Statistical Analysis Plan

Study ID: 218407

Official Title of Study: Prospective cohort study to monitor the emergence of SARSCoV-2 spike viral variants in immunocompromised nonhospitalised patients exposed to sotrovimab in Great Britain: LUNAR study

Date of Document: 18-July-2023 (the latest date has been redacted as PI on page 3)

Statistical Analysis Plan for Real World Research Studies

Sponsor Name: GlaxoSmithKline (GSK)

Protocol Number: 218407
Protocol Title: PROSPECTIVE COHORT STUDY TO MONITOR THE EMERGENCE OF SARS-COV-2 SPIKE VIRAL VARIANTS IN IMMUNOCOMPROMISED NON-HOSPITALISED PATIENTS EXPOSED TO SOTROVIMAB IN GREAT BRITAIN: LUNAR STUDY

Protocol Version and Date:
Version 01, 04-May-2022

Syneos Health Project Code: 7035538

Authors: PPD , Sr Biostatistician

Notice of Confidential and Proprietary Information:

1. Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owners	Revision Summary
1.0	12-Jan-2023	PPD	Initial Release Version (Interim Analysis)
2.0	14-Jul-2023		Updates for Final Analysis

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD , Senior Biostatistician	PPD	
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
PPD , Mgr, statistical Programmer	PPD	
Name, Title Lead Statistical Programmer	Signature	Date (DD-Mmm-YYYY)
PPD		
Name, Title Senior Reviewing Biostatistician	Signature	Date (DD-Mmm-YYYY)

GlaxoSmithKline Approval

PPD , Lead Biostatistician	PPD	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
PPD , Virology Lead	PPD	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
PPD , Clinical Science Lead	PPD	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
PPD , Scientific Lead, Epidemiology	PPD	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)
PPD , Study Delivery Lead	PPD	
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

2. Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AA	Amino Acid
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CMDU	COVID-19 Medicine Delivery Units
COVID-19	Coronavirus Disease 2019
DIA	Data Import Agreement
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GB	Great Britain
GISAID	Global Initiative on Sharing All Influenza Data
GSK	GlaxoSmithKline
HCP	HealthCare Professional
has	Health Security Agency
his	Human Safety Information
IC	Immunocompromised
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
QC	Quality Control
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PASS	Post Authorisation Safety Study
PCR	Polymerase Chain Reaction
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE(s)	Severe Adverse Event(s)
SAP	Statistical Analysis Plan

TFL	Tables Figures Listings
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SFTP	Secure File Transfer Protocol
SOP	Standard Operating Procedure
SYNH	Syneos Health
TEAE	Treatment Emergent Adverse Events
UCL	University College of London
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
VOC	Variant of Concern
VUI	Variant Under Investigation
WHO	World health Organization
EOS	End of Study
EAP	External Alliance Portal

2. Purpose

The purpose of this statistical analysis plan (SAP) is to document the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used to ensure they are complete and appropriate to allow valid conclusions regarding the study objectives.

This genomic surveillance study will aim to describe changes in the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spike protein observed in Immunocompromised (IC) patients receiving sotrovimab in sentinel sites at a national level to assess potential emergence of viral variants in Great Britain (GB).

2.1 Responsibilities

Syneos Health (SYNH) will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2 Timings of Analyses

As part of this genomic surveillance study, an interim and final analysis to United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) has been committed by GlaxoSmithKline (GSK). Interim analysis was performed half-way in to the recruitment period (i.e., 6 months over the whole recruitment period of 1 year) and the final analysis will be conducted after all participants complete the final study visit or terminate early from the study.

Tables, Figures and Listings pertaining to Interim and Final analysis can be found (See Section 14, 15, 16).

3. Study Objectives

Primary Objectives
1. Evaluate the proportion of patients eligible for sequence analysis that have any amino acid (AA) change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days)
2. . Evaluate the proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein in samples collected at Day 7, 14 and 28 (+/-2 days)
Secondary Objectives
1. Evaluate the proportion of patients eligible for sequence analysis with variants of concern (VOC) and under investigation (VUI) on the earliest possible sample including baseline
2. Evaluate the proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) by reverse transcriptase polymerase chain reaction (RT-PCR)
3. Evaluate the proportion of patients with key clinical outcomes (hospital admission, requirement for respiratory support, intensive care unit [ICU] admission and death) through Day 28 post sotrovimab administration
4. Describe AA (detected at >5% allelic frequency) changes in SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay
5. Describe AA changes in the consensus sequence (>50%) of SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads below the threshold for detection of AA changes at >5% allelic frequency but with sufficient levels to generate consensus sequencing data
Exploratory Objectives
1. Describe viral characteristics (e.g. viral load, VOC/VUI, AA changes) in patients who subsequently require hospital admission or die due to COVID-19 post sotrovimab treatment
2. Establish whether changes in AA from baseline identified in the SARS-CoV-2 spike protein are reported sequences in genomic databases (e.g. Global initiative on sharing all influenza data [GISAID])
3. Explore the feasibility of linkage with routinely collected samples (as per standard of clinical care) for spike protein monitoring in patients who remain SARS-CoV-2 positive beyond 28 days as part of a longer follow-up for this sub-population.

4. Study Details/Design

4.1 Brief Description

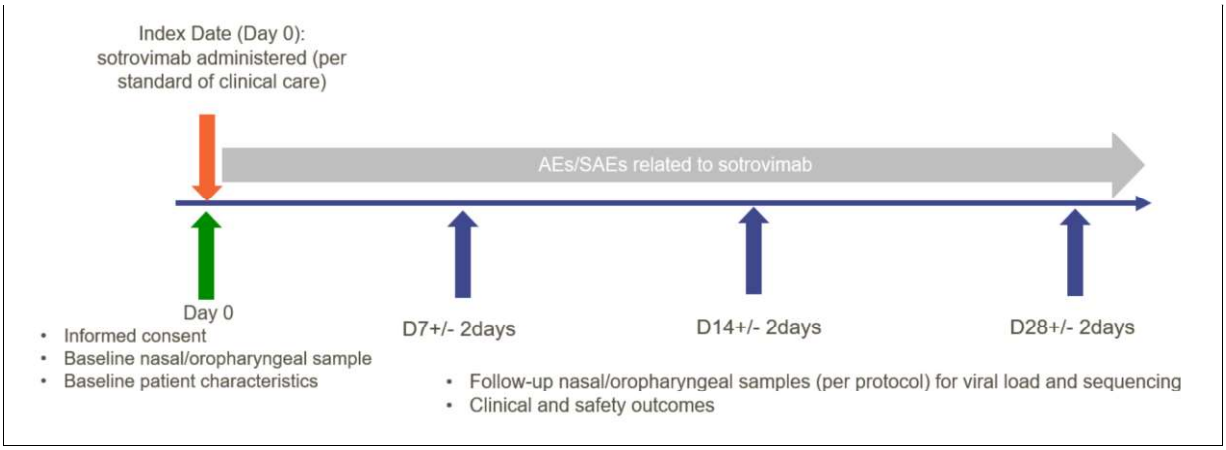
Sotrovimab was granted a conditional marketing authorisation for the treatment of early coronavirus disease 2019 (COVID-19) infection in GB on December 01, 2021. Sotrovimab is an early treatment that will be prescribed to patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who are at risk to progress to severe disease in non-hospitalised settings. There is a theoretical risk of monoclonal antibodies selecting for viral variants which could have the potential for increased transmissibility and/or reduced susceptibility to sotrovimab or to vaccine derived immunity. IC patients, who are on a prioritised list to receive treatment should they become infected, present a particular risk for variants because of their potential for prolonged viral shedding, and thus, present a risk for the emergence of mutations and potential onward community transmission. This genomic surveillance study will aim to describe changes in the SARS-CoV-2 spike protein observed in IC patients receiving sotrovimab in sentinel sites at a national level to assess potential emergence of viral variants.

4.2 Study Design

This is a phase IV, prospective cohort study amongst IC non-hospitalised patients treated with sotrovimab as part of standard clinical care to monitor the emergence of SARS-CoV-2 spike viral variants.

Patients will be followed for 28 days from the time they received sotrovimab treatment (index date (D0)) in one of the clinical sites. Data and samples will be collected following the schedule below (see also Table 1)

Figure 1



- Non-hospitalised patients who are being treated with sotrovimab as part of standard of clinical care will be screened and enrolled if eligible (Day 0 = baseline). Informed consent, patient characteristics (demographic and clinical), and treatment history (related to COVID-19 and underlying diseases) will also be recorded at Day 0.
- Baseline nasal/oropharyngeal swab sample will be collected on site, as per protocol, under supervision after training and sent to the central analytical laboratory.
- Follow-up nasal/oropharyngeal swab samples (Day 7, 14 and 28 (+/-2 days)) will be collected by the patients using home test kits or by healthcare professionals (HCP) in case of hospitalisation, as per protocol, with samples sent to the central analytical laboratory.

- Sequencing analyses will be conducted on all SARS-CoV-2 positive nasal/oropharyngeal swab samples that meet the threshold criteria for the sequencing assay.

4.3 Participant Selection

4.3.1 Inclusion Criteria

The inclusion criteria for are defined in the protocol section 8.2.1.

4.3.2 Exclusion Criteria

The exclusion criteria are defined in the protocol section 8.2.2.

4.4 Determination of Sample Size

As a sentinel surveillance study, the aim will be to collect 500 (and up to 625) patients over the course of a year across the whole of GB to meet the target sample size. Flexible enrolment caps per site and per month will be considered. The aim is to ensure continuous enrolment with appropriate geographical representation over the 12-month study period, to reflect the fast - evolving COVID-19 pandemic. In addition, the target sample size will be re-assessed after the first 200-300 patients are enrolled in regard to progression towards achieving the primary objective, with the potential to decrease or increase the target number accordingly.

For Further details please refer protocol section 8.5.

4.5 Treatment Assignment and Blinding

Not Applicable.

4.6 Administration of Study Medication

Sotrovimab Xevudy TM, dose and administration per standard of clinical care.

4.7 Study Procedures and Flowchart

Table 1:

	Baseline **(Day 0, sotrovimab index date)**	**Follow Up Call 1** **(Day 7 ± 2)[p]**	**Follow Up Call 2** **(Day 14 ± 2)[p]**	**Follow Up Call 3** **(Day 28 ± 2)[pq]**
Pre-screening[a]	√			
Confirmation of sotrovimab prescription[b]	√			
Informed Consent [c]	√			
Eligibility confirmation[d]	√			
Enrolment[e]	√			
Nasal nasal/oropharyngeal swab	√[f]	√[g]	√[g]	√[g]
Sotrovimab administration[h]	√			
Demography[i]	√			
Co-morbidities[j]	√			
Disease characterisation[k]	√			
Concomitant medications[l]	√	√	√	√
Vaccination status[m]	√	√	√	√
Clinical Outcomes[n]		√	√	√
Adverse events related to sotrovimab treatment[o]	√	√	√	√

[a] Pre-screening of potential patients is encouraged to make the eligibility and consent process as efficient as possible and reduce delay to sotrovimab administration.
[b] Evidence that the decision to administer sotrovimab was taken prior to consenting the patient to join the study must be documented in the patient's medical records.
[c] Informed consent must be taken prior to any study specific procedures being conducted with the patient.
[d] Evidence that all inclusion and no exclusion criteria have been met must be documented in the patient's medical records prior to enrolment.
[e] Register patient in EDC (Electronic Data Capture) system. Assign subject identification number to patient and document on enrolment log and patient materials (ICF [Informed consent form], contact card) and sample collection kits.
[f] The nasal/oropharyngeal swab at baseline must be taken prior to the administration of sotrovimab or as close as possible to the end of sotrovimab infusion. Patients must be trained in the self-administration of nasal/oropharyngeal swabs at baseline to support sample collection at follow up timepoints. Three sample collection kits must be provided to the patient for at home sample collection at follow up timepoints, staff must ensure correct subject identification number is present on each kit.
[g] Nasal/oropharyngeal swabs at follow up timepoints will be self-administered by the patient or HCP in case of hospitalisation. Samples must be returned to the central analytical laboratory by post as soon as

practically possible. Use of priority post boxes is encouraged to ensure samples reach the central analytical laboratory within the analysis window.

[h] Sotrovimab administration is to be performed as per local standard of care and is not part of this study protocol.

[i] Demographic data including age (year and range), sex, smoking status, ethnicity and BMI (range) to be collected and documented in the patient's medical records.

[j] Refer to Section 8.3.3.1for list of relevant co-morbidities. Co-morbidities should be documented in the patient's medical record at baseline.

[k] Disease characterisation data including duration of COVID-19 symptoms (days), previous SARS-CoV-2 infection and serostatus (if available) to be collected at baseline and documented in the patient's medical records.

[l] Concomitant medications, both related to and non-related to SARS-CoV-2 infection, must be collected at baseline and during follow up calls and must be documented in the patient's medical.

[m] COVID-19 vaccination status, including number of vaccinations, date (month) and brand, must be collected at baseline and during follow up calls and documented in the patient's medical record.

[n] Clinical outcomes including hospital admission, respiratory support, ICU admission and death will be collected and recorded in the patient's medical records during follow up calls.

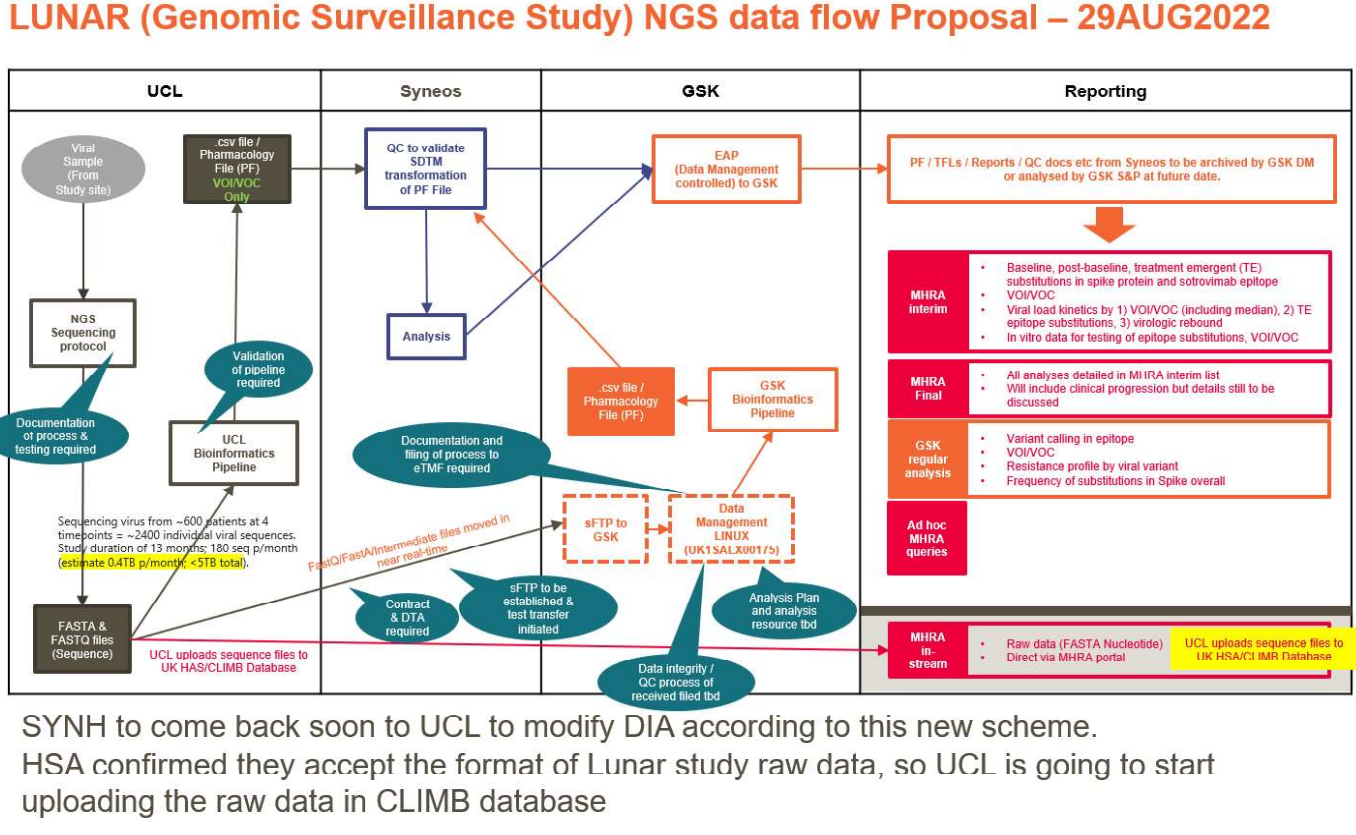
[o] Refer to Section 11.3 for details on safety events to be reported.

[p] Patients who progress to severe disease and may require COVID-19 related hospitalisation should be actively contacted and followed-up where possible by site staff to obtain samples and follow up data as per protocol.

[q] Patients with a persistent positive sample at the end of the 28 day follow up period will have their positive results reported back to the sites (as described in the study reference manual) and should have appropriate medical follow-up under standard clinical care by their treating healthcare team arranged.

5. SARS-CoV-2 Genomic Analysis Results Workflow

Figure 2



SYNH to come back soon to UCL to modify DIA according to this new scheme.
HSA confirmed they accept the format of Lunar study raw data, so UCL is going to start uploading the raw data in CLIMB database

University College of London (UCL) Central Analytical Laboratory:

SARS-CoV-2 Genomic analysis will be performed by the assigned central analytical laboratory, University College of London (UCL), receiving all study patients nasal/oropharyngeal swab samples as described in the Study Lab Manual. Figure 2 shows genomic and viral load data movement between UCL, Syneos Health, and GSK. UCL generates the raw sequencing FASTA/FASTQ and related files which would then be uploaded to UK HSA/CLIMB database by UCL as part of MHRA requirements in-stream. UCL also takes the responsibility to upload the raw sequencing files to GSK via sFTP in near real-time which GSK will be using for bioinformatic analysis of amino acid substitutions in spike protein. UCL uses its bioinformatic pipeline to create a Pharmacology File (PF) having only viral variant calling VOC/VUI information based on the whole genome sequence and sends it to Syneos Health for analysis and MHRA reporting.

GlaxoSmithKline (GSK)

GSK receives the raw sequencing files from UCL and create its own bioinformatic pipeline to create another Pharmacology File consisting of amino acid substitutions in spike protein and sends it to Syneos Health for statistical analysis and MHRA reporting. The interim and final reports would be shared with MHRA directly by GSK.

Syneos Health (SYNH)

Syneos Health receives Pharmacology Files (PF) from both UCL and GSK and will perform study management, clinical data management and statistical analysis for MHRA interim and final analysis.

UCL will share PF (VOC/VUI based on the whole genome sequence) and viral load data in excel (.csv) format using dedicated SFTP according to agreed Data Import Agreement (DIA) with SYNH. Likewise, GSK will share the bioinformatic analysis of amino acid substitutions in spike protein file under excel (.csv) format using dedicated SFTP according to agreed Data Import Agreement (DIA) with SYNH. The data transfer from GSK and UCL to SYNH would be in cumulative fashion, and all reporting would also be cumulative each time. The data will be stored at SYNH server (M: Drive).

SYNH would merge the sequencing data (PF) coming from GSK with UCL (VOC/VUI based on the whole genome sequence and "AA Change from Baseline" will be derived for analyses (i.e., Interim and Final).

Viral load data will be received from UCL and SYNH takes responsibility for conversion of copies/mL into log10 copies/mL for analysis.

All the raw data (FASTA/ FASTQ/BAM/VCF files) will be directly uploaded to GSK's SFTP in near-real time by UCL and SYNH will not be involved in this process.

6. Endpoints

Primary Endpoints

1. Proportion of patients eligible for sequence analysis that have any Amino Acid change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days) (Primary Objective 1)
2. Proportion of patients eligible for sequence analysis that have any Amino Acid change from baseline in the spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) (Primary Objective 2)

Secondary Endpoints

3. Proportion of patients eligible for sequence analysis with SARS CoV-2 VOC or VUI on the earliest possible sample (Secondary Objective 1)
   • Variant identification, pango lineage and AA changes in VOC and VUI in addition to their defining mutations will be reported
4. Proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 2)
5. Clinical outcomes through Day 28 post sotrovimab treatment (Secondary Objective 3):
   - Proportion of all cause hospital admissions and related to COVID-19
   - Proportion of patients requiring new or increased oxygen support (supplemental oxygen [not high flow], non-invasive ventilation or high-flow, invasive mechanical ventilation or Extracorporeal membrane oxygenation [ECMO])
   - Proportion of all cause ICU admissions
   - Proportion of all cause deaths and COVID-19 related deaths
6. AA (detected at >5% allelic frequency) changes in the SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay (Secondary Objective 4)
7. AA changes in the SARS-CoV-2 spike consensus sequences from baseline in samples where viral load is insufficient for >5% allelic frequency analysis but sufficient to generate consensus level sequencing data (Secondary Objective 5)

Exploratory Endpoints

1. Describe viral characteristics (e.g. viral load, VOC/VUI, AA changes) in patients who subsequently require hospital admission or die due to COVID-19 post sotrovimab treatment.

The following separate tables will be presented to support the above viral characteristics endpoint:

- Please refer Table 1.26 for analysis on VOC/VUI for hospitalized patients.
- Summary of viral load results by clinical outcomes (Please refer Table 1.49 of TLF shells).
- Summary of proportion of subjects with undetectable viral load by clinical outcomes. (Please refer Table 1.50 of TLF shells).
- Summary of proportion of amino acid substitutions at baseline and post-baseline in spike protein - consensus sequence (allelic frequency >50%) in patients with clinical outcomes. (Please refer Table 1.51 of TLF shells).

2. Establish whether changes in AA from baseline identified in the SARS-CoV-2 spike protein are reported sequences in the genomic databases (e.g. GISAID).

   We will explore the feasibility of extracting the virology data from the GISAID database for the final report and cross-refer to output Table 1.11.

3. Explore the feasibility of linkage with routinely collected samples (as per standard of clinical care) for spike protein monitoring in patients who remain SARS-CoV-2 positive beyond 28 days as part of a longer follow-up for this sub-population.

   Feasibility was assessed during the interim analyses with UKHSA and the linkage was not an option. Therefore, it will not be part of Final Analysis.

7. Analysis Sets

7.1 Screened Set

The Screened Set will include all patients who were screened at Visit Day 0 (i.e. gave informed consent). This set will be used for the listing and summarization of subject disposition.

7.2 Safety Set

The Safety Set (SS) will include all participants who were enrolled and exposed to study intervention.

7.3 Virology Set

The Virology Set (VS) will include all participants who were enrolled and exposed to study intervention with a positive PCR test by GOSH qPCR having Viral load above lower limit of detection (i.e., viral load >= LLOD) as threshold at baseline.

7.4 Safety Completers Set

The Safety Completers Set (SCS) will include all participants who were enrolled, exposed to study intervention (Sotrovimab) and who have been followed for 30 days (i.e., enrolled prior to 01Jan2023) or withdrew from the study early. This population will be used for outputs relating to Clinical Outcomes for the planned Interim Analysis only.

8. General Aspects for Statistical Analysis

8.1 General Methods

- All participants entered into the database will be included in participant data listings.

- Quantitative (continuous) data including absolute values and changes from baseline, where appropriate, will be summarized with number of observations (n), mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum.

- For the summary statistics of all continuous variables unless otherwise specified, minimum and maximum will be presented to the same number of decimal places as the raw data. Mean, median, Q1, Q3, and IQR will be presented to one more decimal places than the raw data, and SD will be presented to two more decimal places than the raw data.

- Qualitative (categorical) data will be summarized using number of observations (n), and frequency and percentages of patients. Unless stated otherwise, the calculation of percentages will be based on the total number of patients with non-missing data. For some of the endpoints, 95% CI of proportion will also be displayed.

- All statistical analyses will be conducted using SAS® for Windows® Version 9.4 or higher.

8.2 Key Definitions

End of Study (EOS)
The EOS is defined as the date the last participant completes the last visit as shown in the Schedule of Activities in Section 4.8.

Study day
Event date can be adverse events, labs, or any other assessments during the study.
If the event date ≥ date of first dose of sotrovimab, study day = event date – date of first dose of sotrovimab + 1.
If the event date < date of first dose of sotrovimab, study day = event date – date of first dose of sotrovimab.

Baseline Value
Baseline value will be defined as the last non-missing value recorded prior to sotrovimab administration or as close as possible to the end of sotrovimab infusion.
Retrospective collection of baseline data with the patient or directly with patient HCP will be conducted when not possible at Day 0. In all cases baseline is defined to be Day 0.

Change from Baseline (CFB)
CFB = Post-baseline value – Value at baseline

Treatment Emergent
Treatment emergent amino acid substitutions include subjects where baseline and post-baseline records exist.
Treatment emergence for consensus will include baseline records of allelic frequency >5% and post-baseline >50% as thresholds, whereas treatment emergence for minority will include baseline records of allelic frequency >5% and post-baseline >5% as thresholds.

Consensus sequence is defined as allelic frequency >50% and minority species with allelic frequency >5%.

Lower Limit of Detection (LLOD)
LLOD of the assay is defined as 453 copies/mL (equivalent to Ct=38).

Lower Limit of Quantification (LLOQ)
LLOQ of the assay is defined as 1570 copies/mL (equivalent to Ct=36.18).

Viral load Negatives
The threshold to declare a viral load negative is the LLOD.

8.3 Missing Data

For participants who are withdrawn from the study prior to the end of the study, all data collected up to the point of discontinuation will be used for analysis.

Imputation will be performed on post-baseline viral loads depending on the viral load results as below:

Viral loads that are missing or less than the LLOD (453) will be imputed as 0.5*LLOD = 0.5*453=226.5 copies/ml = 2.36 log10c/ml.
Viral loads that are above the LLOD but lower than the LLOQ (1570) will be imputed as LLOQ – 0.5*(LLOQ-LLOD) = 1011.5 copies/ml = 3.00 log10c/ml.

Possible VL results	**LLOD**	**LLOQ**	**Reported in the listings as:**	**Imputation for analysis:**
Missing (as Ct>45)	453	1570	NEG	Half LLOD = 226.5 copies/ml = 2.36 log10c/ml
<LLOD, e.g. 400	453	1570	NEG	Half LLOD = 226.5 copies/ml = 2.36 log10c/m
Between LLOD and LLOQ, e.g. 1000	453	1570	<1570	LLOQ – 0.5*(LLOQ-LLOD) = 1011.5 copies/ml = 3.00 log10c/ml
>LLOQ, e.g 2000	453	1570	Numeric result	None – use numeric result

For calculating age, birth date will be imputed as follows:
For all subjects, the missing date and month will have this imputed as '30th June'.
Birth date will be presented in listings as 'YYYY'.
Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the subject will not be calculated and will remain missing.

8.3.1 Missing Adverse Events (AE) and Medication Dates

Incomplete/missing AE/ Concomitant medication start and end dates are not expected, in case of incomplete/missing AE/Concomitant medication start and end dates, imputation will be performed as stated below.

<table>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table><tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
○ If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.</td></tr></table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>
Else set start date = 1st of month.
</td></tr>
<tr><td>Missing start day and month</td><td>

If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
Else if study treatment start date is not missing:

If year of start date = year of study treatment start date then

If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
Else set start date = study treatment start date.

Else set start date = January 1.

</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
Completely missing start or end dates will remain missing, with no imputation applied.
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:

If month and year of start date = month and year of study intervention start date, then

If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:

If year of start date = year of study intervention start date, then

If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
Else set start date = study. intervention start date.

Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
</table>
</td></tr>
</table>

	Completely missing start/end date	No imputation
	•	

8.4 Visit Windows

Analysis will be based on nominal visit, excluding all the unscheduled visits. Unscheduled assessments will be listed but will not be included in the summarization.

8.5 Pooling of Centers

Not Applicable since no adjustment for center or by center analyses are planned.

8.6 Subgroups

Not Applicable.

9. Demographic, Other Baseline Characteristics and Medication

9.1 Subject Disposition and Withdrawals

Subject disposition will be summarized for all subjects in the Screened Set. The summary table will show the number of subjects screened, the number of screen failures and reason for screen failures, and who discontinued the study prematurely along with the primary reasons for discontinuation.
Reasons for discontinuation of study will also be listed, including the time in days before discontinuation from study.
Eligibility criteria, and informed consent information will be listed for all subjects in the Safety Set.
Screening failures (including screen failure date and primary reason for failure) will be listed separately.

9.2 Protocol Deviations

Protocol deviations will be identified periodically throughout the trial following the 'Protocol Deviation and Non-compliance Management Plan' (Syneos Health SOP and WI, 3101 and 3101.W02). Final definition of protocol deviations and categorization into Not Important / Important will be performed in the Data Review Meeting (DRM) prior to database lock.
All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, dosing, and sampling procedures or patient assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor, the principal investigator and the study statistician, and finalized before database lock during the DRM. All protocol deviations (Not important and Important) observed during the conduct of the study will be listed. Important protocol deviations (patients with at least one important PD overall and split by PD category) will be summarized for safety population.

9.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, age group, sex, race, ethnicity, body mass index (BMI), current smoking status will be summarized for safety population using standard descriptive statistics. Further separate summary tables including demographic and baseline characteristics for subjects who did not clear the virus at D28 (viral load above LLOD at D28) and for subjects with sequence data available will also be presented.

In addition, duration of COVID-19 symptoms (days) prior to receiving sotrovimab, previous SARS-CoV-2 infection, Serostatus, if available the test used for serology, COVID-19 Disease History, Number of days since initial COVID-19 positive test result, Test used for COVID-19 testing, number of previous COVID-19 infections, COVID-19 Vaccination status, Product name of COVID-19 vaccine, number of doses of vaccine will also be summarized using standard descriptive statistics.

All demography data will be listed.

9.4 Medical History and Concomitant Diseases

Medical history, as recorded at screening/baseline and concomitant diseases, will be summarized separately for the safety population presenting the number and percentages of subjects within each CRF pre-defined classified conditions. Concomitant diseases are all events which are ongoing at first intake of study medication. A separate summary of medical conditions and comorbidities for subjects who did not clear the virus at D28 (viral load above LLOD at D28) and subjects with sequence data available will also be presented.

9.5 Prior and Concomitant Medication

Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHO-DD). Medications will be classified as concomitant or prior and summarized by ATC class (level 2, therapeutic subgroup) and preferred drug name for all subjects in the safety population.
Prior medication is defined as any medication taken before the date of the first dose of study treatment.
Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment.

Concomitant medication will be recorded, including the medication name, daily dose, unit, regimen, administration route, reason for administration (text field) and medication start and end dates or ongoing.
All prior and concomitant medications will be listed, with a flag identifying prior medications, for all subjects in the Safety population.
The summary tables will show the frequency and percentage of subjects in each group with at least one usage of medication on the sub-class level within each ATC class sorted alphabetically.

10. Efficacy

Treatment Emergent Amino acid Substitutions/Amino acid Change from Baseline is defined as any amino acid substitutions detected at post-baseline visits compared to baseline sequence.

10.1 Primary Efficacy Endpoint and Analysis

Primary efficacy analyses will be conducted for the safety populations.
The primary endpoints in this study are

- Proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding.

The proportion of subjects with epitope amnio acid change from baseline will be summarized showing the counts and percentages of patients in each epitope substitution change by post-baseline visits (Day 7, 14 and 28 (+/-2 days)) and overall and will be presented separately for Minority species (>5% allelic frequency) as well as consensus sequence (>50% allelic frequency).

Proportion of patients with epitope substitution change by VOC/VUI for Consensus Sequence (Allelic frequency >50%) and for Minority species (>5% allelic frequency) was also presented by visit for interim analysis reporting, but will not be included in the final analysis.

- Proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike.

The proportion of subjects with spike amnio acid change from baseline will be summarized showing the counts and percentages of patients in each spike substitution change by post-baseline visits (Day 7, 14 and 28 (+/-2 days)) and overall and will be presented separately for Minority species (>5% allelic frequency) as well as consensus sequence (>50% allelic frequency).

10.2 Secondary Efficacy Endpoint and Analysis

Secondary efficacy analyses will be conducted for the safety populations, unless otherwise stated.

The secondary endpoints in this study are:

- Proportion of patients eligible for sequence analysis with SARS CoV-2 VOC/VUI on the earliest possible sample.

The proportion of patients with VOC/VUI will be summarized showing the counts and percentages of patients by each variants based on WHO classification and Pango sub-lineage for the earliest possible VOC/VUI sample including baseline. A data listing including WHO label and Pango sub-lineage will be provided.

- Proportion of patients with undetectable virus (i.e. viral load < LLOD)

Summary of proportion of patients with undetectable virus would be based on safety population and summarized by Day 7, 14 and 28 (+/-2 days).

- Clinical outcomes through Day 28 post-sotrovimab treatment:

The following clinical outcomes will be summarized by count and percentage of patients and its 95% CI by VOC/VUI, Non-VOC/VUI, and Overall:

  - Proportion of patient with all-cause hospital admissions
  - Proportion of patient with COVID-19 related hospital admissions.
  - Proportion of patients requiring new or increased oxygen support (supplemental oxygen [not high flow], non-invasive ventilation or high-flow, invasive mechanical ventilation, or Extracorporeal membrane oxygenation [ECMO])
  - Proportion of patient with all-cause ICU admissions.
  - Proportion of patient with COVID-19 related ICU admissions.
  - Proportion of patient who died through Day 28.
  - Proportion of patient who died through Day 28 due to COVID-19.

In addition, the clinical outcomes would also be summarized by VOC/VUI variants and also by Medical Condition/Comorbidity.

The above outputs for Clinical outcomes will be based on the Safety Completers Population for the Interim Analysis and safety population for Final Analysis.

Data listings on clinical outcomes separately for hospital admission, ICU admission, oxygen support, death will be listed.

- AA (detected at >5% allelic frequency) changes in the SARS-CoV-2 spike protein in samples collected at Day 7, 14 and 28 (+/-2 days) compared to baseline following sotrovimab administration for samples with viral loads above the threshold of the sequencing assay
- AA changes in the SARS-CoV-2 spike consensus sequences from baseline in samples where viral load is insufficient for >5% allelic frequency analysis but sufficient to generate consensus level sequencing data

  For the above endpoints, Baseline and post-baseline (Day 7, 14 and 28 (+/-2 days)) AA substitutions will be summarized by showing the counts and percentages of patients in spike and epitope substitutions separately for Minority species (>5% allelic frequency) as well as consensus sequence (>50% allelic frequency).

  Treatment emergent AA substitutions in spike as well as epitope for minority species and consensus sequence would be listed separately.

  A similar baseline and post-baseline AA substitutions summary were presented by VOC/VUI variants for the interim but will not be included in the final analysis..

  Data listings will be provided for all the baseline and post-baseline AA substitutions in spike as well as epitope for minority species and consensus sequence separately.

- Viral load

  Absolute and change from baseline viral load summaries will be based on Safety and Virology population respectively on log10 copies/mL.

  An overall summary of viral load (log10 copies/mL) with actual values and change from baseline values of viral load as well as by Day 0, Day 7, 14 and 28 (+/-2 days) using descriptive statistics will be displayed and presented graphically over time.

  In addition, viral load (log10 copies/mL) with actual values and change from baseline values will also be summarized by VOC/VUI variants, and for Epitope Substitutions by Residue and presented graphically over time. Also, individual subject profile plots of viral load by VOC/VUI will be graphically presented based on viral load imputed values.

  .A summary of viral load (log10 copies/mL) with actual values using descriptive statistics will be presented for the subset of subjects who had missing viral load at Baseline, and separately for the subset of subjects who had a viral load available at Baseline.

  Listings will be provided for all viral load data as well as a separate listing including only epitope substitution.

- Viral Rebound

  A subject has experienced a virologic rebound when following conditions are met:

  If subject is in the safety population and:

  - Viral load increases >1 log10 copies/mL at any point in time following any previous sample.
    OR
  - Viral load becomes quantifiable after having been below the limit of quantification (LLOQ) or limit of detection (LLOD).

A table will be summarized with number of subjects who met viral rebound and will also list out their viral load information.

11. Safety

All safety analyses will be conducted using the safety population.

In this study, only events considered related to sotrovimab are collected and referred to adverse drug reactions (ADRs). Therefore, any reference to AE in subsequent sections indicates ADR, unless otherwise stated.

Safety will be assessed on the basis of reporting and analyzing of AE .
Only descriptive statistics will be produced.

11.1 Adverse Events

All subjects in the safety population will be included in the AE summaries. Adverse events will be summarized by the system organ class (SOC) and preferred term (PT) based on the MedDRA dictionary version 25.0.
Treatment emergent adverse events are defined as adverse events that occurred or worsened on or after the first dose of the study treatment. The summary tables will include the number of subjects and the number of events. Percentages will be based on the number of subjects. For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level.
For summaries by SOC, PT, and maximum severity, a subject will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, subjects may only contribute once to each PT and once to each SOC level. The summaries presenting frequency of AEs by SOC and PT will be ordered in the descending frequency of SOC and then, within a SOC in descending frequency of PT.
.
In addition, summary tables for AESIs of hypersensitivity reactions and anaphylactic reactions using MedDRA Hypersensitivity SMQ Code 20000214 BROAD Search and Anaphylactic reaction SMQ Code 20000021 Narrow Search plus the Algorithmic PT search defined in MedDRA will also be generated.

The following tables will be provided:

- An overall summary of the number and percentage of subjects reporting TEAEs, serious TEAEs, Severe TEAEs, TEAEs leading to TEAEs leading to Study Discontinuation and TEAEs resulting in death.
- TEAEs by system organ class (SOC) and preferred term (PT)
- TEAEs by system organ class, preferred term and maximum severity
- Serious TEAEs by System Organ Class and Preferred Term
- TEAES leading to Withdrawal from Study by System Organ Class and Preferred Term
- Fatal treatment-emergent serious adverse events by System Organ Class and Preferred Term
- AESIs of hypersensitivity reaction
- AESIs of anaphylactic reaction

TEAEs will be summarized and listed accordingly. Additional listings will be provided for serious adverse events (SAEs; defined in Section 11 of the Protocol), fatal SAEs.

11.2 Vital Signs

No vital signs parameters were collected.

12. Programming Considerations

12.1 General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file
- Output files will be delivered in Word format (RTF) and portable document format pdf

12.2 Table, Figures, and Listing Format

12.2.1 General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- Legends will be used for all figures with more than one variable, group, or item displayed
- TFLs will be in black and white (no color), unless otherwise specified

- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below)
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate
- The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

12.2.2 Headers

All output will have the following header at the top left of each page:

- GlaxoSmithKline, Protocol 218407
- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page

12.2.3 Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Listing 1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line

Protocol: 218407 Page x of y
Population: Safety Data as of (DDMMMYYYY)

Table x.y.z
First Line of Title
Second Line of Title if Needed

12.2.4 Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters
- In the case of effectiveness tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include 'unit' in column or row heading when appropriate
- Analysis set sizes will be presented in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set

12.2.5 Body of the Data Display

12.2.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned

12.2.5.2 Table Conventions

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects

- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics which cannot be estimated will be reported as '-'

- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

12.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time

- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DDMMMYYYY': e.g: 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study
- Units will be included where available

12.2.5.4 Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

12.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible
- Subject specific footnotes are avoided, where possible
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

13. Quality Control

SAS programs are developed to produce output such as analysis datasets, summary tables, figures, and data listings, or statistical analyses. An overview of the development of programs is detailed in Developing Statistical Programs SOP (3907).

The Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan (3906A) describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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Listing	1.5	Listing of all Baseline and Post-baseline Epitope Amino Acid Substitutions – Minority species (Allelic frequency >5%)	Safety	Interim, Final
Listing	1.6	Listing of all Baseline and Post-baseline Epitope Substitutions – Consensus Sequence (Allelic frequency >50%)	Safety	Interim, Final
Listing	1.7	Listing of all Treatment-emergent Spike protein Amino Acid Substitutions – Minority species (Allelic frequency >5%)	Safety	Interim, Final
Listing	1.8	Listing of all Treatment-emergent Spike protein Amino Acid Substitutions – Consensus sequence (Allelic frequency >50%)	Safety	Interim, Final
Listing	1.9	Listing of all Treatment-emergent Epitope Amino Acid Substitutions – Minority species (Allelic frequency >5%)	Safety	Interim, Final
Listing	1.10	Listing of all Treatment-emergent Epitope Amino Acid Substitutions – Consensus sequence (Allelic frequency >50%)	Safety	Interim, Final
Listing	1.11	Listing of all Treatment-emergent Epitope Amino Acid Substitutions – Minority species (Allelic frequency >5%) by VOI/VUI	Safety	Interim
Listing	1.12	Listing of Variant of Concern/Under Investigation (VOC/VUI)	Safety	Interim, Final

Listing	1.131	Listing of Nasal/oropharyngeal swab SARS CoV2 Viral Load	Safety	Interim, Final
Listing	1.132	Listing of Nasal/oropharyngeal swab SARS CoV2 Viral Load for subjects with missing baseline viral load	Safety	Interim, Final
Listing	1.14	Listing of Nasal/oropharyngeal swab SARS CoV2 viral load by epitope substitution	Safety	Interim
Listing	1.15	Listings of Hospital Admission	Safety	Interim, Final
Listing	1.16	Listings of ICU Hospital Admissions	Safety	Interim, Final
Listing	1.17	Listings of requirement for Oxygen Support, Non-invasive, Invasive ventilation, ECMO	Safety	Interim, Final
Listing	1.18	Listings of Deaths	Safety	Interim, Final
Listing	1.19	Listings of All Adverse Events	Safety	Interim, Final
Listing	1.20	Listings of All Serious Adverse Events	Safety	Interim, Final
Listing	1.21	Listings of Hypersensitivity Adverse Reactions	Safety	Interim, Final
Listing	1.22	Listings of Anaphylactic Adverse Reactions	Safety	Interim, Final
Listing	1.23	Listings of All Serious Adverse Events	Safety	Interim, Final
		Additional Listings for Final Analysis		
Listing	1.24	Listings of All Protocol Deviations	Safety	Final
Listing	1.25	Listings of Medical History	Safety	Final
Listing	1.26	Listings of Prior and Concomitant Medications	Safety	Final
Listing	1.27	Listing of Nasal/oropharyngeal swab SARS CoV2 Viral Load of Participants Meeting Criteria for Viral Rebound	Safety	Final
Listing	1.28	Listing of All S Protein Substitutions (Allelic frequency >1%)	Safety	Final
Listing	1.29	Listing of Screen Failures	Safety	Final

17. Shells

17.1 Table Shells

Please refer TLF shells document.

17.2 Figure Shells

Please refer TLF shells document.

18. Appendices

Not Applicable.

GSK_218407_LUNAR_RAP_Final_v2.0_14JUL2023_Clean

Final Audit Report 2023-07-18

Created:	2023-07-14
By:	PPD
Status:	Signed
Transaction ID:	CBJCHBCAABAARfsjYSnuM0Q8jBsifnW8y6afMlCaijkx

"GSK_218407_LUNAR_RAP_Final_v2.0_14JUL2023_Clean" History

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