Journal of Infection 91 (2025) 106510

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Infectious Disease Practice

Monitoring the emergence of resistance with sotrovimab in immunocompromised patients with COVID-19: LUNAR study

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ARTICLE INFO

Article history:
Accepted 11 May 2025
Available online 19 May 2025

Keywords:
Immunocompromised
Omicron
SARS-CoV-2
Sotrovimab

SUMMARY

Objectives: To assess outcomes in sotrovimab-treated immunocompromised patients in the United Kingdom.
Methods: Multicenter, prospective, observational, descriptive study in immunocompromised, non-hospitalized adults infected with SARS-CoV-2 who received intravenous sotrovimab 500 mg as standard-of-care (July 1, 2022–June 30, 2023; Omicron predominance). Virology analyses included determination of SARS-CoV-2 viral load, spike sequencing, and determination of amino-acid substitutions in the spike protein and sotrovimab epitope.
Results: The proportion of participants (N = 217) with undetectable SARS-CoV-2 RNA was 25.1% at day 7, 65.8% at day 14%, and 83.5% at day 28. Of 156 participants with paired sequences, 101 (64.7%) and 47 (30.1%) had treatment-emergent substitutions at > 50% allelic frequency in the spike protein and sotrovimab epitope, respectively, at any post-baseline timepoint. Ten treatment-emergent substitutions (at positions 337, 340, and 356) were identified in the epitope at > 50% allelic frequency. Five of 18 (27.8%) participants with, versus 22/30 (73.3%) of those without, treatment-emergent epitope substitutions at day 14 achieved undetectable SARS-CoV-2 RNA levels at day 28.
Conclusions: In this immunocompromised population infected with SARS-CoV-2 who received early treatment with sotrovimab, most participants (83.5%) experienced substantial viral load reductions by day 28. Treatment-emergent substitutions occurred in the sotrovimab epitope, including substitutions known to reduce susceptibility in vitro. Several treatment-emergent substitutions were associated with viral persistence.

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https://doi.org/10.1016/j.jinf.2025.106510

Introduction

The outbreak of coronavirus 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) in March 2020.[1] In May 2023, the WHO declared COVID-19 to be an established and ongoing health issue that no longer constitutes a public health emergency of international concern.[1] Nevertheless, SARS-CoV-2 remains problematic in high-risk groups and those who do not respond durably to vaccination.[2–4] In particular, immunocompromised individuals are at higher risk of infection and of hospitalization or death in the event of developing symptomatic COVID-19 than non-immunocompromised individuals, even when fully vaccinated.[5,6] They are also more likely to transmit the virus to household contacts (leading to larger clusters of infection),[7] and more likely to shed the virus for longer (potentially increasing the risk of emergent variants).[7–9]

Sotrovimab is a dual-action Fc-engineered neutralizing human monoclonal antibody (mAb) with potent activity against the spike protein of SARS-CoV-2.[10,11] The safety and efficacy of sotrovimab in non-hospitalized patients with COVID-19 at high risk of severe disease were demonstrated in the COMET-ICE trial (NCT04545060),[12,13] which was conducted when the wild-type Wuhan strain of SARS-CoV-2 was predominant: a single intravenous (IV) infusion of sotrovimab 500 mg reduced the risk of all-cause > 24-hour hospitalization or death *versus* placebo by 79%.[12,13] Since then, numerous variants of SARS-CoV-2 have emerged, and there remains considerable uncertainty around their transmissibility, virulence, and potential for evading vaccine-induced immunity or developing resistance against antivirals and neutralizing mAbs (NmAbs). The potential for NmAbs to select for viral variants with reduced susceptibility to treatment, that can evade vaccine-derived immunity, or have properties which increase viral transmissibility, is of particular concern in immunocompromised individuals due to the propensity for prolonged viral replication and shedding.[14–18] We therefore assessed the emergence of SARS-CoV-2 spike variants in immunocompromised non-hospitalized patients in the United Kingdom (UK) treated with sotrovimab for symptomatic COVID-19, and the impact of detected changes on clinical and virological outcomes.

Methods

This was a multicenter, prospective, observational, descriptive study conducted across nine sites in England and Wales.

Study population

Immunocompromised, symptomatic, non-hospitalized adults aged ≥18 years infected with SARS-CoV-2 (diagnosed by a positive polymerase chain reaction [PCR] or antigen test) who received sotrovimab 500 mg IV treatment as standard of care between July 1, 2022 and June 30, 2023 were screened for eligibility. The list of immunocompromised populations eligible to receive sotrovimab was derived from the NHS Clinical Commissioning Policy applicable at the time of recruitment.[19] Patients who required hospitalization at baseline, or who initiated treatment with sotrovimab in an inpatient setting, were excluded. Full eligibility criteria are shown in Supplementary Table 1.

No formal sample-size calculations were conducted. The aim was to collect data for a period of 12 months, or until the enrollment of up to 625 patients (based on the rate of treatment-emergent [TE] substitutions in the COMET-ICE study[12,13]). Due to a change in guidance in the UK in March 2023[20] and the subsequent reduced use of sotrovimab, 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.

Study endpoints

Primary end points were the proportion of patients eligible for sequence analysis who had any amino acid (AA) change from baseline in the epitope of sotrovimab binding, and in the spike protein, in samples collected at days 7, 14, and 28 (± 2 days) after treatment.

Secondary end points included: the proportion of patients with SARS-CoV-2 variants of concern (VOC) or variants under investigation (VUI) (Supplementary Table 2) on the earliest possible sample, including at baseline (pre-treatment); the proportion of patients with undetectable virus assessed by reverse transcription PCR at days 7, 14, and 28 (± 2 days); clinical outcomes (all-cause and COVID-19-related hospital admissions, intensive care unit [ICU] admissions, and deaths) through day 28 post-sotrovimab administration; AA changes detected at (i) minority (> 5%) allelic frequency and (ii) consensus (> 50%) level in the SARS-CoV-2 spike protein in samples collected at days 7, 14, and 28 (± 2 days) compared with baseline following sotrovimab administration.

Exploratory end points (and associated results) are included in the Supplementary Material.

Data collection

Baseline characteristics, treatment history, and initial adverse events (AEs) observed during sotrovimab treatment (eg, infusion-related reactions) were collected during the baseline visit (day of sotrovimab infusion). Subsequent events were collected retrospectively from the participant or their regular healthcare professionals during the follow-up period using an electronic Case Report Form. Participants received a follow-up phone call on days 7, 14, and 28 (± 2 days) to collect clinical and safety outcome information, details of co-medications, and vaccination status.

Virology analyses

Virology analyses included determination of SARS-CoV-2 RNA (viral load), SARS-CoV-2 spike sequencing, AA substitutions, and VOC/VUI. Participant samples needed to be received at the Great Ormond Street Hospital testing lab within 7 days of the date of the positive SARS-CoV-2 test or the results were excluded from the analysis. Full details of the virology analysis methods are included in the Supplementary Material.

Analysis sets and statistical analysis

The safety population comprised all participants who were enrolled in the study and treated with sotrovimab; the virology population included all participants who were enrolled and treated with sotrovimab who had a positive PCR test and viral load above the limit of detection at baseline. The safety population was also used to assess virology outcomes, except for the change from baseline in viral load and viral rebound analyses, which used the virology population set.

No formal statistical analyses were conducted. Demographic and baseline characteristics were summarized for the safety population using standard descriptive statistics. Study end points were also analyzed descriptively and summarized using the number of observations and percentages of participants (with the latter based on the total number of participants with non-missing data). For participants who withdrew before the end of the study, all data collected up to the point of discontinuation were used for analysis. All analyses were conducted using SAS® for Windows® Version 9.4.

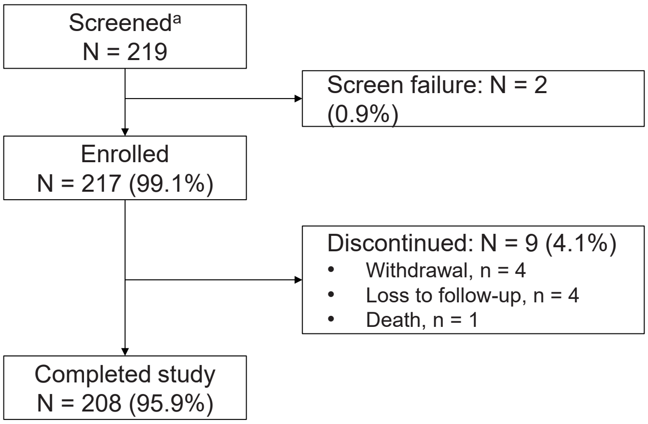

Fig. 1. Flow chart of study participants. [a]The screened set comprised all participants who provided informed consent.

Results

Patient disposition and baseline characteristics

Of the 219 patients who provided informed consent and were screened, 217 (99.1%) were eligible for enrollment and comprised the safety population (Fig. 1). Nine participants (4.1%) discontinued the study early due to withdrawal (n = 4), loss to follow-up (n = 4), and death (n = 1). A total of 209 participants were included in the virology population. Baseline characteristics are shown in Table 1. Among the 217 participants, 123 (56.7%) were female and the median age at enrollment was 58 years. The majority (87.1%) were of self-reported White ethnicity, and all except three participants (1.4%) had received ≥1 dose of a COVID-19 vaccine before study enrollment (212/214 had ≥2 doses). Participants had received sotrovimab within a mean (standard deviation) of 2.6 (1.4) days after testing positive for SARS-CoV-2.

The three most frequent immunocompromising conditions were immune-mediated inflammatory disorders meeting the criteria for immunodeficiency as per the commissioning policy (30.4%), solid-organ transplant (25.8%), and renal disease meeting the criteria for immunodeficiency (24.0%) (Table 1). Other frequently reported co-morbid conditions included being overweight, obesity, hypertension, cardiovascular disease, and chronic kidney disease.

Eight participants (3.7%) were enrolled in the study despite not being immunocompromised (as defined in the protocol). All completed the study without being withdrawn, and their data contributed to the study results. Further details of these participants are included in the Supplementary Material.

Sequencing results

Next-generation sequencing (NGS) of the SARS-CoV-2 genome was performed on swab samples with sufficient viral RNA to qualify for the sequencing assay (n = 208/217). Data on VOC/VUI and baseline polymorphisms are reported in the Supplementary Material.

A total of 156 participants had paired (baseline and post-baseline) sequences available for analysis; the number at days 7, 14, and 28 was 153, 71 and 33, respectively.

Treatment-emergent AA substitutions at > 50% allelic frequency

Among the 156 participants with paired sequences, 101 (64.7%) and 47 (30.1%) had TE substitutions at > 50% allelic frequency in the spike protein and sotrovimab epitope, respectively, at any post-baseline timepoint. Ten TE substitutions were identified in the sotrovimab epitope at > 50% allelic frequency, with substitutions observed at positions 337, 340, and 356 (Table 2). Depending on the residue, the frequency of participants having TE substitutions in the sotrovimab epitope at > 50% allelic frequency ranged from 1.1–3.3%, 3.8–11.5%, and 7.7–23.1% at days 7, 14, and 28, respectively. However,

Table 1
Baseline Characteristics (Safety Population).

Characteristic	Safety population (N = 217), n (%)
Sex	
Female	123 (56.7)
Male	94 (43.3)
Age (years)	
Mean (SD)	56.5 (15.66)
Median	58.0
Min–max	20–92
Ethnicity	
White	189 (87.1)
De-identified[a]	28 (12.9)
BMI (kg/m^2)[b]	
< 24.9	78 (36.3)
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	
Mean (SD)	2.6 (1.36)
Median	2.0
Min–max	0–8
Received ≥1 COVID-19 vaccine dose prior to study enrollment	
Yes	214 (98.6)
No	3 (1.4)
Immunocompromising condition reported	
Participants with an immunocompromising	209 (96.3)[c]
condition reported	66 (30.4)
IMID	56 (25.8)
Solid-organ transplant	52 (24.0)
Renal disease	44 (20.3)
Hematological disease and/or recipient of stem-cell	41 (18.9)
transplant	26 (12.0)
Solid cancer	26 (12.0)
Immune deficiency	
De-identified[a]	
Common comorbidities (≥6% of participants)	
Overweight (including obesity)	107 (49.3)
Hypertension	90 (41.5)
Obesity	67 (30.9)
Cardiovascular disease	47 (21.7)
CKD	44 (20.3)
Asthma	38 (17.5)
Diabetes mellitus	35 (16.1)
Chronic respiratory disease	24 (11.1)
Cerebrovascular disease	14 (6.5)
Chronic liver disease	14 (6.5)
COPD	13 (6.0)

Participants were enrolled in the study on the basis that they belonged to an immunocompromised population eligible to be treated with sotrovimab.[19] Individual participants may have reported more than one immunocompromising condition.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; eCFR, electronic Case Report Form; IMID, immune-mediated inflammatory disorder; max, maximum; min, minimum; SD, standard deviation.

[a] Cell counts < 11 are grouped to avoid identification.

[b] Data available for 215 patients.

[c] Eight of the 217 participants had no immunocompromising condition recorded in the eCRF. Following queries to the sites after database lock, two participants were considered to be immunocompromised as a result of being treated with mepolizumab for severe asthma (one patient) and being treated with adalimumab for psoriasis (one patient). The other six participants were not considered to be immunocompromised. In addition, there were two participants for whom the site recorded an immunocompromising condition in the eCRF that was later determined not to meet the definition in the protocol. The immunocompromising conditions of these participants (renal disease and solid cancer for one patient each) are included in this table.

Table 2
Summary of treatment-emergent epitope substitutions at > 50% allelic frequency (consensus analysis).

	Post-baseline safety population (N = 217)					
	Day 7		Day 14		Day 28	
	n'	Participants with change per residue in epitope, n (%)[b]	n'	Participants with change per residue in epitope, n (%)[b]	n'	Participants with change per residue in epitope, n (%)[b]
Participants with sequence, n (%)[a]	91–92 (41.9–42.4)		26 (12.0)		12–13 (5.5–6.0)	
Substitution list						
P337L	92	1 (1.1)	26	1 (3.8)	–	0 (0)
P337S	92	3 (3.3)	26	1 (3.8)	13	2 (15.4)
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)
K356R	–	0 (0)	–	0 (0)	12	1 (8.3)
K356T	–	0 (0)	26	1 (3.8)	–	0 (0)

n' = the number of participants with sequencing data available at the specific amino acid position.
n = the number of participants with substitutions in the epitope at the specific amino acid position.
– = the number of participants without a specific substitution cannot be determined.
[a] Denominator is N.
[b] Denominator is n' for residue at specified visit.

we note that the presence of substitutions could not be accurately determined in many samples, especially at later timepoints, due to a lack of available sequencing or gaps in the epitope sequence. Among the 32 participants with detectable viral load at day 28, only one definitively harbored no substitutions in the sotrovimab epitope (11 participants had substitutions detected and 20 had missing sequence; Supplementary Table 3). The epitope residue with the most frequent TE substitutions observed at > 50% allelic frequency at any time post-baseline was E340 (Table 2). E340Q was the most prevalent change at day 7 and day 28. At day 14, E340D and E340Q had the same prevalence and were the most prevalent TE epitope substitutions observed. All of the TE substitutions observed in the sotrovimab epitope are known to cause reduced susceptibility to sotrovimab in *in vitro* neutralization assays.[21]

Outside of the sotrovimab epitope, one TE substitution present at > 50% allelic frequency in the spike protein (deletion at Y114) was observed in more than one participant at day 28 (Supplementary Table 4).

Viral load

The proportion of participants with undetectable SARS-CoV-2 RNA increased over time; 25.1% at day 7, 65.8% at day 14%, and 83.5% at day 28 (Fig. 2). Median viral load declined over the course of the study from 7.42 $\log^{10}$ copies/mL at baseline to 2.36 $\log^{10}$ copies/mL at day 28 (Fig. 3); viral rebound was observed in 16 (7.8%) participants, five of whom went on to clear the virus by day 28. Of the 11 participants with a rebound who did not clear the virus by day 28, five had TE epitope substitutions at day 28 and a further three could not be determined (gaps in sequence in the epitope region). In total, 32 participants had a positive viral load at day 28; details of TE epitope substitutions, medical history, and concomitant medications for these participants are included in Supplementary Table 3. On inspection, the immunocompromising conditions reported in these participants appeared to be consistent with those reported by the overall study population (Table 1).

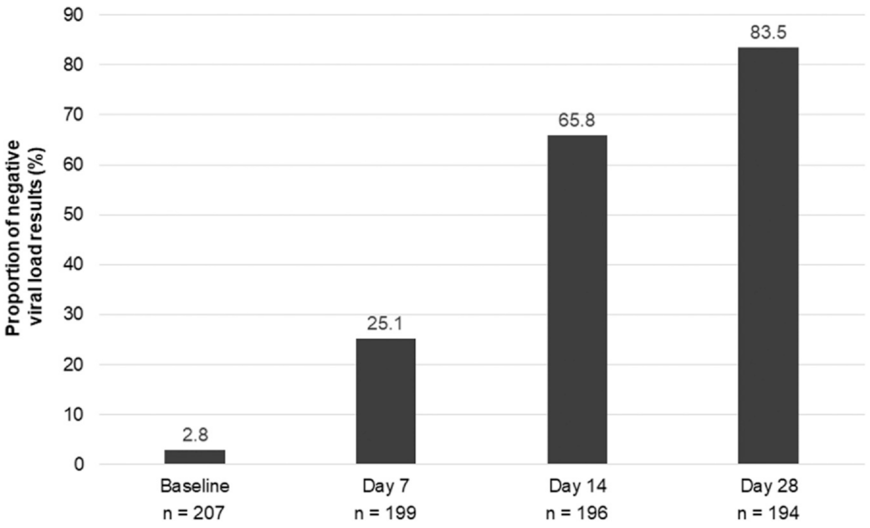

Fig. 2. Summary of the percentage of negative viral-load results at baseline and post-baseline. Negative viral loads are defined as below the lower limit of detection (453 copies/mL). n = number of participants with a non-missing viral-load result on the day listed.

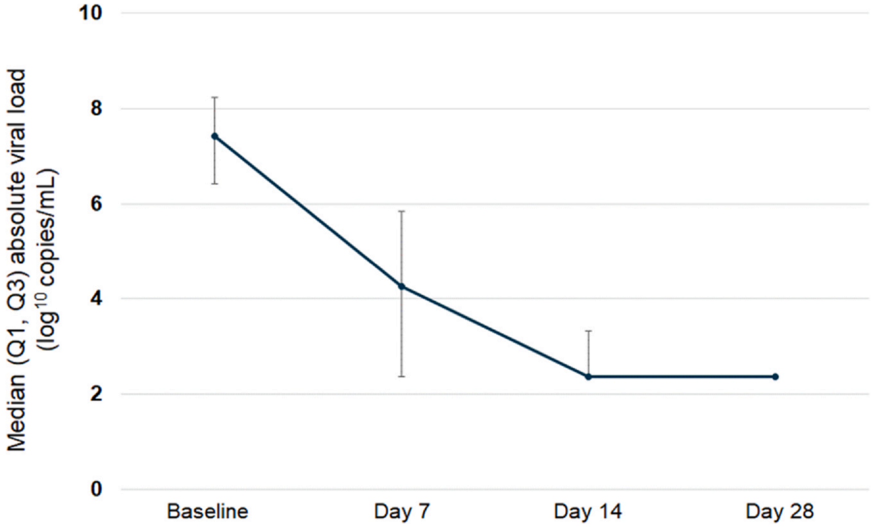

Fig. 3. Summary of absolute viral load ($\log^{10}$ copies/mL) through day 28 as measured by qRT-PCR from nasal/oropharyngeal swabs. Baseline viral load is defined as the non-missing assessment taken at day 0 and excludes the negative viral-load results. The post-baseline viral-load records with viral loads below the LLOD (453 copies/mL) are imputed to 226.5 copies/mL. Viral loads above the LLOD and below the LLOQ (1570 copies/mL) are imputed to 1011.5 copies/mL. These imputed values are used to derive $\log^{10}$ viral loads. Participants with major protocol deviation (out-of-visit window, samples received late at Great Ormond Street Hospital, or return more samples than expected) at specific visits were excluded from the analysis. Abbreviations: LLOD, lower limit of detection; LLOQ, lower limit of quantitation; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

Among the eight participants in the study who were considered not immunocompromised on review, six had a reported viral load below the lower limit of detection at day 28, and viral rebound was observed in one participant (no day-28 data were available for the other participant).

Viral load by epitope substitutions

The presence of substitutions in the sotrovimab epitope that cause a decrease in the *in vitro* susceptibility of sotrovimab might impact the clearance of SARS-CoV-2 virus, so we assessed the proportion of participants with undetectable virus at days 7, 14, and 28 in participants with or without epitope substitutions at > 5% allelic frequency. The majority of participants with or without TE substitutions in the sotrovimab epitope at day 7 achieved undetectable viral load at day 28 (63.9% and 81.0%, respectively) (Fig. 4). However, only 5/18 (27.8%) participants with, *versus* 22/30 (73.3%) of those without, TE epitope substitutions at day 14 achieved undetectable viral load at day 28 (Fig. 4). Seventeen of the 18 participants with TE substitutions at day 14 (including the five with undetectable viral load at day 28) had substitutions that are known to reduce the susceptibility of sotrovimab in *in vitro* assays, including the P337L/S and E340D/K/Q substitutions which reduce *in vitro* activity of sotrovimab by > 50-fold relative to the control.[20]

We also assessed if the presence of epitope substitutions impacted the longitudinal decline in SARS-CoV-2 virus; results are included in the Supplementary Material.

Clinical outcomes and safety findings

Seven participants (3.2%) were hospitalized during the study; all were considered by investigators to be unrelated to COVID-19. No

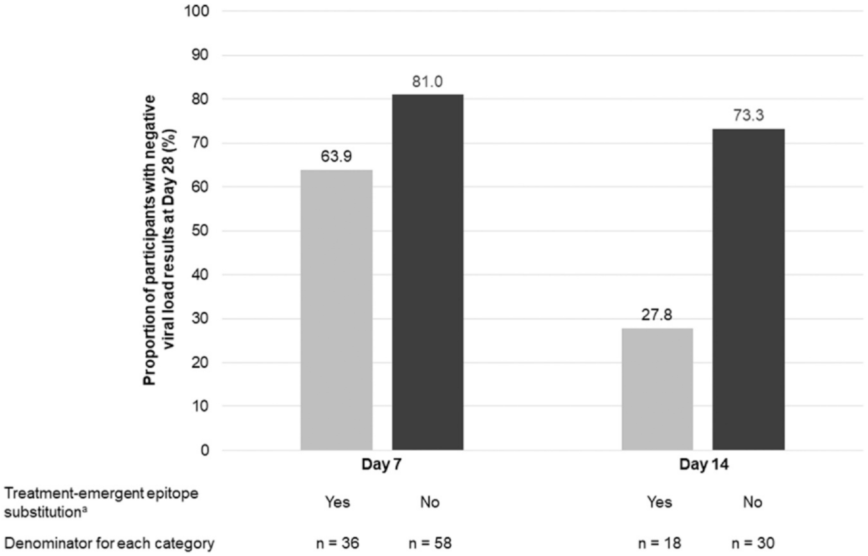

Fig. 4. Summary of day 28 viral-load status based on presence of treatment-emergent substitutions in the sotrovimab epitope (> 5% allelic frequency). [a]Excludes participants who did not have a valid result for the day 28 viral load.

participants required ICU admission during the study. One participant (0.5%) died during the study after requiring high-flow/non-invasive mechanical ventilation. The death occurred after discharge from the hospital, and was considered by the investigator as due to the participant's underlying condition (type-2 respiratory failure and aspiration pneumonia).

No serious AEs or deaths related to sotrovimab were reported, and there were no events leading to interruption and/or incomplete sotrovimab infusion or leading to withdrawal. Five non-serious AEs (in four participants [1.8%]) were considered related to sotrovimab (see the Supplementary Material for further details).

Discussion

We assessed the emergence of SARS-CoV-2 spike variants and the impact of detected changes on virological and clinical outcomes, in predominantly immunocompromised, symptomatic, non-hospitalized patients in the UK treated with sotrovimab for COVID-19. Most study participants successfully cleared the virus by day 28, but TE epitope substitutions were identified in some (n = 11) of those who did not. No COVID-19-related hospitalizations were reported, and no new safety issues were identified.

The overall frequency of TE epitope substitutions (> 5% allelic frequency) in LUNAR (30.1%) was numerically higher than reported in other studies of sotrovimab 500 mg IV (COMET-PEAK [13.5%], COMET-TAIL [20.8%], COMET-ICE [23.5%]; all of which included non-immunocompromised patients).[22,23] Most of the participants in LUNAR were immunocompromised, a group known to have a prolonged duration of virus shedding (which can lead to selection for resistance) compared with non-immunocompromised patients.[7,9,24] However, the time to virus clearance may vary depending on the type and severity of immunosuppression. In a recent study comparing 56 immunocompromised *versus* 184 non-immunocompromised adults with COVID-19,[8] the time to viral clearance for those with severe immunosuppression due to hematological malignancy or transplant (solid organ or hematopoietic stem cell; 72 days; n = 12) was significantly longer than for those with other types of severe immunosuppression (autoimmune/B-cell-deficient; 10 days; n = 13), those with non-severe immunosuppression (12 days, n = 31), and non-immunocompromised groups (13 days; n = 184) (all $P < .01$). Severely immunocompromised participants also had greater SARS-CoV-2 evolution and a higher risk of developing resistance against mAbs compared with the non-severe and non-immunocompromised groups. These findings highlight the varied risk of persistent COVID-19 across a broad range of immunosuppressive conditions, which may dictate response to treatment with mAbs.[8,25] In our study, there was a range of underlying diseases in participants with a persistently positive viral load at day 28 (Supplementary Table 3), with no obvious over-representation of one condition. This emphasizes the importance of aiming for viral clearance in all immunocompromised individuals.

The majority of sotrovimab-treated patients had reduced viral load by day 7, which further decreased through day 28, despite most participants being immunocompromised and all being infected with Omicron subvariants. Reduced activity for sotrovimab has been reported for some Omicron variants (relative to Wuhan-Hu-1 wild type) based on *in vitro* neutralization assays.[26] However, it remains unclear if reduced *in vitro* activity translates to reduced clinical effectiveness, especially for antibodies such as sotrovimab that also have potent effector functions.[27,28] Indeed, other studies using *in vitro* methods have reported that sotrovimab retains neutralizing activity against Omicron variants at clinically relevant concentrations.[29,30] Several studies have also indicated that sotrovimab is effective against Omicron variants in the real-world clinical setting, including in high-risk immunocompromised patients.[26,31–34] In addition, 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 (1.7–2.0% during BA.2; 3.4% during combined BA.2 and BA.5 periods).[35] At day 28 of LUNAR, 83.5% of participants (n = 162/194) had undetectable viral load compared with 93.2% (n = 261/280) and 80.6% (50/62) in the sotrovimab 500 mg IV arm of COMET-TAIL and COMET-PEAK (Part B), respectively.

Participants in the LUNAR study were infected with different SARS-CoV-2 viral variants, which may impact viral clearance. Sotrovimab had a 22.6-fold shift in activity against Omicron BA.5 in *in vitro* neutralization assays,[26] and the spike amino acid sequence for Omicron BA.5.1, BA.5.2, BA.5.2.1 and BE.1 is the same as Omicron BA.5. As such, viral clearance would be expected to be similar across these variants. Although no formal comparison was made, VL clearance across these variants appeared similar, with median viral load below the lower limit of quantitation at Day 14 and below the lower limit of detection at Day 28.

A smaller proportion of participants in LUNAR who had TE substitutions at day 14 (5/18 [27.8%]) achieved undetectable virus at day 28 than participants with no TE substitutions at day 14 (22/30 [73.3%]). This implies that in this small number of participants, the presence of TE epitope substitutions at day 14 potentially contributed to the continued virus detection at day 28. Only one of 32 participants with detectable viral load at day 28 definitely had no TE sotrovimab epitope substitutions, with substitutions detected in the other 11 participants with available sequence (and sequencing gaps in all others). Of the 11 participants who experienced viral rebound and had detectable viral load at day 28, five had TE substitutions in the sotrovimab epitope at day 28. However, none of the participants with viral rebound who were positive for viral RNA at day 28 experienced COVID-19 disease progression during the study (albeit two participants were admitted to the hospital for non-COVID-19-related reasons).

Some study limitations should be considered. Firstly, the LUNAR study only included sites in England and Wales, which may not be representative of the rest of the UK or elsewhere. Secondly, this was a single-arm observational study, which potentially limits any inference about the association between sotrovimab and the development of novel viral mutations. However, inclusion of an untreated control arm would have been unethical, while an active comparator arm would have potentially introduced bias (eg, confounding by indication). Thirdly, only descriptive analyses were performed, with no adjustments for differences in patient characteristics; therefore, definitive conclusions cannot be drawn about the clinical relevance of the reported TE substitutions. Finally, eight non-immunocompromised patients were included, potentially biasing findings in favor of sotrovimab; however, they account for only 3.7% of the study population, so their impact on results is likely to be minimal. Additional limitations include: the limited duration of follow-up may have impacted the development of resistance if it occurred later in cases of prolonged infection; post-baseline swabs were self-collected by participants and may not have been handled correctly; there is potential for false-negative results due to variable distribution of virus across the respiratory tract[36]; the one reported death may represent observer bias as the cause was not formally evaluated (beyond the investigator's opinion); further outcome classification may have occurred due to mixed infections not being detected through sequencing; we did not collect data on levels of SARS-CoV-2 antibodies before study participants received sotrovimab, and so are unable to comment on the possible impact of such antibodies on viral clearance.

In conclusion, in this immunocompromised population with COVID-19 who received early sotrovimab treatment, most participants (83.5%) experienced substantial reductions in viral load by day 28. TE substitutions were seen in the sotrovimab epitope, including substitutions known to cause reduced susceptibility in *in vitro* neutralization assays. Several TE substitutions were numerically associated with persistence of virus.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis or interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the manuscript; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Ethics approval

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by an Ethics Committee (IRAS reference 1005346; reference number 22/SC/0099) in accordance with ethical principles founded in the Declaration of Helsinki (version 2008) and applicable UK requirements. Written informed consent was obtained from each participant prior to the performance of any study-specific procedures.

Funding

This study was supported by GSK (study number 218407).

Data availability

For requests for access to anonymised subject-level data, please contact the corresponding author.

Declaration of Competing Interest

All authors at clinical sites received costing support for their sites from GSK.

M.D., J.W., J.H., A.A., M.V.D., H.J.B., E.M., W.J., K.G., A.S., and I.A.G. are employed by and hold financial equities in GSK.

J.U. is supported by the Medical Research Council (grant number MR/T023791/1) and has received honoraria for advisory boards from Celltrion Healthcare, Gilead Sciences, and GSK.

E.G.K. is supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

A.L.G. receives funding to support salary from the Medical Research Council (MC_UU_00004/05).

J.B. and D.M.L. received a research grant and consultancy fees, all paid to their institution, for this study. D.M.L. has also received personal fees from Gilead for an educational video and from Merck for a roundtable discussion; speaker fees from AstraZeneca, Biotest, and Takeda; support to attend a conference from Octapharma; and a research grant from Bristol Myers Squibb. J.B. is a NIHR Senior Investigator and received support from the UCLUCLH NIHR Biomedical Research Centre.

M.B., C.G., C.A.W., J.R.B., R.W., L.B. and C.B. have nothing to disclose.

E.H. has received consultancy fees from MSD.

Acknowledgments

Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables, grammatical editing, and referencing) was provided by Tony Reardon, OPEN Health Communications, in accordance with Good Publication Practice (GPP) guidelines (www.ismpp.org/gpp-2022). The support was funded by GSK.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106510.

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