iDRC composition and role. **Phase 1:** • Participants aged 18-50 years. • 13 groups enrolled in parallel (12 mRNA groups and 1 control group), detailed in Table 6 of the protocol. • Approximate number of participants: 312 (24 participants per group). • Blinding: single-blind. Refer to Section 6.4 of the protocol for more information on blinding. • Study interventions administered in Phase 1 will be manufactured as separate components and mixed at site by the site staff/pharmacist based on the scheme provided in the Table 6 of the protocol, before dosing each participant. This approach will only be applicable in the Phase 1 part. **Phase 2:** • Participants aged 18-64 and 65-85 years. • Up to 8 groups enrolled in parallel (up to 3 mRNA groups and 1 control group for each age range), Table 7 of the protocol. Dependent upon immunogenicity data generated in the Phase 1 part of the study, not all mRNA groups may be started. • Approximate number of participants: 960 (120 participants per group). Dependent upon immunogenicity data generated in the Phase 1 part of the study, not all mRNA groups may be started which would reduce the planned number of participants. • Blinding: observer-blind. Refer to Section 6.4 of the protocol for more information on blinding. • An CCI [redacted] will be defined for additional immunogenicity analyses and will consist of approximately 50 participants of each group (Flu mRNA and Control). • Final number of groups, number of participants, and dose levels will be described in a protocol amendment prior to initiation of the Phase 2 part of the study.
Study intervention	All study interventions are administered as single-dose intramuscularly (IM). • Up to 12 mRNA formulations may be assessed in phase 1 (refer to Table 6 of the protocol) while up to 3 mRNA formulations are expected to be assessed within each age group in Phase 2 (refer to Table 7 of the protocol). • CCI [redacted]

Overview of Study Design and Key Features	
	• CCI [redacted]
Study intervention Assignment	All participants will be centrally assigned to randomized study intervention using an automated Internet-based system. Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used. • In Phase 1 of the study, the randomization algorithm will use a minimization procedure accounting for sentinel status as a stratification factor, and study, country, center, and flu vaccination history during past 2 years as minimization factors. • For Phase 2, the randomization algorithm will use a minimization procedure accounting for age group and sentinel status (in OA group only) as a stratification factors, and study, country, center, and flu vaccination history during past 2 years as minimization factors. In addition, CCI [redacted] In the randomization algorithm, allocation within the levels of the minimization factors will be based on equal weights.
Interim Analysis	In addition to the analyses detailed below, additional analyses e.g., safety analyses, may be conducted to support the SRT, iSRC and iDRC decisions, as described in Section 8.3.7.1 of the protocol. Refer to Section 10.1.6 of the protocol for the SRT, iSRC and iDRC roles. Two interim analyses are foreseen and will be conducted upon availability of all primary endpoints up to Day 29 for participants in Phase 1 and Phase 2, respectively. The interim analysis in Phase 2 will serve to inform future Phase 3 study(ies) preparation.

2. STATISTICAL HYPOTHESES

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

2.1. Multiplicity Adjustment

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

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	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 the dose of study intervention as per protocol, had immunogenicity results pre- and Day 29 post-dosing for at least one [redacted], without intercurrent conditions (influenza disease, new malignancy and immunocompromised condition) that may interfere with immunogenicity and without prohibited concomitant medication/vaccination before Day 29. 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 9 and Table 10) as well as results obtained after intercurrent conditions (influenza disease, new malignancy and immunocompromised condition) that may interfere with immunogenicity or after prohibited concomitant medication/vaccination during this period will be excluded from the PPS.	Immunogenicity, demography

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).

Participants will be analysed according to the age group stratum that was used at the time of randomization but with the actual vaccine received. For other minimization factors, the actual value will be considered for analysis.

4.1.1. General Methodology

Enrolled participants who withdraw from the 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 functional titers, 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.

For calculations regarding polypositive CCI frequencies, frequencies below 590 per 10^6 cells will be replaced by 590.

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. Reactogenicity and Safety Endpoints

The analysis of reactogenicity and safety endpoints will be based on the ES. All analyses will be done separately for OAs and YAs according to study phase, unless specified otherwise.

4.2.1.1. Solicited AEs

All solicited events must be recorded into the eDiary during the first 7 days following administration of the dose of study intervention (Day 1 to Day 7 included), irrespective of occurrence or intensity. Solicited events ongoing after Day 7 will continue to be recorded into the eDiary from Day 8 to Day 28 and followed-up until the event has resolved, subsided, stabilized, disappeared, or until the event is otherwise explained, the participant is lost to follow up, or study is completed.

The following administration site events will be solicited:

- Pain
- Redness

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

The following systemic events will be solicited:

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

Note: Participants will be instructed to measure and record the axillary temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the eDiary.

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 except for fever (refer to Section 6.2.2.3). When available, solicited AE information (e.g., occurrence, grading) collected by study staff when daily eDiary 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 and medically attended events) and solicited systemic event (any grade, Grade ≥2, Grade ≥3 and medically attended events) within the 7-day follow up period (i.e., Day 1-Day 7 post-dosing) will be tabulated for each group according to the maximum grading in Day 1-Day 7.

The same summaries will be generated for any, administration site solicited AEs, any systemic solicited AEs and any solicited AEs.

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 clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

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 is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The investigator will use clinical judgment to determine the relationship.

The percentage of participants with any unsolicited AEs within the 28-day follow up period (i.e., Day 1-Day 28 post-dosing) with its exact 95% confidence interval (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

The following events are considered as AESIs in this study.

Severe hypersensitivity reactions within 24 hours after study intervention administration

Myocarditis/pericarditis. Refer to Section 8.3.4 of the protocol for myocarditis/pericarditis assessment and definitions.

The summary of event characteristics will be provided for each AESI as well as any potential immune-mediated diseases [pIMDs] (new onsets and exacerbations) 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), with at least 1 report of MAE and with at least 1 report of AESI, respectively, classified by the MedDRA SOC and PT and reported from Dose 1 up to study end 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

Protocol-required Safety Laboratory Tests (Phase 1 only)

The following laboratory assessments will be performed:

Assay type	System	Component	Method
Hematology	Whole Blood	White Blood Cells count and differentials	As per local laboratory procedures
	Whole Blood	Erythrocytes	
	Whole Blood	Hemoglobin	
	Whole Blood	Glycated hemoglobin (Hba1c) *	
	Whole Blood	Platelets	
Biochemistry	Serum	Blood urea nitrogen/Urea	
		Creatinine	
		Alanine aminotransferase (ALT)	
		Aspartate aminotransferase (AST)	
		Troponin (Troponin I and/or Troponin T)	
Urinalysis*, **	Urine	Leukocytes, Blood, Proteins, Glucose, Ketones, Bilirubin, Urobilinogen, Nitrite, Specific gravity, pH	

* Only applicable for screening visit in Phase 1.
** Urinalysis will be done by dipstick.

Individual safety laboratory measurements for hematology, chemistry, and urinalysis laboratory panel will be provided. All listings will include the age group, study group, participants ID, laboratory test name and 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 will be 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 and clinical chemistry. 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: Bayesian Logistic Regression Model (BLRM)

An adaptive BLRM will be used to inform on the posterior probability of the true Grade 3 solicited event rate for all dose levels used in Phase 1 study groups. 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. [Rogatko, 2007] and is one of the key elements of the FDA's Critical Path Initiative.

The modified version of the 2-parameter BLRM described by Neuenschwander et al., 2008 [Neuenschwander, 2008] which accounts for the total amount of HA and NA in each mRNA formulation will be used to assess reactogenicity and recommend the mRNA doses to proceed to Phase 2 of the study.

The BLRM is specified as follows:

$\text{logit}(p(f)) = \log(\alpha) + \beta 1 * \log(d_{HA}/d^*) + \beta 2 * \log(d_{NA}/d^*)$

where

- p(f) = percentage of participants with Grade 3 solicited event at mRNA formulation, f
- logit(p) = log(p/(1-p))
- d* = 50 µg is the reference dose representing the total mRNA dose
- α is the intercept parameter
- β1 is a dose effect due to total amount of HA
- β2 is a dose effect due to total amount of NA

Since no prior information is available, the uncertainty about the dose-tolerance relationship (parameters α and β [i.e., β1 and β2]) is expressed by a mixture of 2 bivariate normal distributions as follows:

- 80% weight for minimally informative component: log(α) ≈ normal (mean= -1.516, var=1) and log(β) ≈ normal (mean= -1.553, var=1), a priori assuming 10% and 18% Grade 3 solicited event rate at 2 µg and 50 µg, respectively.
- 20% weight for toxicity component: log(α) ≈ normal (mean= -0.708, var=1) and log(β) ≈ normal (mean= -1.143, var=1), a priori assuming 15% and 33% Grade 3 solicited event rate at 2 µg and 50 µg, respectively.

A zero covariance between priors is assumed. The same prior information is assumed for β1 and β2 reflecting *a priori* no difference between the same amounts of HA and NA on adverse reaction.

A greater than 50% posterior probability that the Grade 3 solicited event rate ≥ 18% at a given mRNA dose will indicate that the dose may not be tolerable. The result of the BLRM will be available to the SRT and iSRC at each meeting as a recommendation tool for deciding if non-sentinel participants should be enrolled for each dose level and what dose levels to proceed to Phase 2 of the study.

4.2.2. Co-primary and Secondary Immunogenicity Endpoints

At each phase and for OA and YA separately, the group difference between each mRNA group and the control group will be assessed separately as follows for CCI

- At each post-dosing timepoint separately, the 2-sided CI for group GMT ratio between investigational study intervention dose and (over) the control group will be derived from an ANCOVA model on log10 transformed concentration. The ANCOVA model will include group (i.e., each of the investigational study intervention and the control group), actual age of participants, country, flu vaccination history and log10-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 lower level of quantification (LLOQ) will be replaced by half the assay LLOQ.
- For a given age group, the 2-sided 95% CI on group difference in SCR between an investigational study intervention and (minus) the control group will be computed at Day 29 based on the method of Miettinen and Nurminen [Miettinen, 1985].
- CCI

All analyses will be performed separately for each age group, where applicable.

Abbreviation/term	Definition
GMI	The geometric mean of the ratios of the post-dosing titer over the Day 1 titer.
CCI	The percentage of dosed participants who have either a CCI and a post-dosing CCI or a CCI and at least a 4-fold increase in post-dosing CCI.
CCI	The percentage of dosed participants who have either a CCI and a post-dosing CCI or a pre-dose CCI and at least a 4-fold increase in post-dosing CCI.
CCI	The percentage of dosed participants with a CCI
S+ (seropositive)	Titer ≥LLOQ

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 age;
    LSMEANS trt01a / CL;
RUN;
```

For the purpose of analysis, previous flu vaccination history reported as 'Unknown' will be classified as 'No'.

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

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

The assays used in this study and their LLOQs are presented in Table 3.

Table 3 Assay cut-off values for various assays in Phase 1

Assay	Unit	Test ID	LLOQ
CCI			

Table 4 Assay cut-off values for various assays in Phase 2

Assay	Unit	Test ID	LLOQ
CCI [redacted]			

4.3. Secondary Endpoint(s) Analyses

To evaluate the humoral immune response induced by the investigational study intervention. The CCI [redacted] for each strain on Day 92 and Day 183 will be assessed as follows:

- CCI [redacted] at Day 92 and Day 183 (GMT)
- Fold increase in CCI [redacted] from Day 1 to Day 92 (GMI)
- Fold increase in CCI [redacted] from Day 1 to Day 183 (GMI)
- CCI [redacted] at Day 183 (SPR)
- CCI [redacted] at Day 92 and Day 183 (GMT)
- Fold increase in CCI [redacted] from Day 1 to Day 92 (GMI)
- Fold increase in CCI [redacted] from Day 1 to Day 183 (GMI)

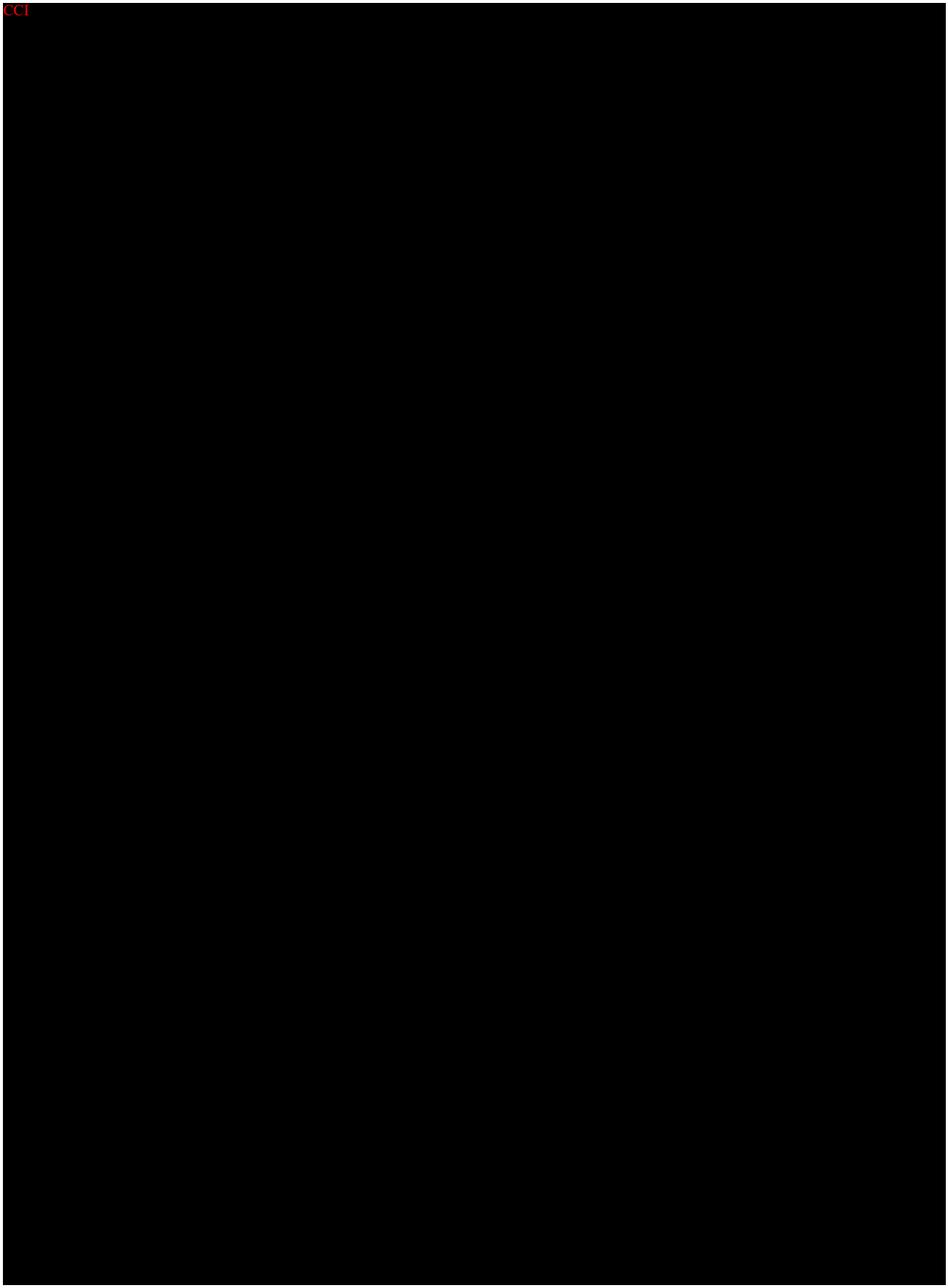
4.3.1. Main Analytical Approach

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

4.4. Tertiary/Exploratory Endpoint(s) Analyses

CCI [redacted]

CCI



CCI

[redacted]

CCI

4.5. Safety Analyses

Refer to Section 4.2.1

4.5.1. Safety Review Team (SRT) & Internal Safety Review Committee (iSRC)

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

For Phase 1, the SRT will receive unblinded summaries of safety data that will be generated by the independent Data Analysis Centre (iDAC) who will have access to the randomization scheme. The unblinded summaries will include all results from the safety analysis by study group. For Phase 2, the SRT and iSRC will respectively receive blinded and unblinded summaries of safety data that will be generated by the iDAC. The blinded summaries will include all results from the safety analysis by age group while the unblinded summaries will include all results from the safety analysis by age and study group.

The safety holding rules for Phase 1 and Phase 2, are defined in Table 5 and Table 6 respectively. If met, holding rules will trigger a hold of the study intervention administration. Holding rules 1a-f will be assessed by the investigator on a continuous basis. Holding rules 2a and 2b will be assessed by the iSRC and/or SRT as applicable

during the safety evaluations of the data. Meeting any of these holding rules will trigger a hold of study intervention administration irrespective of number of participants enrolled and/or timing of the event, for all the study groups.

If a holding rule was met or safety signal observed during the SRT or iSRC 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 or iSRC, a decision to continue, suspend or modify the conduct of the study will be taken by the committee.

In addition to the BLRM analysis (Phase 1 only), the following statistical analyses will be conducted on holding rules in both Phase 1 and 2:

- 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 5 Study holding rules for Phase 1

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	Necrosis at the injection site	≥1
1e	Confirmed myocarditis or pericarditis events not clearly attributable to any cause other than study vaccine	≥1
1f	Laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention	≥1
2a	Maximum number of participants with the same **Grade 3 solicited local or systemic AE** in an investigational vaccine group, with onset within the 7-day (Day 1-7) post-dosing period	≥2
2b	Maximum number of participants with the **same or similar Grade 3 related unsolicited AE in an investigational vaccine group, including events with an identical MedDRA High Level Term** and events assessed as clinically similar. *Includes any Grade 3 or above laboratory abnormalities* of clinical relevance, symptomatic or not, as determined by the investigator*	≥2

* 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". N/A: not applicable

Table 6 Study holding rules for Phase 2

Holding rule	*Events, per dose and per individual study group*	*Number of participants to pause dosing in all groups, pending further evaluation by the iSRC*
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	Necrosis at the injection site	≥1
1d	Confirmed myocarditis or pericarditis events not clearly attributable to any cause other than study vaccine	≥1
1e	Laryngospasm, bronchospasm, or anaphylaxis within 24 hours after administration of study intervention	≥1
2a	Maximum number of participants with the same **Grade 3 solicited local or systemic AE (same solicited AE lasting 2 consecutive days [48 hours] or more as grade 3)*** in an investigational vaccine group, with onset within the 7-day (Day 1-7) post-dosing period	≥5% (and ≥2)
2b	Maximum number of participants with the **same or similar Grade 3 related unsolicited AE in an investigational vaccine group, including events with an identical MedDRA High Level Term** and events assessed as clinically similar.	≥5% (and ≥2)

* E.g., 2 cases of grade 3 fever occurring 2 consecutive days in 2 participants in the same group

The TFLs to be generated to support SRT and iSRC reviews will be detailed in a dedicated output programming specification (OPS).

4.5.2. Internal Data Review Committee (iDRC)

An iDRC will be set up in the study for the purpose of reviewing all available data and recommending the composition of the investigational study intervention formulations to be assessed Phase 2. Statistical interim analyses will be performed to support iDRC data reviews at pre-planned time points (Section 4.7). Refer to Section 4.3 of the protocol for details on selection of doses for further assessment for the next phase of the study.

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, additional analyses, e.g., safety analyses, may be conducted to support the SRT, iSRC and iDRC decisions, as described in Section 8.3.7.1 of the protocol. Refer to Section 10.1.6 of the protocol for the SRT, iSRC and iDRC roles.

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. All interim analyses will be based on the ES.

4.7.1. Sequence of Analyses

Two interim analyses are foreseen and will be conducted upon availability of all primary endpoints up to Day 29 for participants in Phase 1 and Phase 2, respectively. CCI [redacted] For the observer-blinded Phase 2 interim analyses, a restricted study team will be unblinded to individual participant data and all efforts will be made to ensure the participants, investigators and monitoring staff blinding is maintained up to study end. The rest of the study team will have access to group data but will remain blinded to individual participant data and treatment assignment until the end of the study. It is possible, however, due to the limited sample size, that unblinding occurs for a few participants having a specific AE or SAE (e.g., an AE/SAE occurring only in a single participant). Therefore, anyone having access to the results could become unblinded regarding those few specific cases.

An analysis with all primary and secondary endpoints obtained until the last visit (Day 183) will be performed and made available to the investigators and submitted to regulatory authorities, as appropriate. This may be performed separately for each phase. Analysis of tertiary endpoints may be performed at a later stage. Tertiary analyses deemed futile due to the other study results will not be analyzed nor reported.

4.8. Changes to Protocol Defined Analyses

The BLRM described on Section 4.2.1.5 has been modified to include 2 slope parameters accounting separately for the total amounts of CCI [redacted] in each formulation which deviates from that specified in the protocol amendment 1 (Dated: 07 April 2023) where only one slope accounting for the sum of total amounts of both CCI [redacted] in each formulation was planned.To focus the laboratory testing, only participants exposed to mRNA vaccines with CCI [redacted] in the formulation and control group will be included in the subset for CCI [redacted] testing. In CCI [redacted]

Section 5.2 is updated to reflect the actual unevaluable rate and lower half-width used for Phase 2 sample size estimation.

5. SAMPLE SIZE DETERMINATION

5.1. Sample Size Determination for Phase 1

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 vaccine. For each investigational study intervention group, it is expected that 24 participants will be enrolled. 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 7 provides the estimate and 95% credibility interval for a given observed number of participants for a sample size of 24 participants per study group (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 7 Posterior probability estimates of Grade 3 solicited event rate <18%

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 10.7 of the protocol.

5.2. Sample size determination for Phase 2

The primary objective is to explore how the different formulation(s) or dose level(s) of mRNA-based vaccine compare to licensed control group(s).

The sample size of 108 evaluable participants in each dose level cohort and age group, is expected to provide a 95% CI for group difference in SCR with a lower half-width below 13.3% for difference in seroconversion rates for the different strains (Table 8) and a 95% CI with an expected half-width of 1.36-fold for the group geometric mean concentration ratio considering a population standard deviation of 0.5 in log10 transformation concentration post-dosing and 10% of unevaluable participants per group.

Table 8 Half-width of 95% CI for the group difference in seroconversion

Control	Strain	Proportion (%)	95% CI of Proportion (%)*	Lower half-width of 95 CI (%)
CCI [redacted]				

*Obtained from meta-analysis of historical data CCI [redacted]

CCI [redacted]

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, sex, 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, 65-84 and ≥85 based on the Enrolled 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
- Participants randomized using the wrong stratification factor (incorrect age group)

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

- Influenza disease infection, new malignancy and immunocompromised condition
- 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 9 and Table 10)
- CCI [redacted]
- 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 28 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). The important PDs leading to elimination from the PPS will be summarized for the ES and the important PDs leading to elimination from the ES will be summarized for the Enrolled Set.

Table 9 Intervals between study visits. Phase 1

Interval*	Planned visit interval	Allowed interval range
Screening Visit** → Visit 1	1-28 days	1 – 28 days
Visit 1 → Contact 1***	1 day	1 day
Visit 1 → Contact 2	2 days	2-3 days
Visit 1 → Visit 2	7 days	6-8 days
Visit 1 → Visit 3	28 days	28-35 days
Visit 1 → Visit 4‡	91 days	84-98 days
Visit 1 → Visit 5‡	182 days	180-210 days

* Interval is computed as the difference between 2 dates

** Screening Visit is planned for participants enrolled in Phase 1 and needs to be performed within 28 days before Visit 1, with sufficient time to receive/review the hematology, biochemistry, HbA1c 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. In this case, all screening procedures must be completed within 28 days before Visit 1 (Day 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 only be applicable for the sentinel participants in Phase 1. Remaining Phase 1 participants will not have a visit or contact at Day 2.

‡ Visit 4 and 5 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.

Table 10 Intervals between study visits. Phase 2

Interval*	Planned visit interval	Allowed interval range
Visit 1 → Visit 2**	1 day	1 day
Visit 1 → Contact 1***	1 day	1 day
Visit 1 → Contact 2	2 days	2-3 days
Visit 1 → Visit 3†	7 days	6-8 days
Visit 1 → Visit 4	28 days	28-35 days
Visit 1 → Visit 5‡	91 days	84-98 days
Visit 1 → Visit 6‡	182 days	180-210 days

* Interval is computed as the difference between 2 dates

** Visit 2 (Day 2) will only be applicable for participants in the CCI [redacted] subset in Phase 2. Remaining Phase 2 participants will not have a visit at Day 2.

*** Contact 1 (Day 2) will only be applicable for the sentinel OA participants in Phase 2. Remaining Phase 2 participants will not have a contact at Day 2.

† Visit 3 (Day 8) will be replaced by a Contact for all non-subset participants in Phase 2 and if participant did not report any adverse events that would require physical examination on site.

‡ Visit 5 and 6 will be replaced by a Contact if participant has received the standard of care vaccination against seasonal flu after Day 29 and prior to this visit and did not report any adverse events that would require physical examination on site.

6.1.5. Prior and 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 a 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-dosing) will be summarized by group.

This antipyretic list may be revised based on WHO dictionary version.

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, with the exclusion of [redacted] data, 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 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:

- Study day prior to dosing will be calculated as: date of assessment – date of the study intervention administration
- 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 1 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 and unsolicited 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.

Accordingly for the summary presenting the number and percentage of participants reporting any solicited and unsolicited adverse events excluding SAE, a solicited AE starting within the solicited period (day 1-7) will be counted as one event while unsolicited AE, excluding prolonged solicited AE will be counted as different event when these are associated to different MedDRA Primary Term or different start date. For instance, a participant with fatigue for several days within the solicited period, with fatigue prolonged beyond the solicited period and with fatigue restarting later in the unsolicited period will contribute as 2 occurrence of fatigue.

6.2.1.11. AESIs

GSK MedDRA queries will be used to identify AESI:

- pIMD: refer to Table 15 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.

These pIMD, myocarditis and pericarditis queries may be revised based on MedDRA dictionary version.

AESI summaries will include AEs identified by either the investigator or the MedDRA queries.

6.2.2. Handling of Partial Dates

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., Creatinine results may be 1.91).

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 Creatinine and therefore 1.91 will be rounded to 1.9 and Grade as 2).

Table 11 FDA toxicity grading scales for biochemistry parameters evaluated in the current study

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**	Conversion factor (new unit)
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis	0.3571 (mmol/L)
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis	88.4 (µmol/L)
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN	

ULN is the upper limit of the normal range.

* 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.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the participant had a new seizure associated with the low sodium value.

Table 12 FDA toxicity grading scales for hematology parameters evaluated in the current study

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)	Conversion factor (new unit)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 –10.9	8.0 – 9.4	< 8.0	10 (g/L)
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0	10 (g/L)
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5	10 (g/L)
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0	10 (g/L)
WBC Increase - cell/mm^3	10 800 – 15 000	15 001 – 20,000	20 001 – 25 000	> 25 000	0.001 (10^9/L)
WBC Decrease - cell/mm^3	2 500 – 3 500	1 500 – 2 499	1 000 – 1 499	< 1 000	0.001 (10^9/L)
Lymphocytes Decrease - cell/mm^3	750 – 1 000	500 – 749	250 – 499	< 250	0.001 (10^9/L)
Neutrophils Decrease - cell/mm^3	1 500 – 2 000	1 000 – 1 499	500 – 999	< 500	0.001 (10^9/L)
Eosinophils - cell/mm^3	650 – 1 500	1 501 – 5 000	> 5 000	Hypereosinophilic	0.001 (10^9/L)
Platelets Decreased - cell/mm^3	125 000 – 140 000	100 000 – 124 000	25 000 – 99 000	< 25 000	0.001 (10^9/L)

* 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.

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:

Administration Site (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***	Present but 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]

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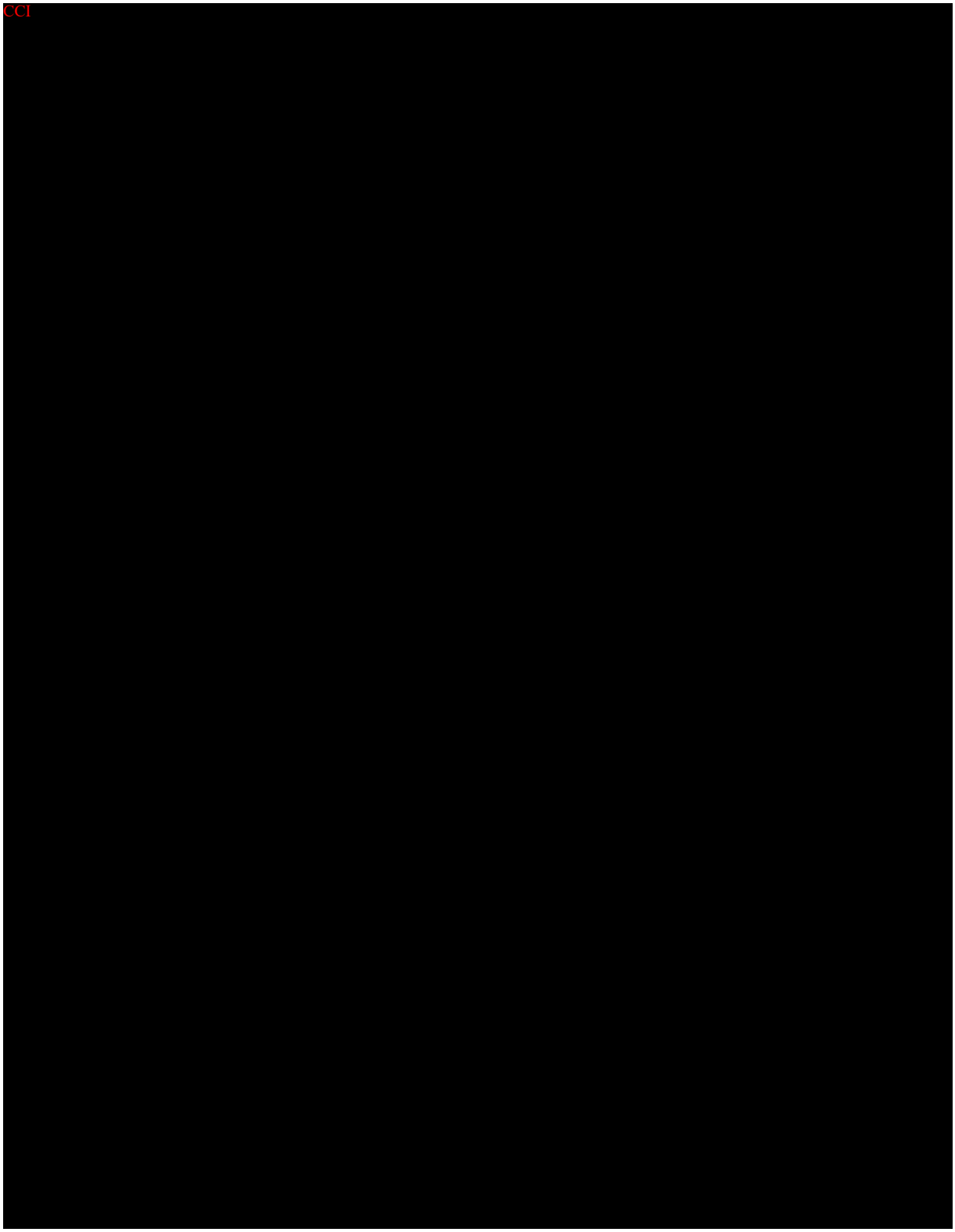

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Instructions – General Principles of Scoring

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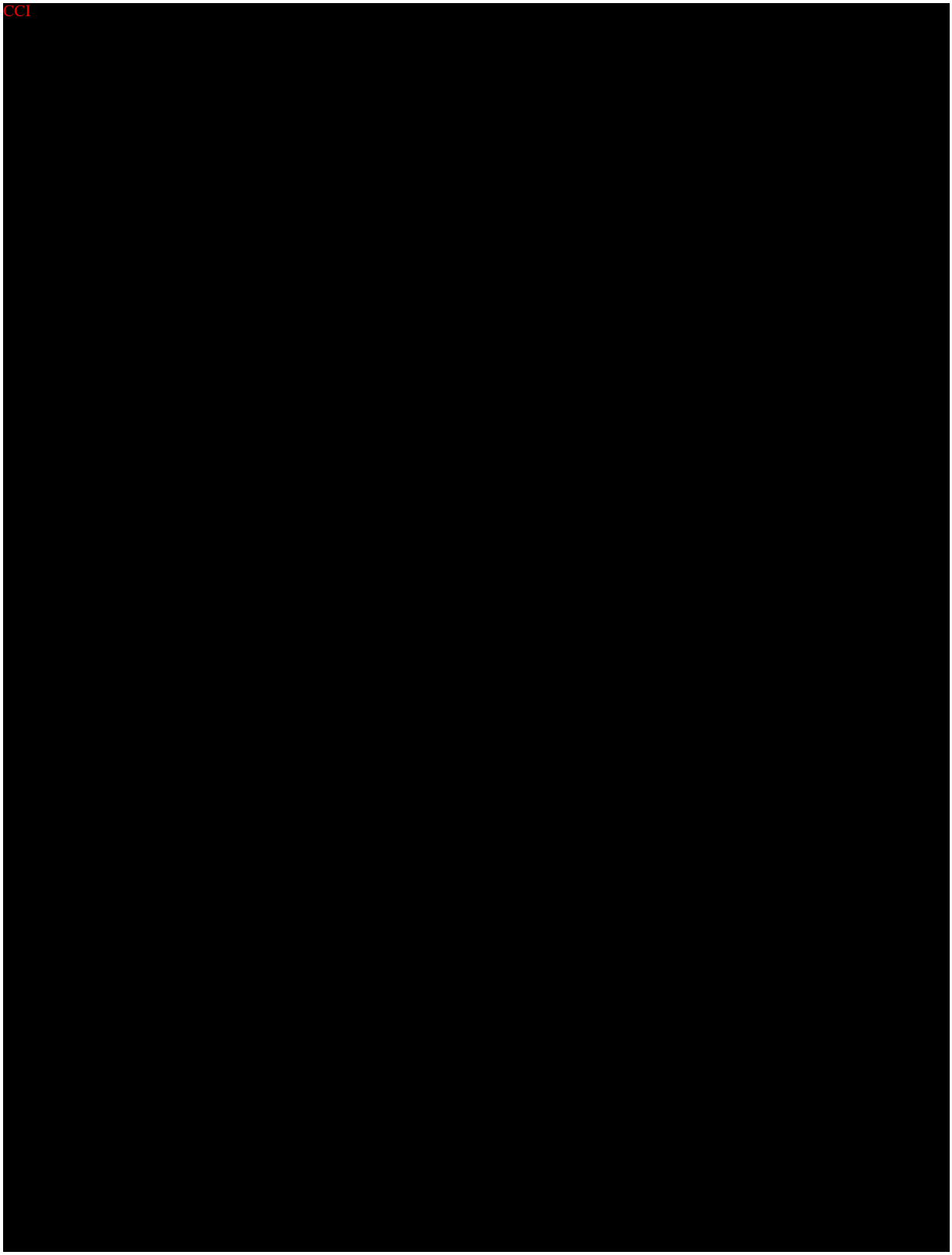

6.2.6. Trademarks

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