

# Sotrovimab for treatment of COVID-19 infections

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## Abstract

The COVID-19 pandemic necessitates the development of therapeutic agents for high-risk infected patients. Sotrovimab is a monoclonal antibody with efficacy against SARS-CoV-2 and other sarbecoviruses. Its efficacy has been shown in the COMET-ICE trial, where a 500 mg infusion in non-hospitalized patients with mild to moderate COVID-19 infections and at least one risk factor for progression was associated with reduced disease progression, hospitalization and death. There was a small but statistically significant increase in self-limiting diarrhoea with sotrovimab. For hospitalized patients, there is no strong evidence of benefit with sotrovimab. The emergence of the Omicron variant was associated with reduced efficacy of sotrovimab, with subsequent increased resistance to sotrovimab by the BA.2 sub-lineage. The risk of developing resistance to monoclonal antibodies with increased use, efficacy with the emergence of variants and safety monitoring should continue to provide ongoing risk-benefit analysis of their use.

**Keywords:** COVID-19, monoclonal antibodies, therapeutics

## Introduction

The COVID-19 pandemic has significant implications for the health of older people, ranging from the higher risk of COVID-19 infection related complications and mortality, to the morbidity from delays in seeking medical attention and mental health sequelae [1]. COVID-19 vaccines have been rolled out globally to reduce the risk of infections, hospitalisations or death. This has been shown to be effective in high-risk groups, particularly older people and those with underlying medical conditions, such as diabetes mellitus, chronic obstructive pulmonary disease, chronic renal disease and obesity [2].

In addition to preventive measures such as vaccination, social isolation, use of masks and hand hygiene measures, therapeutic agents are required especially for high-risk patients infected with the *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2). This includes monoclonal antibodies (mAbs), which ideally bind to the SARS-CoV-2 virus in a region separate to the frequently evolving receptor-binding motif. In this paper, the mAb,

Sotrovimab, and relevant papers pertaining to its efficacy in COVID-19 infections and safety are described.

## Efficacy and safety of sotrovimab

MABs were previously isolated from the SARS-CoV-1 virus, which caused the SARS outbreak approximately twenty years ago. Subsequently, sotrovimab (VIR-7831) was developed as an engineered human mAb that has the ability to neutralize SARS-CoV-2 and other sarbecoviruses. It has two-amino acid Fc modifications to prolong its half-life and to improve bioavailability in the respiratory mucosa. Unlike several other mAbs developed against COVID-19, sotrovimab does not depend on binding to the *angiotensin-converting enzyme 2* (ACE2) receptor, which is prone to mutations [3].

A phase 3, double-blind, placebo-controlled trial (COMET-ICE) was performed in multiple centres in the United States, Canada, Brazil and Spain, to evaluate the effects of a single dose of sotrovimab 500 mg infusion in preventing progression of COVID-19 infection severity in high-risk, non-hospitalised patients. Patients included in the trial had confirmed COVID-19 infections on reverse-transcriptase polymerase-chain-reaction or antigen SARS-CoV-2 testing, had symptom onset within five days and were considered high-risk of hospitalisation or death from the infection due to at least one risk factor or older age. Patients with severe COVID-19 infections evidenced by dyspnoea at rest, hypoxia or requiring supplemental oxygen were excluded from the study.

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In a pre-specified interim analysis based on an intention-to-treat sample of 583 patients (291 with sotrovimab, 292 with placebo), there were 3 patients (1%) and 21 (7%) who progressively worsened, leading to hospitalization and death in the sotrovimab and placebo groups respectively. This was a relative risk reduction of 85%, which was statistically significant. Five patients were admitted to intensive care, all of whom were from the placebo group. In terms of safety, 17% and 19% reported adverse events in the sotrovimab and placebo groups respectively. For the sotrovimab group, the most common adverse event was diarrhoea, occurring in 1%. One patient in the sotrovimab group developed an infusion-related reaction, with symptoms of moderate dyspnoea. Based on the interim analysis of the COMET-ICE trial, sotrovimab appeared safe and effective in reducing the risk of disease progression for outpatient mild to moderate COVID-19 patients who are considered high risk [3].

By the time the COMET-ICE study was completed, patient recruitment had extended to 57 sites, with the addition of Peru to the list of countries [4]. However, enrollment was stopped earlier at a prespecified interim analysis due to efficacy. There were 1057 randomly selected patients, with one-fifth being 65 years of age and older and more than half being Latinx. The sotrovimab group was associated with a significant reduction of all-cause hospitalization and death compared to placebo (1% vs 6%, relative risk 0.21, absolute difference -4.91%, number needed to treat 20.4). In terms of safety, while there were more adverse events in the placebo group, self-limiting diarrhoea was reported by more patients receiving sotrovimab (2%) compared to placebo (< 1%). There was no significant difference between groups for systemic infusion-related reactions. Overall, the COMET-ICE study supported sotrovimab as a treatment for high-risk outpatients with mild to moderate COVID-19 infections [4].

In a retrospective study from Obaidullah Hospital, United Arab Emirates, 220 patients who received Sotrovimab were monitored in terms of progression to severe disease. Among these patients, 177 (80.5%) improved, while 43 (19.5%) deteriorated in terms of shortness of breath, cough and worsening of radiological findings on chest x-ray. The rate of hospitalization was 18.6% with sotrovimab. However, there was overall statistically significant improvement after sotrovimab in terms of vital signs, inflammatory markers, hepatic and renal functions [5].

An observational cross-sectional study was carried out in the National Centre for Infectious Diseases (NCID), the largest COVID-19 treatment centre in Singapore. Out of 410 COVID-19 inpatients, 94 met the inclusion criteria of confirmed COVID-19 admitted within five days, not requiring oxygen and did not receive full doses of COVID-19 vaccination. Among these patients, 19 (20.2%) received pre-emptive sotrovimab treatment. Although the sotrovimab group was significantly older (mean age 73 years) and had more comorbidities, there were less patients who progressed to requiring oxygen (31.6% vs 54.7%), admission to intensive care (10.5% vs 24.0%) or death (5.3% vs 13.3%). This suggested that sotrovimab

may be useful for early treatment of high-risk inpatients with mild-to-moderate COVID-19 infections [6].

However, this was not demonstrated in a randomized-controlled trial comparing the efficacy of sotrovimab and BII-196 plus BII-198 (amubarvimab/romlusevimab). This was a multi-centred study performed across 43 hospitals in the United States, Denmark, Switzerland and Poland. There were 546 patients who were admitted with moderate to severe COVID-19 infections without organ failure and presented with symptoms for less than 12 days. They were administered a single dose of the study product over 60 minutes, and monitored for infection complications, organ failure, co-infections and death. However, an interim futility analysis showed that there was no improvement in clinical outcomes for sotrovimab or BII-196 plus BII-198 in this group of patients, resulting in the study being terminated early [7]. This may be contributed by the extended length of time before receiving the infusion.

Overall, the available evidence suggests that sotrovimab is useful for outpatient use for patients presenting within 5 days of symptoms with mild-moderate COVID-19 infections who are considered high risk of developing complications. Its use for inpatients or those with severe COVID-19 infections currently remains unproven.

### Efficacy of sotrovimab in COVID-19 variants

The effectiveness of mAbs, including casirivimab, imdevimab and sotrovimab has been confirmed for the Delta variant [8]. An observational study from the University of Pittsburgh School of Medicine showed that the 3558 patients who received the mAb infusions at an outpatient center had a reduced risk of hospitalization or death compared to those without treatment. There was a relative risk reduction of 0.31 and 0.60 for casirivimab/imdevimab and sotrovimab respectively. Although there was no statistically significant difference in the effectiveness of both mAbs, there was an 86% probability of inferiority of sotrovimab compared to casirivimab/imdevimab against the Delta variant [8].

Currently, the main SARS-CoV-2 variant is Omicron (B.1.1.529) with multiple mutations (37 amino acid substitutions) in the spike protein, including 15 in the receptor-binding domain (RBD). This was associated with a loss of *in-vitro* neutralizing activity against Omicron for 26 out of 29 mAbs which target the RBD motif, leaving three mAbs with retained potency. For the broadly neutralizing sarbecovirus mAbs, sotrovimab, in addition to S2X259 and S2H97 retained their potency [9]. In another study, pooled human IgG from convalescent and vaccinated donors had a reduced potency of 16-fold with the variant, while among the therapeutic mAbs tested, only sotrovimab resulted in significant neutralization of Omicron [10].

These findings were replicated in two other *in-vitro* studies. The first assessed nine mAbs and 115 serum samples from recovered patients or vaccine recipients. This study found that serum from Pfizer or AstraZeneca vaccine

recipients, or those with previous infections at least 6 months prior, had low or no neutralizing activity against Omicron. Serum from recipients of Pfizer booster doses elicited a response, but at titres 6 to 23-fold lower compared to against the Delta variant [11]. The second study found that over 85% of their tested neutralizing mAbs had limited efficacy, including LY-CoV016, LY-CoV555, REGN10933, REGN10987, AZD1061, AZD8895 and BRII-196. However, VIR-7831 and DXP-604 had some efficacy, albeit a reduced one [12].

Subsequently, a report demonstrating the presence and persistence of viable Omicron SARS-CoV-2 virus despite treatment with sotrovimab suggested the possibility of development of resistance against mAbs due to the rapid development of mutations on the spike protein [13]. The Erasmus University Medical Centre in Rotterdam assessed viral evolution in immunocompromised patients (from solid organ transplant or previous B-cell depleting therapy) infected by Omicron BA.1 or 2 and treated with sotrovimab. Four patients had viral RNA detected for a longer duration, up to 28 days. These patients had spike protein mutations at position 337 or 340, with an associated reduction in susceptibility [14]. This development of treatment resistant SARS-CoV-2 variants was also identified in a similar study from Toulouse University Hospital [15]. Thus, consideration should be given to ensure confirmed viral clearance after treatment to avoid these patients becoming a source of new variants. This also suggests the need for mAb stewardship and raised concerns regarding future treatment failure with ongoing mAbs use. The Omicron BA.1 variant is being replaced by the BA.2 sub-lineage with different spike protein mutations, with a gain of 8 new and loss of 13 spike alterations compared to BA.1. A further reduction in neutralizing efficacy of Sotrovimab by 50% with BA.2 was initially suggested [16]. Since then, further testing showed the BA.2 variant developed significant resistance to 17 of 19 neutralising monoclonal antibodies, including sotrovimab [17]. This highlighted the necessity of active, ongoing monitoring of mAb efficacy and amending treatment options accordingly based on the main variant causing SARS-CoV-2 infections. For the BA.2 sublineage, this includes use of bebtelovimab (LY-CoV1404) [17], or considering combination therapy with sotrovimab to ensure a broader spectrum of cover [18].

Overall, during the Delta pandemic, mAbs generally held significant promise in neutralizing the SARS-CoV-2 virus. Casirivimab/imdevimab which was potentially more effective than sotrovimab at that time has been rendered useless by the Omicron variant; while sotrovimab retained some efficacy against BA.1 [19]. However, there is increasing resistance through rapid mutations by the SARS-CoV-2 virus with a further reduction in efficacy against the BA.2 sub-lineage. Eventually, the United States Food and Drug Administration (FDA) limited the use of sotrovimab in areas where Omicron BA.2 variant contributed to more than half the COVID-19 cases on March 30th, 2022, with a subsequent withdrawal of their authorization to use sotrovimab on April 5th, 2022, when the BA.2 variant became the main cause of COVID-19 infections in all

regions in the United States [20].

### Safety monitoring of sotrovimab

In addition to monitoring for ongoing efficacy against COVID-19 variants, safety monitoring is also required. Pharmacovigilance for adverse events should be considered, rather than symptoms assumed to be due to the progression of COVID-19. This was illustrated in a case of a patient who developed alveolar haemorrhage post-infusion, which was initially thought to be due to COVID-associated pneumonia [21]. The long-term sequelae of monoclonal antibody use, particularly effects on the immune system should also be monitored.

As all therapeutics can potentially result in side effects, there is a view that it may no longer be appropriate to carry out studies for mAbs in hospitalized COVID-19 patients [22]. Other than severe immunocompromised patients where studies may be appropriate, the lack of efficacy for hospitalized patients with moderate to severe COVID-19 infections has already been demonstrated in multiple mAb studies [22].

### Conclusion

Sotrovimab is a mAb with demonstrable efficacy in reducing the risk of progression to hospitalization, clinical deterioration and death for high-risk outpatients with mild to moderate COVID-19 infections. However, it has not been found to be effective for inpatient treatment, and is gradually becoming less effective with the development of COVID-19 variants, including Omicron and the BA.2 sub-lineage. Subsequently, the FDA withdrew emergency use authorization of Sotrovimab when the Omicron BA.2 variant eventually became the main cause of COVID-19 infections in the United States.

### Declarations

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