

A Detailed Guide for the Use of Sotrovimab

Under Emergency Use Authorization (EUA)

June 2021

AUTHORIZED USE

Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for use in patients: who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).
- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Sotrovimab is not FDA-approved and is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sotrovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Please see [Important Safety Information](#), most current [Fact Sheet for Healthcare Providers](#) and [Fact Sheet for Patients, Parents, and Caregivers](#), and [FDA Letter of Authorization](#) for sotrovimab.

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Executive Summary

Sotrovimab is a human immunoglobulin G-1 (IgG1-kappa) monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Sotrovimab does not compete with human ACE2 receptor binding. Sotrovimab requires 1 single-dose vial, 1 infusion bag, 30 minutes of infusion time, and 60 minutes of post-infusion observation. See complete [Dose Preparation and Administration](#) instructions in this guide and in Section 2.4 of the [Fact Sheet for Healthcare Providers](#).

The FDA has found it reasonable to believe that sotrovimab may be effective for the treatment of mild-to-moderate COVID-19 in certain at-risk patients as specified in the [Fact Sheet for Healthcare Providers](#). The FDA has also found it reasonable to believe that, when used under the conditions described in the [FDA Letter of Authorization](#) for sotrovimab, the known and potential benefits of sotrovimab outweigh its known and potential risks. Healthcare providers should review the [Mandatory Requirements for Administration of Sotrovimab Under EUA](#) in this resource and in Section 8 of the [Fact Sheet for Healthcare Providers](#). This guide provides you with available [Clinical Trial Information](#) and [Important Safety Information](#). The FDA may contact you and ask you to provide information to help with the assessment of the use of the product during this emergency.

Healthcare providers should review the [Microbiology/Resistance Information](#) in the Appendix of this resource for details regarding specific variants and resistance (also available in Section 15 of the [Fact Sheet for Healthcare Providers](#)).

This *Detailed Guide for the Use of Sotrovimab* is intended to help healthcare providers and healthcare facilities plan and operationalize ordering, administration, and reimbursement for sotrovimab. It has been developed using clinical trial experience with sotrovimab, with guidance from the National Infusion Center Association (NICA), and includes links to available resources. NICA guidance is identified for you at key points throughout this resource.

Information provided in this guide should not supersede local requirements and guidelines for sites of care or substitute for the medical judgment of treating healthcare professionals.

Important information for healthcare providers

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued an EUA, as requested by GlaxoSmithKline, for the unapproved product, sotrovimab, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. As a healthcare provider, you must comply with the mandatory requirements of this EUA.

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that sotrovimab may be effective for the treatment of mild-to-moderate COVID-19 in certain at-risk patients as specified in the [Fact Sheet for Healthcare Providers](#). You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for sotrovimab will end when the Secretary determines that the circumstances justify the EUA no longer exist or when there is a change in the approval status of the product such that an EUA may no longer be needed.

Section 1

Population for treatment and requirements for administration under EUA

- Population for treatment
- Mandatory requirements for administration of sotrovimab under EUA
- IMPORTANT SAFETY INFORMATION

Population for treatment and requirements for administration under EUA

Population for treatment

AUTHORIZATION FOR USE

Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for use in patients: who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).
- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

This patient population corresponds to those in stages 1 and 2 in the WHO Ordinal Scale for Clinical Improvement.¹

Patients with **mild** COVID-19 illness may exhibit a variety of signs and symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell). They do not have shortness of breath, dyspnea, or abnormal chest imaging. **Moderate** COVID-19 illness is defined as evidence of lower respiratory disease during clinical assessment or imaging and an oxygen saturation (SpO₂) ≥94% on room air at sea level.²

Sotrovimab should be administered by intravenous (IV) infusion as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Please see Dosage and Administration section within the [Fact Sheet for Healthcare Providers](#) for more information.

Sotrovimab is not FDA-approved and is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sotrovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

References: 1. WHO R&D Blueprint. Novel coronavirus: COVID-19 therapeutic trial synopsis. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf. Accessed May 14, 2021. 2. National Institutes of Health. Clinical Spectrum of SARS-CoV-2 Infection. <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>. Accessed May 14, 2021.

Population for treatment (*cont'd*)



Having at least ONE of the following may place patients at higher risk for progression to severe COVID-19:

Older age (for example, ≥ 65 years of age)

Obesity or being overweight (for example, adults with BMI > 25 kg/m², or if 12 to 17, have BMI ≥ 85 th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)

Pregnancy

Chronic kidney disease

Diabetes

Immunosuppressive disease or immunosuppressive treatment

Cardiovascular disease (including congenital heart disease) or hypertension

Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)

Sickle cell disease

Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)

Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on these medical conditions and factors, see the [CDC website](#). Healthcare providers should consider the benefit-risk for an individual patient.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Healthcare providers should review the Antiviral Resistance information in Section 15 of the [Fact Sheet for Healthcare Providers](#) for details regarding specific variants and resistance, and refer to the [CDC website](#) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Mandatory requirements for administration of sotrovimab under EUA

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of sotrovimab, the following steps are required. Use of sotrovimab under this EUA is limited to the following (all requirements **must** be met):

- 1 Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.
- 2 As the healthcare provider, communicate to your patient or parent/caregiver information consistent with the [Fact Sheet for Patients, Parents, and Caregivers](#) prior to the patient receiving sotrovimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
 - a. given the Fact Sheet for Patients, Parents, and Caregivers,
 - b. informed of alternatives to receiving authorized sotrovimab, and
 - c. informed that sotrovimab is an unapproved drug that is authorized for use under this EUA.
- 3 Patients with known hypersensitivity to any ingredient of sotrovimab must not receive sotrovimab.
- 4 The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "**Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)**" in the description section of the report.

• **Submit adverse event reports to FDA MedWatch using one of the following methods:**

- Complete and submit the report online at fda.gov/medwatch/report.htm, OR
- Complete and submit a postage-paid FDA Form 3500 (available at fda.gov/media/76299/download) and return by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), OR
- Call 1-800-FDA-1088 to request a reporting form.
- Submitted reports should include in the field name "Describe Event, Problem, or Product Use/Medication Error" the statement "**Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)**."

***Serious adverse events that must be reported to FDA MedWatch are defined as:**

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

Mandatory requirements for administration of sotrovimab under EUA (*cont'd*)

- 5 The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of sotrovimab.
- 6 Other reporting requirements:
In addition, please provide a copy of all FDA MedWatch forms to:
GlaxoSmithKline, Global Safety
Fax: 919-287-2902
Email: WW.GSKAEReportingUS@gsk.com
OR call the GSK COVID Contact Center at 1-844-GSK-COVID (844-475-2684) to report adverse events.



See Sections 8 and 9 of the [Fact Sheet for Healthcare Providers](#) for reporting requirements.

Approved available alternatives

There is no adequate, approved, and available alternative to sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Additional information on COVID-19 treatments can be found at [covid19treatmentguidelines.nih.gov/](https://www.covid19treatmentguidelines.nih.gov/). The healthcare provider should visit clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

Contact Information

For additional information, visit sotrovimabinfo.com.
If you have questions, please contact 1-844-GSK-COVID (844-475-2684).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with sotrovimab use.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include: fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (eg, atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (eg, pre-syncope, syncope), dizziness and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (eg, atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, sotrovimab is not authorized for use in patients: who are hospitalized due to COVID-19, OR who require oxygen therapy due to COVID-19, OR who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

ADVERSE EVENTS

The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (2%) and diarrhea (1%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo.

Reporting Adverse Events:

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

IMPORTANT SAFETY INFORMATION (*cont'd*)

ADVERSE EVENTS (*cont'd*)

Reporting Adverse Events (*cont'd*):

Submit adverse event reports to FDA MedWatch using one of the following methods:

- Complete and submit the report online at <http://www.fda.gov/medwatch/report.htm>, or
- Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by: Mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or Call 1-800-FDA-1088 to request a reporting form.

In addition, please provide a copy of all FDA MedWatch forms to: GlaxoSmithKline, Global Safety; Fax: 919-287-2902; Email: WW.GSKAEReportingUS@gsk.com; Or call the GSK COVID Contact Center at 1-844-GSK-COVID (844-475-2684) to report adverse events.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Sotrovimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Lactation

There are no available data on the presence of sotrovimab in human milk, the effects on the breastfed infant, or the effects on milk production. Individuals with COVID-19 who are breastfeeding should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Section 2

Availability, ordering, and support

- Product availability
- Ordering from AmerisourceBergen
- Customer support

Availability, ordering, and support

Product availability

Sotrovimab is only available through AmerisourceBergen during the Emergency Use Authorization period approved by the FDA for infusion in appropriate patients as defined in the Sotrovimab Fact Sheet for Healthcare Providers.

Ordering from AmerisourceBergen

Sotrovimab is available for customers to purchase directly with AmerisourceBergen as the sole Specialty Distributor during the Emergency Use Authorization period. Customers can purchase directly by:

- Placing purchase order through the customer ordering portal at abcorder.amerisourcebergen.com
- Calling AmerisourceBergen Customer Service at 1-800-746-6273 Monday through Thursday 7:00 AM to 6:30 PM, and Friday 7:00 AM to 6:00 PM CT or
- Placing the purchase order through any of the AmerisourceBergen ordering platforms. Customers may search by product name, material item number, or NDC. For new customers please call AmerisourceBergen Customer Service or email c19therapies@amerisourcebergen.com

The sotrovimab material item number is **10258949**. Please include the item number when placing your order.

Please allow 1 to 2 days for product arrival following order placement. For new customers, please allow up to 2 days for the initial order following receipt of the required customer documentation. For any additional information regarding orders, product availability, or access/log-in information, please email c19therapies@amerisourcebergen.com or contact AmerisourceBergen's Customer Service Department.

Other available AmerisourceBergen customer service contacts

Emails	Phone numbers
<ul style="list-style-type: none">• service@asdhealthcare.com• service@besse.com	ASD: 1-800-746-6273 Besse: 1-800-543-2111 Oncology Supply: 1-800-633-7555

Ordering from AmerisourceBergen (cont'd)

Sites will be required to¹:

- Provide AmerisourceBergen with a board of pharmacy license or physician letter of authorization if not already on file
- Attest to their designated class of trade and that they will administer sotrovimab according to terms of the FDA-issued EUA

Additional information

- Product availability may be subject to established criteria for minimum and maximum amounts based on previous orders and utilization history
- GSK and AmerisourceBergen will ensure that the authorized labeling (ie, Fact Sheets) will accompany the authorized sotrovimab. Please see most current [Fact Sheet for Healthcare Providers](#) and [Fact Sheet for Patients, Parents, and Caregivers](#)
- GSK and AmerisourceBergen will ensure that appropriate storage and cold chain is maintained until the product is delivered to healthcare facilities and/or healthcare providers
- GSK and AmerisourceBergen will ensure that the terms of the sotrovimab EUA are made available to all relevant stakeholders (eg, U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized sotrovimab
- GSK will provide all relevant stakeholders a copy of the FDA Letter of Authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (ie, Fact Sheets)

Customer support

GSK Customer Support and Resources

GSK has established a dedicated team to help customers with medical, product, and disease state information, as well as reimbursement support and other resources, and to provide information regarding clinical trial programs. Customers can call the GSK COVID Contact Center directly Monday through Friday 9 AM to 6 PM ET at 1-844-GSK-COVID (844-475-2684) or go to contactus.gsk.com/callback/covid.html.

HCP and healthcare settings should report all product quality claims directly to the GSK COVID Contact Center. For more information regarding GSK's Product Replacement Policies, please call the GSK Pharma Service Center at 1-800-877-1158 option 4 Monday through Friday 8 AM to 6 PM ET.

Reference: 1. Overview of Direct Order Process for COVID-19 Therapeutics, Public Health Emergency. <https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Documents/Overview%20of%20direct%20order%20process%20Fact%20Sheet-508.pdf>. Accessed May 14, 2021.

Section 3

Infusion site of care recommendations

- Ordering treatment with sotrovimab
- How supplied/dosage form and packaging
- Dosage
- Storage and handling
- Dose preparation and administration

Infusion site of care recommendations

Ordering treatment with sotrovimab

If using an electronic system to order treatment, you may have to enter details of preparation and administration. Always be cautious when using abbreviations. If you are unsure whether you should use an abbreviation, write out your directions completely.

See: Sample sotrovimab order form provided in the Appendix.

How supplied/dosage form and packaging

Drug Name	Sotrovimab
Strength	500 mg/8 mL (62.5 mg/mL)
Formulation	Sterile, preservative-free, clear, colorless or yellow to brown solution in a single-dose vial
Quantity	1
NDC	0173-0901-86



Sotrovimab is supplied in a carton containing one single-dose glass vial with a rubber vial stopper (not made with natural rubber latex) and a flip-off cap.

Dosage

The dosage of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is a single IV infusion of 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single intravenous infusion over 30 minutes.

Sotrovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.



Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on renal impairment, during pregnancy, while lactating, or for geriatric patients. Sotrovimab is not authorized for patients under 12 years of age or pediatric patients weighing less than 40 kg. See Section 11 of the [Fact Sheet for Healthcare Providers](#).

Storage and handling



Storage Prior to Dilution

- Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.



Storage After Dilution

- The solution of sotrovimab in the vial is preservative-free and requires dilution prior to administration. The diluted solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.
- Sotrovimab is preservative-free. Discard unused portion.

Additional Guidance from NICA



Guidance on Medication Stability & Storage from the National Infusion Center Association¹

Storage must not exceed 4 hours *unless* the product was prepared in an environment with at least ISO Class 5 air quality in accordance with United States Pharmacopeia (USP) General Chapter <797> pharmacy standards for compounding sterile products. Check with USP <797> operational considerations for sterile compounding during COVID-19 pandemic.

This is true even if storage/stability information in product labeling indicates that prepared medications may be stored for durations that exceed 4 hours.

Stability and storage duration data supplied in product labeling typically:

- Refers to chemical/physical stability rather than microbiological purity and safety, and
- Does not consider the preparation procedures used (eg, aseptic technique) or environmental conditions (eg, ISO air classification)

The longer the prepared medication is stored before administration, the more time microbial pathogens—which may be introduced via contamination during preparation—have to replicate. While the medication molecules themselves may be physically stable beyond 4 hours, the infection risk is too great.

Please visit infusioncenter.org/bestpractices for more information from NICA.

Reference: 1. NICA Notes: Medication Stability & Storage. National Infusion Center Association. http://infusioncenter.org/wp-content/uploads/2021/01/Medication-Stability-and-Storage_0113.pdf. Accessed May 14, 2021.

Dose preparation and administration

Preparation

Sotrovimab is supplied in a single-dose vial and must be diluted prior to administration.

Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique.

- Gather the materials for preparation:



- Polyvinyl chloride (PVC) or polyolefin (PO), sterile prefilled infusion bag. Choose one of the following sizes: prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, and
- One vial of sotrovimab (500 mg/8 mL).



- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded, and a fresh solution prepared.
 - Sotrovimab is a clear, colorless or yellow to brown solution.



- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**



- Withdraw 8 mL sotrovimab from one vial and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection.



- Discard any product remaining in the vial.



- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.



- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately.
 - If immediate administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Alteration of protein structure of monoclonal antibody medications can result from shaking or forceful aspiration or injection during preparation. Withdraw and inject sotrovimab slowly to avoid creating turbulence or foaming.¹

Reference: 1. Laptos T, Omersel J. The importance of handling high-value biologicals: physico-chemical instability and immunogenicity of monoclonal antibodies (review). *Exp Ther Med*. 2018;15:3161-3168. DOI: 10.3892/etm.2018.5281

Dose preparation and administration (cont'd)

Administration

Sotrovimab infusion solution should be administered by a qualified healthcare professional.



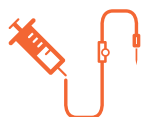
- Gather the materials for infusion:
 - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set
 - Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set with 0.9% Sodium Chloride Injection.
- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.



- **Do not** administer as an IV push or bolus.



- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.



- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.



- If the infusion must be discontinued due to an infusion reaction, discard unused product.



- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Sotrovimab requires 1 single-dose vial, 1 infusion bag, 30 minutes of infusion time, and 60 minutes of post-infusion observation.

Patients treated with sotrovimab should continue to self-isolate and use infection control measures (eg, wear a mask, isolate, practice social distancing, avoid sharing personal items, clean and disinfect “high touch” surfaces, and wash hands frequently) according to CDC guidelines. Also see [Fact Sheet for Patients, Parents, and Caregivers](#).

Section 4

Coding and reimbursement

- Additional considerations

Coding and reimbursement

The following information is for informational purposes only and is not intended to guarantee or provide reimbursement or legal advice. This information is subject to change without notice. Payer coding requirements vary, and may change over time. Please check with the patient's health plan to confirm payer-specific requirements.

ICD-10-CM Diagnosis Code

Code ¹	Description	Notes
U07.1	COVID-19	A confirmed diagnosis of COVID-19 as documented by the provider or documentation of a confirmed diagnosis with a positive COVID-19 test

Level II HCPCS Code

Code ²	Description
Q0247 (for product)	Injection, sotrovimab, 500 mg
M0247 (for administration)	Intravenous infusion, sotrovimab, includes infusion and post-administration monitoring
M0248 (for administration)	Intravenous infusion, sotrovimab, includes infusion and post-administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the COVID-19 public health emergency.

NDC Number

Code	Concentration	Package size
0173-0901-86	500 mg/8 mL	1 vial per carton

HCPCS = Healthcare Common Procedure Coding System; ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification; NDC = National Drug Codes.

References: 1. Centers for Disease Control. ICD-10-CM Official Guidelines for Coding and Reporting FY 2021 (October 1, 2020 - September 30, 2021). Chapter 1: Certain Infectious and Parasitic Diseases, U07.1. <https://www.cdc.gov/nchs/data/icd/10cmguidelines-FY2021.pdf>. Accessed May 14, 2021.
2. Centers for Medicare & Medicaid Services. Medicare Part B Payment for COVID-19 Vaccines and Certain Monoclonal Antibodies during the Public Health Emergency. <https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monoclonal-antibodies>. Accessed June 10, 2021.

Additional considerations

Medicare¹

The Centers for Medicare & Medicaid Services has released a set of toolkits for providers, states, and insurers to help the healthcare system prepare and assist in swiftly administering monoclonal antibodies once they become available during the public health emergency. These resources are designed to increase the number of providers that can administer the products and ensure adequate reimbursement for administration in Medicare. Medicare will publish codes and rates for administering new products as the FDA approves or authorizes each product. For more information on payment allowances and other related information for these products, review the [COVID-19 provider toolkit](#).

Medicaid/CHIP²

States and the federal government fund Medicaid and the Children's Health Insurance Program (CHIP) jointly. The programs are administered by states according to federal requirements and comprehensive benefits offered to people who are determined eligible by states. For information on benefits offered in your state, where to access services, and how to apply for coverage, visit [medicaid.gov](https://www.medicaid.gov). For additional information on the coverage of monoclonal antibody products to treat COVID-19, visit [CMS.gov](https://www.cms.gov).

Uninsured³

The Health Resource and Service Administration (HRSA) is providing support to healthcare providers fighting the COVID-19 pandemic through the COVID-19 Claims Reimbursement to Health Care Providers and Facilities for Testing, Treatment, and Vaccine Administration for the Uninsured Program. This program provides reimbursements on a rolling basis directly to eligible providers for claims that are attributed to the testing, treatment, and vaccine administration for COVID-19 for uninsured individuals. For more information, see [FAQs for COVID-19 Claims Reimbursement to Health Care Providers and Facilities for Testing, Treatment and Vaccine Administration](#).

Reimbursement from commercial payers

Commercial payer reimbursement for sotrovimab will vary based on the payer, hospital system, region, and payer policy during the public health emergency. Reimbursement and administration for sotrovimab will be based on the patient's health plan, coverage policy, and the provider's fee schedule. Please contact the reimbursement department for the patient's payer or health system with specific questions regarding billing and coverage.

Co-pay assistance

GSK may be able to help eligible commercially insured patients with their out-of-pocket costs. Subject to program rules and limitations. Please call the GSK COVID Contact Center at 1-866-GSK-COVID (475-2684) for questions regarding the co-pay program eligibility requirements and find out how to enroll.

References: 1. Medicare Monoclonal Antibody COVID-19 Infusion Program Instruction. CMS.gov. <https://www.cms.gov/files/document/covid-medicare-monoclonal-antibody-infusion-program-instruction.pdf>. Accessed May 14, 2021. 2. The Children's Health Insurance Program (CHIP). Medicaid.gov. <https://www.medicaid.gov/chip/index.html>. Accessed May 14, 2021. 3. COVID-19 Claims Reimbursement to Health Care Providers and Facilities for Testing, Treatment, and Vaccine Administration for the Uninsured. Health Resources & Services Administration. <https://www.hrsa.gov/CovidUninsuredClaim>. Accessed May 14, 2021.

Appendix

- Sample order form for sotrovimab infusion
- Recommended NICA administration instructions
- Responding to patient questions about COVID-19
- Monoclonal antibodies and COVID-19
- Clinical trial information
- Microbiology/resistance information

Sample order form for sotrovimab infusion

[Click here for latest NICA order form](#)

		Patient Name: _____ DOB: _____ Age: _____													
SOTROVIMAB INFUSION ORDERS															
Drug Allergies: _____		Weight: (must weigh at least 40 kg)													
Date of Positive Test: _____		Date of Symptom Onset: _____													
Primary diagnosis: <input checked="" type="checkbox"/> U07.1 COVID-19 infection															
Diagnoses placing patient at high-risk for severe COVID-19 illness - include ICD-10 code(s) and description(s): _____															
Prescriber must indicate <i>all</i> of the following requirements have been met:															
<input type="checkbox"/> Patient/caregiver has been given the Fact Sheet for Patients and Parents/Caregivers <input type="checkbox"/> Patient/caregiver has been informed of alternatives to receiving sotrovimab <input type="checkbox"/> Patient/caregiver has been informed that sotrovimab is an unapproved product that is authorized for use under an Emergency Use Authorization. <input type="checkbox"/> Patient/caregiver has been informed of the significant known and potential risks and benefits of sotrovimab and the extent to which such risks and benefits are unknown.															
Pre-Infusion:		<input checked="" type="checkbox"/> Obtain baseline vital signs <input checked="" type="checkbox"/> Establish vascular access													
Infusion Orders:		<input checked="" type="checkbox"/> If infusion-related reaction occurs, stop infusion and treat per orders/protocol as clinically indicated.													
<input checked="" type="checkbox"/> Using dilution and administration instructions per table below, add sotrovimab 500 mg/8 mL to prefilled bag of 0.9% sodium chloride and administer intravenously using a sterile, in-line, low protein-binding 0.2-micron filter . <input checked="" type="checkbox"/> May use any diluent volume (and associated infusion rate) permitted per EUA unless prohibited by prescriber below.															
Prescriber: If patient requires specific diluent volumes/infusion rates, check appropriate box at right to indicate desired selection. If no box is checked, administering clinician will use facility protocol to determine diluent volume/infusion rate per EUA.		<table border="1"> <thead> <tr> <th>Diluent Volume</th> <th>Total Volume to be Infused</th> <th>MAXIMUM Infusion Rate</th> <th>MINIMUM Infusion Time</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/> 50 mL</td> <td>58 mL</td> <td>116 mL/hr</td> <td>30 minutes</td> </tr> <tr> <td><input type="checkbox"/> 100 mL</td> <td>108 mL</td> <td>216 mL/hr</td> <td>30 minutes</td> </tr> </tbody> </table>	Diluent Volume	Total Volume to be Infused	MAXIMUM Infusion Rate	MINIMUM Infusion Time	<input type="checkbox"/> 50 mL	58 mL	116 mL/hr	30 minutes	<input type="checkbox"/> 100 mL	108 mL	216 mL/hr	30 minutes	
Diluent Volume	Total Volume to be Infused	MAXIMUM Infusion Rate	MINIMUM Infusion Time												
<input type="checkbox"/> 50 mL	58 mL	116 mL/hr	30 minutes												
<input type="checkbox"/> 100 mL	108 mL	216 mL/hr	30 minutes												
Post-Infusion:															
<input checked="" type="checkbox"/> Flush administration set with 0.9% sodium chloride to deliver residual volume. <input checked="" type="checkbox"/> Leave IV in place for observation period; remove prior to discharge. <input checked="" type="checkbox"/> Monitor patient for hypersensitivity reaction for a period of 60 minutes following infusion. <input checked="" type="checkbox"/> Record vital signs immediately following infusion and prior to discharge. <input checked="" type="checkbox"/> Provide patient with discharge instructions. <input checked="" type="checkbox"/> Send record of treatment to prescriber at fax number below.															
Prescriber Name (print): _____		Fax: _____													
Prescriber signature: _____		Date: _____													
Reviewed 6/1/21															

- Individual infusion site documentation requirements may vary; contact site to confirm the medical records that must accompany a sotrovimab order (eg, positive test result for SARS-CoV-2)
- Visit the [NICA COVID-19 Antibody Treatment Resource Center](#) to find order sets, referral guides, patient education, the infusion center locator, and other resources to support the safe use of sotrovimab at infusioncenter.org/
- For more information about basic equipment and medical supplies, see [NICA Minimum Standards for In-Office Infusion](#)

Additional Guidance from NICA

Recommended NICA administration instructions



General guide to preparation of parenteral medications

According to the National Infusion Center Association Standards, prepared product is intended for immediate administration to an individual patient. Administration of parenteral medications should begin immediately, ideally within 1 hour of beginning preparation. If extenuating circumstances preclude immediate administration, manufacturer guidelines and National Infusion Center Association standards regarding stability, storage, and preparation must be followed.¹

Sotrovimab requires 1 single-dose vial, 1 infusion bag, 30 minutes of infusion time, and 60 minutes of post-infusion observation.

*NICA Recommended Administration Instructions**

Diluent Volume	Total Volume to Be Infused (VTBI)	MAXIMUM Infusion Rate	MINIMUM Infusion Time
50 mL	58 mL	100 mL/hr	34 minutes
100 mL	108 mL	200 mL/hr	32 minutes

*VTBI and minimum infusion times above differ from those provided earlier in this guide because they account for the addition of 8 mL sotrovimab to the prefilled saline bag, resulting in a slightly larger volume and consequently a slightly longer infusion time.

Calculating drip rate for gravity infusion²

For gravity infusions, use the following formula to calculate drip rate:

$$\frac{\text{desired rate (mL/hr)} \times \text{drop factor (gtts/mL)}}{60 \text{ min/hr}} = \text{gtts/min}$$

View [drip rate tables](#) for monoclonal antibody administration at the NICA webpage.

- Staff are responsible for ensuring that sotrovimab is handled, stored, prepared, administered, and disposed of properly
- Responsibilities include maintaining a clean, designated area for the preparation of parenteral medications that is free from potential sources of contamination and compliance with USP General Chapter <797> when applicable (eg, batch preparation, anticipatory preparation, and storage for future use)

gtts=drops.

References: 1. NICA Minimum Standards for In-Office Infusion. <https://infusioncenter.org/wp-content/uploads/2019/06/2019-06-19-NICA-Minimum-Standards-for-In-Office-Infusion.pdf>. Accessed May 28, 2021. 2. NICA Drip Rate Tables. http://infusioncenter.org/wp-content/uploads/2021/06/Sotrovimab-Drip-Rate-Tables_0520.pdf. Accessed June 5, 2021.

Responding to patient questions about COVID-19

As a healthcare provider, you understand that vaccines may help prevent COVID-19, and monoclonal antibodies may help treat COVID-19.¹ Patients, caregivers, and others, however, may have questions about monoclonal antibodies for COVID-19 treatment and how they work. The following information, which is written in patient-friendly language, may be helpful when you are discussing treatment options with your patients.

Terminology

Vaccines provide active immunity by stimulating the body's immune response in order to fight an infectious viral disease.² Vaccines are not intended to treat people with active infections.³ There are FDA-authorized vaccines to prevent COVID-19 for people 12 years of age and older.³ The need and timing for repeat vaccines are not known at this time.³

Monoclonal antibodies provide passive immunity by providing antibodies that were manufactured to target a specific disease or virus. They are used when there is an infection and there is not enough time for the body to develop its own response.⁴ Immunity is provided immediately, but is temporary.⁴

Variants are genetic mutations of the SARS-CoV-2 virus. Viruses constantly change and become more diverse. Scientists monitor these changes, including changes to the spikes on the surface of the virus. By carefully studying viruses, scientists can learn how changes to the virus might affect how it spreads and how sick people will get from it.⁵

For more information on SARS-CoV-2 variants, visit: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html>.

References: 1. Combat COVID. <https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients>. Accessed May 14, 2021. 2. Vaccines & Immunizations. Centers for Disease Control and Prevention. <https://www.cdc.gov/vaccines/vac-gen/immunity-types.htm>. Updated March 10, 2021. Accessed May 14, 2021. 3. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Centers for Disease Control and Prevention. <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>. Updated May 14, 2021. Accessed May 30, 2021. 4. The science of COVID-19 vaccines and monoclonal antibodies. <https://www.coronaviruspreventionnetwork.org/coronavirus-vaccine-and-antibody-science/>. Accessed May 14, 2021. 5. About Variants of the Virus that Causes COVID-19. Centers for Disease Control and Prevention. <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant.html>. Updated May 20, 2021. Accessed May 28, 2021.

Monoclonal antibodies and COVID-19

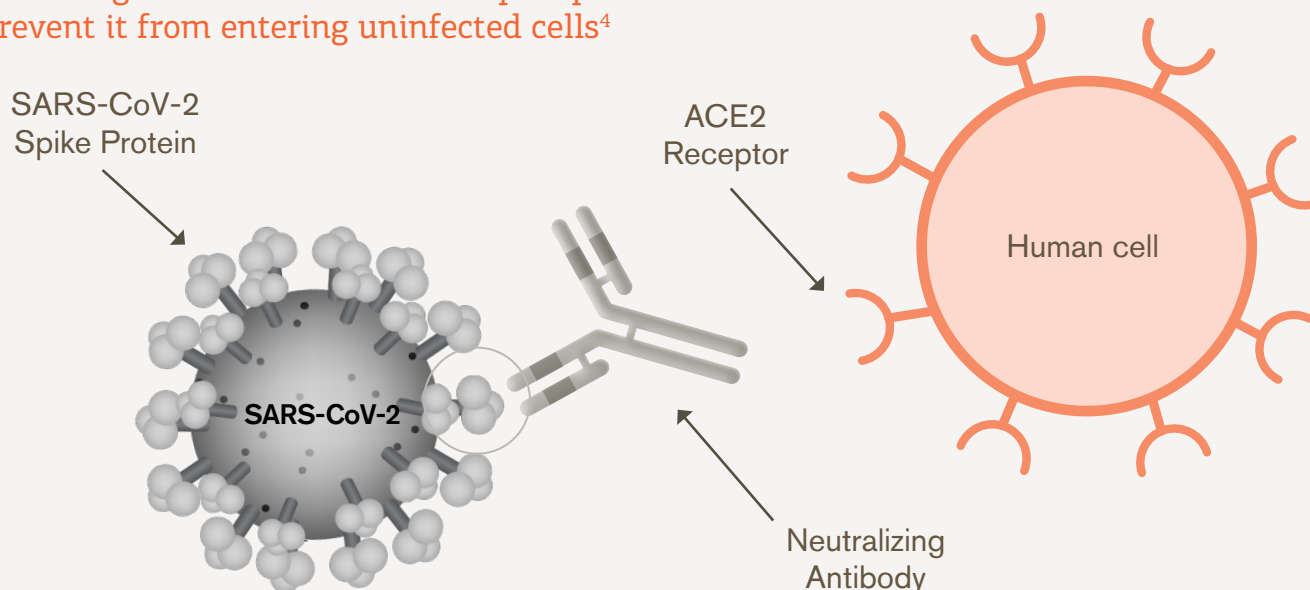
Sotrovimab is a monoclonal antibody (mAb). mAbs are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance, or mimic the immune system's attack on pathogens. Sotrovimab is designed to block viral attachment and entry into human cells, thus neutralizing the virus.¹

mAb treatment is intended to help patients who²:

- Have a positive COVID-19 test, and
- Have symptoms for 10 days or less, and
- Are at high risk for progression to severe COVID-19, including hospitalization or death

Monoclonal antibody treatment may also be an option for individuals who do not develop an adequate immune response after vaccination or cannot receive a vaccine.³

Neutralizing antibodies bind to the spike protein on the SARS-CoV-2 virus to prevent it from entering uninfected cells⁴



For individuals who are already infected, mAb treatment immediately provides the antibodies the body needs to fight the virus.²

Early evidence suggests that treatment with monoclonal antibodies can reduce the SARS-CoV-2 viral load (the amount of virus in the body). Lowering the viral load may result in milder symptoms and reduce the likelihood of hospitalization.²

You can find more information about monoclonal antibody drugs from the CDC, state health departments, and the following resources:

[CombatCOVID.HHS.gov](https://www.combatcovid.hhs.gov)

[coronaviruspreventionnetwork.org](https://www.coronaviruspreventionnetwork.org)

[NICA COVID-19 Antibody Therapy Resource Center](https://www.nica-covid-19-antibody-therapy-resource-center.org)

References: 1. US Food and Drug Administration. Frequently Asked Questions on the Emergency Use Authorization of Sotrovimab. <https://www.fda.gov/media/149535/download>. Accessed June 4, 2021. 2. Combat COVID. <https://combatcovid.hhs.gov/i-have-covid-19-now/monoclonal-antibodies-high-risk-covid-19-positive-patients>. Accessed May 14, 2021. 3. The science of COVID-19 vaccines and monoclonal antibodies. <https://www.coronaviruspreventionnetwork.org/coronavirus-vaccine-and-antibody-science/>. Accessed May 11, 2021. 4. Pinto D, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature*. 2020;583:290-295.

Clinical trial information

Study design

Clinical data supporting the sotrovimab EUA are based on an interim analysis from the Phase 1/2/3 COMET-ICE trial (NCT #04545060) that occurred after 583 randomized subjects had the opportunity to complete at least Day 29 of the trial.

- COMET-ICE is an ongoing, randomized, double-blind, placebo-controlled trial studying sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized)
- Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma, or were 55 years of age and older regardless of comorbidities
- The study included symptomatic patients with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 5 days of enrollment
- Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization and severely immunocompromised patients were excluded from the trial
- Subjects were treated with a single 500-mg infusion of sotrovimab (n = 291) or placebo (n = 292) over 1 hour (Intent to Treat [ITT] population at interim analysis 1)

Baseline study population characteristics

At baseline, the median age was 53 years (range:18 to 96); 22% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 7% Black or African American, 6% Asian, 63% Hispanic or Latino.

- Fifty-eight percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 42% within 4 to 5 days
- The three most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), and diabetes requiring medication (23%)
- Overall, baseline demographic and disease characteristics were well balanced between the treatment arms

Clinical trial information (cont'd)

Primary endpoint

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 85% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo ($p = 0.002$). The table below provides the results of the primary endpoint and a key secondary endpoint of COMET-ICE.

Interim Efficacy Results in Adults with Mild-to-Moderate COVID-19

	Sotrovimab n = 291	Placebo n = 292
Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)		
Proportion (n, %)	3 (1%)	21 (7%)
Adjusted Relative Risk Reduction (97.24% CI)		85% (44%, 96%)
p-value		0.002
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	1 (<1%)

Analysis of change from baseline in viral load in COMET-ICE is not yet possible because data are not available in the majority of trial participants.

Safety summary

The ongoing Phase 1/2/3 double-blind, placebo-controlled, randomized study enrolled 1,057 non-hospitalized patients with COVID-19 (COMET-ICE). The safety of sotrovimab is primarily based on an interim analysis from 868 patients through Day 15.

- All patients received a single 500-mg infusion of sotrovimab ($n = 430$) or placebo ($n = 438$). Two patients experienced treatment interruptions due to infusion site extravasation; infusion was completed for each.
- Infusion-related reactions, including immediate hypersensitivity reactions, have been observed in 1% of patients treated with sotrovimab and 1% of patients treated with placebo in COMET-ICE. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate)
- One case of anaphylaxis was reported following sotrovimab infusion in a study in hospitalized patients; the infusion was immediately discontinued, and the patient received epinephrine. The event resolved but recurred within 2 hours; the patient received another dose of epinephrine and improved with no additional reactions. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following sotrovimab infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. Sotrovimab is not authorized for use in patients hospitalized due to COVID-19
- The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (2%) and diarrhea (1%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo

Microbiology/resistance information

Antiviral Activity

The neutralization activity of sotrovimab against SARS-CoV-2 (isolate USA WA1/2020) was measured in a concentration response model using cultured Vero E6 cells. Sotrovimab neutralized SARS-CoV-2 with an average EC_{50} value of 0.67 nM (100.1 ng/mL) and an average EC_{90} value of 1.2 nM (186.3 ng/mL).

Sotrovimab demonstrated cell culture FcγR activation using Jurkat reporter cells expressing FcγRIIa (low-affinity R131 and high-affinity H131 alleles), FcγRIIIa (low-affinity F158 and high-affinity V158 alleles) and FcγRIIb. Sotrovimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) in cell culture using isolated human natural killer (NK) cells following engagement with target cells expressing spike protein. Sotrovimab also elicited antibody-dependent cellular phagocytosis (ADCP) in cell-based assays using CD14⁺ monocytes targeting cells expressing spike protein.

Antibody Dependent Enhancement (ADE) of Infection

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 cells, primary human monocytic dendritic cells, and peripheral blood mononuclear cells. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS CoV-2 in the presence of concentrations of sotrovimab from 1-fold down to 1000-fold below the EC_{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, lung weight, total viral RNA in the lungs, or infectious virus levels based on TCID₅₀ measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

An E340A amino acid substitution in the spike protein emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay. This substitution is in the conserved epitope of sotrovimab, which is comprised of 23 amino acids. A pseudotyped VLP assessment in cell culture showed that epitope amino acid sequence polymorphisms P337H/L/R/T and E340A/K/G conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: E340K (>297), P337R (>276), P337L (180), E340A (>100), E340G (27), P337H (7.5), and P337T (5.4). The presence of the highly prevalent D614G variant, either alone or in combination, did not alter neutralization of sotrovimab. Pseudotyped VLP assessments indicate that sotrovimab retains activity against the UK (2.3-fold change in EC_{50} value; B.1.1.7: H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), South Africa (0.6-fold change in EC_{50} value; B.1.351: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V), Brazil (0.35-fold change in EC_{50} value; P.1: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F), California (0.7-fold change in EC_{50} value; CAL.20C: S13I, W152C, L452R, D614G), New York (0.6-fold change in EC_{50} value; B.1.526: L5F, T95I, D253G, E484K, D614G, A701V), and India (0.7-fold change in EC_{50} value; B.1.617; T95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H) variant spike proteins. Microneutralization data using authentic SARS-CoV-2 variant virus indicate that sotrovimab retains activity against the UK (3-fold change in EC_{50} value), South Africa (1.2-fold change in EC_{50} value) and Brazil (1.6-fold change in EC_{50} value) variants.



Microbiology/resistance information (cont'd)

Authentic SARS-CoV-2 and Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Sotrovimab

Lineage with Spike Protein Substitution	Key Substitutions Tested ^a	Fold Reduction in Susceptibility (Pseudotyped VLP)	Fold Reduction in Susceptibility (Authentic Virus)
B.1.1.7 (UK origin)	N501Y	No change ^b	No change ^b
B.1.351 (South Africa origin)	K417N + E484K + N501Y	No change ^b	No change ^b
P.1 (Brazil origin)	K417T + E484K + N501Y	No change ^b	No change ^b
B.1.427/B.1.429 (California origin)	L452R	No change ^b	nd ^d
B.1.526 (New York origin) ^c	E484K	No change ^b	nd ^d
B.1.617 (India origin)	L452R + E484Q	No change ^b	nd ^d

^aFor variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is (are) listed. ^bNo change: <5-fold reduction in susceptibility. ^cNot all isolates of the New York lineage harbor the E484K substitution (as of February 2021). ^dNot determined.

Limited nucleotide sequencing data from a total of 218 participants, at the time of authorization, indicated that 9 participants (5 placebo and 4 treated with sotrovimab) enrolled in COMET-ICE were infected with the CAL.20C variant (S13I, W152C, L452R), and one subject treated with sotrovimab progressed to require hospitalization. Two additional participants in the placebo group carried the L452R variant only. None of the participants were infected with SARS-CoV-2 that contained the full complement of spike substitutions characteristic of the UK (B.1.1.7), South African (B.1.351), or Brazilian (P.1) variants. One participant in the placebo group carried the N501Y variant at baseline.

In COMET-ICE, post-baseline epitope variants were detected in eight participants in the cohort receiving sotrovimab (spike protein substitutions E340K [4 subjects: ≥99.7% allele frequency]; A344V [6.2%]; K356R [7.5%]; S359G [2 subjects: 12.2% and 8.3%]). Of the variants detected at baseline and post-baseline, L335F, G339C, E340A, E340K, R346I, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. E340A and E340K substitutions confer reduced susceptibility to sotrovimab (>100-fold and >297-fold changes in EC₅₀ value, respectively). Sotrovimab retains susceptibility against L335F (0.8-fold change in EC₅₀ value), G339C (1.2-fold change in EC₅₀ value), R346I (1.7-fold change in EC₅₀ value), K356N (1.1-fold change in EC₅₀ value), K356R (0.8-fold change in EC₅₀ value), R357I (1-fold change in EC₅₀ value), I358V (0.7-fold change in EC₅₀ value), and S359G (0.8-fold change in EC₅₀ value) substitutions. The clinical impact of these variants is not yet known. Data collection and analysis is still ongoing.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

Please see [Important Safety Information](#), most current [Fact Sheet for Healthcare Providers](#) and [Fact Sheet for Patients, Parents, and Caregivers](#), and [FDA Letter of Authorization](#) for sotrovimab.

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