In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

INTERVENTIONAL PASS REPORT

TITLE PAGE

Division: Pharma Research and Development

Information Type: Interventional PASS End of Study report.

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.
Phase of study	4
Compound Number:	GSK4182136.
Effective Date:	21 Feb 2024
Subject:	SARS-CoV-2 infection.
Author(s):	PPD (Scientific lead, Epidemiology, VEO), PPD (Clinical Biomarker Lead, Virology), PPD (ID & Virology Clinical Sciences), PPD (Programmer), PPD (Statistics Lead), PPD (Senior Clinical Development Lead), PPD (Study Delivery Lead), PPD (PPD), PPD (PPD), PPD (PPD), PPD (Medical Writer, Epidemiologist, Syneos Health), PPD (Epidemiologist, Syneos Health), PPD (Senior Epidemiologist, Syneos Health), PPD (PI), PPD (PI).
Indication Studied:	Early treatment for SARS-CoV-2 infection.

STUDY INFORMATION

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.
Report version identifier	218407
Date of last version of Report	12 June 2023
EU PAS (ENCEPP) register number	EUPAS46386.
Active substance	Sotrovimab (also known as VIR-7831 and GSK4182136) ATC code: J06BD05
Medicinal product	XEVUDY (Sotrovimab) 500 mg concentrate for solution for infusion
Product reference	PLGB 19494/0301
Procedure number	Not Applicable
Marketing authorization holder(s)	GlaxoSmithKline UK Limited 980 Great West Road Brentford Middlesex TW8 9GS UK
Joint PASS	No.
Research question and objectives	The primary and secondary objectives of the study were assessed among IC non-hospitalized patients treated with sotrovimab as part of standard clinical care. Primary Objectives: • Evaluate the proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days).

	• 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: • Evaluate the proportion of patients eligible for sequence analysis with VOC and VUI on the earliest possible sample including baseline. • Evaluate the proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) by RT-PCR. • Evaluate the proportion of patients with key clinical outcomes (hospital admission, requirement for respiratory support, ICU admission and death) through Day 28 post sotrovimab administration. • Describe 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. • 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. Refer to Section 6.3 for details on exploratory objectives.
Country(-ies) of study	UK
Author	PPD Scientific Lead, Epidemiology GlaxoSmithKline Research & Development Limited.

MARKETING AUTHORISATION HOLDER(S) *

Marketing authorization holder(s)	GlaxoSmithKline UK Limited 980 Great West Road Brentford Middlesex TW8 9GS UK
MAH contact person	PPD , Regulatory Project Manager. PPD

SPONSOR SIGNATORY

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.

Compound Number: GSK4182136

Myriam Drysdale, Scientific Lead, Epidemiology GlaxoSmithKline.	Date (DD Month YYYY)
Iain Gillespie, Infectious Disease Epidemiology Head, GlaxoSmithKline.	Date (DD Month YYYY)
Jennifer Han, Senior Clinical Development Director, Infectious Diseases, GlaxoSmithKline.	Date (DD Month YYYY)

INVESTIGATOR REPORT AGREEMENT PAGE

- I have read this report and confirm that to the best of my knowledge the study was carried out as described in this GSK report.
- I acknowledge that I was responsible for overall study conduct. I personally conducted or supervised the described clinical study.
- I ensured that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations. Mechanisms were in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

David Lowe

_____

Investigator Signature | Date (DD Month YYYY)

Judith Breuer

_____

Investigator Signature | Date (DD Month YYYY)

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LIST OF ABBREVIATIONS

AA	Amino acid
AE	Adverse event
AF	Allelic frequency
AIDS	Acquired immune deficiency syndrome
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CDMS	Clinical data management system
CFR	Code of federal regulations
CI	Confidence interval
CKD	Chronic kidney disease
CLIMB	Cloud infrastructure for microbial bioinformatics
CMA	Conditional marketing authorization
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
Ct	Threshold cycle
DM	Diabetes mellitus
EC	Ethics committees
ECMO	Extracorporeal membrane oxygenation
EU	European union
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMR	Electronic medical record
EoS	End of study

GB	Great Britain
GISAID	Global initiative on sharing all influenza data
GOSH	Great Ormond Street Hospital
GSK	GlaxoSmithKline Research & Development Limited
GVP	Good pharmacovigilance practices
HCP	Healthcare professionals
HIV	Human Immunodeficiency Virus
IC	Immunocompromised
ICF	Informed consent form
ICH	International council for harmonisation of technical requirements of pharmaceuticals for human use
ICU	Intensive care unit
IEC	Independent ethics committees
IMID	Immune-mediated inflammatory disorders
IQR	Interquartile range
IR	Implementing regulation
IV	Intravenous
IRB	Institutional Review Board
LLOD	Lower limit of detection
LLOQ	Lower limit of quantitation
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
NGS	Next generation sequencing
NHS	National Health Service
nMABs	Neutralizing monoclonal antibodies

PASS	Post authorization safety study
PDV	Phocine distemper Virus
PI	Principal Investigator
PT	Preferred terms
qPCR	Quantitative polymerase chain reaction
qRT-PCR	Quantitative reverse transcription-polymerase chain reaction.
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical analysis system
SD	Standard deviation
SMA	Site management associate
SMQ	Standardised MedDRA queries
SoC	Standard of care
SOP	Standard operating procedure
TE	Treatment emergent
UCL	University College London
UCLG	University College London Genomics
UK	United Kingdom
UKHSA	UK Health Security Agency
VIR	Vir Biotechnology
VOC	Variants of concern
VSV	Vesicular stomatitis virus

VUI	Variants under investigation
WHO	World Health Organization

TRADEMARK INFORMATION

Trademarks of the GSK group of companies	Trademarks not owned by the GSK group of companies
XEVUDY	Not Applicable.

1. RESPONSIBLE PARTIES

Information regarding the investigators whose patients are included in this EoS analysis, and the associated ECs is provided in the List of Investigators and IECs/IRBs modular appendix. Information regarding study administrative structure is provided in the study administration table modular appendix.

2. SYNOPSIS

Title

Prospective cohort study to monitor the emergence of SARS-CoV-2 spike viral variants in immunocompromised non-hospitalized patients exposed to sotrovimab in Great Britain: LUNAR study.

Keywords

Post authorization safety study (PASS), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) variant, Immunocompromised (IC), Sotrovimab, Omicron.

Rationale and background

Sotrovimab was granted a Conditional marketing authorization (CMA) in GB in December 2021 for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute Coronavirus Disease 2019 (COVID-19) infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection [GlaxoSmithKline UK, 2023]. One of the conditions of the CMA was for GlaxoSmithKline Research & Development Limited (GSK) to conduct a study to further characterize the emergence of viral variants in patients treated with sotrovimab. The Medicines and Healthcare products Regulatory Agency (MHRA) emphasized that this study should be broadly reflective of how the product was to be used clinically, mainly focusing on its use in immunocompromised patients. The protocol for the study was submitted to and agreed by the MHRA. The study was subsequently conducted, and this is the clinical study report.

Immunocompromised patients are more likely to develop prolonged SARS-CoV-2 viral replication and shedding. In such patients, there is a risk that treatment with monoclonal antibodies including sotrovimab may select for viral variants with reduced susceptibility. The ability of these variants to evade vaccine-derived immunity and/or have properties that increase transmissibility is a potential risk [Destras, 2022; Focosi, 2022; Vellas, 2022; Andrés, 2023; Huygens, 2023; Palomino-Cabrera, 2023; Yan, 2023].

Research questions and objectives

The LUNAR genomic surveillance study aimed to identify changes in the SARS-CoV-2 spike protein observed in IC patients treated with sotrovimab in a prospective study designed to robustly characterize resistance profiles.

Primary Objectives

- 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).
- 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

- Evaluate the proportion of patients eligible for sequence analysis with Variants of concern (VOC) and Variants under investigation (VUI) on the earliest possible sample including baseline.
- Evaluate the proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) by reverse transcriptase polymerase chain reaction (RT-PCR).
- 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.
- Describe 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.
- 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

- 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.
- 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]).

Study design

The LUNAR study was a multicenter, single arm, prospective, genomic surveillance study that followed non-hospitalized IC patients who received sotrovimab treatment as per standard of clinical care for COVID-19. As part of the study, follow-up nasal/oropharyngeal swab samples (Day 7, 14 and 28 [+/-2 days]) were collected by the participants using home test kits or by Healthcare Professionals (HCPs) in case of hospitalization. Samples were sent to a central laboratory for analysis. Patients were

recruited over a period of 12 months with a follow-up period for each patient of 28 days. Sequencing analyses were conducted on all SARS-CoV-2 positive nasal/oropharyngeal swab samples that met the threshold criteria for the sequencing assay. Clinical outcomes (as defined in the protocol) and adverse events considered related to sotrovimab were collected by the investigators through Day 28.

Setting

This prospective study was conducted for a period of 12 months across 9 sites in Great Britain (GB).

Subjects and study size

Eligibility Criteria

IC non-hospitalized patients aged ≥18 year old infected with SARS-CoV-2 who received 500 mg Intravenous (IV) sotrovimab treatment as per standard of clinical care for COVID-19 between 01 July 2022 and 30 June 2023 were screened for eligibility.

Inclusion Criteria

- Adult patients aged ≥ 18 years of age.
- IC (as defined and derived from the clinical commissioning policy [NHS, 2022]). The list included specific IC patients within the following cohorts: [GOV.UK, 2023]:
    - Patients with a solid cancer
    - Patients with a hematological disease and stem cell transplant recipients
    - Patients with renal disease
    - Patients with liver disease
    - Patients with Immune-mediated inflammatory disorders (IMID)
    - Patients with immune deficiencies
    - Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome (HIV/AIDS)
    - Solid organ transplant recipients
- A positive polymerase chain reaction (PCR) or antigen test for SARS-CoV-2 through clinical testing or routine screening undertaken as part of clinical management.
- Prescribed treatment with sotrovimab as standard of clinical care
- Able to provide informed consent and willing to adhere to study-related procedures.

Exclusion Criteria

- Patients who require hospitalization (related or not to COVID-19) at baseline

- Patients who initiated sotrovimab therapy in inpatient settings
- Patients unable to perform nasal/oropharyngeal sample collection.
- Blinded patients from other COVID-19 related trials

From the Clinical Commissioning Policy, the following groups were also excluded from this study unless also eligible for sotrovimab under other Clinical Commissioning Policy IC criteria [NHS England, 2023; GOV.UK, 2023]:

- Cohort of patients with rare neurological conditions
- Cohort of patients with Down's Syndrome
- In the cohort of patients with renal disease:
    - Patients with Chronic kidney disease (CKD) stage 4 or 5 (an Estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m2) without immunosuppression (patients with renal disease cohort)
- In the cohort of patients with liver disease:
    - Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease), Child's-Pugh class B or C (decompensated liver disease)

Study Size

As a sentinel surveillance study, the aim was to enroll patients for a period of 12 months, or until the enrollment target of 500 (up to 625) patients was met, or until sotrovimab was no longer used in GB. Due to the change in guidance in the United Kingdom (UK) in November 2022 [NHS England, 2023] and the subsequent low usage of sotrovimab, it was concluded that enrollment numbers could not be achieved and collection of data would end following the recruitment period of 12 months as planned.

Variables and data sources

Treatment Exposure

All participants received a single 500 mg dose of sotrovimab IV infusion as part of their Standard of care (SoC) treatment on the National Health Service (NHS).

Primary Endpoints

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

Secondary Endpoints

- 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.
- Proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 2).
- 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
- 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).
- 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).

Data Sources

Patient informed consent and other data elements required for the study were collected from the patient during baseline visit or during follow up phone calls at Day 7, 14 and 28 (+/- 2 days). Any baseline participant characteristics or treatment history unable to be collected during the baseline visit were collected retrospectively directly from the participant or the participant's regular HCPs during the follow up period. Participating sites also contacted participant's regular HCPs as required, for clinical and safety outcomes data. All baseline and follow-up data were recorded in the Electronic Case Report Form (eCRF).

Results

A total of 217 participants met the inclusion and exclusion criteria, provided informed consent, and were enrolled in the study.

The majority of participants (n=208, 95.9%) completed the study. Nine participants (4.1%) discontinued the study early due to withdrawal (n=4), loss to follow-up (n=4) and death (n=1). No AEs led to study discontinuation.

Among the 217 participants, 56.7% were females and the median age at enrollment was 58 years. The majority (87.1%) were of white race. The 3 most frequent IC conditions were presence of an IMID (30.9%), recipient of a solid organ transplant (25.8%), and presence of a renal disease (24.0%). All participants received a single dose of sotrovimab as part of their SoC treatment at a mean of 2.6 days from testing positive for SARS-CoV-2.

Results of Primary Analyses

There were 101 (64.7%) and 47 (30.1%) out of 156 participants with paired sequences in the LUNAR study with treatment emergent substitutions at >5% allelic frequency in the spike protein and sotrovimab epitope at any post-baseline timepoints respectively. Forty-six out of 156 participants (29.5%) had treatment emergent substitutions in the sotrovimab epitope at >5% allelic frequency that are known to cause reduced susceptibility to sotrovimab in in vitro neutralization assays. There were 88/153 (57.5%), 37/71 (52.1%) and 20/33 (60.6%) participants with treatment emergent substitutions at >5% allelic frequency in the spike protein at Day 7, Day 14 and Day 28, respectively. There were 38/153(24.8%), 18/71 (25.4%) and 11/33 (33.3%) participants with treatment emergent substitutions at >5% allelic frequency in the sotrovimab epitope at Day 7, Day 14 and Day 28, respectively. The most prevalent epitope residue with the treatment emergent substitutions observed at >5% allelic frequency at any time post-baseline was E340 with the E340D substitution being the most prevalent change on Day 7 and the E340Q substitution being the most prevalent change on Day 14 and Day 28.

There were 36 (23.1%) and 23 (14.7%) out of 156 participants with paired sequences in the LUNAR study with treatment emergent substitutions at >50% allelic frequency in the spike protein and sotrovimab epitope at any post-baseline timepoint respectively. There were 19/153 (12.4%), 17/71 (23.9%) and 13/33 (39.4%) participants with treatment emergent substitutions at >50% allelic frequency in the spike protein at Day 7, Day 14 and Day 28, respectively. There were 12/153 (7.8%), 11/71 (15.5%) and 11/33 (33.3%) participants with treatment emergent substitutions at >50% allelic frequency in the sotrovimab epitope at Day 7, Day 14 and Day 28, respectively. The epitope residue with the most frequent treatment emergent substitutions observed at >50% allelic frequency at any time post-baseline was E340. The E340Q substitution was the most prevalent change at Day 7 and Day 28. At Day 14, the E340D and E340Q substitutions had the same prevalence and were the most prevalent treatment emergent epitope substitutions observed.

Results of Secondary Analyses

1. Overall, 208 of 208 (100%) participants with sequencing data out of 217 total participants harbored a SARS-CoV-2 VOC/VUI based on whole genome sequence at the earliest possible visit. Of the 208 participants with a SARS-CoV-2 VOC/VUI, 207 (99.5%) harbored SARS-CoV-2 Omicron viral variants. The most predominant sublineages were Omicron BE.1 (n=48, 23.1%), Omicron BA.5.2 (n=45, 21.6%), Omicron BA.5.2.1 (n=29, 13.9%) and Omicron BA.5.1 (n=28, 13.5%).

2. The proportion of participants that had undetectable viral load in nasal/oropharyngeal swabs was determined by qRT/PCR at Baseline, Day 7, Day 14 and Day 28. The number of samples with undetectable viral ribonucleic acid (RNA) levels increased over time. At Day 7, Day 14 and Day 28, 50 (25.1%) 129 (65.8%) and 162 (83.5%) had undetectable levels of SARS-CoV-2 RNA, respectively.

   An integrated analysis looking at the relationship between treatment emergent epitope substitutions and viral load at Day 28 found the majority of participants with or without treatment emergent substitutions in the sotrovimab epitope at Day 7 achieved negative viral load at Day 28 (63.9% or 81.0%, respectively). However, participants who had treatment emergent substitutions at Day 14 (5/18 [27.8%]) were less likely to achieve undetectable virus at Day 28 than participants with no treatment emergent substitutions at Day 14 (22/30 [73.3%]).

   Evaluation of longitudinal SARS-CoV-2 RNA levels showed that the median viral load for LUNAR participants declined over the course of the study from 7.241 $\log_{10}$ copies/mL at baseline to below the Lower limit of detection (LLOD) at Day 28. This evaluation also showed that 16 (7.8%) participants demonstrated viral rebound, 5 of them went on to clear virus by Day 28. Of the 11 participants with a viral load above the LLOD at Day 28 that had experienced viral rebound, 5 had treatment emergent epitope substitutions at Day 28 and a further 3 did not have sequence in the epitope region.

3. Among all 217 participants, no participants required hospitalization or had an ICU admission due to COVID-19 during the study. Seven participants (3.2%) had ‘all-cause’ hospitalization unrelated to COVID-19 during the study. One participant (0.5%) with progressive neuromuscular disease required high flow/non-invasive mechanical ventilation and died due to their underlying conditions.

4. The most frequent baseline epitope substitutions detected at >5% allelic frequency were the G399D and N440K which are part of the characteristic spike substitution profile for the Omicron viral variants that were detected in this study. At post-baseline, the G339D and N440K substitutions were also observed but for G339D the frequency was lower at later timepoints than at baseline. Post-baseline analysis of the epitope showed that substitutions at residue 340 had the highest prevalence after the substitutions at positions 339 and 440. The most frequent E340 substitution at Day 7 was the E340D and on Day 14 and Day 28 was the E340Q.

5. The most frequent baseline epitope substitutions detected at >50% allelic frequency were the G399D and N440K substitutions which were found in 158 (81.0%) and 185 (100%) participants, respectively. The R346T and G339H were the next most frequent baseline changes. At post-baseline, the G339D and N440K substitutions were also observed but for G339D the frequency was lower from Day 14 than at baseline. Post-baseline analysis of the epitope showed that substitutions at residue 340 were observed frequently in participants. The most frequent E340 substitution on Day 7 and Day 14 were the E340D and E340Q and on Day 28 was the E340Q.

Results of Exploratory Analyses

Longitudinal evaluation of SARS-CoV-2 RNA levels during the LUNAR study demonstrated that only one participant who experienced viral rebound was admitted to a

hospital, and this admission was not considered to be COVID-19 related. None of the other 10 participants with viral rebound that were positive for viral RNA at Day 28 experienced COVID-19-related hospitalizations during the study.

Seven participants were hospitalized during the study. All 7 were infected with Omicron sub-lineages based on whole genome sequence (3 participants had Omicron BE.1 while 1 participant each had Omicron BA.2, BA2.73, BA.5.2, and BA.5.2.1). Three of the 7 had negative viral load levels by Day 7 or 14, 1 experienced significant viral load decline by Day 7 with missing data subsequently, 2 experienced viral load declines before rebounding and 1 participant died who had a viral load decline from baseline of >4 $\log_{10}$ copies/mL at the last available timepoint. Three participants had treatment emergent substitutions in the sotrovimab epitope. P337L/S and E340Q were observed in one of the participants who experienced rebound, E340G was observed in the second participant who experienced rebound and E340K/Q was observed in the participant who died.

The baseline epitope substitutions detected at >5% allelic frequency were G399D, G339H, E340D, E340Q, R346I, R346S, R346T, K356T and N440K. To investigate the conservation of the residues in the sotrovimab epitope, >14,200,000 spike sequences from SARS-CoV-2 deposited in the GISAID Database as of 13 September 2023 were examined for conservation. Among AAs comprising the epitope, ≥99.90% conservation was observed for 19/23 AA positions among currently available sequences, with 12/23 positions being ≥99.99% conserved. Epitope positions 339, 346, and 440 were ≥47.98% conserved, with decreases in conservation driven by G339D/H, R346K/T, and N440K substitutions characteristic of the Omicron variants.

Safety Results

A total of 5 non-serious adverse events (AEs) Preferred terms (PTs): pruritis, diarrhoea, neutrophil count increased, white blood cell count increased and blood creatinine increased) considered related to sotrovimab treatment by the investigator were reported in 4 out of 217 (1.8%) participants during the study. All 5 AEs were of mild intensity, reported as resolved and none led to withdrawal from the study. No SAEs or deaths related to sotrovimab treatment were reported.

Discussion

There were treatment emergent substitutions detected at >5% allelic frequency in the sotrovimab epitope in 24.8%, 25.4% and 33.3% of participants with paired sequencing data at Day 7, Day 14, and Day 28, respectively. There were treatment emergent substitutions detected in the sotrovimab epitope at >50% allelic frequency in 7.8%, 15.5% and 33.3% of participants with paired sequencing data at Day 7, Day 14, and Day 28, respectively.

The numbers of treatment emergent substitutions in the sotrovimab epitope with an allelic frequency of >5% identified at any time during follow up in this study were compared to the substitution frequency of ≥5% allelic frequency in participants treated with 500 mg IV sotrovimab in other GSK/VIR sponsored sotrovimab clinical studies (COMET-ICE,

COMET-TAIL and COMET-PEAK). The overall frequency of treatment emergent epitope substitutions in the LUNAR study (30.1%) was numerically higher than that observed in COMET-ICE (23.5%) and COMET-TAIL (20.8%) clinical studies but in a similar range. The overall frequency of treatment emergent epitope substitutions in the LUNAR study (30.1%) was higher than observed in the COMET-PEAK clinical study (13.5%). The higher frequency of treatment emergent substitutions in LUNAR may be due to the IC population of the study versus the COMET-PEAK study population which did not require participants to have a risk factor for COVID-19 disease progression for inclusion. Patients that are IC may have prolonged duration of virus shedding that can lead to resistance selection.

The overall prevalence of treatment emergent epitope substitutions at position 337 was 17.3% compared to the overall post-baseline prevalence of 4.7%, 5.7% and 5.4% for the 500 mg IV treatment arms in the COMET-ICE [GSK document number RPS-CLIN-032797], COMET-TAIL [GSK Document number RPS-CLIN-040980] and COMET-PEAK [GSK document number RPS-CLIN-049179] clinical studies, respectively. Prevalence of treatment emergent E340 substitutions was similar across all four clinical studies for the 500 mg IV treatment arms.

At Day 28 of the LUNAR study there were 162/194 (83.5%) participants with undetectable viral load compared to 261/280 (93%) and 50/62 (81%) in the sotrovimab 500 mg IV arm of COMET-TAIL [GSK document number RPS-CLIN-047387] and COMET-PEAK (Part B) [GSK document number RPS-CLIN-030208] clinical studies, respectively.

The low rates of severe clinical outcomes reported in this study for patients treated with sotrovimab as SoC are consistent with those reported from other observational studies conducted in the UK across periods of predominant circulating variants [Harman, 2023; Zheng, 2022; Patel, 2023; Zheng 2023; Tazare, 2023].

Conclusions

- Consistent with previous clinical trials of sotrovimab, treatment emergent substitutions were seen in the sotrovimab epitope in the LUNAR study following the administration of sotrovimab 500 mg IV to a highly IC population for the early treatment of COVID-19.
    - Treatment emergent substitutions in the sotrovimab epitope at >50% allelic frequency were observed in 7.8%, 15.5% and 33.3% of participants with paired sequencing data at Day 7, Day 14, and Day 28, respectively.
    - Treatment emergent substitutions in the sotrovimab epitope at >5% allelic frequency were observed in 24.8%, 25.4% and 33.3% of participants with paired sequencing data at Day 7, Day 14, and Day 28, respectively. Of these, 46 (29.5%) had treatment emergent substitutions that are known to cause reduced susceptibility to sotrovimab in in vitro neutralization assays.

- The presence of treatment emergent substitutions in the sotrovimab epitope did not appear to have a negative impact on clinical outcomes during the study follow-up period.
- The majority of participants experienced significant reductions in viral load, with the mean and median viral load being below the LLOQ by Day 28.
- A low number of patients with severe clinical outcomes were reported (protocol defined as hospital admission, requirement for respiratory support, ICU admission and death) and none of them were determined to be due to COVID-19.
- There were 5 non-serious AEs considered related to sotrovimab by the investigator, which were of mild intensity and reported as resolved and there were no reports of hypersensitivity or anaphylaxis.

Reference:

Andrés C, González-Sánchez A, Jiménez M, et al. Emergence of Delta and Omicron variants carrying resistance-associated mutations in immunocompromised patients undergoing sotrovimab treatment with long-term viral excretion. Clin Microbiol Infect. 2023;29(2):240-6.

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3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	03 May 2022	Abstract, Section 8.1 Table Schedule of Activities, Section 8.2.1 Study population and setting, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections. "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"**	The Ethics committee requested more time for participants to review and sign the ICF. To avoid any delay in sotrovimab administration, it was agreed to collect the baseline nasal/oropharyngeal swab just after sotrovimab infusion if it is not possible to collect before. By allowing for the baseline sample to be collected soon after infusion, the participant had additional time to evaluate their participation whilst still enabling a viable sample to be collected.
2	03 May 2022	Abstract and Section 5 Milestones	The text in bold was updated in the appropriate section: Estimated Study Start: First Patient First Visit – **21 June 2022** Estimated Study End: Last Patient Last Visit – **20 July 2023** Start of data collection: Estimated **June 2022** End data collection: Estimated **July 2023** Final report of study results: Estimated **November 2023**	The study start was delayed and new timelines provided in the amendment.
3	20 January 2023	PASS information	The ATC code for sotrovimab, J06BD05, was added	Addition of ATC code
4	20 January 2023	PASS information	Correction of a formatting error that truncated secondary objective 5 in the section	Correction following authority comment

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			Research question and objectives	
5	20 January 2023	Abstract, Section 8.1 Table 1 Schedule of Activities, Section 8.2.1 Study population and setting, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections: "The nasal/oropharyngeal swab at baseline must be taken prior to the administration of sotrovimab **or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion)"**	Clarification of how long after the end of sotrovimab infusion the baseline swab could be taken.
6	20 January 2023	Section 8.1 Table 1 Schedule of Activities, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections: "Persistent positive results will be reported back to the sites **upon site request** (as described in the study reference manual)."	Preference of sites
7	20 January 2023	Section 5 Milestones, Section 8.7.4 Interim Analysis	An interim analysis assessing the primary and secondary objectives was added	Health authority request
8	20 January 2023	Section 8.2 Study Population and Setting	Text in ~~strikethrough~~ was deleted: "It will be conducted for a period of 12 months in approximately 10 sites ~~selected following feasibility assessment from the list of COVID Medicine Delivery Units (CMDUs [https://www.england.nhs.uk/coronavirus/publication/covid-~~	Delivery of COVID-19 therapeutics to non-hospitalized patients was expected to become part of routine NHS services from April 2023 (https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2022/12/C1677 commissioning-framework-

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			~~medicine-delivery-unit-directory/~~]) in GB, or until the enrollment of 500 (up to 625) patients is met, or until sotrovimab is no longer used in GB, whichever comes first."	covid-19-therapeutics-for-non-hospitalisedpatients.pdf)
9	20 January 2023	Abstract, Section 8.4 Data sources, Section 8.7.1.1 Primary objective, Section 8.7.1.2 Secondary objective, Section 8.7.3 General considerations for data analyses, Section 8.9 Limitations of the research methods	The term "reporting plan" was replaced with "statistical analysis plan"	The statistical analysis plan contains all details about what the study will report
10	20 January 2023	Abstract, Section 8.7.2 Exploratory Analyses	The third exploratory analysis was removed: "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"	Exploratory analysis no longer relevant and not feasible
11	20 January 2023	Abstract, Section 8.1 Study Design,	The reference "MHRA. Central Alert System CAS-ViewAlert. Antivirals or neutralizing monoclonal antibodies	Updated recommendations for antiviral treatment in non-

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
		Section 8.2.1 Inclusion criteria, Section 8.2.2 Exclusion criteria, Section 10 References	(nMABs) for non-hospitalized patients with COVID-19 . 27 January 2022. CAS-ViewAlert (mhra.gov.uk)" was replaced with "NHS England. Coronavirus » Interim Clinical Commissioning Policy: Treatments for non-hospitalized patients with COVID-19. 28 November 2022"	hospitalized patients with COVID-19
12	20 January 2023	Section 6.1 Background, Section 10 References	The reference to the Summary of Product Characteristics for XEVUDY (MHRA, 2021) was updated to GlaxoSmithKline UK, 2022	Updated version of Summary of Product Characteristics
13	20 January 2023	Throughout protocol	Minor corrections to punctuation have been made throughout the protocol	Administrative changes

4. MILESTONES

Milestone	Planned date	Actual Date	Comments
Start of data collection	June 2022	01 July 2022	First site activated 27 June 2022
End of data collection	July 2023	17 July 2023	-
Registration in the EU PAS register	March 2022	29 March 2022	-
Interim report 1	Q2 2023	26 May 2023	-
Final report of study results	February 2024*	19 February 2024	-

*Date when report was planned to be complete.

5. RATIONALE AND BACKGROUND

5.1. Background

The novel beta-coronavirus SARS-CoV-2 was first detected in December 2019, with initial reports of its emergence in Wuhan, China. Since this time, the virus, which causes COVID-19 and can include severe pneumonia in infected individuals, has spread throughout the world, causing unprecedented impact on health, economy, and social security [Wu, 2020].

The spectrum of symptomatic COVID-19 ranges from mild disease without pneumonia to critical disease requiring hospitalization with ICU care. Up to 14 December 2023, approximately 21 million cases (people who have had at least 1 positive COVID-19 test result) and approximately 233 791 COVID-19 deaths have been recorded in the UK [GOV.UK, 2023a]. The risk of hospital admission for a person infected with the SARS-CoV-2 Omicron variant appears to be reduced compared to Delta variant [UKHSA, 2022].

COVID-19 vaccination has been fundamental to minimizing the impact of COVID-19, and vaccine effectiveness has reduced the number of hospitalizations and deaths in the setting of high viral circulation [Lopez Bernal , 2021a; Lopez Bernal, 2021b]. Up to 29 March 2023, nearly 50 million people in the UK have received at least 2 doses of vaccine and about 40 million have received a booster/third dose [GOV.UK, 2023a]. Nonetheless, vaccine immunogenicity and effectiveness are lower in certain high-risk groups such as those with immunocompromising conditions [Chodick, 2022; Embi, 2021].

Sotrovimab (VIR-7831; GSK4182136) is a human neutralizing anti-SARS-CoV-2 antibody which contains a 2 AA Fc-modification (“LS”) that is designed to increase half-life. Sotrovimab binds to a conserved epitope on the SARS-CoV-1 and SARS-CoV-2 spike protein outside the receptor-binding motif and has been shown to neutralize SARS-CoV-2 pseudovirus and live virus in vitro [Pinto, 2020]. Sotrovimab neutralization activity against SARS-CoV-2 viral variants is listed in Table 1.

Table 1 Sotrovimab neutralization data for SARS-CoV-2 Viral Variants

SARS-CoV-2 Variant		Fold Reduction in Susceptibility[a]	
Lineage	WHO Nomenclature	Pseudotyped Virus	Authentic Virus
B.1.1.7	Alpha	No change	No change
B.1.351	Beta	No change	No change
P.1	Gamma	No change	No change
B.1.617.2	Delta	No change	No change
AY.1 and AY.2	Delta [+K417N]	No change	Not tested
AY.4.2	Delta [+]	No change	Not tested
B.1.427/B.1.429	Epsilon	No change	Not tested
B.1.526	Iota	No change	Not tested
B.1.617.1	Kappa	No change	No change
C.37	Lambda	No change	Not tested
B.1.621	Mu	No change	Not tested

SARS-CoV-2 Variant		Fold Reduction in Susceptibility[a]	
Lineage	WHO Nomenclature	Pseudotyped Virus	Authentic Virus
B.1.1.529/BA.1	Omicron	No change	No change
BA.1.1	Omicron	No change	No change
BA.2	Omicron	16	15.7[b]
BA.2.12.1	Omicron	16.6	25.1[b]
BA.2.75	Omicron	8.3[b]	15.6
BA.2.75.2	Omicron	10	Not tested
BA.3	Omicron	7.3	Not tested
BA.4	Omicron	21.3	48.4[b]
BA.4.6	Omicron	57.9	Not determined
BA.5	Omicron	22.6[b]	21.6[b]
BF.7	Omicron	74.2	Not tested
BN.1[c]	Omicron	778	Not tested
BQ.1	Omicron	28.5	Not tested
BQ.1.1	Omicron	94	31.2
BR.2	Omicron	10.2	Not tested
CH.1.1	Omicron	12.4	57.3[b]
XBB.1	Omicron	6.5	Not tested
XBB.1.5	Omicron	11.3	33.3[b]
XBF	Omicron	9.4	Not tested
XD	None[d]	Not tested	No change

Source: GSK Study Report 2022N504259_00, GSK Study report 2022N515778_00, GSK Study Report 2022N516891_00, GSK Study Report 2023N527678_00, GSK Study Report 2023N530610_00, GSK Study Report 2022N501240_00, GSK Study report 2022N516788_00, GSK Study report 2022N521597_00, GSK Study Report 2022N523834_00, GSK study report 2023N526908_00; GSK study report 2023N528079_00; GSK study report 2023N530612; GSK study report 2023N535562.

a. Based on EC50 fold change compared to wild-type. No change: ≤5-fold change in EC50 compared to wild-type.
b. Sotrovimab inhibited authentic virus isolates of Omicron BA.2, BA.2.12.1, BA.4, BA.5, CH.1.1 and XBB.1.5 lineages with maximum percentage inhibition in the range of 59% to 100%.
c. The BN.1 variant contains the K356T substitution which is known to confer reduced susceptibility to sotrovimab. Sotrovimab is unlikely to be effective against COVID-19 caused by the Omicron BN.1 variant of SARS-CoV-2.
d. Variant has not been named by the WHO

COMET-ICE, a randomized, double-blind, multicenter, placebo-controlled trial of sotrovimab for the early treatment of COVID-19 in non-hospitalized patients, demonstrated a 79% reduction in disease progression to hospitalization for >24 hours or death among patients treated with sotrovimab compared with placebo. It was the single pivotal study that supported the CMA of sotrovimab in GB when there was no vaccine against SARS-CoV-2 available at the time. The COMET-ICE study was conducted when the wild-type Wuhan-Hu-1 virus was predominant and excluded participants who were severely IC [Gupta, 2021].

The MHRA granted a CMA for sotrovimab for GB on December 2021 for 'the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID infection' [GlaxoSmithKline UK, 2023].

The final summary data on England's shielding list issued at the end of September 2021 showed that about 3.7 million individuals are considered as being at highest risk for

severe COVID-19, or about 6.5% of the population [NHS Digital, 2021; Hippisley-Cox, 2021 Office for National Statistics, 2022]. IC patients, a subset of the shielding list, are not only at higher risk of breakthrough infections and higher risk for hospitalization/death despite good vaccine uptake [Di Fusco, 2021; Hippisley-Cox, 2021], but evidence also shows that this group are more likely to transmit the virus to their household contacts, leading to larger clusters of the disease. This population is also more likely to shed the virus for longer, potentially increasing the risk of emergent variants [Aydillo, 2020; Lewis, 2021; Niyonkuru, 2021]. Immune deficiencies may predispose patients to severe COVID-19 outcomes and the numerous concomitant immune-modulating therapies they are receiving can result in a failure to mount a robust immune response to SARS-CoV-2 following vaccination. IC individuals may also be on some medications contraindicated with nirmatrelvir/ritonavir, one of the first line treatments in early COVID-19 for non-hospitalized patients [NICE, 2023]. For these reasons, treatment options such as sotrovimab are likely to remain important for optimal management of IC patients [Kearns, 2021; Mahase, 2021; NHS, 2022; NICE, 2024].

5.2. Rationale

Since December 2020, a number of variants of SARS-CoV-2 have emerged globally, with a high level of uncertainty around their transmissibility, severity and potential for evading vaccine-induced immunity or developing resistance against antivirals and monoclonal antibodies. SARS-CoV-2 variants can undergo mutations that alter the AAs in the spike protein of the virus [Harvey, 2021]. In the UK, many of these variants have been detected and have since remained under surveillance by UKHSA through routine surveillance [UKHSA, 2023]. Variants may be designated as VOC or VUI, depending on the evidence at the time of their discovery [WHO, 2023].

Sotrovimab is an early treatment designed to be prescribed to SARS-CoV-2 patients at risk of progression to severe disease in a non-hospitalized setting. The potential that monoclonal antibodies might select for viral variants with reduced susceptibility to sotrovimab or to vaccine-derived immunity and/or properties that increase viral transmissibility has been highlighted as a risk in IC patients because of their propensity for prolonged viral replication and shedding [Destras, 2022; Focosi, 2022; Vellas, 2022; Andrés, 2023; Huygens, 2023; Palomino-Cabrera, 2023; Yan, 2023].

One of the conditions of the CMA granted in GB was for GSK to conduct a study to further characterize the emergence of viral variants in patients treated with sotrovimab. The MHRA emphasized that this study should be broadly reflective of how the product was to be used clinically, mainly focusing on its use in IC patients. An interim report was developed to cover the study period from 01 July 2022 to 30 December 2022 including 195 patients [Breuer, 2023]. This interim report was a subset of this final report which presents the results of the entire study period from 01 July 2022 to 30 June 2023 including all patients who were enrolled in the study.

6. RESEARCH QUESTION AND OBJECTIVE(S)

The aim of the LUNAR genomic surveillance study was to identify changes in the SARS-CoV-2 spike protein observed in IC non-hospitalized patients treated with sotrovimab in a prospective study designed to robustly characterize resistance profiles.

6.1. Primary Objectives

1. Evaluate the proportion of patients eligible for sequence analysis that have any 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).

6.2. Secondary Objectives

1. Evaluate the proportion of patients eligible for sequence analysis with VOC and 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 RT-PCR.
3. Evaluate the proportion of patients with key clinical outcomes (hospital admission, requirement for respiratory support, ICU admission and death) through Day 28 post sotrovimab administration.
4. Describe 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.
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.

6.3. 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., GISAID).

7. RESEARCH METHODS

7.1. Study Design

This was a multicenter single-arm observational, genomic surveillance study to describe changes in the SARS-CoV-2 spike protein observed in IC patients receiving sotrovimab to assess the potential emergence of viral variants.

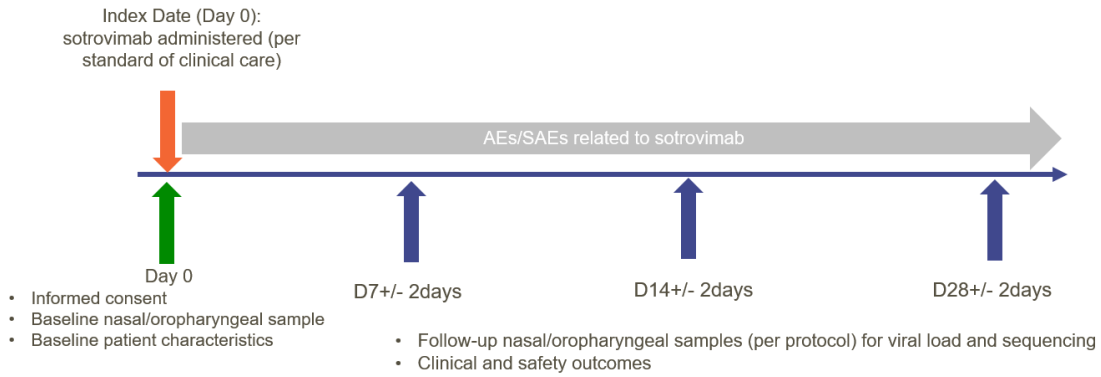
The study enrolled IC non-hospitalized patients aged ≥18 year old infected with SARS-CoV-2 and who had received sotrovimab treatment as per standard of clinical care for COVID-19. Due to the risk of progression to more severe disease and high mortality rate in this population, it was considered unethical to include a placebo-control group in this study.

Data from participants who were enrolled at 9 sites in England and Wales between 01 July 2022 and 30 June 2023 were included in the analysis. All participants consented to be enrolled in the study. Participant characteristics (demographic and clinical) and treatment history (related to COVID-19 and underlying diseases) were recorded at enrollment (Day 0). Baseline nasal/oropharyngeal swab samples were 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]) were collected by the participants using home test kits or by HCPs in case of hospitalization, as per protocol, with samples sent to the central analytical laboratory.

Sequencing analyses were conducted on all SARS-CoV-2 positive nasal/oropharyngeal swab samples that met the threshold criteria for the sequencing assay. Clinical outcomes (defined in the protocol as hospital admission, requirement for respiratory support, ICU admission and death), and adverse events considered related to sotrovimab were collected by the investigators through Day 28.

Figure 1 Study Design



7.2. Study Population/Subjects and Setting

This prospective study was conducted for a period of 12 months across 9 sites in GB, to understand the risk of treatment emergent substitutions and its potential impact on clinical and virological outcomes.

Eligibility Criteria

IC non-hospitalized patients aged ≥18 years infected with SARS-CoV-2 who received 500 mg IV sotrovimab treatment as per standard of clinical care for COVID-19 between 01 July 2022 and 30 June 2023 were screened for eligibility.

Inclusion Criteria

1. Adult patients aged 18 years.
2. IC (as defined in the clinical commissioning policy [NHS, 2022]).
3. A positive PCR or antigen test for SARS-CoV-2 through clinical testing or routine screening undertaken as part of clinical management.
4. Prescribed treatment with sotrovimab as standard of clinical care.
5. Able to provide informed consent and willing to adhere to study-related procedures.

The list of IC populations eligible to receive sotrovimab was derived from the IC cohorts outlined in the interim Clinical Commissioning Policy: nMABs or antivirals for non-hospitalized patients with COVID-19. Patient cohorts considered at highest risk from COVID-19 and to be prioritized for treatment with nMABs [NHS England, 2023; GOV.UK, 2023b]. The list included specific IC patients within the following cohorts:

- Patients with a solid cancer.
- Patients with a haematological disease and stem cell transplant recipients.
- Patients with renal disease.
- Patients with liver disease.
- Patients with IMID.
- Immune deficiencies.
- HIV/AIDS.
- Solid organ transplant recipients.

Exclusion Criteria

1. Patients who require hospitalization (related or not to COVID-19) at baseline.
2. Patients who initiated sotrovimab therapy in inpatient settings.
3. Patients unable to perform nasal/oropharyngeal sample collection.
4. Blinded patients from other COVID-19 related trials.

From the Clinical Commissioning Policy, the following groups were also excluded from this study unless also eligible for sotrovimab under other Clinical Commissioning Policy IC criteria [NHS England, 2023; GOV.UK, 2023b]:

5. Cohort of patients with rare neurological conditions.
6. Cohort of patients with Down's Syndrome.
7. In the cohort of patients with renal disease:
    - Patients with CKD stage 4 or 5 (an eGFR less than 30 mL/min/1.73m^2) without immunosuppression (patients with renal disease cohort)
8. In the cohort of patients with liver disease:
    - Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease), Child's-Pugh class B or C (decompensated liver disease)

Withdrawal Criteria

Participation in this study was voluntary and participants could withdraw from the study at any time without prejudice. If the participant withdrew or was withdrawn, the reason was collected in the eCRF. The ICF explained that in case of withdrawal, all study data collected before withdrawal would be kept in the study database.

If the participant withdrew consent for disclosure of future information, the sponsor could retain and continue to use any data collected before such a withdrawal of consent. If a participant withdrew from the study, they could request destruction of any samples taken and not tested, and the investigator documented this in the site study records.

The Sponsor reserved the right, at any time, to discontinue enrollment of additional participants into the study, at any site; or to discontinue the study, for medical or administrative reasons.

7.3. Variables

7.3.1. Exposure definitions

Treatment Exposure

All participants received a single 500 mg dose of sotrovimab IV infusion as part of their SoC treatment on the NHS.

7.3.2. Outcome definitions

The primary and secondary endpoints are summarized below.

7.3.2.1. Primary endpoints

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

7.3.2.2. Secondary endpoints

1. 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.
2. Proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 2).
3. 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 ECMO)
    - Proportion of all cause ICU admissions
    - Proportion of all cause deaths and COVID-19 related deaths
4. 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).
5. 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).

7.3.2.2.1. VOC and VUI

The SARS-CoV-2 virus isolates were classified by whole genome sequencing. Some of these lineages were designated VOC and VUI as defined below.

A SARS-CoV-2 VOC has been defined by the WHO as one that meets the definition of a VUI (see definition below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology, OR

- Increase in virulence or change in clinical disease presentation, OR
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

A SARS-CoV-2 VUI has been defined by the WHO as a variant:

- With genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND
- Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

For determination of VOC/VUI, analysis was performed to determine the variants described in Annex 2.

7.3.2.3. Exploratory endpoints

1. Viral characteristics (e.g., viral load, VOC/VUI, AA changes) in patients who subsequently require hospital admission or died due to COVID-19 post sotrovimab treatment.
2. AA changes in the SARS-CoV-2 spike protein from baseline that were reported sequences in the genomic databases (e.g., GISAID).

7.3.3. Confounders and effect modifiers

The following patient characteristics were captured to inform on alternative explanations for the emergence of viral variants in sotrovimab-treated patients, if observed.

7.3.3.1. Patients characteristics

Demographics (at baseline):

- Age (year)
- Age range (year): 18-64; 65-74; 75-84; ≥ 85
- Sex
- Current smoking status (Yes = current smoker, No = ex-smoker, never smoker),
- Ethnicity
- BMI (kg/m^2): <18.5; 18.5-24.9; 25-29.9; 30-34.9; 35-39.9; ≥40.

Comorbidities (at baseline):

- Immunocompromising condition
  - The specific conditions will be grouped by set of immunocompromising conditions for analytic purposes.

  - Solid cancer
  - Hematological diseases and stem cell transplant
  - IMIDs
  - Solid organ transplant recipients
  - Renal diseases
  - Liver diseases
  - Immune deficiencies
  - HIV/AIDS.
- Obesity (BMI $\geq$ 30 kg/m^2) and overweight (BMI $\geq$ 25 kg/m^2).
- Cardiovascular disease (including congenital heart disease) or hypertension.
- Cerebrovascular disease
- COPD
- Asthma
- Other chronic respiratory disease (moderate-to-severe), interstitial lung disease, cystic fibrosis and pulmonary hypertension
- CKD and stage
- Chronic liver disease
- DM
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Pregnancy
- Sickle cell disease
- Having a medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])
- Other.

Disease characteristics (at baseline):

- Duration of COVID-19 symptoms (days) prior to receiving sotrovimab
- Previous SARS-CoV-2 infection
- Serostatus, if available, test used (i.e., assay manufacturer; test for antibodies to spike protein or test for nucleocapsid protein or other) and date.

Co-medications (data collected at baseline and follow-up time points):

- Related to SARS-CoV-2 infection:

- Corticosteroids (inhaled, systemic)
- Remdesivir
- IL-6 inhibitors
- Other mAbs (casirivimab and imdevimab, or other agents if licensed during the study period)
- Antivirals (molnupiravir, nirmatrelvir and ritonavir, other)
- Others following national guidance
- Experimental drugs

- Non-related to SARS-CoV-2 infection (e.g., immunosuppressant treatment).

COVID-19 vaccination status (data collected at baseline and follow-up time points):

- Number of vaccinations, date (month) and brand of each vaccination.

7.4. Data Sources

After obtaining informed consent, data on inclusion/exclusion criteria, baseline patient characteristics and treatment history were collected and documented. Any initial AEs observed during sotrovimab treatment (e.g., infusion-related reaction), completion of baseline nasal/oropharyngeal sample collection, and dispensing of home lab kits to the patients were documented prior to patient discharge. Any baseline patient characteristics or treatment history data which was not possible to be collected during the baseline visit were collected retrospectively directly from the patient or the patient's regular HCPs during the follow up period. Patients received a follow up phone call at Day 7, 14 and 28 (+/- 2 days) to collect clinical and safety outcomes information and any new or changes in co-medications/vaccination status. During follow up, patients were reminded to complete at home nasal/oropharyngeal sample collection at the required timepoints (see Section 7.5.1 for details). Participating sites also contacted patient's regular HCPs as required, for clinical and safety outcomes data. All baseline and follow-up data were recorded in the eCRF.

7.5. Study Assessments and Procedures

This study enrolled IC non-hospitalized patients aged ≥18 year old infected with SARS-CoV-2 and receiving 500 mg IV sotrovimab treatment as per standard of clinical care for COVID-19 in selected facilities. All patients who consented to be enrolled in the study were followed up for up to 28 days post sotrovimab treatment. Participant and disease characteristics (e.g. demographics, number of days of COVID-19 symptoms [if symptomatic] and number of days since initial COVID-19 positive test result at time of receiving treatment, co-morbidities including immunocompromising condition and risk factors for COVID-19 progression, COVID-19 vaccination status, previous SARS-CoV-2 infection, serostatus [if available] and treatment history [e.g. immunosuppressant treatment]) were collected at baseline (index date; D0), which corresponded to the sotrovimab administration date. Information on other treatments for COVID-19 infection

involving antivirals or other monoclonal antibodies were collected at baseline and follow-up, as required.

The decision to treat patients with sotrovimab was made by the patient's healthcare team prior to and independently from the decision to enroll patients into this study. ICF completion and baseline sample collection were done prior to sotrovimab administration; when this was not possible, then this was conducted either during the sotrovimab infusion or as close as possible to the end of the sotrovimab infusion (within ≤ 2 hours of the end of the sotrovimab infusion). This study therefore included patients who had received sotrovimab as part of their standard clinical care.

Selected key clinical outcome data (e.g., hospital admission, respiratory support, ICU admission and death) were collected from patients and medical records at Day 7, 14 and 28 (+/-2 days); participating sites could also have contacted patient's regular HCPs for clinical and safety outcomes data as required. All baseline and follow-up data were recorded in the eCRF. Phone calls to the participants by the study research staff were conducted at these 3 follow-up time points with the aim to complete the eCRF and to remind the participants to collect their follow-up nasal/oropharyngeal sample.

If a participant progressed to severe disease that required hospitalization they were actively contacted and followed up where possible by the study research staff from the site where sotrovimab was administered. The research staff or HCPs involved in the patient's clinical care may have collected samples whilst the participant was hospitalized. Participants were given a contact card and asked to notify the site if they could not be contacted for the follow-up calls. To reduce loss to follow up of hospitalized participants, preference was given to sites where it was likely that participants who require hospitalization following enrollment would have been readmitted to the study site. This was assessed as part of site feasibility.

Table 2 Schedule of Activities

	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)[p,q]
Pre-screening[a]	√			
Confirmation of sotrovimab prescription[b]	√			
Informed Consent c	√			
Eligibility confirmation[d]	√			
Enrollment[e]	√			
Nasal/oropharyngeal swab	√ [f]	√[g]	√[g]	√[g]
Sotrovimab administration[h]	√			
Demography[i]	√			
Co-morbidities[j]	√			
Disease characterization[k]	√			
Concomitant medications[l]	√	√	√	√
Vaccination status[m]	√	√	√	√
Clinical Outcomes[n]		√	√	√
Adverse events related to sotrovimab treatment[o]	√	√	√	√

a Pre-screening of potential participants was 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 was documented in the patient's medical records.

c Informed consent was taken prior to any study specific procedures being conducted with the patient.

d Evidence that all inclusion and no exclusion criteria have been met was documented in the patient's medical records prior to enrollment.

e Patent was registered in EDC system. Subject identification number was assigned to patient and documented on enrollment log and patient materials (ICF, contact card) and sample collection kits.

f The nasal/oropharyngeal swab at baseline was taken prior to the administration of sotrovimab or as close as possible to the end of sotrovimab infusion. Participants were trained in the self-administration of nasal/oropharyngeal swabs at baseline to support sample collection at follow up timepoints. Three sample collection kits were provided to the participant for at home sample collection at follow up timepoints, staff ensured correct subject identification number was present on each kit.

g Nasal/oropharyngeal swabs at follow up timepoints were self-administered by the participant or HCP in case of hospitalization. Samples were returned to the central analytical laboratory by post as soon as practically possible. Use of priority post boxes was encouraged to ensure samples reached the central analytical laboratory within the analysis window.

h Sotrovimab administration was performed as per local SoC and was not part of this study protocol.

i Demographic data including age (year and range), sex, smoking status, ethnicity and BMI (range) were collected and documented in the participant's medical records.

j Refer to Section 8.3.3.1 of the Protocol for list of relevant co-morbidities. Co-morbidities were documented in the participant's medical record at baseline.

k Disease characterization data including duration of COVID-19 symptoms (days), previous SARS-CoV-2 infection and serostatus (if available) were collected at baseline and documented in the participant's medical records.
l Concomitant medications, both related to and non-related to SARS-CoV-2 infection, were collected at baseline and during follow up calls and were documented in the participant's medical records.
m COVID-19 vaccination status, including number of vaccinations, date (month) and brand, were collected at baseline and during follow up calls and documented in the participant's medical record.
n Clinical outcomes including hospital admission, respiratory support, ICU admission and death were collected and recorded in the participant's medical records during follow up calls.
o Refer to Section 11.3 of the protocol for details on safety events reported.
p Participants who progressed to severe disease and required COVID-19 related hospitalization were actively contacted and followed-up where possible by site staff to obtain samples and follow up data as per protocol.
q Participants with a persistent positive sample at the end of the 28 day follow up period had their positive results reported back to the sites upon site request (as described in the study reference manual) and had appropriate medical follow-up under standard clinical care by their treating healthcare team arranged.

7.5.1. Clinical assessment

Patients were followed for 28 days from the time they received sotrovimab treatment (index date [D0]) in one of the clinical sites. Data and samples were collected following the schedule below (see also Table 2):

- Day 0 On-site screening:
  - Confirmation that decision to administer sotrovimab (per standard of clinical care) was made by the treating HCP.
  - Informed consent and enrollment.
  - Baseline sample collection under supervision after training (nasal/oropharyngeal) prior to sotrovimab administration or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion). Data collection of patient and disease characteristics (e.g., demographic, medications, and comorbidities) when possible.
  - Three sample collection kits were provided to the patient for home collection at each follow up timepoints (D7, D14, D28 [+/-2days]), with subject identification present on each kit (as per guidance in the study reference manual).
- Day 7 +/-2 days
  - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes.
  - Reminder to follow-up sample collection (nasal/oropharyngeal) – Home kit.
  - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0.
- Day 14 +/-2 days
  - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes.
  - Reminder to follow-up sample collection (nasal/oropharyngeal) – Home kit.

- Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0.

- Day 28 +/-2 days
  - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes.
  - Reminder to follow-up sample collection (nasal/oropharyngeal) – Home kit.
  - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0.

Patients who required hospitalization were actively contacted and followed-up where possible by the study research staff from the site where sotrovimab was administered. They or HCPs involved in the patient's clinical care collected samples whilst the patient was hospitalized. Patients were given a contact card and asked to notify the site if they could not be contacted for the follow-up calls. To reduce loss to follow-up of hospitalized patients, preference was given to sites where it was likely that patients who require hospitalization following enrollment would be readmitted to the study site.

7.5.2. Safety events

Only AEs considered related to sotrovimab by the investigator were collected.

The investigator or site staff were responsible for detecting, documenting, and reporting events that met the definition of an AE or SAE related to sotrovimab. AE information volunteered by the participant, discovered by investigator questioning or detected by other means was collected from treatment with sotrovimab until the last follow-up contact. The following information on only AEs related to sotrovimab was obtained from the investigators:

- Duration (start and stop dates).
- Severity (mild, moderate, severe).
- Causality (reasonable possibility yes/no).
- Actions taken and outcome.

The AE and SAE definitions are provided in the protocol, Section 11.1.

7.6. Methodology for Virology Analysis

7.6.1. Clinical sample collection, shipping, and handling information

Nasal/oropharyngeal swab samples for resistance surveillance were collected by HCPs at baseline and by participants at Day 7, Day 14 and Day 28, as defined in the clinical study protocol. Briefly, nylon flocked swabs (MedDX respiratory virus swab sample collection kit, KT388) were provided to swab 1 nostril and throat. Swabs were placed into 1 mL Virocult transport media (supplied in the kit) for shipment at ambient temperature to

GOSH. At GOSH swabs were processed which involved aliquoting into 3 aliquots; 1 aliquot containing lysis buffer for RNA extraction and detection of SARS-CoV-2 by 1-step real-time RT-PCR and 2 aliquots containing swab sample without lysis buffer for virus culture. The purified RNA from samples positive for SARS-CoV-2 by PCR were then transferred to UCLG [London, UK] for NGS analysis.

7.6.2. Methodology for determination of viral load

SARS-CoV-2 RNA was quantified using the RT-qPCR assay developed and qualified by GOSH. Viral RNA was extracted from the sample on the Microlab STAR automated platform. Every sample was spiked with PDV during the extraction process to control extraction failures. Each batch of samples extracted included a negative sample extraction control. Following extraction, samples were tested for SARS-CoV-2 and PDV by multiplex targeted one-step real-time RT/PCR using a Quantstudio 5. Every PCR run included a SARS-CoV-2 positive control and a no-template control. Following analysis, results were automatically uploaded to and reported on Epic EMR. The LLOD and the LLOQ of the assay were 453 copies/mL (equivalent to Ct=38) and 1570 copies/mL (equivalent to Ct=36.18), respectively. It was possible for this assay to detect SARS-CoV-2 RNA at lower concentrations, but with less than 95% confidence. When calculating median and mean viral load values when values below the LLOD were reported for a given sample, half the lowest value of the LLOD was imputed (226.5 copies/mL). When values above the LLOD but below the LLOQ were reported for a given sample, the LLOQ minus half the difference between LLOQ and LLOD was imputed (1011.5 copies/mL).

Viral loads were assigned using a standard curve. The standard curve was generated using a 10-fold dilution series of SARS-CoV-2 RNA of known quantity and imported to the PCR analysis to generate a viral load in copies/mL for each positive sample. The viral load was calculated using the QuantStudio5 PCR analysis software. Viral loads were reported as copies/mL. Viral load results, exported from the PCR analysis software, were automatically merged with the Epic EMR data export before transferring it to UCL. Viral loads were not recorded in Epic EMR as Epic EMR allows entry of only qualitative and not quantitative results.

7.6.3. Methodology for sequence analysis

NGS was conducted at UCL using RNA isolated during the viral load assay. The SARS-CoV-2 genome was amplified in 400 bp overlapping fragments by RT-PCR using the ARTIC v4.1 primer sets. The amplicons were prepared for sequencing using a modified version of the Illumina DNA prep tagmentation protocol [Baker, 2021]) either on the Agilent Bravo workstation or manually. Each batch of samples processed included at least 1 negative and 1 positive control. Samples were pooled and sequenced on the appropriate Illumina platform (MiniSeq, MiSeq or NextSeq) dependent on the number of samples (UCLG_SOP_0076). A viral load cut-off of 2.65 $\log_{10}$ copies/mL was applied, below which samples were not subjected to NGS analysis.

The analyzed NGS data with at least 50% genome-wide coverage and 10 distinct reads per covered position was uploaded to CLIMB Database.

7.6.4. Analysis of SARS-CoV-2 spike next-generation sequencing data

Next-generation sequencing data for the spike gene were analyzed at GSK using an analysis pipeline created by GSK Bioinformatics (Post-Text Methods section).

Reads were processed and mapped using the following steps:

Data from the 2 non-overlapping pools of fragments were pooled in silico and mapped against the same reference sequence (Wuhan-Hu-1, GenBank: MN908947.3).

Individual mapped reads were trimmed to remove primer derived data, followed by generation of a consensus sequence.

For AA substitutions calling, filtering was applied for each substitution, with a minimum of 500 coverage and Q>20.

Sequencing results including full changes or mixtures were reported as change from reference sequence. When a baseline and a post-baseline sequence was available, post-baseline sequences were compared to the respective baseline sequence and change from baseline was reported. AA substitutions were reported as minority substitutions detected at >5% allelic frequency and consensus at ≥50% allelic frequency. The location of gaps in the sequence are presented in Table 44. Gaps in the sequence were accounted for in the substitution analysis. For baseline and post-baseline analysis, the number of participants with sequence data available at a specific residue and visit was determined by subtracting the number of participants with a gap at the residue at the specific timepoint from the total number of available sequences for the specific timepoint. For the treatment emergent substitution determination, participants required paired sequences (sequence data available at both baseline and the specific timepoint) to be included (Primary Endpoint). The number of participants at the specific residue with a gap at baseline or the specific timepoint was subtracted from the total number of participants with paired data. Substitutions detected at ≤5% allelic frequency have been shown to be nonspecific and are not shown in this report but are available in Source Listing 1.28.

Sequencing results from each sample were classified as having no change from reference (no substitutions detected), or having substitutions detected in the spike sequence. AA changes in the spike protein were further classified as being substitutions in the epitope of sotrovimab (“epitope”). For substitutions in the epitope, positions 332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, and 509 were defined as the epitope positions.

Analysis was also performed at a per participant level. For participants with sequencing data available for more than 1 visit, substitutions detected at any visit (baseline or post-baseline) were included in the results for a given participant. Substitutions could only be determined to be treatment emergent if there was a baseline sample available.

7.6.4.1. VOC and VUI

The SARS-CoV-2 virus isolates were classified by whole genome sequencing based on the first available sequencing result. Some of these lineages were designated VOC and VUI as defined in Section 7.3.2.2.1.

For determination of VOC/VUI, analysis was performed to determine the variants described in the Post-Text Methods Section.

7.7. Bias

Selection bias

Since participants who were hospitalized for non-COVID-19 reasons or who were unable to collect nasal/oropharyngeal swabs were excluded, there was a possibility of selection bias in recruiting a somewhat healthier population. Furthermore, participants were requested to provide informed consent to be enrolled in the study. This may have potentially selected participants more willing to participate.

Testing procedures

The baseline sample was a nasal/oropharyngeal swab collected on site and supervised by a HCP, while a pragmatic, participant-focused solution asked study participants to collect their follow up samples at 7-, 14-, and 28-days using home test kits. Study staff were not able to verify whether samples were collected and handled properly, which would impact the sensitivity of subsequent sequencing testing of participant samples. However, this collection approach was considered more acceptable than asking COVID-19 positive, IC participants to seek testing outside their residence.

Geographical coverage

The geographical coverage was limited to the sentinel sites that agreed to participate in this study. This may have impacted the generalizability of the results. All participating sites were in major towns or cities. The identification and hence distribution of viral variants in the IC participants may not be generalizable to all parts of the UK. Furthermore, whilst included sites were distributed widely across England and Wales, no sites in Scotland were included.

Loss to follow up/ Attrition Bias

Although the duration of follow up was relatively short (28 days +/- 2 days) all data were collected remotely, and samples were provided by post, which relied on participant compliance with protocol procedures. Similarly, not all IC conditions are the same and different IC conditions may increase or decrease the propensity for prolonged viral replication and shedding of SARS-CoV2. Consequently, the distribution of IC conditions among those participants eligible for sequence analysis at different time points in the study may change.

7.8. Study Size

7.8.1. Sample size considerations

As a sentinel surveillance study, the aim was to collect data for a period of 12 months, or until the enrollment of 500 (up to 625) patients was met, or until sotrovimab is no longer used in GB. Due to the change in guidance in the UK in November 2022 [NHS England, 2023] and the low usage of sotrovimab since then, it was concluded that enrollment numbers would not be met and enrollment of patients would end following the data collection period of 12 months as planned.

7.9. Data Analysis

Analysis Sets

Screened Set:

The Screened Set included all participants who were screened at Visit Day 0 (i.e., gave informed consent). This set was used for the listing and summarization of subject disposition.

Safety Set:

The Safety Set, or Safety population, included all participants who were enrolled and treated with sotrovimab.

Virology Set:

The Virology Set, or Virology Population, included all participants who were enrolled and treated with sotrovimab with a positive PCR test by GOSH qPCR having viral load above the limit of detection (i.e., viral load >= LLOD) as threshold at baseline.

7.9.1. Statistical analysis overview

Participant disposition was summarized for all participants in the Screened Set. The summary table captured the number of participants screened, the number of screen failures and reason, the number of participants who discontinued from the study prematurely and the primary reason for discontinuation.

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, participant management, dosing, and sampling procedures or participant assessments were reviewed by the Sponsor, the PI, and the study statistician and categorized into Not Important/Important during a Data Review Meeting prior to database lock. All protocol deviations (Not Important and Important) observed during the conduct of the study are available in data listings. Important protocol deviations (participants with at least one Important protocol deviation and split by protocol deviation category) were summarized for the Safety population.

Demographic and baseline characteristics, including age, age group, sex, race, ethnicity, BMI, and current smoking status were summarized for the Safety population using standard descriptive statistics.

Medical history, as recorded at screening/baseline and concomitant diseases, were summarized separately for the Safety population with the number and percentages of participants within each of the CRF pre-defined conditions.

Prior and concomitant medications were coded by the ATC classification system according to the WHO Drug Dictionary. Medications were classified as concomitant or prior and summarized by ATC class (level 2, therapeutic subgroup) and preferred drug name for all participants in the Safety population. Prior medication was defined as any medication taken before the date of the first dose of treatment with sotrovimab. Concomitant medication was defined as any medication taken on or after the date of the first dose of treatment with sotrovimab.

This was a descriptive study. All participants entered into the database were included in participant data listings. Quantitative (continuous) data including absolute values and changes from baseline, where appropriate, were summarized with number of observations (n), mean, SD, median, IQR, minimum, and maximum. Qualitative (categorical) data were summarized using number of observations (n), and frequency and percentages of participants. Unless stated otherwise, the calculation of percentages was based on the total number of participants with non-missing data. For some of the endpoints, 95% CI of proportion was also displayed. For participants who withdrew or were withdrawn from the study prior to the end of the study, all data collected up to the point of discontinuation was used for analysis.

All statistical analyses were conducted using SAS® for Windows® Version 9.4.

7.9.1.1. Missing Data

Missing or incomplete data for viral load

Imputation was performed on post-baseline viral loads depending on the viral load results below:

Viral loads that were missing or less than the LLOD (453) were imputed as 0.5*LLOD = 0.5*453 = 226.5 copies/mL = 2.36 $\log_{10}$ copies/mL. Viral loads that were above the LLOD but lower than the LLOQ (1570) were imputed as LLOQ – 0.5*(LLOQ-LLOD) = 1011.5 copies/mL = 3.00 $\log_{10}$ copies/mL.

Missing or incomplete dates for age

Age was calculated for all participants using birth date. If necessary, birth date was imputed as follows:

- For all participants with birth year available, the missing date and month were imputed as ‘30th June’.

- Birth date was presented in listings as 'YYYY'.

Completely missing dates of birth remained missing, with no imputation applied. Consequently, the age of these participants was not calculated and was reported as missing.

7.9.2. Analysis of SARS-CoV-2 spike next-generation sequencing data for AA substitutions and VOC/VUI

Next-generation sequencing data for the spike gene were analyzed for AA substitutions in spike protein at GSK using an analysis pipeline created by GSK Bioinformatics (Post-Text Methods Section). NGS data for the whole genome was analyzed at UCL for VOC/VUI determination (Post-Text Methods Section).

7.9.3. Primary analysis

7.9.3.1. Main analytical approach

The primary analysis was conducted on the Safety population. For the primary objectives, only descriptive analysis was performed.

Analysis of primary objectives included:

1. The proportion of participants with epitope AA change from baseline was summarized showing the count and percentages of participants in each epitope substitution change by post-baseline visits (Day 7, 14 and 28 [+/-2 days]) and overall. These proportions were also presented separately for Minority species (>5% allelic frequency) and consensus sequence (>50% allelic frequency).
2. The proportion of participants with spike AA change from baseline was summarized showing the count and percentages of participants in each spike substitution change by post-baseline visits (Day 7, 14 and 28 [+/-2 days]) and overall. These proportions were also presented separately for Minority species (>5% allelic frequency) and consensus sequence (>50% allelic frequency).

Data were summarized using number of observations (n), and percentages of participants. The calculation of percentages was based on the total number of participants with non-missing data. The method of sequencing analysis used for this study is given in Section 7.6.3. Details regarding analysis of SARS-CoV-2 Spike Next-Generation Sequencing are provided in Section 7.6.4. Information regarding protocol deviation leading to sample excluded from analysis is given in Section 9.1.2.

7.9.3.1. Data handling conventions/data transformations

Detailed information on the data handling convention is provided in Section 7.6.1. For participants who withdrew or were withdrawn from the study prior to the end of the study, all data collected up to the point of discontinuation was used for analysis. Participant samples were considered ineligible for viral analysis if the sample was

missing, sample had undetected RNA, sample had invalid NGS, sample failed NGS, sample failed NA NGS and sample failed sequencing (Table 8).

7.9.3.2. Sensitivity analyses

Not applicable.

7.9.4. Secondary analysis/exploratory analysis

All secondary and exploratory analyses were conducted on the Safety population, unless otherwise stated.

Analysis of secondary endpoints included:

1. Proportion of patients eligible for sequence analysis with SARS-CoV-2 VOC and VUI on the earliest possible sample. Proportions were summarized showing the counts and percentages of patients by each variant based on WHO classification and Pango sub-lineage.
2. Proportion of patients with undetectable virus (e.g., viral load < LLOD) were summarized by Day 7, 14, and 28 (+/-2 days).
3. Clinical outcomes through Day 28 post sotrovimab administration were summarized by count and percentage of patients and its 95% CI by VOC/VUI, Non-VOC/VUI, by VOC/VUI variants, Medical Condition/Comorbidity, and overall:
    - Proportion of patients with all-cause hospital admission
    - Proportion of patients with COVID-19 related hospital admission
    - Proportion of patients requiring new or increased oxygen support (supplemental oxygen [not high flow], non-invasive ventilation or high-flow, invasive mechanical ventilation, or ECMO)
    - Proportion of patients with all-cause ICU admissions
    - Proportion of patients with COVID-19 related ICU admissions
    - Proportion of patients who died through Day 28
    - Proportion of patients who died through Day 28 due to COVID-19
4. 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.
5. 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 secondary endpoints 4 and 5, baseline and post-baseline (Day 7, 14, and 28 [+/-2 days]) AA substitutions were 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 were listed separately.

Exploratory analyses included:

1. Viral characteristics (e.g., viral load, VOC/VUI, AA changes) in patients who subsequently required hospital admission or died due to COVID-19, post sotrovimab treatment.
2. Whether AA changes in SARS-CoV-2 spike protein from baseline had been reported in the genomic databases (e.g., GISAID).

7.9.5. Amendments to statistical plan

The interim analysis included VOC/VUI determined using spike consensus sequences and whole genome sequence. There were gaps in the spike consensus sequences for participants in the clinical trial which impacts the ability to definitively determine the VOC/VUI so the whole genome sequence approach was viewed as generating results with higher confidence. Therefore, in this final report the VOC/VUI determination was reported only from the whole genome sequence of the virus. While the proportion of participants with epitope substitution change by VOC/VUI for Consensus Sequence (allelic frequency >50%) and for Minority species (>5% allelic frequency) was presented by visit for interim analysis reporting, it was not planned to be included in the final analysis.

Two additional tables were generated post-hoc for the viral sequencing data:

- Table to report the frequency of participants with treatment emergent AA substitutions in the spike protein and the sotrovimab epitope.
- Table to report the frequency of participants with baseline or treatment emergent substitutions in the sotrovimab epitope at >5% allelic frequency that impact the activity of sotrovimab.

7.10. Quality Control and Quality Assurance

Syneos Health and GSK were responsible for following SOPs to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All sites were trained by the SMA on the protocol, study logistics, and the EDC system.

Veeva Vault CDMS was the EDC system used to manage data collection during this study; it is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies. All participant data relating to the study was recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator was responsible for ensuring prospective data were entered in a timely manner and verifying that data were accurate and correct by physically or electronically signing the eCRF. Guidance on completion of CRFs was provided in the eCRF Guidelines.

On-line logic checks were built into the EDC system as much as possible, so that missing or illogical data were not submitted. If inconsistent data persisted, queries were issued electronically to the clinical study site and answered electronically by the study site personnel.

Participant data was entered into GSK-defined eCRFs, transmitted electronically to Syneos Health and combined with data provided from other sources (e.g., laboratory data) in a validated data system before being transmitted to GSK.

Verification of data accuracy and adherence to protocol requirements was achieved through regular monitoring visits of each investigational site and remote site calls. Subsequent data handling and reporting processes were performed according to processes detailed in Syneos Health and GSK's SOPs. AEs and concomitant medications were coded using company standard dictionaries, MedDRA and GSK Drug.

Any SAE, consistent with the data collected for other AEs, was entered into the database and quality assured, including reconciliation with the GSK Global Safety Database.

All investigators and responsible study site staff attended a study site initiation visit to review study protocol procedures, study requirements, and responsibilities. Investigators and staff were given the opportunity to discuss any aspect of the study protocol and study requirements. Training records were reviewed to ensure investigators and staff were qualified to conduct the study and to document training.

PIs signed the investigator page of the protocol to confirm their commitment to conduct the study in accord with the protocol. The signed documents have been archived within individual investigator study files.

7.10.1. Critical to quality factors

To ensure compliance with all applicable regulatory requirements, the Sponsor conducted one or more quality assurance audits.

Responsible IEC/Competent Authority and/or the Sponsor's clinical quality assurance group, or its designee, requested access to all source documents, case report forms, and other study documentation as necessary for on-site audits or inspections. Direct access to these documents had to be guaranteed by the Investigator, who also had to always provide support for these activities.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical Approval and Subject Consent

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center EC or IRB, in accordance with ethical principles founded in the Declaration of Helsinki (version 2008) [WMA, 2023] and applicable country-specific requirements, including US 21 CFR 312.3(b) for constitution of IECs, and related

guidances, especially Directive 2001/83/EC, Regulation (EC) No 726/2004 and Commission Implementing Regulation (EU) No 520/2012 (IR) as detailed in GVP Modules V, VI and VIII. Ethics committee or IRB approvals are maintained in the Sponsor's study file.

Investigators were trained to conduct the study in accordance with the study protocol. Written commitments were obtained from investigators to conduct the study in accordance with all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki (version 2008) [WMA, 2023], and to conduct the study in accordance with the protocol.

Written informed consent was obtained from each participant prior to the performance of any study-specific procedures. The investigator agreed to provide the participant as much time as necessary, within the constraints of the study protocol, to review the document, to inquire about details of the trial, and to decide whether to participate in the study. The informed consent was signed and dated by the study participant and by the person who conducted the informed consent discussion. Case report forms were provided for each participant's data to be recorded. The participant was also informed that his/her medical records could be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities. The medical record had to include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

8.2. Subject Confidentiality

Participants were assigned a unique identifier by the sponsor. Any participant records or datasets that were transferred to the sponsor contained the identifier only; participant names or any information which would make the participant identifiable were not transferred.

The ICF complied with relevant data protection and privacy legislation in the UK. The participant was informed that his/her personal study-related data would be used by the sponsor in accordance with local data protection law. The level of disclosure was also explained to the participant who was required to give consent for their data to be used as described in the informed consent.

9. RESULTS

9.1. Participants

On 17 July 2023, data collection in the study closed with the last participant last visit. A total of 219 participants had been screened from 9 sites. Of the screened participants, 217 (99.1%) met the inclusion and exclusion criteria, provided informed consent, and enrolled in the study.

9.1.1. Disposition of participants

Table 3 presents participant disposition. The majority of enrolled participants (n=208, 95.9%) completed the study. Nine participants (4.1%) discontinued the study early due to withdrawal (n=4), loss to follow-up (n=4) and death (n=1). No AEs led to study discontinuation.

Table 3 Participant Disposition

Disposition	N (%)
Screened[a]	219
Screen Failure	2 (0.9)
Met eligibility, not enrolled	0
Enrolled	217 (99.1)
Study Status after Enrollment[b]	217
Completed the Study	208 (95.9)
Discontinued from Study	9 (4.1)

Source: Table 1.1
a. Percentages based on the number of screened participants.
b. Percentages based on the number of enrolled participants.

9.1.2. Protocol deviations

There were 52 participants (24.0%) with one or more recorded major protocol deviations during the study (Table 45 in the Annex 2). A selection of major protocol deviations is described below.

Eight participants were enrolled in the study without being eligible because they were not immunocompromised as defined in the protocol. Because the study enrolled patients who received sotrovimab as per local standard of clinical care, it was decided to keep these eight patients in the analysis sets. The study ineligibility of 6 of these 8 participants was identified after database lock and completion of the statistical analysis; therefore, their protocol deviations are not recorded in the database and not included in Table 45 in the Annex 2.

Among all 8 participants, 5 were enrolled on the basis of multiple sclerosis, 1 on the basis of pulmonary disease (bronchiectasis, asthma, and COPD), and 1 on the basis of stage-4 chronic kidney disease. The eighth participant was enrolled because the site was unaware that the patient was no longer receiving active treatment for breast cancer following surgical resection. The lack of active treatment for cancer was only identified after the participant had completed the study. None of the 8 participants were hospitalized, admitted to an ICU, or had sotrovimab-related AEs reported during the study.

The virological outcomes for all 8 participants who were enrolled in the study despite not meeting eligibility criteria are summarized below. The viral load, VOC/VUI and treatment emergent substitution data for each participant can be found in Listing 1.131, Listing 1.12 and Listing 1.9.

Participant PPD had a baseline viral load of 6.45 log_{10} copies/mL. The viral load declined over time to below LLOD on Day 14 and then rebounded to 5.60 log_{10} copies/mL on Day 28. This participant had the Omicron BE.1 viral variant based on whole genome sequence at Baseline. However, there was no sequence available at Days 7 and 14 as the levels of viral RNA were below the threshold set for the sequencing assay (2.65 log_{10} copies/mL). There was no sequencing data available for Day 28 even though viral RNA levels detected in this sample were above the threshold set for the sequencing assay.

Participant PPD had a baseline viral load of 8.36 log_{10} copies/mL. The viral load declined to below LLOD on Day 14 and remained below LLOD on Day 28. This participant had the Omicron BA.5.2.1 viral variant based on whole genome sequence at Baseline and although sequence was available Post-Baseline at Day 7 and Day 28 there was no sequence of the sotrovimab epitope to evaluate for substitutions.

Participant PPD had a baseline viral load of 8.30 log_{10} copies/mL. The viral load declined to below LLOD on Day 7 and remained below LLOD on Day 14 and Day 28. This participant had the Omicron BE.1 viral variant based on whole genome sequence at Baseline however there was no sequence available at Days 7, 14 and 28 as the levels of viral RNA were below the threshold set for the sequencing assay (2.65 log_{10} copies/mL).

Participant PPD had a negative viral load result at Baseline and all Post-Baseline time points. Viral NGS analysis could not be performed at any timepoint due to the levels of viral RNA being below the threshold for the assay (2.65 log_{10} copies/mL) so there are no results for substitution or viral variant analysis for this participant.

Participant PPD had a baseline viral load of 6.46 log_{10} copies/mL. The viral load declined to below LLOD on Day 28. This participant had the Omicron BA.5.1 viral variant based on whole genome sequence at Baseline. No treatment emergent substitutions in the sotrovimab epitope were detected at Day 7. There was no sequence available for the sotrovimab epitope at Day 14 to perform the substitution analysis. There was no sequence available at Day 28 as the levels of viral RNA were below the threshold set for the sequencing assay (2.65 log_{10} copies/mL). The sequence for this participant had a gap in epitope sequence except 509.

Participant PPD had a baseline viral load of 7.03 log_{10} copies/mL. The viral load declined to below LLOD on Day 14. This participant had the Omicron BA.4 viral variant based on whole genome sequence at Baseline. There were no treatment emergent substitutions observed in the sotrovimab epitope at Day 7 but there was only sequence available for part of the epitope. There was no sequence available at Day 14 as the level of viral RNA were below the threshold set for the sequencing assay (2.65 log_{10} copies/mL).

Participant PPD had a baseline viral load of 2.67 log_{10} copies/mL. The viral load declined to below LLOD on Day 7 and remained below LLOD on Day 14 and Day 28. There was no sequencing data available at Baseline for viral variant determination even though viral RNA levels detected in this sample was above the threshold set for the sequencing assay (2.65 log_{10} copies/mL). Viral NGS analysis could not be performed at any post-baseline timepoint due to the viral RNA levels being below the threshold (2.65 log_{10} copies/mL) for the assay so there are no results for substitution or viral variant analysis for this participant.

Participant PPD had a baseline viral load of 7.12 log_{10} copies/mL. The viral load declined to below LLOD on Day 14 and remained below LLOD at Day 28. This participant had the Omicron BA.5.2 viral variant based on whole genome sequence at baseline. Although sequence was available post-baseline at Day 7 and Day 14 there was no sequence of the sotrovimab epitope to evaluate for substitutions.

Another category of protocol deviation was non-compliance to study procedures. A total of 55 samples from 43 unique participants were identified with a deviation leading to their exclusion from the viral load analysis as described in Table 4 below.

No noncompliance issues leading to participant exclusion from analysis were identified by monitoring or audit. Protocol deviations by participant are provided in Listing 1.24.

Table 4 Protocol Deviations Leading to Sample Exclusion from Analysis

Deviation Type	Number of Samples (N)[a]	Number of Participants (N)[b]
Participant has returned more samples than expected	3	3
Sample completed out of window	25	24
Sample received late at central laboratory	27	20

Source: Table 1.39; Listing 1.24.
a. Excluded only from viral load analysis.
b. One participant can have more than one deviation type.

9.1.3. Analysis sets analyzed

A total of 217 participants were included in the Safety population to assess demographic and baseline characteristics, safety, and clinical outcomes.

The Safety population was also used to assess virology outcomes, except for the change from baseline in viral load analyses which used the Virology Set. A total of 209 participants were included in the Virology Set.

9.2. Descriptive Data Including Baseline Characteristics.

Among the 217 participants in the Safety population, 56.7% were female and the median age at enrollment was 58 years (Table 5). The majority (87.1%) were of white race. All except 3 participants (1.4%) had received at least 1 dose of a COVID-19 vaccine before study enrollment. Participants were treated with sotrovimab in a mean of 2.6 days (median 2 days) after testing positive for SARS-CoV-2.

Table 5 Summary of Demographic and Baseline Characteristics

Characteristic	Sotrovimab (N=217) n (%)
Sex	
Female	123 (56.7)
Male	94 (43.3)
Age (Years)	
Mean (SD)	56.5 (15.66)
Median	58.0

Characteristic	Sotrovimab (N=217) n (%)
Min – Max	20-92
Age Group (Years)	
18-34	21 (9.7)
35-49	52 (24.0)
50-64	68 (31.3)
65-74	44 (20.3)
75-84	30 (13.8)
≥85	2 (0.9)
Ethnicity	
Hispanic or Latino	1 (0.5)
Not Hispanic or Latino	199 (91.7)
Unknown	17 (7.8)
Race	
Asian	9 (4.1)
Black or African American	9 (4.1)
White	189 (87.1)
Unknown	4 (1.8)
Mixed Race	6 (2.8)
BMI (kg/m^2)[a]	
<18.5	3 (1.4)
18.5-24.9	75 (34.9)
25-29.9	51 (23.7)
30-34.9	42 (19.5)
35-39.9	28 (13.0)
≥40	16 (7.4)
COVID-19 Disease History[b]	
Symptomatic	212 (98.6)
Asymptomatic	3 (1.4)
Number of days since initial COVID-19 positive test result at time of receiving treatment[b]	
Mean (SD)	2.6 (1.36)
Median	2.0
Min – Max	0-8
Received a COVID-19 vaccine prior to study enrollment	
Yes	214 (98.6)
No	3 (1.4)

Source: Table 1.2.
N = number of participants in the Safety population.
a. BMI was available for 215 subjects.
b. Among 215 participants for whom COVID-19 disease history was known.

Participants were enrolled in the study on the basis that they belonged to an IC population eligible to be treated with sotrovimab [NHS England, 2023]. A summary of the study population immunocompromising medical conditions is provided in Table 6 below. The three most frequent IC conditions were IMID (30.4%), solid organ transplant (25.8%), and renal disease (24.0%).

Table 6 Summary of study population immunocompromising medical conditions

Immunocompromising Condition Reported	Sotrovimab (N=217) n (%)
Participants with IC reported	209 (96.3)
IMID	66 (30.4)
Solid organ transplant recipients	56 (25.8)
Renal diseases	52 (24.0)
Hematological diseases and recipient of stem cell transplant	44 (20.3)
Solid cancer	41 (18.9)
Immune deficiencies	26 (12.0)
Liver diseases	23 (10.6)
HIV/AIDS	3 (1.4)

Source: Table 1.40.
N= number of participants in Safety population.
Note: Participants may have reported more than 1 IC condition. Eight of the 217 participants had no immunocompromising condition recorded in the eCRF. Following queries to the sites after database lock, 2 of the 8 participants were considered to be immunocompromised as a result of being treated with mepolizumab for severe asthma (1 patient) and being treated with adalimumab for psoriasis (1 patient). The other 6 participants were not considered to be immunocompromised. In addition, there were 2 other participants for whom the site recorded an IC condition in the eCRF that was later determined not to meet the definition in the protocol. The IC conditions of these participants (renal disease and solid cancer for one patient each; Listing 1.24) are included in this table.

Other protocol defined co-morbidities that were frequently reported (>20% of participants) included overweight [including obesity, 107 participants, (49.3%)], hypertension [90 participants (41.5%)], obesity [67 participants (30.9%)], cardiovascular disease [47 participants (21.7%)] and CKD [44 participants (20.3%)]. Co-morbidities reported in 6-<20% participants were asthma [38 participants (17.5%)], DM [35 participants (16.1%)], other chronic respiratory disease [24 participants (11.1%)], cerebrovascular disease [14 participants (6.5%)], chronic liver disease [14 participants (6.5%)], and COPD [13 participants (6.0%)].

9.3. Prior and Concomitant Medications

A summary of concomitant medications taken at the time of receiving treatment with sotrovimab is presented in Table 7.

Table 7 Summary of Concomitant Medications

Main Pharmacological Group (ATC 1st Level)	Sotrovimab (N=217) n (%)
Participants with any concomitant medication	175 (80.6)
Alimentary tract and metabolism	149 (68.7)
Cardiovascular system	132 (60.8)
Antineoplastic and immunomodulating agents	129 (59.4)

Main Pharmacological Group (ATC 1st Level)	Sotrovimab (N=217) n (%)
Dermatologicals	120 (55.3)
Nervous system	119 (54.8)
Sensory organs	109 (50.2)
Respiratory system	104 (47.9)
Blood and blood forming organs	100 (46.1)
Genito urinary system and sex hormones	91 (41.9)
Musculo-skeletal system	87 (40.1)
Systemic hormonal preparations, excl. sex hormones and insulins	75 (34.6)
Antiinfectives for systemic use	59 (27.2)
Various	39 (18.0)
Antiparasitic products, insecticides and repellents	7 (3.2)

Source: Table 1.41.
N = number of participants in the Safety population.
Notes: Participants may have reported more than one concomitant medication. One medication may be included in more than one ATC level category.

A detailed participant description of prior and concomitant medications is available in Listing 1.26.

9.4. Exposure and Treatment Compliance

All participants received a single dose of sotrovimab as part of their SoC treatment. There were no cases of early cessation of the IV infusion as a result of infusion-related events, therefore all participants are considered to have received the prescribed 500 mg dose of sotrovimab.

9.5. Outcome Data

The main outcomes of interest included both virology and clinical endpoints.

The primary endpoint analyses were conducted on the 217 participants included in the Safety population. The secondary endpoint analyses (Secondary Objective 1-3) were also conducted on the 217 participants included in the Safety population.

Absolute change from baseline viral load summaries (Secondary Objective 4 and 5) were based on the 209 participants included in the Virology Set.

9.6. Results of Primary Analyses

9.6.1. Virology results

9.6.1.1. SARS-CoV-2 spike sequence analysis study population

SARS-CoV-2 spike analysis was carried out by nucleotide sequencing of the SARS-CoV-2 spike protein by NGS analysis of participant nasal/oropharyngeal swab samples. The nucleotide sequences were translated, and the AA sequences aligned and compared to a reference sequence. AA substitutions compared to the reference strain are presented for baseline, Day 7, Day 14 and Day 28. The reference strain used in the LUNAR clinical study is Wuhan-Hu-1 (GenBank: MN908947.3). Treatment emergent substitutions are defined as AA differences in a post-baseline sample that were not present at baseline at the defined threshold for minority and consensus analysis. These data are presented at 2 different thresholds of allelic frequency: minority (>5%) and consensus (>50%). The individual allelic frequencies are not shown in most tables within the study report. These can be found in the listings included in the modular appendices.

Number of participants with sequence available for the minority and consensus baseline and post-baseline analysis can be found in Table 8.

Table 8 Distribution of Samples for Virology Analysis in the LUNAR Study

	N = 217			
	Baseline	Post-baseline		
		Day 7	Day 14	Day 28
Participants with Spike Protein sequence data n (%)[a]	80-208 (36.9-95.9%)[b]	65-149 (30.0-68.7%)[b]	3-62 (1.4-28.6%)[b]	5-25 (2.3-11.5%)[b]
Participants with Sotrovimab Epitope Sequence, n (%)[a]	185-195 (85.3-89.9%)[b]	68-97 (31.3-44.7%)[b]	18-48 (8.3-22.1%)[b]	5-13 (2.3-6.0%)[b]
Sample information				
Number of failed NGS samples because of Equivocal results[c]	1	19	42	28
Number of invalid NGS samples	0	0	1	0
Number of failed NA NGS samples	0	4	0	0
Number of samples where RNA was not detected	7	35	97	149
Number of missing samples	0	5	8	10
Number of failed sequences	2	1	3	7

	N = 217			
	Baseline	Post-baseline		
		Day 7	Day 14	Day 28

Source: Table 1.7, Table 1.8; Table 1.9; Table 1.10.
N = number of participants in the Safety population. n = participants with sequence available at specified day.
Note: Participants may be counted in more than one subcategory.
a. Denominator is N.
b. Each amino acid residue in the spike protein or the epitope has a specific number of participants with sequencing data available for substitution analysis at that residue, and the range of n's observed is presented.
c. Equivocal results are samples with Ct value >38 (the cut off is 38), so cannot be determined as it may not be a true positive.

9.6.1.2. SARS-CoV-2 spike sequencing treatment emergent AA substitution analysis (Primary Objective)

The primary endpoint was evaluated for AA changes from baseline, referred to as treatment emergent substitutions in subsequent sections, at both >5% and >50% allelic frequency thresholds. Sequencing results from each sample were classified as having no change from reference (no substitutions detected) or having AA changes detected in the spike. This analysis has accounted for gaps in the spike sequence which are listed in Table 44. AA substitutions were compared to reference sequence at the specific AA residue and were not recorded if there is a gap in the sequence.

9.6.1.2.1. Proportion of participants with treatment emergent substitutions at >5% and >50% allelic frequency in the spike protein and the sotrovimab epitope in samples collected at Day 7, 14 and 28

A total of 156 paired baseline and post-baseline sequences were obtained and analyzed by NGS for minority and consensus analysis (Table 9). There were 153 (70.5%), 71 (32.7%) and 33 (15.2%) participants with paired sequences at Day 7, Day 14 and Day 28, respectively (Table 9).

There were 101 (64.7%) and 47 (30.1%) participants in the LUNAR study with treatment emergent substitutions at >5% allelic frequency in the spike protein and sotrovimab epitope, respectively at any post-baseline timepoint (Table 9). There were 88 (57.5%), 37 (52.1%) and 20 (60.6%) participants with treatment emergent substitutions at >5% allelic frequency in the spike protein at Day 7, Day 14 and Day 28, respectively (Table 9). There were 38 (24.8%), 18 (25.4%) and 11 (33.3%) participants with treatment emergent substitutions at >5% allelic frequency in the sotrovimab epitope at Day 7, Day 14 and Day 28, respectively (Table 9).

There were 36 (23.1%) and 23 (14.7%) participants in the LUNAR study with treatment emergent substitutions at >50% allelic frequency in the spike protein and sotrovimab epitope, respectively at any post-baseline timepoint. There were 19 (12.4%), 17 (23.9%) and 13 (39.4%) participants with treatment emergent substitutions at >50% allelic frequency in the spike protein at Day 7, Day 14 and Day 28, respectively (Table 9). There were 12 (7.8%), 11 (15.5%) and 11 (33.3%) participants with treatment emergent substitutions at >50% allelic frequency in the sotrovimab epitope at Day 7, Day 14 and Day 28, respectively (Table 9).

Table 9 Summary of Treatment Emergent AA Substitutions >5% and >50% Allelic Frequency in the Spike Protein and the sotrovimab Epitope on Day 7, 14 and 28

	(N=217)			
		Post-baseline		
Participant Category	Total	Day 7	Day 14	Day 28
Participants with Paired Sequences, n (%)[a]	156 (71.9%)	153 (70.5%)	71 (32.7%)	33 (15.2%)
>5% Allelic Frequency				
Participants with No TE Substitution detected at >5% AF, n (%)[b]	55 (35.3%)	65 (42.5%)	34 (47.9%)	13 (39.4%)
Participants with a TE Spike Protein[c] Substitution >5% AF, n (%)[b]	101 (64.7%)	88 (57.5%)	37 (52.1%)	20 (60.6%)
Participants with a TE Sotrovimab Epitope Substitution >5% AF, n (%)[b]	47 (30.1%)	38 (24.8%)	18 (25.4%)	11 (33.3%)
Participant with TE Sotrovimab Epitope Substitution >5% AF at 337, 340, 345, 356 or 441 that causes a reduction in sotrovimab activity in in vitro assays, n (%)[d]	46 (29.5%)	38 (24.8%)	17 (23.9%)	11 (33.3%)
>50% Allelic Frequency				
Participants with No TE Substitution detected at >50% AF, n (%)[b]	120 (76.9%)	134 (87.6%)	54 (76.1%)	20 (60.6%)
Participants with a TE Spike Protein[c] Substitution >50% AF, n (%)[b]	36 (23.1%)	19 (12.4%)	17 (23.9%)	13 (39.4%)
Participants with a TE Sotrovimab Epitope Substitution >50% AF, n (%)[b]	23 (14.7%)	12 (7.8%)	11 (15.5%)	11 (33.3%)
Participant with TE Sotrovimab Epitope Substitution >50% AF at 337, 340, 345, 356 or 441 that causes a reduction in sotrovimab activity in in vitro assays, n (%)[d]	23 (14.7%)	12 (7.8%)	11 (15.5%)	11 (33.3%)

Source: Table 1.11, Table 1.12; Table 1.13, Table 1.14; Table 1.52; Table 1.53; Listing 1.9; Listing 1.10.
In the total participants column, N = total number of participants in the LUNAR Safety population; n= number of participants. TE = treatment emergent; S = spike protein, AF = allelic frequency.
a. The denominator is N. Refer to Table 34 for listings of participants with paired sequence.
b. The denominator is the number of paired sequences either total or available on the specified day.
c. The number of participants with TE substitutions in the spike protein reflects participants that had a TE change in the spike protein at any position including the sotrovimab epitope.
d. Participants may have more than one epitope substitutions at the positions listed

9.6.1.2.2. Summary of treatment emergent substitutions in the epitope of sotrovimab at >5% allelic frequency

NGS analysis identified treatment emergent epitope substitutions with >5% allelic frequency at AA positions 337, 339, 340, 346, 356 and 509 of the sotrovimab epitope (Table 10). The predominant treatment emergent epitope substitutions observed in LUNAR participants at >5% allelic frequency were P337L, P337S, E340D, E340Q and K356T. Phenotypic data for single AA substitutions in the sotrovimab epitope observed in LUNAR can be found in Table 35, Table 36, Table 37 and Table 38.

Table 10 Summary of Treatment Emergent Epitope Substitutions >5% Allelic Frequency

	Post-baseline (N=217)					
	Day 7		Day 14		Day 28	
	n'	Number of Participants with Change Per Residue in Epitope n (%)[b]	n'	Number of Participants with Change Per Residue in Epitope n (%)[b]	n'	Number of Participants with Change Per Residue in Epitope n (%)[b]
Participants with Sequence n (%)[a]	90-92 (41.5-42.4%)		26-48 (12.0-22.1%)		12-13 (5.5-6.0%)	
Substitution list						
P337 any change	92	22 (23.9)	26	11 (42.3)	13	2 (15.4)
P337A	92	2 (2.2)	-	0 (0)	-	0 (0)
P337H	92	2 (2.2)	26	1 (3.8)	13	1 (7.7)
P337L	92	8 (8.7)	26	4 (15.4)	-	0 (0)
P337R	92	2 (2.2)	26	1 (3.8)	-	0 (0)
P337S	92	14 (15.2)	26	6 (23.1)	13	2 (15.4)
G339 any change	91	1 (1.1)	-	0 (0)	-	0 (0)
G339R	91	1 (1.1)	-	0 (0)	-	0 (0)
G339Y	91	1 (1.1)	-	0 (0)	-	0 (0)
E340 any change	91	28 (30.8)	26	14 (53.8)	13	8 (61.5)
E340A	91	3 (3.3)	-	0 (0)	13	1 (7.7)
E340D	91	15 (16.5)	26	5 (19.2)	13	1 (7.7)
E340G	91	5 (5.5)	26	4 (15.4)	13	2 (15.4)
E340K	91	6 (6.6)	26	5 (19.2)	13	1 (7.7)
E340Q	91	14 (15.4)	26	7 (26.9)	13	4 (30.8)
E340V	91	2 (2.2)	26	2 (7.7)	13	2 (15.4)
R346T	-	0 (0)	26	1 (3.8)	-	0 (0)
K356 any change	90	8 (8.9)	26	1 (3.8)	12	2 (16.7)
K356M	90	1 (1.1)	-	0 (0)	-	0 (0)
K356R	90	1 (1.1)	-	0 (0)	12	1 (8.3)
K356T	90	6 (6.7)	26	1 (3.8)	12	1 (8.3)
R509T	-	0 (0)	48	1 (2.1)	-	0 (0)

Source: Table 1.14

- = the number of participants without a specific substitution cannot be determined.

N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid position. n is number of participants with substitutions in the epitope at the specific amino acid position.

a. Denominator is N.

b. Denominator is n' for residue at specified visit.

9.6.1.2.3. Summary of treatment emergent substitutions in the epitope of sotrovimab at >50% allelic frequency

NGS analysis identified treatment emergent epitope substitutions with >50% allelic frequency at AA positions 337, 340 and 356 of the sotrovimab epitope at the consensus level (Table 11). The most predominant treatment emergent epitope substitutions detected at >50% allelic frequency were P337S, E340D and E340Q. Phenotypic data for single AA substitutions in the sotrovimab epitope observed in LUNAR can be found in Table 35, Table 36, Table 37 and Table 38.

Table 11 Summary of Treatment Emergent Epitope Substitutions >50% Allelic Frequency

	Post-baseline (N=217)					
	Day 7		Day 14		Day 28	
Participants with Sequence, n (%)[a]	91-92 (41.9-42.4%)		26 (12.0%)		12-13 (5.5-6.0%)	
	n'	Number of Participants with Change Per Residue in Epitope, n (%)[b]	n'	Number of Participants with Change Per Residue in Epitope, n (%)[b]	n'	Number of Participants with Change Per Residue in Epitope, n, (%)[b]
Substitution list						
P337 any change	92	4 (4.3)	26	2 (7.7)	13	2 (15.4)
P337L	92	1 (1.1)	26	1 (3.8)	-	0 (0)
P337S	92	3 (3.3)	26	1 (3.8)	13	2 (15.4)
E340 any change	91	8 (8.8)	26	8 (30.8)	13	8 (61.5)
E340A	91	1 (1.1)		(0)	13	1 (7.7)
E340D	91	2 (2.2)	26	3 (11.5)	13	1 (7.7)
E340G	91	1 (1.1)		(0)	13	1 (7.7)
E340K	91	1 (1.1)	26	1 (3.8)	13	1 (7.7)
E340Q	91	3 (3.3)	26	3 (11.5)	13	3 (23.1)
E340V	-	0 (0)	26	1 (3.8)	13	1 (7.7)
K356 any change	-	0 (0)	26	1 (3.8)	12	1 (8.3)
K356R	-	0 (0)	-	0 (0)	12	1 (8.3)
K356T	-	0 (0)	26	1 (3.8)	-	0 (0)

Source: Table 1.12
A dash (-) = the number of participants without a specific substitution cannot be determined.
N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid. n is number of participants with substitutions in the epitope at the specific amino acid position.
a. Denominator is N.
b. Denominator is n' for residue at specified visit.

9.6.1.2.4. Summary of treatment emergent substitutions in the spike protein at >5% allelic frequency

NGS analysis was performed on the entire spike protein to identify changes with >5% allelic frequency. Only treatment emergent spike protein substitutions present in >1 participant and excluding the sotrovimab epitope were included in the analysis presented in Table 12. The entire list of substitutions can be found in Table 40.

NGS analysis identified treatment emergent spike protein substitutions of >5% allelic frequency at positions 139, 140, 141, 142, 143, 144, 330, 660, 777, 1049 and 1254 (Table 12). The most predominant treatment emergent spike protein substitution was C1254*.

Table 12 Summary of Treatment Emergent Substitutions in the Spike Protein at >5% Allelic Frequency Found in >1 Participant in the LUNAR Study

	Post-baseline (N=217)					
	Day 7		Day 14		Day 28	
Participants with Sequence n (%)[a]	85-145 (39.2-66.8%)		39-50 (18.0-23.0%)		18-22 (8.3-10.1%)	
	n'	Number of Participants with Change Per Residue in Spike Protein n (%)[a]	n'	Number of Participants with Change Per Residue in Spike Protein n (%)[a]	n'	Number of Participants with Change Per Residue in Spike Protein n (%)[a]
Substitution list						
P139#	-	0 (0)	39	2 (5.1)	-	0 (0)
F140#	-	0 (0)	39	2 (5.1)	-	0 (0)
L141#	-	0 (0)	39	2 (5.1)	-	0 (0)
G142#	-	0 (0)	39	2 (5.1)	-	0 (0)
V143#	-	0 (0)	38	2 (5.3)	-	0 (0)
Y144#	-	0 (0)	39	3 (7.7)	18	5 (27.8)
P330S	85	2 (2.4)	-	0 (0)	-	0 (0)
Y660H	145	2 (1.4)	-	0 (0)	-	0 (0)
N777#	136	2 (1.5)	-	0 (0)	-	0 (0)
L1049F	137	2 (1.5)	-	0 (0)	-	0 (0)
C1254*	139	20 (14.4)	50	7 (14.0)	22	5 (22.7)

Source: Table 1.13
A dash (-) = the number of participants without a specific substitution cannot be determined.
N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid position. n is number of participants with substitutions in the epitope at the specific amino acid position.
* = Stop codon; # = deletion.
a. Denominator is n' for residue at specified visit.

9.6.1.2.5. Summary of treatment emergent substitutions in the spike protein at >50% allelic frequency

NGS analysis was performed on the entire spike protein to identify changes with >50% allelic frequency. Only spike protein substitutions present in >1 participant and excluding the sotrovimab epitope were included in the analysis presented in (Table 13).

The entire list of substitutions can be found in Table 42. NGS analysis identified treatment emergent spike protein substitutions of >50% allelic frequency at position 144 (Table 13).

Table 13 Summary of Treatment Emergent Substitutions in the Spike Protein >50% Allelic Frequency Found in >1 Participant in the LUNAR Study

	Post-baseline (N=217)					
	Day 7		Day 14		Day 28	
	n'	Number of Participants with Change Per Residue in Spike Protein n(%)[a]	n'	Number of Participants with Change Per Residue in Spike Protein n (%)[a]	n'	Number of Participants with Change Per Residue in Spike Protein n (%)[a]
Substitution list						
Y144#	-	0 (0)	-	0 (0)	18	3 (16.7)

Source: Table 1.11
- = the number of participants without a specific substitution cannot be determined.
N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid position and is the denominator for the percentage. n is number of participants with substitutions in the epitope at the specific amino acid position.
# = deletion.
a. Denominator is n' for residue at specified visit.

9.7. Results of Secondary Analyses

9.7.1. Virology results

9.7.1.1. SARS-CoV-2 spike sequencing AA baseline and post-baseline substitution analysis.

Analysis was conducted to determine the presence of AA substitutions at the minority (>5% allelic frequency) and consensus (>50% allelic frequency) level in the sotrovimab epitope of SARS-CoV-2 spike protein as well as in the entire spike protein at baseline and post-baseline.

9.7.1.1.1. Analysis of AA substitutions detected in the epitope of sotrovimab at baseline and post-baseline at >5% allelic frequency.

Analysis was conducted to determine the presence of AA substitutions at >5% allelic frequency in the epitope of sotrovimab in baseline or post-baseline sequences (Table 14). The most frequent baseline epitope substitutions detected at >5% allelic frequency were the G399D and N440K substitutions which were found in 158 (81.0%)-and 185 (100%) participants, respectively (Table 14). These AA changes are part of the characteristic spike substitution profile for the Omicron viral variants that were detected in the LUNAR clinical study and thus the presence of these substitutions at baseline reflects the spike sequences of the viral variant infecting the participants enrolled in the study (Table 14). The other epitope substitutions observed at baseline were G339H, E340D, E340Q, R346I, R346S, R346T and K356T which were observed in 36 (18.5%), 1 (0.5%), 1 (0.5%), 1 (0.5%), 3 (1.5%), 82 (42.1%) and 8 (4.1%) participants, respectively (Table 14).

Post-baseline, the G339D and N440K substitutions were also observed but for G339D the frequency was lower at later timepoints than at baseline (Table 14). Post-baseline

analysis of the epitope showed that substitutions at residue 340 had the highest prevalence after the substitutions at positions 339 and 440. Overall, there were 30 (31.9%), 14 (51.9%) and 8 (61.5%) participants at Day 7, 14 and 28, respectively with substitutions at position 340. The most frequent E340 substitution at Day 7 was the E340D (17 participants [18.1%]) and on Day 14 and 28 was the E340Q (7 participants [25.9%] on day 14; 4 participants [30.8%] on Day 28]) (Table 14). Other substitutions observed at E340 post-baseline in the LUNAR study were E340A, E340G, E340K and E340V.

Post-baseline, substitutions were also observed at the P337, G339, R346, K356 and R509 epitope residues (Table 14). The most prevalent change at these residues was the P337S and the K356T. The frequency of participants with the P337S, R346T and K356T substitutions was 15.4-22.2%, 41.2-59.3%, and 3.7-16.7%, respectively. The other substitutions at these residues were observed in ≤8 participants.

Table 14 Proportion of AA Substitutions in the Sotrovimab Epitope >5% Allelic Frequency at Baseline and Post-Baseline

	N=217							
			Post-baseline					
	Baseline		Day 7		Day 14		Day 28	
Substitution	n'	Number of Participants with Change per Residue in Epitope n (%)[a]	n'	Number of Participants with Change per Residue in Epitope n (%)[a]	n'	Number of Participants with Change per Residue in Epitope n (%)[a]	n'	Number of Participants with Change per Residue in Epitope n (%)[a]
P337 any change	-	0 (0)	95	23 (24.2)	27	11 (40.7)	13	2 (15.4)
P337A	-	0 (0)	95	2 (2.1)	27	0 (0)	-	(0)
P337H	-	0 (0)	95	2 (2.1)	27	1 (3.7)	13	1 (7.7)
P337L	-	0 (0)	95	8 (8.4)	27	4 (14.8)	-	0 (0)
P337R	-	0 (0)	95	2. (2.1)	27	1 (3.7)	-	0 (0)
P337S	-	0 (0)	95	15 (15.8)	27	6 (22.2)	13	2 (15.4)
G339 any change	195	194 (99.5)	94	93 (98.9)	27	27 (100)	13	13 (100)
G339D	195	158 (81.0)	94	76 (80.9)	27	18 (66.7)	13	8 (61.5)
G339H	195	36 (18.5)	94	17 (18.1)	27	9 (33.3)	13	5 (38.5)
G339R	-	0 (0)	94	1 (1.1)	-	0 (0)	-	0 (0)
G339Y	-	0 (0)	94	1 (1.1)	-	0 (0)	-	0 (0)
E340 any change	195	2 (1.0)	94	30 (31.9)	27	14 (51.9)	13	8 (61.5)
E340A	-	0 (0)	94	3 (3.2)	-	0 (0)	13	1 (7.7)
E340D	195	1 (0.5)	94	17 (18.1)	27	5 (18.5)	13	1 (7.7)
E340G	-	0 (0)	94	5 (5.3)	27	4 (14.8)	13	2 (15.4)
E340K	-	0 (0)	94	6 (6.4)	27	5 (18.5)	13	1 (7.7)
E340Q	195	1 (0.5)	94	15 (16.0)	27	7 (25.9)	13	4 (30.8)
E340V	-	0 (0)	94	2 (2.1)	27	2 (7.4)	13	2 (15.4)
R346 any change	195	86 (44.1)	97	43 (44.3)	27	16 (59.3)	13	8 (61.5)
R346I	195	1 (0.5)	97	1 (1.0)	-	0 (0)	-	0 (0)
R346S	195	3 (1.5)	97	2 (2.1)	-	0 (0)	13	1 (7.7)
R346T	195	82 (42.1)	97	40 (41.2)	27	16 (59.3)	13	7 (53.8)

	N=217							
	Baseline		Post-baseline					
			Day 7		Day 14		Day 28	
K356 any change	195	8 (4.1)	93	10 (10.8)	27	1 (3.7)	12	3 (25.0)
K356M	-	0 (0)	93	1 (1.1)	-	0 (0)	-	0 (0)
K356R	-	0 (0)	93	1 (1.1)	-	0 (0)	12	1 (8.3)
K356T	195	8 (4.1)	93	8 (8.6)	27	1 (3.7)	12	2 (16.7)
N440K	185	185 (100)	68	67 (98.5)	18	18 (100)	5	5 (100)
R509T	-	0 (0)	-	0 (0)	48	1 (2.1)	-	(0)

Source: Table 1.10

- = the number of participants without a specific substitution cannot be determined. N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid position. n is number of participants with substitutions in the epitope at the specific amino acid position. Substitutions in bold are part of the characteristic spike substitution profile for one or more SARS-CoV-2 viral variants identified in participants in the LUNAR study.

a. Denominator is n'.

9.7.1.1.2. Analysis of AA substitutions detected in the epitope of sotrovimab at baseline and post-baseline at >50% allelic frequency.

Analysis was conducted to determine the presence of AA substitutions at >50% allelic frequency in the epitope of sotrovimab in baseline or post-baseline sequences (Table 15). The most frequent baseline epitope substitutions detected at >50% allelic frequency were the G399D and N440K substitutions which were found in 158 (81.0%) and 185 (100%) participants, respectively (Table 15). These AA changes are part of the characteristic spike substitution profile for the Omicron viral variants that were detected in the LUNAR clinical study and thus the presence of these substitutions at baseline reflects the spike sequences of the viral variant infecting the participants enrolled in the study (Table 16). The R346T and G339H were the next most frequent baseline changes which were found in 82 (42.1%) and 36 (18.5%) of participants at baseline. The other epitope substitutions observed at baseline were R346I, R346S, and K356T which were observed in 1 (0.5%), 3 (1.5%) and 7 (3.6%) participants, respectively (Table 15).

Post-baseline the G339D and N440K substitutions were also observed but for G339D the frequency was lower from Day 14 than at baseline (Table 15). Post-baseline analysis of the epitope showed that substitutions at residue 340 were observed frequently in participants. Overall, there were 9 (9.6%), 8 (29.6%) and 8 (61.5%) participants at Day 7, 14 and 28, respectively, with substitutions at >50% allelic frequency at position 340.

The most frequent E340 substitution on Day 7 were the E340D and E340Q substitutions (2 participants [2.1%] and 4 participants [4.3%] respectively), on Day 14 was the E340D and E340Q substitution (3 participants each [11.1%]) and was the E340Q substitution on Day 28 (3 participants [23.1%]) (Table 15). Other substitutions observed at E340 post-baseline in the LUNAR study were E340A, E340G, E340K and E340V.

Post-baseline substitutions were also observed at the G339, P337, R346 and K356 epitope residues (Table 15). The most prevalent change at these residues was the R346T, which had a frequency range of 41.2-55.6%.

Table 15 Proportion of AA Substitutions in the Sotrovimab Epitope >50% Allelic Frequency at Baseline and Post-Baseline

	N=217							
			Post-baseline					
	Baseline		Day 7		Day 14		Day 28	
Substitution	n'	Number of Participants with Change per Residue in Epitope n (%)[a]	n'	Number of Participants with Change per Residue in Epitope n (%)[a]	n'	Number of Participants with Change per Residue in Epitope n (%)[a]	n'	Number of Participants with Change per Residue in Epitope n (%)[a]
P337 any change	-	0 (0)	95	4 (4.2)	27	2 (7.4)	13	2 (15.4)
P337L	-	0 (0)	95	1 (1.1)	27	1 (3.7)	-	0 (0)
P337S	-	0 (0)	95	3 (3.2)	27	1 (3.7)	13	2 (15.4)
G339 any change	195	194 (99.5)	94	93 (98.9)	27	27 (100)	13	13 (100)
G339D	195	158 (81.0)	94	76 (80.9)	27	18 (66.7)	13	8 (61.5)
G339H	195	36 (18.5)	94	17 (18.1)	27	9 (33.3)	13	5 (38.5)
E340 any change	-	0 (0)	94	9 (9.6)	27	8 (29.6)	13	8 (61.5)
E340A	-	0 (0)	94	1 (1.1)	-	0 (0)	13	1 (7.7)
E340D	-	0 (0)	94	2 (2.1)	27	3 (11.1)	13	1 (7.7)
E340G	-	0 (0)	94	1 (1.1)	-	0 (0)	13	1 (7.7)
E340K	-	0 (0)	94	1 (1.1)	27	1 (3.7)	13	1 (7.7)
E340Q	-	0 (0)	94	4 (4.3)	27	3 (11.1)	13	3 (23.1)
E340V	-	0 (0)	-	0 (0)	27	1 (3.7)	13	1 (7.7)
R346 any change	195	86 (44.1)	97	43 (44.3)	27	15 (55.6)	13	8 (61.5)
R346I	195	1 (0.5)	97	1 (1.0)	-	0 (0)	-	0 (0)
R346S	195	3 (1.5)	97	2 (2.1)	-	0 (0)	13	1 (7.7)
R346T	195	82 (42.1)	97	40 (41.2)	27	15 (55.6)	13	7 (53.8)
K356 any change	195	7 (3.6)	93	2 (2.2)	27	1 (3.7)	12	2 (16.7)
K356R	-	0 (0)	-	0 (0)	-	0 (0)	12	1 (8.3)
K356T	195	7 (3.6)	93	2 (2.2)	27	1 (3.7)	12	1 (8.3
N440K	185	185 (100)	68	67 (98.5)	18	18 (100)	5	5 (100)

Source: Table 1.8
- = the number of participants without a specific substitution cannot be determined. N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid position. n is number of participants with substitutions in the epitope at the specific amino acid position. Substitutions in bold are part of the characteristic spike substitution profile for one or more SARS-CoV-2 viral variants identified in participants in the LUNAR study.
a. Denominator is n'.

9.7.1.1.3. Analysis of AA substitutions detected in the spike protein outside of the sotrovimab epitope at baseline and post-baseline at >5% allelic frequency.

Analysis was conducted to determine the presence of AA substitutions at the minority (>5% allelic frequency) level in the SARS-CoV-2 spike protein at baseline and post-baseline. The complete data analysis is shown in Table 40 at the end of the document. This summary focuses on substitutions that occur in >1 participant and excludes the residues in the sotrovimab epitope that is reported in Table 14.

There were 77 substitutions observed at baseline or post-baseline, 68 of which were at baseline and 68 were post baseline in the spike protein, 33 of which were known to be part of the characteristic spike substitution profile for the SARS-CoV-2 Omicron viral variants identified in the LUNAR study (Table 39, Figure 19). Of the 44 substitutions that

are not part of a SARS-CoV-2 viral variant spike substitution profile, the most prevalent baseline and post-baseline substitution was N460K (Table 40).

9.7.1.1.4. Analysis of AA substitutions detected in the spike protein outside of the sotrovimab epitope at baseline and post-baseline at >50% allelic frequency.

An analysis was conducted to determine the presence of AA substitutions at the consensus (>50% allelic frequency) level in the SARS-CoV-2 spike protein at baseline and post-baseline. The complete data set is shown in Table 42 at the end of the document. This summary focuses on substitutions that occur in >1 participant and excludes the residues in the sotrovimab epitope that are reported in Table 15.

There were 61 substitutions observed at baseline or post-baseline, 59 of which were at baseline and 57 at post baseline in the spike protein, respectively, 33 of which were known to be part of the characteristic spike substitution profile for the SARS-CoV-2 Omicron viral variants identified in the LUNAR study (Figure 19). Of the 28 substitutions that were not part of a SARS-CoV-2 viral variant spike substitution profile, the most prevalent baseline and post-baseline substitution was N460K (Table 42).

9.7.1.2. Analysis of VOC and VUI based on whole genome sequencing.

In this final analysis, NGS results from 208 participants at 1 or more visits were available. Available sequences at any available visit were assessed to determine if any participant carried a variant of concern or a variant under investigation. The consensus NGS data for the whole SARS-CoV-2 genome was used to assess if a participant was infected with an VOC/VUI.

Overall, 208 of 208 (100%) participants with sequencing data out of 217 total participants harbored a SARS-CoV-2 VOC/VUI based on whole genome sequence at the earliest possible visit. Of the 208 participants with a SARS-CoV-2 VOC/VUI, 207 (99.5%) harbored SARS-CoV-2 Omicron viral variants. The most predominant sublineages were Omicron BE.1 (n=48, 23.1%), Omicron BA.5.2 (n=45, 21.6%), Omicron BA.5.2.1 (n=29, 13.9%) and Omicron BA.5.1 (n=28, 13.5%) (Table 16).

Table 16 Summary of VOC and VUI Detected in Participants in LUNAR by Whole Genome Sequencing

Variant of Concern, Variant under Investigation Identified by Whole Genome Sequencing	Total in LUNAR (N=217) n (%)[a]
Subjects with sequencing data	208
Omicron	207 (99.5)
Omicron BA.2	13 (6.3)
Omicron BA.2.1	4 (1.9)
Omicron BA.2.10	2 (1.0)
Omicron BA.2.17	1 (0.5)
Omicron BA.2.73	17 (8.2)
Omicron BA.4	11 (5.3)
Omicron BA.5	4 (1.9)
Omicron BA.5.1	28 (13.5)

Variant of Concern, Variant under Investigation Identified by Whole Genome Sequencing	Total in LUNAR (N=217) n (%)[a]
Subjects with sequencing data	208
Omicron	207 (99.5)
Omicron BA.5.2	45 (21.6)
Omicron BA.5.2.1	29 (13.9)
Omicron BA.5.3	1 (0.5)
Omicron BA.5.3.1	2 (1.0)
Omicron BE.1	48 (23.1)
Omicron BF.1	1 (0.5)
Unassigned	1 (0.5)
Possible Omicron	1 (0.5)
Unassigned	1 (0.5)

Source: Table 1.15
N = number of participants in Safety population in the LUNAR study. n = number of participants with VOC/VUI
a. denominator is the number of participants with sequencing data available

The viral variants identified by whole genome sequencing in the LUNAR study were evaluated in phenotypic assays using pseudotyped VSV viruses and/or authentic live virus to determine sotrovimab activity (Table 39; Phenotyping Section).

9.7.1.3. SARS-CoV-2 viral RNA analysis.

9.7.1.3.1. Undetectable virus at Day 7, 14 and 28 (+/-2 days).

The proportion of participants that had undetectable viral load in nasal/oropharyngeal swabs was determined by qRT/PCR at Baseline, Day 7, Day 14 and Day 28 (Table 17). The number of samples with undetectable viral RNA levels increased over time. At Day 7, Day 14 and Day 28, 50 (25.1%) 129 (65.8%) and 162 (83.5%) had undetectable levels of SARS-CoV-2 RNA, respectively.

Table 17 Summary of the Percentage of Positive and Negative Viral Load Results at Baseline and Post-Baseline

Visit		Sotrovimab (500 mg IV) (N=217)
Baseline	n	213 (98.2%)
	Positive	207 (97.2%)
	Negative	6 (2.8%)
Day 7	n	199 (91.7%)
	Positive	149 (74.9%)
	Negative	50 (25.1%)
Day 14	n	196 (90.3%)
	Positive	67 (34.2%)
	Negative	129 (65.8%)
Day 28	n	194 (89.4%)
	Positive	32 (16.5%)
	Negative	162 (83.5%)

Source: Table 1.18.
N = number of participants in Safety population in the LUNAR study. n = number of participants with a non-missing viral load result on the day listed. Positive = number of participants with non-negative viral load results on the day listed. Negative = number of participants with an undetectable viral load result.
Note: Negative viral loads are defined as below LLOD (453 copies/mL).

9.7.1.3.2. Analysis of participants based on SARS-CoV-2 viral RNA positivity or negativity at Day 28.

Analysis of TE epitope substitutions in participants with positive viral load at Day 28.

A total of 32 participants had a positive viral load at Day 28 for SARS-CoV-2 viral RNA (Table 18 and Table 19). Of these, 24 (75%), 14 (44%) and 12 (38%) had sequence data available at Day 7, 14 and 28, respectively. Of the participants that were positive by viral load at Day 28 and had sequence data available, 13 (54%), 13 (93%) and 11 (92%) had treatment emergent epitope substitutions at Day 7, Day 14 and Day 28, respectively.

By contrast a total of 162 participants had a negative viral load at Day 28 for SARS-CoV-2 viral RNA (Table 18 and Table 43). Of these, 56 (35%) and 13 (8%), had sequence data available at Day 7 and Day 14 respectively. There were no sequence data available at Day 28 from participants that were negative for viral load at Day 28. Of the participants that were negative by viral load at Day 28 and had sequence data available, 23 (41%) and 5 (39%) had treatment emergent epitope substitutions at Day 7 and Day 14 respectively.

Table 18 Summary of Treatment Emergent Epitope Substitutions for Participants with Positive or Negative Viral Load at Day 28 at >5% allelic frequency

	Participants with positive or negative viral load at Day 28 that have Treatment Emergent Substitutions in the Sotrovimab Epitope		
	Day 7 n/N (%)	Day 14 n/N (%)	Day 28 n/N (%)
Positive Viral Load at Day 28	13/24 (54%)	13/14 (93%)	11/12 (92%)
Negative Viral Load at Day 28	23/56 (41%)	5/13 (39%)	NA

Source: Listing 1.131; Listing 1.9; n = number of participants with TE substitutions at the day indicated; N= number of participants with sequence in the sotrovimab epitope on the day indicated. NA = Not applicable

Table 19 Treatment Emergent Epitope Substitutions for Participants with Positive Viral Load at Day 28 at >5% Allelic Frequency.

TE epitope substitutions in participants with positive viral load at Day 28			
Participants with Positive viral load at Day 28	**Day 7**	**Day 14**	**Day 28**
PPD	no TE substitution	P337L (5.59%), E340G (42.1%)	gap in epitope sequence
PPD	P337L (10.2%), E340D (9.24%), E340Q (53.1%)	E340Q (91.1%)	E340Q (96.4%)
PPD	no TE substitution	gap in epitope sequence	gap in epitope sequence

TE epitope substitutions in participants with positive viral load at Day 28			
Participants with Positive viral load at Day 28	**Day 7**	**Day 14**	**Day 28**
PPD	P337H (31.9%), P337L (25.3%), P337R (6.21%), E340G (30.2%)	P337L (87%), E340G (6.06%)	gap in epitope sequence
	no TE substitution	P337S (7.81%), E340G (18.1%), E340V (68.3%)	E340G (28.6%), E340V (69.9%)
	no sequence	no sequence	no sequence
	G339R (11.1%), G339Y (26%), E340D (13.7%)	no sequence	gap in epitope sequence except 332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 509
	gap in epitope sequence except 509	gap in epitope sequence	gap in epitope sequence except 509
	E340D (19.8%), E340G (19.9%), K356T (15.6%)	gap in epitope sequence	gap in epitope sequence
	no sequence	E340K (9.03%), E340Q (42.8%), E340V (26.5%)	E340Q (89%), E340V (10%), K356T (7.91%)
	P337L (9.41%), P337S (75%)	P337S (96.4%)	P337S (100%)
	gap in epitope sequence	no TE substitution	E340A (98.4%)
	no TE substitution	gap in epitope sequence	gap in epitope sequence
	gap in epitope sequence	gap in epitope sequence	gap in epitope sequence
	no TE substitution	R509T (23.5%) gap in epitope sequence	gap in epitope sequence
	P337S (14.8%), E340G (17.3%), E340K (7.44%), E340V (13.9%), K356R (6.9%)	gap in epitope sequence	gap in epitope sequence
	E340K (16.2%), K356T (6.31%)	K356T (71.2%)	gap in epitope sequence
	P337S (10.7%), E340G (86.1%)	no sequence	no TE substitution
	no TE substitution	E340G (12.2%), E340Q (86.4%)	K356R (99.7%)
	no TE substitution	gap in epitope sequence	gap in epitope sequence
	P337L (21.8%), P337S (14%)	no sequence	E340Q (99.6%)
	P337L (20%), K356T (5.68%)	no sequence	gap in epitope sequence
	E340D (29.9%), E340Q (56.9%), E340V (5.09%)	P337L (12.9%), E340D (20.9%), E340K (52.4%), E340Q (11.2%)	gap in epitope sequence
	P337H (21%), E340D (60.5%)	P337H (24.3%), P337S (20.4%), E340D (50.6%)	P337H (46.3%), P337S (51.2%)
	gap in most epitope sequence	P337R (43.2%), E340K (12.2%), E340Q (36.8%)	E340D (58.7%), E340Q (37%)
	no TE substitution	gap in epitope sequence	gap in epitope sequence

TE epitope substitutions in participants with positive viral load at Day 28			
Participants with Positive viral load at Day 28	**Day 7**	**Day 14**	**Day 28**
PPD	gap in epitope sequence	no sequence	gap in epitope sequence
	no TE substitution	gap in epitope sequence	gap in epitope sequence
	gap in epitope sequence except 440, 441, 509	gap in epitope sequence except 440, 441, 509	gap in epitope sequence except 509
	no TE substitution	gap in epitope sequence	gap in epitope sequence
	E340D (49.5%), E340K (18.1%), E340Q (24.1%)	E340K (38.3%), E340Q (60.4%)	E340K (97.1%)
	no TE substitution	gap in epitope sequence	E340G (98.3%)

Source: Listing 1.9; Table 44.

Analysis of viral load status at Day 28 for participants with treatment emergent substitutions at Day 7 and Day 14.

An analysis was performed to look at the impact of treatment emergent substitutions in the sotrovimab epitope on clearance of SARS-CoV-2 virus as assessed by viral positivity or negativity at Day 28. The majority of participants with or without treatment emergent substitutions in the sotrovimab epitope at Day 7 achieved negative viral load at Day 28 (63.9% or 81.0%, respectively) (Table 20). Participants who had treatment emergent substitutions at Day 14 were less likely to achieve a negative viral load at Day 28 than participants who did not have treatment emergent substitutions at Day 14 (27.8% compared to 73.3%, respectively) (Table 20).

Table 20 Summary of Day 28 Viral Load Status Based on Presence of Treatment Emergent Substitutions in the Sotrovimab Epitope

	Day 7		Day 14	
	Participants with TE Epitope Substitution[a] (n' = 36)	**Participants with no TE Epitope Substitution[a] (n'=58)**	**Participants with TE Epitope Substitution[a] (n'=18)**	**Participants with no TE Epitope Substitution[a] (n'=30)**
Day 28 Positive Viral Load n (%)[b]	13 (36.1%)	11 (19.0%)	13 (72.2%)	8 (26.7%)
Day 28 Negative Viral Load n (%)[b]	23 (63.9%)	47 (81.0%)	5 (27.8%)	22 (73.3%)

Source: Table 1.13; Table 1.14, Listing 1.131; Listing 1.7; Listing 1.9.
a. Excludes participants that do not have a valid result for Day 28 viral load.
b. Denominator is n' for each category.

9.7.1.3.3. Kinetics of SARS-CoV-2 viral RNA.

The absolute viral load in nasal/oropharyngeal swabs was determined by qRT-PCR at Baseline, Day 7, Day 14 and Day 28 (Table 21). The mean viral load declined over time

to 2.684 log_{10} copies/mL at Day 28. The median viral load declined over time to a level below the LLOD by Day 28 (LLOD = 2.66 log_{10} copies/mL).

Table 21 Summary of Absolute Viral Load (log_{10} copies/mL) Through Day 28 as Measured by qRT-PCR from Nasal/Oropharyngeal Swabs

Visit			Sotrovimab (500 mg IV) (N=217)
Baseline	Viral Load (log_{10} copies/mL)	N	207
		Mean (SD)	7.241 (1.3214)
		Median (Min, Max)	7.420 (2.46, 9.52)
Day 7	Viral Load (log_{10} copies/mL)	N	199
		Mean (SD)	4.419 (1.7414)
		Median (Min, Max)	4.260 (2.36, 8.51)
Day 14	Viral Load (log_{10} copies/mL)	N	196
		Mean (SD)	3.092 (1.3065)
		Median (Min, Max)	2.360 (2.36, 8.43)
Day 28	Viral Load (log_{10} copies/mL)	N	194
		Mean (SD)	2.684 (0.8910)
		Median (Min, Max)	2.360 (2.36, 8.35)

Source: Table 1.161.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

9.7.1.3.4. Change from baseline in SARS-CoV-2 viral RNA.

The mean change from baseline at Day 7, Day 14 and Day 28 of viral load as measured by qRT/PCR in nasal/oropharyngeal swabs was calculated (Table 22 and Figure 2). By Day 7 there was a mean reduction in the viral load of -2.778 log_{10} copies/mL (n=189) with a mean reduction of -4.134 log_{10} copies/mL (n=186) and - 4.580 log_{10} copies/mL (n=185) at Day 14 and Day 28, respectively.

Table 22 Summary of Change from Baseline in SARS-CoV-2 Viral Load (log_{10} copies/mL) Through Day 28 as Measured by qRT-PCR from Nasal/Oropharyngeal Swabs.

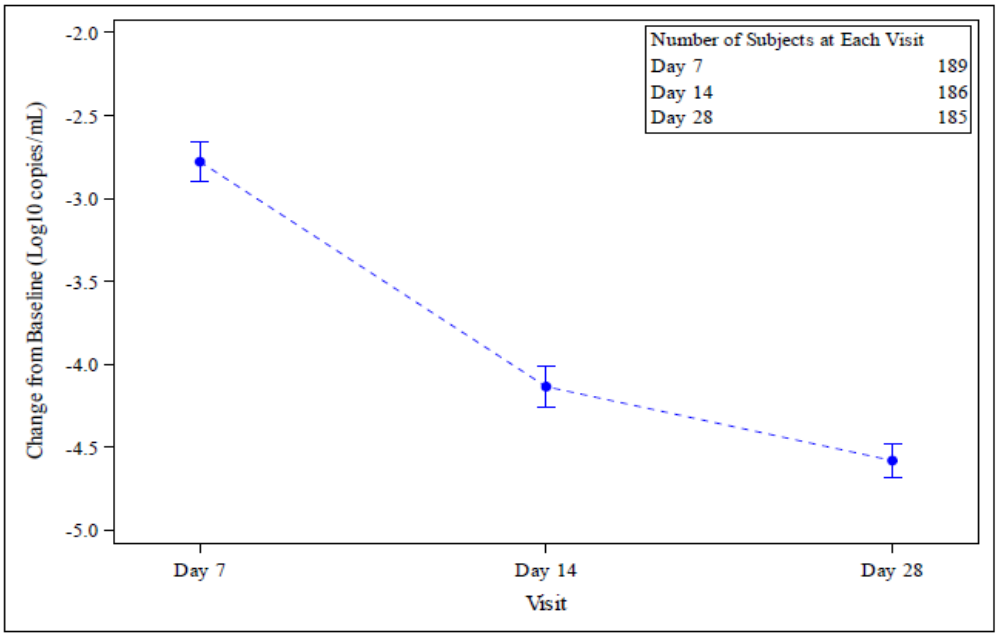
Visit			Sotrovimab (500 mg IV) (N=209)
Day 7	Change from Baseline Viral Load (log_{10} copies/mL)	n	189
		Mean (SD)	-2.778 (1.6753)
		Median (Min, Max)	-2.950 (-6.75, 1.25)
Day 14	Change from Baseline Viral Load (log_{10} copies/mL)	n	186
		Mean (SD)	-4.134 (1.7012)
		Median (Min, Max)	-4.465 (-6.94, 0.35)
Day 28	Change from Baseline Viral Load (log_{10} copies/mL)	n	185
		Mean (SD)	-4.580 (1.3983)
		Median (Min, Max)	-4.760 (-7.16, -0.32)

Visit			Sotrovimab (500 mg IV) (N=209)

Source: Table 1.164

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 2 Mean (+/- SE) Change in Baseline in SARS-CoV-2 Viral Load (log_{10} copies/mL).



Source: Figure 1.1.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

9.7.1.3.5. Analysis of participants with viral rebound.

The viral load data were analyzed to determine if participants experienced virologic rebound during the study. Virologic rebound is defined as participants who experience an increase of >1 log_{10} copies/mL in viral load at any point in time following any previous sample, or viral load becomes quantifiable after having been below the limit of quantification (LLOQ).

In LUNAR, 209 participants were eligible for the viral rebound analysis and 16 (7.8%) participants experienced viral rebound at any visit. The frequency of viral rebound was 0.5%, 3.2% and 4.8% on Day 7, Day 14 and Day 28, respectively (Table 23).

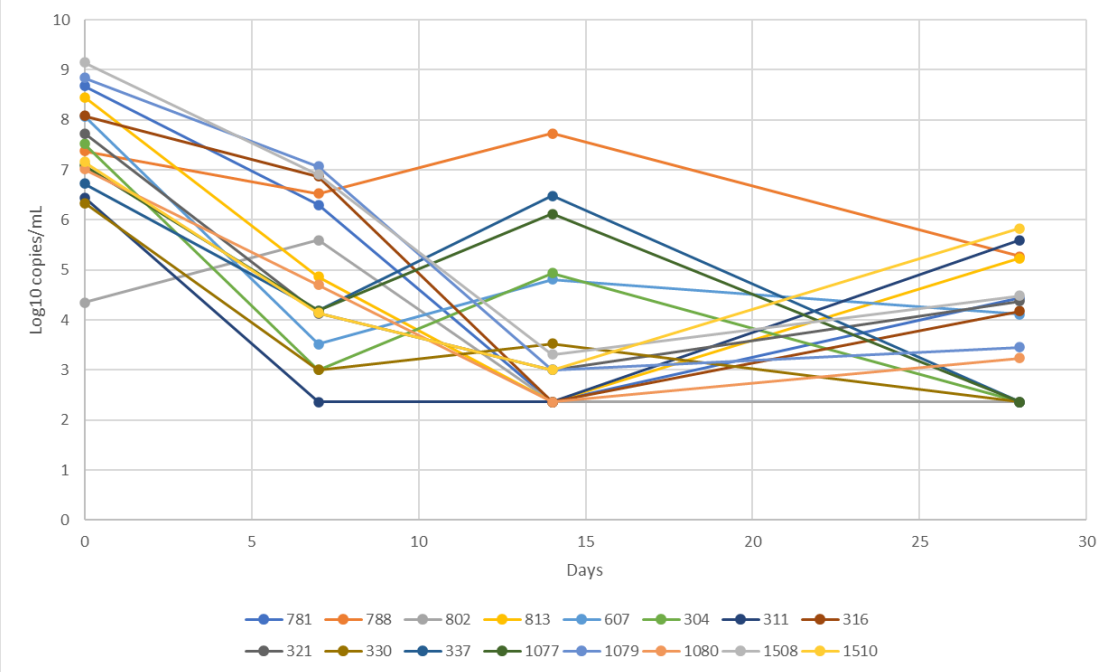
Table 23 Summary of Viral Rebound Analysis

Visit	n (%) (N=209)	Participants with Viral Load Rebound n' (%)
Any visit	204 (97.6)	16 (7.8%)
Day 7	196 (93.8)	1 (0.5%)
Day 14	189 (90.4)	6 (3.2%)
Day 28	188 (90.0)	9 (4.8%)

Source Table 1.44.
n = number of participants in virology population at respective visit. N= number of total participants in the virology population. n'= number of participants with viral rebound at the respective visit Percentages for n are based on N as denominator. Percentages for n' are based on n as the denominator for the respective visit.

The viral load kinetics for the 16 participants who experienced viral rebound at any time in the study are shown in Figure 3. Five of the 16 (31.3%) participants experiencing viral rebound had viral load <LLOD at Day 28. The eleven participants experiencing viral rebound that did not resolve viral excretion by Day 28 had SARS-CoV-2 RNA levels of 3.24-5.83 $\log_{10}$ copies/mL at Day 28 (Source Listing 1.131 and Source Listing 1.27). The day of viral rebound, SARS-CoV-2 viral variant and treatment emergent epitope substitution profile for the 11 participants positive for viral load at Day 28 can be found in Table 24. Five of the 7 participants with sequence of the epitope available at Day 28 had treatment emergent epitope substitutions.

Figure 3 Viral Load Kinetics for Participants Experiencing Viral Rebound



Source: Listing 1.131; Listing 1.27.
Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log_{10}$ viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Table 24 Summary of Viral Variant and TE Epitope Substitutions at >5% Allelic Frequency for Participants Experiencing Viral Rebound with Positive Viral Load at Day 28.

Participant	Day of Virus Rebound	Viral Variant[a]	TE epitope substitutions[b] (% Allelic Frequency)
PPD	28	Omicron BE.1	Day 7: P337S (10.7%), E340G (86.1%) Day 14: No sequence Day 28: None
	14	Omicron BA.5.2	Day 7: None Day 14: E340G (12.2%), E340Q (86.4%) Day 28: K356R (99.7%)
	28	Omicron BE.1	Day 7: P337L (21.8%), P337S (14%); Gap for 440, 441 Day 14: No sequence Day 28: E340Q (99.6%)
	14	Omicron BA.5.1	Day 7: Gap in sequence for epitope except 509 Day 14: Gap for 440 and 441 Day 28: E340A (98.4%), Gap for 440 and 441
	28	Omicron BE.1	Day 7: No sequence Day 14: No sequence Day 28: No sequence
	28	Omicron BA.2.73	Day 7: G339R (11.1%), G339Y (26%), E340D (13.7%) Day 14: No sequence Day 28: None
	28	Omicron BA.5.2	Day 7: Gap in sequence for epitope except 509. Day 14: Gap in sequence for epitope Day 28 Gap in sequence for epitope except 332, 333, 334, 509.
	14	Omicron BA.5.1	Day 7: None Day 14: Gap in sequence for epitope Day 28 Gap in sequence for epitope
	28	Omicron BE.1	Day 7: Gap in sequence for epitope except 509 Day 14: No sequence Day 28: No sequence
	28	Omicron BA.2.73	Day 7: E340D (49.5%), E340K (18.1%), E340Q (24.1%) Day 14: E340K (38.3%), E340Q (60.4%). Day 28: E340K (97.1%)
	28	Omicron BA.2	Day 7: None Day 14: Gap in sequence for epitope Day 28: E340G (98.3%);

Source: Listing 1.27, Listing 1.11, Listing 1.12, Listing 1.9, Listing 1.3.
TE = Treatment emergent.
a. Viral variant determined by whole genome sequence.
b. Epitope substitutions observed in minority species analysis (>5% allelic frequency).

Of the participants with viral rebound, only one PPD was admitted to hospital (Listing 1.15).

9.7.1.3.6. Kinetics of SARS-CoV-2 viral RNA for VOC/VUI.

The absolute viral load and change from baseline in viral load measured by qRT/PCR in nasal/oropharyngeal swabs was analysed according to the VOC/ VUI that was present by whole genome sequencing analysis. The kinetics of SARS-CoV-2 Viral RNA for participants in the study with VOC/VUI based on whole genome sequencing analysis are shown in Table 25, Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9 and Figure 10. The median change from baseline in SARS-CoV-2 Viral RNA for participants in the study with VOC/VUI based on whole genome sequencing analysis are shown in Table 26.

For participants infected with any VOC/VUI (n=205), the median viral load declined from 7.440 $\log_{10}$ copies/mL at baseline to 2.360 $\log_{10}$ copies/mL (<LLOD) on Day 28 (Table 25). For participants infected with an Omicron viral variant (n=204), the median viral load declined from 7.445 $\log_{10}$ copies/mL to 2.360 $\log_{10}$ copies/mL (<LLOD) on Day 28 (Table 25). For participants infected with all Omicron sub-lineages except Omicron BA.2.10, Omicron BA.2.17 and Omicron BA.5.3.1 viral variants, the median viral load declined over time from baseline to 2.360 $\log_{10}$ copies/mL (<LLOD) on Day 28 (Table 25, Figure 4, Figure 6, Figure 7, Figure 8, Figure 9 and Figure 10).

Participants infected with Omicron BA.2.10 (n=2) had a median baseline viral load of 7.555 $\log_{10}$ copies/mL at baseline that deceased over time to 4.695 $\log_{10}$ copies/mL at Day 28 (Table 25, Figure 5). The viral load for one participant (Participant PPD) infected with the Omicron BA.2.10 viral variant declined over time to <LLOD at Day 28 (Source Listing 1.131). The viral load for the other participant PPD infected with Omicron BA.2.10 viral variant had a persistently high viral load (>7 log10 copies/mL) for all visits. The persistently high viral load is likely due to the presence of treatment emergent substitutions at > 5% allelic frequency in the sotrovimab epitope [Day 7: P337L (10.2%), E340D (9.24%), E340Q (53.1%); Day 14: E340Q (91.1%); Day 28: E340Q (96.4%)] that are known to impact sotrovimab activity and not the specific viral variant as the consensus spike sequence for Omicron BA.2.10 is the same as for Omicron BA.2 and BA.2.1 (Figure 19; Source Listing 1.4, Source Listing 1.9, Source Listing 1.12, Source Listing 1.131, Phenotype Section).

The participant (PPD) infected with the Omicron BA.2.17 viral variant had a baseline viral load of 6.550 $\log_{10}$ copies/mL that decreased over time to 3.22 $\log_{10}$ copies/mL at Day 28 (Table 25, Figure 5). There was no sequence of the sotrovimab epitope available at Day 14 and Day 28 but as of Day 7 there were no treatment emergent substitutions in the sotrovimab epitope observed (gap at 440 and 441). The consensus spike sequence for Omicron BA.2.17 is the same as for Omicron BA.2 and BA.2.1 (Figure 19).

The participants infected with the Omicron BA.5.3.1 viral variant (n=2) had a median baseline viral load of 8.295 $\log_{10}$ copies/mL that decreased over time to 5.675 $\log_{10}$ copies/mL at Day 28 (Table 25, Figure 9). One participant (PPD) infected with Omicron BA.5.3.1 had a baseline viral load of 7.810 $\log_{10}$ copies/mL that declined >4 $\log_{10}$ copies/mL to 3 $\log_{10}$ copies/mL at Day 28 even with treatment emergent substitutions observed in the epitope [Day 7: E340K (16.2%), K356T (6.31%); Day 14: K356T (71.2%)] (Source Listing 1.4, Source Listing 1.9, Source Listing 1.12, Source Listing 1.131). The other participant (PPD) infected with Omicron BA.5.3.1 had

persistently high viral load (>8.3$\log_{10}$ copies/mL) at baseline, Day 14 and Day 28. No viral load data was available at Day 7. Treatment emergent substitutions were observed in the sotrovimab epitope [Day 14: E340K (9.03%), E340Q (42.8%), E340V (26.5%); Day 28: E340Q (89%), E340V (10%), K356T (7.91%)] (Source Listing 1.4, Source Listing 1.9, Source Listing 1.12, Source Listing 1.131). The persistently high viral load is likely due to the presence of the epitope substitutions that are known to impact sotrovimab activity as the consensus spike sequence for Omicron BA.5.3.1 is the same as for Omicron BA.4, BA.5 and BE.1 (Phenotype section; Figure 19).

Table 25 Summary of Median Absolute Viral Load (log_{10} copies/mL) Through Day 28 as Measured by qRT-PCR from Nasal/Oropharyngeal Swabs by VOC/VUI

	Visit							
	Median Viral Load [Min, Max] (log_{10} copies/mL) (N=217)							
	Baseline		Day 7		Day 14		Day 28	
VOC/VUI	n		n		n		n	
With any VOC/VUI	205	7.440 [2.73, 9.52]	191	4.520 [2.36, 8.51]	188	2.360 [2.36, 8.43]	187	2.360 [2.36, 8.35]
Omicron	204	7.445 [3.75, 9.52]	190	4.520 [2.36, 8.51]	187	2.360 [2.36, 8.43]	186	2.360 [2.36, 8.35]
BA.2	13	7.060 [5.83, 9.02]	11	4.140 [2.36, 8.48]	11	3.000 [2.36, 6.76]	11	2.360 [2.36, 5.83]
BA.2.1	4	7.020 [4.02, 7.92]	3	6.730 [3.00, 6.75]	3	2.360 [2.36, 4.97]	4	2.360 [2.36, 3.00]
BA.2.10	2	7.555 [6.35, 8.76]	2	5.085 [2.36, 7.81]	2	4.970 [2.36, 7.58]	2	4.695 [2.36, 7.03]
BA.2.17	1	6.550 [6.55, 6.55]	1	3.320 [3.32, 3.32]	1	3.630 [3.63, 3.63]	1	3.220 [3.22, 3.22]
BA.2.73	16	7.385 [5.58, 9.16]	15	4.490 [2.36, 6.91]	16	3.000 [2.36, 6.48]	15	2.360 [2.36, 4.91]
BA.4	11	7.830 [6.89, 9.17]	11	5.110 [2.36, 7.03]	11	2.360 [2.36, 3.62]	9	2.360 [2.36, 2.36]
BA.5	4	7.750 [5.97, 8.80]	4	5.515 [3.34, 6.62]	3	3.380 [2.36, 5.12]	4	2.360 [2.36, 3.85]
BA.5.1	28	7.875 [5.36, 9.36]	25	5.560 [2.36, 8.51]	24	2.680 [2.36, 5.55]	27	2.360 [2.36, 5.7]
BA.5.2	45	7.320 [4.53, 9.52]	42	4.500 [2.36, 7.98]	42	2.360 [2.36, 7.73]	38	2.360 [2.36, 5.27]
BA.5.2.1	29	7.480 [3.75, 9.30]	27	4.180 [2.36, 7.55]	26	2.360 [2.36, 5.84]	26	2.360 [2.36, 3.00]
BA.5.3	1	7.820 [7.82, 7.82]	1	3.630 [3.63, 3.63]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]
BA.5.3.1	2	8.295 [7.81, 8.78]	1	6.930 [6.93, 6.93]	2	6.945 [5.46, 8.43]	2	5.675 [3.00, 8.35]
BE.1	46	7.290 [4.35, 8.89]	45	3.990 [2.36, 7.02]	43	2.360 [2.36, 6.45]	44	2.360 [2.36, 5.60]
BF.1	1	7.740 [7.74, 7.74]	1	5.340 [5.34, 5.34]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]
Unassigned	1	5.410 [5.41, 5.41]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]
Probable Omicron	1	2.730 [2.73, 2.73]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]
Unassigned	1	2.730 [2.73, 2.73]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]	1	2.360 [2.36, 2.36]

Source: Table 1.171

N = number of participants in Safety population in the LUNAR study. n = number of participants with a non-missing viral load result on the day listed.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Table 26 Summary of Median Change from Baseline in Viral Load (log_{10} copies/mL) Through Day 28 as Measured by qRT-PCR from Nasal/Oropharyngeal Swabs by VOC/VUI

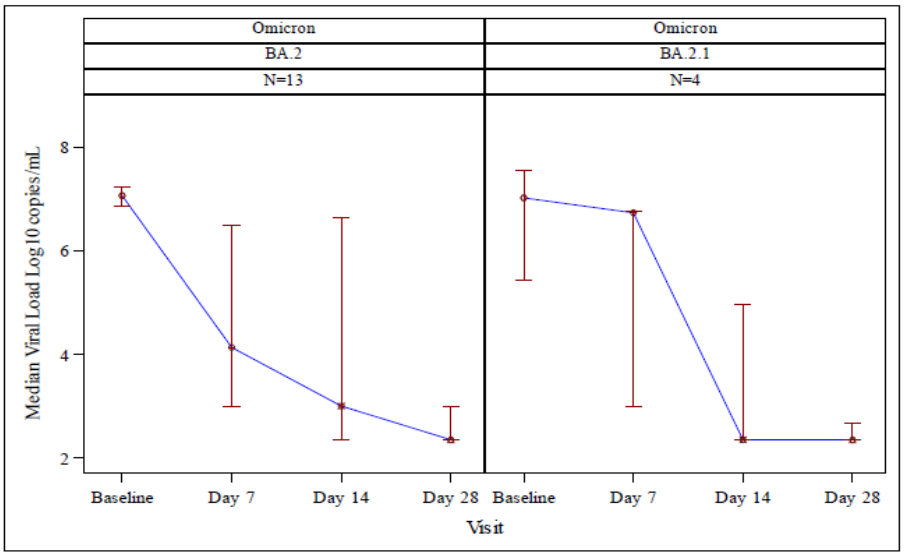
	Visit					
	Median Viral Load [Min, Max] (log_{10} copies/mL) (N=209)					
VOC/VUI	n	Day 7	n	Day 14	n	Day 28
With any VOC/VUI	188	-2.950 [-6.75, 1.25]	185	-4.470 [-6.94, 0.35]	184	-4.785 [-7.16, -0.38]
Omicron	187	-2.950 [-6.75, 1.25]	184	-4.480 [-6.94, 0.35]	183	-4.810 [-7.16, -0.44]
BA.2	11	-2.120 [-5.89, -0.25]	11	-3.060 [-6.54, -0.29]	11	-4.460 [-6.66, -1.33]
BA.2.1	3	-1.170 [-3.84, -0.46]	3	-2.210 [-5.57, -1.66]	4	-4.335 [-5.57, -1.66]
BA.2.10	2	-2.470 [-4.00, -0.94]	2	-2.590 [-4.00, -1.18]	2	-2.865 [-4.00, -1.73]
BA.2.17	1	-3.230 [-3.23, -3.23]	1	-2.920 [-2.92, -2.92]	1	-3.340 [-3.34, -3.34]
BA.2.73	14	-3.565 [-5.87, -0.87]	15	-4.460 [-5.87, -0.25]	14	-4.520 [-6.81, -2.18]
BA.4	11	-3.220 [-5.67, -0.82]	11	-5.380 [-6.82, -4.54]	9	-5.500 [-6.82, -4.54]
BA.5	4	-1.875 [-4.29, -1.24]	3	-3.680 [-4.49, -3.61]	4	-5.110 [-5.51, -3.61]
BA.5.1	25	-2.330 [-5.03, -0.14]	24	-4.340 [-6.53, -2.67]	27	-4.950 [-7.00, -2.91]
BA.5.2	42	-2.435 [-6.75, 0.34]	42	-4.495 [-6.75, 0.35]	38	-4.830 [-7.16, -2.11]
BA.5.2.1	27	-2.460 [-6.38, 0.07]	26	-5.040 [-6.94, -0.47]	26	-5.020 [-6.91, -1.40]
BA.5.3	1	-4.190 [-4.19, -4.19]	1	-5.460 [-5.46, -5.46]	1	-5.460 [-5.46, -5.46]
BA.5.3.1	1	-0.880 [-0.88, -0.88]	2	-1.350 [-2.35, -0.35]	2	-2.625 [-4.81, -0.44]
BE.1	43	-3.300 [-5.94, 1.25]	41	-4.670 [-6.54, -0.79]	42	-4.675 [-6.54, -0.84]
BF.1	1	-2.400 [-2.40, -2.40]	1	-5.380 [-5.38, -5.38]	1	-5.380 [-5.38, -5.38]
Unassigned	1	-3.060 [-3.06, -3.06]	1	-3.060 [-3.06, -3.06]	1	-3.060 [-3.06, -3.06]
Probable Omicron	1	-0.380 [-0.38, -0.38]	1	-0.380 [-0.38, -0.38]	1	-0.380 [-0.38, -0.38]
Unassigned	1	-0.380 [-0.38, -0.38]	1	-0.380 [-0.38, -0.38]	1	-0.380 [-0.38, -0.38]

Source: Table 1.172

N = number of participants in Safety population in the LUNAR study. n = number of participants with a non-missing viral load result on the day listed.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

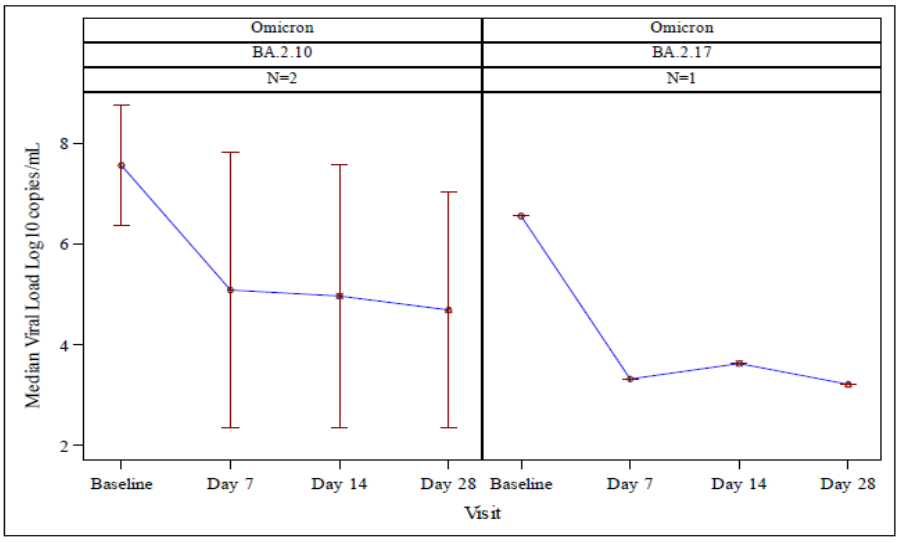
Figure 4 Median Viral Load Kinetics for Participants with Omicron BA.2 or BA.2.1 Viral Variants



Source: Figure 1.2.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log_{10}$ viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 5 Median Viral Load Kinetics for Participants with Omicron BA.2.10 or BA.2.17 Viral Variants

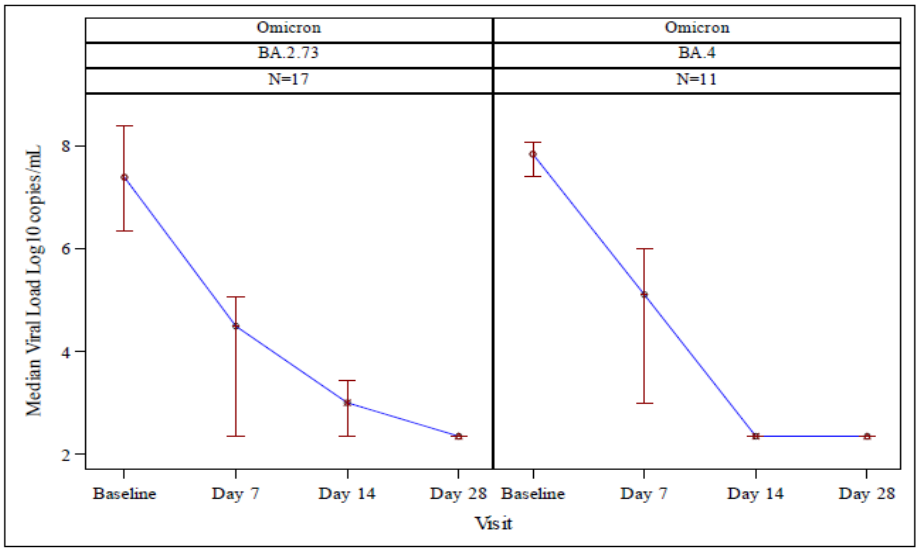


Source: Figure 1.2.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log_{10}$ viral loads. Subjects with major protocol deviation (out of visit

window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

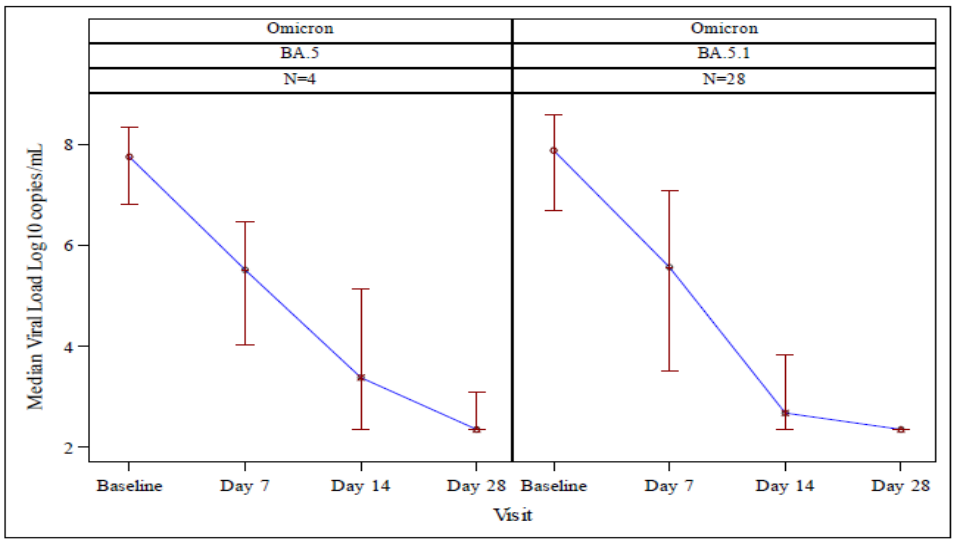
Figure 6 Median Viral Load Kinetics for Participants with Omicron BA.2.73 or BA.4 Viral Variants



Source: Figure 1.2.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log_{10}$ viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 7 Median Viral Load Kinetics for Participants with Omicron BA.5 or BA.5.1 Viral Variants

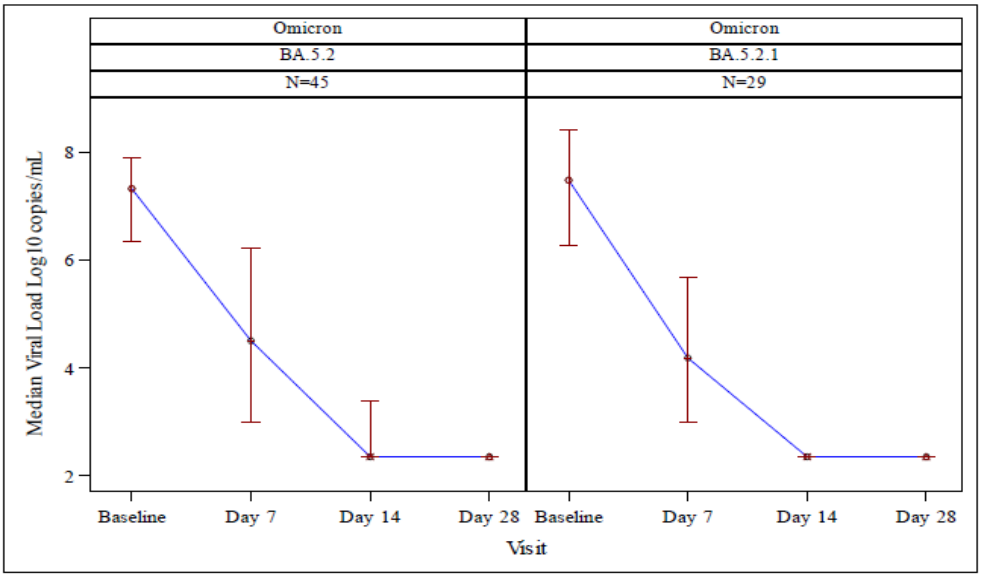


Source: Figure 1.2.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to

226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log_{10}$ viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

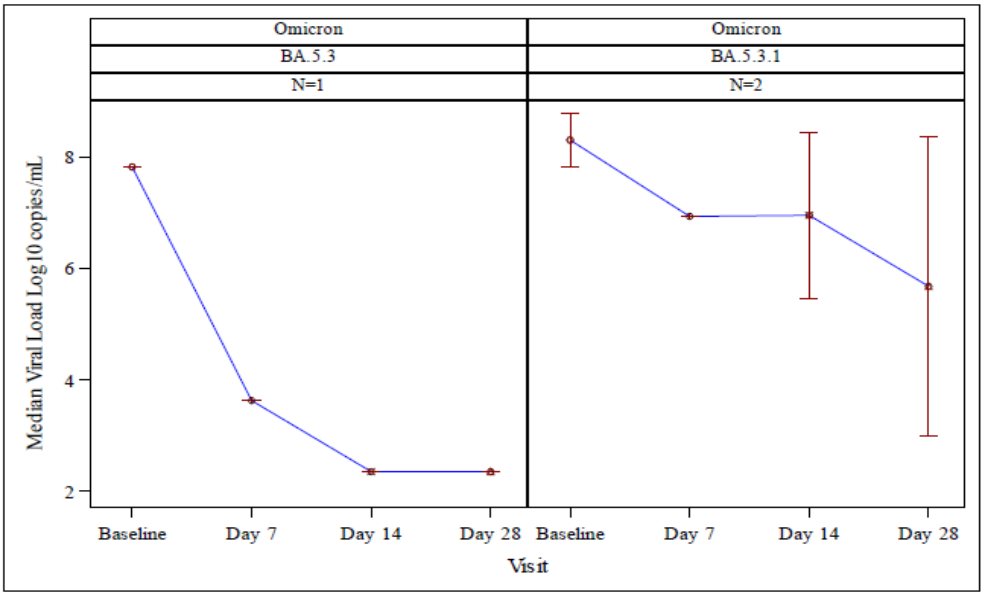
Figure 8 Median Viral Load Kinetics for Participants with Omicron BA.5.2 or BA.5.2.1 Viral Variants



Source: Figure 1.2.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log_{10}$ viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

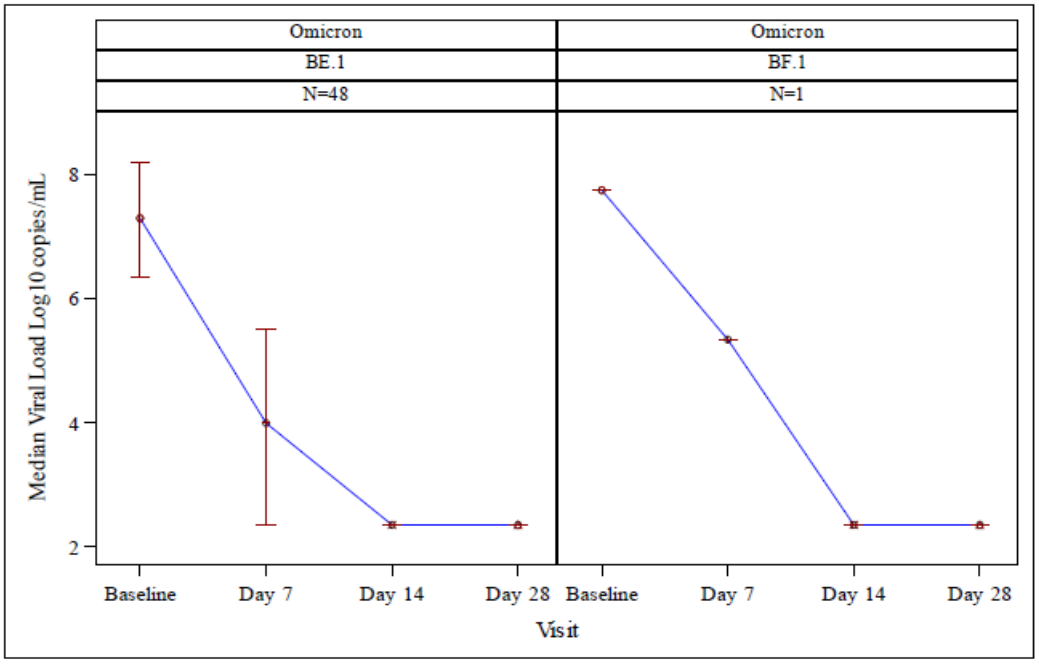
Figure 9 Median Viral Load Kinetics for Participants with Omicron BA.5.3 or BA.5.3.1 Viral Variants



Source: Figure 1.2.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log_{10}$ viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 10 Median Viral Load Kinetics for Participants with Omicron BE.1 or BF.1 Viral Variants



Source: Figure 1.2.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

9.7.1.3.7. Viral Load by Epitope Substitutions

The absolute and change from baseline in viral load measured by qRT/PCR in nasal/oropharyngeal swabs was analyzed in participants according to the epitope substitution (>5% allelic frequency) present in the virus (Table 27 and Table 28). The viral kinetics of SARS-CoV-2 viruses with epitope substitutions are shown in Figure 11, Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, Figure 17 and Figure 18. Participants who have epitope substitutions at more than one residue were included in more than one category.

Participants with any sotrovimab epitope substitution observed at >5% allelic frequency at any study visit (n=202) had a median baseline viral load of 7.470 log_{10} copies/mL that declined over time to <LLOD at Day 14 and Day 28 (Table 27; Figure 11). Participants with AA substitutions in at least one of the sotrovimab epitope residues 339 (n=194), 346 (n=85), and 440 (n=184) at >5% allelic frequency had baseline median viral load ranging from 7.2-7.575 log_{10} copies/mL that declined to <LLOD at Day 14 and was sustained <LLOD through Day 28 (Table 27; Figure 13, Figure 15, Figure 17). Participants with AA substitutions in at least one of the sotrovimab epitope residues 337 (n=28), 340 (n=39) and 356 (n=18) had baseline median viral load ranging from 7.88-8.07 log_{10} copies/mL that declined to <LLOD at Day 28 (Table 27, Figure 12, Figure 14, Figure 16). One participant had a substitution at epitope position 509 and had a baseline viral load of 6.696 log_{10} copies/mL that declined to <LLOQ at Day 28 (Table 27; Figure 17).

Participants with any sotrovimab epitope substitution observed at >5% allelic frequency at any visit (n=193) had a median change from baseline of -4.875 log_{10} copies/mL by Day 28 (Table 28). When assessed by substitution, the change from baseline in viral load at Day 28 was -3.950 log_{10} copies/mL for a participant with a substitution at >5% allelic frequency at epitope residue 509 and the median change from baseline ranged from -4.46 to -4.95 log_{10} copies/mL for participants with at least one substitution at >5% allelic frequency at epitope positions 337, 339, 340, 346, 356 and 440 of the sotrovimab epitope (Table 28).

Table 27 Summary of Median Absolute Viral Load (log_{10} copies/mL) by Epitope Residue with a Substitution Through Day 28 as Measured by qRT-pCR from Nasal/Oropharyngeal Swabs

Epitope Residue [n]	Median Viral Load (log_{10} copies/mL) (N=217)							
	Baseline		Day 7		Day 14		Day 28	
	n'	Median [Min, Max]	n'	Median [Min, Max]	n'	Median [Min, Max]	n'	Median [Min, Max]
Any [202]	199	7.470 [4.35, 9.52]	186	4.530 [2.36, 8.51]	182	2.360 [2.36, 8.43]	181	2.360 [2.36, 8.35]
337 [28]	28	8.060 [6.47, 9.02]	27	6.490 [4.05, 8.51]	26	5.050 [2.36, 7.58]	27	2.360 [2.36, 7.03]
339 [197]	194	7.475 [4.35, 9.52]	182	4.520 [2.36, 8.51]	179	2.360 [2.36, 8.43]	176	2.360 [2.36, 8.35]
340 [39]	39	8.070 [5.83, 9.15]	37	6.440 [3.52, 8.51]	36	4.785 [2.36, 8.43]	37	2.360 [2.36, 8.35]
346 [88]	85	7.200 [4.35, 9.30]	79	4.520 [2.36, 8.48]	80	2.360 [2.36, 8.43]	78	2.360 [2.36, 8.35]
356 [18]	17	7.880 [5.58, 9.16]	17	5.900 [2.36, 7.65]	16	3.190 [2.36, 8.43]	18	2.360 [2.36, 8.35]
440 [186]	184	7.575 [4.35, 9.52]	170	4.730 [2.36, 8.51]	167	2.360 [2.36, 8.43]	167	2.360 [2.36, 8.35]
509 [1]	1	6.696 [6.96, 6.96]	1	5.950 [5.95, 5.95]	1	4.440 [4.44, 4.44]	1	3.000 [3.00, 3.00]

Source: Table 1.231.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis. n= number of participants with substitutions at the amino acid residue at any time point. n' = number of participants with viral load at the specific amino acid residue at the specified time point. Participants can be included in more than one category.

a. Bold residue indicates substitution is part of the characteristic of the spike profile of SARS-CoV-2 Omicron viral variants observed in the LUNAR study. This data includes the characteristic change but also other changes at that residue

Table 28 Summary of Median Change from Baseline Viral Load (log_{10} copies/mL) by Epitope Residue Through Day 28 as Measured by qRT-pCR from Nasal/Oropharyngeal Swabs

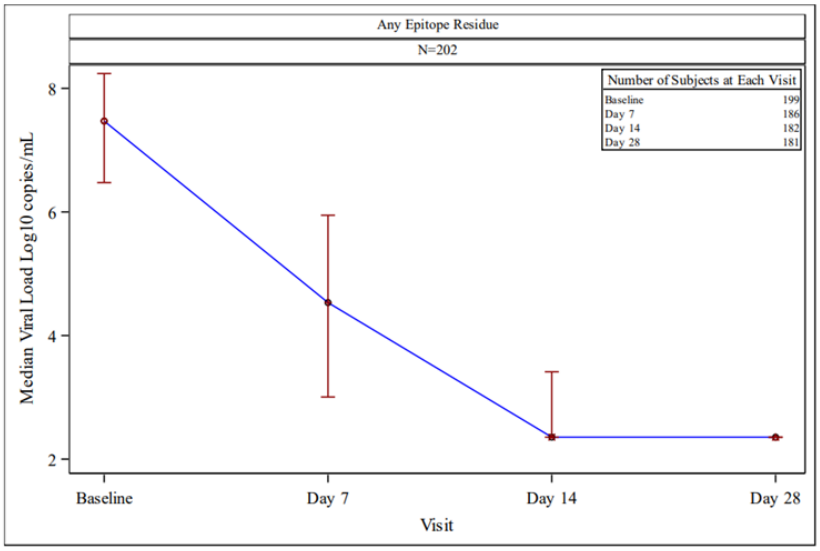
Epitope Residue [n]	Median Change in Viral Load [Min, Max] (log_{10} copies/mL) (N=209)					
	Day 7		Day 14		Day 28	
	n'	Median [Min, Max]	n'	Median [Min, Max]	n'	Median [Min, Max]
Any [193]	183	-2.970 [-6.75, 1.25]	179	-4.490 [-6.94, 0.35]	178	-4.875 [-7.16, -0.44]
337 [27]	27	-1.170 [-3.85, 0.10]	26	-3.155 [-6.33, -0.58]	27	-4.950 [-6.66, -1.73]
339 [188]	179	-2.970 [-6.75, 1.25]	176	-4.490 [-6.94, 0.35]	173	-4.880 [-7.16, -0.44]
340 [38]	37	-1.470 [-4.56, 0.10]	36	-3.365 [-6.54, 0.35]	37	-4.670 [-6.66, -.0.44]
346 [81]	76	-2.370 [-6.38, 1.25]	77	-4.110 [-6.94, -0.25]	75	-4.460 [-6.91, -0.44]
356 [17]	16	-1.625 [-4.94, -0.55]	15	-3.650 [-6.54, 0.35]	17	-4.810 [-6.81, -0.44]
440 [178]	168	-3.030 [-6.75, 1.25]	165	-4.720 [-6.94, 0.35]	165	-4.950 [-7.16, -0.44]
509 [1]	1	-1.010 [-1.01, -1.01]	1	-2.520 [-2.52, -2.52]	1	-3.950 [-3.95, -3.95]

Source: Table 1.232.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis. n= number of participants with substitutions at the amino acid residue at any time point. n' = number of participants with viral load at the specific amino acid residue. Participants can be included in more than one category.

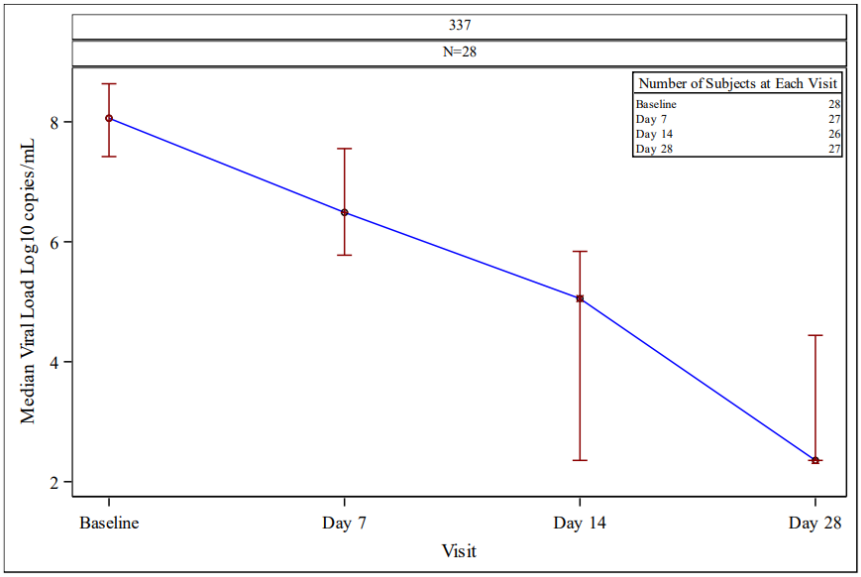
a. Bold residue indicates substitution is part of the characteristic of the spike profile of SARS-CoV-2 Omicron viral variants observed in the LUNAR study. This data includes the characteristic change but also other changes at that residue.

Figure 11 Median Viral Load Kinetics for Participants with Substitutions at Any Residue in Sotrovimab Epitope at >5% Allelic Frequency



Source: Figure 1.3. Baseline log_{10} viral load is defined as the non-missing assessment taken at Day 0 and excluding the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

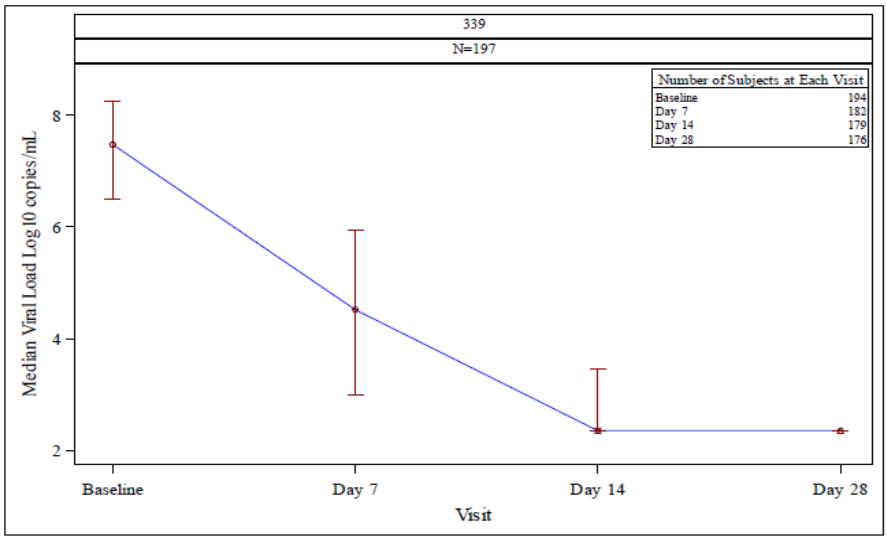
Figure 12 Median Viral Load Kinetics for Participants with Substitutions at Residue 337 in Sotrovimab Epitope at >5% Allelic Frequency



Source: Figure 1.3. Baseline log_{10} viral load is defined as the non-missing assessment taken at Day 0 and excluding the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol

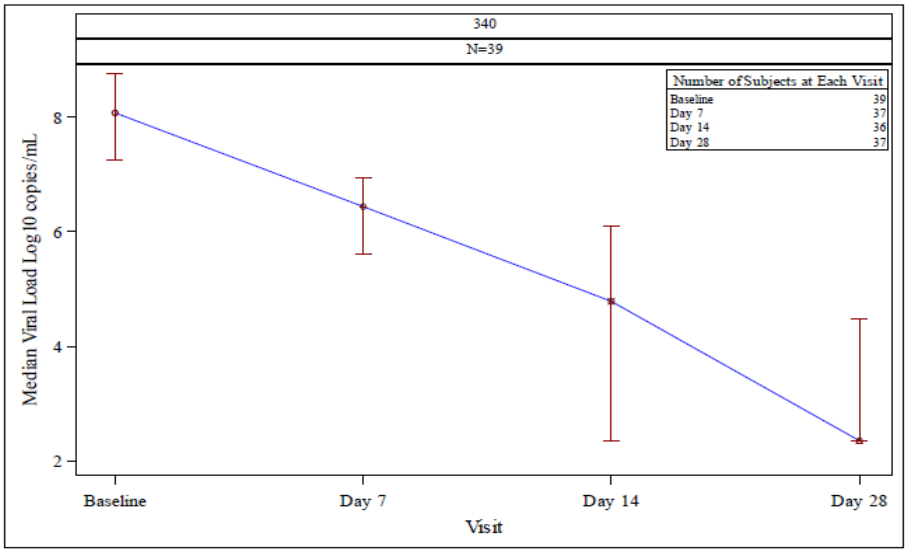
deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 13 Median Viral Load Kinetics for Participants with Substitutions at Residue 339 in Sotrovimab Epitope at >5% Allelic Frequency



Source: Figure 1.3. Baseline log_{10} viral load is defined as the non-missing assessment taken at Day 0 and excluding the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

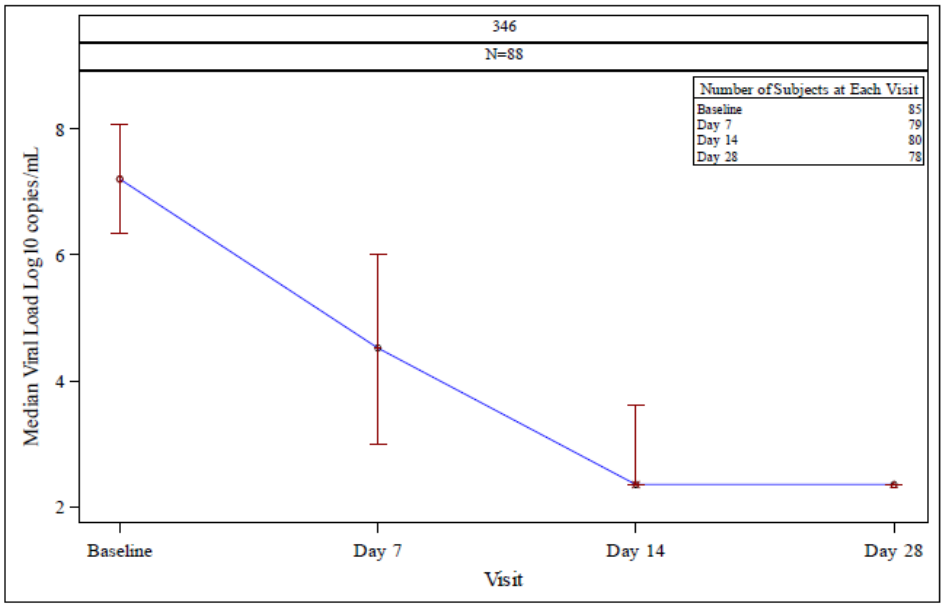
Figure 14 Median Viral Load Kinetics for Participants with Substitutions at Residue 340 in Sotrovimab Epitope at >5% Allelic Frequency



Source: Figure 1.3. Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to

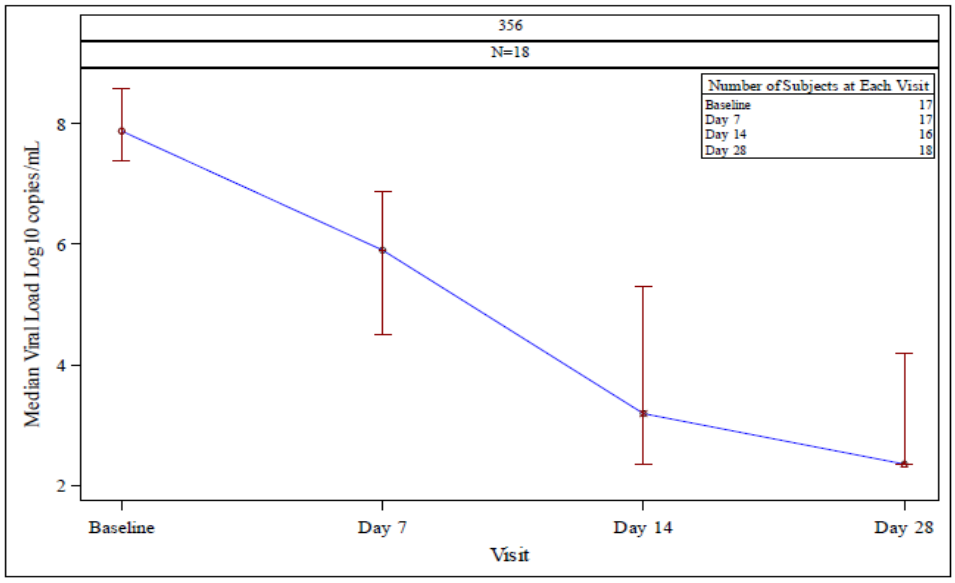
1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 15 Median Viral Load Kinetics for Participants with Substitutions at Residue 346 in Sotrovimab Epitope at >5% Allelic Frequency



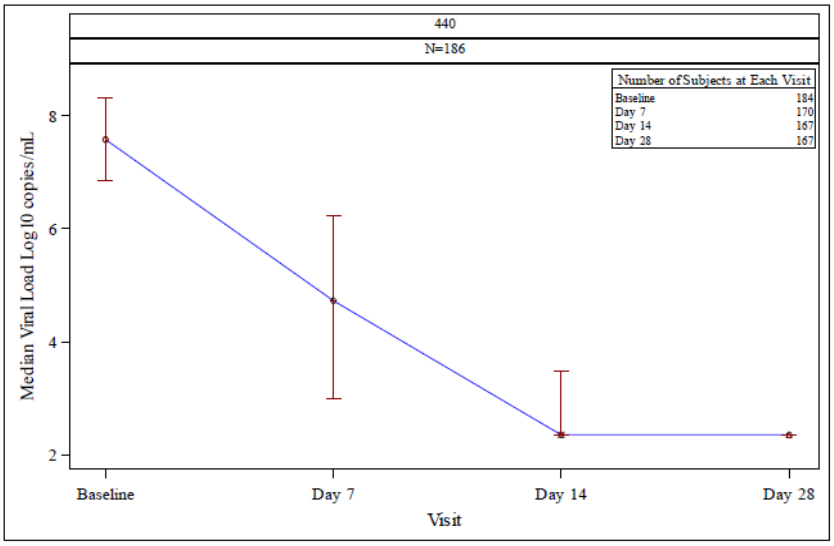
Source: Figure 1.3. Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 16 Median Viral Load Kinetics for Participant with Substitutions at Residue 356 in Sotrovimab Epitope at >5% Allelic Frequency



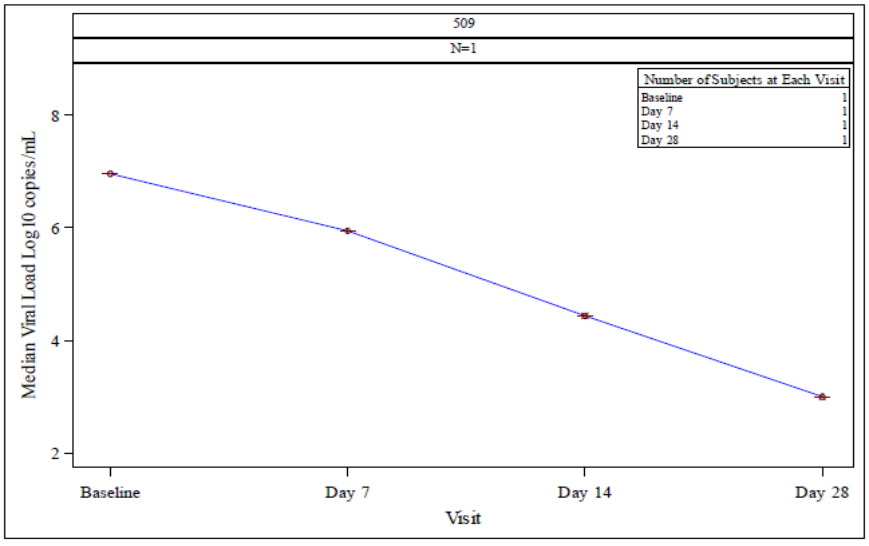
Source: Figure 1.3. Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 17 Median Viral Load Kinetics for Participants with Substitutions at Residue 440 in Sotrovimab Epitope at >5% Allelic Frequency



Source: Figure 1.3. Baseline log_{10} viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

Figure 18 Median Viral Load Kinetics for Participant with Substitutions at Residue 509 in Sotrovimab Epitope at >5% Allelic Frequency



Source: Figure 1.3. Baseline log_{10} viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis.

9.7.1.3.8. Viral load by treatment emergent epitope substitutions

The absolute and change from baseline in viral load measured by qRT/PCR in nasal/oropharyngeal swabs was analyzed in participants according to the treatment emergent epitope substitution at > 5% allelic frequency present in the virus (Table 29 and Table 30).

Participants harbouring at least one treatment emergent epitope substitution at >5% allelic frequency had a baseline median viral load of 8.07 log_{10} copies/mL which declined over time to 2.36 log_{10} copies/mL by Day 28 (Table 29). Participants with at least one treatment emergent epitope substitution at > 5% allelic frequency at 337, 340 or 356 had a median viral load that declined to the LLOD or LLOQ levels by Day 28.

Participants with at least 1 treatment emergent epitope substitution in the sotrovimab epitope had a median reduction in viral load at Day 7 of -1.470 log_{10} copies/mL (Table 30). The median decline at Day 28 for participants with specific treatment emergent epitope substitutions at > 5% allelic frequency was similar and ranged from -4.670 to -5.160 log_{10} copies/mL.

Table 29 Summary of Median Absolute Viral Load (log_{10} copies/mL) by Treatment Emergent Epitope Substitution >5% AF Through Day 28 as Measured by qRT-PCR from Nasal/Oropharyngeal Swabs

	Median Viral Load [Min, Max] (log_{10} copies/mL) (N=217)							
TE Epitope Residue [n]	Baseline		Day 7		Day 14		Day 28	
	n'		n'		n'		n'	
Any [47]	47	8.070 [5.83, 9.15]	45	6.410 [3.52, 8.51]	44	4.315 [2.36, 8.43]	45	2.360 [2.36, 8.35]
337 [27]	27	8.200 [6.47, 9.02]	26	6.530 [4.19, 8.51]	25	5.130 [2.36, 7.58]	26	2.360 [2.36, 7.03]
340 [37]	37	8.080 [5.83, 9.15]	35	6.490 [3.52, 8.51]	34	4.890 [2.36, 8.43]	35	3.000 [2.36, 8.35]
356 [10]	10	8.345 [7.38, 8.94]	9	6.620 [5.79, 7.65]	9	5.130 [2.36, 8.43]	10	3.000 [2.36, 8.35]

Source: Table 1.241.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis. TE = treatment emergent; AF = allelic frequency; n= number of participants in the category for TE epitope substitution. n'= number of participants in category at specified amino acid residue. Participants can be included in more than one category

Table 30 Summary of Median Change from Baseline Viral Load (log_{10} copies/mL) by Treatment Emergent Epitope Substitution >5% AF Through Day 28 as Measured by qRT-pCR from Nasal/Oropharyngeal Swabs

	Median Viral Load [Min, Max] (log_{10} copies/mL) (N=209)					
TE Epitope Residue [n]	Day 7		Day 14		Day 28	
	n'		n'		n'	
Any [46]	45	-1.470 [-4.56, 0.10]	44	-3.575 [-6.54, 0.35]	45	-4.810 [-6.66, -0.44]
337 [26]	26	-1.100 [-3.66, 0.10]	25	-3.050 [-6.33, -0.58]	26	-4.920 [-6.66, -1.73]
340 [36]	35	-1.470 [-4.56, 0.10]	34	-3.365 [-6.54, 0.35]	35	-4.670 [-6.66, -0.44]
356 [10]	9	-1.240 [-3.04, -0.55]	9	-2.740 [-6.54, 0.35]	10	-5.160 [-6.58, -0.44]

Source: Table 1.242.

Note: Baseline viral load is defined as the non-missing assessment taken at Day 0 and excludes the negative viral load results. The post-baseline viral load records with viral loads below LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above LLOD and below LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive log_{10} viral loads. Subjects with major protocol deviation (out of visit window/samples received late at GOSH/return more samples than expected) at specific visits were excluded from analysis. TE = treatment emergent; AF = allelic frequency; n= number of participants in the category for TE epitope substitution. n'= number of participants in category at specified amino acid residue. Participants can be included in more than one category.

9.7.2. Clinical outcome results

Among the 217 participants in the Safety population, no participants required hospitalization due to COVID-19 [Table 31]. Seven participants (3.2%) had 'all-cause' hospitalizations reported during the study. More details on these participants can be found in Annex 2 and Listing 1.15.

One participant with progressive neuromuscular disease required high flow oxygen/non-invasive mechanical ventilation; this participant died on Day 18 of the study and their death was deemed not to be COVID-19 related by the investigator (Listing 1.18). Their death was attributed to decompensated type 2 respiratory failure due to chest infection on a background of progressive myotonic dystrophy, as well as aspiration pneumonia.

No participants required ICU admission during the study. A summary of the clinical outcomes for the 7 participants requiring hospital stays, by VOI/VOC as determined by whole genome sequencing are summarized in Table 31.

Table 31 Summary of Clinical Outcomes Overall and by VOI/VUI

Clinical Outcome	**Sotrovimab (500 mg IV) (N=217) n (%)**
Number of participants with Hospital Stay 'all-cause'	7 (3.2)
Omicron	7 (100)
BA.2	1 (14.3)
BA.2.73	1 (14.3)
BA.5.2	1 (14.3)

Clinical Outcome	Sotrovimab (500 mg IV) (N=217) n (%)
BA.5.2.1	1 (14.3)
BE.1	3 (42.9)
Number of participants with ICU Hospital Stay 'all-cause'	0 (0)
Number of participants requiring oxygen support (new or increased oxygen support)	1 (0.5)[a]
Omicron	1 (100)
BA.2.73[a]	1 (100)[a]
Number of participants requiring Non-invasive ventilation or high flow oxygen	1 (0.5)
Omicron	1 (100)
BA.2.73	1 (100)[a]
Number of participants requiring Invasive ventilation	0 (0)
Number of participants requiring ECMO	0 (0)
Number of participants who died through Day 28 'all-cause'	1 (0.5)
Omicron	1 (100)
BA.2.73	1 (100)[a]
Number of participants requiring hospitalization (COVID-19 Related)	0 (0)
Number of participants requiring ICU hospitalization (COVID-19 Related)	0 (0)
Number of participants who died through Day 28 due to COVID-19	0 (0)

Source: Table 1.25, 1.26, 1.27, 1.28, 1.29, 1.30
Notes: N = Number of participants in Safety population; n = Number of participants with data available.
a. The same participant who received oxygen support was also the same participant who was hospitalized and died due to their existing underlying conditions.
Cross-reference: Listing 1.15, Listing 1.16, Listing 1.17 and Listing 1.18

9.7.2.1. Virological data for hospitalized study participants

The virological outcomes for the 7 participants who were hospitalized during the study are summarized below. Further details relating to each of these participants can be found in Listing 1.15 and Listing 1.16. The viral load, VOC/VUI and treatment emergent substitution data for each participant can be found in Listing 1.131, Listing 1.12 and Listing 1.9.

Participant PPD had a baseline viral load of 8.74 $\log_{10}$ copies/mL. The viral load declined over the course of the study and was negative at both Day 14 and Day 28. The participant had the Omicron BA.5.2.1 viral variant based on whole genome sequence at baseline. However, there was no sequence available at Days 7, 14 and 28 as the levels of viral RNA were below the threshold set for the sequencing assay (2.65 $\log_{10}$ copies/mL).

Participant PPD had a baseline viral load of 5.98 $\log_{10}$ copies/mL. The viral load decreased to negative on Day 7 and remained negative on Days 14 and 28. The

participant had the Omicron BE.1 viral variant based on whole genome sequence at baseline, however, no sequence was available on Days 7, 14 and 28 as the level of viral RNA was below the threshold set for the sequencing assay (2.65 log_{10} copies/mL).

Participant PPD had a baseline viral load of 8.43 log_{10} copies/mL. The viral load decreased to 5.46 log_{10} copies/mL on Day 7 and no further viral load data was available for this participant. The participant had the Omicron BE.1 viral variant based on whole genome sequence at baseline. Sequencing data were available for the region of the spike protein including the residues in the sotrovimab epitope where substitutions are known to impact sotrovimab activity, and no treatment emergent substitutions were detected in the epitope on Day 7. Sequencing was not available for this participant on Days 14 and 28.

Participant PPD had a baseline viral load of 8.45 log_{10} copies/mL. The viral load declined to 2.36 log_{10} copies/mL on Day 14 then rose to 5.24 log_{10} copies/mL on Day 28. The participant had the Omicron BE.1 viral variant based on whole genome sequence at baseline. Treatment emergent substitutions were detected in the epitope at Day 7 [P337L (21.8%), P337S (14%)] and Day 28 [E340Q (99.6%)].

Participant PPD had a baseline viral load of 8.24 log_{10} copies/mL. The viral load declined to 3.78 log_{10} copies/mL on Day 14. This is the last data point for viral load for this participant who died on Day 18. The participant had the Omicron BA.2.73 viral variant based on whole genome sequence at baseline. Treatment emergent substitutions were observed in the sotrovimab epitope on Day 7 [E340K (42.4%), E340Q (20.2%)]. There was a gap in the sequencing of the virus from this participant on Day 14 so no data is available on the epitope substitution profile.

Participant PPD had a baseline viral load of 7.45 log_{10} copies/mL. The viral load declined to negative at Day 7 and remained negative through Days 14 and 28. The participant had the Omicron BA.5.2 viral variant based on whole genome sequence at baseline, however no sequence was available on Days 7, 14 and 28 as the level of viral RNA was below the threshold set for the sequencing assay (2.65 log_{10} copies/mL).

Participant PPD had a baseline viral load of 7.16 log_{10} copies/mL. The viral load declined to 3.0 log_{10} copies/mL at Day 14 then rose to 5.83 log_{10} copies/mL at Day 28. The participant had the Omicron BA.2 viral variant based on whole genome sequencing. Sequencing results were available at baseline, Day 7 and Day 28 with a treatment emergent substitution observed at Day 28 [E340G (98.3%)].

9.7.2.2. Outcomes and characteristics of participants with SARS-CoV-2 viral load >5 log_{10} copies/mL at Day 28

The clinical outcomes, co-morbidities, concomitant medicines, and virology sequencing results for epitope substitutions are summarized in Table 32 for participants that had a viral load of >5 log_{10} copies/mL at Day 28.

Table 32 Summary of participants with SARS-CoV-2 Viral Load >5 log_{10} copies/mL at Day 28 by Demographics, Medical Condition/Co-morbidities

Participant ID Age Sex Race	Clinical Outcomes	Virology Sequencing Outcomes: Treatment Emergent Epitope Substitutions (allelic frequency)	Co-morbidities	Concomitant medications
PPD	None	Day 7: P337L (10.2%), E340D (9.24%), E340Q (53.1%) Day 14: E340Q (91.1%) Day 28: E340Q (96.4%)	Low folate Stem cell transplant for Acute Myeloid Leukaemia	Ciclosporin, folic acid, magnesium aspartate, sorafemib
	None	No Post-Baseline sequence available	Multiple sclerosis	Data not available.
	None	Day 7: E340D (19.8%), E340G (19.9%), K356T (15.6%)	Sarcoidosis Cardiovascular disease DM Medical-related technological dependence	Data not available.
	None	Day 14: E340K (9.03%), E340Q (42.8%), E340V (26.5%) Day 28: E340Q (89%), E340V (10%), K356T (7.91%)	CLL stem cell transplant prostate cancer Bowen's disease CLL Stem cell transplant 2000	Data not available.
	None	Day 14: E340Q (86.4%) Day 28: K356R (99.7%)	Atrial fibrillation Benign prostatic hyperplasia Heart valve disease Non-Hodgkin's follicular lymphoma Skin cancer Hematological diseases and stem cell transplant (Follicular lymphoma) Solid cancer (Skin cancer) Asthma Cardiovascular disease Hypertension Obesity Overweight	Bisoprolol, finasteride, furosemide, rivaroxaban irbesartan, Loratadine, Rituximab, Rosuvastatin, salbutamol

Participant ID Age Sex Race	Clinical Outcomes	Virology Sequencing Outcomes: Treatment Emergent Epitope Substitutions (allelic frequency)	Co-morbidities	Concomitant medications
PPD	Hospitalization unrelated to COVID-19	Day 7: P337L (21.8%), P337S (14%) Day 28: E340Q (99.6%).	DM type II steroid induced Renal transplant Sarcoidosis with pulmonary fibrosis Other renal disease (CKD) Renal disease Renal transplant recipients Solid organ transplant recipients (Renal Transplant X 2 1st 1999, 2nd 2014) CKD Chronic liver disease DM Overweight	Alfacalcidol, Allopurinol, Atorvastatin, Calcichew, ciprofloxacin, co-amoxiclav, domperidone, folic acid, Humulin M3, Mycophenolate Mofetil, Omeprazole, Prednisolone Sodium Bicarbonate, Tacrolimus
	None	No treatment emergent epitope substitutions	CVID Immune deficiencies Hypertension Overweight	Co-trimoxazole, Immunoglobulin, Losartan, Vitamin D
	Hospitalization unrelated to COVID-19	Day 28 E340G (98.3%)	Immune deficiencies Liver diseases Other immune deficiencies (hypogammaglobulinemia) Other liver diseases (Granulomatous liver disease)	Data not available.

Source: Table 1.42; Listing 1.15; Listing 1.16; Listing 1.2; Listing 1.9; Listing 1.131, Listing 1.26
Note: CKD = chronic kidney disease; CVID = Common variable immunodeficiency; DM = Diabetes Mellitus.
[a]Participant was enrolled in the study despite not meeting eligibility criteria. Refer to Section 9.1.2 for further details on protocol deviations.

9.8. Results of Exploratory Analyses

9.8.1. Variant analysis and treatment-emergent substitutions in participants who were hospitalized during the study

Seven participants were hospitalized during the study, all of whom were infected with Omicron sub-lineages based on whole genome sequence; 3 participants had Omicron BE.1 while 1 participant each had Omicron BA.2, BA.2.73, BA.5.2, and BA.5.2.1. Details regarding treatment emergent substitutions / variants for the 7 hospitalized participants is provided in Section 9.7.2.1.

Three of the 7 participants had negative viral load levels by Day 7 or 14, 1 experienced significant viral load declines through Day 7 with missing data subsequently, 2

experienced viral load declines before rebounding and 1 participant died who had a viral load decline from baseline of >4 log_{10} copies/mL at the last available timepoint.

Three participants had treatment emergent substitutions in the sotrovimab epitope; P337L/S and E340Q were observed in one of the participants who experienced rebound, E340G was observed in the second participant who experienced rebound and E340K/Q was observed in the participant who died.

9.8.2. Assessment of baseline substitutions in the SARS-cov-2 sotrovimab epitope in the GISAID Genomic Database

The baseline epitope substitutions detected at >5% allelic frequency were G399D, G339H, E340D, E340Q, R346I, R346S, R346T, K356T and N440K (Table 14) To investigate the conservation of the residues in the sotrovimab epitope, > 14,200,000 spike sequences from SARS-CoV-2 deposited in the GISAID database as of 13 September 2023 were examined for conservation. Among AAs comprising the epitope, ≥99.90% conservation was observed for 19/23 AA positions among currently available sequences, with 12/23 positions being ≥99.99% conserved. Epitope positions 339, 346, and 440 were ≥47.98% conserved, with decreases in conservation driven by G339D/H, R346K/T, and N440K substitutions characteristic of the Omicron variants [GSK Study Report 2023N540840].

The G339D/H substitutions observed at Baseline are part of the characteristic profile of spike substitutions for Omicron viral variants observed in LUNAR. This residue is only 47.98% conserved in the GISAID Database which likely reflects the prevalence of Omicron viral variants sequences in the database [GSK Study Report 2023N540840].

The E340D/Q substitutions were identified at baseline in LUNAR were present in the GISAID Database as 2 of 16 observed insertions/deletions/substitutions. The E340 residue was found to be 99.96% conserved, so although substitutions were observed including the two identified at baseline in LUNAR they were present in a small number of overall sequences [GSK Study Report 2023N540840].

The R346I/K/T substitutions were observed at baseline in the LUNAR study with R346K/T being part of the characteristic spike AA sequence for Omicron variants (Table 14). These substitutions were 3 of 17 insertions/deletions/substitutions observed in the GISAID Database at position 346. The R346 residue was found to be 82.08% conserved [GSK Study Report 2023N540840].

The K356T substitution was observed at baseline in LUNAR and was 1 of 17 insertions/deletions/substitutions observed in the GISAID Database. The K346 residue was 99.43% conserved showing the substitution was present in a small number of overall sequences [GSK Study Report 2023N540840].

9.9. Adverse Events/Adverse reactions

In this study only AEs/SAEs considered by the investigator related to sotrovimab were collected.

Hypersensitivity reactions including infusion related reactions and anaphylactic reactions were identified using MedDRA Hypersensitivity SMQ (narrow) and Anaphylactic Reaction SMQ (narrow).

9.9.1. Drug related AEs

A total of 5 AEs considered related to sotrovimab by the investigator were reported in 4 out of 217 (1.8%) participants during the study. These AEs are summarised below:

- A PPD participant reported a non-serious event of pruritus (verbatim PPD ') of mild intensity 2 days after receiving sotrovimab. The event resolved within 3 days.
- A PPD participant had two non-serious adverse events reported: neutrophil count increased and white blood cell count increased, both events occurred 12 days after receiving sotrovimab, were of mild intensity and resolved within 8 days.
- A PPD participant had a non-serious event of diarrhoea of mild intensity reported 1 day after receiving sotrovimab, which resolved within 2 days.
- A PPD had a non-serious event of blood creatinine increased mild intensity reported 20 days after receiving sotrovimab The event resolved within 29 days.

9.9.1.1. Drug related serious and other significant AEs

No SAEs or deaths were reported that were considered related to sotrovimab (Table1.34, Table 1.36). Treatment emergent adverse events were reported in 6 participants (Table 1.31: Table 1.32). One death not related to sotrovimab was reported – see Section 10.1.2 for details.

There were no events leading to interruption and/or incomplete sotrovimab infusion or leading to withdrawal from the study (Table 1.35). There were no events of infusion related reactions including anaphylactic reaction (Table 1.38) or any other hypersensitivity reactions (Table 1.37) reported in this study.

9.9.1.2. Clinical laboratory evaluations

No study-specific samples were taken for clinical chemistry or hematology analysis. Samples were only taken where necessary as part of clinical care and these data were not captured as part of the study.

9.9.2. Virological data for participants with sotrovimab related AEs

Sotrovimab-related AEs were reported by 4 participants during the study. Section 9.7.2.1. describes the virology outcome for Participant PPD. For the remaining three participants, the virology outcome is described below:

- Participant PPD had a baseline viral load of 8.2 $\log_{10}$ copies/mL. Their viral load decreased over time to negative at Day 14 and remained negative at Day 28. ParticipantPPD had the Omicron BE.1 viral variant based on whole genome

sequence at baseline. No treatment emergent substitutions were observed on Day 7 and sequencing data was available for the region of spike including the residues in the epitope where substitutions are known to impact sotrovimab in vitro activity. No sequencing data was available at Days 14 and 28 as the level of viral RNA was below the threshold set for the sequencing assay (2.65 log_{10} copies/mL).

- No virus could be isolated at any timepoint from the nasal or nasopharyngeal swabs of Participant PPD, therefore no sequence data are available, and the infecting viral strain is unknown.
- Virus could only be isolated at baseline from Participant PPD and had a viral load of 7.06 log_{10} copies/mL and all samples from Day 7 onwards were negative. Participant PPD had the Omicron BA.2 viral variant based on whole genome sequence at baseline.

9.9.3. Pregnancies

There were no pregnancies reported during the study.

10. DISCUSSION

10.1. Key Results

10.1.1. Virology results

One of the primary objectives of the LUNAR study was to identify the treatment emergent changes in the sotrovimab epitope of the SARS-CoV-2 spike protein in IC participants following treatment with sotrovimab. In this study, treatment emergent substitutions in the sotrovimab epitope at >5% allelic frequency were observed in 24.8%, 25.4% and 33.3% of participants in LUNAR with paired sequencing data at Day 7, Day 14 and Day 28, respectively. Treatment emergent substitutions in the sotrovimab epitope at >50% allelic frequency were observed in 7.8%, 15.5% and 33.3% of participants in LUNAR with paired sequencing data at Day 7, Day 14 and Day 28, respectively. Furthermore, a total of 101 (64.7%) and 36 (23.1%) participants with paired sequencing data had treatment emergent substitutions at >5% and >50% allelic frequency, respectively, in the spike protein at any time post-baseline. At any visit post-baseline, a total of 47 (30.1%) and 23 (14.7%) participants had treatment emergent substitutions in the sotrovimab epitope at >5% and >50% allelic frequency, respectively.

The substitution profile seen in this study aligns with the results of previous GSK/VIR sponsored clinical studies with sotrovimab where substitutions in the sotrovimab epitope were observed in a proportion of participants following administration of sotrovimab [GSK document number RPS-CLIN-032797;GSK Document number RPS-CLIN-040980; GSK document number RPS-CLIN-048775].

Treatment emergent substitutions were observed at residues 337, 339, 340, 346, 356 and 509 in the sotrovimab epitope at >5% allelic frequency. Treatment emergent substitutions at >5% allelic frequency were most frequent at E340 with 28 (30.8%), 14 (53.8%) and 8 (61.5%) participants having substitutions at E340 on Day 7, Day 14 and Day 28, respectively. The frequency of detection of treatment emergent E340 substitutions at >5% allelic frequency was similar at Day 14 and Day 28 with the E340D/G/K/Q/V specific substitutions observed but was higher at Day 7 for E340D and E340Q. Treatment emergent substitutions at E340 were also the most frequent substitutions observed in the consensus sequence analysis although fewer participants had these substitutions at >50% allelic frequency (Day 7=8 [8.8%], Day 14=8 [30.8%] and Day 28=8 [61.5%] participants) than in the analysis at >5% allelic frequency.

Treatment emergent substitutions at >5% allelic frequency at P337 were most prevalent at Day 7 (22 participants [23.9%]) and Day 14 (11 participants [42.3%]) with the P337A/H/L/R/S specific substitutions observed and the most prevalent being P337S. In the analysis of treatment emergent substitutions at >50% allelic frequency, fewer participants had these treatment emergent substitutions than had them at >5% allelic frequency with only 4 (4.3%) and 2 (7.7%) participants having treatment emergent substitutions at Day 7 and Day 14 at >50% allelic frequency. In the consensus sequence analysis only P337L/S were observed.

It has been well documented with other viruses that resistance substitutions can reduce the replicative capacity but the determination of fitness in SARS-CoV-2 cannot be done with the currently available cell systems [Lampejo, 2020]. Fitness deficient viruses may not be able to replicate to higher levels of allelic frequency that would be identified in the >50% allelic frequency data set. This may account for the differences in the detection of the P337 and E340 substitutions at >5% or >50% allelic frequency [Lampejo, 2020].

Treatment emergent substitutions at 339, 346, 356 and 509 were less frequent, with the G339R/Y, R346T, K356M/R/T and R509T substitutions observed at least once post-baseline in the minority variant analysis. In the consensus analysis, treatment emergent substitutions at K356R/T were observed in one participant at two time points.

Baseline substitutions were observed in LUNAR at the epitope residues 339, 346, 356 and 440 at >5% and >50% allelic frequency. Two of these 8 substitutions are part of the characteristic profile of spike substitutions in several of the Omicron sub-lineages so the appearance of these changes at baseline was expected. No baseline substitutions were observed at sotrovimab resistance epitope position 337 at >5% or 337 and 340 at >50% allelic frequency. At post-baseline time points, substitutions were observed at residues 337, 339, 340, 346, 356, 440 and 509 in both the >5% and >50% allelic frequency analyses.

Six of the 18 treatment emergent substitutions and 6 of 23 post-baseline substitutions observed in the sotrovimab epitope at >5% allelic frequency in LUNAR are known to cause reduced susceptibility to sotrovimab in in vitro neutralization assays. Data from previously reported in vitro neutralisation studies demonstrate that the P337L/R and E340A/K/Q/V substitutions resulted in significant EC50 shifts (>50-fold) for sotrovimab indicating reduced susceptibility in vitro when evaluated in the Wuhan-hu-1 spike

background in a pseudotyped virus assay (Table 35). The P337H/S, E340D and K356T substitutions led to >609-fold change in activity when evaluated in the Omicron BA.1 protein in a pseudotyped virus assay compared to the activity on the wild-type Omicron BA.1 spike protein (Table 36). The P337H/S/T, E340D/G and K356M/T substitutions caused significant shift in sotrovimab EC50 values (>117-fold) when evaluated in the Omicron BA.2 protein in a pseudotyped virus assay compared to the activity on the wild-type Omicron BA.2 spike protein (Table 37). The P337H/S, E340D/G and K356 M/R/T substitutions caused a significant shift in sotrovimab activity (>690-fold) when evaluated in the Omicron BA.5 protein in a pseudotyped virus assay compared to the activity on the wild-type Omicron BA.5 spike protein (Table 38). Epitope substitutions that led to reduction in sotrovimab activity in the Wuhan-hu-1 spike protein background in vitro neutralization pseudotyped virus assays are assumed to lead to resistance in the Omicron spike protein backgrounds and were not retested in the Omicron BA.1, BA.2 and BA.5 spike protein background.

The numbers of treatment emergent substitutions in the sotrovimab epitope with an allelic frequency of >5% identified in this study were compared to the substitution frequency of ≥5% allelic frequency in patients treated with 500 mg IV sotrovimab in other GSK/VIR sponsored sotrovimab clinical studies (COMET-ICE, COMET-TAIL and COMET-PEAK) in Table 33. The overall frequency of treatment emergent epitope substitutions in the LUNAR study (30.1%) was numerically higher than that observed in COMET-ICE (23.5%) and COMET-TAIL (20.8%) clinical studies but in a similar range. The overall frequency of treatment emergent epitope substitutions in the LUNAR study (30.1%) was higher than observed in the COMET-PEAK clinical study (13.5%) [Table 33]. The higher frequency of treatment emergent substitutions in LUNAR may be due to the IC population of the study versus the COMET-PEAK clinical study population which did not require participants to have a risk factor for COVID-19 disease progression for inclusion. Patients that are IC may have prolonged duration of virus shedding that can lead to resistance selection.

Table 33 Treatment Emergent Substitutions Selected during treatment with 500 mg IV sotrovimab in GSK/VIR Sponsored Sotrovimab Clinical Studies.

		Treatment Emergent Substitution >5% or ≥5% Allelic Frequency[a], n/N[b] (%)[c]						
Clinical Study (Timepoints as Appropriate)	Sotrovimab Treatment Group	Epitope	Spike Protein	Residue 337	Residue 340	Residue 345	Residue 356	Residue 441
LUNAR (Total)	500 mg IV	47/156 (30.1%)	101/156 (64.7%)	27/156 (17.3%)	37/156 (22.7%)	0	10/156 (6.4%)	0
COMET-ICE[d]	500 mg IV	40/170 (23.5%)	138/170 (81.2%)	8/170 (4.7%)	23/170 (13.6%)	0	2/170 (1.2%)	0
COMET-TAIL[d]	500 mg IV	33/159 (20.8%)	110/159 (69.2%)	9/159 (5.7%)	28/159 (17.6%)	0	0	0
COMET-PEAK[d]	500 mg IV	15/111 (13.5%)	79/111 (71.2%)	6/111 (5.4%)	13/111 (11.7%)	0	0	0

Source: Listing 1.9; Table 1.52.
Reference: m5.3.5.4 COMET-ICE Virology Study Report: GSK document number RPS-CLIN-032797; m5.3.5.4 COMET-TAIL Virology Study Report: GSK Document number RPS-CLIN-040980; m5.3.5.4 COMET-PEAK Virology Study Report: GSK document number RPS-CLIN-049179.
a. The threshold for minority variant calling was >5% for LUNAR and ≥5% for COMET-ICE, COMET-TAIL and COMET-PEAK.
b. n = Number of participants with TE substitutions listed. N= number of paired sequences available for analysis.
c. Denominator is the number of participants with paired sequences for that category.
d. TE substitutions were total counts in the study and not broken down by post-baseline study day. In the COMET-ICE, COMET-TAIL and COMET-PEAK clinical studies, samples could be evaluated out through Day 29 based on specified criteria.

The specific substitution profile observed for sotrovimab in LUNAR was similar to published studies that report the appearance of P337A/H/L/R/S/T, E340A/D/G/K/Q/V, R346T and K356T substitutions following the administration of sotrovimab to individuals that are IC and infected with SARS-CoV-2 Omicron lineages [Andres, 2023; Huygens, 2023; Destras, 2022; Focosi, 2022; Palomino-Cabrera, 2023; Vellas, 2022; Yan, 2023].

Characterization of changes in the spike protein outside of the sotrovimab epitope in the IC population was also a goal of the LUNAR study. The overall prevalence of treatment emergent substitutions at >5% allelic frequency in the spike protein was similar to that observed for the 500 mg IV arms of the COMET-ICE, COMET-TAIL, COMET-PEAK clinical trials (Table 33).

Another goal of the LUNAR study was to evaluate the spike sequences for the presence of VOC/VUI. The COMET-ICE, COMET-TAIL and COMET-PEAK clinical studies all utilized consensus spike sequence to identify SARS-CoV-2 viral variants. The viral variant present in some LUNAR participants could not be definitively identified by spike consensus sequence because of gaps in the sequence data and the similarities between the spike protein in the different Omicron sub-lineages. Whole genome sequencing was therefore performed which enabled an assessment of VOC/VUI using the whole genome of SARS-CoV-2 [GSK document number RPS-CLIN-032797, GSK document number RPS-CLIN-049179, GSK Document number RPS-CLIN-040980].

Fourteen Omicron sub-lineages were definitively identified in LUNAR participants by whole genome sequencing. Sotrovimab activity across the consensus spike sequences for these variants has similar activity (16-22.6-fold change in EC50 value from wild type) in in vitro neutralization assays (Table 39).

The median viral load for the majority of participants declined to LLOD by Day 28 when analysed by VOC/VUI. The exception was the participants that were infected with Omicron BA.5.3.1 which declined from a median viral load at baseline of 8.295 to a median viral load of 6.945 $\log_{10}$ copies/mL at Day 28. There were only 2 participants identified with Omicron BA.5.3.1 viral variant and one had E340Q (89%) and E340V (10%) epitope substitutions at Day 28 and a viral load that did not significantly change over the course of the study. The spike sequence for Omicron BA.5.3.1 is the same as for Omicron BA.4 and BA.5 and sotrovimab has been shown to retain activity against this viral variant, although a 22.6-fold change in susceptibility to pseudotyped virus expressing the consensus BA.5 spike sequence was observed (Table 38). The E340 substitutions observed in the virus circulating in this participant (E340Q and E340V) cause a >50-fold change in sotrovimab in vitro neutralization activity and are the likely cause of the virus persistence through Day 28 in a participant with significant immune deficiency (Table 35).

Another goal of the LUNAR study was to determine the number of participants with undetectable viral load at the end of the study (Day 28). The mean viral load for LUNAR participants declined over the course of the study from 7.241 log10 copies/mL at baseline to below the LLOD at Day 28. At Day 28 of the LUNAR study there were 32 (16.5%) of 194 participants that had a positive viral load. Of these, 21 (n=32, 66%) participants had treatment emergent substitutions in the epitope at 1 or more post-baseline timepoints. This compares to 24 (n=162, 17%) that had treatment emergent epitope substitutions at 1 or more post-baseline samples and were negative for viral load at Day 28. The majority of participants with or without treatment emergent substitutions in the sotrovimab epitope at Day 7 achieved negative viral load at Day 28 (63.9% or 81.0%, respectively). Participants who had treatment emergent substitutions at Day 14 (5 /18 [27.8%]) were less likely to achieve undetectable virus at Day 28 than participants with no treatment emergent substitutions at Day 14 (22/30 [73.3%]). This implies that the treatment emergent substitutions contributed to the continued virus secretion at Day 28.

Of the treatment emergent substitutions observed in both the participants with positive or negative viral load at Day 28, there were 10 epitope substitutions common to both groups (P337A/L/R/S, G339D, E340A/D/G/Q, K356T) and 9 of these are known to reduce susceptibility to sotrovimab based on in vitro neutralization assays (Table 35, Table 36, Table 37 and Table 38). This suggests that the emergence of these epitope substitutions alone does not lead to persistent viral load. In the viral load negative at Day 28 group, a smaller proportion of participants developed these changes and the viruses with the substitutions were cleared by Day 28.

In the COMET-TAIL clinical study 19/280 (7%) patients in the sotrovimab 500 mg IV group were positive for viral RNA in nasal secretions at Day 29 [GSK document number RPS-CLIN-047387]. In Part B of the COMET-PEAK clinical trial 12/62 (19%) of patients that received sotrovimab 500 mg IV were positive for viral RNA in nasal

secretion at Day 29 [GSK document number RPS-CLIN-030208]. The findings in the LUNAR study showed 32 (16.5%) participants positive for viral RNA at Day 28. It should be noted that the LUNAR study used a different viral load assay that was not validated, with a different LLOD than the assay that was utilized in both COMET-TAIL and COMET-PEAK studies. The COMET-ICE clinical study used a different viral RNA quantitation assay than LUNAR, COMET-TAIL and COMET-PEAK and thus was not included in this comparison.

In general, participants with epitope substitutions achieved a median viral load below the level of detection of the viral load assay by Day 28 including for participants with E340 substitutions. It is worth noting that one participant in this category had E340 treatment emergent changes at Day 14 and Day 28 at high allelic frequency and did not have significant reduction in viral load during the study. The substitutions observed in this participant are known to cause >50-fold change in sotrovimab activity in in vitro neutralization assays.

The majority of participants in the LUNAR study experienced viral load decline over time and achieved a viral load below LLOD at Day 28. However, 16 (7.8%) participants demonstrated viral rebound, five of which went on to achieve LLOD by Day 28. Of the 11 participants that experienced viral rebound and had detectable viral load at Day 28, 5 had treatment emergent substitutions in the sotrovimab epitope at Day 28 and a further 3 did not have sequence available in the epitope region. Only one participant who experienced viral rebound was admitted to hospital, and this admission was not considered to be COVID-19 related. None of the other 10 participants with viral rebound that were positive for viral RNA at Day 28 experienced COVID-19 disease progression during the study. Therefore, the presence of treatment emergent substitutions in the sotrovimab epitope in participants with viral rebound did not appear to have a negative impact on clinical outcomes in the IC participant population enrolled in this study within the follow-up period.

10.1.2. Clinical outcomes

During the study 7 participants (3.2%) were hospitalized due to their underlying co-morbidities, of these 1 participant (0.5%) required high flow/non-invasive mechanical intervention and died on Day 18 of the study. The death was deemed not to be COVID-19 related by the investigator and was attributed to decompensated type 2 respiratory failure due to chest infection on a background of progressive myotonic dystrophy, as well as aspiration pneumonia. Please refer to Section 9.7.2.1 and Section 9.8.2 for details regarding treatment emergent substitution/variant for the 7 hospitalized patients. Observational studies conducted in the UK have reported consistent low rates of hospitalization due to COVID-19 in highest-risk patients (mostly IC as defined in the clinical commissioning policy [NHS England, 2022]) treated with sotrovimab as SoC across periods of predominant circulating variants [Harman, 2023; Zheng, 2022; Patel, 2023b; Zheng 2023; Tazare, 2023].A recent systematic literature review that included 14 observational studies and evaluated clinical outcomes associated with sotrovimab use among high risk participants during Omicron BA.2 and BA.5 predominance reported similar low rates of all-cause hospitalization or mortality (1.7% to 2.0% during BA.2; 3.4% during combined BA.2 and BA.5 periods) [Drysdale, 2023].

10.2. Limitations

There were several limitations in the study design or its conduct which may impact on study findings or the interpretation of the results of this study, summarized below:

Design

This surveillance study aimed to monitor the emergence of changes in spike protein over time following the administration of sotrovimab. The aim was to monitor the changes in the entire spike protein, but some substitutions, deletions or insertions of concern may have occurred outside of the spike protein. The participant population in this study is of public health interest for sentinel surveillance in the detection of variants of interest and concern, and this study contributes valuable information to the effort being undertaken by UKHSA. This study was a single arm study; due to the risk of progression to more severe disease, and high mortality rate in this population, it was considered unethical to include a placebo control in this study. The lack of an untreated comparator group in the study design limits the ability to provide meaningful inference into the association between treatment with sotrovimab and the development of novel viral mutations. Therefore, published literature and findings from previous clinical trials were used to contextualize the results of this study.

Selection bias

While participants who were hospitalized or who were unable to collect nasal/oropharyngeal swabs were not eligible to participate, the study participants enrolled were representative of a non-hospitalized IC participant population per the eligibility criteria. Please refer to Table 6 for more details.

Requiring participants to provide informed consent to be enrolled in the study may have potentially selected participants more willing to participate, however, participant disposition shows that only 2/219 participants screened (0.9%) were ineligible, or refused to or could not provide informed consent.

Eight patients were enrolled in the study despite not being immunocompromised as defined in the protocol. These participants completed the study without being withdrawn, and their data contribute to the results of this report.

Sample selection bias could have been introduced if different IC conditions increased or decreased the propensity for prolonged viral replication and shedding of SARS-CoV2, leading to changes in the distribution of IC conditions among those participants eligible for sequence analysis at different time points in the study may change. This does not appear to have occurred in the current study as the distribution of patients' underlying conditions in the sequenced populations remained relatively constant (Table 41).

Testing procedures

While study staff were not able to verify whether at-home samples (Days 7, 14, 28 [+/-2 days]) were collected and handled properly, self-collected nasal/oropharyngeal swabs have demonstrated comparable sensitivity and good viral load correlation to clinician

collected nasopharyngeal swabs (considered as the gold standard) for SARS-CoV-2 detection [Kojima, 2021; Alemany, 2021]. The participants were trained to increase the likelihood that the swabs were performed correctly.

One limitation of this study is that the SARS-CoV-2 viral load and NGS sequencing assays were performed in an accredited laboratory but the assays were not validated.

Distribution of virus across the respiratory tract may have varied between participants. Therefore, an infected participant may have had detectable virus in sputum but not in nasal/oropharyngeal swabs. This limitation and the potential for false negative results when using nasal/oropharyngeal swabs were acknowledged.

Loss to follow up

It was expected that there would be challenges obtaining follow-up information and samples from enrolled participants. However, clinical sites proactively contacted participants on at least 3 occasions over a period of 4 days (+/- 2 days from expected date of follow up samples) in order to reduce loss to follow-up. Attempts were also made by the study staff to contact or follow-up participants if they were admitted to the hospital. Perhaps it was due to these measures that just 4 out of the 217 enrolled participants (1.8%) were recorded as lost-to-follow-up. We cannot exclude the possibility that these participants may have experienced a severe clinical outcome such as hospital admission or death within 28 days.

By evaluating clinical outcomes and safety events at later time points, it was possible that participants experiencing adverse clinical outcomes or safety events were either more or less likely to maintain contact with study staff. The data from participants who remained under observation may be biased for related outcomes.

Geographical coverage

The study was conducted in 9 sites across England and Wales. It is therefore acknowledged that the identification and hence distribution of viral variants and the occurrence of treatment emergent substitutions in the IC participants may not be generalizable to all parts of the UK. However, based on similar variants circulating across the UK during the study period, we shouldn't expect different results in the IC population from different parts of the country [UKHSA, 2023].

Duration of follow-up

Concerns about the development of SARS-CoV-2 viruses that are resistant to sotrovimab in participants who are IC were based in part on the tendency of these participants to develop prolonged infections [Gupta 2022]. The design may not be able to detect the development of resistance if it developed later in the course of a prolonged infection, or if the viral load failed to rise above the threshold of detection for the sequencing assay.

Uncontrolled confounding

This was a descriptive study which was analyzed without adjustment for potential confounders, so other factors could also have contributed to findings. The observation that participants who had treatment emergent substitutions at Day 14 were less likely to achieve undetectable virus at Day 28, compared with participants with no treatment emergent substitutions at Day 14, could, for example, also be explained by the type of immunocompromising conditions for patients in that analysis.

10.3. Interpretation of Results

Virology

Emergence of resistance substitutions during treatment with sotrovimab in this IC population was in line with other studies; the number of treatment emergent epitope substitutions appeared to be numerically higher than those detected in the COMET-ICE and COMET-TAIL clinical studies but were in a similar range. In addition, the prevalence in LUNAR was higher than observed in the COMET-PEAK clinical study. However, the presence of treatment emergent substitutions in the sotrovimab epitope did not appear to have a negative impact on clinical outcomes in the IC participant population enrolled in this study during the follow-up period.

Clinical

A low number of clinical outcomes were reported in the IC population studied. There was 1 death reported, which was not considered by the investigator to be related to COVID-19. And while 7 participants were hospitalized, no participants required hospitalization, admission to the ICU, or respiratory support due to their COVID-19 infection. Of the 7 hospitalized participants, all were infected with Omicron sub-lineages based on spike consensus sequence.

Safety

There were 5 non-serious AEs considered related to sotrovimab treatment by the investigators. There were no infusion related reactions including anaphylaxis or other hypersensitivity reactions reported among 217 participants who were treated with sotrovimab 500 mg IV dose. The reported 5 non serious adverse events considered related to sotrovimab by the investigator did not identify any new safety issues.

10.4. Generalizability

The specific amino acid substitution profiles observed for sotrovimab-treated patients in LUNAR are only applicable to non-hospitalized patients who are IC and infected with SARS-CoV-2 Omicron lineages in GB. The outcomes results from the LUNAR study are not generalizable to hospitalized or non-immunocompromised participants treated with sotrovimab.

11. OTHER INFORMATION

Not Applicable

12. CONCLUSIONS

- Consistent with previous clinical trials of sotrovimab, treatment emergent substitutions were seen in the sotrovimab epitope in the LUNAR study following the administration of sotrovimab 500 mg IV to a highly IC population for the early treatment of COVID-19.
    - Treatment emergent substitutions in the sotrovimab epitope at >50% allelic frequency were observed in 7.8%, 15.5% and 33.3% of participants with paired sequencing data at Day 7, Day 14, and Day 28, respectively.
    - Treatment emergent substitutions in the sotrovimab epitope at >5% allelic frequency were observed in 24.8%, 25.4% and 33.3% of participants with paired sequencing data at Day 7, Day 14, and Day 28, respectively. Of these, forty six (29.5%) had treatment emergent substitutions that are known to cause reduced susceptibility to sotrovimab in in vitro neutralization assays.
- The presence of treatment emergent substitutions in the sotrovimab epitope did not appear to have a negative impact on clinical outcomes during the study follow-up period.
- The majority of participants experienced significant reductions in viral load, with the mean and median viral load being below the LLOQ by Day 28.
- A low number of patients with severe clinical outcomes were reported (protocol defined as hospital admission, requirement for respiratory support, ICU admission and death) and none of them were determined to be due to COVID-19.
- There were 5 non-serious AEs considered related to sotrovimab by the investigator, which were of mild intensity and reported as resolved, and there were no reports of hypersensitivity or anaphylaxis.

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ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1.	218407	04 May 2022	LUNAR Epidemiology PASS Protocol Version 2.0
2.	TMF-18060855	14 July 2023	LUNAR Statistical Analysis Plan for Real World Research Studies Version 2.0
3.	TMF-14485507 TMF-14659649 TMF-16093200	01 March 2022 04 May 2022 24 January 2023	Protocol Amendments
4.	TMF-18060858	11 May 2022	Sample Case Report Form
5	TMF-18561594	17 July 2023	List of Investigators and Independent Ethics
6	Obtained once CSR core text is final	Obtained once CSR core text is final	Sponsor's Signature Page
7	TMF-18061842 TMF-18061867 TMF-18061875 TMF-18061888 TMF-18061896 TMF-18061914 TMF-18061931 TMF-18061939 TMF-18061951 TMF-18428915	20 June 2022 23 June 2022 14 June 2022 25 July 2022 26 July 2022 08 June 2022 29 September 2022 06 June 2022 10 June 2022 30 January 2024	Principal Investigator's Signature Page
8	TMF-18551824 TMF-15151913	12 October 2023 21 April 2022	Publications based on the study
9	TMF-16152566 TMF-16152563	15 March 2022 24 March 2023	Sample Consent Forms
10	TMF-16152958 TMF-16152980 TMF-16209304 TMF-16153152 TMF-16153013 TMF-16152950 TMF-16153021 TMF-16153087 TMF-16152940	20 June 2022 06 June 2022 12 November 2022 23 June 2022 08 June 2022 23 February 2022 29 July 2022 28 July 2022 13 June 2022	Investigator Brief CVs/Biographies
11	TMF-18561594	17 July 2023	Study Administrative Table
12	TMF-18559365 TMF-18559661 TMF-18559665 TMF-18559666 TMF-18559677 TMF-18559686 TMF-18559688 TMF-18559692 TMF-18559693 TMF-18559706 TMF-18559710 TMF-18559714	03 November 2023 03 November 2023 03 November 2023 03 November 2023 04 December 2023 03 November 2023 03 November 2023 04 December 2023 04 December 2023 03 November 2023 03 November 2023 03 November 2023	ICH/Other Data Listings

No.	Document Reference No	Date	Title
	TMF-18559718 TMF-18559721 TMF-18559724 TMF-18559729	03 November 2023 03 November 2023 23 November 2023 23 November 2023	
13	TMF-16152640 TMF-16152634	14 March 2022 01 November 2022	Audit Certificates
14	TMF-16152651 TMF-16152650 TMF-16152649	29 June 2022 28 September 2022 10 February 2023	Documentation of inter-laboratory standardization methods and quality assurance procedures (if used)
15	TMF-18551909 TMF-18551936	24-February-2022 30-May-2022	Important publications referenced in the report

ANNEX 2 ADDITIONAL INFORMATION

Listing of Participants

Table 34 Listing of Participants with Paired Sequence Data

List of Participants with Paired Sequence		
Day 7	Day 14	Day 28
PPD		

List of Participants with Paired Sequence		
Day 7	**Day 14**	**Day 28**
PPD		

List of Participants with Paired Sequence		
Day 7	**Day 14**	**Day 28**
PPD		

List of Participants with Paired Sequence		
Day 7	**Day 14**	**Day 28**
PPD		

PHENOTYPIC RESULTS

Phenotypic evaluation of single AA substitutions in the epitope of sotrovimab.

The data sets in this section are the in vitro neutralization data for sotrovimab against single AA substitutions in the epitope observed in the LUNAR study that have previously been reported in non-clinical study reports by GSK/VIR.

Data are currently available for 22 of the 23 unique substitutions detected in the epitope in the Wuhan-Hu-1 spike protein background. The R509T substitution has not been evaluated in the pseudotyped virus system. Of the substitutions with available data, sotrovimab effectively neutralized 13 of the epitope substitutions tested in the Wuhan-Hu-1 spike background with fold changes in EC50 ranging from 0.48 to 2.45 relative to wild-type (Table 35). The P337H, E340G and K356T substitutions resulted in modest shifts in potency ranging from 5.13-18.21-fold indicating reduced susceptibility to sotrovimab in vitro (Table 35). The P337L, P337R, E340A, E340K, E340Q, and E340V substitution resulted in significant EC50 shifts (>50-fold) indicating reduced susceptibility to sotrovimab in vitro (Table 35).

Table 35 Neutralization Activity of Sotrovimab Against Wuhan-Hu-1 Pseudotyped Virus Containing Epitope Substitutions

Epitope Reference Amino Acid	Amino Acid Changes in Spike Protein	Geomean Neutralization EC50 (ng/mL)	Average Fold EC50 Change Relative to Reference[a]	Source Report
P337	P337A, D614G	57.79	0.97	PC-7831-0143
	P337H, D614G	185.29	5.13	PC-7831-0133
	P337L, D614G	>10000	>192	PC-7831-0133
	P337R, D614G	>10000	>192	PC-7831-0133
	P337S, D614G	127.69	1.26	PC-7831-0124
G339	G339D, D614G	117.38	1.18	PC-7831-0107, PC-7831-0124
	G339H, D614G	52.34	0.79	PC-7831-0143
	G339R, D614G	28.46	0.48	PC-7831-0143
	G339Y, D614G	43.40	0.80	PC-7831-0143
E340	E340A	>10000	>100	PC-7831-0109, PC-7831-0124
	E340D, D614G	81.46	2.45	PC-7831-0136
	E340G, D614G	640.07	18.21	PC-7831-0133
	E340K	>10000	>297	PC-7831-0124
	E340Q, D614G	>2500	>50	PC-7831-0133
	E340V, D614G	>10000	>200	PC-7831-0143
R346	R346I, D614G	65.39	1.72	PC-7831-0129
	R346S, D614G	42.87	1.13	PC-7831-0129
	R346T, D614G	89.04	1.25	PC-7831-0131
K356	K356M, D614G	64.09	1.03	PC-7831-0133
	K356R, D614G	29.61	0.78	PC-7831-0129
	K356T, D614G	281.13	5.9	PC-7831-0133
N440	N440K, D614G	19.99	0.48	PC-7831-0124
R509	R509T	Not determined		

Epitope Reference Amino Acid	Amino Acid Changes in Spike Protein	Geomean Neutralization EC50 (ng/mL)	Average Fold EC50 Change Relative to Reference[a]	Source Report

Source: Listed in Column 4 labelled "Source Report"
ND: not determined
The neutralizing capacity of sotrovimab against SARS-CoV-2 pseudotyped virus. Geomean and average are calculated from at least 2 independent experiments.
a. Fold change calculated relative to wild type sequence YP_009724390.1 for GSK Study Report 2020n456987-00; GSK study report 2021N470274, GSK Study Report 2021n477635-00; GSK Study Report 2022N504260_00; fold change calculated relative to D614G for YP_009724390.1 for GSK Study Report 2021n471870-00.

Data are currently available for 4 of the 23 unique substitutions detected in the epitope in the Omicron BA.1 spike protein background. In the Omicron BA.1 spike variant background, significant shifts in potency were observed for substitutions P337H, P337S, E340D, and K356T (>609 fold change in EC50 relative to Omicron BA.1 spike protein), indicating reduced susceptibility to sotrovimab when the substitutions occur in the Omicron BA.1 spike protein (Table 36). The average fold changes relative to the Wuhan-Hu-1 spike protein are listed in Table 36.

Table 36 Neutralization Activity of Sotrovimab Against Omicron BA.1 Spike Variant Pseudotyped Virus Containing Epitope Substitutions

Epitope Reference Amino Acid[a]	Amino Acid Changes in the Spike Protein	Geomean Neutralization EC_{50} (ng/mL)[b]	Average Fold-Change in EC_{50} Relative to Wuhan-Hu-1[c]	Average Fold-Change in EC_{50} Relative to Omicron BA.1[d]
P337	P337H	>100,000	>1872	>631
	P337S	>100,000	>1410	>609
E340	E340D	>100,000	>1410	>609
K356	K356T	>100,000	>1872	>631

Source: GSK study report 2024N546629 .
Geometric mean (Geomean) and average fold-change in EC50 values are calculated from at least 2 independent experiments. Substitution E340G could not be evaluated for neutralization in the Omicron BA.1 variant due to low infectivity of the pseudotyped virus containing the substitution.
a. Wuhan-Hu-1 wild-type sequence (YP_009724390.1) used as reference for the numbering of amino acid positions.
b. Neutralization assays were performed using VeroE6 cells.
c. Fold change calculated relative to Wuhan-Hu-1 wild-type sequence YP_009724390.1
d. Fold change calculated relative to Omicron BA.1 variant sequence, which includes the spike substitutions listed in Table 6 of GSK Study report 2023N538089.

Data are currently available for 9 of the 23 unique substitutions detected in the epitope in the Omicron BA.2 spike protein background. In the Omicron BA.2 spike variant, significant shifts in potency were observed for substitutions P337H, P337S, P337T, E340D, E340G, K356M, K356R, and K356T (>117-fold-change in EC50 relative to Omicron BA.2 spike protein), indicating reduced susceptibility to sotrovimab when the substitutions occur in the Omicron BA.2 spike protein (Table 37). In the Omicron BA.2 spike variant, the R346T substitution led to a 2.95-fold change relative Omicron BA.2. The average fold-changes relative to the Wuhan-Hu-1 spike protein are listed in Table 37. The R509T substitution could not be evaluated in the Omicron BA.2 spike variant due to low infectivity of the pseudotyped virus.

Table 37 Neutralization Activity of Sotrovimab Against Omicron BA.2 Spike Variant Pseudotyped Virus Containing Epitope Substitutions

Epitope Reference Amino Acid[a]	Amino Acid Changes in the Omicron BA.2 Spike Protein	Geomean Neutralization EC_{50} (ng/mL)[b]	Average Fold-Change in EC_{50} Relative to Wuhan-Hu-1[c]	Average Fold-Change in EC_{50} Relative to Omicron BA.2[d]
P337	P337H	>100,000	>1365	>117
	P337S	>100,000	>1410	>117
	P337T	>100,000	>1365	>117
E340	E340D	>100,000	>1410	>117
	E340G	>100,000	>1365	>117
R346	R346T	2,084	32.2	2.95
K356	K356M	>100,000	>1789	>132
	K356R	13,373	219	22.0
	K356T	>100,000	>1365	>117

Source: GSK study report 2024N546629 .

a. Geometric mean (Geomean) and average fold-change in EC_{50} values are calculated from at least 2 independent experiments. Wuhan-Hu-1 wild-type sequence (YP_009724390.1) used as reference for the numbering of amino acid positions.
b. Neutralization assays were performed using VeroE6 cells.
c. Fold change calculated relative to Wuhan-Hu-1 wild-type sequence YP_009724390.1.
d. Fold change calculated relative to Omicron BA.2 variant sequence, which includes the spike substitutions listed in Table 6 of GSK Study report 2023N538089.

Data are currently available for 8 of the 23 unique substitutions detected in the epitope in the Omicron BA.5 spike protein background. In the Omicron BA.5 spike variant, significant shifts in potency were observed for substitutions P337A, P337H, P337S, E340D, E340G, K356M, K356R and K356T with fold changes of >69.0 observed relative to Omicron BA.5 (Table 38). The average fold changes relative to the Wuhan-Hu-1 spike protein are listed in Table 38.

Table 38 Neutralization Activity of Sotrovimab Against Omicron BA.5 Spike Variant Pseudotyped Virus Containing Epitope Substitutions

Epitope Reference Amino Acid[a]	Amino Acid Changes in the Omicron BA.5 Spike Protein	Geomean Neutralization EC_{50} (ng/mL)[b]	Average Fold-Change in EC_{50} Relative to Wuhan-Hu-1[c]	Average Fold-Change in EC_{50} Relative to Omicron BA.5[d]
P337	P337A	>100,000	>2,698	>133
	P337H	>100,000	>2,133	>120
	P337S	>100,000	>2,589	>152
E340	E340D	>100,000	>2,244	>91.4
	E340G	>100,000	>2,244	>91.4
K356	K356M	>100,000	>2,233	>86.1
	K356R	>100,000	>1,275	>69.0
	K356T	>100,000	>2,244	>91.4

Source: GSK study report 2024N546629 .

a. Geometric mean (Geomean) and average fold-change in EC_{50} values are calculated from at least 2 independent experiments. Wuhan-Hu-1 wild-type sequence (YP_009724390.1) used as reference for the numbering of amino acid positions.
b. Neutralization assays were performed using VeroE6 cells.
c. Fold change calculated relative to Wuhan-Hu-1 wild-type sequence YP_009724390.1.

Epitope Reference Amino Acid[a]	Amino Acid Changes in the Omicron BA.5 Spike Protein	Geomean Neutralization EC_{50} (ng/mL)[b]	Average Fold-Change in EC_{50} Relative to Wuhan-Hu-1[c]	Average Fold-Change in EC_{50} Relative to Omicron BA.5[d]
P337	P337A	>100,000	>2,698	>133
	P337H	>100,000	>2,133	>120
	P337S	>100,000	>2,589	>152

d. Fold change calculated relative to Omicron BA.5 variant sequence, which includes the spike substitutions listed in Table 6 of GSK Study report 2023N538089.

Phenotypic Analysis of Circulating SARS-CoV-2 Virus VOC or VUI

The data sets in this section are the in vitro neutralization data for sotrovimab against VOC/VUIs identified in LUNAR either in pseudotyped virus assays or authentic live virus assays that has been previously reported in non-clinical study reports by GSK/VIR

Fourteen SARS-CoV-2 viral variants were identified in the VOC/VUI analysis in LUNAR by whole genome sequencing. Amongst the 14 viral variants identified, there were the three distinct spike consensus sequences. Sotrovimab neutralized the pseudotyped virus expressing the Omicron BA.2 consensus spike protein with an EC50 value of 1139 ng/mL and a 16-fold change from wild type (Table 39). The consensus spike sequences for Omicron BA.4, BA.5, BA.5.1, BA.5.2, BA.5.2.1, BA.5.3, BA.5.3.1, BE.1 and BF.1 are the same and sotrovimab neutralized the pseudotyped virus expressing the consensus spike protein for these variants with an EC50 value of 1556 ng/mL and a 22.6-fold change from wild type (Table 39). The consensus sequence for Omicron BA.2.73 has the characteristic profile of Omicron BA.2 with an additional substitution in the spike protein at G257S.This substitution is outside of the sotrovimab epitope and is not expected to impact activity.

Sotrovimab neutralized authentic SARS-CoV-2 Omicron BA.2 and BA.5 live virus with EC50 values of 972.8 and 1001.2 ng/mL, respectively. The fold changes in EC50 values were 15.7 and 21.6 for SARS-CoV-2 Omicron BA.2 and BA.5 viral variants, respectively [PC-7831-0155, PC-23-0117].

Table 39 Neutralization Activity of Sotrovimab Against Circulating SARS-CoV-2 Virus Variants Identified by Whole Genome Sequencing (Pseudovirus Assay)

SARS-CoV-2 Variant	Amino Acid Changes in Spike Protein	Geomean Neutralization EC_{50} (ng/mL)	Average Fold Change in EC_{50} [a]	Source Report[a]
Omicron BA.2/BA.2.1/BA.2.10/ BA.217	T19I, del24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K,	1139	16	PC-7831-0149

SARS-CoV-2 Variant	Amino Acid Changes in Spike Protein	Geomean Neutralization EC_{50} (ng/mL)	Average Fold Change in EC_{50} [a]	Source Report[a]
	P681H, N764K, D796Y, Q954H, N969K			
Omicron BA.4/ BA.5/BA.5.1/ BA.5.2/ BA.5.2.1/ BA.5.3/ BA.5.3.1/ BE.1/ BF.1[b]	T19I, del24-26, A27S, del69-70, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K	1556	22.6	PC-7831-0157

Source: GSK Study Report 2022N500862_00; GSK study report 2022N508878.

The neutralizing capacity of sotrovimab against SARS-CoV-2 pseudotyped virus. Geomean and average are calculated from at least 2 independent experiments.

a. Fold change calculated relative to wild type sequence YP_009724390.1.

b. The consensus spike sequence for Omicron BA.4 and BA.5 were determined to be the same when the spike sequences were defined based on sequences in the GISAID Database on 02-Feb-2023. At the time of pseudotyped testing the Omicron BA.4 spike variant the defined consensus sequence included a V3G substitution, and this was included in the consensus sequence for Omicron BA.4 in GSK study report 2022N508878. This substitution is no longer part of the consensus for this variant and the value reported in table represents the value for the current consensus sequence which is labelled as Omicron BA.5 in the study report.

ADDITIONAL POST-TEXT TABLES

Table 40 Proportion of AA Substitutions >5% Allelic Frequency at Baseline and Post-Baseline in the Spike Protein Outside of the Sotrovimab Epitope Found in >1 Participant in the LUNAR Study

N=217								
	Baseline		Post-baseline					
			Day 7		Day 14		Day 28	
Substitution	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]
L5F	207	6 (2.9)	142	7 (4.9)	55	4 (7.3)	-	0 (0)
L5F?	207	4 (1.9)	142	4 (2.8)	55	2 (3.6)	-	0 (0)
T19I	207	207 (100)	143	142 (99.3)	57	56 (98.2)	24	24 (100)
L24S	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
P25#	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
P26#	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
A27#	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
H69#	207	170 (82.1)	138	113 (81.9)	53	37 (69.8)	22	15 (68.2)
V70#	207	170 (82.1)	138	113 (81.9)	53	37 (69.8)	22	15 (68.2)
D80Y	207	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
V83A	207	20 (9.7)	139	14 (10.1)	54	10 (18.5)	22	4 (18.2)
P139#	-	0 (0)	-	0 (0)	40	2 (5.0)	-	0 (0)
F140#	-	0 (0)	-	0 (0)	40	2 (5.0)	-	0 (0)
L141#	-	0 (0)	-	0 (0)	40	2 (5.0)	-	0 (0)
G142D	202	202 (100)	115	115 (100)	40	40 (100)	18	18 (100)
V143#	-	0 (0)	-	0 (0)	39	2 (5.1)	-	0 (0)
Y144#	202	38 (18.8)	115	20 (17.4)	40	14 (35.0)	18	9 (50)
H146Q	202	19 (9.4)	115	11 (9.6)	39	7 (17.9)	18	3 (16.7)
K147E	202	17 (8.4)	115	9 (7.8)	39	5 (12.8)	18	3 (16.7)
N148#	202	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
W152L	202	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
W152R	202	17 (8.4)	112	8 (7.1)	38	5 (13.2)	18	3 (16.7)
F157L	202	18 (8.9)	112	9 (8.0)	38	5 (13.2)	18	3 (16.7)
Q183E	203	19 (9.4)	114	11 (9.6)	39	7 (17.9)	18	3 (16.7)
N185D	203	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
I210V	202	17 (8.4)	114	8 (7.0)	38	4 (10.5)	18	3 (16.7)
V213E	203	19 (9.4)	122	11 (9.0)	44	8 (18.2)	18	3 (16.7)
V213G	203	184 (90.6)	122	111 (91.0)	44	35 (79.5)	18	15 (83.3)
G257S	89	8 (9.0)	-	0 (0)	-	0 (0)	-	0 (0)
P330S	-	0 (0)	88	2 (2.3)	-	0 (0)	-	0 (0)
L368I	189	18 (9.5)	87	10 (11.5)	27	6 (22.2)	11	2 (18.2)
S371F	187	185 (98.9)	83	81 (97.6)	27	27 (100)	10	10 (100)
S373P	188	185 (98.4)	83	79 (95.2)	27	27 (100)	10	10 (100)
S375F	187	186 (99.5)	83	82 (98.8)	27	27 (100)	10	10 (100)
T376A	187	186 (99.5)	83	82 (98.8)	27	27 (100)	10	10 (100)
D405N	195	194 (99.5)	80	80 (100)	26	26 (100)	9	8 (88.9)
R408S	193	193 (100)	77	76 (98.7)	25	24 (96.0)	8	8 (100)
K417N	187	185 (98.9)	65	65 (100)	19	19 (100)	6	6 (100)
K444M	188	4 (2.1)	68	2 (2.9)	-	0 (0)	-	0 (0)

N=217								
			Post-baseline					
	Baseline		Day 7		Day 14		Day 28	
K444N	188	2 (1.1)	68	2 (2.9)	-	0 (0)	-	0 (0)
K444R	188	3 (1.6)	-	0 (0)	20	2 (10.0)	-	0 (0)
K444T	188	45 (23.9)	68	13 (19.1)	20	2 (10.0)	5	2 (40.0)
V445P	187	15 (8.0)	68	7 (10.3)	19	3 (15.8)	-	0 (0)
G446S	187	29 (15.5)	68	12 (17.6)	19	4 (21.1)	5	2 (40.0)
L452R	189	162 (85.7)	68	57 (83.8)	20	15 (75.0)	6	4 (66.7)
N460K	191	74 (38.7)	69	26 (37.7)	21	8 (38.1)	6	3 (50.0)
T470N	208	2 (1.0)	134	2 (1.5)	-	0 (0)	-	0 (0)
S477N	208	208 (100)	138	138 (100)	47	47 (100)	22	22 (100)
T478K	208	207 (99.5)	138	138 (100)	47	47 (100)	22	22 (100)
E484A	208	208 (100)	138	138 (100)	51	50 (98.0)	22	22 (100)
F486P	208	17 (8.2)	138	12 (8.7)	51	6 (11.8)	22	4 (18.2)
F486S	208	13 (6.3)	138	7 (5.1)	51	6 (11.8)	22	2 (9.1)
F486V	208	170 (81.7)	138	114 (82.6)	51	39 (76.5)	22	15 (68.2)
F490S	208	26 (12.5)	139	16 (11.5)	53	8 (15.1)	22	4 (18.2)
Q498R	208	208 (100)	137	137 (100)	48	48 (100)	22	22 (100)
N501Y	208	208 (100)	137	136 (99.3)	48	48 (100)	22	22 (100)
Y505H	207	207 (100)	137	136 (99.3)	48	48 (100)	22	22 (100)
T547I	206	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
T547K	-	0 (0)	136	2 (1.5)	47	2 (4.3)	22	2 (9.1)
D614G	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
H625R	208	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
H655Y	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
N658S	208	9 (4.3)	145	7 (4.8)	-	0 (0)	-	0 (0)
Y660H	-	0 (0)	145	2 (1.4)			-	0 (0)
N679K	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
P681H	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
A694S	197	4 (2.0)	-	0 (0)	-	0 (0)	-	0 (0)
S750I	195	2 (1.0)	79	2 (2.5)	-	0 (0)	-	0 (0)
N764K	197	197 (100)	84	83 (98.8)	26	26 (100)	8	8 (100)
N777#	-	0 (0)	136	2 (1.5)	-	0 (0)	-	0 (0)
D796Y	206	206 (100)	136	136 (100)	50	50 (100)	20	20 (100)
Q954H	207	207 (100)	143	143 (100)	54	54 (100)	24	24 (100)
N969K	208	208 (100)	145	145 (100)	59	59 (100)	25	25 (100)
A1020S	207	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
L1049F	-	0 (0)	137	2 (1.5)	-	0 (0)	-	0 (0)
D1199N	207	2 (1.0)	141	2 (1.4)	50	2 (4.0)	-	0 (0)
C1254*	207	52 (25.1)	139	34 (24.5)	50	10 (20.0)	22	6 (27.3)

Source: Table 1.9; Listing 1.7 has the TE spike protein substitutions >5% allelic frequency listed by participant.
- = the number of participants without a specific substitution cannot be determined. N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid position and is the denominator for the percentage. n is number of participants with substitutions in the epitope at the specific amino acid position. Substitutions in bold are part of the characteristic spike substitution profile for one or more SARS-CoV-2 viral variants identified in participants in the LUNAR study
a. A zero means the result was zero or below the threshold (>1) for number of participants for this summary table. Complete results in Source Table 1.9.
b. n' is the denominator.

Table 41 Summary of Demographics/Medical Conditions/Comorbidities for Sequenced Subjects

Number of Sequenced subjects	Baseline (N=210)	Day 7 (N=154)	Day 14 (N=71)	Day 28 (N=33)
Demographics				
Age - Mean (SD)	56.6 (15.76)	57.7 (15.45)	57.7 (16.74)	60.4 (16.63)
Sex				
Male	93 (44.3)	74 (48.1)	34 (47.9)	16 (48.5)
Female	117 (55.7)	80 (51.9)	37 (52.1)	17 (51.5)
Unknown	0	0	0	0
Ethnicity				
Hispanic or Latino	1 (0.5)	1 (0.6)	0	0
Not Hispanic or Latino	192 (91.4)	143 (92.9)	64 (90.1)	29 (87.9)
Unknown	17 (8.1)	10 (6.5)	7 (9.9)	4 (12.1)
Immunocompromising medical conditions	203 (96.7)	150 (97.4)	70 (98.6)	32 (97.0)
Solid cancer	40 (19.0)	26 (16.9)	10 (14.1)	3 (9.1)
Hematological diseases and stem cell transplant	43 (20.5)	33 (21.4)	13 (18.3)	7 (21.2)
Immune-mediated inflammatory disorders (IMID)	62 (29.5)	47 (30.5)	17 (23.9)	7 (21.2)
Solid organ transplant recipients	56 (26.7)	42 (27.3)	23 (32.4)	10 (30.3)
Renal diseases	50 (23.8)	35 (22.7)	19 (26.8)	6 (18.2)
Liver diseases	23 (11.0)	16 (10.4)	6 (8.5)	2 (6.1)
Immune deficiencies	24 (11.4)	17 (11.0)	10 (14.1)	5 (15.2)
HIV/AIDS	3 (1.4)	3 (1.9)	1 (1.4)	2 (6.1)
Other Comorbidities (protocol defined)	179 (85.2)	130 (84.4)	57 (80.3)	26 (78.8)
Obesity	64 (30.5)	47 (30.5)	22 (31.0)	8 (24.2)
Overweight	104 (49.5)	74 (48.1)	32 (45.1)	15 (45.5)
Cardiovascular disease	44 (21.0)	33 (21.4)	14 (19.7)	7 (21.2)
Cerebrovascular disease	13 (6.2)	10 (6.5)	6 (8.5)	4 (12.1)
Hypertension	87 (41.4)	67 (43.5)	30 (42.3)	14 (42.4)
Chronic obstructive pulmonary disease (COPD)	13 (6.2)	7 (4.5)	1 (1.4)	2 (6.1)
Asthma	34 (16.2)	30 (19.5)	13 (18.3)	7 (21.2)
Other chronic respiratory disease	23 (11.0)	20 (13.0)	8 (11.3)	4 (12.1)
Chronic kidney disease	43 (20.5)	29 (18.8)	17 (23.9)	6 (18.2)
Chronic liver disease	14 (6.7)	11 (7.1)	6 (8.5)	2 (6.1)
Diabetes mellitus	33 (15.7)	25 (16.2)	11 (15.5)	7 (21.2)
Sickle cell disease	1 (0.5)	1 (0.6)	0	0
Pregnancy	2 (1.0)	0	0	0
Neurodevelopmental disorders	4 (1.9)	2 (1.3)	0	0
Medical-related technological dependence	6 (2.9)	6 (3.9)	5 (7.0)	3 (9.1)

Source: Table 1.43

Notes: Percentages are based on 'N', i.e., Number of subjects sequenced as denominator.

Cross-reference: Listing 1.2, Listing 1.25

Table 42 Proportion of AA Substitutions >50% Allelic Frequency at Baseline and Post-Baseline in the Spike Protein Outside of the Sotrovimab Epitope Found in >1 Participant in the LUNAR Study

N=217								
	Baseline		Post-baseline					
			Day 7		Day 14		Day 28	
Substitution	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]	n'	Number of Participants with Change per Residue in Epitope n[a] (%)[b]
L5F	207	5 (2.4)	142	6 (4.2)	55	4 (7.3)	-	-
T19I	207	207 (100)	143	142 (99.3)	57	56 (98.2)	24	24 (100)
L24S	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
P25#	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
P26#	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
A27#	207	207 (100)	142	142 (100)	56	55 (98.2)	23	23 (100)
H69#	207	170 (82.1)	138	113 (81.9)	53	37 (69.8)	22	15 (68.2)
V70#	207	170 (82.1)	138	113 (81.9)	53	37 (69.8)	22	15 (68.2)
V83A	207	20 (9.7)	139	14 (10.1)	54	10 (18.5)	22	4 (18.2)
G142D	202	202 (100)	115	115 (100)	40	40 (100)	18	17 (94.4)
Y144#	202	38 (18.8)	115	19 (16.5)	40	12 (30.0)	18	7 (38.9)
H146Q	202	19 (9.4)	115	11 (9.6)	39	7 (17.9)	18	3 (16.7)
K147E	202	17 (8.4)	115	9 (7.8)	39	5 (12.8)	18	3 (16.7)
W152L	202	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
W152R	202	17 (8.4)	112	8 (7.1)	38	5 (13.2)	18	3 (16.7)
F157L	202	18 (8.9)	112	9 (8.0)	38	5 (13.2)	18	3 (16.7)
Q183E	203	19 (9.4)	114	11 (9.6)	39	7 (17.9)	18	3 (16.7)
N185D	203	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
I210V	202	17 (8.4)	114	8 (7.0)	38	4 (10.5)	18	3 (16.7)
V213E	203	19 (9.4)	122	11 (9.0)	44	8 (18.2)	18	3 (16.7)
V213G	203	184 (90.6)	122	111 (91.0)	44	35 (79.5)	18	15 (83.3)
G257S	89	8 (9.0)	-	0 (0)	-	0 (0)	-	0 (0)
L368I	189	18 (9.5)	87	10 (11.5)	27	6 (22.2)	11	2 (18.2)
S371F	187	171 (91.4)	83	79 (95.2)	27	27 (100)	10	10 (100)
S373P	188	185 (98.4)	83	79 (95.2)	27	27 (100)	10	10 (100)
S375F	187	186 (99.5)	83	82 (98.8)	27	27 (100)	10	10 (100)
T376A	187	186 (99.5)	83	82 (98.8)	27	27 (100)	10	10 (100)
D405N	195	194 (99.5)	80	80 (100)	26	26 (100)	9	8 (88.9)
R408S	193	191 (99.0)	77	73 (94.8)	25	22 (88.0)	8	7 (87.5)
K417N	187	185 (98.9)	65	65 (100)	19	19 (100)	6	6 (100)
K444M	188	4 (2.1)	68	2 (2.9)	-	0 (0)	-	0 (0)
K444N	-	0 (0)	68	2 (2.9)	-	0 (0)	-	0 (0)
K444R	188	3 (1.6)	-	0 (0)	20	2 (10.0)	-	0 (0)
K444T	188	45 (23.9)	68	13 (19.1)	20	2 (10.0)	5	2 (40.0)
V445P	187	15 (8.0)	68	7 (10.3)	19	3 (15.8)	-	0 (0)
G446S	187	29 (15.5)	68	12 (17.6)	19	4 (21.1)	5	2 (40.0)
L452R	189	162 (85.7)	68	57 (83.8)	20	15 (75.0)	6	4 (66.7)
N460K	191	73 (38.2)	69	26 (37.7)	21	8 (38.1)	6	3 (50.0)
T470N	-	0 (0)	134	2 (1.5)		0 (0)	-	0 (0)
S477N	208	208 (100)	138	138 (100)	47	47 (100)	22	22 (100)
T478K	208	207 (99.5)	138	138 (100)	47	47 (100)	22	22 (100)

N=217								
	Baseline		Post-baseline					
			Day 7		Day 14		Day 28	
E484A	208	208 (100)	138	138 (100)	51	50 (98.0)	22	22 (100)
F486P	208	17 (8.2)	138	12 (8.7)	51	6 (11.8)	22	4 (18.2)
F486S	208	13 (6.3)	138	7 (5.1)	51	6 (11.8)	22	2 (9.1)
F486V	208	170 (81.7)	138	114 (82.6)	51	39 (76.5)	22	15 (68.2)
F490S	208	26 (12.5)	139	16 (11.5)	53	8 (15.1)	22	4 (18.2)
Q498R	208	208 (100)	137	137 (100)	48	48 (100)	22	22 (100)
N501Y	208	208 (100)	137	136 (99.3)	48	48 (100)	22	22 (100)
Y505H	207	207 (100)	137	136 (99.3)	48	47 (97.9)	22	21 (95.5)
D614G	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
H655Y	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
N658S	208	8 (3.8)	145	7 (4.8)	-	0 (0)	-	0 (0)
N679K	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
P681H	208	208 (100)	145	145 (100)	56	56 (100)	24	24 (100)
S750I	195	2 (1.0)	79	2 (2.5)	-	0 (0)	-	0 (0)
N764K	197	197 (100)	84	83 (98.8)	26	26 (100)	8	8 (100)
D796Y	206	206 (100)	136	136 (100)	50	49 (98.0)	20	20 (100)
Q954H	207	207 (100)	143	143 (100)	54	54 (100)	24	24 (100)
N969K	208	208 (100)	145	145 (100)	59	59 (100)	25	25 (100)
A1020S	207	2 (1.0)	-	0 (0)	-	0 (0)	-	0 (0)
D1199N	207	2 (1.0)	141	2 (1.4)	50	2 (4.0)	-	0 (0)

Source: Table 1.7; Listing 1.8 has the TE spike protein substitutions >50% allelic frequency listed by participant.

- = the number of participants without a specific substitution cannot be determined. N = number of participants in Safety population in the LUNAR study. n' is the number of participants with sequencing data available at the specific amino acid position and is the denominator for the percentage. n is number of participants with substitutions in the epitope at the specific amino acid position. Substitutions in bold are part of the characteristic spike substitution profile for one or more SARS-CoV-2 viral variants identified in participants in the LUNAR study

a. A zero means the result was zero or below the threshold (>1) for number of participants for this summary table. Complete results in Source Table1.7.

b. n' is the denominator.

Table 43 Treatment Emergent Epitope Substitutions for Participants with Negative Viral Load at Day 28

Participant with Negative viral load at D28	TE Substitutions at Day 7 (% AF)	TE Substitutions at Day 14 (% AF)	TE Substitutions at Day 28 (% AF)
PPD	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 440, 441, 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No substitutions	gap in epitope sequence	No Sequence
	No substitutions	No substitutions	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No Sequence	gap in epitope sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	P337L (10.7%)	No Sequence	No Sequence
	E340K (27.3%)	No Sequence	No Sequence
	E340D (9.41%), E340Q (88.5%)	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	gap in epitope sequence	No substitutions	No Sequence
	No substitutions	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No substitutions	P337S (32.3%), E340K (25.1%)	No Sequence
	E340D (85.8%)	E340D (98.1%)	No Sequence
	gap in epitope sequence except 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 509	gap in epitope sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	gap in epitope sequence at BL	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	E340A (41.6%), E340Q (9.03%), K356T (8.18%)	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	gap in epitope sequence	gap in epitope sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence

Participant with Negative viral load at D28	TE Substitutions at Day 7 (% AF)	TE Substitutions at Day 14 (% AF)	TE Substitutions at Day 28 (% AF)
PPD	gap in epitope sequence except 509	No Sequence	No Sequence
	gap in epitope sequence	gap in epitope sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No substitutions	gap in epitope sequence	No Sequence
	E340D (5.18%)	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in BL epitope sequence except 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	gap in epitope sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	No Sequence	gap in epitope sequence except 509	No Sequence
	P337S (47.8%)	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No substitutions	gap in epitope sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No substitutions	No substitutions	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	P337S (7.36%)), E340A (9.12%), E340Q (15.5%)	No substitutions	No Sequence
	No substitutions	gap in epitope sequence except 509	No Sequence
	No substitutions	No Sequence	No Sequence
	P337S (7.51%)	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	No substitutions	gap in epitope sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence

Participant with Negative viral load at D28	TE Substitutions at Day 7 (% AF)	TE Substitutions at Day 14 (% AF)	TE Substitutions at Day 28 (% AF)
PPD	gap in epitope sequence except 509	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No substitutions	gap in epitope sequence	No Sequence
	gap in epitope sequence except 509	gap in epitope sequence	No Sequence
	gap in epitope sequence except 509	gap in epitope sequence except 509	No Sequence
	No substitutions	gap in epitope sequence except 509	No Sequence
	E340Q (7.41%)	No Sequence	No Sequence
	P337S (42.8%), E340D (10.8%), E340Q (10.3%)	P337S (19.6%), E340D (9.51%), E340Q (49.5%), R346T (18%)	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 440, 441, 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	E340Q (16.1%)	gap in epitope sequence except 509	No Sequence
	No substitutions	gap in epitope sequence except 509	No Sequence
	No substitutions	gap in epitope sequence except 509	No Sequence
	gap in epitope sequence except 509	gap in epitope sequence except 509	No Sequence
	No substitutions	No Sequence	No Sequence
	K356T (5.58%)	gap in epitope sequence except 509	No Sequence
	No substitutions	No substitutions	No Sequence
	No Sequence	No Sequence	No Sequence
	P337L (84.3%)	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence

Participant with Negative viral load at D28	TE Substitutions at Day 7 (% AF)	TE Substitutions at Day 14 (% AF)	TE Substitutions at Day 28 (% AF)
PPD	No Sequence	No Sequence	No Sequence
	E340G (15.4%), E340Q (6.19%)	No substitutions	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	gap in epitope sequence except 509	No Sequence
	P337S (20.2%), E340K (51.9%), K356T (14.9%)	gap in epitope sequence except 509	No Sequence
	No substitutions	gap in epitope sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	P337S (6.66%), E340D (8.23%)	No substitutions	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No Substitution	gap in epitope sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	P337A (5.23%), P337S (83.7%), E340D (8.79%)	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	gap in epitope sequence	gap in epitope sequence	No Sequence
	gap in epitope sequence	gap in epitope sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	gap in epitope sequence except 509	No Sequence	No Sequence
	P337R (12.7%), P337S (32.1%), E340D (7.77%), E340Q (14.8%), K356M (27.6%)	gap in epitope sequence except 509	No Sequence
	gap in epitope sequence	No Sequence	No Sequence
	No substitutions	gap in epitope sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	gap in BL epitope sequence	gap in BL epitope sequence	No Sequence
	P337A (23.6%)	No substitutions	No Sequence
	P337S (96.6%)	P337S (9.39%)	No Sequence
	gap in epitope sequence	No Sequence	No Sequence

Participant with Negative viral load at D28	TE Substitutions at Day 7 (% AF)	TE Substitutions at Day 14 (% AF)	TE Substitutions at Day 28 (% AF)
PPD	No Sequence	No Sequence	No Sequence
	E340D (44.8%)	No Sequence	No Sequence
	No substitutions	No Sequence	No Sequence
	P337L (38.1%), E340D (34.1%), E340Q (8.78%)	P337L (15.4%), E340D (62.8%)	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence
	No Sequence	No Sequence	No Sequence

Source: Listing 1.3
AF= allelic frequency; BL= Baseline

Table 44 Gaps in SARS-CoV-2 spike sequencing analysis.

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Baseline (Day 0)	235_423	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	689_1274	
	Baseline (Day 0)	275_283	
	Baseline (Day 0)	235_285	
	Baseline (Day 0)	316_328	
	Baseline (Day 0)	370_376	
	Day 7 (Follow Up Call 1)	120_881	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	898_975	
	Day 7 (Follow Up Call 1)	979_1274	
	Baseline (Day 0)	236_249	
	Baseline (Day 0)	258_282	
	Day 7 (Follow Up Call 1)	198_203	
	Day 7 (Follow Up Call 1)	235_284	
	Day 14 (Follow Up Call 2)	235_291	
	Day 14 (Follow Up Call 2)	310_462	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	692_766	
	Baseline (Day 0)	236_252	
	Baseline (Day 0)	256_283	
	Day 7 (Follow Up Call 1)	235_283	
	Day 14 (Follow Up Call 2)	236_283	
	Baseline (Day 0)	236_287	
	Baseline (Day 0)	315_327	
	Baseline (Day 0)	395_403	
	Baseline (Day 0)	407_463	440, 441
	Day 7 (Follow Up Call 1)	1146_1165	
	Day 7 (Follow Up Call 1)	133_210	
	Day 7 (Follow Up Call 1)	228_290	
	Day 7 (Follow Up Call 1)	309_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_766	
	Baseline (Day 0)	275_281	
	Day 7 (Follow Up Call 1)	1146_1165	
	Day 7 (Follow Up Call 1)	122_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Baseline (Day 0)	235_284	
	Day 14 (Follow Up Call 2)	1000_1274	
	Day 14 (Follow Up Call 2)	122_287	
	Day 14 (Follow Up Call 2)	312_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	690_871	
	Baseline (Day 0)	1_1187	
	Baseline (Day 0)	1194_1274	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	235_284	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_283	
	Day 14 (Follow Up Call 2)	236_284	
	Day 28 (Follow Up Call 3)	117_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	689_788	
	Day 28 (Follow Up Call 3)	796_872	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_283	
	Day 14 (Follow Up Call 2)	235_284	
	Day 28 (Follow Up Call 3)	235_284	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	378_450	440, 441
	Baseline (Day 0)	781_871	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	370_464	440, 441
	Day 7 (Follow Up Call 1)	690_768	
	Baseline (Day 0)	193_207	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	412_451	440, 441
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	365_463	440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 14 (Follow Up Call 2)	143_209	
	Day 14 (Follow Up Call 2)	228_486	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441,
	Day 14 (Follow Up Call 2)	492_555	509
	Day 14 (Follow Up Call 2)	690_767	
	Day 28 (Follow Up Call 3)	1_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441,
	Day 28 (Follow Up Call 3)	594_1274	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	235_284	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 14 (Follow Up Call 2)	235_284	
	Day 14 (Follow Up Call 2)	412_433	
	Day 14 (Follow Up Call 2)	435_451	440, 441,
	Day 28 (Follow Up Call 3)	192_204	
	Day 28 (Follow Up Call 3)	235_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441,
	Day 28 (Follow Up Call 3)	690_767	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	412_462	440, 441
	Baseline (Day 0)	235_284	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	316_324	
	Day 7 (Follow Up Call 1)	370_377	
	Day 7 (Follow Up Call 1)	381_386	
	Day 7 (Follow Up Call 1)	392_463	440, 441
	Day 7 (Follow Up Call 1)	691_766	
	Baseline (Day 0)	273_282	
	Day 7 (Follow Up Call 1)	1_470	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	1000_1274	
	Day 7 (Follow Up Call 1)	690_768	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	1000_1065	
	Day 7 (Follow Up Call 1)	193_210	
	Day 7 (Follow Up Call 1)	234_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	45_113	
	Day 7 (Follow Up Call 1)	690_768	
	Day 14 (Follow Up Call 2)	235_284	
	Day 14 (Follow Up Call 2)	428_441	440, 441
	Day 14 (Follow Up Call 2)	445_460	
	Day 14 (Follow Up Call 2)	693_712	
	Day 14 (Follow Up Call 2)	732_741	
	Day 14 (Follow Up Call 2)	743_751	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_285	
	Day 7 (Follow Up Call 1)	411_461	440, 441
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	236_283	
	Baseline (Day 0)	236_284	
	Baseline (Day 0)	312_396	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	140_168	
	Day 7 (Follow Up Call 1)	179_210	
	Day 7 (Follow Up Call 1)	227_287	
	Day 7 (Follow Up Call 1)	312_341	332, 333, 334, 335, 336, 337, 339, 340, 341
	Day 7 (Follow Up Call 1)	356_464	356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Baseline (Day 0)	235_286	
	Baseline (Day 0)	428_441	440, 441
	Baseline (Day 0)	1090_1166	
	Baseline (Day 0)	122_400	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Baseline (Day 0)	504_555	509
	Baseline (Day 0)	690_766	
	Baseline (Day 0)	898_957	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	236_283	
	Day 28 (Follow Up Call 3)	236_287	
	Day 28 (Follow Up Call 3)	407_463	440, 441
	Day 28 (Follow Up Call 3)	690_871	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	256_282	
	Day 7 (Follow Up Call 1)	274_281	
	Day 14 (Follow Up Call 2)	236_283	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	235_283	
	Day 14 (Follow Up Call 2)	525_550	
	Baseline (Day 0)	236_247	
	Baseline (Day 0)	260_283	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_334	332, 333, 334
	Day 7 (Follow Up Call 1)	356_463	356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	693_718	
	Day 7 (Follow Up Call 1)	732_765	
	Day 14 (Follow Up Call 2)	1_767	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	1195_1273	
	Day 14 (Follow Up Call 2)	898_957	
	Day 7 (Follow Up Call 1)	1_469	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	592_872	
	Day 7 (Follow Up Call 1)	255_283	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 28 (Follow Up Call 3)	235_287	
	Day 28 (Follow Up Call 3)	359_366	359, 360, 361
	Day 28 (Follow Up Call 3)	368_464	440, 441
	Day 28 (Follow Up Call 3)	690_766	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	318_331	
	Day 7 (Follow Up Call 1)	393_463	440, 441
	Day 7 (Follow Up Call 1)	690_766	
	Baseline (Day 0)	273_281	
	Baseline (Day 0)	311_372	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	390_463	440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 7 (Follow Up Call 1)	1195_1259	
	Day 7 (Follow Up Call 1)	235_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_768	
	Day 7 (Follow Up Call 1)	896_1065	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_768	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_871	
	Day 14 (Follow Up Call 2)	121_1260	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	235_333	332, 333
	Day 28 (Follow Up Call 3)	335_465	335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 28 (Follow Up Call 3)	689_767	
	Baseline (Day 0)	236_247	
	Baseline (Day 0)	273_282	
	Day 7 (Follow Up Call 1)	259_283	
	Day 14 (Follow Up Call 2)	234_441	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 28 (Follow Up Call 3)	122_215	
	Day 28 (Follow Up Call 3)	221_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 28 (Follow Up Call 3)	692_766	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	259_283	
	Baseline (Day 0)	261_266	
	Baseline (Day 0)	268_282	
	Day 14 (Follow Up Call 2)	275_281	
	Baseline (Day 0)	236_284	
	Day 7 (Follow Up Call 1)	1096_1101	
	Day 7 (Follow Up Call 1)	1126_1166	
	Day 7 (Follow Up Call 1)	121_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_771	
	Baseline (Day 0)	236_284	
	Day 7 (Follow Up Call 1)	236_282	
	Day 14 (Follow Up Call 2)	235_283	
	Day 28 (Follow Up Call 3)	198_203	
	Day 28 (Follow Up Call 3)	232_302	
	Day 28 (Follow Up Call 3)	323_328	
	Day 28 (Follow Up Call 3)	353_465	354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 28 (Follow Up Call 3)	690_768	
	Baseline (Day 0)	235_287	
	Day 7 (Follow Up Call 1)	119_489	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	492_555	509
	Day 7 (Follow Up Call 1)	66_73	
	Day 7 (Follow Up Call 1)	690_874	
	Day 7 (Follow Up Call 1)	877_882	
	Day 7 (Follow Up Call 1)	898_975	
	Day 7 (Follow Up Call 1)	979_1166	
	Day 14 (Follow Up Call 2)	1_1274	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Baseline (Day 0)	275_283	
	Baseline (Day 0)	236_284	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	319_332	332
	Baseline (Day 0)	359_463	359, 360, 361, 440, 441
	Baseline (Day 0)	693_766	
	Day 7 (Follow Up Call 1)	1141_1165	
	Day 7 (Follow Up Call 1)	122_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_768	
	Baseline (Day 0)	235_283	
	Baseline (Day 0)	235_283	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	122_127	
	Day 14 (Follow Up Call 2)	192_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	690_872	
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	258_283	
	Day 7 (Follow Up Call 1)	1091_1101	
	Day 7 (Follow Up Call 1)	1122_1166	
	Day 7 (Follow Up Call 1)	122_472	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	496_555	509
	Day 7 (Follow Up Call 1)	690_766	
	Day 14 (Follow Up Call 2)	595_1274	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	235_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	39_107	
	Day 14 (Follow Up Call 2)	595_1274	
	Baseline (Day 0)	236_284	
	Day 7 (Follow Up Call 1)	122_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_766	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	383_464	440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Baseline (Day 0)	235_286	
	Baseline (Day 0)	312_334	332, 333, 334
	Baseline (Day 0)	359_396	359, 360, 361
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	338_439	339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	690_766	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	1092_1115	
	Day 7 (Follow Up Call 1)	1120_1166	
	Day 7 (Follow Up Call 1)	120_471	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_774	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	1195_1274	
	Day 7 (Follow Up Call 1)	689_873	
	Day 7 (Follow Up Call 1)	999_1186	
	Baseline (Day 0)	192_209	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	312_334	332, 333, 334
	Baseline (Day 0)	359_463	359, 360, 361, 440, 441
	Baseline (Day 0)	692_766	
	Day 7 (Follow Up Call 1)	102_108	
	Day 7 (Follow Up Call 1)	118_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	1251_1258	
	Day 7 (Follow Up Call 1)	39_96	
	Day 7 (Follow Up Call 1)	690_789	
	Day 7 (Follow Up Call 1)	792_871	
	Day 14 (Follow Up Call 2)	235_287	
	Day 14 (Follow Up Call 2)	398_463	440, 441
	Day 14 (Follow Up Call 2)	750_766	
	Day 28 (Follow Up Call 3)	235_287	
	Day 28 (Follow Up Call 3)	313_331	
	Day 28 (Follow Up Call 3)	370_376	
	Day 28 (Follow Up Call 3)	394_463	440, 441
	Day 28 (Follow Up Call 3)	691_766	
	Baseline (Day 0)	235_297	
	Baseline (Day 0)	307_397	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	235_285	
	Day 7 (Follow Up Call 1)	407_463	440, 441
	Day 7 (Follow Up Call 1)	693_765	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	1082_1166	
	Day 14 (Follow Up Call 2)	119_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	690_770	
	Day 28 (Follow Up Call 3)	1_10	
	Day 28 (Follow Up Call 3)	112_1274	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	21_27	
	Day 28 (Follow Up Call 3)	39_93	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	1_1187	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	1192_1274	
	Baseline (Day 0)	235_283	
	Baseline (Day 0)	273_282	
	Day 7 (Follow Up Call 1)	151_158	
	Day 7 (Follow Up Call 1)	191_210	
	Day 7 (Follow Up Call 1)	235_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 28 (Follow Up Call 3)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	1195_1274	
	Day 28 (Follow Up Call 3)	689_1187	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	1000_1065	
	Day 7 (Follow Up Call 1)	1195_1262	
	Day 7 (Follow Up Call 1)	122_872	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	235_287	
	Day 28 (Follow Up Call 3)	313_403	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 28 (Follow Up Call 3)	40_108	
	Day 28 (Follow Up Call 3)	412_418	
	Day 28 (Follow Up Call 3)	424_462	440, 441
	Day 28 (Follow Up Call 3)	690_766	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	273_282	
	Day 7 (Follow Up Call 1)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	1195_1274	
	Day 7 (Follow Up Call 1)	689_768	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	236_283	
	Day 7 (Follow Up Call 1)	236_284	
	Day 7 (Follow Up Call 1)	412_426	
	Baseline (Day 0)	236_247	
	Baseline (Day 0)	274_281	
	Baseline (Day 0)	236_244	
	Baseline (Day 0)	273_282	
	Day 7 (Follow Up Call 1)	133_209	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	229_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 7 (Follow Up Call 1)	236_283	
	Baseline (Day 0)	274_280	
	Day 14 (Follow Up Call 2)	235_320	
	Day 14 (Follow Up Call 2)	325_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_767	
	Baseline (Day 0)	121_220	
	Baseline (Day 0)	256_283	
	Day 7 (Follow Up Call 1)	122_286	
	Day 7 (Follow Up Call 1)	395_403	
	Day 7 (Follow Up Call 1)	407_462	440, 441
	Baseline (Day 0)	275_283	
	Day 7 (Follow Up Call 1)	148_160	
	Day 7 (Follow Up Call 1)	162_167	
	Day 7 (Follow Up Call 1)	191_210	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	691_766	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	122_284	
	Baseline (Day 0)	411_462	440, 441
	Day 7 (Follow Up Call 1)	121_287	
	Day 7 (Follow Up Call 1)	385_464	440, 441
	Day 14 (Follow Up Call 2)	60_76	
	Day 14 (Follow Up Call 2)	118_873	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	999_1274	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	120_873	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	1096_1101	
	Day 7 (Follow Up Call 1)	1126_1131	
	Day 7 (Follow Up Call 1)	1140_1166	
	Baseline (Day 0)	235_284	
	Baseline (Day 0)	411_463	440, 441
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	410_463	440, 441
	Day 14 (Follow Up Call 2)	236_286	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 14 (Follow Up Call 2)	409_462	440, 441
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_284	
	Day 14 (Follow Up Call 2)	235_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_767	
	Day 28 (Follow Up Call 3)	1_1175	
	Day 28 (Follow Up Call 3)	1196_1207	
	Day 28 (Follow Up Call 3)	1233_1266	
	Baseline (Day 0)	235_285	
	Day 7 (Follow Up Call 1)	121_475	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	515_555	509
	Day 7 (Follow Up Call 1)	689_780	
	Day 7 (Follow Up Call 1)	795_870	
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	1_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	1000_1065	
	Day 7 (Follow Up Call 1)	594_741	
	Day 7 (Follow Up Call 1)	757_871	
	Day 7 (Follow Up Call 1)	276_282	
	Day 7 (Follow Up Call 1)	236_287	
	Day 14 (Follow Up Call 2)	1_11	
	Day 14 (Follow Up Call 2)	1000_1065	
	Day 14 (Follow Up Call 2)	1096_1101	
	Day 14 (Follow Up Call 2)	1147_1164	
	Day 14 (Follow Up Call 2)	1189_1274	
	Day 14 (Follow Up Call 2)	133_210	
	Day 14 (Follow Up Call 2)	227_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	23_120	
	Day 14 (Follow Up Call 2)	594_873	
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	256_282	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	411_463	440, 441
	Day 14 (Follow Up Call 2)	235_287	
	Day 14 (Follow Up Call 2)	312_403	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 14 (Follow Up Call 2)	423_457	440, 441
	Day 14 (Follow Up Call 2)	692_766	
	Day 28 (Follow Up Call 3)	235_288	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 28 (Follow Up Call 3)	312_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 28 (Follow Up Call 3)	691_766	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_285	
	Day 7 (Follow Up Call 1)	405_464	440, 441
	Day 7 (Follow Up Call 1)	691_766	
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	256_283	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	316_324	
	Day 7 (Follow Up Call 1)	396_464	440, 441
	Day 7 (Follow Up Call 1)	691_766	
	Baseline (Day 0)	236_249	
	Baseline (Day 0)	268_282	
	Day 7 (Follow Up Call 1)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	689_1274	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	407_463	440, 441
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	256_266	
	Baseline (Day 0)	268_282	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	236_284	
	Day 14 (Follow Up Call 2)	413_419	
	Day 28 (Follow Up Call 3)	1_872	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	1000_1065	
	Day 28 (Follow Up Call 3)	1156_1163	
	Day 28 (Follow Up Call 3)	1189_1274	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	1090_1115	
	Day 14 (Follow Up Call 2)	1118_1170	
	Day 14 (Follow Up Call 2)	1178_1186	
	Day 14 (Follow Up Call 2)	1189_1274	
	Day 14 (Follow Up Call 2)	690_1070	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	428_441	440, 441
	Baseline (Day 0)	447_453	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	235_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	595_766	
	Day 7 (Follow Up Call 1)	898_957	
	Baseline (Day 0)	196_203	
	Baseline (Day 0)	235_285	
	Baseline (Day 0)	406_464	440, 441
	Baseline (Day 0)	697_716	
	Baseline (Day 0)	733_765	
	Day 7 (Follow Up Call 1)	133_210	
	Day 7 (Follow Up Call 1)	226_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	255_283	
	Baseline (Day 0)	236_282	
	Day 7 (Follow Up Call 1)	1_872	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	1000_1261	
	Baseline (Day 0)	236_247	
	Baseline (Day 0)	258_282	
	Day 7 (Follow Up Call 1)	1_10	
	Day 7 (Follow Up Call 1)	117_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	1200_1205	
	Day 7 (Follow Up Call 1)	1233_1263	
	Day 7 (Follow Up Call 1)	20_35	
	Day 7 (Follow Up Call 1)	38_92	
	Day 7 (Follow Up Call 1)	689_1171	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	236_283	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	313_333	332, 333
	Baseline (Day 0)	359_463	359, 360, 361, 440, 441
	Baseline (Day 0)	693_715	
	Baseline (Day 0)	721_765	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_345	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345
	Day 7 (Follow Up Call 1)	354_463	354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_766	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	236_249	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Baseline (Day 0)	258_266	
	Baseline (Day 0)	268_282	
	Day 7 (Follow Up Call 1)	1096_1101	
	Day 7 (Follow Up Call 1)	1126_1166	
	Day 7 (Follow Up Call 1)	121_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_769	
	Day 7 (Follow Up Call 1)	236_284	
	Day 7 (Follow Up Call 1)	693_725	
	Day 7 (Follow Up Call 1)	733_740	
	Day 14 (Follow Up Call 2)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	1089_1274	
	Day 14 (Follow Up Call 2)	689_890	
	Day 14 (Follow Up Call 2)	896_957	
	Day 7 (Follow Up Call 1)	131_210	
	Day 7 (Follow Up Call 1)	225_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	43_126	
	Day 7 (Follow Up Call 1)	690_766	
	Day 14 (Follow Up Call 2)	1_10	
	Day 14 (Follow Up Call 2)	100_479	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	1002_1007	
	Day 14 (Follow Up Call 2)	1090_1274	
	Day 14 (Follow Up Call 2)	39_96	
	Day 14 (Follow Up Call 2)	495_555	509
	Day 14 (Follow Up Call 2)	689_871	
	Baseline (Day 0)	236_248	
	Baseline (Day 0)	260_266	
	Baseline (Day 0)	268_282	
	Baseline (Day 0)	239_244	
	Baseline (Day 0)	272_282	
	Day 7 (Follow Up Call 1)	122_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 14 (Follow Up Call 2)	1_114	
	Day 14 (Follow Up Call 2)	1190_1274	
	Day 14 (Follow Up Call 2)	149_159	
	Day 14 (Follow Up Call 2)	162_167	
	Day 14 (Follow Up Call 2)	191_210	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 14 (Follow Up Call 2)	235_467	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	593_873	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	235_286	
	Day 14 (Follow Up Call 2)	1090_1166	
	Day 14 (Follow Up Call 2)	133_211	
	Day 14 (Follow Up Call 2)	221_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_768	
	Day 7 (Follow Up Call 1)	236_283	
	Day 28 (Follow Up Call 3)	235_287	
	Day 28 (Follow Up Call 3)	396_462	440, 441
	Day 28 (Follow Up Call 3)	690_766	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	236_283	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	235_286	
	Day 14 (Follow Up Call 2)	236_283	
	Baseline (Day 0)	235_283	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	312_333	332, 333
	Baseline (Day 0)	367_386	
	Baseline (Day 0)	391_464	440, 441
	Baseline (Day 0)	691_766	
	Day 7 (Follow Up Call 1)	1090_1168	
	Day 7 (Follow Up Call 1)	119_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	690_769	
	Baseline (Day 0)	275_281	
	Baseline (Day 0)	236_251	
	Baseline (Day 0)	254_283	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	236_283	
	Day 28 (Follow Up Call 3)	236_283	
	Day 7 (Follow Up Call 1)	131_181	
	Day 7 (Follow Up Call 1)	183_188	
	Day 7 (Follow Up Call 1)	191_208	
	Day 7 (Follow Up Call 1)	235_400	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Baseline (Day 0)	133_167	
	Baseline (Day 0)	191_210	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Baseline (Day 0)	232_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Baseline (Day 0)	690_767	
	Baseline (Day 0)	235_284	
	Baseline (Day 0)	420_453	440, 441
	Baseline (Day 0)	455_460	
	Baseline (Day 0)	698_708	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	316_330	
	Day 7 (Follow Up Call 1)	359_462	359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	693_741	
	Day 7 (Follow Up Call 1)	743_765	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	316_331	
	Day 7 (Follow Up Call 1)	394_463	440, 441
	Day 7 (Follow Up Call 1)	693_762	
	Day 14 (Follow Up Call 2)	235_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_767	
	Day 28 (Follow Up Call 3)	1089_1113	
	Day 28 (Follow Up Call 3)	1115_1168	
	Day 28 (Follow Up Call 3)	120_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	689_873	
	Baseline (Day 0)	274_281	
	Day 7 (Follow Up Call 1)	235_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Baseline (Day 0)	236_286	
	Baseline (Day 0)	370_376	
	Day 7 (Follow Up Call 1)	134_175	
	Day 7 (Follow Up Call 1)	177_209	
	Day 7 (Follow Up Call 1)	235_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	690_767	
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	411_427	
	Baseline (Day 0)	1_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Baseline (Day 0)	1000_1065	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Baseline (Day 0)	1195_1259	
	Baseline (Day 0)	690_871	
	Baseline (Day 0)	235_290	
	Baseline (Day 0)	310_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Baseline (Day 0)	690_767	
	Day 7 (Follow Up Call 1)	121_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_768	
	Day 7 (Follow Up Call 1)	896_957	
	Baseline (Day 0)	267_283	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	1_476	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	1069_1175	
	Day 14 (Follow Up Call 2)	687_788	
	Day 14 (Follow Up Call 2)	796_846	
	Day 14 (Follow Up Call 2)	851_869	
	Baseline (Day 0)	236_284	
	Baseline (Day 0)	412_431	
	Baseline (Day 0)	719_730	
	Day 7 (Follow Up Call 1)	236_284	
	Day 7 (Follow Up Call 1)	312_328	
	Day 7 (Follow Up Call 1)	690_766	
	Day 14 (Follow Up Call 2)	1000_1065	
	Day 14 (Follow Up Call 2)	122_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	689_872	
	Baseline (Day 0)	254_283	
	Day 14 (Follow Up Call 2)	1194_1274	
	Day 14 (Follow Up Call 2)	121_478	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	587_787	
	Day 14 (Follow Up Call 2)	999_1065	
	Baseline (Day 0)	274_283	
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	312_404	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	423_460	440, 441
	Day 7 (Follow Up Call 1)	690_766	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 14 (Follow Up Call 2)	121_467	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_767	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	395_463	440, 441
	Baseline (Day 0)	690_766	
	Day 7 (Follow Up Call 1)	236_283	
	Day 7 (Follow Up Call 1)	273_282	
	Day 14 (Follow Up Call 2)	234_308	
	Day 14 (Follow Up Call 2)	337_465	337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_767	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	413_427	
	Day 14 (Follow Up Call 2)	235_284	
	Day 14 (Follow Up Call 2)	411_462	440, 441
	Day 14 (Follow Up Call 2)	693_718	
	Day 14 (Follow Up Call 2)	721_729	
	Day 14 (Follow Up Call 2)	732_741	
	Day 14 (Follow Up Call 2)	743_756	
	Baseline (Day 0)	259_283	
	Day 7 (Follow Up Call 1)	192_207	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	315_333	332, 333
	Day 7 (Follow Up Call 1)	359_463	359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	693_757	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	256_283	
	Day 7 (Follow Up Call 1)	235_284	
	Baseline (Day 0)	268_282	
	Day 7 (Follow Up Call 1)	236_285	
	Day 7 (Follow Up Call 1)	693_708	
	Day 7 (Follow Up Call 1)	710_715	
	Day 7 (Follow Up Call 1)	732_741	
	Day 7 (Follow Up Call 1)	743_756	
	Day 14 (Follow Up Call 2)	1090_1166	
	Day 14 (Follow Up Call 2)	122_286	
	Day 14 (Follow Up Call 2)	396_463	440, 441
	Day 14 (Follow Up Call 2)	595_767	
	Baseline (Day 0)	236_244	
	Baseline (Day 0)	274_281	
	Baseline (Day 0)	274_281	
	Day 7 (Follow Up Call 1)	236_284	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	411_462	440, 441
	Day 7 (Follow Up Call 1)	693_718	
	Day 7 (Follow Up Call 1)	733_740	
	Day 28 (Follow Up Call 3)	235_283	
	Baseline (Day 0)	236_248	
	Baseline (Day 0)	274_281	
	Day 7 (Follow Up Call 1)	197_203	
	Day 7 (Follow Up Call 1)	235_298	
	Day 7 (Follow Up Call 1)	308_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_766	
	Day 14 (Follow Up Call 2)	121_478	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	497_555	509
	Day 14 (Follow Up Call 2)	690_768	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	1_472	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	1090_1168	
	Day 14 (Follow Up Call 2)	589_957	
	Baseline (Day 0)	273_282	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	1_479	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	1091_1101	
	Day 14 (Follow Up Call 2)	1118_1257	
	Day 14 (Follow Up Call 2)	491_555	509
	Day 14 (Follow Up Call 2)	689_772	
	Day 14 (Follow Up Call 2)	927_957	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	235_283	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	312_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Baseline (Day 0)	692_766	
	Day 7 (Follow Up Call 1)	193_208	
	Day 7 (Follow Up Call 1)	235_291	
	Day 7 (Follow Up Call 1)	311_463	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_766	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	236_250	
	Day 7 (Follow Up Call 1)	260_282	
	Day 14 (Follow Up Call 2)	1090_1166	
	Day 14 (Follow Up Call 2)	235_287	
	Day 14 (Follow Up Call 2)	313_331	
	Day 14 (Follow Up Call 2)	395_555	440, 441, 509
	Day 14 (Follow Up Call 2)	690_767	
	Day 14 (Follow Up Call 2)	897_957	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	359_366	359, 360, 361
	Day 7 (Follow Up Call 1)	370_464	440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 14 (Follow Up Call 2)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	689_874	
	Day 14 (Follow Up Call 2)	927_942	
	Day 14 (Follow Up Call 2)	950_973	
	Day 14 (Follow Up Call 2)	996_1274	
	Baseline (Day 0)	275_283	
	Day 7 (Follow Up Call 1)	236_283	
	Day 28 (Follow Up Call 3)	1_783	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	796_804	
	Day 28 (Follow Up Call 3)	829_852	
	Day 28 (Follow Up Call 3)	860_869	
	Day 28 (Follow Up Call 3)	896_1274	
	Baseline (Day 0)	236_251	
	Baseline (Day 0)	256_283	
	Day 7 (Follow Up Call 1)	148_158	
	Day 7 (Follow Up Call 1)	162_172	
	Day 7 (Follow Up Call 1)	183_210	
	Day 7 (Follow Up Call 1)	235_290	
	Day 7 (Follow Up Call 1)	309_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	698_767	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	422_451	440, 441
	Day 7 (Follow Up Call 1)	122_412	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	690_1259	
	Day 7 (Follow Up Call 1)	236_286	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 14 (Follow Up Call 2)	1_112	
	Day 14 (Follow Up Call 2)	1000_1065	
	Day 14 (Follow Up Call 2)	1195_1274	
	Day 14 (Follow Up Call 2)	235_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	562_788	
	Day 14 (Follow Up Call 2)	796_871	
	Baseline (Day 0)	275_283	
	Day 7 (Follow Up Call 1)	1000_1065	
	Day 7 (Follow Up Call 1)	13_104	
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	337_464	337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	4_10	
	Day 7 (Follow Up Call 1)	595_766	
	Baseline (Day 0)	1_1274	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	1000_1065	
	Day 7 (Follow Up Call 1)	1194_1259	
	Day 7 (Follow Up Call 1)	122_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	689_789	
	Day 7 (Follow Up Call 1)	792_872	
	Day 14 (Follow Up Call 2)	1_114	
	Day 14 (Follow Up Call 2)	122_1274	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	236_284	
	Baseline (Day 0)	238_248	
	Baseline (Day 0)	269_282	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_333	332, 333
	Day 7 (Follow Up Call 1)	359_386	359, 360, 361
	Day 7 (Follow Up Call 1)	391_403	
	Day 7 (Follow Up Call 1)	411_463	440, 441
	Day 7 (Follow Up Call 1)	693_765	
	Baseline (Day 0)	236_283	
	Day 14 (Follow Up Call 2)	236_283	
	Day 28 (Follow Up Call 3)	1126_1136	
	Day 28 (Follow Up Call 3)	1140_1165	
	Day 28 (Follow Up Call 3)	121_466	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 28 (Follow Up Call 3)	690_767	
	Baseline (Day 0)	274_281	
	Day 7 (Follow Up Call 1)	198_203	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_345	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345
	Day 7 (Follow Up Call 1)	355_464	356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	693_765	
	Day 14 (Follow Up Call 2)	1090_1166	
	Day 14 (Follow Up Call 2)	138_210	
	Day 14 (Follow Up Call 2)	229_469	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_768	
	Day 7 (Follow Up Call 1)	196_204	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 14 (Follow Up Call 2)	1_489	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	1150_1164	
	Day 14 (Follow Up Call 2)	491_555	509
	Day 14 (Follow Up Call 2)	690_777	
	Day 14 (Follow Up Call 2)	896_1065	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	411_463	440, 441
	Day 7 (Follow Up Call 1)	121_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	690_769	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	236_251	
	Baseline (Day 0)	256_282	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	194_203	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Baseline (Day 0)	236_251	
	Baseline (Day 0)	256_283	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	133_210	
	Day 14 (Follow Up Call 2)	227_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_767	
	Baseline (Day 0)	235_284	
	Baseline (Day 0)	423_441	440, 441
	Baseline (Day 0)	445_460	
	Day 7 (Follow Up Call 1)	1_556	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 7 (Follow Up Call 1)	689_1274	
	Baseline (Day 0)	236_251	
	Baseline (Day 0)	256_283	
	Day 7 (Follow Up Call 1)	235_286	
	Day 7 (Follow Up Call 1)	412_460	440, 441
	Day 14 (Follow Up Call 2)	1194_1273	
	Day 14 (Follow Up Call 2)	120_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	689_1186	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	236_249	
	Day 7 (Follow Up Call 1)	260_266	
	Day 7 (Follow Up Call 1)	269_282	
	Day 14 (Follow Up Call 2)	236_283	
	Day 28 (Follow Up Call 3)	235_287	
	Day 28 (Follow Up Call 3)	394_462	440, 441
	Day 28 (Follow Up Call 3)	718_736	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_284	
	Day 7 (Follow Up Call 1)	423_459	440, 441
	Baseline (Day 0)	1128_1136	
	Baseline (Day 0)	1140_1165	
	Baseline (Day 0)	122_400	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Baseline (Day 0)	524_555	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	316_325	
	Day 7 (Follow Up Call 1)	359_463	359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_766	
	Day 14 (Follow Up Call 2)	236_284	
	Day 14 (Follow Up Call 2)	423_460	440, 441
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	235_284	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	411_460	440, 441
	Day 7 (Follow Up Call 1)	693_766	
	Day 14 (Follow Up Call 2)	236_284	
	Baseline (Day 0)	236_250	
	Baseline (Day 0)	256_283	
	Day 7 (Follow Up Call 1)	235_398	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 14 (Follow Up Call 2)	236_284	
	Day 14 (Follow Up Call 2)	411_431	
	Day 28 (Follow Up Call 3)	235_287	
	Day 28 (Follow Up Call 3)	383_463	440, 441
	Day 28 (Follow Up Call 3)	717_766	
	Day 7 (Follow Up Call 1)	275_282	
	Day 14 (Follow Up Call 2)	121_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	690_1274	
	Day 28 (Follow Up Call 3)	1_555	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	1195_1274	
	Day 28 (Follow Up Call 3)	562_789	
	Day 28 (Follow Up Call 3)	796_1187	
	Baseline (Day 0)	236_400	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	235_462	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	719_737	
	Day 28 (Follow Up Call 3)	1_1274	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	236_284	
	Day 14 (Follow Up Call 2)	693_718	
	Day 14 (Follow Up Call 2)	743_762	
	Baseline (Day 0)	236_284	
	Baseline (Day 0)	411_459	440, 441
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	311_464	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	692_766	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	359_464	359, 360, 361, 440, 441
	Baseline (Day 0)	714_767	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	312_334	332, 333, 334

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 7 (Follow Up Call 1)	359_463	359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_767	
	Day 14 (Follow Up Call 2)	1_1274	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_283	
	Baseline (Day 0)	236_283	
	Baseline (Day 0)	236_283	
	Day 7 (Follow Up Call 1)	235_287	
	Day 7 (Follow Up Call 1)	394_462	440, 441
	Day 14 (Follow Up Call 2)	235_460	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_767	
	Day 28 (Follow Up Call 3)	1_957	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	1090_1274	
	Baseline (Day 0)	235_287	
	Baseline (Day 0)	374_403	
	Day 7 (Follow Up Call 1)	235_462	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 7 (Follow Up Call 1)	690_766	
	Day 14 (Follow Up Call 2)	1_1186	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 14 (Follow Up Call 2)	1195_1274	
	Baseline (Day 0)	310_396	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 7 (Follow Up Call 1)	308_398	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 14 (Follow Up Call 2)	308_398	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 28 (Follow Up Call 3)	235_404	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361
	Day 28 (Follow Up Call 3)	426_441	440, 441
	Day 28 (Follow Up Call 3)	444_459	
	Day 7 (Follow Up Call 1)	267_283	
	Baseline (Day 0)	236_284	
	Baseline (Day 0)	413_419	
	Baseline (Day 0)	254_283	
	Day 7 (Follow Up Call 1)	235_284	
	Day 14 (Follow Up Call 2)	133_210	
	Day 14 (Follow Up Call 2)	233_462	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Day 14 (Follow Up Call 2)	692_766	
	Day 28 (Follow Up Call 3)	119_467	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 28 (Follow Up Call 3)	1195_1274	
	Day 28 (Follow Up Call 3)	689_872	
	Baseline (Day 0)	236_285	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	120_465	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Day 14 (Follow Up Call 2)	690_1163	
	Day 28 (Follow Up Call 3)	1_788	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	796_1274	
	Day 7 (Follow Up Call 1)	235_286	
	Day 7 (Follow Up Call 1)	411_431	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2)	236_283	
	Day 14 (Follow Up Call 2)	411_462	440, 441
	Day 14 (Follow Up Call 2)	693_715	
	Day 14 (Follow Up Call 2)	743_751	
	Day 28 (Follow Up Call 3)	236_287	
	Day 28 (Follow Up Call 3)	393_402	
	Baseline (Day 0)	235_284	
	Day 7 (Follow Up Call 1)	236_283	
	Day 14 (Follow Up Call 2	235_283	
	Baseline (Day 0)	235_283	
	Day 7 (Follow Up Call 1)	236_287	
	Day 7 (Follow Up Call 1)	315_330	
	Day 7 (Follow Up Call 1)	370_377	
	Day 7 (Follow Up Call 1)	391_463	
	Day 7 (Follow Up Call 1)	700_707	
	Day 14 (Follow Up Call 2)	122_1259	332, 333, 334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441, 509
	Day 28 (Follow Up Call 3)	235_284	
	Day 28 (Follow Up Call 3)	411_451	440, 441
	Day 28 (Follow Up Call 3)	453_462	
	Baseline (Day 0)	235_283	
	Baseline (Day 0)	235_283	
	Baseline (Day 0)	235_332	
	Baseline (Day 0)	334_463	334, 335, 336, 337, 339, 340, 341, 343, 344, 345, 346, 354, 356, 357, 358, 359, 360, 361, 440, 441
	Baseline (Day 0)	690_766	

Participant ID	Visit	Amino Acid Positions of Sequencing Gaps	Gap Overlap with Sotrovimab Epitope
PPD	Baseline (Day 0)	235_293	
	Baseline (Day 0)	370_398	

Source: Listing 1.28.

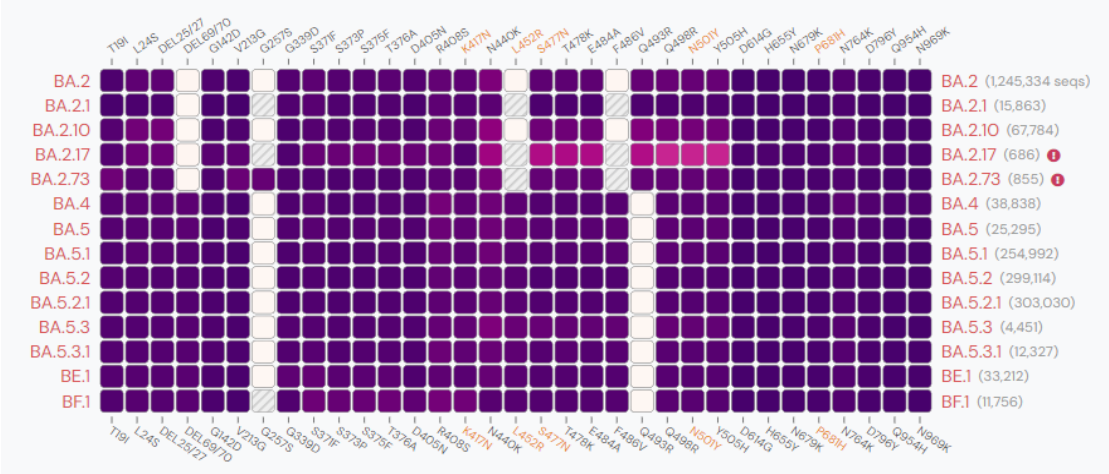
Table 45 Summary of Important Protocol Deviations

Deviation Type	Overall (N=217) n (%)
Any important protocol deviations	52 (24.0)
ELIGIBILITY CRITERIA NOT MET	2 (0.9)
Eligibility criteria not met	2 (0.9)
INFORMED CONSENT	1 (0.5)
Wrong consent/assent version	1 (0.5)
OTHER PROTOCOL DEVIATION CATEGORY	7 (3.2)
Other deviation from study procedures	7 (3.2)
STUDY PROCEDURES	30 (13.8)
Biological sample specimen procedures	3 (1.4)
Lid of swab tube was not secured tightly causing total leakage of VTM. Insufficient VTM for processing and storage.	2 (0.9)
Participant has returned more samples than expected	2 (0.9)
Participant returned more samples than expected	1 (0.5)
RNA extraction failure	1 (0.5)
Sample received late at GOSH	19 (8.8)
Sample was received late at GOSH	1 (0.5)
Swab tube was received empty	1 (0.5)
VISIT, ASSESSMENT OR TIMEPOINT WINDOW	24 (11.1)
Out of window assessment	24 (11.1)

Source: Table 1.39

ADDITIONAL POST-TEXT FIGURES

Figure 19 Comparison of Spike Sequences in the SARS-CoV-2 Viral Variants Identified by Whole Genome Sequences



Source : Outbreak.info on (08 November -2023) ; [Khare, 2021; Gangavarapu, 2023].

Box color varies on a scale between white and dark purple to represent the increasing prevalence of each substitution in the lineage. White boxes represent a prevalence of 0%. Dark purple represents a prevalence of 100%. Boxes with diagonal stripes depict a substitution that is not found the lineage. Sequences were accessed on 08 November 2023.

ADDITIONAL POST-TEXT METHODS

Process to create AA substitution analysis pipeline for LUNAR study (218407)

This document describes the steps and procedures to produce AA substitution data from raw sequencing data ('fastq' files) generated by UCL and transferring the resulting file ('PF file') to Syneos for further analysis.

AA substitution calling was centered on the approach used for the GENCOV pipeline [Jacot, 2021]] and is dependent on the following tools [GNU Bash, 2020; Barnett, 2011; Cingolani, 2012b; Chen, 2018; Danecek, 2021;BASH, 2023; GitHub, 2024a; Github, 2024b; Broadinstitute, 2024; GitHub; 2024d]:

- bash
- fastp
- bwa
- samtools
- bamtools
- picard
- freebayes
- bcftools
- snpeff

All dependencies (with exception of bash) were install into individual anaconda python3.6 environments then added to .bashrc (bash configuration file)

Pipeline steps (based on NC_045512.2 (equivalent to MN908947.3) genome):

1. Read trimming and mapping (fastp > bwa > samtools > bamtools)

- Removal of illumina sequencing adaptors
- Removal of low complexity regions
- Removal of low-quality stretches
- fastp paramaters:
    - qualified_quality_phred 20
    - length_required 50
    - low_complexity_filter
    - overrepresentation_analysis

2. Samtools mpileup (used for downstream gap identification)

- Parameters:
    - A

- min_MQ 10
- min_BQ 0
- d 0

3. Variant calling (freebayes)

- Parameters:
  - pooled-continous
  - min-alternate-fraction 0.01
  - min-coverage 500
  - min-alternate-count 1
  - min-base-quality 20
  - min-mapping-quality 10
  - haplotype-length 3
  - p 1

4. Left alignment and normalization (bcftools)

- Parameters:
  - norm
  - m
  - both

5. Variant annotation (snpeff)

- Parameters:
  - ann
  - nodownload
  - formatEff
  - classic
  - noStats
  - noLog
  - quiet
  - no-upstream
  - no-downstream

6. Variable extraction (bcftools)

- Parameters:
  - query

- f'%CHROM %POS %ID %REF %ALT %QUAL %MQM %AF %AB %AO %RO %DP %QA %SAF %SAR %EFF\n'

7. Addition of ID column containing provided sample name (sed)
8. PF table creation

- STUDYID, USUBJID, and VISITNUM are derived from filename
- Filter for Spike Region using position (start = 21563, end = 25384)
- Various calculations:
  - Alternate allele frequency ((AO/DP) * 100)
  - Variant average quality (QA/AO)
  - Variant forward reverse score (SAF/SAR)
    - Small pseudo count of 1E-8 added to SAR for above calculation (values > 9999999 are annotated as "> 9999999")
  - Identifying start/end of spike protein (21563 – 25384)
  - AA position (converting nucleotide position to AA location)
  - Gap identification
    - Identify segments where average number of reads (#reads for 3 nucleotides making up AA/3 is below 500
    - Gaps called only for regions that span 6 or more AAs to ensure deletion calls are not mis-specified
- STUDYID, USUBJID, and VISITNUM are used as join keys to extract ARM, PFREFID, and PFDTC from UCL sample manifest
- PFRESCAT attributes are further simplified into 4 major categories (SUBSTITUTION, DELETION, REFERENCE, or GAP)
  - MISSENSE -> SUBSTITUTION
  - SILENT -> REFERENCE
  - NONSENSE -> SUBSTITUTION
  - NON_SYNONYMOUS_CODING+CODON_DELETION -> DELETION
  - FRAME_SHIFT+NON_SYNONYMOUS_CODING-> SUBSTITUTION
  - NON_SYNONYMOUS_CODING+CODON_CHANGE_PLUS_CODON_DELETION -> DELETION
  - STOP_GAINED+CODON_CHANGE_PLUS_CODON_DELETION -> DELETION
  - CODON_CHANGE_PLUS_CODON_DELETION -> DELETION
  - NON_SYNONYMOUS_CODING -> SUBSTITUTION
  - FRAME_SHIFT+STOP_GAINED -> SUBSTITUTION

- FRAME_SHIFT -> DELETION
- CODON_DELETION -> DELETION
- STOP_GAINED -> SUBSTITUTION

Updates completed for EoS analysis:

Merging of identical substitutions and deconvolution of complex substitutions:

The current pipeline described above may produce seemingly duplicated AA substitutions with differing allelic frequencies. This reflects differences in the underlying nucleotide changes. We will correct for this by converting MNPs to SNPs prior to annotation. In scenarios where identical output AA substitutions are encountered it will be required to merge and sum alternate allele counts and allelic depths to ensure overall frequencies are conserved and sum to 1 then manually; this update will also lead to deconvolution of complex substitutions that are currently present in the PF table (e.g. GVY142DV would become G142D and Y144).

LUNAR processing of amplicon raw sequencing data

Amplicon raw sequencing data generated from Illumina sequencing platforms (MiniSeq, MiSeq, NextSeq) were demultiplexed based on a sample sheet to output paired Fastq files for each sample. The demultiplexed Fastq along with a metadata sample sheet form the input to the analysis pipeline. **nf-core/viralrecon** is the pipeline used for LUNAR sequences, the pipeline is built using Nextflow, a workflow tool to run tasks across multiple compute infrastructures in a very portable manner [Patel, 2023a]). Detailed description of the stages of the pipeline are as follows:

1. Pre-processing

Read QC (FastQC) step provides a simple way to do quality control checks on raw sequence data coming from high throughput sequencing pipelines. It imports data from fastQ files and outputs graphs and tables allowing assess of the data [Andrews, 2023]. **Adapter trimming** (fastp) step produce comprehensive quality profiling for both before and after filtering data, filter out bad reads, cut low quality bases for per read in its 5' and 3' by evaluating the mean quality from a sliding window, trim all reads in front and tail, cut adapters, correct mismatched base pairs in overlapped regions of paired end reads (if one base is with high quality while the other is with ultra low quality trim polyG in 3' ends, which is commonly seen in NovaSeq/NextSeq data) [Chen, 2018]

2. Alignment and BAM post-processing

Read alignment (Bowtie2) step [Langmead, 2012] aligns fastq files to SARS-CoV-2 reference (MN908947.3) producing BAM files which are then piped to the **sort and index alignments** (Samtools) step, to sort them by coordinate, for indexing, as well as to generate read mapping statistics [Danecek, 2021]. The next step is the **primer sequence removal** (iVar) to trim amplicon primer sequences from the aligned reads. iVar uses ARTIC primer 4.1 positions supplied in a BED file to soft clip primer sequences from previously aligned and sorted BAM files by using a sliding window approach (Basically the windows slides

from the 5' end to the 3' end and if at any point the average base quality in the window falls below the threshold, the remaining read is soft clipped. If after trimming, the length of the read is greater than the minimum length specified, the read is written to the new trimmed BAM file) [Grubaugh, 2019]. **Duplicate read marking** (picard) step which locates and tags duplicate reads in a BAM file [Broadinstitute, 2024].

3. SARS-CoV-2 Viral Variant Calling by Whole Genome Sequencing

SARS-CoV-2 viral variant calling (iVar) was performed using iVar tool as contains functions broadly useful for viral amplicon-based sequencing [Grubaugh, 2019], followed by **Variant annotation** (snpEFF and SnpSift) step. snpEFF annotates and predicts the effects of genetic variants on genes and proteins and SnpSift help filter large genomic datasets in order to find the most significant variants [Cingolani, 2012a; Cingolani, 2012b] .

4. Consensus calling

iVar was used in this pipeline to call variants and for the **consensus** sequence generation (iVar) with the following parameters: Minimum frequency threshold of 0.5; minimum quality score threshold to count base of 30; minimum read depth to call variants of 10 [Grubaugh, 2019]. A **Consensus assessment report** was also generated as a single report allowing to evaluate the quality of the consensus sequence [Gurevich, 2013; Mikheenko, 2018]. **Lineage analysis** (Pangolin) step to assign lineages to SARS-CoV-2 genome sequenced sample [GitHub, 2024c]. **Clade assignment, mutation calling and sequence quality checks** (Nextclade) step to perform viral genome clade assignment, mutation calling and sequence quality checks for the consensus sequences generated [Aksamentov, 2021]. Finally, variants long format table was generated, collating per-sample information for individual variants (iVar), functional effect prediction (SnpSift) and lineage analysis (Pangolin).

5. Final QC

Present QC and visualization for raw read, alignment, assembly and viral variant calling results [Ewels,2016].

A PF report file was shared with Syneos as per DIA version 3. The following files per samples were shared with GSK: raw data (fastq files), sorted BAM files, vcf files, and consensus files.

Additional Details for Hospitalized Patients

Sex -Subject Age Race Status	Date of Dose	Date of admission/ Reason for admission	Date of Discharge	Duration in hospital (Days)	Comorbidities	Concomitant medications
PPD Completed	PPD 2022	PPD 2022/ Breathlessness day after infusion not related to sotrovimab as confirmed by study doctor and PI	PPD 2022	4	Diabetes mellitus, Glaucoma, High Cholesterol, T2DM, Non-Hodgkin's Lymphoma, Insomnia, Lung Cancer, Osteoporosis	Calceos, Pembrolizumab, Simvastatin, Promethazine Hydrochloride, Latanoprost, Sodium Hyaluronate, Doxycycline, Magnesium powder (NOS)
PPD Completed	PPD 2022	PPD 2022/ Pain, poor appetite, ascites and constipation	Not available	Not available	Hypertension, High cholesterol, Renal transplant 2012, Gynaecological cancer diagnosed – likely ovarian, IgG kappa para-protein, Hysterectomy, G6PD, Hypertension	Amlodipine, Lactulose, Sodium docusate, Amitriptyline, calcium carbonate, Oromorph, Atorvastatin, Bisoprolol, Irbesartan, Aspirin, Adaport, Mycophenolate, Prednisolone (COVID), Vitamin
PPD Withdrawal by Subject PPD 2022	PPD 2022	PPD 2022/ Unknown, but unrelated to COVID-19	Not available Withdrew from study on PPD 2022(burden of procedures) and date of discharge not recorded in medical records	Not available	Obesity, Cardiovascular disease, Hypertension Other chronic respiratory disease, Diabetes mellitus, High cholesterol, Interstitial lung disease, Hypothyroidism, Bronchiecstasis, Rheumatoid arthritis, Osteopenia, Chronic Hepatitis C infection, T2DM, Hypertension, Ischaemic heart disease	Celecoxib, Irbesartan, Entecavir, Ivabradine, Atorvastatin, Angitil SR, Clopidogrel, Levothyroxine, Rituximab, Promixin, GTN spray, Prednisolone, Vilanterol Laba (Umeclidinium LAMA), Ranolizine MR, Adcal D3 (calcium carbonate and vitamin D3 (200iu, equivalent to

Sex -Subject Age Race Status	Date of Dose	Date of admission/ Reason for admission	Date of Discharge	Duration in hospital (Days)	Comorbidities	Concomitant medications
						10Î¼g cholecalciferol), Glucophage SR, Aspirin, Clotrimazole 1% cream, Empagliflozin, Ozempic, Lansoprazole
PPD Completed	PPD 2022	Not available/ Blocked urethra	Not available	Not available	Other renal diseases, Chronic kidney disease, Diabetes mellitus, Sarcoidosis with Pulmonary fibrosis, Diabetes Mellitus Type II– steroid induced, Renal transplant	Alfacalcidol (Vitamin D Analogues, Tacrolimus, Prednisolone, Mycophenolate mofetil, Calcichew, Co-Amoxiclav, ciprofloxacin from 20/12/22 until 29/12/22; Humulin M3; Allopurinol; Atorvastatin, Domperidone, Folic acid, Sodium bicarbonate, Omeprazole
PPD PPD 2022	PPD 2022	PPD 2022/ Decompensated type 2 respiratory failure due to chest infection on background of declining myotonic dystrophy, as well as aspiration pneumonia	PPD 2022PPD	10	Other immune deficiencies, Cardiovascular disease, Other chronic respiratory disease: Myotonic dystrophy with. ventilatory failure	Hypromellose, Beclometasone, Cetirizine, Carbocisteine, furosemide, Apixaban, bisoprolol, Atorvastatin, Ramipril
PPD Completed	PPD 2022	PPD 2022/ Initial reason for hospitalization was dehydration. Patient had routine bloods done as an outpatient which confirmed severe dehydration, patient	Not available	Not available (patient wasn't discharged before the end of the study follow-up period)	Sigmoid colon cancer Cerebrovascular disease Hypertension Hypertension Diverticular disease CVA 2018	Apixaban, Finastaride, isosorbide mononitrate, alfuzosin, lansoprazole, Furosemide, atorvastatin,paracetamol, capecitabine

Sex -Subject Age Race Status	Date of Dose	Date of admission/ Reason for admission	Date of Discharge	Duration in hospital (Days)	Comorbidities	Concomitant medications
		was then admitted the same day for fluid			Ischaemic heart disease-CABG 2018. Atrial fibrillation. HFrEF-ECHO March Severe heart failure	
PPD Completed		PPD Unknown but unrelated to COVID-19	Not available	Not available (patient wasn't discharged before the end of the study follow-up period)	Hypogammaglobulinemia, Granulomatous liver disease	Chest infection. Decompensated liver disease

Abbreviation: CABG= Coronary artery bypass graft, COVID-19= Coronavirus disease 2019, CVA= Cerebrovascular accident, G6PD =Glucose-6-phosphate dehydrogenase, GTN= Glyceryl trinitrate, HFrEF-ECHO = Heart failure with reduced ejection fraction-electrocardiogram, LAMA= Long-acting muscarinic antagonist, MR= Modified release, NOS= Nitric oxide synthase SR= Sustained release, T2DM= Type 2 diabetes mellitus.

Note: Except for patient PPD information obtained by direct communication with sites as it was not collected in the eCRF. Reason for hospitalization was not collected in the eCRF until post-interim.

TITLE PAGE

Division: Pharma Research and Development
Information Type: Epidemiology PASS 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

Compound Number:	GSK4182136
Development Phase	IV
Effective Date:	24 January 2023
Subject:	SARS-CoV-2 infection
Author(s):	PPD

Indication Studied: Early treatment for SARS-CoV-2 infection

PASS information *

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 identifier	Version 2
Date of last version of protocol	04 May 2022
EU PAS (ENCEPP) register number	EUPAS46386
Active substance	Sotrovimab [recommended INN] (also known as VIR-7831 and GSK4182136) ATC code: J06BD05
Medicinal product	Xevudy™ 500 mg concentrate for solution for infusion
Product reference	PLGB 19494/0301
Procedure number	N/A
Marketing authorisation holder(s)	GlaxoSmithKline UK Limited 980 Great West Road Brentford Middlesex TW8 9GS UK
Joint Post Authorisation Safety Study **PASS**	No

Research question and objectives	Amongst immunocompromised non-hospitalised patients treated with sotrovimab as part of standard clinical care: 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 the Severe Acute Respiratory Syndrome Coronavirus 2 (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

Country of study	Great Britain
Author	PPD , PhD, PharmD, MPH PPD , Value Evidence and Outcomes

MARKETING AUTHORISATION HOLDER(S) *

Marketing authorisation holder(s)	GlaxoSmithKline UK Limited 980 Great West Road Brentford Middlesex TW8 9GS UK
MAH contact person	PPD

TABLE OF CONTENTS

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1. LIST OF ABBREVIATIONS

AA	Amino Acid
ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
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
HSA	Health Security Agency
HSI	Human Safety Information
IC	Immunocompromised
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
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
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMP	Safety Management Plan
SOP	Standard Operating Procedure
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency
VOC	Variant of Concern
VUI	Variant Under Investigation
WHO	World health Organization

Trademark Information

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None

2. RESPONSIBLE PARTIES

Co-Principal Investigator: Professor Judith Breuer, University College London

Co-Principal Investigator: Dr David Mark Lowe, University College London

Qualified Person for Pharmacovigilance (QPPV): Heather Stein

SPONSOR SIGNATORY:

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

Compound Number: GSK4182136

PPD

Myriam Drysdale
Scientific Lead, Epidemiology, VEO, GSK

Date

PPD

Melissa Van Dyke
Immunology Head, Epidemiology, VEO, GSK

Date

Heather Stein
TA Head, Global Safety, GSK

Date

SPONSOR INFORMATION PAGE

Study ID: 218407

Sponsor Legal Registered Address and Sponsor Contact Address:

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980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Medical Monitor Contact Information: Medical Monitor Name and Contact Information will be provided separately

Sponsor Serious Adverse Events (SAE) Contact Information: Refer to Safety Management Plan (SMP)

Regulatory Agency Identifying Number(s): EudraCT number 2022-000754-29

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

_____

_____ _____

Date

Investigator Signature

_____ _____

STUDY ADVISORY COMMITTEE

N/A

3. ABSTRACT

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

Rationale and background

Sotrovimab was granted a conditional marketing authorisation for the treatment of early coronavirus disease 2019 (COVID-19) infection in Great Britain (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. Immunocompromised (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.

Research question and objective(s)

Amongst IC non-hospitalised patients treated with sotrovimab as part of standard clinical care:

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

Study design

Prospective cohort study

- 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.

Population, including the setting and study population

Inclusion criteria:

1. Adult patients ≥18-year-old
2. IC (as defined in the clinical commissioning policy [NHS England, 2022])
3. A positive PCR or antigen test for SARS-CoV-2 through clinical testing or routine screening undertaken as part of clinical management
4. Prescribed treatment with sotrovimab as standard of clinical care
5. Able to provide informed consent and willing to adhere to study-related procedures

Exclusion criteria:

1. Patients who require hospitalisation (related or not to COVID-19) at baseline
2. Patients who initiated sotrovimab therapy in in-patient settings
3. Patients unable to perform follow-up sample collection

4. Blinded patients from other COVID-19 related trials

From the Clinical Commissioning Policy, the following groups will also be excluded from this study unless also eligible for sotrovimab under other Clinical Commissioning Policy IC criteria not listed below [NHS England, 2022]*:*

5. Cohort of patients with rare neurological conditions
6. Cohort of patients with Down's syndrome
7. In the cohort of patients with renal disease::
    - Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m2) without immunosuppression (patients with renal disease cohort)
8. In the cohort of patients with liver disease:
    - Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease), class B or class C (decompensated liver disease)

The decision to treat patients with sotrovimab will be made prior to and independently from the decision to enroll patients into the study by the patient's healthcare team. This is to ensure that sotrovimab is prescribed as per standard of clinical care. The patient will then be screened and enrolled in the study with informed consent and baseline sample collection taken prior to sotrovimab administration or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion). A patient who declines to be enrolled in the study will still receive sotrovimab when eligible for the treatment.

Variables (for primary and secondary objectives)

- Exposure: Sotrovimab administration
- Primary endpoint:
    - Proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding in samples collected at Day 7, 14 and 28 (+/-2 days) (Primary Objective 1)
    - 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) (Primary Objective 2)
- Secondary endpoints:
    - Proportion of patients eligible for sequence analysis with VOC and VUI on the earliest possible sample including baseline (Secondary Objective 1)
    - Proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 2)
    - Clinical outcomes at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 3):
        - Proportion of patients that are admitted to hospital for any cause and for COVID-19 reasons
        - Proportion of patients requiring new or increased oxygen support

  - Proportion of patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
  - Proportion of all cause ICU admission
  - Proportion of all cause deaths and COVID-19 related deaths
- 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)
- 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)

Covariables:

Patient characteristics measured at baseline (demographics, number of days of COVID-19 symptoms (if symptomatic) and number of days since initial COVID-19 positive test result at time of receiving treatment, co-morbidities including immunocompromising condition, treatment history including immunosuppressant treatment, previous SARS-CoV-2 infections, COVID-19 vaccination status, serostatus if available, other treatment for COVID-19 including antivirals or other monoclonal antibodies).

Data sources:

After obtaining informed consent, inclusion/exclusion and baseline patient characteristics and treatment history data will be collected and documented. Any adverse event (AE) (serious and non-serious) observed during sotrovimab treatment (e.g., infusion-related reaction) and considered related to sotrovimab will be collected. Completion of baseline nasal/oropharyngeal sample collection and dispensing of at home lab kits to the patient will be completed and documented prior to patient discharge. Any baseline patient characteristics or treatment history unable to be collected during the baseline visit can be collected retrospectively from the patient or the patient's regular HCPs during the follow up period. Patients will receive a phone call at Day 7, 14 and 28 (+/- 2 days) to collect follow-up clinical outcomes and safety information (AEs) with a reminder for completion of at home nasal/oropharyngeal sample collection at the required timepoints. Participating sites may also contact patient's regular HCPs for clinical outcomes and safety information data as required. All baseline and follow-up data will be recorded in the electronic case report form (eCRF).

Virology data will be reported following the central analytical laboratory analysis of baseline, day 7, 14 and day 28 (+/-2 days) nasal/oropharyngeal samples as detailed in the statistical analysis plan (SAP).

Study size:

As a sentinel surveillance study, the aim will be to set up approximately 10 sites that are geographically spread across all 3 GB countries and collect data from a target of 500 (up to 625) patients over the course of a year. Flexible enrolment caps per site and per month may 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.

Data analysis:

Essential analyses

- Sequencing of samples on a regular basis (as detailed in the study laboratory manual) is required.
    - For patients eligible for sequencing analysis, proportion of patients with AA change from baseline in the epitope of sotrovimab (Primary Objective 1)
    - For patients eligible for sequencing analysis, proportion of patients with AA change from baseline in the spike protein (Primary Objective 2)
    - For samples with viral load above the threshold for allelic frequency determination, AA changes in SARS-CoV-2 spike protein at >5% allelic frequency compared to baseline will be reported as described in the SAP (Secondary Objective 4)
    - For samples with viral load below the threshold for low (5%) allelic frequency analysis, but above the threshold for consensus sequence generation, AA changes in the SARS-CoV-2 spike protein consensus sequence from baseline will be reported as described in the SAP (Secondary Objective 5)
- For patients eligible for sequencing analysis, VOC, VUI and other lineages information as classified by UKHSA (United Kingdom Health Security Agency) and WHO (World Health Organization) will be identified from sequencing data (Secondary Objective 1)
    - This analysis will be done on the earliest possible sample and reported only once per patient as described in the SAP
- Comorbidities, clinical outcomes, patients with undetectable virus and safety events data will be described and reported with counts and proportions (Secondary Objective 2 and 3).

Exploratory analyses

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])

Milestones:

Actual Study Start: First Patient First Visit – 21 June 2022
Estimated Study End: Last Patient Last Visit – 20 July 2023

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	03 May 2022	Abstract, Section 8.1 Table 1 Schedule of Activities, Section 8.2.1 Study population and setting, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections. "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**"	The Ethics committee requested more time for patients to review and sign the ICF. To avoid any delay in sotrovimab administration, it was agreed to collect the baseline nasal/oropharyngeal swab just after sotrovimab infusion if it is not possible to collect before. By allowing for the baseline sample to be collected soon after infusion, the patient will have additional time to evaluate their participation whilst still enabling a viable sample to be collected.
2	03 May 2022	Abstract and Section 5 Milestones	The text in bold was updated in the appropriate section: Estimated Study Start: First Patient First Visit **– 21 June 2022** Estimated Study End: Last Patient Last Visit **– 20 July 2023** Start of data collection: Estimated **June 2022** End data collection: Estimated **July 2023** Final report of study results: Estimated **November 2023**	The study start has been delayed and new timelines are now proposed in the amendment

3	20 January 2023	PASS information	The ATC code for sotrovimab, J06BD05, was added	Addition of ATC code
4	20 January 2023	PASS information	Correction of a formatting error that truncated secondary objective 5 in the section Research question and objectives	Correction following authority comment
5	20 January 2023	Abstract, Section 8.1 Table 1 Schedule of Activities, Section 8.2.1 Study population and setting, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections: "The nasal/oropharyngeal swab at baseline must be taken prior to the administration of sotrovimab **or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion)**"	Clarification of how long after the end of sotrovimab infusion the baseline swab can be taken
6	20 January 2023	Section 8.1 Table 1 Schedule of Activities, Section 8.6.1 Timing of assessment during follow-up	The text in bold was added in the relevant sections: "Persistent positive results will be reported back to the sites **upon site request** (as described in the study reference manual)."	Preference of sites
7	20 January 2023	Section 5 Milestones, Section 8.7.4 Interim Analysis	An interim analysis assessing the primary and secondary objectives was added	Health authority request
8	20 January 2023	Section 8.2 Study Population and Setting	Text in ~~strikethrough~~ was deleted: "It will be conducted for a period of 12 months in approximately 10 sites ~~selected following feasibility assessment from the list of COVID Medicine~~	Delivery of COVID-19 therapeutics to non-hospitalised patients is expected to become part of routine NHS services from April 2023 (https://www.england.nhs.uk/coronavirus/wp-

			~~Delivery Units (CMDUs [https://www.england.nhs.uk/coronavirus/publication/covid-medicine-delivery-unit-directory/])~~ in GB, or until the enrollment of 500 (up to 625) patients is met, or until sotrovimab is no longer used in GB, whichever comes first."	content/uploads/sites/52/2022/12/C1677-commissioning-framework-covid-19-therapeutics-for-non-hospitalised-patients.pdf)
9	20 January 2023	Abstract, Section 8.4 Data sources, Section 8.7.1.1 Primary objective, Section 8.7.1.2 Secondary objective, Section 8.7.3 General considerations for data analyses, Section 8.9 Limitations of the research methods	The term "reporting plan" was replaced with "statistical analysis plan"	The statistical analysis plan contains all details about what the study will report
10	20 January 2023	Abstract, Section 8.7.2 Exploratory Analyses	The third exploratory analysis was removed: "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"	Exploratory analysis no longer relevant and not feasible
11	20 January 2023	Abstract, Section 8.1 Study	The reference "MHRA. Central Alert System CAS-ViewAlert. Antivirals or	Updated recommendations for antiviral treatment in

		Design, Section 8.2.1 Inclusion criteria, Section 8.2.2 Exclusion criteria, Section 10 References	neutralising monoclonal antibodies (nMABs) for non-hospitalised patients with COVID-19 . 27 January 2022. CAS-ViewAlert (mhra.gov.uk)" was replaced with "NHS England. Coronavirus » Interim Clinical Commissioning Policy: Treatments for non-hospitalised patients with COVID-19. 28 November 2022"	non-hospitalised patients with COVID-19
12	20 January 2023	Section 6.1 Background, Section 10 References	The reference to the Summary of Product Characteristics for Xevudy (MHRA, 2021) was updated to GlaxoSmithKline UK, 2022	Updated version of Summary of Product Characteristics
13	20 January 2023	Throughout protocol	Minor corrections to punctuation have been made throughout the protocol	Administrative changes

5. MILESTONES

Milestone	Planned date
Start of data collection	June 2022
End of data collection	Estimated July 2023
Interim report of study results	Q2 2023
Registration in the EU PAS register	March 2022
Final report of study results	Estimated November 2023

6. RATIONALE AND BACKGROUND

6.1. Background

The novel beta-coronavirus SARS-CoV-2 (Coronavirus disease 2019 [COVID-19]) was first detected in December 2019, with initial reports of its emergence in Wuhan, China. Since this time, the virus, which can cause severe pneumonia in infected individuals, has spread throughout the world, causing unprecedented impacts on health, economy, and social security [Wu Z, 2020].

The spectrum of symptomatic COVID-19 ranges from mild disease without pneumonia to critical disease requiring hospitalisation with intensive care unit (ICU) care. As of 18 February 2022, approximately 18.5 million cases (people who have had at least one positive COVID-19 test result) and approximately 181,424 COVID-19 deaths have been recorded in the United Kingdom (UK) [GOV.UK, 2022]. The risk of hospital admission for a person detected as a case of Omicron appears to be reduced compared to a case of Delta [UKHSA, 2022].

COVID-19 vaccination remains the foundation for SARS-CoV-2 control, and vaccine effectiveness has reduced the magnitude of hospitalisations and deaths despite continued high viral circulation [Lopez Bernal J, 2021a; Lopez Bernal J, 2021b]. More than 48 million people in the UK have received at least two doses of vaccine and about 38 million have received a booster/third dose [GOV.UK, 2022]. Nonetheless, vaccine immunogenicity and effectiveness are lower in certain high-risk groups such as those with immunocompromising conditions [Chodick, 2021; Embi, P. J, 2021].

Sotrovimab (VIR-7831; GSK4182136) is a human neutralising anti-SARS-CoV-2 antibody which contains a 2 AA Fc-modification ("LS") that is designed to improve bioavailability in the respiratory mucosa and increase half-life. Sotrovimab binds to a conserved epitope on the SARS-CoV and SARS-CoV-2 spike protein outside the receptor-binding motif and has been shown to neutralise pseudovirus and live virus in several independent laboratories [Pinto, 2020]. This unique binding site may retain activity against emerging SARS-CoV-2 variants that may be resistant to other mAbs [Wang, 2021]. COMET-ICE, a randomised, double-blind, multi-centre, placebo-controlled trial of sotrovimab for the early treatment of COVID-19 in non-hospitalised patients, demonstrated 79% reduction in disease progression to hospitalisation or death

among patients treated with sotrovimab compared with placebo [Gupta A, 2021]. This single pivotal study supported the Marketing Authorisation Application (MAA) in Great Britain (GB).

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a conditional marketing authorisation for sotrovimab for the treatment of people with mild to moderate COVID-19 who are at high risk of developing severe disease [GlaxoSmithKline UK, 2022]. The final summary data on England's shielding list issued at the end of September 2021, showed that about 3.7 million individuals were included as being at highest risk for severe COVID-19, or about 6.5% of the population [NHS Digital, 2021; Office for National Statistics, 2021; Hippisley-Cox J, 2021]. Immunocompromised (IC) patients, a subset of the shielding list, are not only subject to increased risk of severe outcomes such as hospitalisation and mortality, but evidence also shows that this group are more likely to transmit the virus to their household contacts, leading to increased clusters of the virus. This population is also more likely to shed the virus for a longer duration, potentially increasing the risk of emergent variants [Lewis, 2021; Aydillo, 2020; Niyonkuru, 2021].

The impact of the recently detected Omicron variant on the effectiveness of vaccines and therapeutics is unknown pending further research, though very early findings suggest that the Omicron variant may have greater reinfection risk than Beta or Delta variants. *In vitro* studies of sotrovimab suggest that it retains antiviral activity against viral mutations in the spike proteins of Alpha, Beta, Gamma, Delta, Kappa, and Omicron BA.1 variants, whilst there is evidence of reduced antiviral activity of other currently authorised mAbs or vaccines [Torjesen, 2021; Pulliam, 2021; Cathcart, 2022]. In February 2022, GSK submitted preliminary *in vitro* data on the antiviral activity of sotrovimab against the BA.2 variant to the MHRA. These data are currently under assessment. GSK will provide all new relevant *in vitro* data on the variants of concern (VOC) and variants under investigation (VUI) of SARS-CoV-2 to the MHRA (UK). The protocol will not be updated for each new VOC or VUI, but GSK *in vitro* data will be published contemporaneously (e.g. in the Cathcart et al pre-print [Cathcart, 2022]).

The epitope to which sotrovimab binds is comprised of 23 AAs. Amino acids comprising the epitope are highly conserved with >99.68% conservation among >5,500,000 spike sequences from SARS-CoV-2 deposited in the GISAID database as of 15 December 2021 (https://www.gisaid.org). In vitro pseudotyped virus assessment shows that the epitope sequence polymorphisms P337H/K/L/R/T and E340A/K/G/Q/V confer reduced susceptibility to sotrovimab [Cathcart, 2022].

Sotrovimab is thus a potentially critical therapeutic in the fight against COVID-19, for which there remains a high unmet medical need despite the recent success of preventative measures such as vaccines. Challenges with access to vaccines, vaccine hesitancy, medical contraindications to vaccines, IC individuals who may not respond to a vaccine, and importantly, the potential emergence of variant viruses that escape vaccine-derived immunity, will all contribute to what is likely to be an unfortunately large and enduring number of COVID-19 cases in need of treatment.

IC individuals have been shown to be at higher risk of breakthrough infections and are at higher risk for hospitalisation and death despite high vaccine uptake [Di Fusco, 2021; Hippisley-Cox J, 2021]. The same immune deficiencies that may predispose patients to severe COVID-19 outcomes can also result in a failure to mount robust immunity to SARS-CoV-2 following vaccination, which is why it is likely that IC patients will highly benefit from sotrovimab administration [Kearns, P, 2021; Mahase, 2021; NHS England, 2022; NICE, 2021].

6.2. Rationale

Since December 2020, a number of variants of SARS-CoV-2 have emerged globally, with a high level of uncertainty around their transmissibility, severity and potential for evading vaccine-induced immunity or developing resistance against antivirals and mAbs. SARS-CoV-2 variants can undergo mutations that alter the AAs in the spike protein of the virus [Harvey W.T, 2021]. In the UK, many of these variants have been detected and have since remained under surveillance by UKHSA through routine surveillance [UKHSA, 2021]. Variants may be designated as VOC or VUI, depending on the evidence at the time of their discovery.

Sotrovimab is an early treatment that will be prescribed to SARS-CoV-2 patients 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.

Thus, 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.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Amongst IC non-hospitalised patients treated with sotrovimab as part of standard clinical care:

7.1. Primary Objectives

1. Evaluate the proportion of patients eligible for sequence analysis that have any 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)

7.2. Secondary Objectives

1. Evaluate the proportion of patients eligible for sequence analysis with VOC and 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 RT-PCR
3. Evaluate the proportion of patients with key clinical outcomes (hospital admission, requirement for respiratory support, ICU admission and death) through Day 28 post sotrovimab administration
4. Describe 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
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

8. RESEARCH METHODS

8.1. Study Design

This study is a prospective cohort study (Figure 1).

This study will enrol IC non-hospitalised patients aged ≥18-year-old infected with SARS-CoV-2 and receiving sotrovimab treatment as per standard of clinical care for COVID-19 in selected facilities. Patients who require hospitalisation for COVID-19 are currently not eligible to receive sotrovimab [NHS England, 2022] and will be excluded; there is other ongoing research that will evaluate this population if sotrovimab is administered to this patient population. Patients prescribed sotrovimab who were hospitalised for non-COVID-19 reasons at baseline will also be excluded; this population being already eligible for other national genomic surveillance and requiring a different operational model. All participants that consent to be enrolled in the study will be followed up for up to 28 days post sotrovimab treatment. Patient and disease characteristics (e.g. demographics, number of days of COVID-19 symptoms (if symptomatic) and number of days since initial COVID-19 positive test result at time of receiving treatment, co-morbidities including immunocompromising condition and risk factors for COVID-19 progression, COVID-19 vaccination status, previous SARS-CoV-2 infection, serostatus if available) and treatment history (e.g. immunosuppressant treatment) will be collected at baseline (index date (D0), which corresponds to sotrovimab administration date). Other treatments for COVID-19 including antivirals or other monoclonal antibodies will be collected at baseline and follow-up if any.

Nasal/oropharyngeal samples for virological analysis will be collected at baseline and at three follow-up time points (Day 7, 14 and 28 (+/-2 days)), as per protocol (see Table 1).

Patients will be asked to take a throat and nasal sample with the same swab at each follow-up time point.

Collected nasal mid-turbinate swabs have demonstrated comparable sensitivity and good viral load correlation to clinician collected nasopharyngeal swabs (considered as the gold standard) for COVID-19 detection [Kojima, 2021; Alemany, 2021]. While the nasal/oropharyngeal sample will be collected on site at baseline under supervision after training (as detailed in the study reference manual), home test kits will be provided to the patients with clear explanations on the appropriate technique to collect the follow-up samples as well as instructions for return to the central analytical laboratory. The patient's subject identification number must be present on each of the home test kits (follow guidance in the study reference manual) and checked by study research staff, when these are provided to the patient to take home. Collection of the follow-up samples may also be performed by an HCP in case of hospitalisation. Home test kits are proposed to minimise patients' exposure to healthcare settings that in-person visits would require and to improve patient adherence to study-related procedures and follow up. All the samples will be sent to a central analytical laboratory for testing (i.e., viral load, and sequencing analyses amongst SARS-CoV-2 positive samples with sufficient viral load) (see Section 8.3.2).

Select key clinical outcomes data (e.g. hospital admission, respiratory support, ICU admission and death) will be collected at Day 7, 14 and 28 (+/-2 days) and documented in the eCRF. Phone calls to the patients by the study research staff will be planned at these three follow-up time points with the aim to complete the eCRF and to remind the patients to collect their follow-up nasal/oropharyngeal sample.

Table 1 Schedule of Activities

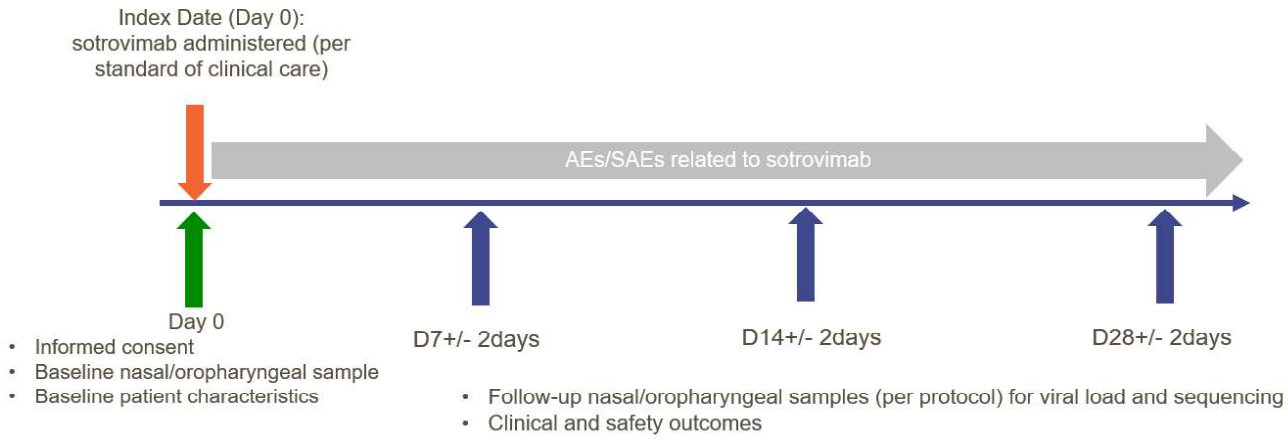
	Baseline **(Day 0, sotrovimab index date)**	**Follow Up Call 1** **(Day 7 ± 2)**[p]	**Follow Up Call 2** **(Day 14 ± 2)**[p]	**Follow Up Call 3** **(Day 28 ± 2)**[pq]
Pre-screening[a]	√			
Confirmation of sotrovimab prescription[b]	√			
Informed Consent [c]	√			
Eligibility confirmation[d]	√			
Enrolment[e]	√			
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 if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the 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 upon site request (as described in the study reference manual).

Patients who progress to severe disease and may require COVID-19 related hospitalisation will be actively contacted and followed-up where possible by the study research staff from the site where sotrovimab was administered. They or HCPs involved in the patient's clinical care may collect samples whilst the patient is hospitalised. Patients will be given a contact card and asked to notify the site if they cannot be contacted for the follow-up calls. To reduce loss to follow up of hospitalised patients, preference will be given to sites where it is likely that patients who require hospitalisation following enrolment will be readmitted to the study site. This will be assessed as part of site feasibility.

Figure 1 Study Design



8.2. Study Population and Setting

This post approval study will aim to start as soon as possible since sotrovimab is now deployed in GB (England, Scotland, Wales). It will be conducted for a period of 12 months in approximately 10 sites in GB, or until the enrollment of 500 (up to 625) patients is met, or until sotrovimab is no longer used in GB, whichever comes first. The aim will be to identify sites that are geographically spread across all three of the home nations. Preference will be given to sites where it is likely that patients who require hospitalisation following enrolment will be readmitted to the study site. Another key factor considered when selecting study sites will be the capacity to start the study quickly, from both a staffing and governance perspective.

This study is intended to cover a fixed period of vulnerability when a limited number of drugs and vaccines are available to generate evidence to understand the risk of variant emergence. UKHSA may continue to monitor the evolving variants and their impact on COVID-19 therapeutic and vaccine effectiveness as part of their routine surveillance activity.

8.2.1. Inclusion Criteria

1. Adult patients aged ≥18 years
2. IC (as defined in the clinical commissioning policy [NHS England, 2022])
3. A positive PCR or antigen test for SARS-CoV-2 through clinical testing or routine screening undertaken as part of clinical management
4. Prescribed treatment with sotrovimab as standard of clinical care
5. Able to provide informed consent and willing to adhere to study-related procedures

The list of IC population eligible to receive sotrovimab will be derived from the IC cohorts outlined in the interim Clinical Commissioning Policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19. Patient cohorts considered at highest risk from COVID-19 and to be prioritised for treatment with nMABs [NHS England, 2022]. The list may include specific IC patients within the following cohorts:

- Patients with a solid cancer
- Patients with a haematological disease and stem cell transplant recipients
- Patients with renal disease
- Patients with liver disease
- Patients with immune-mediated inflammatory disorders (IMID)
- Immune deficiencies
- HIV/AIDS
- Solid organ transplant recipients

Of note, the criteria for the IC cohorts are subject to change as they will follow the latest NHS guidance. The protocol will not be amended to accommodate updates to MHRA guidance, but the criteria will be updated accordingly in the study reference manual.

The decision to treat patients with sotrovimab will be made prior to and independently from the decision of enrolling patients into this study by the patient's healthcare team. Informed consent form and baseline sample collection will be taken prior to sotrovimab administration or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion). This study will therefore include patients who have received sotrovimab dosed as part of their standard clinical care

8.2.2. Exclusion Criteria

1. Patients who require hospitalisation (related or not to COVID-19) at baseline
2. Patients who initiated sotrovimab therapy in inpatient settings
3. Patients unable to perform nasal/oropharyngeal sample collection
4. Blinded patients from other COVID-19 related trials

From the Clinical Commissioning Policy, the following groups will also be excluded from this study unless also eligible for sotrovimab under other Clinical Commissioning Policy IC criteria not listed below [NHS England, 2022]*:*

5. Cohort of patients with rare neurological conditions
6. Cohort of patients with Down's Syndrome
7. In the cohort of patients with renal disease:
    - Patients with chronic kidney stage (CKD) 4 or 5 (an eGFR less than 30 ml/min/1.73m^2) without immunosuppression (patients with renal disease cohort)
8. In the cohort of patients with liver disease:
    - Patients with cirrhosis Child's-Pugh class A who are not on immune suppressive therapy (compensated liver disease), Child's-Pugh class B or C (decompensated liver disease)

8.3. Variables

8.3.1. Exposure Definitions

Sotrovimab Xevudy^{TM}, dose and administration per standard of clinical care

8.3.2. Outcome definitions

8.3.2.1. Primary Endpoint (Primary Objective)

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

Laboratory process

Samples will be dispatched by sites (baseline sample) and patients or HCPs if patients are hospitalised (follow-up samples) to a central analytical laboratory which will follow its own procedures for sequencing techniques.

Sequence analysis of the SARS-CoV-2 spike gene will be attempted on swab samples from all participants eligible for sequence analysis. Viral load will also be measured for all samples. Changes in the spike protein that arise following treatment will be determined by comparing baseline and post-baseline sequencing data for a given patient. More detailed information will be available in the overarching study laboratory manual.

8.3.2.2. Secondary Endpoints

1. 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
2. Proportion of patients with undetectable virus at Day 7, 14 and 28 (+/-2 days) (Secondary Objective 2)
3. 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
4. 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)
5. 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)

Of note, exploratory endpoints will be defined and pre-specified in the statistical analysis plan (SAP).

8.3.3. Confounders and Effect Modifiers

8.3.3.1. Patients Characteristics

Demographic (at baseline)

- Age (year)
- Age range: 18-64; 65-74; 75-84; ≥85
- Sex

- Current smoking status (Yes = current smoker, No = ex-smoker, never smoker),
- Ethnicity
- Body mass index (BMI) (kg/m2): <18.5; 18.5-24.9; 25-29.9; 30-34.9; 35-39.9; ≥40

Comorbidities (at baseline) see Section 8.4 for data source and collection

- Immunocompromising condition
    - The specific conditions will be grouped by set of immunocompromising conditions for analytic purposes
- Obesity (BMI ≥ 30 kg/m^2) and overweight (BMI ≥ 25 kg/m^2)
- Cardiovascular disease (including congenital heart disease) or hypertension
- Cerebrovascular disease
- Chronic obstructive pulmonary disease (COPD)
- Asthma
- Other chronic respiratory disease (moderate-to-severe), interstitial lung disease, cystic fibrosis and pulmonary hypertension
- Chronic kidney disease and stage
- Chronic liver disease
- Diabetes mellitus (DM)
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Pregnancy
- Sickle cell disease
- Having a medical-related technological dependence (e.g. tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])
- Other

Disease characteristic (at baseline)

- Duration of COVID-19 symptoms (days) prior to receiving sotrovimab
- Previous SARS-CoV-2 infection
- Serostatus, if available, test used (i.e. assay manufacturer; test for antibodies to spike protein or test for nucleocapsid protein or other) and date

Co-medication (data collected at baseline and follow-up time points)

- Related to SARS-CoV-2 infection
    - Corticosteroids (inhaled, systemic)
    - Remdesivir
    - IL-6 inhibitors
    - Other mAbs (casirivimab and imdevimab, or other agents if licensed during the study period)
    - Antivirals (molnupiravir, nirmatrelvir and ritonavir, other)
    - Others following national guidance
    - Experimental drugs

- Non-related to SARS-CoV-2 infection (e.g. immunosuppressant treatment)

COVID-19 vaccination status (data collected at baseline and follow-up time points)

- Number of vaccinations, date (month) and brand of each vaccination

8.4. Data Sources

After obtaining informed consent, inclusion/exclusion and baseline patient characteristics and treatment history data will be collected and documented. Any initial AEs observed during sotrovimab treatment (e.g., infusion-related reaction), completion of baseline nasal/oropharyngeal sample and dispensing of at home lab kits to the patient will be completed and documented prior to patient discharge. Any baseline patient characteristics or treatment history unable to be collected during the baseline visit can be collected retrospectively directly from the patient or the patient's regular HCPs during the follow up period. Patients will receive a phone call at Day 7, 14 and 28 (+/- 2 days) to collect follow-up clinical and safety outcomes information, any new or changes in co-medications/ vaccination status, with a reminder for completion of at home nasal/oropharyngeal sample collection at the required timepoints. Participating sites may also contact patient's regular HCPs for clinical and safety outcomes data as required. All baseline and follow-up data will be recorded in the eCRF.

Virology (viral load and viral sequencing) data will be reported following the central analytical laboratory analysis of baseline, day 7, 14 and day 28 (+/-2 days) nasal/oropharyngeal samples as detailed in the SAP.

(For patients progressing to severe COVID-19 and being hospitalised – see Section 8.1)

8.5. Study Size

The primary endpoints are the proportion of patients eligible for sequence analysis that have any AA change from baseline i) in the epitope of sotrovimab binding and ii) in the spike protein at Day 7, 14 and 28 (+/-2 days). The AA changes from baseline in the spike protein will be submitted to MHRA at the individual-patient level as part of ongoing surveillance reporting. Precision around the estimates of the primary endpoints will help to define the target sample size. No prior information about these precise endpoints is available, and the closest comparable available data are derived from the COMET-ICE clinical trial (i.e. conducted in immunocompetent patients with co-morbidities). Preliminary analyses of these sequencing data reported:

- The percentage of sotrovimab treated patients that had treatment emergent AA changes detected **in the epitope of sotrovimab binding** at the consensus sequencing level was approximately 20% (when emergent changes were defined at 5% allelic frequency), and approximately 9% (when defined at 15% frequency)
- The percentage of sotrovimab treated patients that had emergent AA changes more broadly **across the spike protein** was approximately 80% and 52% (defined at 5% and 15% allelic frequency respectively).

A higher prevalence is expected in IC patients.

Precision calculations based on this information, and some additional values, are presented below (output from the software PASS (NCSS, LLC, Version 19.0.1). They show that, for example:

- If 50% of patients with AA changes that meet the criteria for the variable of interest (i.e. the estimated percentage that gives the widest confidence interval (CI)) is observed, then a sample size of 500 patients will give reasonable precision around the estimate (95% CI 45.5%-54.5%).
- If 9% of patients that meet the criteria is observed, a target sample size of 500 patients will also yield reasonable precision around the estimate (95% CI 6.7%-11.9%).

Table 2 Numerical Results for Two-Sided Confidence Intervals for One Proportion – Confidence Interval Formula: Score with Continuity Correction [Fleiss, 2003; Newcombe, 1998]

Confidence Level	Sample Size (N)	Actual Width	Proportion (P)	Lower Limit	Upper Limit
0.950	500	0.041	0.050	0.033	0.074
0.950	500	0.052	0.090	0.067	0.119
0.950	500	0.055	0.100	0.076	0.131
0.950	500	0.078	0.250	0.213	0.291
0.950	500	0.089	0.500	0.455	0.545
0.950	500	0.089	0.520	0.475	0.564
0.950	500	0.072	0.800	0.762	0.834
0.950	500	0.065	0.850	0.815	0.880

- Confidence level is the proportion of cIs (constructed with this same confidence level, sample size, etc.) that would contain the population proportion.
- N is the size of the sample draw from the population.
- Width is the distance from the lower limit to the upper limit.
- Actual width is the value of the width that is obtained from the procedure.
- Proportion (P) is the assumed sample proportion.
- Lower Limit is the lower limit of the CI.
- Upper Limit is the upper limit of the CI.

Using an estimate of 20% of patients being lost to follow-up, the plan will be to increase recruitment up to 625 patients to meet the target sample size of 500. It is also anticipated that in some patients, the viral load in samples collected at days 7, 14, and 28 (+/-2 days) will be too low for determination of the variable of interest. While undetectable viral load is a goal for treatment, this would further reduce the number of patients contributing to the assessment of the primary endpoint. Nonetheless, there remains adequate precision if

there are fewer patients contributing to analyses at day 7, for example (e.g. if there were 400 patients with a detectable viral load and 50% had AA changes that meet the criteria of interest, then the precision would be 95% CI 45.0-55.0%).

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 GB to meet the target sample size. Flexible enrolment caps per site and per month may 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.

8.6. Data Management

Data collection and data source is described in Section 8.4.

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan (DMP) or equivalent contract research organisation (CRO) document.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations [CROs]).

More granular level process for data management will be described in the overarching study DMP.

8.6.1. Timings of Assessment during Follow-up

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):

- Day 0 On-site screening:
    - Confirmation that decision to administer sotrovimab (per standard of clinical care) has been made by the treating HCP
    - Informed consent and enrolment
    - Baseline sample collection under supervision after training (nasal/oropharyngeal) prior to sotrovimab administration or if not possible, then either during sotrovimab infusion or as close as possible to the end of sotrovimab infusion (within ≤2 hours of the end of the sotrovimab infusion).

Data collection of patient and disease characteristics (e.g. demographic, medications and comorbidities) when possible
    - Three sample collection kits must be provided to the patient for home collection at each follow up timepoints (D7, D14, D28 [+/-2days]), with subject identification present on each kit (as per guidance in the study reference manual).
- Day 7 +/-2 days
    - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes
    - Follow-up sample collection (nasal/oropharyngeal) – Home kit
    - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0
- Day 14 +/-2 days
    - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes
    - Follow-up sample collection (nasal/oropharyngeal) – Home kit
    - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0
- Day 28 +/-2 days
    - Phone call: Data collection of clinical outcomes and any treatment related AEs reported by the patient, concomitant medications if any changes
    - Follow-up sample collection (nasal/oropharyngeal) – Home kit
    - Retrospective collection of baseline data with the patient or directly with patient HCP when not possible at Day 0

For patients progressing to severe COVID-19 and being hospitalised – see Section 8.1.

The follow-up of patients with a persistent positive sample at the end of the study period (i.e. Day 28) is described in Section 8.7.2 as an exploratory analysis. Persistent positive results will be reported back to the sites upon site request (as described in the study reference manual).

8.7. Data analysis

8.7.1. Essential Analysis

This study is descriptive. Categorical variables will be described using counts, proportions and 95% CI and continuous variables will be described using measures of central tendency (e.g. mean, interquartile range, etc.)

8.7.1.1. Primary Objective

- Sequencing of samples on a regular basis (as detailed in the study laboratory manual) is required.
- The primary analysis of data will include:
    - Proportion of patients eligible for sequence analysis that have any AA change from baseline in the epitope of sotrovimab binding

- Proportion of patients eligible for sequence analysis that have any AA change from baseline in the spike protein
- More details on any sub-analyses performed by sub-groups will be described in the SAP.

8.7.1.2. Secondary Objective

- VOC, VUI and other lineages information as classified by UKHSA and WHO will be identified from sequencing data for patients eligible for sequencing analysis (Secondary Objective 1)
    - This analysis will be done on the earliest possible sample and reported only once per patient as described in the SAP

- Comorbidities, clinical outcomes, patients with undetectable SARS-VoV-2 viral ribonucleic acid and safety events data will be described and reported with counts and proportions with a 95% CI (Secondary Objective 2 and 3).

- 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)

- 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)

8.7.2. Exploratory Analysis

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 the genomic databases (e.g. GISAID)

8.7.3. General Considerations for Data Analyses

More granularity for data analyses and reporting will be available in the overarching project SAP.

8.7.4. Interim Analysis

An interim analysis is planned to be conducted to support regulatory health authority post authorisation commitments. The analysis aims to assess the primary and secondary objectives and is due in Q2 2023. For details about the analysis refer to the SAP.

8.8. Quality control and Quality Assurance

To ensure compliance with all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 8.8.5 for more details regarding the audit process.

8.8.1. Data Quality Assurance

Syneos Health and GSK are responsible for following standard operating procedures (SOPs) to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All sites will be trained by the Site Management Associate (SMA) on the protocol, study logistics, and the EDC system.

Veeva Vault CDMS (Clinical Data Management System) will be the EDC system used to manage data collection during this study; it is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies. All participant data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (*e.g.*, laboratory data). The investigator is responsible for ensuring prospective data is entered in a timely manner and verifying that data are accurate and correct by physically or electronically signing the eCRF. Guidance on completion of CRFs will be provided in the eCRF Guidelines.

On-line logic checks will be built into the EDC system as much as possible, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study site and answered electronically by the study site personnel.

8.8.2. Access to Source Data/Documents

The Investigator will allow Sponsor representatives, contract designees, authorised regulatory authority inspectors, and Independent Ethics Committee (IEC) to have direct access to all documents pertaining to the study.

8.8.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. All study materials will be returned to the Sponsor after the study has been completed.

Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations. According to International Council on Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

8.8.4. Study Monitoring

Subject data will be monitored using a risk-based approach, with remote monitoring being preferred to reduce burden on sites. The monitoring strategy will be documented in the study Site Management (monitoring) Plan and will include flexibility in approach to account for COVID-19 restrictions that may change during the study.

8.8.5. Audits and Inspections

Responsible IEC/Competent Authority and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

8.9. Limitations of the Research Methods

Strengths of the proposed study include its prospective design, which provides clear temporal information, and use of advanced laboratory methods to describe AA changes in viral genetic sequence in an IC population that is at risk for both poor clinical outcomes and the development of novel substitutions, deletions or insertions in the spike protein of SARS-CoV-2 virus.

There are several limitations to the interpretation of the results of this study, summarised below:

Design

This surveillance study will aim to monitor the emergence of changes in spike protein over time following the administration of sotrovimab. The aim will be to monitor the changes in the entire spike protein, but some substitutions, deletions or insertions of concern may occur outside of the spike. All changes that are identified in the SARS-CoV-2 spike protein will be recorded and reported per the SAP.

Selection bias

Since patients who are hospitalised for non-COVID-19 reasons or who are unable to collect nasal/oropharyngeal swabs will be excluded, there is a possibility of selection bias in recruiting a somewhat healthier population. However, it is expected that the impact on the primary outcome will be minimal. Immunosuppressed status, regardless of hospitalisation status, should be the main factor impacting the AA changes in the spike protein. Since the study will enrol a range of highly IC patients, selection bias should be minimal.

Testing procedures

The baseline sample will be a nasal/oropharyngeal swab collected on site and supervised by a HCP, while pragmatic, patient-focused solutions will ask study participants to

collect their follow up samples at 7-, 14- and 28-days using home test kits. Study staff will not be able to verify whether samples are collected and handled properly, which may impact the sensitivity of subsequent sequencing testing of patient samples. However, this collection approach was weighed against asking COVID-19 positive, IC people having to seek testing outside their residence. Self-collected nasal/oropharyngeal swabs have demonstrated comparable sensitivity and good viral load correlation to clinician collected nasopharyngeal swabs (considered as the gold standard) for SARS-CoV-2 detection [Kojima, 2021; Alemany, 2021]. The patients will also be trained to increase chances of getting the appropriate samples. Finally, nasopharyngeal swabs generally should not be done in patients with significant thrombocytopenia or bleeding disorders, which some of this IC population would likely have.

Distribution of virus across the respiratory tract may vary between patients. Therefore, an infected patient may have detectable virus in sputum but not in nasal/oropharyngeal swabs. This limitation and the potential for false negative results when using nasal/oropharyngeal swabs are acknowledged. Regular re-assessments of the sample collection strategy to ensure the appropriate capture of the primary outcome will be planned.

Loss to follow up

Although the duration of follow up is relatively short (28 day +/- 2 days) all data will be collected remotely, and samples will be provided by post and relies on patient compliance with protocol procedures. It is expected that there may be challenges obtaining follow up information and samples from enrolled patients. Clinical sites will proactively contact patients on at least 3 occasions over a period of 4 days (+/- 2 days from expected date) in order to reduce loss to follow-up. Reasons for loss-to-follow-up will be recorded in the eCRF if available. Attempts will also be made by the study staff to contact or follow-up patients if they are admitted to the hospital.

In evaluating clinical outcomes and safety events at later time points, it is possible that loss to follow up will be differential, with patients experiencing adverse clinical outcomes or safety events either more or less likely to maintain contact with study staff. In the presence of differential loss to follow up, the data from participants who remain under observation would be biased for related outcomes. Substantial baseline characteristic data on patients should be available to quantitatively evaluate whether there are significant differences between patients lost to follow-up and patients with complete follow-up.

Geographical coverage

The geographical coverage will be limited to the sentinel sites that agree to participate in this study. The identification of viral variants in the IC patients may not be generalisable to all parts of GB.

Duration of follow-up

Concerns about the development of novel viral variants resulting from infections in immunosuppressed patients are based in part on the tendency of these patients to develop prolonged infections. The proposed design may not be able to detect the development of these variants if they develop later in the course of a prolonged infection (>28 days), or if they fail to rise above the threshold of detection for the sequencing assay. 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 Day 28 will be explored (see Section 8.7.2).

Role of Sotrovimab

Immunosuppressed populations are of particular concern for the development of novel variants because of their tendency to develop prolonged infections, which can expose SARS-CoV-2 to the host's antibodies (or therapeutic antibodies or donor-derived antibodies in normal human immunoglobulin products) without viral clearance and create selective pressure for viral mutations allowing for immune evasion. This patient population is of public health interest for sentinel surveillance in the detection of variants of interest and concern, and the proposed study will contribute valuable information to the effort being undertaken by UKHSA. However, the lack of an untreated comparator group in the proposed study design means that it will not allow for any meaningful inference into the association between treatment with sotrovimab and the development of novel viral mutations. Genomic databases (e.g. GISAID) will be used to contextualise the changes in AA from baseline that are identified in the SARS-CoV-2 spike protein in this study.

8.10. Study Closure/Uninterpretability of Results

Information Bias

Relying on investigators to fill out the assessment forms might induce the presence of missing data, which can result in bias. Entry of prospectively collected data into eCRFs will minimise missing or incorrect data by having automated queries. Clear instructions and engagement with the study staff with appropriate training will minimise the amount of missing data.

Rules about how missing data will be handled will be included in the SAP.

Patients Lost to Follow-up or without Follow-up Data

See Section 8.9

8.11. Other Aspects

Not Applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Approval and Subject Consent

9.1.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (version 2008) and applicable legal and regulatory requirements and related guidances, especially Directive 2001/83/EC, Regulation (EC) No 726/2004 (REG) and Commission Implementing Regulation (EU) No 520/2012 (IR) as detailed in Good Pharmacovigilance Practices (GVP) Modules V, VI and VIII.

It is the responsibility of GSK and the Investigators to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., ICFs), if applicable, from the IEC/Competent Authorities. Any necessary extensions or renewals of IEC approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
- Notifying the IEC of SAE or other significant safety findings as required by IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines (if applicable), the IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

9.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.1.3. Informed Consent Process

Informed consent will be obtained from all patients before enrolment into the study. Each investigator will ensure that each patient who needs to provide informed consent is given full and adequate oral and written information about the nature and purpose of the study. The patient will be given the opportunity to ask questions and allowed time to consider the information provided. All parties will ensure protection of participant personal data and will not include names on any sponsor forms, reports, publications, or in any other disclosures, except where required by the local laws and regulations.

The signed and dated informed consent must be obtained before any study procedures including sample collection or data entry into the eCRF. The investigator must store the original, signed ICF. A copy of the signed ICF must be given to the patient. If the patient decides not to participate, the reason will be collected in the eCRF. The option of using e-Consent will be explored and the process by which consent is collected will be updated as needed and provided to sites via other means.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about sotrovimab or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have sotrovimab approved for medical use or approved for payment coverage.

9.2. Participant Withdrawal

Participation in this study is voluntary and patients may withdraw from the study at any time without prejudice. If the patient withdraws or is withdrawn, the reason will be collected in the eCRF. The ICF will explain that in case of withdrawal, all study data collected before withdrawal will be kept in the study database.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The process of managing subject samples collected but not analysed at the time of withdrawal will be managed following the process as described in the study reference manual. The Sponsor reserves the right, at any time, to discontinue enrolment of additional patients into the study, at any site; or to discontinue the study, for medical or administrative reasons.

9.3. Subject Confidentiality

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The ICF will incorporate wording that complies with relevant data protection and privacy legislation in the UK. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

Study Use means the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the product studied and the disease/condition studied. This includes bringing the product to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Key Definitions

This study adopts the following ICH definitions:

Adverse event: Any untoward medical occurrence in a patient, or clinical investigation subject, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

- An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product including those used in combination with a medical device. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an AE), and AEs associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse or those related to a deficiency occurring with a medical device or combination product.

Adverse Drug Reaction (ADR): A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Serious adverse event: any untoward medical occurrence that at any dose that 1) results in death, 2) is life threatening, 3) requires inpatient hospitalisation or prolongs existing hospitalization, 4) results in persistent or significant disability/incapacity or 5) is a congenital anomaly.

Spontaneous events:

- Those AEs observed related to the GSK product under evaluation but exempted from collection, if justified, are reported as spontaneous events.

- Those AEs observed related to any other GSK product (not under evaluation)are reported as spontaneous events.
- If any ADRs are observed related to drug product(s) not related to the Sponsor (GSK), the Investigator should report the ADRs to the appropriate marketing authorisation application of the product(s) or Health Authority per local regulations.

More detailed definitions of AE types are provided in the SMP.

The Investigator or Sponsor must provide a causality assessment regarding the relationship of any AE to the medicinal product.

Further details of the causality assessment can be provided in the protocol or the reader can be referred to the SMP.

11.2. Collection of adverse events/reactions

Adverse events (serious and non-serious) will be collected following the administration of sotrovimab if considered related to sotrovimab. Events should only be collected if they are new or worsening when compared to the patient's usual health status. Safety data will be collected by the study research HCP on site at baseline and by phone at Day 7, 14 and 28 (+/-2 days). Only safety events related to sotrovimab will be collected. The study population is likely to have many comorbidities and AEs may be symptoms of their underlying diseases.

As they are not related to study objectives, spontaneously captured AEs related to other GSK products, or non-GSK products, are not systematically collected, but are reported (see adverse event reporting in Section 11.3 below).

11.3. Reporting of adverse events/reactions

All AEs (serious and non-serious) systematically collected and considered causally related to sotrovimab will be entered into the CRF, as well as pregnancy exposures, and should be reported to the GSK Case Management Group. These will be classified as individual case safety reports (ICSRs). Reporting process and timelines are provided in the SMP.

AEs related to any other GSK product, will be classified as spontaneous reports and reported to the Safety department as such.

HCPs (and any study vendor) can report these spontaneous adverse reactions to GSK via the following web link:

https://www.gsk.com/en-gb/contact-us/report-a-possible-side-effect/

Adverse reactions related to non-GSK product, will also be classified as spontaneous reports. Healthcare professionals (and any study vendor) will be informed of the possibility to report these spontaneous adverse reactions to the marketing authorisation holder of the suspected medicinal product (studied or not) OR to the concerned competent authority via the national spontaneous reporting system.

It is the responsibility of the Sponsor of the product in question rather than the Investigator to report these spontaneous ADRs to the Regulatory Authorities according to applicable regulations.

11.4. Safety collection and reporting study documentation

A Safety Management Plan (SMP) will be developed for the study and will provide detailed information on the study specific pharmacovigilance processes and procedures.

- This plan will include the following elements to ensure a comprehensive approach to safety event collection and reporting:
- Supplier pharmacovigilance training
- Investigator and site staff pharmacovigilance training
- Safety-specific roles
- AEs collection, pregnancy exposures and reporting processes
- Health safety information (HSI) collection processes
- Causality assessment
- HSI Reporting processes
- HSI reporting tools/forms Frequency of data review
- Reviewing and reporting results
- Interim reports
- PVP oversight process
- Provision of final study report

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

GSK and/or a designated party will prepare safety and other summary reports, as required by the appropriate regulatory authority. In addition, these data may be summarised periodically for presentation at professional conferences and sessions, as appropriate. GSK is responsible for presentations and/or publications. For studies that are fully or partially conducted by investigators who are not employees of the GSK group of companies, GSK and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. GSK should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. Results from this study will be submitted for publication in international peer-reviewed journals and will be disseminated appropriately to inform MHRA and other regulatory agencies, public health guidance and risk assessment, as well as to relevant expert clinical groups. Any public reporting will contain aggregate data and will avoid any risk of deductive disclosure.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Contact details of all Investigators participating in the study will be kept in stand-alone documents.

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

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PPD , Virology Lead	PPD	
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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

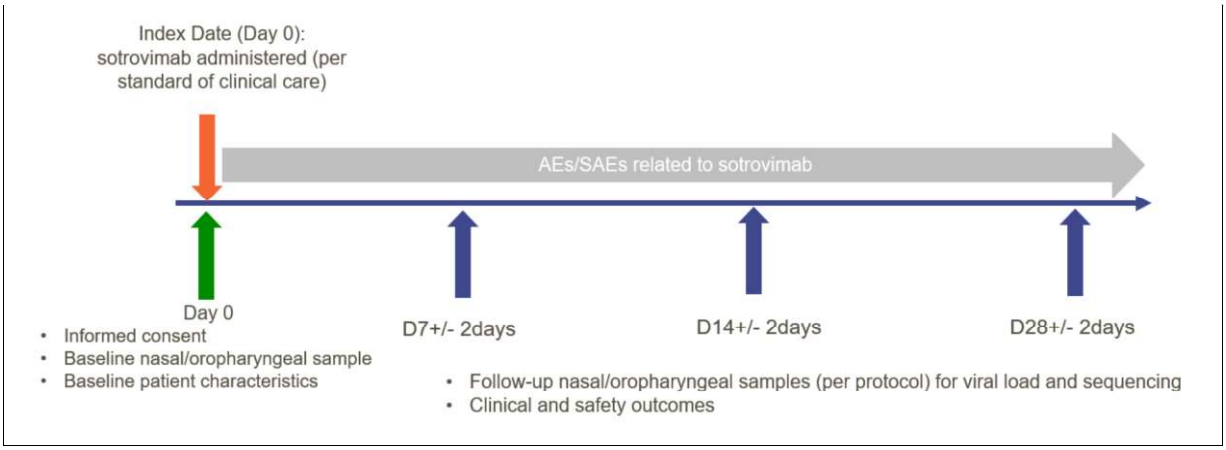
Sotrovimab was granted a conditional marketing authorisation for the treatment of early coronavirus disease 2019 (COVID-19) infection in GB on December 01, 2021. Sotrovimab is an early treatment that will be prescribed to patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection 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.

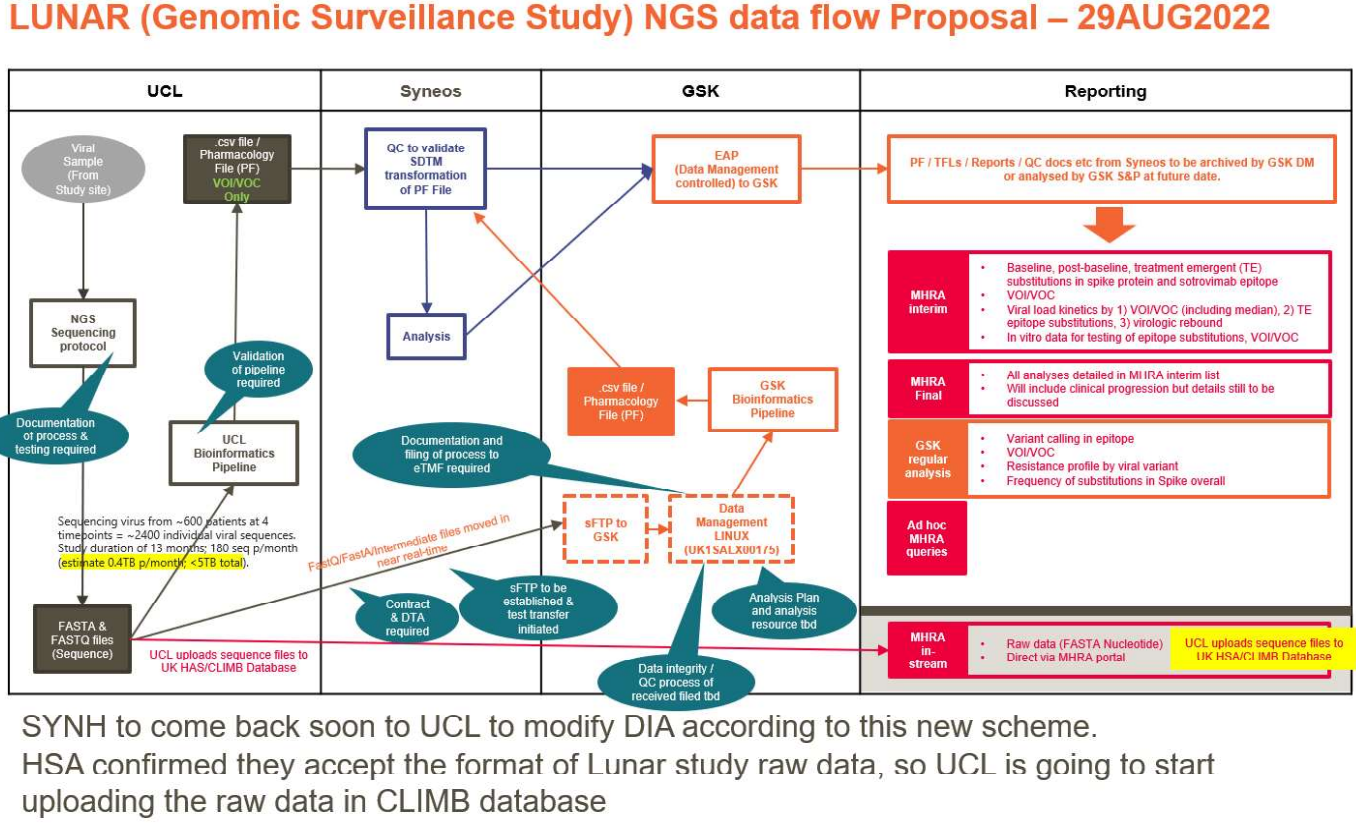
[o] Refer to Section 11.3 for details on safety events to be reported.

[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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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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Agreement completed.

2023-07-18 - 7:45:05 AM GMT

Study	218407_DEV1
Casebook Definition Name	InitialVersion
Casebook Definition External ID	InitialVersion
Generation Mode	Blank CRFs
Include Annotations	Yes
Casebook Version	1.8
Generated	11-May-2022 08:20:20
Specification Version	

Subject Identification(ev_SUBJ) (Short Label: Subject Identification) (External ID: ev_SUBJ)

Event Date	**External ID: ev_SUBJ** **Offset Days: 0** **Future Date**

Subject Identification

External ID: SUBID_RD

Design Object Name: SUBID_RD

Short Label: SUB ID

Restricted: No

Subject Identification (ig_SI) (External ID: ig_SI)	
Subject ID Number	**Name: SUBJID** **External ID: SUBJID** **Required** **Hint Label: 6 digits** **Max Length: 6**

Informed Consent(ev_ICE) (Short Label: Informed Consent) (External ID: ev_ICE)

Event Date	_____	**External ID: ev_ICE** **Offset Days: 0** **Future Date**

Informed Consent

External ID: PROT_CONSENT_RD

Design Object Name: PROT_CONSENT_RD

Short Label: INF CONSENT

Restricted: No

Informed Consent - Main Study Details (ig_PROTCONSENT_STD) (External ID: ig_PROTCONSENT_STD)		
Study Consent Date	_____	**Name: DSSTDT_ICF** **External ID: DSSTDT_ICF** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Study Site Informed Consent Version Number	_____	**Name: ICSTV_ICF** **External ID: ICSTV_ICF** **Required** **Max Length: 40**
Study Consent for Primary Research Use	○ Yes (Y) ○ No (N)	**Name: CNSOBT_PR** **External ID: CNSOBT_PR** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_CNSWD_PR_SHOW**
Study Consent for Primary Research Use Withdrawn	○ Yes (Y) ○ No (N)	**Name: CNSWD_PR** **External ID: CNSWD_PR** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_DSPMSTDTC_ICFWDPR_DT_SHOW**
Study Consent Primary Research Withdrawn Date	_____	**Name: DSSTDT_ICFWDPR** **External ID: DSSTDT_ICFWDPR** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**

Study Consent for Further Research Use	○ Yes (Y) ○ No (N) ○ Not applicable (NA)	**Name: CNSOBT_FR** **External ID: CNSOBT_FR** **Required** **Codelist: cl_NY_NYNA** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_CNSWD_FR_SHOW**
Study Consent for Further Research Use Withdrawn	○ Yes (Y) ○ No (N)	**Name: CNSWD_FR** **External ID: CNSWD_FR** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_DSPMSTDTC_ICFWDFR_DT_SHOW**
Study Consent Further Research Withdrawn Date		**Name: DSSTDT_ICFWDFR** **External ID: DSSTDT_ICFWDFR** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**

Informed Consent - Additional Consent Details (ig_PROTCONSENT_ADD) (Repeats, Max: 999) (External ID: ig_PROTCONSENT_ADD)		
Consent Type	○ Study (STUDY)	**Name: DSSCAT_ICFADD** **External ID: DSSCAT_ICFADD** **Required** **Codelist: cl_DSPMSCAT_ICF** **Codelist Style: Radio Buttons - Vertical**
Consent Date		**Name: DSSTDT_ICFADD** **External ID: DSSTDT_ICFADD** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Study Site Informed Consent Version Number		**Name: ICSTV_ICFADD** **External ID: ICSTV_ICFADD** **Required** **Max Length: 40**

Consent for Primary Research Use	○ Yes (Y) ○ No (N)	**Name: CNSOBT_PR_ADD** **External ID: CNSOBT_PR_ADD** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_CNSWD_PR_ADD_SHOW**
Consent for Primary Research Use Withdrawn	○ Yes (Y) ○ No (N)	**Name: CNSWD_PR_ADD** **External ID: CNSWD_PR_ADD** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_DSPMSTDTC_ICFWDPR_ADD_DT_SHOW**
Consent Primary Research Withdrawn Date		**Name: DSSTDT_ICFWDPR_ADD** **External ID: DSSTDT_ICFWDPR_ADD** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Consent for Further Research Use	○ Yes (Y) ○ No (N) ○ Not applicable (NA)	**Name: CNSOBT_FR_ADD** **External ID: CNSOBT_FR_ADD** **Required** **Codelist: cl_NY_NYNA** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_CNSWD_FR_ADD_SHOW**
Consent for Further Research Use Withdrawn	○ Yes (Y) ○ No (N)	**Name: CNSWD_FR_ADD** **External ID: CNSWD_FR_ADD** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_DSPMSTDTC_ICFWDFR_ADD_DT_SHOW**
Consent Further Research Consent Withdrawn Date		**Name: DSSTDT_ICFWDFR_ADD** **External ID: DSSTDT_ICFWDFR_ADD** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**

Baseline (Day 0)(ev_BASE) (Short Label: Baseline (Day 0)) (External ID: ev_BASE)

Event Date	_____	**External ID: ev_BASE** **Offset Days: 0** **Future Date**

Visit Type

External ID: VIS_TYP

Design Object Name: VIS_TYP

Short Label: VIS_TYP

Restricted: No

Visit Type (ig_VIS_TYP) (External ID: ig_VIS_TYP)		
Visit Type	○ Site inpatient (SITE INPATIENT) ○ Home visit (HOME VISIT)	**Name: VIS_TYP** **External ID: VIS_TYP** **Required** **Codelist: cl_VIS_TYP** **Codelist Style: Radio Buttons - Vertical**

Demography

External ID: DEMO_RD

Design Object Name: DEMO_RD

Short Label: DEMO

Restricted: No

Demography (ig_DEMO) (External ID: ig_DEMO)		
Birth Year	_____	**Name: BRTHYY** **External ID: BRTHYY** **Required** **(4.0)**
Sex	○ Male (MALE) ○ Female (FEMALE) ○ Unknown (UNKNOWN)	**Name: SEX** **External ID: SEX** **Required** **Codelist: LAB_Sex** **Codelist Style: Radio Buttons - Horizontal**
Ethnicity	○ Hispanic or Latino (HISPANIC OR LATINO) ○ Not Hispanic or Latino (NOT HISPANIC OR LATINO) ○ Unknown (UNKNOWN)	**Name: ETHNIC** **External ID: ETHNIC** **Required** **Codelist: cl_ETHNIC** **Codelist Style: Radio Buttons - Vertical**

Race (ig_RACE) (External ID: ig_RACE)		
Check all that apply		**Name: lbl_CHECKALL** **External ID: lbl_CHECKALL**
American Indian or Alaska Native	☐	**Name: RACE_AMINALN** **External ID: RACE_AMINALN**
Asian	☐	**Name: RACE_ASIAN** **External ID: RACE_ASIAN** **Rule for Disable: R_DISPLAY_RACEASIAN_S01325_SHOW,R_DISPLAY_RACEASIAN_S01324_SHOW,R_DISPLAY_RACEASIAN_S01326_SHOW,R_DISPLAY_RACEASIAN_S01323_SHOW**
Asian - Central/South Asian Heritage	☐	**Name: CRACE_ASIAN_CS** **External ID: CRACE_ASIAN_CS**
Asian - East Asian Heritage	☐	**Name: CRACE_ASIAN_E** **External ID: CRACE_ASIAN_E**

Asian - Japanese Heritage	☐	**Name: CRACE_ASIAN_JPN** **External ID: CRACE_ASIAN_JPN**
Asian - South East Asian Heritage	☐	**Name: CRACE_ASIAN_SE** **External ID: CRACE_ASIAN_SE**
Black or African American	☐	**Name: RACE_BLAA** **External ID: RACE_BLAA**
Native Hawaiian or Other Pacific Islander	☐	**Name: RACE_NHOPI** **External ID: RACE_NHOPI**
White	☐	**Name: RACE_WHT** **External ID: RACE_WHT** **Rule for Disable: R_DISPLAY_RACEWHITE_S20231_SHOW,R_DISPLAY_S01328_SHOW**
White - Arabic/North African Heritage	☐	**Name: CRACE_WHT_ARBNAH** **External ID: CRACE_WHT_ARBNAH**
White - White/Caucasian/European Heritage	☐	**Name: CRACE_WHT_WCEH** **External ID: CRACE_WHT_WCEH**
Unknown	☐	**Name: RACE_UNKNOWN** **External ID: RACE_UNKNOWN**

Eligibility - Study

External ID: ELIG_RD

Design Object Name: ELIG_RD

Short Label: ELIG

Restricted: No

Eligibility - Study (ig_ELIG_STD) (External ID: ig_ELIG_STD)		
Protocol Amendment Number *(Refer to the protocol cover page for the Protocol Amendment Number. Enter the digit part only (e.g. 0 for original, 1 for amendment 1, 2 for amendment 2, etc.). Country-specific version information is not required.)*	_____	**Name: PROTVER** **External ID: PROTVER** **Required** **(2.0)**
Subject Met All Eligibility Criteria	○ Yes (Y) ○ No (N)	**Name: IEYN_ZZ** **External ID: IEYN_ZZ** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ig_ELIG_CRIT_SHOW**

Eligibility Category Not Met (ig_ELIG_CRIT) (Repeats, Max: 999) (External ID: ig_ELIG_CRIT)		
Criterion Category	○ Inclusion (INCLUSION) ○ Exclusion (EXCLUSION)	**Name: IECAT** **External ID: IECAT** **Required** **Codelist: cl_IECAT** **Codelist Style: Radio Buttons - Horizontal**
Criterion Identifier *(Enter the identifier of the criterion the subject did not meet (e.g. 1,2a,etc..).)*	_____	**Name: IESPID** **External ID: IESPID** **Required** **Max Length: 3**

Sotrovimab Administration

External ID: EX2

Design Object Name: EX2

Short Label: EX2

Restricted: No

Drug Administration (ig_EX2) (External ID: ig_EX2)		
Administration Date *((dd-Mmm-yyyy))*	_____	**Name: EXDAT** **External ID: EXDAT** **Required** **Future Date** **Hint Label: dd-Mmm-yyyy**
Start Time	_____ : _____ 24 hour clock	**Name: STTIMEX2** **External ID: STTIMEX2** **Required** **Hint Label: HH:mm**
End Time	_____ : _____ 24 hour clock	**Name: ENTIMEX2** **External ID: ENTIMEX2** **Required** **Hint Label: HH:mm**
Route of Administration	○ Intravenous (INTRAVENOUS)	**Name: ROUTE** **External ID: ROUTE** **Required** **Codelist: cl_STROUTE** **Codelist Style: Radio Buttons - Vertical**
Dose Administered	_____	**Name: DOSE_EX2** **External ID: DOSE_EX2** **Hint Label: mg** **(4.0)**

Home Sample Collection Kit Dispensation

External ID: OP3

Design Object Name: OP3

Short Label: OP3

Restricted: No

Swab sample collection kits (ig_OP3) (External ID: ig_OP3)		
Lab kits dispensed to subject	○ Yes (Y) ○ No (N)	**Name: LKTOP3** **External ID: LKTOP3** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Baseline Kit Number	_____	**Name: BKTNOP3** **External ID: BKTNOP3** **Max Length: 6**
Kit Number 1	_____	**Name: KTNOP31** **External ID: KTNOP31** **Max Length: 6**
Kit Number 2	_____	**Name: KTNOP32** **External ID: KTNOP32** **Max Length: 6**
Kit Number 3	_____	**Name: KTNOP33** **External ID: KTNOP33** **Max Length: 6**

Central Laboratory - Samples

External ID: LAB_CSMP_RD

Design Object Name: LAB_CSMP_RD

Short Label: LAB CSMP

Restricted: No

Samples (ig_LABCSMPL) (External ID: ig_LABCSMPL)		
Samples Collected at this Visit	○ Yes (Y) ○ No (N)	**Name: LBPERF_CSMP_ZZ** **External ID: LBPERF_CSMP_ZZ** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ig_LABC_SMPL_DETAILS_SHOW**

Samples Details (ig_LABCSMP_DET) (External ID: ig_LABCSMP_DET)		
Lab Specimen Collection Date	_____	**Name: LBDT_CSMP** **External ID: LBDT_CSMP** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Lab Specimen Collection Time	_____ : _____ 24 hour clock	**Name: LABTIM** **External ID: LABTIM** **Hint Label: HH:mm**
Lab Specimen Type Collected	○ Nasal swab (NASAL SWAB) ○ Oropharyngeal swab (OROPHARYNGEAL SWAB) ○ Nasal and Oropharyngeal swab (NASAL AND OROPHARYNGEAL SWAB)	**Name: LBCAT_ZZ** **External ID: LBCAT_ZZ** **Required** **Codelist: cl_SPECTYPE_CSMP** **Codelist Style: Radio Buttons - Vertical**

COVID-19 Vaccination Status

External ID: CM1

Design Object Name: CM1

Short Label: CM1

Restricted: No

Vaccine History (ig_CM1) (External ID: ig_CM1)		
Did the subject receive a COVID-19 vaccine prior to study enrollment?	○ Yes (Y) ○ No (N)	**Name: PRIORCM** **External ID: PRIORCM** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_DOSENUMCM_SHOW,R_DISPLAY_ig_CM1_DET_SHOW,R_DISPLAY_VXDAT_SHOW**
Number of doses received?	_____	**Name: DOSENUMCM** **External ID: DOSENUMCM** **Required** **Max Length: 2**

Vaccine History Details (ig_CM1_DET) (Repeats, Max: 20) (External ID: ig_CM1_DET)		
Product name of COVID-19 vaccine	○ Moderna (MODERNA) ○ Pfizer-BioNTech (PFIZER-BIONTECH) ○ AstraZeneca (ASTRAZENECA) ○ J&J Janssen (J&J JANSSEN) ○ Novavax (NOVAVAX) ○ Other (OTHER) ○ Unknown (UNKNOWN)	**Name: VXNAME** **External ID: VXNAME** **Required** **Codelist: cl_COV_VX** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_VXOTHER_SHOW**
If Other, specify	_____	**Name: VXOTHER** **External ID: VXOTHER** **Max Length: 1500**

Date of vaccine _____	**Name: VXDAT** **External ID: VXDAT** **Required** **Future Date** **Hint Label: DD-Mmm-YYYY**

Vital Signs

External ID: VITALS_A_RD

Design Object Name: VITALS_A_RD

Short Label: VITALS A

Restricted: No

Vital Signs - Measurements (ig_VITALS_A_MEAS) (External ID: ig_VITALS_A_MEAS)			
Date of Measurements	_____		**Name: VSDT** **External ID: VSDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Height	_____		**Name: VSORRES_HEIGHT** **External ID: VSORRES_HEIGHT** **Required** **Hint Label: cm** **(3.0)**
Weight	_____	(xxx.y)	**Name: VSORRES_WEIGHT** **External ID: VSORRES_WEIGHT** **Required** **Hint Label: kg** **(3.1)**
Body Mass Index (calculated)	_____	(xxxx.yy)	**Name: VSORRES_BMI_C** **External ID: VSORRES_BMI_C** **Hint Label: kg/m^2** **(4.2)** **Read Only**

Substance Use History

External ID: SUBUSE_HIST_RD

Design Object Name: SUBUSE_HIST_RD

Short Label: SUBUSE HIST

Restricted: No

Tobacco (ig_SUBUSE_TBHIST) (External ID: ig_SUBUSE_TBHIST)		
Used Tobacco	○ Never (NEVER) ○ Former (FORMER) ○ Current (CURRENT)	**Name: SUNCF_T** **External ID: SUNCF_T** **Required** **Codelist: cl_NCF** **Codelist Style: Radio Buttons - Horizontal**

COVID-19 Disease History

External ID: MH1

Design Object Name: MH1

Short Label: MH1

Restricted: No

COVID-19 Disease History (ig_MH1) (External ID: ig_MH1)		
Was subject symptomatic?	○ Yes (Y) ○ No (N)	**Name: SYYNMH1** **External ID: SYYNMH1** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_SYMPDAT_SHOW,R_DISPLAY_DURPRIOR_SHOW**
Date of earliest symptom	_____	**Name: SYMPDAT** **External ID: SYMPDAT** **Required** **Future Date**
Duration of COVID-19 symptoms (days) prior to receiving sotrovimab	_____	**Name: DURPRIOR** **External ID: DURPRIOR** **Required** **(5.0)**
Number of days since initial COVID-19 positive test result at time of receiving treatment	_____	**Name: TRTNUM** **External ID: TRTNUM** **Required** **(5.0)**
Test used for COVID-19 testing	○ Antigenic tests (Lateral flow) (ANTIGENIC TESTS (LATERAL FLOW)) ○ Polymerase chain reaction (PCR) (POLYMERASE CHAIN REACTION(PCR))	**Name: TESTCOV** **External ID: TESTCOV** **Required** **Codelist: cl_COV_TEST** **Codelist Style: Radio Buttons - Vertical**
Previous SARS-CoV-2 infection	○ Yes (Y) ○ No (N)	**Name: PREVCOVID** **External ID: PREVCOVID** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_NPRVCOV_SHOW**

Number of previous COVID-19 infections	_____	**Name: NPRVCOV** **External ID: NPRVCOV** **Required** **(2.0)**

Previous SARS-CoV-2 infection (ig_MH1_DET) (Repeats, Max: 20) (External ID: ig_MH1_DET)		
Year of infection	_____	**Name: YRCOV** **External ID: YRCOV** **Required** **(4.0)**

Serology status (ig_MH1_SER) (External ID: ig_MH1_SER)		
Serology status (presence/absence of antibodies)	○ Present (PRESENT) ○ Absent (ABSENT) ○ Not assessed (NOT ASSESSED) ○ Unknown (UNKNOWN)	**Name: SEROST** **External ID: SEROST** **Required** **Codelist: cl_SERO_ST** **Codelist Style: Radio Buttons - Vertical**
Date of serology test	_____	**Name: SERODAT** **External ID: SERODAT** **Future Date**
Test used for serology	○ Antibodies to spike protein test (ANTIBODIES TO SPIKE PROTEIN TEST) ○ Nucleocapsid protein test (NUCLEOCAPSID PROTEIN TEST) ○ Other (OTHER) ○ Unknown (UNKNOWN)	**Name: SEROTEST** **External ID: SEROTEST** **Codelist: cl_SERO_TEST** **Rule for Disable: R_DISPLAY_OTHERMH1_SHOW**
If Other, specify	_____	**Name: OTHERMH1** **External ID: OTHERMH1** **Max Length: 1500**

Medical Conditions - Immunocompromising condition

External ID: MH3

Design Object Name: MH3

Short Label: MH3

Restricted: No

Immunocompromising conditions (ig_MH3) (External ID: ig_MH3)		
Solid cancer	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: SLDCMH3** **External ID: SLDCMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_IYSMH3_SHOW**
If yes, specify		**Name: IYSMH3** **External ID: IYSMH3** **Required** **Max Length: 200**
Hematological diseases and stem cell transplant	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: HMGMH3** **External ID: HMGMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_IYS1MH3_SHOW**
If yes, specify		**Name: IYS1MH3** **External ID: IYS1MH3** **Required** **Max Length: 200**
Immune-mediated inflammatory disorders (IMID)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: IMIDMH3** **External ID: IMIDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_IYS2MH3_SHOW**

If yes, specify		**Name: IYS2MH3** **External ID: IYS2MH3** **Required** **Max Length: 200**
Solid organ transplant recipients	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: SOTRMH3** **External ID: SOTRMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_IYS3MH3_SHOW**
If yes, specify		**Name: IYS3MH3** **External ID: IYS3MH3** **Required** **Max Length: 200**

Renal diseases (ig_RD_MH3) (External ID: ig_RD_MH3)		
Renal diseases	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: REDMH3** **External ID: REDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_RETRMH3_SHOW,R_DISPLAY_ORDMH3_SHOW,R_DISPLAY_RENTMH3_SHOW**
Renal transplant recipients (including those with failed transplants within the past 12 months)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: RETRMH3** **External ID: RETRMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Non-transplant patients who have received a comparable level of immunosuppression	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: RENTMH3** **External ID: RENTMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**

Other renal diseases	○ Yes (Y) ○ No (N)	**Name: ORDMH3** **External ID: ORDMH3** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OTSPMH3_SHOW**
Other specify	_____	**Name: OTSPMH3** **External ID: OTSPMH3** **Required** **Max Length: 200**

Liver diseases (ig_LD_MH3) (External ID: ig_LD_MH3)		
Liver diseases	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: LDMH3** **External ID: LDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OLDMH3_SHOW ,R_DISPLAY_LPIMH3_SHOW, R_DISPLAY_LIVTMH3_SHOW**
Liver transplant	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: LIVTMH3** **External ID: LIVTMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Liver patients on immune suppressive therapy (including patients with and without liver cirrhosis)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: LPIMH3** **External ID: LPIMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Other liver diseases	○ Yes (Y) ○ No (N)	**Name: OLDMH3** **External ID: OLDMH3** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OTSP1MH3_SHOW**

Other specify	_____	**Name: OTSP1MH3** **External ID: OTSP1MH3** **Required** **Max Length: 200**

Immune deficiencies (ig_ID_MH3) (External ID: ig_ID_MH3)		
Immune deficiencies	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: IDMH3** **External ID: IDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_ID5MH3_SHOW, R_DISPLAY_ID10MH3_SHOW ,R_DISPLAY_ID4MH3_SHOW, R_DISPLAY_ID8MH3_SHOW, R_DISPLAY_ID1MH3_SHOW, R_DISPLAY_ID7MH3_SHOW, R_DISPLAY_ID2MH3_SHOW, R_DISPLAY_ID9MH3_SHOW, R_DISPLAY_ID3MH3_SHOW, R_DISPLAY_ID6MH3_SHOW**
Common variable immunodeficiency (CVID)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID1MH3** **External ID: ID1MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID2MH3** **External ID: ID2MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Hyper-IgM syndromes	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID3MH3** **External ID: ID3MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**

Good's syndrome (thymoma plus B-cell deficiency)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID4MH3** **External ID: ID4MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Severe Combined Immunodeficiency (SCID)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID5MH3** **External ID: ID5MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Autoimmune polyglandular syndromes/autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID6MH3** **External ID: ID6MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Primary immunodeficiency associated with impaired type I interferon signalling	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID7MH3** **External ID: ID7MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID8MH3** **External ID: ID8MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Secondary immunodeficiency 14 receiving, or eligible for, immunoglobulin replacement therapy	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ID9MH3** **External ID: ID9MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**

Other immune deficiencies	○ Yes (Y) ○ No (N)	**Name: ID10MH3** **External ID: ID10MH3** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OTSP2MH3_SHOW**
Other specify	_____	**Name: OTSP2MH3** **External ID: OTSP2MH3** **Required** **Max Length: 200**

HIV/AIDS (ig_HIV_MH3) (External ID: ig_HIV_MH3)		
HIV/AIDS	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: HIV1MH3** **External ID: HIV1MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_HIV4MH3_SHOW,R_DISPLAY_HIV3MH3_SHOW,R_DISPLAY_HIV2MH3_SHOW**
High levels of immune suppression, have uncontrolled/untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: HIV2MH3** **External ID: HIV2MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
HIV with CD4 350 cells/mm3 and additional risk factors	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: HIV3MH3** **External ID: HIV3MH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical**
Other HIV/AIDS conditions	○ Yes (Y) ○ No (N)	**Name: HIV4MH3** **External ID: HIV4MH3** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OTSP3MH3_SHOW**

Other specify	**Name: OTSP3MH3** **External ID: OTSP3MH3** **Required** **Max Length: 200**

Medical Conditions - Protocol Specific

External ID: MH2

Design Object Name: MH2

Short Label: MH2

Restricted: No

Protocol Specific Medical History (ig_MH2) (External ID: ig_MH2)		
Obesity	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: OBEMH3** **External ID: OBEMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH31_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH31** **External ID: OABMH31** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Overweight	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: OVRMH2** **External ID: OVRMH2** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH22_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH22** **External ID: OABMH22** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Cardiovascular disease	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: CARMH3** **External ID: CARMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH32_SHOW**

Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH32** **External ID: OABMH32** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Cerebrovascular disease	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: CERMH3** **External ID: CERMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH33_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH33** **External ID: OABMH33** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Hypertension	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: HYPMH3** **External ID: HYPMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH34_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH34** **External ID: OABMH34** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Chronic obstructive pulmonary disease (COPD)	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: COPDMH3** **External ID: COPDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH35_SHOW**

Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH35** **External ID: OABMH35** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Asthma	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: ASTMH3** **External ID: ASTMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH36_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH36** **External ID: OABMH36** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Other chronic respiratory disease	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: OCRMH3** **External ID: OCRMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH37_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH37** **External ID: OABMH37** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OTHMH3_SHOW**
Other specify	_____	**Name: OTHMH3** **External ID: OTHMH3** **Required** **Max Length: 200**

Chronic kidney disease	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: CKDMH3** **External ID: CKDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH38_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH38** **External ID: OABMH38** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_STAGEMH3_SHOW**
Stage	○ 1 (1) ○ 2 (2) ○ 3 (3) ○ 4 (4)	**Name: STAGEMH3** **External ID: STAGEMH3** **Required** **Codelist: cl_STAGE** **Codelist Style: Radio Buttons - Vertical**
Chronic liver diseases	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: CLDMH2** **External ID: CLDMH2** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH23_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH23** **External ID: OABMH23** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Diabetes mellitus	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: DMMH3** **External ID: DMMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH39_SHOW**

Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH39** **External ID: OABMH39** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Sickle cell disease	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: SCDMH3** **External ID: SCDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH310_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH310** **External ID: OABMH310** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Pregnancy	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: PREMH3** **External ID: PREMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH311_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH311** **External ID: OABMH311** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Neurodevelopmental disorders	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: NDMH3** **External ID: NDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH312_SHOW**

Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH312** **External ID: OABMH312** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Medical-related technological dependence	○ Yes (YES) ○ No (NO) ○ Not assessed (NOT ASSESSED)	**Name: MRTDMH3** **External ID: MRTDMH3** **Required** **Codelist: cl_NY_NYA** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_OABMH313_SHOW**
Ongoing at baseline	○ Yes (Y) ○ No (N)	**Name: OABMH313** **External ID: OABMH313** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**

Medical History - Other

External ID: MEDHIST_OTHER_RD

Design Object Name: MEDHIST_OTHER_RD

Short Label: MEDHX OTH

Restricted: No

Repeats, Max: 999

Linked Form(s): AE_RD

Medical History (ig_MH) (External ID: ig_MH)		
Medical Condition or Event		**Name: MHTERM** **External ID: MHTERM** **Required** **Max Length: 200**
Ongoing at Baseline	○ Yes (Y) ○ No (N)	**Name: MHONGO** **External ID: MHONGO** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal**

Screening Status

External ID: SUBJSTATUS_SCREEN_RD

Design Object Name: SUBJSTATUS_SCREEN_RD

Short Label: SUBJSTAT SCR

Restricted: No

Baseline Status (ig_SUBJSTATUS_SCREEN) (External ID: ig_SUBJSTATUS_SCREEN)		
Date of Subject Completion or Failure		**Name: DSSTDT_SCREEN** **External ID: DSSTDT_SCREEN** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Subject Status	○ Completed (COMPLETED) ○ Screen Failure (SCREEN FAILURE)	**Name: DSTERM_SCREEN** **External ID: DSTERM_SCREEN** **Required** **Codelist: cl_DSFAIL** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ig_SUBJSTATUS_SCREEN_SF_SHOW,R_DISPLAY_ig_SUBJSTATUS_SCREEN_CMP_SHOW**

Completed Details (ig_SUBJSTATUS_SCREEN_CMP) (External ID: ig_SUBJSTATUS_SCREEN_CMP)		
Subject Entered into Trial	○ Entered into trial (ENTERED INTO TRIAL) ○ Met eligibility criteria but not needed (MET ELIGIBILITY CRITERIA BUT NOT ENROLLED)	**Name: DSTERM_DSENRL** **External ID: DSTERM_DSENRL** **Required** **Codelist: cl_DSENRL** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_DSENRLDTC_DT_SHOW_1**
Date Subject Entered Trial		**Name: DSSTDT_DSENRL** **External ID: DSSTDT_DSENRL** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**

Screen Failure Reasons (ig_SUBJSTATUS_SCREEN_SF) (External ID: ig_SUBJSTATUS_SCREEN_SF)		
Check all that apply		**Name: lbl_CHECKALL** **External ID: lbl_CHECKALL**

Did Not Meet Inclusion/Exclusion Criteria	☐	**Name: DSTERM_INCEXC** **External ID: DSTERM_INCEXC**
Lost to Follow-up	☐	**Name: DSTERM_LTFU** **External ID: DSTERM_LTFU**
Physician Decision	☐	**Name: DSTERM_PHYDCSN** **External ID: DSTERM_PHYDCSN** **Rule for Disable: R_DISPLAY_DSRSSP_PDEC_SHOW**
Physician Decision, Specify	_____	**Name: DSTERSP1** **External ID: DSTERSP1** **Required** **Max Length: 200**
Protocol Deviation	☐	**Name: DSTERM_PROTDEV** **External ID: DSTERM_PROTDEV**
Study Terminated by Sponsor	☐	**Name: DSTERM_STDYTERM** **External ID: DSTERM_STDYTERM**
Withdrawal by Subject	☐	**Name: DSTERM_WDSUBJ_STDY** **External ID: DSTERM_WDSUBJ_STDY** **Rule for Disable: R_DISPLAY_DSRSSP1_SHOW**
Withdrawal by Subject, Specify	_____	**Name: DSTERSP2** **External ID: DSTERSP2** **Required** **Max Length: 200**

Day 7 (Follow Up Call 1)(ev_D7) (Short Label: Day 7 (Follow Up Call 1)) (External ID: ev_D7)

Event Date		**External ID: ev_D7** **Day Range Early: 2** **Day Range Late: 2** **Offset Days: 7** **Overdue Days: 2** **Offset Event: Baseline (Day 0)** **Future Date**

Visit Type

External ID: VIS_TYP

Design Object Name: VIS_TYP

Short Label: VIS_TYP

Restricted: No

Visit Type (ig_VIS_TYP) (External ID: ig_VIS_TYP)		
Visit Type	○ Site inpatient (SITE INPATIENT) ○ Home visit (HOME VISIT)	**Name: VIS_TYP** **External ID: VIS_TYP** **Required** **Codelist: cl_VIS_TYP** **Codelist Style: Radio Buttons - Vertical**

Central Laboratory - Samples

External ID: LAB_CSMP_RD

Design Object Name: LAB_CSMP_RD

Short Label: LAB CSMP

Restricted: No

Samples (ig_LABCSMPL) (External ID: ig_LABCSMPL)		
Samples Collected at this Visit	○ Yes (Y) ○ No (N)	**Name: LBPERF_CSMP_ZZ** **External ID: LBPERF_CSMP_ZZ** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ig_LABC_SMPL_DETAILS_SHOW**

Samples Details (ig_LABCSMP_DET) (External ID: ig_LABCSMP_DET)		
Lab Specimen Collection Date	_____	**Name: LBDT_CSMP** **External ID: LBDT_CSMP** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Lab Specimen Collection Time	_____ : _____ 24 hour clock	**Name: LABTIM** **External ID: LABTIM** **Hint Label: HH:mm**
Lab Specimen Type Collected	○ Nasal swab (NASAL SWAB) ○ Oropharyngeal swab (OROPHARYNGEAL SWAB) ○ Nasal and Oropharyngeal swab (NASAL AND OROPHARYNGEAL SWAB)	**Name: LBCAT_ZZ** **External ID: LBCAT_ZZ** **Required** **Codelist: cl_SPECTYPE_CSMP** **Codelist Style: Radio Buttons - Vertical**

Day 14 (Follow Up Call 2)(ev_D14) (Short Label: Day 14 (Follow Up Call 2)) (External ID: ev_D14)

Event Date		**External ID: ev_D14** **Day Range Early: 2** **Day Range Late: 2** **Offset Days: 14** **Overdue Days: 2** **Offset Event: Baseline (Day 0)** **Future Date**

Visit Type

External ID: VIS_TYP

Design Object Name: VIS_TYP

Short Label: VIS_TYP

Restricted: No

Visit Type (ig_VIS_TYP) (External ID: ig_VIS_TYP)		
Visit Type	○ Site inpatient (SITE INPATIENT) ○ Home visit (HOME VISIT)	**Name: VIS_TYP** **External ID: VIS_TYP** **Required** **Codelist: cl_VIS_TYP** **Codelist Style: Radio Buttons - Vertical**

Central Laboratory - Samples

External ID: LAB_CSMP_RD

Design Object Name: LAB_CSMP_RD

Short Label: LAB CSMP

Restricted: No

Samples (ig_LABCSMPL) (External ID: ig_LABCSMPL)		
Samples Collected at this Visit	○ Yes (Y) ○ No (N)	**Name: LBPERF_CSMP_ZZ** **External ID: LBPERF_CSMP_ZZ** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ig_LABC_SMPL_DETAILS_SHOW**

Samples Details (ig_LABCSMP_DET) (External ID: ig_LABCSMP_DET)		
Lab Specimen Collection Date	_____	**Name: LBDT_CSMP** **External ID: LBDT_CSMP** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Lab Specimen Collection Time	_____ : _____ 24 hour clock	**Name: LABTIM** **External ID: LABTIM** **Hint Label: HH:mm**
Lab Specimen Type Collected	○ Nasal swab (NASAL SWAB) ○ Oropharyngeal swab (OROPHARYNGEAL SWAB) ○ Nasal and Oropharyngeal swab (NASAL AND OROPHARYNGEAL SWAB)	**Name: LBCAT_ZZ** **External ID: LBCAT_ZZ** **Required** **Codelist: cl_SPECTYPE_CSMP** **Codelist Style: Radio Buttons - Vertical**

Day 28 (Follow Up Call 3)(ev_D28) (Short Label: Day 28 (Follow Up Call 3)) (External ID: ev_D28)

Event Date		**External ID: ev_D28** **Day Range Early: 2** **Day Range Late: 2** **Offset Days: 28** **Overdue Days: 2** **Offset Event: Baseline (Day 0)** **Future Date**

Visit Type

External ID: VIS_TYP

Design Object Name: VIS_TYP

Short Label: VIS_TYP

Restricted: No

Visit Type (ig_VIS_TYP) (External ID: ig_VIS_TYP)		
Visit Type	○ Site inpatient (SITE INPATIENT) ○ Home visit (HOME VISIT)	**Name: VIS_TYP** **External ID: VIS_TYP** **Required** **Codelist: cl_VIS_TYP** **Codelist Style: Radio Buttons - Vertical**

Central Laboratory - Samples

External ID: LAB_CSMP_RD

Design Object Name: LAB_CSMP_RD

Short Label: LAB CSMP

Restricted: No

Samples (ig_LABCSMPL) (External ID: ig_LABCSMPL)		
Samples Collected at this Visit	○ Yes (Y) ○ No (N)	**Name: LBPERF_CSMP_ZZ** **External ID: LBPERF_CSMP_ZZ** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ig_LABC_SMPL_DETAILS_SHOW**

Samples Details (ig_LABCSMP_DET) (External ID: ig_LABCSMP_DET)		
Lab Specimen Collection Date	_____	**Name: LBDT_CSMP** **External ID: LBDT_CSMP** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Lab Specimen Collection Time	_____ : _____ 24 hour clock	**Name: LABTIM** **External ID: LABTIM** **Hint Label: HH:mm**
Lab Specimen Type Collected	○ Nasal swab (NASAL SWAB) ○ Oropharyngeal swab (OROPHARYNGEAL SWAB) ○ Nasal and Oropharyngeal swab (NASAL AND OROPHARYNGEAL SWAB)	**Name: LBCAT_ZZ** **External ID: LBCAT_ZZ** **Required** **Codelist: cl_SPECTYPE_CSMP** **Codelist Style: Radio Buttons - Vertical**

End of Study(ev_EOS) (Short Label: End of Study) (External ID: ev_EOS)

Event Date	_____	**External ID: ev_EOS** **Offset Days: 0** **Future Date**

Study Conclusion

External ID: CONC_STUDY_RD

Design Object Name: CONC_STUDY_RD

Short Label: CONC

Restricted: No

Study Conclusion (ig_CONC) (External ID: ig_CONC)		
Date of Study Completion or Discontinuation	_____	**Name: DSSTDT_DSCONC** **External ID: DSSTDT_DSCONC** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Date of Last Contact	_____	**Name: DSENDT_DSCONC** **External ID: DSENDT_DSCONC** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Subject's Status or Reason Subject Did Not Complete	○ Completed (COMPLETED) ○ Death (DEAD) ○ Adverse event (ADVERSE EVENT) ○ Lost to follow-up (LOST TO FOLLOW-UP) ○ Physician decision (PHYSICIAN DECISION) ○ Protocol deviation (PROTOCOL DEVIATION) ○ Site terminated by sponsor (SITE TERMINATED BY SPONSOR) ○ Study terminated by sponsor (STUDY TERMINATED BY SPONSOR) ○ Withdrawal by subject (WITHDRAWAL BY SUBJECT)	**Name: DSPRIMRY_DSCONC** **External ID: DSPRIMRY_DSCONC** **Required** **Codelist: cl_NCOMPLT_CONC_SC** **Rule for Disable: R_DISPLAY_COVIMP_CONC_SHOW,R_DISPLAY_ig_DSRSCD_SITETRM_SHOW,R_DISPLAY_ig_DSRSCD_PROTDEV_SHOW,R_DISPLAY_ig_DSRSCD_LFUP_SHOW,R_DISPLAY_ig_DSRSCD_PHYDEC_SHOW,R_DISPLAY_ig_DSRSCD_WDSUBJ_SHOW**

Subject Discontinued/Withdrew from the Study due to COVID-19 Pandemic	○ Yes (Y) ○ No (N) ○ Unknown (U)	Name: PNRELIND_STUDY External ID: PNRELIND_STUDY Required Codelist: cl_NY_NYUNK

Lost To Follow-up (ig_DSRSCD_LFUP) (External ID: ig_DSRSCD_LFUP)

Check all that apply		Name: lbl_CHECKALL External ID: lbl_CHECKALL
Subject Relocated	☐	Name: DSTERM_LFUPRELO External ID: DSTERM_LFUPRELO
Subject was Incarcerated	☐	Name: DSTERM_LFUPINCAR External ID: DSTERM_LFUPINCAR
Other	☐	Name: DSTERM_LFUPOTH External ID: DSTERM_LFUPOTH
Follow-up Phone Contact Attempted 3 Times	○ Yes (Y) ○ No (N)	Name: FUPCONT3 External ID: FUPCONT3 Required Codelist: cl_NY_NY Codelist Style: Radio Buttons - Horizontal
Follow-up Certified Letter Mailed	○ Yes (Y) ○ No (N)	Name: FUCERTLM External ID: FUCERTLM Required Codelist: cl_NY_NY Codelist Style: Radio Buttons - Horizontal

Physician Decision (ig_DSRSCD_PHYDEC) (External ID: ig_DSRSCD_PHYDEC)

Physician Decision, Specify	_____	Name: DSTERSP1 External ID: DSTERSP1 Required Max Length: 200

Protocol Deviation (ig_DSRSCD_PROTDEV) (External ID: ig_DSRSCD_PROTDEV)

Protocol Deviation, Specify	_____	Name: DSTERM_PDEV_STDY External ID: DSTERM_PDEV_STDY Required Max Length: 200

Site Terminated By Sponsor (ig_DSRSCD_SITETRM) (External ID: ig_DSRSCD_SITETRM)		
Site Terminated by Sponsor, Specify	_____	Name: DSTERM_ST_SP External ID: DSTERM_ST_SP Required Max Length: 200

Withdrawal By Subject (ig_DSRSCD_WDSUBJ) (External ID: ig_DSRSCD_WDSUBJ)		
Check all that apply		Name: lbl_CHECKALL External ID: lbl_CHECKALL
Burden of Procedure	☐	Name: DSTERM_WDSUBJBPROC External ID: DSTERM_WDSUBJBPROC
Subject Relocated	☐	Name: DSTERM_WDSUBJRELO External ID: DSTERM_WDSUBJRELO
Other	☐	Name: DSTERM_WDSUBJOTH External ID: DSTERM_WDSUBJOTH Rule for Disable: R_DISPLAY_DSSBRSSP_SHOW
Other, Specify	_____	Name: DSTERM_SP External ID: DSTERM_SP Required Max Length: 200

Logs(ev_LOGS) (Short Label: Logs) (External ID: ev_LOGS)

Event Date _____	**External ID: ev_LOGS** **Offset Days: 0**

Log Prompt

External ID: OP2

Design Object Name: OP2

Short Label: OP2

Restricted: No

Log Prompt (ig_OP2) (External ID: ig_OP2)		
Did the subject experience any serious or non-serious adverse drug reaction related to Sotrovimab during the study?	○ Yes (Y) ○ No (N)	**Name: AEOP2** **External ID: AEOP2** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Were any concomitant medications taken by the subject prior to baseline and/or during the study?	○ Yes (Y) ○ No (N)	**Name: CMOP2** **External ID: CMOP2** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Did the subject die during the study?	○ Yes (Y) ○ No (N)	**Name: SUBJDEATH** **External ID: SUBJDEATH** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Were any additional swab samples kits dispensed to the subject?	○ Yes (Y) ○ No (N)	**Name: SWABOP2** **External ID: SWABOP2** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**

Adverse Drug Reaction

External ID: AE_RD

Design Object Name: AE_RD

Short Label: AE

Restricted: No

Repeats, Max: 999

Linked Form(s): AE_SER_RD, CONMEDS_RD, MEDHIST_OTHER_RD

Adverse Drug Reaction (ig_AE_EVT) (External ID: ig_AE_EVT)		
Add an entry for each non-serious and serious adverse drug reaction on this form		**Name: lbl_AE_EVT** **External ID: lbl_AE_EVT**
Adverse Drug Reaction		**Name: AETERM** **External ID: AETERM** **Required** **Max Length: 200**
Start Date		**Name: AESTDT** **External ID: AESTDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Outcome	○ Recovered/Resolved (1) ○ Recovering/Resolving (2) ○ Not recovered/Not resolved (3) ○ Recovered/Resolved with sequelae (4) ○ Fatal (5)	**Name: AEOUT** **External ID: AEOUT** **Required** **Codelist: cl_OUT_E2B** **Rule for Disable: R_DISPLAY_AEENDT_SHOW**
End Date		**Name: AEENDT** **External ID: AEENDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Maximum Severity of the Adverse Drug Reaction	○ Mild (MILD) ○ Moderate (MODERATE) ○ Severe (SEVERE)	**Name: AESEV** **External ID: AESEV** **Required** **Codelist: cl_AESEV_E2B**

Related to Study Treatment	○ Yes (Y) ○ No (N)	**Name: AEREL** **External ID: AEREL** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal**
Action Taken with Study Treatment(s)	○ Dose not changed (4) ○ Action(s) taken (Y) ○ Not applicable (X)	**Name: AEACN** **External ID: AEACN** **Required** **Codelist: cl_ACN_E2B_2A** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_lbl_AEACN_TRT_SHOW_1,R_DISPLAY_AEACN_TRT_DGW_SHOW,R_DISPLAY_AEACN_TRT_DGID_SHOW,R_DISPLAY_AEACN_TRT_DSI_SHOW,R_DISPLAY_AEACN_TRT_DSR_SHOW**
Check all Action(s) Taken with Study Treatment(s) that apply..		**Name: lbl_AEACN_TRT** **External ID: lbl_AEACN_TRT**
Drug Withdrawn	☐	**Name: AEACN_DGW** **External ID: AEACN_DGW**
Drug Interrupted/Delayed	☐	**Name: AEACN_DGID** **External ID: AEACN_DGID**
Dose Reduced	☐	**Name: AEACN_DSR** **External ID: AEACN_DSR**
Dose Increased	☐	**Name: AEACN_DSI** **External ID: AEACN_DSI**
Serious	○ Yes (Y) ○ No (N)	**Name: AESER** **External ID: AESER** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ig_AESER_REASON_SHOW,R_DISPLAY_OUTSIDECOUNTRY_SHOW**
Check if the Serious Adverse Drug Reaction Case Occurred outside of the Country of the Subject	☐	**Name: OUTSIDECOUNTRY** **External ID: OUTSIDECOUNTRY** **Rule for Disable: R_DISPLAY_SAECOUNTRY_SHOW**

Country where Adverse Drug Reaction Occurred	○ Afghanistan (AF) ○ Åland Islands (AX) ○ Albania (AL) ○ Algeria (DZ) ○ American Samoa (AS) ○ Andorra (AD) ○ Angola (AO) ○ Anguilla (AI) ○ Antarctica (AQ) ○ Antigua and Barbuda (AG) ○ Argentina (AR) ○ Armenia (AM) ○ Aruba (AW) ○ Australia (AU) ○ Austria (AT) ○ Azerbaijan (AZ) ○ Bahamas (BS) ○ Bahrain (BH) ○ Bangladesh (BD) ○ Barbados (BB) ○ Belarus (BY) ○ Belgium (BE) ○ Belize (BZ) ○ Benin (BJ) ○ Bermuda (BM)	**Name: SAECOUNTRY** **External ID: SAECOUNTRY** **Required** **Codelist: cl_SAECOUNTRY**

- ○ Bhutan (BT)
- ○ Bolivia (BO)
- ○ Bonaire, Sint Eustatius and Saba (BQ)
- ○ Bosnia and Herzegovina (BA)
- ○ Botswana (BW)
- ○ Bouvet Island (BV)
- ○ Brazil (BR)
- ○ British Indian Ocean Territory (IO)
- ○ Brunei Darussalam (BN)
- ○ Bulgaria (BG)
- ○ Burkina Faso (BF)
- ○ Burundi (BI)
- ○ Cabo Verde (CV)
- ○ Cambodia (KH)
- ○ Cameroon (CM)
- ○ Canada (CA)
- ○ Cayman Islands (KY)
- ○ Central African Republic (CF)
- ○ Chad (TD)
- ○ Chile (CL)
- ○ China (CN)
- ○ Christmas Island (CX)
- ○ Cocos (Keeling) Islands (CC)
- ○ Colombia (CO)

- ○ Comoros (KM)
- ○ Congo (the Democratic Republic of the) (CD)
- ○ Congo (CG)
- ○ Cook Islands (CK)
- ○ Costa Rica (CR)
- ○ Côte d'Ivoire (CI)
- ○ Croatia (HR)
- ○ Cuba (CU)
- ○ Curaçao (CW)
- ○ Cyprus (CY)
- ○ Czechia (CZ)
- ○ Denmark (DK)
- ○ Djibouti (DJ)
- ○ Dominica (DM)
- ○ Dominican Republic (DO)
- ○ Ecuador (EC)
- ○ Egypt (EG)
- ○ El Salvador (SV)
- ○ Equatorial Guinea (GQ)
- ○ Eritrea (ER)
- ○ Estonia (EE)
- ○ Eswatini (SZ)
- ○ Ethiopia (ET)
- ○ Falkland Islands (Malvinas) (FK)

- ○ Faroe Islands (FO)
- ○ Fiji (FJ)
- ○ Finland (FI)
- ○ France (FR)
- ○ French Guiana (GF)
- ○ French Polynesia (PF)
- ○ French Southern Territories (TF)
- ○ Gabon (GA)
- ○ Gambia (GM)
- ○ Georgia (GE)
- ○ Germany (DE)
- ○ Ghana (GH)
- ○ Gibraltar (GI)
- ○ Greece (GR)
- ○ Greenland (GL)
- ○ Grenada (GD)
- ○ Guadeloupe (GP)
- ○ Guam (GU)
- ○ Guatemala (GT)
- ○ Guernsey (GG)
- ○ Guinea (GN)
- ○ Guinea-Bissau (GW)
- ○ Guyana (GY)
- ○ Haiti (HT)

- ○ Heard Island and McDonald Islands (HM)
- ○ Holy See (VA)
- ○ Honduras (HN)
- ○ Hong Kong (HK)
- ○ Hungary (HU)
- ○ Iceland (IS)
- ○ India (IN)
- ○ Indonesia (ID)
- ○ Iran (Islamic Republic) (IR)
- ○ Iraq (IQ)
- ○ Ireland (IE)
- ○ Isle of Man (IM)
- ○ Israel (IL)
- ○ Italy (IT)
- ○ Jamaica (JM)
- ○ Japan (JP)
- ○ Jersei (JE)
- ○ Jordan (JO)
- ○ Kazakhstan (KZ)
- ○ Kenya (KE)
- ○ Kiribati (KI)
- ○ Korea (the Democratic People's Republic of) (KP)
- ○ Korea (the Republic of) (KR)
- ○ Kuwait (KW)

- ○ Kyrgystan (KG)
- ○ Lao People's Democratic Republic (LA)
- ○ Latvia (LV)
- ○ Lebanon (LB)
- ○ Lesotho (LS)
- ○ Liberia (LR)
- ○ Libya (LY)
- ○ Liechtenstein (LI)
- ○ Lithuania (LT)
- ○ Luxembourg (LU)
- ○ Macao (MO)
- ○ North Macedonia (MK)
- ○ Madagascar (MG)
- ○ Malawi (MW)
- ○ Malasia (MY)
- ○ Maldives (MV)
- ○ Mali (ML)
- ○ Malta (MT)
- ○ Marshall Islands (MH)
- ○ Matinique (MQ)
- ○ Mauritania (MR)
- ○ Mauritius (MU)
- ○ Mayotte (YT)
- ○ Mexico (MX)

- ○ Micronesia (Federated States if) (FM)
- ○ Moldova (the Republic of) (MD)
- ○ Monaco (MC)
- ○ Mongolia (MN)
- ○ Montenegro (ME)
- ○ Montserrat (MS)
- ○ Morocco (MA)
- ○ Mozambique (MZ)
- ○ Mynanmar (MM)
- ○ Namibia (NA)
- ○ Nauru (NR)
- ○ Nepal (NP)
- ○ Netherlands (NL)
- ○ New Caledonia (NC)
- ○ New Zeland (NZ)
- ○ Nicaragua (NI)
- ○ Niger (NE)
- ○ Nigeria (NG)
- ○ Niue (NU)
- ○ Norfolk Island (NF)
- ○ Northern Mariana Islands (MP)
- ○ Norway (NO)
- ○ Oman (OM)
- ○ Pakistan (PK)

- ○ Palau (PW)
- ○ Palestine, State of (PS)
- ○ Panama (PA)
- ○ Papua New Guinea (PG)
- ○ Paraguay (PY)
- ○ Peru (PE)
- ○ Philippines (PH)
- ○ Pitcairn (PN)
- ○ Poland (PL)
- ○ Portugal (PT)
- ○ Puerto Rico (PR)
- ○ Qatar (QA)
- ○ Réunion (RE)
- ○ Romania (RO)
- ○ Russian Federation (RU)
- ○ Rwanda (RW)
- ○ Saint Barthélemy (BL)
- ○ Saint Helena - Ascension Island - Tristan da Cunha (SH)
- ○ Saint Kitts and Nevis (KN)
- ○ Saint Lucia (LC)
- ○ Saint Martin (French part) (MF)
- ○ Saint Pierre and Miquelon (PM)
- ○ Saint Vincent and the Grenadines (VC)
- ○ Samoa (WS)

- ○ San Marino (SM)
- ○ Sao Tome and Principe (ST)
- ○ Saudi Arabia (SA)
- ○ Senegal (SN)
- ○ Serbia (RS)
- ○ Seychelles (SC)
- ○ Sierra Leone (SL)
- ○ Singapore (SG)
- ○ Sint Maarten (Dutch part) (SX)
- ○ Slovakia (SK)
- ○ Slovenia (SI)
- ○ Somolon Islands (SB)
- ○ Somalia (SO)
- ○ South Africa (ZA)
- ○ South Georgia and the South Sandwich Islands (GS)
- ○ South Sudan (SS)
- ○ Spain (ES)
- ○ Sri Lanka (LK)
- ○ Sudan (SD)
- ○ Suriname (SR)
- ○ Svalbard - Jan Mayen (SJ)
- ○ Sweden (SE)
- ○ Switzerland (CH)
- ○ Syrian Arab Republic (SY)

- ○ Taiwan (Province of China) (TW)
- ○ Tajikistan (TJ)
- ○ Tanzania, the United Republic of (TZ)
- ○ Thailand (TH)
- ○ Timor-Leste (TL)
- ○ Togo (TG)
- ○ Tokelau (TK)
- ○ Tonga (TO)
- ○ Trinidad and Tobago (TT)
- ○ Tunisia (TN)
- ○ Turkey (TR)
- ○ Turkmenistan (TM)
- ○ Turks and Caicos Islands (TC)
- ○ Tuvalu (TV)
- ○ Uganda (UG)
- ○ Ukraine (UA)
- ○ United Arab Emirates (AE)
- ○ United Kingdom of Great Britain and Northern Ireland (GB)
- ○ United States Minor Outlying Islands (UM)
- ○ United States of America (US)
- ○ Uruguay (UY)
- ○ Uzbekistan (UZ)
- ○ Vanuatu (VU)
- ○ Venezuela (Bolivarian Republic of) (VE)

	○ Venezuela (Bolivarian Republic of) (VE) ○ Viet Nam (VN) ○ Virgin Islands (British) (VG) ○ Virgin Islands (U.S.) (VI) ○ Wallis and Futuna (WF) ○ Western Sahara (EH) ○ Yemen (YE) ○ Zambia (ZM) ○ Zimbabwe (ZW)	
Check if the event is probable, confirmed, suspected COVID-19	☐	**Name: COVDIAG** **External ID: COVDIAG** **Rule for Disable: R_DISPLAY_FAORRES_C19CSDIA_SHOW**
Case Diagnosis	○ Confirmed (CONFIRMED) ○ Probable (PROBABLE) ○ Suspected (SUSPECTED)	**Name: FAORRES_C19CSDIA** **External ID: FAORRES_C19CSDIA** **Required** **Codelist: cl_COVDIAG_CASE** **Codelist Style: Radio Buttons - Vertical**
Caused study discontinuation	○ Yes (Y) ○ No (N)	**Name: AEDIS** **External ID: AEDIS** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**

Seriousness Reason (ig_AESER_REASON) (External ID: ig_AESER_REASON)		
Check all Reason(s) for considering this a serious adverse drug reaction.		**Name: lbl_AESER_REAS** **External ID: lbl_AESER_REAS**
Results in death	☐	**Name: AESDTH** **External ID: AESDTH** **Rule for Disable: R_DISPLAY_AULABEL1_SHOW,R_DISPLAY_DDORRES_AUTOPIND_SHOW**

Autopsy Done	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: DDORRES_AUTOPIND** **External ID: DDORRES_AUTOPIND** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_DDORRES_AUTOPRES_SHOW**
If Yes, summarize findings in General Narrative Comments section of the Adverse Drug Reaction Continued form.		**Name: AULABEL1** **External ID: AULABEL1**
Autopsy Results Available	○ Yes (Y) ○ No (N)	**Name: DDORRES_AUTOPRES** **External ID: DDORRES_AUTOPRES** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical**
Is life-threatening	☐	**Name: AESLIFE** **External ID: AESLIFE**
Requires subject hospitalisation or prolongation of existing hospitalisation	☐	**Name: AESHOSP** **External ID: AESHOSP**
Results in persistent or significant disability/incapacity	☐	**Name: AESDISAB** **External ID: AESDISAB**
Is a congenital anomaly/birth defect	☐	**Name: AESCONG** **External ID: AESCONG**
Possible Hy’s law case	☐	**Name: AESPROT** **External ID: AESPROT**
Other medically important serious event, specify within general narrative comment	☐	**Name: AESMIE** **External ID: AESMIE**

Adverse Drug Reaction Continued

External ID: AE_SER_RD

Design Object Name: AE_SER_RD

Short Label: SAE CASE

Restricted: No

Repeats, Max: 999

Linked Form(s): AE_RD

Adverse Drug Reaction (ig_AESER_CASE) (External ID: ig_AESER_CASE)		
Link this Adverse Drug Reaction to all clinically or temporally related Adverse Drug Reaction entries on Adverse Drug Reaction form.		**Name: lbl_AESER_AE** **External ID: lbl_AESER_AE**
Summary of Event(s)	_____	**Name: SAE_SUMM** **External ID: SAE_SUMM** **Required** **Max Length: 200**
ADR Related to Study Participation Activities other than Study Treatment *((e.g. procedures, blood draws, washout, etc.))*	○ Yes (Y) ○ No (N)	**Name: AERELNST** **External ID: AERELNST** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal**

Relevant Medical Conditions/Risk Factors (ig_AESER_MHX) (Repeats, Max: 999) (External ID: ig_AESER_MHX)		
Medical Condition	_____	**Name: SAEMHTRM** **External ID: SAEMHTRM** **Required** **Max Length: 100**
Start Date	_____	**Name: SAEMHSTDT** **External ID: SAEMHSTDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Continuing	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: SAEMHCONT** **External ID: SAEMHCONT** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_MHLSTOCDT_SHOW_1**

Date of Last Occurrence	_____	Name: MHLSTOCDT External ID: MHLSTOCDT Required Future Date Hint Label: dd-MMM-yyyy

Relevant Diagnostic Lab Results (ig_AESER_LAB) (Repeats, Max: 999) (External ID: ig_AESER_LAB)

Test Name	○ Chemistry - All (CHEM ALL) ○ Chemistry - Alanine Aminotransferase (ALT) ○ Chemistry - Aspartate Aminotransferase (AST) ○ Chemistry - Albumin (ALB) ○ Chemistry - Alkaline Phosphatase (ALP) ○ Chemistry - Bilirubin (BILI) ○ Chemistry - Direct Bilirubin (BILDIR) ○ Chemistry - Brain Natriuretic Peptide (BNP) ○ Chemistry - C Reactive Protein (CRP) ○ Chemistry - Calcium (CA) ○ Chemistry - Calcium, Ionized (CAION) ○ Chemistry - Calcium Corrected for Albumin (CACRALB) ○ Chemistry - Chloride (CL) ○ Chemistry - Creatine Kinase (CK) ○ Chemistry - Creatinine (CREAT) ○ Chemistry - Creatinine Clearance (CREATCLR) ○ Chemistry - Ferritin (FERRITIN) ○ Chemistry - Triiodothyronine, Free (T3FR) ○ Chemistry - Thyroxine, Free (T4FR) ○ Chemistry - Gamma Glutamyl Transferase (GGT) ○ Chemistry - Glucose (GLUC) ○ Chemistry - Lactate Dehydrogenase (LDH)	**Name: SAELBTST** **External ID: SAELBTST** **Required** **Codelist: SAELBTST** **Rule for Disable: R_DISPLAY_SAELBOTH_SHOW_1**

- ○ Chemistry - Magnesium (MG)
- ○ Chemistry - Phosphate (PHOS)
- ○ Chemistry - Potassium (K)
- ○ Chemistry - Protein (PROT)
- ○ Chemistry - Sodium (SODIUM)
- ○ Chemistry - Thyrotropin (TSH)
- ○ Chemistry - Carbon Dioxide (CO2)
- ○ Chemistry - Troponin I (TROPONI)
- ○ Chemistry - Troponin T (TROPONT)
- ○ Chemistry - Tryptase (TRYPTASE)
- ○ Chemistry - Urea (UREA)
- ○ Chemistry - Urea Nitrogen (UREAN)
- ○ Chemistry - Urate (URATE)
- ○ CBC - All (HEMA ALL)
- ○ CBC - Hemoglobin (HGB)
- ○ CBC - Hematocrit (HCT)
- ○ CBC - Erythrocytes (RBC)
- ○ CBC - Platelets (PLAT)
- ○ CBC - Leukocytes (WBC)
- ○ CBC - Neutrophils (NEUT)
- ○ CBC - Neutrophils/Leukocytes (NEUTLE)
- ○ CBC - Lymphocytes (LYM)
- ○ CBC - Lymphocytes/Leukocytes (LYMLE)

- ○ CBC - Monocytes (MONO)
- ○ CBC - Monocytes/Leukocytes (MONOLE)
- ○ CBC - Eosinophils (EOS)
- ○ CBC - Eosinophils/Leukocytes (EOSLE)
- ○ CBC - Basophils (BASO)
- ○ CBC - Basophils/Leukocytes (BASOLE)
- ○ CBC - Ery. Mean Corpuscular Hemoglobin (MCH)
- ○ CBC - Ery. Mean Corpuscular HGB Concentration (MCHC)
- ○ CBC - Ery. Mean Corpuscular Volume (MCV)
- ○ CBC - Reticulocytes (RETI)
- ○ Coagulation - All (COAG ALL)
- ○ Coagulation - Activated Partial Thromboplastin Time (APTT)
- ○ Coagulation - Prothrombin Time (PT)
- ○ Coagulation - Partial Thromboplastin Time (PTT)
- ○ Coagulation - Prothrombin Intl. Normalized Ratio (INR)
- ○ Urinalysis - All (URIN ALL)
- ○ Urinalysis - Glucose (GLUCU)
- ○ Urinalysis - Ketones (KETONES)
- ○ Urinalysis - Occult Blood (OCCBLD)
- ○ Urinalysis - pH (PHU)
- ○ Urinalysis - Protein (PROTU)
- ○ Urinalysis - Specific Gravity (SPGRAV)

- ○ Urinalysis - Protein Excretion Rate (PROTEXR)
- ○ Urinalysis - Monocytes (MONOU)
- ○ Urinalysis - Monocytes/Leukocytes (MONOULE)
- ○ Urinalysis - Leukocyte Esterase (LEUKASE)
- ○ Urinalysis - Erythrocytes (RBCU)
- ○ Urinalysis - Granular Casts (CSGRAN)
- ○ Urinalysis - Hyaline Casts (CSHYAL)
- ○ Urinalysis - Cellular Casts (CSCELL)
- ○ Urinalysis - Calcium Corrected for Albumin (CACRALBU)
- ○ GFR - All (GFR ALL)
- ○ GFR - GFR from Creat,UreaN,Alb Adj BSA (GFRBSCUA)
- ○ GFR - GFR from Creatinine Adjusted for BSA (GFRBSCRT)
- ○ BMA - All (BMA ALL)
- ○ BMA - Plasma Cells/Total Cells (PLSCECEA)
- ○ BMA - Erythroid Cells/Total Cells (ERCECE)
- ○ BMA - Myeloid Cells/Nucleated Cells (MYCENCE)
- ○ BMB - All (BMB ALL)
- ○ BMB - Plasma Cells/Total Cells (PLSCECEB)
- ○ BMB - Cellularity (CELLULAR)
- ○ Monoclonal Protein Excretion Rate (MPROTEXRZ)

	○ Spot Urine - Albumin/Creatinine (ALBCREAT) ○ Other (OTHER)	
Other, specify		**Name: SAELBOTH** **External ID: SAELBOTH** **Required** **Max Length: 1500**
Test Date		**Name: AETESTDAT** **External ID: AETESTDAT** **Required** **Future Date** **Hint Label: DD-mmm-yyyy**
Test Result		**Name: AETESTRESL** **External ID: AETESTRESL** **Required** **Max Length: 50**
Test Units		**Name: AETESTUNIT** **External ID: AETESTUNIT** **Required** **Max Length: 1500**
Normal Low Range		**Name: AENLR** **External ID: AENLR** **Required** **Max Length: 50**
Normal High Range		**Name: AENHR** **External ID: AENHR** **Required** **Max Length: 50**

Rechallenge (ig_AESER_TRTRECH) (External ID: ig_AESER_TRTRECH)		
Reported Event(s) Recur When Study Treatments Stopped Temporarily and Restarted	○ Yes (Y) ○ No (N) ○ Not applicable (NA)	**Name: AESRECHA** **External ID: AESRECHA** **Codelist: cl_NY_NYNA** **Codelist Style: Radio Buttons - Horizontal**

General Narrative Comments (ig_AESER_SAECOM) (External ID: ig_AESER_SAECOM)

Provide a brief narrative description of ADR, possible other causes of the event (e.g. lack of efficacy, withdrawal of study treatment(s), the disease under study or other medical conditions) and details of the treatment.		**Name: lbl_AESER_SAECOM** **External ID: lbl_AESER_SAECOM**
General Narrative Comments		**Name: SAECOMM** **External ID: SAECOMM** **Required** **Max Length: 1500**
General Narrative Comments Continuation		**Name: SAECOMM1** **External ID: SAECOMM1** **Max Length: 1500**

Safety System Case (Added by Integration ONLY) (SAECASES) (External ID: SAECASES)		
Safety System Case		**Name: SAECASE** **External ID: SAECASE** **Hint Label: Set by integration** **Max Length: 30** **Read Only**

Concomitant Medication/Therapy

External ID: CONMEDS_RD

Design Object Name: CONMEDS_RD

Short Label: CONMEDS

Restricted: No

Repeats, Max: 999

Dynamic Add (by rule: Z_ADD_FR_CONMEDS)

Linked Form(s): AE_RD

Concomitant Medication/Therapy (ig_CM) (External ID: ig_CM)		
Medication or Therapy		**Name: CMTRT** **External ID: CMTRT** **Required** **Max Length: 200**
Start Date		**Name: CMSTDT** **External ID: CMSTDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Ongoing	○ Yes (Y) ○ No (N)	**Name: CMONGO** **External ID: CMONGO** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_CMENDT_SHOW**
End Date		**Name: CMENDT** **External ID: CMENDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Indication		**Name: CMINDC** **External ID: CMINDC** **Required** **Max Length: 200**

Medication related to SARS-CoV-2 infection	○ Yes (Y) ○ No (N)	**Name: MEDCON** **External ID: MEDCON** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_MEDTYPE_SHOW,R_DISPLAY_TYPECON_SHOW**
Type of medication(SARS-CoV-2 related medication)	○ Corticosteroids (inhaled, systemic) (CORTICOSTEROIDS (INHALED, SYSTEMIC)) ○ Remdesivir (REMDESIVIR) ○ IL-6 inhibitors (IL-6 INHIBITORS) ○ Other mAbs (casirivimab and imdevimab) (OTHER mABs (CASIRIVIMAB AND IMDEVIMAB)) ○ Antivirals (molnupiravir, nirmatrelvir and ritonavir, other) (ANTIVIRALS (MOLNUPIRAVIR, NIRMATRELVIR AND RITONAVIR, OTHER)) ○ Others following national guidance (OTHERS FOLLOWING NATIONAL GUIDANCE) ○ Experimental drugs (EXPERIMENTAL DRUGS)	**Name: TYPECON** **External ID: TYPECON** **Required** **Codelist: cl_TYPE_MED** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_SPEXD_SHOW,R_DISPLAY_OTYPEMED_SHOW**
Other specify	_____	**Name: OTYPEMED** **External ID: OTYPEMED** **Required** **Max Length: 200**
Specify experimental drugs	_____	**Name: SPEXD** **External ID: SPEXD** **Required** **Max Length: 200**

Type of medication	○ Immunosuppressant treatment (IMMUNOSUPPRESSANT TREATMENT) ○ Other (OTHER)	**Name: MEDTYPE** **External ID: MEDTYPE** **Required** **Codelist: cl_MED_TYPE** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_TYPEOMED_SHOW**
Other specify		**Name: TYPEOMED** **External ID: TYPEOMED** **Required** **Max Length: 200**
Dose per Administration		**Name: CMDOSE** **External ID: CMDOSE** **Required** **Max Length: 15**

Dose Unit	○ % (%) ○ 10^6 IU (10^6 IU) ○ 10^6 U (10^6 U) ○ 100 IU/mL (100 IU/mL) ○ Ampule (AMPULE) ○ Application (APPLICATION) ○ Bottle (BOTTLE) ○ Caplet (CAPLET) ○ Capsule (CAPSULE) ○ Cubic centimeter (CUBIC CENTIMETER) ○ Cup (CUP) ○ Drop (DROP) ○ Fingertip unit (FINGERTIP UNIT) ○ g (g) ○ g/kg (g/kg) ○ g/L (g/L) ○ g/m2 (g/m2) ○ g/m2/12h (g/m2/12h) ○ g/mL (g/mL) ○ gtt (gtt) ○ Inhalation (INHALATION) ○ IU (IU) ○ IU/kg (IU/kg) ○ IU/kg/h (IU/kg/h)	**Name: CMDOSU** **External ID: CMDOSU** **Required** **Codelist: cl_UNIT_CM**

- ○ IU/mL (IU/mL)
- ○ L (L)
- ○ L/min (L/min)
- ○ Lozenge (LOZENGE)
- ○ MBq (MBq)
- ○ mCi (mCi)
- ○ mEq (mEq)
- ○ mg (mg)
- ○ mg/h (mg/h)
- ○ mg/kg (mg/kg)
- ○ mg/kg/h (mg/kg/h)
- ○ mg/kg/min (mg/kg/min)
- ○ mg/m2 (mg/m2)
- ○ mg/mL (mg/mL)
- ○ mg/wk (mg/wk)
- ○ mL (mL)
- ○ mL/h (mL/h)
- ○ mL/kg (mL/kg)
- ○ mL/min (mL/min)
- ○ mmol (mmol)
- ○ mmol/kg (mmol/kg)
- ○ mmol/mL (mmol/mL)
- ○ Nebule (NEBULE)
- ○ ng (ng)
- ○ oz (oz)

- ○ Package (PACKAGE)
- ○ Patch (PATCH)
- ○ Puff (PUFF)
- ○ Ring (RING)
- ○ Sachet (SACHET)
- ○ Spray (SPRAY)
- ○ Suppository (SUPPOSITORY)
- ○ Tablet (TABLET)
- ○ Tbsp (Tbsp)
- ○ Troche (TROCHE)
- ○ tsp (tsp)
- ○ U (U)
- ○ U/g (U/g)
- ○ U/h (U/h)
- ○ U/kg/min (U/kg/min)
- ○ U/min (U/min)
- ○ ug (ug)
- ○ ug/g (ug/g)
- ○ ug/h (ug/h)
- ○ ug/kg (ug/kg)
- ○ ug/kg/min (ug/kg/min)
- ○ ug/min (ug/min)
- ○ ug/mL (ug/mL)
- ○ uL (uL)
- ○ umol (umol)

- ○ Vial (VIAL)
- ○ Unknown (UNKNOWN)

Frequency	○ Continuous (CONTINUOUS) ○ Once (ONCE) ○ PRN (PRN) ○ QH (QH) ○ Q2H (Q2H) ○ Q4H (Q4H) ○ Q6H (Q6H) ○ Q8H (Q8H) ○ Q12H (Q12H) ○ QD (QD) ○ BID (BID) ○ TID (TID) ○ QID (QID) ○ 5 times per day (5 TIMES PER DAY) ○ QOD (QOD) ○ Q3D (Q3D) ○ Q4D (Q4D) ○ 1 time per week (1 TIME PER WEEK) ○ 2 times per week (2 TIMES PER WEEK) ○ 3 times per week (3 TIMES PER WEEK) ○ 4 times per week (4 TIMES PER WEEK) ○ 5 times per week (5 TIMES PER WEEK) ○ Every 2 weeks (EVERY 2 WEEKS)	**Name: CMDOSFRQ** **External ID: CMDOSFRQ** **Required** **Codelist: cl_FREQ_CMFREQ**

- ○ Every 3 weeks (EVERY 3 WEEKS)
- ○ QM (QM)
- ○ Q3M (Q3M)
- ○ Unknown (UNKNOWN)

Route of Administration	○ Auricular (OTIC) (AURICULAR (OTIC)) ○ Buccal (BUCCAL) ○ Conjunctival (CONJUNCTIVAL) ○ Dental (DENTAL) ○ Endotracheal (ENDOTRACHEAL) ○ Epidural (EPIDURAL) ○ Inhalation (INHALATION) ○ Intra-arterial (INTRA-ARTERIAL) ○ Intra-articular (INTRA-ARTICULAR) ○ Intrabursal (INTRABURSAL) ○ Intracardiac (INTRACARDIAC) ○ Intradermal (INTRADERMAL) ○ Intragastric (INTRAGASTRIC) ○ Intrajejunal (INTRAJEJUNAL) ○ Intralesional (INTRALESIONAL) ○ Intramuscular (INTRAMUSCULAR) ○ Intraocular (INTRAOCULAR) ○ Intraosseous (INTRAOSSEOUS) ○ Intraperitoneal (INTRAPERITONEAL) ○ Intrapleural (INTRAPLEURAL) ○ Intrathecal (INTRATHECAL) ○ Intrauterine (INTRAUTERINE) ○ Intravenous (INTRAVENOUS)	**Name: CMROUTE** **External ID: CMROUTE** **Required** **Codelist: cl_ROUTE_CM**

- ○ Intravesical (INTRAVESICAL)
- ○ Nasal (NASAL)
- ○ Nasogastric (NASOGASTRIC)
- ○ Ophthalmic (OPHTHALMIC)
- ○ Oral (ORAL)
- ○ Other (OTHER)
- ○ Parenteral (PARENTERAL)
- ○ Rectal (RECTAL)
- ○ Subconjunctival (SUBCONJUNCTIVAL)
- ○ Subcutaneous (SUBCUTANEOUS)
- ○ Sublingual (SUBLINGUAL)
- ○ Topical (TOPICAL)
- ○ Transdermal (TRANSDERMAL)
- ○ Transmucosal (TRANSMUCOSAL)
- ○ Urethral (URETHRAL)
- ○ Vaginal (VAGINAL)
- ○ Unknown (UNKNOWN)

Death

External ID: DEATH_RD

Design Object Name: DEATH_RD

Short Label: DEATH

Restricted: No

Dynamic Add (by rule: Z_ADD_FR_DEAT)

Primary Cause of Death (ig_PRIMARY)	**(External ID: ig_PRIMARY)**	
Date of Death	_____	**Name: DTHDT** **External ID: DTHDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Primary Cause of Death	○ Cancer (CANCER) ○ Cardiac arrhythmia (CARDIAC ARRHYTHMIA) ○ Haemorrhage (HAEMORRHAGE) ○ Heart failure (HEART FAILURE) ○ Myocardial infarction (MYOCARDIAL INFARCTION) ○ Other cardiovascular diagnosis (OTHER CARDIOVASCULAR DIAGNOSIS) ○ Pulmonary embolism (PE) (PULMONARY EMBOLISM (PE)) ○ Sepsis (SEPSIS) ○ Stroke (STROKE) ○ Suicide (SUICIDE) ○ Trauma (TRAUMA) ○ COVID19 disease (COVID19 DISEASE) ○ Other (OTHER) ○ Unknown (UNKNOWN)	**Name: DDORRES_PRCDTH** **External ID: DDORRES_PRCDTH** **Required** **Codelist: cl_DTH_CAUSE_PRIM**

Pregnancy Information

External ID: PREG_F_RD

Design Object Name: PREG_F_RD

Short Label: PREG

Restricted: No

Dynamic Add (by rule: Z_ADD_FR_PREG)

Pregnancy Information (ig_PREG_F) (External ID: ig_PREG_F)		
Date of Assessment	_____	**Name: RPDT** **External ID: RPDT** **Required** **Future Date** **Hint Label: dd-MMM-yyyy**
Subject Become Pregnant during the Study	○ Yes (Y) ○ No (N)	**Name: RPORRES_PREGST_F** **External ID: RPORRES_PREGST_F** **Required** **Codelist: cl_NY_NY** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_lbl_RPORRES_PREGF_SHOW**
If Yes, complete the paper Pregnancy Notification form.		**Name: lbl_RPORRES_PREGF** **External ID: lbl_RPORRES_PREGF**

Additional Sample Collection Kit Dispensation

External ID: OP4

Design Object Name: OP4

Short Label: OP4

Restricted: No

Dynamic Add (by rule: Z_ADD_FR_OP4)

Swab sample collection kits (ig_OP4) (External ID: ig_OP4)		
Kit Number 4		**Name: KT5OP4** **External ID: KT5OP4** **Required** **Max Length: 6**
Date of Dispensation		**Name: KTDESPDAT** **External ID: KTDESPDAT** **Required** **Future Date**
Reason for dispensing additional kit		**Name: RESN5OP4** **External ID: RESN5OP4** **Required** **Max Length: 200**
Kit Number 5		**Name: KT6OP4** **External ID: KT6OP4** **Max Length: 6**
Date of Dispensation		**Name: KTDESPDAT1** **External ID: KTDESPDAT1** **Future Date**
Reason for dispensing additional kit		**Name: RESN6OP4** **External ID: RESN6OP4** **Max Length: 200**
Kit Number 6		**Name: KT7OP4** **External ID: KT7OP4** **Max Length: 6**
Date of Dispensation		**Name: KTDESPDAT2** **External ID: KTDESPDAT2** **Future Date**

Reason for dispensing additional kit		**Name: RESN7OP4** **External ID: RESN7OP4** **Max Length: 200**
Kit Number 7		**Name: KT8OP4** **External ID: KT8OP4** **Max Length: 6**
Date of Dispensation		**Name: KTDESPDAT3** **External ID: KTDESPDAT3** **Future Date**
Reason for dispensing additional kit		**Name: RESN8OP4** **External ID: RESN8OP4** **Max Length: 200**

Hospitalizations

External ID: HOSPLOG

Design Object Name: HOSPLOG

Short Label: HOSPLOG

Restricted: No

Repeats, Max: 999

Dynamic Add (by rule: Z_ADD_FR_HOSP_LOG)

Hospitalizations (ig_HOSPLOG) (External ID: ig_HOSPLOG)		
Hospital admission	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: HOSADM** **External ID: HOSADM** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_ADMDAT_SHOW,R_DISPLAY_HOSCOV_SHOW,R_DISPLAY_ICUYN_SHOW,R_DISPLAY_DISHOSP_SHOW**
Hospitalization related to COVID-19	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: HOSCOV** **External ID: HOSCOV** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical**
Hospital admission date	_____	**Name: ADMDAT** **External ID: ADMDAT** **Required** **Future Date**
Was the patient discharged from hospital before the end of the study follow-up period (within 28 day from sotrovimab administration)?	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: DISHOSP** **External ID: DISHOSP** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_DISDAT_SHOW**
Hospital discharge date	_____	**Name: DISDAT** **External ID: DISDAT** **Required** **Future Date**

Was subject admitted to an intensive care unit (ICU) at this hospitalization ?	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: ICUYN** **External ID: ICUYN** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Horizontal** **Rule for Disable: R_DISPLAY_ICHOSP_SHOW, R_DISPLAY_ICUADMDT_SHOW**
Date of admission to ICU		**Name: ICUADMDT** **External ID: ICUADMDT** **Required** **Range 2021-03-01-2025-12-31** **Future Date**
Was the patient discharged from ICU before the end of the study follow-up period (within 28 day from sotrovimab administration)?	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: ICHOSP** **External ID: ICHOSP** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_ICUDISDT_SHOW**
Date of discharge from ICU		**Name: ICUDISDT** **External ID: ICUDISDT** **Required** **Range 2021-03-01-2025-12-31** **Future Date**
Did the subject require new or increased oxygen support?	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: HOSOXY** **External ID: HOSOXY** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical** **Rule for Disable: R_DISPLAY_HOSSUPOXY_SHOW,R_DISPLAY_NIVHHOS_SHOW,R_DISPLAY_HOSINOXY_SHOW,R_DISPLAY_HOSECMO_SHOW**
Supplemental oxygen(not high flow)	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: HOSSUPOXY** **External ID: HOSSUPOXY** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical**

Non-invasive ventilation or high-flow	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: NIVHHOS** **External ID: NIVHHOS** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical**
Invasive mechanical ventilation	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: HOSINOXY** **External ID: HOSINOXY** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical**
Extracorporeal membrane oxygenation (ECMO)	○ Yes (Y) ○ No (N) ○ Unknown (U)	**Name: HOSECMO** **External ID: HOSECMO** **Required** **Codelist: cl_NY_NYUNK** **Codelist Style: Radio Buttons - Vertical**