# Early COVID-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab

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## Background and objective

- COVID-19 disproportionately results in hospitalization and death in older individuals and in those with comorbidities, such as obesity, diabetes mellitus, chronic pulmonary diseases, and chronic kidney disease.[1-4]
- Sotrovimab is a pan-sarbecovirus monoclonal antibody that binds to a highly conserved epitope of the SARS-CoV-2 receptor binding domain, predicted to be retained as the virus evolves.[5-7]
  - Sotrovimab retains *in vitro* activity against spike protein VOIs and VOCs, including alpha, beta, gamma, delta, and lambda.[7-9]
- This study evaluated the efficacy and safety of treatment with sotrovimab in high-risk individuals with mild-to-moderate COVID-19, as part of the COMET-ICE clinical trial (NCT04545060).[10]

## Methods

### Study design and population

- Multicenter, double-blind, Phase 2/3 trial that enrolled non-hospitalized individuals with symptomatic mild-to-moderate COVID-19 between August 2020 and March 2021 (**Figure 1**).
  - Eligible participants were randomized 1:1 to an IV infusion of sotrovimab 500mg or placebo.
- Eligibility criteria:
  - **Inclusion:** Adults (aged ≥18 years) with a positive SARS-CoV-2 test, oxygen saturation ≥94% on room air, symptom onset ≤5 days prior to treatment, and at high risk of COVID-19 disease progression (**Figure 1**).[5,10]
  - **Exclusion:** Participants with signs or symptoms of severe or critical COVID-19, defined as shortness of breath at rest, respiratory distress, or need for supplemental oxygen.[5]

### Primary and secondary efficacy outcomes

- The primary outcome was the proportion of participants with hospitalization for >24 hours for acute management of illness or death through Day 29; hospitalization and death were also reported as serious AEs.
- Secondary outcomes included the following key endpoints:
  - Proportion of participants with an ER visit, hospitalization of any duration, or death due to any cause
  - Proportion of participants who progressed to requiring supplemental oxygen (severe disease) or mechanical ventilation (critical disease)
  - Mean change in viral load from baseline to Day 8
  - Symptoms as measured by mean change in total score from baseline (AUC through Day 7) in the COVID-19 adaptation of the FLU-PRO Plus tool
  - All-cause mortality at Day 29.

### Safety outcomes

- Occurrence of AEs, SAEs, and AESIs regardless of relationship to COVID-19 was assessed.
  - IRR and potential ADE were protocol defined AESIs.

### Statistical analysis

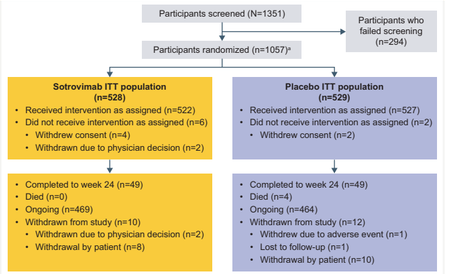
- The primary and secondary clinical progression endpoints were analyzed in the ITT population using a Poisson regression model adjusted for the duration of symptoms, age, and sex.
  - Missing data were imputed using MI under the MAR assumption.
- Mean change in viral load from baseline was analyzed using an MMRM model adjusting for baseline value by visit, age, duration of symptoms, and sex.
- Mean change in total FLU-PRO Plus score from baseline (AUC through Day 7) was assessed using an ANCOVA model, adjusted for baseline value, age group, time to symptom onset, sex, and region.
- No statistical analysis was performed on the all-cause mortality secondary endpoint due to the low number of events through Day 29.
- The analyses of the secondary outcomes were adjusted for multiplicity using hierarchical testing.
- Safety was assessed in all participants, according to intervention received.
- Post-hoc review of safety narratives was used to determine the causes of hospitalizations and deaths.

## Results

### Study population

- Of the 1351 participants screened, 1057 were randomized to sotrovimab (n=528) or placebo (n=529, **Figure 1**).

**Figure 1. Study participants**




[a]Eligible participants had ≥1 of the following risk factors: ≥55 years of age, diabetes requiring medication, obesity (BMI >30 kg/m$^2$), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate-to-severe asthma. [b]Safety was assessed in all participants according to treatment received (523 and 526 participants in the sotrovimab and placebo groups, respectively). One participant randomized to placebo received sotrovimab and was therefore included in the sotrovimab safety population.

- The median age was 53 years, with 20% of participants aged ≥65 years. The majority of participants (65%) were Latinx (**Table 1**).
- The most common risk factors for COVID-19 progression were obesity (BMI >30kg/m$^2$), age ≥55 years, and diabetes requiring medication (**Table 1**).
- Enrollment in the COMET-ICE study was halted prematurely due to the profound efficacy of sotrovimab observed at the interim analysis.

### Efficacy outcomes

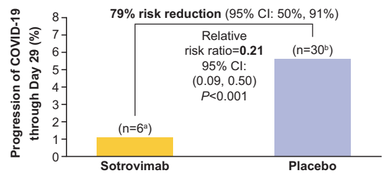
- The risk of COVID-19 progression was significantly reduced among participants treated with sotrovimab versus placebo (adjusted relative risk reduction: 79% [95% CI: 50%, 91%]; *P*<0.001) through Day 29 (**Figure 2**).
  - These results are consistent in magnitude with the profound efficacy observed at the interim analysis of this trial.[5]
- All secondary endpoints tested in the hierarchy met statistical significance except all-cause mortality, which was not formally analyzed due to the low number of events through Day 29.
- Progression of COVID-19 (defined as ER visit, hospitalization of any duration, or death due to any cause) was reduced by 66% following treatment with sotrovimab versus placebo (95% CI: 37%, 81%; *P*<0.001).
- Similarly, treatment with sotrovimab significantly reduced progression to severe and/or critical respiratory COVID-19 compared with placebo (adjusted relative risk reduction: 74% [95% CI: 41%, 88%]; *P*=0.002).
  - No participants treated with sotrovimab required high-flow oxygen, oxygen via a non-rebreather mask, or mechanical ventilation.
  - Of the participants who received placebo, 10 required oxygen support (high-flow nasal cannula, non-rebreather mask, or non-invasive ventilation) and four required mechanical ventilation.
- By Day 29, there were no deaths in the sotrovimab group and two deaths in the placebo group.

**Table 1. Participant demographics and clinical characteristics**

| Characteristic | Sotrovimab (n=528) | Placebo (n=529) | Total (n=1057) |
|---|---|---|---|
| **Age in years, median (range)** | 53 (18–96) | 53 (17–88) | 53 (17–96) |
| **Female sex, n (%)** | 299 (57) | 273 (52) | 572 (54) |
| **Race,[a] n (%)** | | | |
| White | 458 (87) | 463 (88) | 921 (87) |
| Black or African American | 40 (8) | 42 (8) | 82 (8) |
| Asian | 24 (5) | 21 (4) | 45 (4) |
| Mixed race | 4 (<1) | 0 | 4 (<1) |
| American Indian or Alaska Native | 1 (<1) | 2 (<1) | 3 (<1) |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latinx | 345 (65) | 346 (65) | 691 (65) |
| Not Hispanic or Latinx | 183 (35) | 183 (35) | 366 (35) |
| **Duration of symptoms,[b] n (%)** | | | |
| ≤3 days | 314 (59) | 310 (59) | 624 (59) |
| 4–5 days | 213 (40) | 219 (41) | 432 (41) |
| **Any risk factor for COVID-19 progression, n (%)** | 525 (>99) | 526 (>99) | 1051 (>99) |
| Obesity (BMI >30kg/m$^2$) | 330 (63) | 341 (64) | 671 (63) |
| Age ≥55 years | 243 (46) | 256 (48) | 499 (47) |
| Diabetes requiring medication | 119 (23) | 109 (21) | 228 (22) |
| Moderate-to-severe asthma | 90 (17) | 88 (17) | 178 (17) |
| Chronic obstructive pulmonary disease | 34 (6) | 27 (5) | 61 (6) |
| Chronic kidney disease (eGFR <60 by MDRD) | 5 (<1) | 8 (2) | 13 (1) |
| Congestive heart failure (NYHA class II or more) | 4 (<1) | 3 (<1) | 7 (<1) |
| **Number of concurrent risk factors for COVID-19 progression, n (%)** | | | |
| 0 | 3 (<1) | 3 (<1) | 6 (<1) |
| 1 | 290 (55) | 304 (57) | 594 (56) |
| 2 | 178 (34) | 153 (29) | 331 (31) |
| ≥3 | 57 (11) | 69 (13) | 126 (12) |

[a]Race data were not available for 1 participant in each treatment group.
[b]One participant in the sotrovimab group had a symptom duration of 6 days.

**Figure 2. Primary outcome: hospitalization for >24 hours for acute management of illness or death through Day 29**




[a]In a post-hoc review of safety narratives of the six sotrovimab-treated participants who were hospitalized, three were likely hospitalized due to non-COVID-19 causes including small bowel obstruction, lung cancer, and a diabetic foot ulcer. [b]In a post-hoc review of safety narratives of the 30 participants in the placebo group who met the primary endpoint (29 were hospitalized and two died) all were found to be due to events potentially related to COVID-19.

**Table 2. Secondary efficacy outcomes**

| Secondary outcomes (through Day 29)[a] | Sotrovimab (n=528) | Placebo (n=529) |
|---|---|---|
| **ER visit, hospitalization, or death due to any cause** | | |
| Any event, n (%) | 13 (2) | 39 (7) |
| Hospitalized for acute management of any illness, any duration | 7 (1) | 29 (5) |
| ER visit due to any cause | 6 (1) | 10 (2) |
| Death due to any cause | 0 | 2 (<1)[b] |
| Relative risk ratio (95% CI) | 0.34 (0.19, 0.63) | |
| Adjusted relative risk reduction (95% CI) | 66% (37%, 81%) | |
| *P* value | *P*<0.001 | |
| **Change (95% CI) in viral load from baseline to Day 8 (virology population)[c]** | -2.59 (-2.71, -2.47) n=294 | -2.36 (-2.48, -2.24) n=305 |
| LS mean difference, log copies/mL (95% CI) | -0.23 (-0.40, -0.07) | |
| *P* value | *P*=0.007 | |
| **Progression to severe and/or critical respiratory COVID-19[d]** | | |
| Any progression, n (%) | 7 (1) | 28 (5) |
| Category 2: Low flow nasal cannulae/face mask | 7 (1) | 12 (2) |
| Category 3: high flow nasal cannulae/non-invasive ventilation | 0 | 10 (2) |
| Category 4: Mechanical ventilation or ECMO | 0 | 4 (<1) |
| Relative risk ratio (95% CI) | 0.26 (0.12, 0.59) | |
| Adjusted relative risk reduction (95% CI) | 74% (41%, 88%) | |
| *P* value | *P*=0.002 | |
| **Mean change (95% CI) from baseline of COVID-19–related illness as measured by FLU-PRO Plus total score (AUC through Day 7)** | -3.05 (-3.27, -2.83) n=412 | -1.98 (-2.20, -1.76) n=399 |
| LS mean difference (95% CI) | -1.07 (-1.38, -0.76) | |
| *P* value | *P*<0.001 | |
| **All-cause mortality at Day 29, n (%)** | 0 | 2 (<1) |

[a]Hierarchical statistical testing of secondary outcomes was performed in order of presentation, except for all-cause mortality which could not be assessed due to the low number of events. [b]One participant died at home due to COVID-19 pneumonia without hospitalization and one participant died in the hospital due to pneumonia. [c]The virology population included participants with quantifiable viral load at baseline. [d]Severe and/or critical respiratory COVID-19 was defined as requirement for supplemental oxygen (severe disease) and mechanical ventilation (critical disease).

### Safety outcomes

- The incidence of AEs was similar between treatment arms and SAEs were more common in the placebo arm; no SAEs were considered treatment-related.
- No deaths were reported in participants receiving sotrovimab, compared with four deaths reported among participants receiving placebo, with two occurring before and two occurring after Day 29; two of the deaths were classified as COVID-19 pneumonia, one as pneumonia, and one as respiratory failure (**Table 3**).

**Table 3. Summary of AEs in the safety population**

| | Sotrovimab (n=523) | Placebo (n=526) |
|---|---|---|
| **Any AE, n (%)** | 114 (22) | 123 (23) |
| Related to study treatment[a] | 8 (2) | 9 (2) |
| Leading to dose interruption/ delay | 2 (<1)[b] | 0 |
| **Any infusion-related reaction,[c] n (%)** | 6 (1) | 6 (1) |
| Related to study treatment[a] | 0 | 3 (<1) |
| **Any grade 3 or 4 AE, n (%)** | 15 (3) | 36 (7) |
| **Any serious AE, n (%)** | 11 (2) | 32 (6) |
| Related to study treatment[a] | 0 | 2 (<1) |
| Fatal[d] | 0 | 4 (<1) |
| **Most common (≥1% of participants in either group) AEs, n (%)** | | |
| COVID-19 pneumonia | 5 (<1) | 22 (4) |
| Headache | 4 (<1) | 11 (2) |
| Nausea | 5 (<1) | 9 (2) |
| Diarrhea | 8 (2) | 4 (<1) |

[a]Relatedness was determined by individual study investigators while blinded to study treatment. [b]For both participants, the adverse event was infusion extravasation; both infusions were completed. [c]Infusion-related reactions were defined as adverse events with preferred terms of pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reaction within 24 hours of study drug administration. [d]Two deaths were before Day 29 and two deaths were after Day 29.

### Conclusions

- Treatment with sotrovimab 500mg IV resulted in a clinically and statistically significant reduction in COVID-19 progression to hospitalization or death in participants with mild-to-moderate disease.
- The incidence of healthcare utilization and supplemental oxygen use were also significantly reduced among participants who received sotrovimab compared with those who received placebo.
- Sotrovimab was well tolerated, and no safety signals were identified in this study.
- Results from the COMET-ICE trial strongly support the use of sotrovimab for the early treatment of COVID-19 in adults at high risk for disease progression.

### Abbreviations

ADE, antibody-dependent enhancement; AE, adverse events; AESI, adverse events of special interest; ANCOVA, analysis of covariance; AUC, area under the curve; BMI, body mass index; CI, confidence interval; COMET-ICE, COVID-19 Monoclonal antibody Efficacy Trial – Intent to Care Early; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; ER, emergency room; FLU-PRO Plus, influenza patient-reported outcome questionnaire; IRR, infusion-related reaction; ITT, intent-to-treat; IV, intravenous; MAR, missing at random; MDRD, modification of diet in renal disease; MI, multiple imputation; MMRM, mixed model for repeated measures; NYHA, New York Heart Association; PRO, patient-reported outcome; SAE, serious adverse event; SD, standard deviation; VOCs, variants of concern; VOIs, variants of interest.

### Disclosures

This study was sponsored by Vir Biotechnology, Inc., in collaboration with GlaxoSmithKline (NCT04545060).

On behalf of all authors, and with their permission, an audio recording of this poster was prepared by AS, who did not receive any payment for this recording.

**AKG**, **YGR**, **EJ**, **MCC**, **JM**, **DRF**, **EHS**, **JS**, **AF**, **CCB**, and **AS** are investigators in the COMET-ICE study, sponsored by Vir Biotechnology, Inc., in collaboration with GlaxoSmithKline. In addition, **DRF** has received grants from Gilead Sciences, honoraria from Pfizer and United Medical, meeting support from MSD, and has participated in advisory boards for GlaxoSmithKline. **CB** has received honoraria from Gilead Sciences and ViiV Healthcare and has participated in advisory boards for Gilead Sciences and ViiV Healthcare. **HZ**, **ALC**, **CMH**, **JES**, **EM**, **ELA**, **WWY**, and **MA** are employees of Vir Biotechnology, Inc. **HZ**, **ALC**, **CMH**, **JES**, **WWY**, and **MA** own stocks in Vir Biotechnology, Inc. **ALC** also owns stocks in Gilead Sciences. **EM** and **ELA** are equity holders in Vir Biotechnology, Inc. **NS**, **DA**, and **AP** are employees of and hold shares in GlaxoSmithKline. **DA** is also an unpaid member of the UK Government advisory committee as a subgroup of SAGE.

### Acknowledgements

Medical writing support was provided by Brandy Menges of Fishawack Indicia, UK, part of Fishawack Health, and was funded by GSK and Vir Biotechnology, Inc.

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**Presented at IDWeek, Virtual Conference, September 29–October 03, 2021**