# Statistical Analysis Plan Amendment 2

**Study ID:** 219112

**Official Title of Study:** Exploratory, FTIH, observer-blind, randomized, controlled study to evaluate safety, reactogenicity and immunogenicity of various doses of GSK's investigational mRNA-CR-04 vaccine when administered intramuscularly in healthy adults 18 to 49 years of age

**NCT number:** NCT05972993

**Date of Document:** 15 Feb 2024

| | |
|---|---|
| **Information Type:** | Statistical Analysis Plan (SAP) |

# TITLE PAGE

| | |
|---|---|
| **Protocol Title:** | Exploratory, FTIH, observer-blind, randomized, controlled study to evaluate safety, reactogenicity and immunogenicity of various doses of GSK's investigational mRNA-CR-04 vaccine when administered intramuscularly in healthy adults 18 to 49 years of age |
| **Study Number:** | 219112 |
| **Compound Number:** | GSK4768069A |
| **Abbreviated Title:** | MRNA CLINRES-001 |

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

**Regulatory Agency Identifier Number(s)**

| **Registry** | **ID** |
|---|---|
| Clintrials.gov | IND 29606 |

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

# TABLE OF CONTENTS

**PAGE**

# LIST OF TABLES

**PAGE**

## LIST OF FIGURES

**PAGE**

# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ab | Antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| BMI | Body mass index |
| CI | Confidence interval |
| COVID-19 | Coronavirus disease 2019 |
| CRF | Case report form |
| CSR | Clinical study report |
| eCRF | electronic Case report form |
| EKG | Electrocardiogram |
| EoS | End-of-study |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FTIH | First time in human |
| GMC | Geometric mean concentration |
| GMR | Geometric mean ratio |
| GMT | Geometric mean titer |
| GSK | GlaxoSmithKline Biologicals SA |
| ICE | Intercurrent events |
| IgG | Immunoglobulin G |
| iSRC | Internal safety review committee |
| LLOQ | Lower limit of quantitation |
| MAAE | Medically attended adverse event |
| MedDRA | Medical dictionary for regulatory activities |
| mRNA-CR vaccine | SARS-CoV-2 Omicron variant S glycoprotein vaccine |

| | |
|---|---|
| N | Nucleocapsid |
| PCR | Polymerase chain reaction |
| pIMD | Potential immune-mediated disease |
| PP | Per Protocol |
| PPS | Per Protocol Set |
| PT | Preferred term |
| RT-PCR | Real-time polymerase chain reaction |
| S | Spike |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SOC | System organ class |
| $SpO_2$ | Pulse oximetry |
| SRT | Safety review team |
| TC | Telephone call |
| ULN | Upper limit of normal |
| WT | SARS-CoV2 Wuhan ancestral strain or Wild type strain |

# VERSION HISTORY

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| SAP | 31 July 2023 | Final: (11 May 2023) | Not Applicable | Original version |
| SAP Amendment 1 | 20 November 2023 | Protocol amendment 2 (15 November 2023) | Updated the SAP to follow the changes in protocol amendment.<br><br>Changed the intercurrent event strategy from Principal Stratum Strategy to Hypothetical strategy for the immunogenicity endpoints (Section 1.1).<br><br>Removed the temperature by 0.5°C summary table. Only grading summary will be kept (Section 4.2.1.1).<br><br>Updated the shift of hematological and biochemical laboratory abnormality table (Section 4.2.1.1).<br><br>Added the management of solicited symptoms when | Version 2.0 |

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| | | | the investigators provide input (Section 4.2.1.2.1).<br><br>Added the analyses of tertiary endpoints (Section 4.4).<br><br>Clarified that RT-PCR at screening and Day 1 do not contribute to SARS-CoV-2 infection (Section 4.9).<br><br>Updated the partial data handling rules (Section 6.2.2). | |
| SAP Amendment 2 | 15 Feb 2024 | Protocol amendment 3 (07 February 2024) | Updated the SAP to align with the changes in protocol amendment 3.<br><br>This study is divided into two parts (Parts A and B). Part B will commence only after all Part A participants have completed their Day 15 study visits and the Day 15 interim analysis is | |

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| | | | completed. In Part B, 42 more participants will be enrolled in parallel and randomly assigned in a 3:3:1 ratio to receive:<br><br>(a) 3 µg mRNA-CR-04 vaccine, or (b) 10 µg mRNA-CR-04 vaccine, or (c) saline placebo. (Section 1.2).<br><br>Clarified that the descriptive statistical analyses will be performed separately for study Part A and Part B , and for combined part A & B with aggregated common groups (Section 4.1.1, Section 6.1.2.2, Section 6.1.3, and Section 6.1.4). | |

| | | | | |
|---|---|---|---|---|
| | | | Updated the management of solicited symptoms when the investigators provide input, i.e., the update of solicited symptoms was not allowed if solicited symptoms is missing (Section 4.2.1.2.1).<br><br>Updated AE of SARS-CoV-2 infection categories to be consistent with protocol (Section 4.6.1).<br><br>Added text to perform a Day 31 interim analysis on Part A participants and to allow for potential Day 15 and Day 31 interim analyses for Part B participants (Section 4.8.1).<br><br>The GSK statistical team will be unblinded after Part A Day 15 interim analyses (Section 4.8.1). | |

# 1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for 219112 (MRNA CLINRES-001).

## 1.1. Objectives, Endpoints, and Estimands

### Table 1 Study objectives, and endpoints

| Objective(s) | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the safety and reactogenicity of investigational mRNA-CR-04 vaccine up to D31 | • Solicited administration site events and systemic events during the 7-day follow-up period after study vaccine administration (day of study vaccine administration and 6 subsequent days);<br>• Unsolicited AEs during the 30-day follow-up period after study vaccine administration (day of study vaccine administration and 29 subsequent days);<br>• Any hematological and biochemical laboratory abnormality during the 15-day follow-up period after study vaccine administration (day of study vaccine administration and 14 subsequent days);<br>• MAAEs; SAEs; AESIs* up to D31. |
| **Secondary Safety** | |
| • To assess safety of investigational mRNA-CR-04 vaccine from study vaccine administration up to study conclusion. | • MAAEs; SAEs; AESIs* up to study conclusion (M6). |
| **Secondary Immunogenicity** | |
| • To evaluate the Ab functionality (neutralizing capacity induced by the mRNA-CR-04 vaccine against vaccine encoded SARS-CoV-2 and WT strains) up to study conclusion. | • Neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint (D1, D15, D31, M6).<br>• GMR from baseline (D1) of neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint.<br>• Vaccine response rate based on neutralizing titers against vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint. |
| **Tertiary** | |
| • To describe serum-binding antibody (IgG) responses induced by the mRNA-CR-04 vaccine specific for vaccine encoded SARS-CoV-2 and WT strains S protein up to study conclusion. | • GMCs of binding IgG Ab specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains at each timepoint (D1, D15, D31, M6). |

| Objective(s) | Endpoints |
|---|---|
| | • GMR from baseline of binding IgG Ab specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains S proteins at each timepoint.<br>• Seroresponse rates based on binding IgG concentrations specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains S protein at each timepoint. |
| • To describe cell-mediated immune responses induced by the mRNA-CR-04 vaccine up to study conclusion. | • Frequency of CD4+/CD8+ T-cells specific for S protein encoded by the vaccine SARS-CoV-2 and WT strains measured by intracellular cytokine staining assay at each time point (D1, D15, D31, M6).<br>• Cellular immune responses including, but not limited to Th1 and Th2 profiles as determined by flow cytometry using ICS at each time point (D1, D15, D31, M6). |
| • To describe the incidence of confirmed symptomatic and asymptomatic SARS-CoV-2 infection. | • Percentage of laboratory-confirmed (N protein seroconversion) asymptomatic SARS-CoV-2 infection at each time point (D1, D15, D31, M6).<br>• Percentage of laboratory-confirmed (RT-PCR) symptomatic SARS-CoV-2 infection at D8, D15, as well as at unscheduled visits. |
| • To evaluate the genetic sequence of SARS-CoV-2 variant S protein in confirmed (RT-PCR) SARS-CoV-2 positive participants. | • Comparison of SARS-CoV-2 S protein genetic sequence of viral isolates (when available) to the vaccine mRNA sequence<br>• Identification of SARS-CoV-2 variants. |
| • To further characterize the humoral response (including, but not limited to functionality of antibodies) and cellular response, specific for the vaccine encoded SARS-CoV-2, WT and other relevant strains. | • S-specific responses at D1, D15, D31, M6<br>• Other read-outs may be performed if deemed necessary. |

Ab: Antibody; AE: Adverse event; AESI: Adverse events of special interest; D: Day; GMR: Geometric mean ratio; GMT: Geometric mean titer; ICS: intracellular cytokine staining; IgG: Immunoglobulin G; M: Month; MAAE: Medically attended adverse events; N: Nucleocapsid; pIMD: potential Immune-mediated disease; RT-PCR: Real-time polymerase chain reaction; S: Spike; SAE: Serious adverse event; VAED: Vaccine associated enhanced disease; WT: Wild type.

*AESI include pIMDs, myocarditis/pericarditis, virologically confirmed COVID-19 cases and anaphylaxis or severe hypersensitivity within 24 hours after study vaccination (Protocol Section 8.4.4).

## Table 2 Estimands

| Estimand | Attributes | | | | | Summary measure |
|---|---|---|---|---|---|---|
| | Treatment | Population | Endpoint (Variable) | Intercurrent events (ICEs) | | |
| | | | | Description | Handling strategy | |
| Primary | One dose of the investigational mRNA-CR vaccine. | Healthy adults, 18 to 49 years of age, who were primed and received booster dose(s) of an authorized or licensed mRNA COVID -19 vaccine with the last booster dose administered at least 6 months or more prior to screening, inclusive at the time of the vaccination. | • Solicited administration site events and systemic events with onset during the 7-day follow-up period after study vaccine administration (day of study vaccine administration and 6 subsequent days);<br>• Unsolicited AEs with onset during the 30-day follow-up period after study vaccine administration (day of study vaccine administration and 29 subsequent days);<br>• Any hematological and biochemical laboratory abnormality during | • Study vaccination not administered as per protocol<br>• Any intercurrent conditions or any concomitant medication/vaccination that may confound the safety investigational product causality assessment prior to D31 | The data collected from all participants receiving one dose of investigational vaccine will be used regardless of whether the intercurrent event occurs (Treatment policy)<br><br>Rationale: treatment policy strategy is used as all data will contribute to evaluate the safety parameters. | Proportion of participants in each treatment group for each endpoint |

| Estimand | Attributes | | | | | Summary measure |
|---|---|---|---|---|---|---|
| | Treatment | Population | Endpoint (Variable) | Intercurrent events (ICEs) | | |
| | | | | Description | Handling strategy | |
| | | | the 15-day follow-up period after study vaccine administration (day of study vaccine administration and 14 subsequent days);<br>• MAAEs; SAEs; AESIs up to D31. | | | |
| Secondary | One dose of the investigational mRNA-CR vaccine. | Healthy adults, 18 to 49 years of age, who were primed and received booster dose(s) of an authorized or licensed mRNA COVID -19 vaccine with the last booster dose administered at least 6 months or more prior to screening, | MAAEs; SAEs; AESIs from Day 1 up to study conclusion (M6). | • Study vaccination not administered as per protocol<br>• Any intercurrent conditions or any concomitant medication/vaccination that may confound the safety investigational product causality assessment prior to M6 | The data collected from all participants receiving one dose of investigational vaccine will be used regardless of whether the intercurrent event occurs (Treatment policy)<br>Rationale: treatment policy strategy is used as all data will contribute to evaluate the safety parameters | Proportion of participants in each treatment group for each endpoint |

| Estimand | Attributes | | | | | Summary measure |
|---|---|---|---|---|---|---|
| | Treatment | Population | Endpoint (Variable) | Intercurrent events (ICEs) | | |
| | | | | Description | Handling strategy | |
| | | inclusive at the time of the vaccination. | | | | |
| Secondary | One dose of the investigational mRNA-CR vaccine. | Healthy adults, 18 to 49 years of age, who were primed and received booster dose(s) of an authorized or licensed mRNA COVID -19 vaccine with the last booster dose administered at least 6 months or more prior to screening, inclusive at the time of the vaccination. | Neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint (D1, D15, D31, M6). | • Study vaccination not administered as per protocol<br>• A condition that has the capability of altering the immune response (e.g., HIV, lymphoma, COVID) to the study intervention or is confirmed to have an alteration of the participant's initial immune status<br>• Major protocol deviations including out of visit window blood samples. | The Hypothetical strategy will be used. The data after the ICEs will be ignored.<br>Rationale: To estimate the treatment effect on participants who are dosed and have no major protocol deviations. | Geometric Mean Titer for each treatment group |

| Estimand | Attributes | | | | | Summary measure |
|---|---|---|---|---|---|---|
| | Treatment | Population | Endpoint (Variable) | Intercurrent events (ICEs) | | |
| | | | | Description | Handling strategy | |
| Secondary | One dose of the investigational mRNA-CR vaccine. | Healthy adults, 18 to 49 years of age, who were primed and received booster dose(s) of an authorized or licensed mRNA COVID -19 vaccine with the last booster dose administered at least 6 months or more prior to screening, inclusive at the time of the vaccination. | GMR from baseline (D1) of neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint. | • Study vaccination not administered as per protocol<br>• A condition that has the capability of altering the immune response (e.g. HIV, lymphoma, COVID) to the study intervention or is confirmed to have an alteration of the participant's initial immune status<br>• Major protocol deviations including out of visit window blood samples. | The Hypothetical strategy will be used. The data after the ICEs will be ignored.<br>Rationale: To estimate the treatment effect on participants who are dosed and have no major protocol deviations. | Geometric Mean Ratio for each treatment group |
| Secondary | One dose of the investigational mRNA-CR vaccine. | Healthy adults, 18 to 49 years of age, who were primed and received booster | Vaccine response rate based on neutralizing titers against vaccine encoded SARS-CoV-2 and WT | • Study vaccination not administered as per protocol<br>• A condition that has the capability of altering the immune | The Hypothetical strategy will be used. The data after the ICEs will be ignored.<br>Rationale: To estimate the treatment effect on participants | Vaccine response rate in each treatment group for each endpoint |

| Estimand | Attributes | | | | | Summary measure |
|---|---|---|---|---|---|---|
| | Treatment | Population | Endpoint (Variable) | Intercurrent events (ICEs) | | |
| | | | | Description | Handling strategy | |
| | | dose(s) of an authorized or licensed mRNA COVID -19 vaccine with the last booster dose administer at least 6 months or more prior to screening, inclusive at the time of the vaccination. | strains at each collection timepoint. | response (e.g. HIV, lymphoma, COVID) to the study intervention or is confirmed to have an alteration of the participant's initial immune status<br>• Major protocol deviations including out of visit window blood samples. | who are dosed and have no major protocol deviations. | |

## 1.2. Study Design

This is an exploratory, FTIH, observer-blind, randomized, controlled study.

In part A of this study, three doses (10 µg, 30 µg, and 100 µg) of the mRNA-CR-04 vaccine will be evaluated. Approximately 72 eligible healthy adults, 18 to 49 years, inclusive, will be enrolled with 24 participants per group (Group 1, Group 2 and Group 3). Within each group, participants will be randomly assigned in a 3:1 ratio:

- 18 participants will receive the investigational mRNA-CR-04 vaccine and
- 6 participants will receive a saline placebo (sodium chloride [NaCl] isotonic solution [0.9%]).

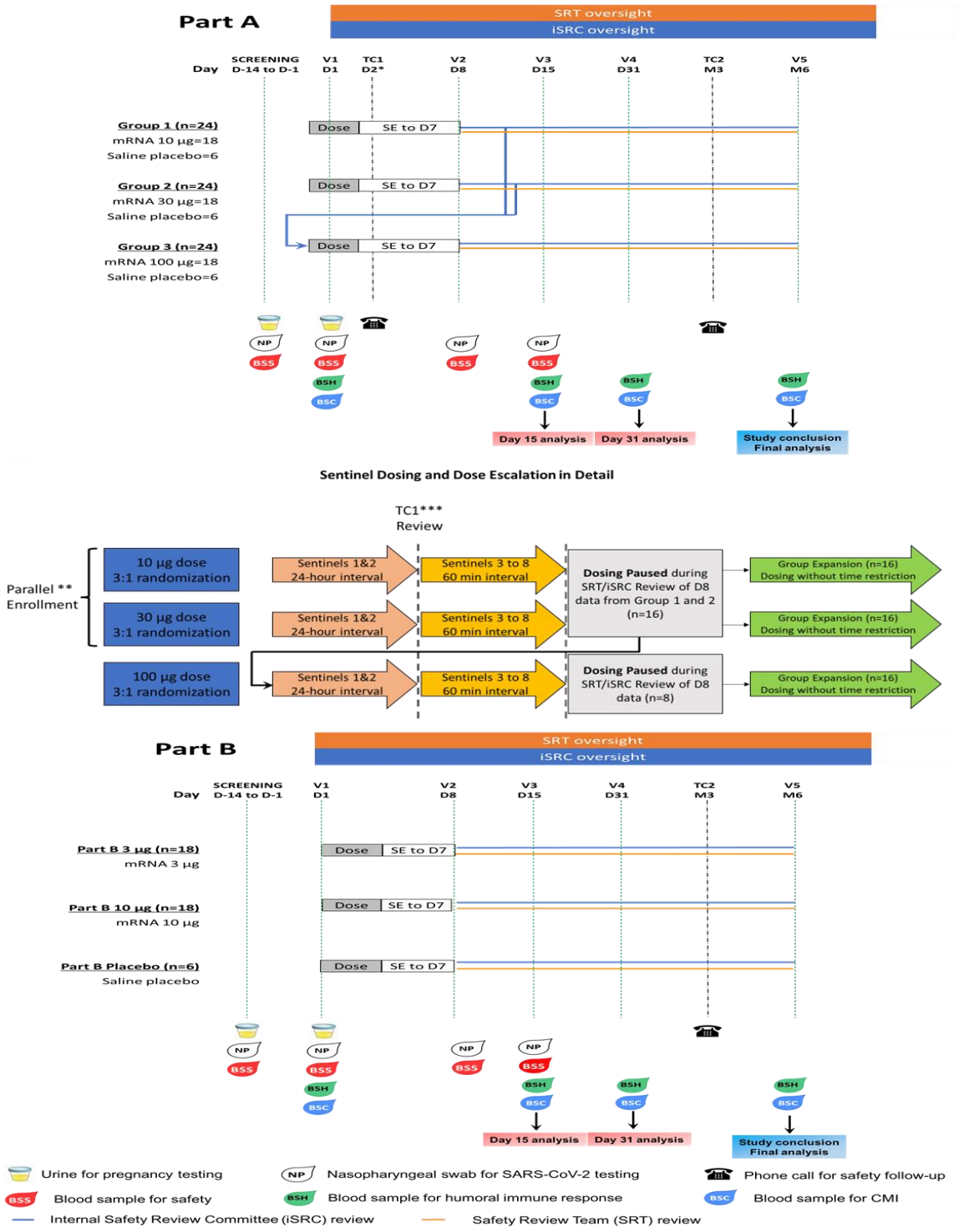
In Part B of the study, 2 doses (3 µg and 10 µg) of the mRNA-CR-04 vaccine will be evaluated. Approximately 42 eligible healthy adults, 18 to 49 years, inclusive, will be enrolled in Part B and will be randomly assigned in a 3:3:1 ratio:

- 18 participants will receive 3 µg of the investigational mRNA-CR-04 vaccine and
- 18 participants will receive 10 µg of the investigational mRNA-CR-04 vaccine and
- 6 participants will receive a saline placebo (sodium chloride [NaCl] isotonic solution [0.9%]).

Study duration for all the participants will be approximately 6 months, and they will be evaluated for safety, reactogenicity and immunogenicity. Safety monitoring and safety data review will be performed by a GSK SRT (blinded data review until Part A Day 15 interim analysis, unblinded review subsequently) and a GSK iSRC (unblinded data review).

Overview of the study design is presented in Figure 1.

**Figure 1 Study design overview**




CMI: Cell-mediated immunity; D: Day; M: Month; mRNA: mRNA-CR-04 vaccine; n: Number of participants; SE: Solicited events; TC: Telephone call; V: Visit.

* TC1 D2 only for sentinel participants in each group. ** The first participant is to be enrolled in Group 1. In addition to the defined intervals between doses within each group, an interval of at least 60 minutes will be maintained between the vaccination of sentinel participants across Group 1 and Group 2. *** TC1 review will be performed by the SRT on blinded data.

Table 3 and Table 4 describe the Part A and Part B study groups, interventions, and blinding, respectively.

**Table 3 Part A study groups, intervention and blinding**

| Study groups | Number of participants | Age (Min-Max years of age) | Study intervention(s)/vaccine(s) mode of administration | | Blinding |
|---|---|---|---|---|---|
| | | | | | Screening→Visit5 |
| Group 1 | 18 | 18 – 49 | mRNA-CR-04 vaccine 10 µg | Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm. | Observer-blind |
| | 6 | 18 – 49 | Saline placebo (NaCl [0.9%]) | | |
| Group 2 | 18 | 18 – 49 | mRNA-CR-04 vaccine 30 µg | Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm. | Observer-blind |
| | 6 | 18 – 49 | Saline placebo (NaCl [0.9%]) | | |
| Group 3 | 18 | 18 – 49 | mRNA-CR-04 vaccine 100 µg | Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm. | Observer-blind |
| | 6 | 18 – 49 | Saline placebo (NaCl [0.9%]) | | |

NaCl: Sodium chloride.

**Table 4 Part B study groups, interventions, and blinding**

| Study groups | Number of participants | Age (Min-Max years of age) | Study intervention(s)/vaccine(s) mode of administration | | Blinding |
|---|---|---|---|---|---|
| Part B 3 µg | 18 | 18 – 49 | mRNA-CR-04 vaccine 3 µg | Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm. | Observer-blind (except sponsor) |
| Part B 10 µg | 18 | 18 – 49 | mRNA-CR-04 vaccine 10 µg | Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm. | Observer-blind (except sponsor) |
| Part B Placebo | 6 | 18 – 49 | Saline placebo (NaCl [0.9%]) | Intramuscular injection into the deltoid muscle, preferably of the non-dominant arm. | Observer-blind (except sponsor) |

NaCl: Sodium chloride.

# 2. STATISTICAL HYPOTHESES

There is no hypothesis testing in this study; all analysis will be performed in a descriptive manner. Means and proportions for different objectives will be computed with their 95% confidence intervals (CIs).

## 2.1. Multiplicity Adjustment

N/A

# 3. ANALYSIS SETS

## 3.1. Definition

**Table 5 Analysis sets**

| Analysis set | Description | Analyses Evaluated |
|---|---|---|
| **Screened** | All participants who were screened for eligibility. | Study Population |
| **Enrolled** | Participants who completed the informed consent process, meet screening/eligibility criteria and undergone an invasive procedure.<br>Note: screening failures (who never passed screening even if re-screened) 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** | All participants who received the dose of the study intervention. Analysis per group using the enrolled set based on the administered intervention. | Safety excluding solicited AE |
| **Per Protocol** | All eligible participants who received dose of study intervention as per protocol, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination, and who have values for pre-dose and post-dose neutralizing titer against pseudovirus bearing BA. 5 S protein data for the relevant timepoint, and without major protocol deviations.<br>The PPS for immunogenicity will be defined by time point. | Immunogenicity |
| **Solicited Safety** | All participants who received the dose of the study intervention (Exposed Set) who have reported the presence or absence of any solicited AE at least once. | Safety |

AE: Adverse event; D: Day; S: Spike; PPS: Per Protocol Set

# 4. STATISTICAL ANALYSES

## 4.1. General Considerations

Standard data derivation rules and statistical methods are described in section 6.2.

Unless otherwise specified, analysis of safety endpoints will be performed on the Exposed Set. The primary analysis of the immunogenicity endpoints will be performed on the Per Protocol Set (PPS).

### 4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

For a given participant and given immunogenicity measurement, missing or non-evaluable measurements will neither be imputed nor be replaced, and therefore will not be included in immunogenicity analysis.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category. Unless otherwise specified, summary table will be presented by treatment group for Part A and Part B separately (i.e. 10 µg, 10 µg placebo, 30 µg, 30 µg placebo, 100 µg, 100 µg placebo, and pooled placebo for Part A safety analyses, and 10 µg, 30 µg, 100 µg, and pooled placebo for Part A immunogenicity analyses, and 3 µg, 10 µg, and placebo for Part B), and for combined part A & B with aggregated common groups (i.e. 3 µg, 10 µg, 30 µg, 100 µg, placebo).

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

### 4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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

## 4.2. Primary Endpoint(s) Analyses

### 4.2.1. Safety and Reactogenicity

#### 4.2.1.1. Analysis of safety and reactogenicity planned in the protocol

Solicited safety endpoints will be performed on the Solicited Safety Set. Unsolicited safety endpoints will be performed on the Exposed Set. Other adverse events/medically attended events, and safety lab data will be performed on the Exposed Set.

| Primary Safety Endpoints | Statistical Analysis Methods |
|---|---|
| Solicited administration site events and systemic events during the 7-day follow-up period after study vaccine administration (day of study vaccine administration and 6 subsequent days); | Solicited AEs are prespecified as administration site and systemic. Solicited AEs are AEs with onset from Day 1 – Day 7 after the dosing and captured in eDiary.<br><br>The number and percentage with exact 95% CI of participants reporting at least one solicited administration site event, with at least one solicited systemic event, and with any solicited AE during the 7-day period (i.e. with onset from Day 1- Day 7 post vaccination) will be tabulated by treatment group. The same tabulations will be performed for Grade 3 AEs.<br><br>The number and percentage with exact 95% CI of participants reporting each individual solicited administration site event (any grade, Grade 1, Grade 2, Grade 3, medically attended events) and solicited systemic event (any grade, Grade 1, Grade 2, Grade 3, medically attended events) during the 7-day follow-up period (i.e. with onset from Day 1- Day 7 post vaccination) will be tabulated by maximum intensity per participant for each treatment group. |
| Unsolicited AEs during the 30-day follow-up period after study vaccine administration (day of study vaccine administration and 29 subsequent days); | The number and percentage with exact 95% CI of participants reporting at least one unsolicited AE during the 30-day follow-up period (i.e. with onset from Day 1 to Day 30 post vaccination), as classified by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) will be tabulated by treatment group.<br><br>The same tabulations will be performed for Grade 3, any causally related, Grade 3 causally related unsolicited AEs and unsolicited AEs with medically attended visits.<br><br>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. |
| Any hematological and biochemical laboratory abnormality during the 15-day follow-up period after study vaccine administration (day of study vaccine administration and 14 subsequent days); | For each treatment group and for each Hematology and biochemistry parameter:<br>• The number and percentage with exact 95% CI of participants having hematology and biochemistry results below, within, or above the laboratory normal ranges will be tabulated by time point.<br>• The number and percentage of subjects reporting a grading increase from baseline at Day 8 and |

| Primary Safety Endpoints | Statistical Analysis Methods |
|---|---|
| | Day 15 separately. The maximum grading post vaccination up to Day 15 (i.e. Day 1 – Day 15) will be tabulated versus baseline. Grades will be based on the FDA guidance for industry "Toxicity grading scale for healthy adults and adolescent volunteers enrolled in preventive vaccine clinical trials" (Protocol Section 10.2.2).<br>• The listing of safety laboratory results will be provided |
| MAAEs; SAEs; AESIs up to D31. | The number and percentage with exact 95% CI of participants reporting MAAEs, SAEs, and AESIs after the dose up to Day 31 (i.e. with onset from Day 1 to Day 30 post vaccination), as classified by the MedDRA SOC and PT, will be tabulated by treatment group. The same tabulation will be performed for causally related MAAEs, SAEs and AESIs during this period (i.e. with onset from Day 1 to Day 30 post vaccination).<br>The detailed listings of SAEs, AESIs and COVID-19 cases will also be produced. |

#### 4.2.1.2. Additional considerations

##### *4.2.1.2.1. Analysis of solicited events*

The analysis of solicited events will be performed on Solicited Safety Set.

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 [Food and Drug Administration , 2007] with Grades 3 and 4 combined and swelling evaluated using the actual measurement only. Analysis by grade will use the maximum grade from Day 1 to Day 7 post vaccination.

When solicited AE data entered by the participant are incorrect, data collected by study investigator/staff on eDiary Follow-up Assessment form in Subject Case Report Forms will be used in the summaries if available.

The duration of solicited AEs of any grade will be summarized by treatment. 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 report period (i.e. from Day 1 to Day 7) with grade above or equal to specific grade will be summarized by treatment.

Duration in days of solicited administration site and systemic events will be listed. Prolonged solicited AEs that continue beyond Day 7 will be identified using a flag in listing of AEs.

The derivation rule of duration in days for solicited events is detailed in section 6.2.3.8.

#### *4.2.1.2.2. Analysis of unsolicited events*

The analysis of unsolicited events will be performed on Exposed Set.

#### *4.2.1.2.3. Combined solicited events and unsolicited events excluding serious AEs*

The combined analysis of solicited and unsolicited events will be performed on the Exposed Set. A listing of participants with all combined solicited and unsolicited adverse events will be provided.

Solicited adverse events will be coded by MedDRA.

For clintrial.gov posting purposes, a summary of combined solicited and unsolicited adverse events excluding serious AEs will be produced by System Organ Class and preferred terms and according to occurrence of each event.

### 4.2.1.3. Adverse Events of Special Interest

The analysis of adverse events of special interest will be performed on Exposed Set.

For adverse events of special interest (AESI) collected up to study conclusion (M6), the following will be considered for the purpose of analyses:

- pIMDs
- Anaphylaxis or severe hypersensitivity reactions within 24 hours after study intervention administration
- Pericarditis and myocarditis.
- Virologically confirmed COVID-19 cases (Protocol Section 8.4.4.2.2)

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.

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 D1 to D30 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.

## 4.3. Secondary Endpoint(s) Analyses

### 4.3.1. Safety

#### 4.3.1.1. Analysis of safety and reactogenicity planned in the protocol

The analysis of secondary safety endpoints will be performed on the Exposed Set.

| Secondary Safety Endpoints | Statistical Analysis Methods |
|---|---|
| MAAEs; SAEs; AESIs up to study conclusion (M6). | The number and percentage with exact 95% CI of participants reporting MAAEs, SAEs, and AESIs after the dose up to study conclusion (Month 6), as classified by the MedDRA SOC and PT, will be tabulated by treatment group. The same tabulation will be performed for causally related MAAEs, SAEs and AESIs during this period. The detailed listings of SAEs, AESIs and COVID-19 cases will also be produced. The number and percentage with exact 95% CI of participants reporting AEs/SAEs leading to withdrawal from the study will be tabulated. |

### 4.3.2. Immunogenicity

#### 4.3.2.1. Analysis of immunogenicity planned in the protocol

The analysis of the secondary immunogenicity endpoints will be performed on the PPS. The descriptive summary will consist in the number of results available (N), standard deviation, median, interquartile, minimum, and maximum, GMT or GMR, and associated 95% CIs. For the analysis of immunogenicity, missing or non-evaluable measurements will not be replaced. Therefore, a participant will be excluded from an analysis if all measurements are missing or non-evaluable.

If more than 10% of participants with BA.5 immunogenicity data at Day 15 are eliminated from any of the PPS in any treatment group, a sensitivity analysis will be carried out using the Exposed Set.

| Secondary Immunogenicity Endpoints | Statistical Analysis Methods |
|---|---|
| Neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint (D1, D15, D31, M6). | Neutralizing titer (GMT) against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains will be tabulated with 95% CI at baseline and each post vaccination visit by treatment. The 95% CI will be calculated based on the t-distribution of the log-transformed value of GMT, then back-transformed to the original scale for presentation with the assumption that log-transformed concentration is normally distributed with variance specific to each treatment group.<br><br>Bar charts (including 95% CIs) of GMT in log10 scale at each visit by treatment will be provided.<br><br>At each post vaccination timepoint, the adjusted GMTs of neutralizing titer, with their 95% CI, will be obtained using an ANCOVA model on log10 transformed titers with treatment group as a fixed factor, and log10 transformed Day 1 baseline value as a covariable.<br><br>Once Part B data are available, Part A and Part B data will be pooled together for model based analyses. When pooled, the study part will be added as a fixed factor and adjusted GMT will be estimated under Part A condition. Groups common in Part A and Part B will be combined as one group respectively for the pooled analysis. Outputs will be displayed by 3 µg, 10 µg, 30 µg, 100 µg, and pooled placebo.<br><br>Listing of neutralizing titers sorted by treatment and participant number will be provided. |
| GMR from baseline (D1) of neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint. | GMR from baseline of neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains will be tabulated with 95% CI at each post vaccination visit by treatment. The 95% CI will be calculated based on the t-distribution of the log-transformed fold rise value for GMR, then back-transformed to the original scale for presentation.<br><br>Bar charts (including 95% CIs) of GMR in log2 scale at each post vaccination visit by treatment will be provided.<br><br>At each post vaccination timepoint, the adjusted GMRs from baseline of neutralizing titer, with their 95% CI, will be obtained using an ANCOVA on log10 transformed |

| Secondary Immunogenicity Endpoints | Statistical Analysis Methods |
|---|---|
| | titers with treatment group as a fixed factor, and log10 transformed Day 1 baseline value as a covariable. Once Part B data are available, Part A and Part B data will be pooled together for model based analyses. When pooled, the study part will be added as a fixed factor and adjusted GMR will be estimated under Part A condition. Groups common in Part A and Part B will be combined as one group respectively for the pooled analysis. Outputs will be displayed by 3 µg, 10 µg, 30 µg, 100 µg, and pooled placebo.<br><br>In addition, the similar ANCOVA model for GMR from baseline will be performed to further evaluate the linear dose effect, using dose level as a continuous variable. |
| Vaccine response rate based on neutralizing titers against vaccine encoded SARS-CoV-2 and WT strains at each collection timepoint. | The number and percentage with exact 95% CI of participants with vaccine responses of at least a 2, 4, and 8 fold increases from Day 1 baseline, with their exact 95% CI will be tabulated by treatment and visit. |

The following SAS code will be used to calculate GMT/GMR from baseline, where LOGVAL is the log10 transformed GMT/GMR values at each post vaccination point, and Base is log10 transformed pre-dose GMT value. The analyses will be performed on PPS only.

```
Proc sort data = study; by group step; run; /** group will be sorted with order of Placebo, 3, 10 , 30, 100***/;
proc MIXED data=study;
class group (ref='Placebo')  step (ref='1'); /**step='1' indicates Part B,  base=log pre-vaccination titer**/;
    model LOGVAL = BASE group step/ solution noint;
    estimate  'Placebo'    base X    group 0 0 0 0 1 step 1 0/ cl;
    estimate  '3'          base X    group 1 0 0 0 0 step 1 0/ cl;
    estimate '10'          base X    group 0 1 0 0 0 step 1 0/ cl;
    estimate '30'          base X    group 0 0 1 0 0 step 1 0/ cl;
    estimate '100'         base X    group 0 0 0 1 0 step 1 0/ cl;
 ods output estimates=estmrnalin;
quit;
```

where X is GMT at pre-dose across groups for Part A.

The following SAS code will be used to further evaluate the linear dose effect on GMR from baseline of neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-CoV-2 and WT strains, where LOGVAL is the log10 transformed GMR values at each post vaccination point, and Base is log10 transformed pre-dose titer value. The analyses will be performed on PPS only.

```
proc MIXED data=study;
    class step (ref='1'); /**step='1' indicates Part B, base=log pre-vaccination titer**/;
    model LOGVAL = BASE dose step/ solution;
    estimate   'Placebo'    intercept 1 base X  dose 0    step 1 0/ cl;
    estimate   '3'          intercept 1 base X  dose 3    step 1 0/ cl;;
    estimate  '10'          intercept 1 base X dose 10    step 1 0/ CL;
    estimate  '30'          intercept 1 base X dose 30    step 1 0/ CL;
    estimate '100'          intercept 1 base X dose 100   step 1 0/ CL;
    ods output estimates=estmrnalin;
  quit;
```

where X is GMT at pre-dose across groups for Part A.

Geometric mean ratios (GMRs) will be computed at each sampling timepoint after dosing versus baseline (D1). The GMRs and 95% Cis will be constructed by exponentiating (base 10) the means of within-participant differences between log-transformed titers after each sampling timepoint and log-transformed titers at baseline. GMR will be calculated only for participants with valid baseline immunogenicity results.

#### 4.3.2.2. Additional considerations

NA.

## 4.4. Tertiary Endpoint(s) Analyses

The analysis will be based on the PPS.

### 4.4.1. Analysis of Serum-Binding Antibody (IgG)

If more than 10% of participants are eliminated from any of the PPS in any treatment group, a sensitivity analysis will be carried out using the Exposed Set.

#### 4.4.1.1. GMCs and GMR from baseline of binding IgG Ab against SARS-CoV-2 Spike WT (D614), SARS-CoV-2 Spike BA.5, SARS-CoV-2 Spike D614G, SARS-CoV-2 Spike (B.1.617.2, AY.4), SARS-CoV-2 Spike (B.1.1.529, BA.1, BA.1.15), SARS-CoV-2 Spike BQ.1, SARS-CoV-2 Spike XBB.1, SARS-CoV-2 Spike BA.2.275, SARS-CoV-2 Spike XBB.1.5, SARS-CoV-2 Spike XBB.1.16 variants at each collection timepoint

The descriptive summary will consist in the number of results available (N), standard deviation, median, interquartile, minimum, and maximum, GMC/GMR, and associated 95% CIs.

Immunogenicity of the study vaccine will be assessed through GMCs with associated CI at each collection time point before the vaccination (Day 1) and after the vaccination (Day 15, Day 31, M6). Likewise GMRs from baseline, percentage above Lower Limit of Quantitation (LLOQ), and corresponding 95% CI will be reported. The corresponding bar charts for GMC and GMR will be provided in log scale (log10 will be used for GMC while log2 will be used for GMR). For these analyses, CI for GMC and GMR will be derived from a student distribution assuming that log-transformed concentration is normally distributed with variance specific to each treatment group.

Distribution of geometric mean concentration fold changes from baseline for at least 2, 4, and 8 folds, with their exact 95% CI will be tabulated, by study group and visit.

The GMC at each post dose time point, the GMR from baseline, and the 95% CIs in all treatment groups will also be analysed using an ANCOVA model on log10 transformed concentrations with treatment group as fixed in the model, and log10 transformed Day 1 baseline value as covariable.
Once Part B data are available, Part A and Part B data will be pooled together for model based analyses. When pooled, the study part will be added as a fixed factor and adjusted GMC or GMR from baseline will be estimated under Part A condition. Groups common in Part A and Part B will be combined as one group respectively for the pooled analysis. Output will be displayed by 3 µg, 10 µg, 30 µg, 100 µg, and pooled placebo.

#### 4.4.1.2. Seroresponse rates, based on binding IgG Ab concentrations against SARS-CoV-2 Spike WT (D614), SARS-CoV-2 Spike BA.5, SARS-CoV-2 Spike D614G, SARS-CoV-2 Spike (B.1.617.2, AY.4), SARS-CoV-2 Spike (B.1.1.529, BA.1, BA.1.15), SARS-CoV-2 Spike BQ.1, SARS-CoV-2 Spike XBB.1, SARS-CoV-2 Spike BA.2.275, SARS-CoV-2 Spike XBB.1.5, SARS-CoV-2 Spike XBB.1.16 variants.

IgG seroresponse rate is defined as the percentage of participants who have either a baseline concentration < LLOQ and a post-dose concentration ≥4*LLOQ or a baseline concentration ≥LLOQ and at least a 4-fold increase from baseline to post-dose concentration.

The percentage of participants with IgG seroresponse of serum SARS-CoV-2 Spike WT, SARS-CoV-2 Spike BA.5, SARS-CoV-2 Spike D614G, SARS-CoV-2 Spike (B.1.617.2, AY.4), SARS-CoV-2 Spike (B.1.1.529, BA.1, BA.1.15), SARS-CoV-2 Spike BQ.1, SARS-CoV-2 Spike XBB.1, SARS-CoV-2 Spike BA.2.275, SARS-CoV-2 Spike XBB.1.5, SARS-CoV-2 Spike XBB.1.16 variants specific binding IgG from baseline at day 15, Day 31, M6 will be tabulated by study group with 2-sided 95% exact CIs.

### 4.4.2. Analysis of Cell-Mediated Immune Response

CMI Analysis will be performed using the Intracellular Cytokine Staining assay for WT(D614) and BA5 variants.

Descriptive statistics at each timepoint (Day 1, Day 15, Day 31, and M6) and change from baseline will be provided by treatment group for:

1. SARS-COV-2 spike-specific polypositive CD4+ T cell responses (frequency per million CD4) expressing at least 2 different markers with at least one cytokine, among CD40 Ligand (CD40L), 41-BB, IL-2, TNF- α, IFN- γ, IL-13 and IL-17 upon in vitro stimulation
2. SARS-COV-2 spike-specific polypositive CD8+ T cell responses (frequency per million CD8) expressing at least 2 different markers with at least one cytokine, among CD40 Ligand (CD40L), 41-BB, IL-2, TNF- α, IFN- γ, IL-13 and IL-17 upon in vitro stimulation.

Descriptive statistics of

1. CD4 T helper profile expressing at least IFN- γ (Th1);
2. CD4 T helper profile expressing at least IL-13 (Th2);
3. CD4 T helper profile expressing at least IL-17 (Th17)

at each timepoint (Day 1, Day 15, Day 31, and M6) will be provided by treatment group. The descriptive summary will consist in the number of results available (N), standard deviation, median, interquartile, minimum, and maximum, GMF and associated 95% CIs. The 95% CI will be calculated based on the t-distribution of the log-transformed values, then back-transformed to the original scale for presentation.

For polypositive CD4+ T cell and CD8+ T cell frequencies, geometric mean of frequency fold rise from baseline (GMFR) with 95% CI as well as the frequency of cells above LLOQ will also be provided. For the GMF and GMFR computation, titer below the LLOQ will be assigned the LLOQ value.

Bar Charts of each cell-mediated response for cytokines by treatment group and timepoint will also be produced on log10 transformed scale for GMF and log2 transformed scale for GMFR, including fold rise from baseline for polypositive CD4+ T cell and CD8+ T cell frequencies.

Supporting listing of CMI parameters will be sorted by treatment group and participant number.

As the frequency of CD4 (or CD8) by in vitro stimulation is separated for different antigen peptides or spikes, the frequency of antigen specific CD4 (or CD8) T cells for each individual participant will be calculated as follows:

1. For each antigen peptides or spikes, the difference between the frequency of CD4 (or CD8), upon in vitro stimulation with the antigen peptides or spikes (induction condition), and the frequency of CD4 (or CD8), upon in vitro stimulation in medium only (background condition) will be computed. Differences less or equal to one (1)

per $10^6$ CD4 (or CD8) T cells will be imputed to 1 antigen specific CD4 (or CD8) T cell per $10^6$ CD4 (or CD8) T cells.

2. The frequency associated to an antigen will then be obtained by summing the frequency of associated peptides or spikes as applicable:
   - for Wuhan antigen, S1 WU and S2 WU-SA frequencies will be added.
   - for Omicron, P1 Omicron and P2 Omicron frequencies will be added.

The imputation to LLOQ will be done on the frequency sum.

### 4.4.3. Incidence of confirmed symptomatic and asymptomatic SARS-CoV-2 infection

The percentage of participants of laboratory-confirmed SARS-CoV-2 by N protein seroconversion at either (D15, D31, and M6) or RT-PCR at either (D8, D15) will be summarized by treatment.

Percentage of laboratory-confirmed (RT-PCR) SARS-CoV-2 infection reported as AESI post-vaccination will be summarized by treatment.

Percentage of laboratory-confirmed (RT-PCR) SARS-CoV-2 infection reported as AESI or SARS-CoV-2 detected by N-protein and R-PCR post-vaccination will be summarized by treatment.

### 4.4.4. Other Tertiary Endpoints

Genetic sequence of SARS-CoV-2 variant S protein in confirmed (RT-PCR) SARS-CoV-2 positive participants will not be reported.

## 4.5. Analysis Interpretation

All analyses are descriptive.

## 4.6. Other Safety Analysis

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

A participant with an AE of SARS-CoV-2 infection can be categorized as “Asymptomatic SARS-CoV-2 infection”, “COVID-19” or “Severe COVID-19” to the case diagnosis question from the COVID-19 coronavirus infection assessment electronic Case Report Form (eCRF).

Any case of “COVID-19” or “Severe COVID-19” is an AESI; and will be captured and described.

The listing of participants with any category of SARS-CoV-2 infection will be provided based on the Exposed Set.

The listing of participants who had a COVID-19 test performed with their results will be provided on the Exposed Set.

## 4.7. Other Analysis

### 4.7.1. Subgroup analyses

N/A.

## 4.8. Interim Analyses

No interim analysis requiring statistical adjustment will be performed. Immunogenicity analysis will be performed on PPS, while safety analyses will be performed on Solicited Set for solicited AEs, Exposed Set for lab and unsolicited AEs. However, analyses to evaluate objectives and endpoints will be performed in steps. The sequence of analyses is described below.

### 4.8.1. Sequence of analyses

- In preparation of the safety review during the dose-escalation safety lead-in, analyses of available safety data will be performed.
- **Day 15 interim analysis** for each group in Part A of the study will include all the data (Day 1 and Day 15) pertaining to primary and secondary safety endpoints; humoral immunogenicity endpoints (including at least neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-COV-2 endpoints). This analysis will be performed when all data of each study group up to Day 15 (i.e., data that are as clean as possible) are available.
  - Results of this analysis will be presented in a Day 15 statistical analysis report.
  - This analysis will be performed by independent unblinded statistician who will be unblinded for this analysis, who will generate a statistical report by treatment group but no individual listings.
  - GSK restricted unblinded team will have access to the unblinded individual data.
  - The investigators and study participants will stay blinded (i.e., will not have access to the individual participant treatment assignment) until EoS.
  - For subsequent analyses the GSK statistical team will be unblinded to individual participants.
  - A similar to Part A Day 15 interim analysis for each group in Part B of the study may be conducted separately or incorporated into a Day 31 interim analysis.
- **Day 31 interim analysis** for each group in Part A of the study will include all the data (Day 1, Day 15, and Day 31) pertaining to primary and secondary safety endpoints; humoral immunogenicity endpoints (including at least neutralizing titer against pseudovirus bearing S protein from vaccine encoded SARS-COV-2 endpoints). This analysis will be performed when all data of each study group up to Day 31 (i.e., data that are as clean as possible) are available.
  - Results of this analysis will be presented in a Day 31 statistical analysis report.

  - The investigators and study participants will stay blinded (i.e., will not have access to the individual participant treatment assignment) until EoS.

- A similar to Part A Day 31 interim analysis for each group in Part B of the study may be conducted separately or incorporated into the final analysis.

- **The final analysis** will include all data from Part A and B pertaining to primary and secondary safety and immunogenicity endpoints, and any available tertiary endpoint(s). This analysis will be performed at the EoS when all data up to study conclusion (Month 6) are available, this includes Day 1, Day 15, Day 31, and Month 6, as all the data analyzed in the Day 15 and Day 31 analyses will be included in the final analysis as well.

The final study report will contain at least the final analyses of all primary and secondary endpoints, including individual listings.

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

### 4.9. Changes to Protocol Defined Analyses

Because RT-PCR at screening and Day 1 do not contribute to the incidence of SARS-CoV-2 infection they have been removed from the SARS-CoV-2 infection endpoint and summary.

## 5. SAMPLE SIZE DETERMINATION

The sample size is based on clinical considerations to inform dose regimen decisions for continued clinical development.

With 18 participants receiving mRNA-CR-04 vaccine in each group, there is a 60.3% probability to observe at least one participant with an AE if the incidence rate is 5% and 85% probability to observe at least one participant with an AE if the incidence rate is 10%.

With 16 participants receiving mRNA-CR-04 vaccine in each group (PPS for immunogenicity, 10% unevaluable), and a standard deviation of 0.45 for $\log_{10}$ transformed increase from Day 1, the ratio of the upper limit of a 2-sided 95% CI and the point estimate of GMR is 1.74.

# 6. SUPPORTING DOCUMENTATION

## 6.1. Appendix 1 Study Population Analyses

### 6.1.1. Participant Disposition

Participant disposition will be summarized by treatment and overall using descriptive statistics:

- Number of participants screened, randomised, vaccinated including withdrawal reasons will be tabulated.

Withdrawal status will be summarized using descriptive statistics:

- The number of participants exposed as well as the number of participants excluded from PPS analyses will be tabulated at D15, D31, and M6.
- The numbers of withdrawn participants will be tabulated according to the reason for withdrawal.

### 6.1.2. Demographic and Baseline Characteristics

#### 6.1.2.1. Analysis of demographics/baseline characteristics

These analyses will be performed on the Exposed set and PP set at Day 15, Day 31.

The demographic characteristics including height, weight, body mass index (BMI), age at screening in years, sex, race, ethnicity, and N protein) will be summarized by treatment using descriptive statistics.

- Frequency tables will be generated for categorical variable such as sex, race and ethnicity.
- Mean, median, standard error and range will be provided for continuous data such as age, height, weight and BMI.

The distribution of participants will be tabulated as a whole and per treatment group.

#### 6.1.2.2. Additional considerations

- Demographic characteristics will also be summarized on Enrolled Set for web public disclosure for Part A and Part B separately.
- The listing of past medical history and current medical conditions will be provided on the Exposed Set by Medical Dictionary for Regulatory Activities (MedDRA) term for Part A and Part B separately. Un-coded medical conditions or medical history will be listed under ‘Other’ category.
- Vaccination history will be coded using WHODRUG dictionary. The listing of vaccination history will be provided on the Exposed Set for Part A and Part B separately.

### 6.1.3. Protocol Deviations

Important protocol deviations will be listed based on the Exposed Set for Part A and Part B separately.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.
- A listing of protocol deviations will be provided.

Protocol deviations which result in exclusion from the analysis set will also be listed.

- Data will be reviewed prior to freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

In addition to the overall listing of important protocol deviations, separate listings will be produced for important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19 respectively if deemed necessary.

An individual listing of important protocol deviations leading to elimination will be provided.

### 6.1.4. Concomitant Medications

Concomitant medications and vaccinations will be coded using the WHODRUG dictionary.

The listing of participants taking concomitant medications /vaccinations within 7 days following study intervention administration, and 30 days following study intervention administration will be provided for Part A and Part B separately.

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, M03BC, M03BX |
| N02BG, N02AC, N02AG, N02AX, N02B, N02BA, N02BB, N02BE, N02AA |
| R05, R05D, R05X |

The number and percentage with exact 95% CI of participants reporting concomitant medication coded using the WHODRUG dictionary (any medication or any antipyretic) during the 7-day follow-up period (i.e. from Day 1 – Day 7) and during the 30-day

follow-up (i.e. from Day 1- Day 30) will be summarized by treatment group for Part A and Part B separately.

*The analysis will be performed on the Exposed Set.*

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

Depending on how the Covid-19 situation evolves, the SAP might be amended to reflect the analysis corresponding to Covid-19.

## 6.2. Appendix 2 Data Derivations Rule

### 6.2.1. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

### 6.2.2. Handling of missing data

#### 6.2.2.1. Dates

Partial dates will be displayed as captured in participant listing displays.

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

- A missing day will be replaced by 15;
- A missing day and month will be replaced by June 30$^{th}$;
- 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 on the same day as the vaccination but with missing time:
  - Onset day will be day 1.
- Adverse event start dates with missing day:
  - If the event starts in the same month as the study intervention administration, then the imputed start date will match the study dose given during that month.
- Adverse event start dates with missing day and month:
  - If the event starts in the same year as the study intervention administration, the imputed start date will match the study dose given during that year.

- Adverse event end dates with missing day:
  - If the event ends in the same month and year as the end of study date (if it exists) then the imputed end date will match the end of study date;
  - Otherwise, day will be imputed to the last day of the month.
- Adverse event end dates with missing day and missing month:
  - If the event ends in the same year as the end of study date (if it exists) then the imputed end date will match the end of study date
  - Otherwise, day and month will be imputed to the last day and month of the year i.e. 31st DEC

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.

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

Haematology/chemistry laboratory data requiring grading as per the protocol toxicity grading scale, which is based upon the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, may have more decimals than expected or may require conversion to the unit associated to the grade, leading to more decimals than expected.

In order 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. In case an approximation is needed to determine the grading, the result (or the result divided by the upper limit of the normal range (ULN), depending on the test) expressed in the expected unit will be rounded to the number of decimals used for the grading.

**Table 6 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)*** |
|---|---|---|---|---|
| **BUN mg/dL** | 23 – 26 | 27 – 31 | > 31 | Requires dialysis |
| **Creatinine mg/dL** | 1.5 – 1.7 | 1.8 – 2.0 | 2.1 – 2.5 | > 2.5 or requires dialysis |
| **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 |
| **ALP – increase by factor** | 1.1 – 2.0 x ULN | 2.1 – 3.0 x ULN | 3.1 – 10 x ULN | > 10 x ULN |
| **Bilirubin – when liver function test is normal; increase by factor** | 1.1 – 1.5 x ULN | 1.6 – 2.0 x ULN | 2.0 – 3.0 x ULN | > 3.0 x ULN |
| **Bilirubin – when accompanied by any increase in liver function test increase by factor** | 1.1 – 1.25 x ULN | 1.26 – 1.5 x ULN | 1.51 – 1.75 x ULN | > 1.75 x ULN |

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; ULN: upper limit of normal.

* Toxicity grading taken from FDA guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials [Food and Drug Administration , 2007].

** 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 7 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) |
|---|---|---|---|---|
| **Hemoglobin (Female) - gm/dL** | 11.0 – 12.0 | 9.5 – 10.9 | 8.0 – 9.4 | < 8.0 |
| **Hemoglobin (Female) change from baseline value - gm/dL** | Any decrease – 1.5 | 1.6 – 2.0 | 2.1 – 5.0 | > 5.0 |
| **Hemoglobin (Male) - gm/dL** | 12.5 – 13.5 | 10.5 – 12.4 | 8.5 – 10.4 | < 8.5 |
| **Hemoglobin (Male) change from baseline value – gm/dL** | Any decrease – 1.5 | 1.6 – 2.0 | 2.1 – 5.0 | > 5.0 |
| **WBC Increase - cell/mm$^3$** | 10,800 – 15,000 | 15,001 – 20,000 | 20,001 – 25,000 | > 25,000 |
| **WBC Decrease - cell/mm$^3$** | 2,500 – 3,500 | 1,500 – 2,499 | 1,000 – 1,499 | < 1,000 |
| **Lymphocytes decrease - cell/mm$^3$** | 750 – 1 000 | 500 – 749 | 250 – 499 | < 250 |
| **Neutrophils decrease - cell/mm$^3$** | 1,500 – 2,000 | 1,000 – 1,499 | 500 – 999 | < 500 |
| **Eosinophils - cell/mm$^3$** | 650 – 1 500 | 1,501 – 5,000 | > 5,000 | Hypereosinophilic |
| **Platelets decreased - cell/mm$^3$** | 125,000 – 140,000 | 100,000 – 124,000 | 25,000 – 99,000 | < 25,000 |
| **Prothrombin Time – increase by factor** | 1.03 – 1.10 x ULN | 1.11 – 1.20 x ULN | 1.21 – 1.25 x ULN | >1.25 x ULN |

ULN: Upper limit of the normal range; WBC: White blood cell.

* Toxicity grading taken from FDA guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials [Food and Drug Administration , 2007].

** 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

#### *6.2.2.3.1. Studies with electronic diaries*

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.

### 6.2.2.4. Unsolicited adverse events

Unsolicited AE summaries are including SAEs unless specified otherwise.

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

### 6.2.3. Data derivation

#### 6.2.3.1. Weight

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

Weight in kilograms = Weight in pounds / 2.2

#### 6.2.3.2. 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

#### 6.2.3.3. Body mass index (BMI)

BMI will be calculated as follows:

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

#### 6.2.3.4. 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

#### 6.2.3.5. 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 |

* Lower limit of quantitation (LLOQ)

**LLOQs for different assays**

| Antigen | Assay and assay unit | LLOQ |
|---|---|---|
| SARS-CoV-2 Spike BA.5 | PNA (NT50) | 10 |
| SARS-CoV-2 Spike D614G | PNA (NT50) | 10 |
| SARS-CoV-2 Spike Wuhan (D614) | IgG (AU/mL) | 360 |
| SARS-CoV-2 Spike D614G | IgG (AU/mL) | 410 |
| SARS-CoV-2 Spike XBB.1 | IgG (AU/mL) | 120 |
| SARS-CoV-2 Spike B.1.617.2 (Delta) | IgG (AU/mL) | 790 |
| SARS-CoV-2 Spike XBB.1.5 | IgG (AU/mL) | 230 |
| SARS-CoV-2 Spike BA.2.75 | IgG (AU/mL) | 200 |
| SARS-CoV-2 Spike XBB.1.16 | IgG (AU/mL) | 170 |
| SARS-CoV-2 Spike B.1.1.529 (BA.1) | IgG (AU/mL) | 150 |
| SARS-CoV-2 Spike BQ.1 | IgG (AU/mL) | 170 |
| SARS-CoV-2 Spike BA.5 | IgG (AU/mL) | 220 |
| SARS-CoV-2 Spike Wuhan (D614) | Polypositive CD4+ T (10E6 cells) | 590 |
| SARS-CoV-2 Spike Wuhan (D614) | Polypositive CD8+ T (10E6 cells) | 590 |
| SARS-CoV-2 Spike Wuhan (D614) | CD4+ expressing at least IFN- γ (10E6 cells) | N/A |
| SARS-CoV-2 Spike Wuhan (D614) | CD4+ expressing at least IL-13 (10E6 cells) | N/A |
| SARS-CoV-2 Spike Wuhan (D614) | CD4+ expressing at least IL-17 (10E6 cells) | N/A |
| SARS-CoV-2 Spike BA.5 | Polypositive CD4+ T (10E6 cells) | 590 |
| SARS-CoV-2 Spike BA.5 | Polypositive CD8+ T (10E6 cells) | 590 |
| SARS-CoV-2 Spike BA.5 | CD4+ expressing at least IFN- γ (10E6 cells) | N/A |
| SARS-CoV-2 Spike BA.5 | CD4+ expressing at least IL-13 (10E6 cells) | N/A |
| SARS-CoV-2 Spike BA.5 | CD4+ expressing at least IL-17 (10E6 cells) | N/A |

#### 6.2.3.6. Geometric mean titres (GMTs) and GMCs

Geometric Mean Titre (GMT) or 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 6.2.3.5 for the purpose of GMT/GMC calculation. The cut-off value is defined by the laboratory before the analysis. If not otherwise specified, the cut-off refers to the LLOQ.

#### 6.2.3.7. Onset day

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

#### 6.2.3.8. 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.

#### 6.2.3.9. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited AEs, all SAEs might have to be considered general events since the administration site flag is not included in the expedited adverse event CRF pages.

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

#### 6.2.3.10. 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 one occurrence regardless of the number of days on which it occurs.

#### 6.2.3.11. AESIs

GSK MedDRA queries will be used to identify AESI:

- PIMD: refer to Table 12 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 list of MedDRA SMQs will be used: Cardiac arrhythmia, Cardiac failure, Cardiomyopathy, Ischaemic heart disease, Non-infectious myocarditis/ pericarditis, narrow search.
- Virologically confirmed COVID-19 cases: In addition to identification based on the medical and scientific judgement of the investigator, AEs under MedDRA SMQ COVID-19, narrow search will be used

This PIMD, Virologically confirmed COVID- 19 cases, Myocarditis and Pericarditis queries may be revised based on MedDRA dictionary.

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

### 6.2.4. Display of decimals

#### 6.2.4.1. Percentages

Percentages will be displayed with one decimal except for 100% in which case no decimal will be displayed.

#### 6.2.4.2. Differences in percentages

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

#### 6.2.4.3. Demographic/baseline characteristics statistics

The mean, median, and SD for continuous baseline characteristics (height, weight, BMI, pre-dose body temperature) will be presented with one 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 minimum and maximum of transformed height variables will be displayed with no decimals.

The minimum and maximum of transformed weight variables will be displayed with no decimals with the exception of values are below 10kg where one decimal will be displayed.

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

#### 6.2.4.4. Serological summary statistics

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

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

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

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

### 6.2.5. Statistical methodology

#### 6.2.5.1. Exact confidence intervals around proportions

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

# 7. REFERENCES

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

Food and Drug Administration (FDA). Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September, 2007. Accessed 07 April 2023. https://www.fda.gov/media/73679/download