STATISTICAL ANALYSIS PLAN

MERS003 - A study of a new vaccine against MERS Virus in adults aged 50 to 70

Trial Title: A phase I study to determine the safety and immunogenicity of a new vaccine against Middle East Respiratory Syndrome Coronavirus in Adults aged 50 to 70

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1. Introduction

This statistical analysis plan (SAP) describes the analysis methods for evaluation of the objectives of the MERS003 study.

1.1. Description of Study Design

This is a participant-observer blind, randomised, placebo-controlled, phase I trial to assess the safety, tolerability and immunogenicity of two administrations of an intramuscular ChAdOx1 MERS vaccine in adults aged 50 to 70 years. Participants will be considered enrolled in the study once their first vaccination has been administered.

1.2. Sample Size Determination & Randomisation

The trial aims to recruit up to 84 volunteers consisting of approximately 42 participants with no prior history of receiving ChAdOx1 nCoV-19 and approximately 42 participants who have previously received at least two doses of ChAdOx1 nCoV-19. There has been no formal power calculation to determine this figure as the study is primarily descriptive. The number of participants has therefore been chosen to pragmatically reflect logistical and budgetary constraints.

Participants will be randomised to receive either ChAdOx1 MERS or saline placebo with a 5:1 allocation ratio, as outlined in *Table 1*. Randomisation will be stratified by previous ChAdOx1 nCoV-19 vaccination (yes/no). Computerised randomisation will be done using REDCap, with randomisation lists generated by a study statistician. Participants will be replaced only if they have not received a dose of vaccine.

Table 1. Sample Sizes by Group

	At least 2 doses of prior ChAdOx1 nCoV-19 Vaccination (Group 1, n = 42)	**No Prior ChAdOx1 nCoV-19 Vaccination (group 2, n = 42)**
ChAdOx1 MERS Vaccine	n= 35*	n = 35*
Saline Placebo	n = 7*	n = 7*

*Approximate only.

1.3. The Level of Statistical Significance

The analyses for this study will be descriptive in purpose and will not include any hypothesis testing. All confidence intervals for descriptive analyses will be set at 95%.

1.4. Procedure for Accounting for Missing Data

There will be no imputations for missing data and missing data will be treated as missing at random. Participants will be analysed according to the treatment they received, regardless of the group to which they were assigned.

1.5. Objectives

The objectives of the MERS003 study are outlined in Table 2.

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Table 2. Objectives, Outcome Measures and Evaluation Timepoints

Outcome	Objective	Outcome measure	Evaluation Timepoints*
Primary	To assess the safety and tolerability of ChAdOx1 MERS vaccine in healthy volunteers.	a) Occurrence of solicited local reactogenicity signs and symptoms	Within 7 days of each vaccination
		b) Occurrence of solicited systemic reactogenicity signs and symptoms	Within 7 days of each vaccination
		c) Occurrence of unsolicited adverse events (AEs)	Within 28 days of each vaccination
		d) Change from baseline for safety laboratory measures	Within 28 days of each vaccination
		e) SAEs and AESIs	Whole duration of the study
Secondary	To assess the immunogenicity of ChAdOx1 MERS vaccine in healthy adult volunteers.	a) MERS spike protein specific serological response as measured by ELISA	D0, D14, D28, V2, V2+14, V2+28, V2+281
		b) MERS spike protein T cell response measured by IFN-γ ELISPOT	D0, D14, D28, V2, V2+14, V2+28, V2+281
Exploratory**	Immunological Profiling	a) MERS virus neutralising antibodies (using either live or pseudoneutralisation assays) b) Cellular immune response to MERS virus measured by ICS, proliferation and/or whole blood assays	Timepoints will be detailed in the lab analysis plan
	To assess anti-vector immunity following vaccination	a) Binding and/or neutralising antibody responses against ChAdOx1	Timepoints will be detailed in the lab analysis plan
	To investigate a potential relationship between the composition of the gut microbiota and vaccination outcomes	Characterisation of the gut microbiome composition and function	Baseline, D14, V2+14, V2+281

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2. Analysis Populations

Data from participants who withdraw consent to participate in the study will be included up to the date of their study termination (including laboratory data from samples, unless the participant withdraws consent for their samples to be used).

The populations for the analysis are defined in Table 3.

Table 3. Study Populations

Population	Description
Screened population	All volunteers screened for the trial, to be used for reporting of the trial enrolment profile
Enrolled population	All enrolled participants (considered enrolled once the first vaccination has been administered)
Immunology population	All enrolled participants providing at least one evaluable post-vaccination clinical immunology specimen, without a major violation (a protocol violation considered by the investigators to have an impact) which may have an effect on the immunological response.

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3. Analysis of Primary Safety and Tolerability Outcome

The primary outcome is to assess the safety and tolerability of the ChAdOx1 MERS vaccine in healthy volunteers. The analysis population for the primary outcome is "Enrolled population" per Table 3. No between-group comparisons will be performed; all results will be presented separately by treatment arm and prior ChAdOx1 vaccination group. Missing values will be treated as such in each calculation.

3.2. Occurrence of solicited local and systemic reactogenicity signs and symptoms

Each solicited adverse event (local and systemic) will be summarized by treatment arm and prior ChAdOx1 vaccination group for each of days 0-6 after vaccination. The counts and proportions of participants experiencing each adverse event will be reported as a total and for each grade of solicited event (as defined in the protocol), with accompanying 95% Clopper-Pearson confidence intervals. Participants should not be double counted; therefore, the event of greatest severity will be used for participants with more than one episode of the same event.

Similar counts and percentages may be presented for solicited local AEs "Overall" and solicited systemic AEs "Overall" across all 7 days.

3.3. Occurrence of unsolicited adverse events (AEs)

All AEs are unsolicited AEs unless categorised as solicited AEs. Unsolicited AEs will be summarized by treatment arm and prior ChAdOx1 vaccination group for days 0-27 following each study vaccination. These summaries might include the number of unsolicited AEs, the number of participants with unsolicited AEs, the number of AEs with severity grade ≥3, the number of participants with unsolicited AEs grade ≥3, the number of unsolicited AEs assessed by investigator to have a possible, probable, or definite relationship with the study intervention, and the number of participants with potentially related AEs.

Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) will not contribute to the unsolicited AE counts. These are described in section 3.5. Additional descriptive analyses will be presented as appropriate.

3.4. Change from baseline for safety laboratory measures

The counts and proportions of participants with changes in safety laboratory measures compared to the baseline grade (considered as the bloods taken immediately prior to each vaccination) will be determined for each individual laboratory parameter for days 14 and 28 following each vaccination. This will be presented by treatment arm and prior ChAdOx1 vaccination group. Out-of-window safety laboratory tests will be included in the analysis of the corresponding time-point on a case-by-case basis, depending on the extent to which the sample was taken out of window.

3.5. Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs)

SAEs and AESIs will be summarized for the duration of the study. These summaries might include number of SAEs and AESIs by treatment arm and prior ChAdOx1 vaccination group, and number of participants experiencing an SAE or AESI, along with other descriptive analyses as appropriate. SAEs and AESIs will also be listed.

4. Analysis of Secondary Immunogenicity Outcome

The secondary objective is to assess the immunogenicity of ChAdOx1 MERS vaccine in healthy adult volunteers. The analysis population for the secondary outcome is the "Immunology Population" per Table 3. MERS spike protein specific serological response as measured by ELISA and MERS spike protein T cell response measured by IFN-γ ELISPOT will be presented at D0, D14, D28, V2, V2+14, V2+28, and V2+281 timepoints.

Descriptive statistics for geometric mean titres/concentrations (GMTs/GMCs) will include number of participants, geometric mean, 95% CIs, minimum and maximum. Medians, 25th quartiles and 75% quartiles may also be presented. Results reported as lower than the lower limit of detection (LLOD) will have a value equal to half of the LLOD imputed.

GMCs will be calculated as the antilogarithm of Σ (log10 transformed titre)/n, i.e., as the antilogarithm transformation of the mean of the log10 transformed titre, where n is the number of participants in that arm. The 95% CI will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log10 transformed titres.

The geometric mean ratio (GMR) will be calculated as antilogarithm of the difference between the means of the log10 transformed titre at post-vaccination timepoints across the two groups (participants with prior ChAdOx1 vaccination and those without). The two-sided 95% CI of the GMR will be calculated as the antilogarithm transformation of the upper and lower 95% CI limits of the difference of the log10 transformed means. The geometric mean fold rise (GMFR) of MERS spike protein specific serological response as measured by ELISA and MERS spike protein T cell response measured by IFN-γ ELISPOT may be presented between D0 (baseline) and peak response.

Out-of-window safety immunology tests will be included in the corresponding time-point on a case-by-case basis, depending on the extent to which the result is out of window.

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5. Review History

Date	Reviewed by	Review Type	Changes:	Previous version
July 2023	Kerry Conlin Merryn Voysey Daniel Jenkin Ilsa Heuler	New Document	First version	N/A

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