Emergency Use Authorization (EUA) for Sotrovimab 500 mg
Center for Drug Evaluation and Research (CDER) Memorandum

Identifying Information

Application Type (EUA or Pre-EUA)	EUA
EUA Application Number	EUA 000100, SDN 76
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	EUA Sponsor GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK GSK US Point of Contact Debra H. Lake, M.S. Sr. Director Global Regulatory Affairs GlaxoSmithKline 5 Moore Drive PO Box 13398 Research Triangle Park, NC 27709-3398 Email: (b) (6) Phone: (b) (6)
Manufacturer	GlaxoSmithKline, Parma.
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OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Sarita Boyd, Clinical Reviewer Kimberly Struble, Clinical Team Lead Eric Donaldson, Clinical Virology Reviewer Julian O'Rear, Clinical Virology Team Lead Scott Komo, Statistical Reviewer Thamban Valappil, Statistical Team Lead Debra Birnkrant, Division Director, DAV John Farley, Office Director, OID
Proprietary Name	None
Established Name/Other names used during development	Sotrovimab (VIR-7831)
Dosage Forms/Strengths	Sterile solution for injection, 500mg/8 mL vial
Therapeutic Class	SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)
Intended Population	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

I. Review of Fact Sheet Revisions

Key updates to the Fact Sheet for Healthcare Providers (HCP) are discussed below. Corresponding changes, where applicable, were made to the Fact Sheet for Patients, Parents, and Caregivers.

A. Approved Available Alternatives

Sotrovimab was initially authorized for emergency use on May 26, 2021 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. At that time, several other therapeutics were available under EUA, but not FDA-approved, for uses that overlap with the authorized use for sotrovimab.

Subsequently, on January 21, 2022, FDA approved a supplement to New Drug Application (sNDA) 214787 for remdesivir (Veklury) for the treatment of adults and pediatric patients (12 years of age and older who weigh at least 40 kilograms, which is about 88 pounds) with positive results of direct SARS-CoV-2 viral testing, and who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

With FDA's approval of the sNDA described above, remdesivir is an approved alternative to sotrovimab for its authorized use. However, FDA previously determined that remdesivir may not be an adequate alternative to sotrovimab because remdesivir must be administered via IV infusion over the course of 3 days, which may not be feasible or practical for certain patients. For example, it may not be possible for some patients to go to an infusion site for treatment for 3 days. The authorized Fact Sheet for sotrovimab was revised to include language consistent with FDA's determination on this issue.

B. Limitations of Authorized Use

The following Limitation of Authorized Use (LOAU) was added to the sotrovimab Fact Sheet, consistent with the current Fact Sheets for other SARS-CoV-2 monoclonal antibody treatments under EUA. The LOAU will ensure that, based on available information including variant susceptibility to sotrovimab and regional variant frequency, any patient receiving sotrovimab consistent with the terms and conditions of the authorization will likely benefit from the therapy and helps avoid exposing patients to the risk of adverse events from specific treatment agents that are not expected to provide benefits to patients.

- Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible

SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.

- FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[1]

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report using Nowcast for the week ending February 12, 2022, the most common variants of concern in the US are the Omicron B.1.1.529/BA.1and B.1.1.529/BA.1.1 variants, representing an estimated 96.1% combined. Sotrovimab is expected to retain activity against the Omicron B.1.1.529/BA.1 and BA.1.1 variants. The Omicron Omicron B.1.1.529/BA.2 variant, for which sotrovimab susceptibility is uncertain, represents an estimated 3.9% (95% PI: 2.8-5.3%) during the same period. Refer to the Microbiology/Resistance section below for additional information on the Omicron B.1.1.529/BA.2 variant.

In addition the following revisions (in red font) were made for consistency with other monoclonal antibody Fact Sheets.

- Sotrovimab is not authorized for use in the following patient populations[6]:
  - Adults or pediatric patients who are hospitalized due to COVID-19, or
  - Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID- 19, or
  - Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen

C. Dosage and Administration

The authorization of sotrovimab to be administered as a single dose of 500 mg as soon as possible after positive results of direct SARS-CoV-2 viral testing remains unchanged. However, the following changes were made based on efficacy and safety data from COMET-TAIL and safety data from COMET-PEAK. These trials are described in the Appendix and discussed further under Overall Safety Summary as well as Clinical Trial Results and Supporting Data for EUA.

- Sotrovimab should be given within 7 days of symptom onset, reduced from within 10 days of symptom onset.

[1] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- The option to administer the IV infusion over 15 minutes for 50-mL infusion bag was added. The recommendation to administer the IV infusion over 30 minutes for 100-mL infusion bag was retained.

D. Overall Safety Summary: Clinical Trials Experience

A 15-minute IV infusion of sotrovimab 500 mg is supported by a safety database of 481 participants who received sotrovimab in this manner in COMET-TAIL (n=345), COMET-PEAK Part B (n=79), or COMET-PEAK Part C (n=57). Note, the duration of IV infusion for 11 of the 481 participants across trials was <15 minutes. Refer to the Appendix for a description of these trials. The main safety concern with an increased infusion rate is infusion-related reactions including hypersensitivity.

In COMET-TAIL and COMET-PEAK, infusion-related reactions including hypersensitivity reactions were defined as those occurring within 24 hours of the infusion. After the end of infusion, participants were monitored for at least 30 minutes in COMET-TAIL and for at least 30 minutes (and up to 2 hours) in COMET-PEAK depending on the cohort. Importantly, no participants in COMET-TAIL or COMET-PEAK experienced anaphlaxis or any serious hypersensitivity reaction.

In COMET-TAIL, non-serious infusion-related reactions occurred in two participants who received a single IV infusion of sotrovimab 500 mg and included one Grade 2 event (chills) and two Grade 1 events (hypersensitivity and pyrexia). While all participants completed treatment, the participant with Grade 1 hypersensitivity had a temporary interruption of the infusion. All events resolved.

In COMET-PEAK Parts B and C, no reactions were reported within 24 hours of dosing. However, one participant experienced Grade 1 facial rash 5 days after the IV infusion of sotrovimab 500 mg. The facial rash was not reported as resolved.

Based on the analysis of infusion-related reactions in both trials, the data are sufficient to support an option to reduce the infusion time from 30 minutes (as currently specified in the EUA Fact Sheet) to 15 minutes, if sotrovimab is diluted using a 50-mL infusion bag. The 30-minute infusion time will be maintained for dilutions using a 100-mL infusion bag. The reduced infusion time for the 50 mL bag may benefit healthcare providers and facilities when the volume of infections and number of participants requiring treatment are high. The benefit/risk for an option to reduce the infusion time to 15 minutes is favorable based on available information.

E. Use in Specific Populations: Pregnancy

There is now a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy. This information was added to the Fact Sheet, along with a website (https://covid-pr.pregistry.com) and telephone number (1-800-616-3791) for access to the registry.

Consistent with Fact Sheets for other SARS-CoV-2 monoclonal antibodies, language was added to inform about maternal and fetal risks associated with untreated COVID-19, including the following clinical consideration. The language reads as follows:

> *Disease-Associated Maternal and/or Embryo-Fetal Risk*
> COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

F. Microbiology/Resistance Information

Sotrovimab neutralization activity was reduced an average fold change in EC_{50} value of 16-fold based on the geometric mean of 10 replicates against pseudotyped VLPs expressing the SARS-CoV-2 Omicron B.1.1.529/BA.2 spike variant compared to wild-type SARS-CoV-2 (Wuhan-1) in a VSV pseudotyped VLP test system (Study Report (b) (4)). The clinical relevance of the 16-fold reduction in sotrovimab activity against the SARS-CoV-2 Omicron B.1.1.529/BA.2 variant is unknown. It is also not known how pseudotyped VLPs or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome.

The Agency is aware of data from several sources that indicate the following fold shifts in sotrovimab EC_{50} value against the SARS-CoV-2 Omicron B.1.1.529/BA.2 variant but with similar EC_{50} values: 60-fold (Monogram, EC_{50} value = 5.8 nM), 19-fold (Vir data from white paper, EC_{50} value = 11.9 nM), 16-fold (Ho Lab data, EC_{50} value = 4.3 nM), 16-fold shift (Vir data from 10 replicates, EC_{50} value = 7.6 nM), 10-fold (Vir data using full length SARS-CoV-2 Omicron B.1.1.529/BA.2 spike from USG, EC_{50} value = 4.1 nM). Of note, the EC_{50} values across the different assays above vary by a maximum of 2.9-fold; however, fold-shifts vary by as much as 6-fold indicating that the wild type SARS-CoV-2 isolate used for comparison is contributing to this variation. It is not known which SARS-CoV-2 isolate would be most appropriate for assessing susceptibility.

Sotrovimab is expected to retain activity against the following SARS-CoV-2 variants of concern or interest, including the Alpha (B.1.1.7, UK origin), Beta (B.1.351, South Africa origin), Gamma (P1, Brazil origin), Delta (B.1.617.2/AY.4.2, India origin)/(AY.1/AY.2, India origin), Epsilon (B.1.427/B.1.429, USA/California origin), Iota (B.1.526, USA/New York origin), Kappa (B.1.617.1, India origin), Lambda (C.37, Peru origin), Mu (B.1.621, Colombia origin), Omicron/BA.1 (B.1.1.529/BA.1, South Africa origin), and Omicron/BA.1.1 (B.1.1.529/BA.1.1, South Africa origin) variants based on cell culture neutralization data from authentic SARS-CoV-2 assays and/or pseudotyped VLP data. The presence of these variants at baseline in the majority of COMET-TAIL and COMET-PEAK participants is unknown at this time, but the sponsor is continuing to obtain this information.

Treatment-emergent SARS-CoV-2 spike substitutions at positions P337 and E340, which are potential sotrovimab resistance-associated substitutions, were detected in post-baseline samples from subjects in COMET-PEAK Part B (n=8 in the 500 mg IV group) and C (n=3 in the 500 mg IV group). Only 1 subject had a substitution at one of these

positions at baseline (COMET-PEAK Part B 500 mg IV group). There were insufficient data to determine if the presence of substitutions at positions P337 and E340 impacted clinical outcomes. However, the sponsor is continuing to obtain sequencing data in all COMET-TAIL and COMET-PEAK participants to better assess the presence and clinical relevance of substitutions at positions P337 and E340.

G. Clinical Trial Results and Supporting Data for EUA

Clinical trial data are available from the Phase 3 trial COMET-TAIL, which provide additional support for the authorized use of sotrovimab. The results were reviewed, and the following information from COMET-TAIL was added to the Fact Sheet.

COMET-TAIL was a randomized, multi-center, open label trial which evaluated the efficacy, safety, and tolerability of sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Eligible subjects were 12 years of age or older with at least one of the following comorbidities: diabetes, obesity (BMI ≥85th percentile for age/gender based on Centers for Disease Control and Prevention [CDC] growth charts for adolescents or BMI □30 for subjects ≥18 years old), chronic kidney disease, congenital heart disease, congestive heart failure (for subjects ≥18 years old), chronic lung diseases, sickle cell disease, neurodevelopmental disorders, immunosuppressive disease or receiving immunosuppressive medications, or chronic liver disease; or were 55 years of age or older regardless of comorbidities. The trial included symptomatic subjects with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 7 days of enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization were excluded from the trial.

The ITT population consisted of 385 subjects randomized to receive a single 500-mg IV infusion of sotrovimab (345 subjects received the dose over 15 minutes). The primary analysis population, which excluded 7 subjects because they were fully vaccinated and immunocompetent (key inclusion/exclusion violation), consisted of 378 subjects randomized to sotrovimab 500 mg IV . In the primary analysis population at baseline, the median age was 51 years (range:15 to 90, including 2 subjects under 18 years); 25% of subjects were 65 years of age or older and 9% were over 75 years of age; 42% of subjects were male; 96% were White and 4% were Black or African American; 83% were Hispanic or Latino. Forty-eight percent (48%) of subjects received sotrovimab within 3 days of COVID-19 symptom onset, 37% within 4 to 5 days, and 14% within 6-7 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (42%), chronic lung disease (16%), and diabetes requiring medication (13%).

In the primary analysis population, 5 (1.3%) of 378 subjects had progression to COVID-19 defined as hospitalization for >24 hours for acute management of any illness or death due

to any cause through Day 29. No deaths were reported through Day 29.

Importantly, COMET-TAIL supports the update to administer sotrovimab within 7 days of symptom onset. While the previously reviewed pivotal trial COMET-ICE enolled participants within 5 days of symptom onset, the initial recommendation in the Fact Sheet to administer sotrovimab within 10 days of symptom onset was based on consistency with other monoclonal antibodies under EUA and to maximize access to these treatments at a time when routine testing was less readily available and/or test results were less timely compared to today. Updating the Fact Sheet for consistency with clinical trial criteria will provide a more accurate recommendation. Given the efficacy results from COMET-TAIL, administering sotrovimab within 7 days of symptom onset is reasonable.

II. Recommendations

The division recommends updating the Fact Sheet for Healthcare Providers as described above, with corresponding updates to the Fact Sheet for Patients, Parents, and Caregivers.

The updates described above do not alter the conclusion in the initial review to support authorization of EUA 100. However, FDA is continuing to receive and evaluate SARS-CoV-2 neutralization susceptibility data for sotrovimab against the Omicron B.1.1.529/BA.2 variant, which may require additional changes to the Fact Sheet for Healthcare Providers in the coming weeks.

III. Appendix

Table 1. Clinical Trials[a]

Study Number NCT Number	IND, NDA, or Literature Reference	Type of Study	Population (Planned N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
VIR-7831-5008, GSK 217114 (COMET-TAIL) NCT04913675	IND 149315	Efficacy, Safety, PK	N=1020 Outpatient adults and pediatric patients aged 12 years and older with mild/moderate COVID-19 at high risk of progression to severe disease	Phase 3 randomized (1:1:1), open-label, active-controlled non-inferiority trial of IM vs. IV Active control: Single dose of sotrovimab 500 mg via IV infusion (over 15 minutes)	Single dose of sotrovimab via IM injection at two dose levels: - 500 mg (two 4 mL injections, one in each dorsogluteal muscle), or - 250 mg (one 4 mL injection in the dorsogluteal muscle; or two 2 mL injections in each deltoid muscle)	Active Enrollment complete 500 mg IV: n=394 500 mg IM: n=394 250 mg IM: n=194 (stopped early per IDMC recommendation)
VIR-7831-5006, GSK 216912 (COMET-PEAK) NCT04779879	IND 149315	Safety, PK, PD	N=150 (Part B) N=150 (Part C) Outpatients with mild/moderate COVID-19 at high risk of progression to severe disease	Part A: Not applicable to the EUA amendment Parts B and C: Phase 2 randomized (1:1), open-label, active-controlled trial of IM vs. IV Active control: Single dose of sotrovimab 500 mg via IV infusion (over 15 minutes)	Single dose of sotrovimab via IM injection: - Part B: 500 mg (two 4 mL injections, one in each dorsogluteal muscle) - Part C: 250 mg (one 4 mL injection in the dorsogluteal muscle or two 2 mL injections in each deltoid muscle)	Active Enrollment complete Part B: n=166 Part C: n=157

Source: EUA Amendment 6, submitted on 11 Jan 2022
Abbreviations: PK = Pharmacokinetics, IM = intramuscular, IV = intravenous, IDMC = independent data monitoring committee, PD = pharmacodynamic
[a] Efficacy and safety results from the IM sotrovimab arms in COMET-TAIL and COMET-PEAK are not discussed in this review. Sotrovimab remains authorized for emergency use only at a dose of 500 mg and only administered as an IV infusion.

FACT SHEET FOR HEALTHCARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF SOTROVIMAB

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product sotrovimab 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 treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[1]
- Sotrovimab is not authorized for use in the following patient populations:
  - Adults or pediatric patients who are hospitalized due to COVID-19, OR
  - Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, OR
  - Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.
- 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.

RECENT MAJOR CHANGES

- Limitations of Authorized Use - updated authorization for those likely to have been infected with or have been exposed to a susceptible SARS-CoV-2 variant — Revised 02/2022

[1] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- Dosage and Administration (Box and Sections 2.2 and 2.4): updated intravenous infusion time — Revised 02/2022
- Overall Safety Summary, Clinical Trials Experience (Section 6.1, 14.2 and 18): addition of COMET-TAIL safety, PK, and efficacy data — Revised 02/2022
- Microbiology/Resistance Information, Antiviral Resistance (Section 15): addition of information on susceptibility of SARS-CoV-2 variants to sotrovimab — Revised 02/2022
- Overall Safety Summary, Post-Authorization Experience (Section 6.2): addition of anaphylaxis — Revised 11/2021
- Dosage and Administration, Dose Preparation and Administration (Section 2.4): addition of 5% Dextrose injection and updated storage of diluted solution of sotrovimab — Revised 09/2021
- Clinical Trial Results and Supporting Data for EUA (Section 18): updated with efficacy results for the full population — Revised 09/2021

Sotrovimab has been authorized by FDA for the emergency use described above.

Sotrovimab is not FDA-approved for this use.

Sotrovimab 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.

This EUA is for the use of 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 *[see Limitations of Authorized Use]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) 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/m^2, or if 12 to 17 years of age, have BMI ≥85th 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 medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

Sotrovimab must be administered after dilution by intravenous (IV) infusion. See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.

- The authorized dosage for sotrovimab is 500 mg administered as a single IV infusion as soon as possible after a positive viral test for SARS-CoV-2 and within 7 days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18)]*.
- Sotrovimab is available as a concentrated solution and **must be diluted** prior to IV infusion.
- Administer 500 mg of sotrovimab by IV infusion over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag.

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

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.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all SERIOUS ADVERSE EVENTS and MEDICATION ERRORS potentially related to sotrovimab within 7 calendar days from the healthcare provider's awareness of the event. See Sections 8 and 9 of the Full EUA Fact Sheet for reporting requirements.

Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of sotrovimab in COVID-19, please see www.clinicaltrials.gov.

Contraindications

Sotrovimab is contraindicated in patients who have a history of anaphylaxis to sotrovimab or to any of the excipients in the formulation.

Dosing

See Full Fact Sheet for Healthcare Providers for information on dosing *[see Dosage and Administration (2)]*.

Preparation and Administration

See Full Fact Sheet for Healthcare Providers for information on preparation and administration *[see Dosage and Administration (2.4)]*.

Storage

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

Warnings

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 *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*. 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 (e.g., 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 (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care. Clinically monitor patients for at least 1 hour after completion of the infusion for signs and symptoms of hypersensitivity.

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 (e.g., 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 the following patient populations *[see Limitations of Authorized Use]*:

- Adults or pediatric patients who are hospitalized due to COVID-19, OR
- Adults or pediatric patients who require oxygen therapy and/or respiratory support due to

COVID-19, OR

- Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

Side Effects

Adverse events have been reported with sotrovimab *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*.

Additional adverse events associated with sotrovimab, some of which may be serious, may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS

As the healthcare provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents, and Caregivers" (and provide a copy of the Fact Sheet**)** prior to the patient receiving sotrovimab, including:

- FDA has authorized the emergency use of sotrovimab for 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 *[see Limitations of Authorized Use]*.
- The patient or parent/caregiver has the option to accept or refuse sotrovimab.
- The significant known and potential risks and benefits of sotrovimab and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of sotrovimab for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF SOTROVIMAB UNDER EMERGENCY USE AUTHORIZATION

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 *[see Limitations of Authorized Use]*.

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 Emergency Use Authorization.
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 serious adverse events* and medication errors potentially related to sotrovimab within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:
   - Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
   - A statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
   - Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
   - Patient's preexisting medical conditions and use of concomitant products
   - Information about the product (e.g., dosage, route of administration, NDC #)
5. Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:
   - Complete and submit the report online: www.fda.gov/medwatch/report.htm
   - Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:

- Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
- Fax to 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 1-866-GSK-COVID (866-475-2684) to report adverse events.

6. 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.

   *Serious Adverse Events 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;
   - other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

7. OTHER REPORTING REQUIREMENTS

   - Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of 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, who are not hospitalized and have mild-to moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via IV infusion for a total treatment duration of 3 days. Although Veklury is an approved alternative 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. FDA does not consider Veklury to be an adequate alternative to sotrovimab for this authorized use because it may not be feasible or practical for certain patients (e.g., it requires a 3-day treatment duration).

Additional information on COVID-19 treatments can be found at http://www.covid19treatmentguidelines.nih.gov/. The healthcare provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

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 this 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.[2] As a healthcare provider, you must comply with the mandatory requirements of this EUA (see above).

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 this Fact Sheet. 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.

CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

END SHORT VERSION FACT SHEET

Long Version Begins on Next Page

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[2] The healthcare provider should visit https://clinicaltrials.gov/ to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

1 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 *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency.
  - FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.[3]

[3] FDA will monitor conditions to determine whether use in a geographic region is consistent with this scope of authorization, referring to available information, including information on variant susceptibility *[see Microbiology/Resistance Information (15)]*, and CDC regional variant frequency data available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

- Sotrovimab is not authorized for use in the following patient populations:
  - Adults or pediatric patients who are hospitalized due to COVID-19, OR
  - Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, OR
  - Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.
- 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 *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Sotrovimab should be administered as soon as possible after a positive viral test for SARS-CoV-2 and within 7 days of symptom onset in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death *[see Authorized Use (1) and Clinical Trial Results and Supporting Data for EUA (18)]*.

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) 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/m^2, or if 12 to 17, have BMI ≥85th 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 medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

The dosage in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is 500 mg of sotrovimab administered as a single IV infusion. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 7 days of symptom onset.

- Sotrovimab is available as a concentrated solution and **must be diluted** prior to IV infusion.
- Administer 500 mg of sotrovimab by IV infusion over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

2.3 Dosage Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older. Sotrovimab is not authorized for patients under 12 years of age or pediatric patients weighing less than 40 kg *[see Use in Specific Populations (11.3)]*.

Geriatric Use

No dosage adjustment is recommended in geriatric patients *[see Use in Specific Populations (11.4)]*.

Renal Impairment

No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

2.4 Dose Preparation and Administration

Preparation

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

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

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose 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 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 of sotrovimab from one vial and inject into the prefilled infusion bag.
- 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 6 hours at room temperature (up to 25°C [up to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

Sotrovimab infusion solution should be administered by a qualified healthcare professional *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.1)]*.

- Gather the materials for infusion via infusion pump or gravity:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and

- 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.
- Administer the entire infusion solution in the bag over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag. 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 and 5% Dextrose Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride or 5% Dextrose 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.

3 DOSAGE FORMS AND STRENGTHS

Sotrovimab is a sterile, preservative-free, clear, colorless or yellow to brown solution available as:

- Injection: 500-mg/8-mL (62.5-mg/mL) solution in a single-dose vial.

4 CONTRAINDICATIONS

Sotrovimab is contraindicated in patients who have a history of anaphylaxis to sotrovimab or to any of the excipients in the formulation.

5 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.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Overall Safety Summary (6.1)]*. 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 *[see Overall Safety Summary (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., 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 (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care. Clinically monitor patients for at least 1 hour after completion of the infusion for signs and symptoms of hypersensitivity.

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.

5.2 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 (e.g., 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.

5.3 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 the following patient populations *[see Limitations of Authorized Use]*:

- Adults or pediatric patients who are hospitalized due to COVID-19, OR
- Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, OR
- Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The safety of sotrovimab in subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized) is based on analyses from COMET-ICE, a Phase 1/2/3 trial, and COMET-TAIL, a Phase 3 trial *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

In COMET-ICE, subjects received a single 500-mg infusion of sotrovimab (n = 523) or placebo (n = 526). Two subjects experienced treatment interruptions due to infusion site extravasation; infusion was completed for each. In COMET-TAIL, subjects received a single 500-mg IV infusion of sotrovimab (n = 393).

Infusion-Related Reactions Including Hypersensitivity

Infusion-related reactions, including immediate hypersensitivity reactions, were observed in 1% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with IV sotrovimab in COMET-TAIL. 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 subjects; the infusion was immediately discontinued, and the subject received epinephrine. The event resolved but recurred within 2 hours; the subject 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 subjects hospitalized due to COVID-19 *[see Warnings and Precautions (5.1, 5.3)]*.

Hypersensitivity adverse reactions (i.e., adverse events assessed as causally related) were observed in 2% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with sotrovimab in COMET-TAIL. All were Grade 1 (mild) or Grade 2 (moderate), and none of the reactions in either trial led to permanent discontinuation of the infusions. One reaction led to pausing of the infusion *[see Warnings and Precautions (5.1)]*.

Common Adverse Events

The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (1%) and diarrhea (2%), 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.

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of sotrovimab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

Anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1)]*.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during dose administration and observe patients for at least 1 hour after IV infusion is complete *[see Warnings and Precautions (5.1, 5.2) and Overall Safety Summary (6.1)]*.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of sotrovimab are ongoing *[see Overall Safety Summary (6)]*.

The prescribing healthcare provider and/or the provider's designee is/are responsible for the mandatory reporting of all serious adverse events* and medication errors potentially related to sotrovimab within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online at 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 to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - 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 1-866-GSK-COVID (866-475-2684) to report adverse events.

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.

*Serious Adverse Events 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;
- other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of sotrovimab
- Pertinent laboratory and virology information

- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

- In section A, box 1, provide the patient's initials in the Patient Identifier
- In section A, box 2, provide the patient's date of birth
- In section B, box 5, description of the event:
  - Write "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
  - Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
- In section G, box 1, name and address:
  - Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
  - Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

10 DRUG INTERACTIONS

Clinical drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy. Pregnant and recently pregnant individuals can go to https://covid-pr.pregistry.com to enroll or call 1-800-616-3791 to obtain information about the registry.

Risk Summary

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. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

Nonclinical reproductive toxicity studies have not been conducted with sotrovimab. In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab. Since sotrovimab is a recombinant human immunoglobulin G (IgG) containing the LS modification in the Fc domain, it has the potential for placental transfer from the mother to the developing fetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing fetus is not known.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk: COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

11.2 Lactation

Risk Summary

There are no available data on the presence of sotrovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sotrovimab and any potential adverse effects on the breastfed infant from sotrovimab or from the underlying maternal condition. Individuals with COVID-19 who are breastfeeding should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

Sotrovimab is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of sotrovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults.

11.4 Geriatric Use

Of the 528 subjects randomized to receive sotrovimab in COMET-ICE, 20% were 65 years of

age and older and 11% were over 70 years of age. Of the 378 subjects in the primary analysis population receiving sotrovimab in COMET-TAIL, 25% were 65 years of age or older and 8% were over 75 years of age. The difference in pharmacokinetics (PK) of sotrovimab in geriatric patients compared to younger patients has not been quantified.

11.5 Renal Impairment

No clinical trials have been conducted to evaluate the effects of renal impairment on the PK of sotrovimab. Sotrovimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of sotrovimab.

11.6 Hepatic Impairment

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of hepatic impairment on the PK of sotrovimab is unknown.

12 OVERDOSAGE

There is no human experience of acute overdosage with sotrovimab.

There is no specific treatment for an overdose with sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

13 PRODUCT DESCRIPTION

Sotrovimab is a human immunoglobulin G-1 (IgG1-kappa) monoclonal antibody consisting of 2 identical light chain (LC) polypeptides composed of 214 amino acids each and 2 identical heavy chain (HC) polypeptides, each composed of 457 amino acids. Sotrovimab is produced by a Chinese Hamster Ovary cell line and has a molecular weight of approximately 149 kDa.

Sotrovimab injection is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a single-dose vial for IV infusion after dilution.

Each mL contains sotrovimab (62.5 mg), L-histidine (1.51 mg), L-histidine monohydrochloride (2.15 mg), L-methionine (0.75 mg), polysorbate 80 (0.4 mg), and sucrose (70 mg). The solution of sotrovimab has a pH of 6.0.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Sotrovimab is a recombinant human IgG1-kappa mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant (K_D = 0.21 nM) but does not compete with human ACE2 receptor binding (IC_{50} value >33.6 nM [5 µg/mL]). Sotrovimab inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extend antibody half-life, but do not impact wild-type Fc-mediated effector functions in cell culture.

14.2 Pharmacokinetics

A summary of PK parameters following a single 500-mg IV infusion is presented in Table 1:

Table 1. Summary of Derived IV Sotrovimab Serum Pharmacokinetic Parameters

PK Parameter[a]	Sotrovimab (500 mg IV)	n
C_{max}[b], µg/mL	143 (34.5)	102
C_{D29}[b], µg/mL	40.7 (40.3)	135
AUC_{D1-29}[c], day*µg/mL	1410 (25.6)	20

[a] Parameters are reported as geometric mean (%CVb).

[b] C_{max} (end of infusion) and C_{D29} (serum sotrovimab concentration on Study Day 29) estimates are based on cumulative intensive and sparse PK data available to date from the lead and expansion phases of COMET-PEAK B and C.

[c] AUC_{D1-29} (area under the curve from Study Day 1 to 29) estimates are based on noncompartmental analyses of intensive PK from the Lead-in Phases of COMET-PEAK B and C.

Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of sotrovimab is unknown. Renal impairment is not expected to impact the PK of sotrovimab since mAbs with molecular weight >69 kDa do not undergo renal elimination. Similarly, dialysis is not expected to impact the PK of sotrovimab.

15 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, total viral RNA in the lungs, or infectious virus levels based on $TCID_{50}$ 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 choose an authorized therapeutic option with activity against circulating SARS-CoV-2 variants in their state. SARS-CoV-2 variant frequency data for states and jurisdictions can be accessed on the CDC website [4].

Spike protein amino acid substitution E340A 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 substitutions P337H/K/L/R/T, E340A/K/G/Q/V, T345P, K356T, and L441N conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: P337H (5.13), P337K (>304), P337L (>192), P337R (>192), P337T (10.62), E340A (>100), E340G (18.21), E340K (>297), E340Q (>50), E340V (>200), T345P (225), K356T (5.90), and L441N (72). The presence of the highly prevalent D614G substitution, either alone or in combination, did not alter neutralization of sotrovimab. Pseudotyped VLP assessments indicate that sotrovimab retains activity against the B.1.1.7 (Alpha, UK origin: H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H; 2.3-fold change in EC_{50} value), B.1.351 (Beta, South Africa origin: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V; 0.6-fold change in EC_{50} value), P.1 (Gamma, Brazil origin: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F; 0.35-fold change in EC_{50} value), B.1.427/B.1.429 (Epsilon, California origin: S13I, W152C, L452R, D614G; 0.7-fold change in EC_{50} value), B.1.526 (Iota, New York origin: L5F, T95I, D253G, E484K, D614G, A701V; 0.6-fold change in EC_{50} value), B.1.617.1 (Kappa, India origin: T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H; 0.7-fold change in EC_{50} value), B.1.617.2 (Delta, India origin: T19R, G142D, E156G, F157-, R158-, L452R, T478K, D614G, P681R, D950N; 1-fold change in EC_{50} value), AY.1 (Delta [+K417N], India origin: T19R, T95I, G142D, E156G, F157-, R158-, W258L, K417N, L452R, T478K, D614G, P681R, D950N; 1.1-fold change in EC_{50} value), AY.2 (Delta [+K417N], India origin: T19R, V70F, G142D, E156G, F157-, R158-, A222V, K417N, L452R, T478K, D614G, P681R, D950N; 1.3-fold change in EC_{50} value),

[4].https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html

AY.4.2 (Delta, India origin: T19R, T95I, G142D, Y145H, E156G, F157-, R158-, A222V, L452R, T478K, D614G, P681R, D950N; 1.6-fold change in EC_{50} value), C.37 (Lambda, Peru origin: G75V, T76I, del246-252, L452Q, F490S, T859N; 1.5-fold change in EC_{50} value), B.1.621 (Mu, Colombia origin: T95I, Y144T, Y145S, ins146N, R346K, E484K, N501Y, D614G, P681H, D950N; 1.3-fold change in EC_{50} value), B.1.1.529/BA.1 (Omicron, South Africa origin: A67V, del69-70, T95I, G142D, del143-145, del211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F; 2.7-fold change in EC_{50} value), and B.1.1.529/BA.1.1 (Omicron [+R346K], South Africa origin: A67V, del69-70, T95I, G142D, del143-145, del211, L212I, ins214EPE, G339D, R346K, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F; 3.3-fold change in EC_{50} value) variant spike proteins (Table 2). Pseudotyped VLP assessments indicate that sotrovimab neutralizes the B.1.1.529/BA.2 (Omicron, South Africa origin: T19I, del24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K) spike variant with a 16-fold reduction in activity relative to wild-type (Table 2).

It is not known how pseudotyped VLPs or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome.

Table 2. Sotrovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y[a]	No change[b]
B.1.351	South Africa	Beta	K417N+E484K+N501Y[c]	No change[b]
P.1	Brazil	Gamma	K417T+E484K+N501Y[d]	No change[b]
B.1.427/B.1.429	USA (California)	Epsilon	L452R[e]	No change[b]
B.1.526[f]	USA (New York)	Iota	E484K[g]	No change[b]
B.1.617.1	India	Kappa	L452R+E484Q[h]	No change[b]
B.1.617.2/AY.4.2	India	Delta	L452R+T478K[i]	No change[b]
AY.1/AY.2	India	Delta [+K417N]	L452R+T478K+K417N[j]	No change[b]
C.37	Peru	Lambda	L452Q+F490S[k]	No change[b]
B.1.621	Colombia	Mu	R346K+E484K+N501Y[l]	No change[b]

B.1.1.529/BA.1	South Africa	Omicron	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q498R+N501Y+Y505H[m]	No change[b]
B.1.1.529/BA.1.1	South Africa	Omicron	G339D+R346K+S371L+ S373P+S375F+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ G496S+Q498R+N501Y+ Y505H[n]	No change[b]
B.1.1.529/BA.2	South Africa	Omicron	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H[o]	16[p]

[a] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] No change: <5-fold reduction in susceptibility.

[c] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, A701V.

[d] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F.

[e] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: S13I, W152C, L452R, D614G.

[f] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

[g] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L5F, T95I, D253G, E484K, D614G, A701V.

[h] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H.

[i] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: B.1.617.2: T19R, G142D, E156G, del157-158, L452R, T478K, D614G, P681R, D950N; AY.4.2: T19R, T95I, G142D, Y145H, E156G, del157-158, A222V, L452R, T478K, D614G, P681R, D950N.

[j] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from

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wild-type spike protein are found in the variant: AY.1 T19R, T95I, G142D, E156G, del157-158, W258L, K417N, L452R, T478K, D614G, P681R, D950N; AY.2. T19R, V70F, G142D, E156G, del157-158, A222V, K417N, L452R, T478K, D614G, P681R, D950N.

[k] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: G75V, T76I, del246-252, L452Q, F490S, T859N.

[l] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: T95I, Y144T, Y145S, ins146N, R346K, E484K, N501Y, D614G, P681H, D950N.

[m] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: A67V, del69-70, T95I, G142D, del143-145, del211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F.

[n] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: A67V, del69-70, T95I, G142D, del143-145, del211, L212I, ins214EPE, G339D, R346K, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F.

[o] Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: T19I, del24-26, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K.

[p] Clinical relevance of the 16-fold reduction in susceptibility is unknown.

Microneutralization data using authentic SARS-CoV-2 variant viruses indicate that sotrovimab retains activity against the B.1.1.7 (Alpha, UK origin; 3-fold change in EC_{50} value), B.1.351 (Beta, South Africa origin; 1.2-fold change in EC_{50} value), P.1 (Gamma, Brazil origin; 1.6-fold change in EC_{50} value), B.1.617.1 (Kappa, India origin; 0.9-fold change in EC_{50} value), and B.1.617.2 (Delta, India origin; 0.4-fold change in EC_{50} value) variants (Table 3).

Table 3. Sotrovimab Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variants

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions[a]	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	N501Y	No change[b]
B.1.351	South Africa	Beta	K417N+E484K +N501Y	No change[b]
P.1	Brazil	Gamma	K417T+E484K+ N501Y	No change[b]
B.1.617.1	India	Kappa	L452R+E484Q	No change[b]
B.1.617.2	India	Delta	L452R+T478K	No change[b]

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is (are) listed.

[b] No change: <5-fold reduction in susceptibility.

Limited nucleotide sequencing data from a total of 539 COMET-ICE subjects indicated that 36 subjects (16 treated with placebo and 20 treated with sotrovimab) carried the B.1.1.7 (Alpha, UK origin) variant. Four subjects (2 treated with placebo and 2 treated with sotrovimab) carried the N501Y substitution. Thirty-one subjects (19 treated with placebo and 12 treated with sotrovimab) carried the B.1.427/B.1.429 (Epsilon, California origin) variant. Eight additional subjects carried the L452R substitution (6 treated with placebo and 2 treated with sotrovimab). Eleven subjects carried the P.1 (Gamma, Brazil origin) variant (3 treated with placebo and 8 treated with sotrovimab). Three subjects carried the B.1.526 (Iota, New York origin) variant with the E484K substitution (2 treated with placebo and 1 treated with sotrovimab), while 9 subjects (4 treated with placebo and 5 treated with sotrovimab) carried the S477N substitution that has been associated with the B.1.526 (Iota, New York origin) variant. Additionally, 10 subjects carried the E484K substitution (4 treated with placebo and 6 treated with sotrovimab), 2 carried the S494P substitution (1 treated with placebo and 1 treated with sotrovimab), and 3 carried the S494P substitution with the N501Y substitution (2 treated with placebo and 1 treated with sotrovimab). Two subjects in the group receiving sotrovimab (1 carrying the B.1.427/B.1.429 [Epsilon, California origin] variant and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. Four subjects in the placebo group (2 carrying the E484K substitution, 1 carrying the P.1 [Gamma, Brazil origin] variant, and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. None of the subjects with currently available baseline sequences carried the full complement of substitutions characteristic of the B.1.351 (Beta, South Africa origin) or B.1.617 (Delta, India origin) variants.

In COMET-ICE, post-baseline epitope substitutions were detected in 20 subjects in the cohort receiving sotrovimab (spike protein substitutions P337L/E340K [49.4%/54.8% allele frequency]; E340A [99.0%]; E340K [5 subjects: 8.0% to 99.9%]; E340V [73.1%]; A344V [6.2%]; R346G [5.2%]; K356R [7.5%]; S359G [2 subjects: 12.2% and 8.3%]); C361T [7 subjects: 5.0% to

15.7%]. Of the substitutions detected at baseline and post-baseline, L335F, L335S, P337L, G339C, E340A, E340K, A344V, R346G, R346I, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. P337L, E340A, and E340K substitutions confer reduced susceptibility to sotrovimab (>100-fold change in EC_{50} value). Sotrovimab retains activity against L335F (0.8-fold change in EC_{50} value), L335S (0.9-fold change in EC_{50} value), G339C (1.2-fold change in EC_{50} value), A344V (1.1-fold change in EC_{50} value), R346G (0.9-fold change in EC_{50} value), R346I (1.7-fold change in EC_{50} value), K356N (1.1-fold change in EC_{50} value), K356R (0.8-fold change in EC_{50} value), R357I (1-fold change in EC_{50} value), I358V (0.7-fold change in EC_{50} value), and S359G (0.8-fold change in EC_{50} value) substitutions. The clinical impact of these substitutions 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.

16 NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, and reproductive toxicology studies with sotrovimab have not been conducted.

In a toxicology study in monkeys, sotrovimab had no adverse effects when administered intravenously.

In tissue cross reactivity studies using human and monkey adult tissues, no binding of clinical concern was detected for sotrovimab.

In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

In a Syrian Golden hamster model of SARS-CoV-2 infection, antiviral activity was demonstrated using a single dose of sotrovimab which was administered intraperitoneally at 24- or 48-hours prior to infection. Animals receiving 5 mg/kg or more of the antibody showed a significant improvement in body weight loss and significantly decreased total lung SARS-CoV-2 viral RNA compared to vehicle only and control antibody-treated animals. Levels of virus in the lung (as measured by $TCID_{50}$) were significantly decreased versus controls in hamsters receiving 0.5 mg/kg or more of the antibody.

Protection was also observed in the Syrian Golden hamster model using the SARS-CoV-2 B.1.351 (Beta, South Africa origin) variant. Significant reductions in total and replication competent virus were observed on Day 4 post-infection in animals receiving a single intraperitoneal dose of 0.5, 2, 5, or 15 mg/kg sotrovimab compared to isotype control antibody-treated animals.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

The clinical data supporting this EUA are based on the analysis of the Phase 1/2/3 COMET-ICE trial (NCT04545060) with supporting data from the Phase 3 COMET-TAIL trial (NCT04913675).

COMET-ICE Trial

COMET-ICE was a, randomized, multi-center, 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 trial included symptomatic subjects 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 subjects were excluded from the trial.

A total of 1,057 eligible subjects were randomized to receive a single 500-mg infusion of sotrovimab (n = 528) or placebo (n = 529) over 1 hour (Intent to Treat [ITT] population at Day 29). At baseline, the median age was 53 years (range:17 to 96); 20% 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, 8% Black or African American, 4% Asian, 65% Hispanic or Latino. Fifty-nine percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 41% within 4 to 5 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medication (22%), and moderate-to-severe asthma (17%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 79% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo. Table 4 provides the results for the primary and key secondary endpoint of COMET-ICE.

Table 4. Efficacy Results in Adults with Mild-to-Moderate COVID-19 in COMET-ICE at Day 29

	Sotrovimab n = 528	**Placebo n = 529**
Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)[a]		
Proportion (n, %)	6 (1.1%)	30 (5.7%)
Adjusted Relative Risk Reduction (95% CI)	79% (50%, 91%)	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	2 (<1%)

[a] The determination of primary efficacy was based on a planned interim analysis of 583 subjects, which had similar findings to those seen in the full population above. The adjusted relative risk reduction was 85% with a 97.24% CI of (44%, 96%) and p-value = 0.002.

Within the subset of the ITT population who had a central laboratory confirmed, virologically quantifiable nasopharyngeal swab at Day 1 and Day 8 (n = 639), the mean decline from baseline in viral load at Day 8 was greater in subjects treated with sotrovimab (-2.610 $\log_{10}$ copies/mL) compared to that in subjects treated with placebo (-2.358); mean difference = -0.251, 95% CI: (-0.415, -0.087).

COMET-TAIL Trial

COMET-TAIL was a randomized, multi-center, open label trial which evaluated the efficacy, safety, and tolerability of sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Eligible subjects were 12 years of age or older with at least one of the following comorbidities: diabetes, obesity (BMI ≥85th percentile for age/gender based on Centers for Disease Control and Prevention [CDC] growth charts for adolescents or BMI ≥30 for subjects ≥18 years old), chronic kidney disease, congenital heart disease, congestive heart failure (for subjects ≥18 years old), chronic lung diseases, sickle cell disease, neurodevelopmental disorders, immunosuppressive disease or receiving immunosuppressive medications, or chronic liver disease; or were 55 years of age or older regardless of comorbidities. The trial included symptomatic subjects with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 7 days of enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization were excluded from the trial.

The ITT population consisted of 385 subjects randomized to receive a single 500-mg IV infusion of sotrovimab over 15 minutes. The primary analysis population, which excluded 7 subjects because they were fully vaccinated and immunocompetent (key inclusion/exclusion violation), consisted of 378 subjects.

In the primary analysis population at baseline, the median age was 51 years (range:15 to 90,

including 2 subjects under 18 years); 25% of subjects were 65 years of age or older and 8% were over 75 years of age; 42% of subjects were male; 96% were White and 4% were Black or African American; 83% were Hispanic or Latino. Forty-eight percent (48%) of subjects received sotrovimab within 3 days of COVID-19 symptom onset, 37% within 4 to 5 days, and 14% within 6 to 7 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (42%), chronic lung disease (16%), and diabetes requiring medication (13%).

In the primary analysis population, 5 (1.3%) of 378 subjects had progression to COVID-19 defined as hospitalization for >24 hours for acute management of any illness or death due to any cause through Day 29. No deaths were reported through Day 29.

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Sotrovimab injection 500 mg (62.5 mg/mL) is a sterile, preservative-free, clear, colorless or yellow to brown solution 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 (NDC 0173-0901-86).

Storage and Handling

Sotrovimab is preservative-free. Discard unused portion.

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.

The solution of sotrovimab in the vial is preservative-free and requires dilution prior to IV administration. The diluted infusion 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 6 hours at room temperature (up to 25°C [up 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.

20 PATIENT COUNSELING INFORMATION

Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines. Also, see “Fact Sheet for Patients, Parents, and Caregivers”.

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy *[see Use in Specific Populations (11.1)]*.

21 CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

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STR:XFS-HCP

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DETACH HERE AND GIVE FACT SHEET TO PATIENT, PARENT OR CAREGIVER.

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FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS
Emergency Use Authorization (EUA) of Sotrovimab for the Treatment of Coronavirus Disease 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you or your child with **sotrovimab** for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. This Fact Sheet contains information to help you understand the potential risks and potential benefits of receiving sotrovimab, which you or your child have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make sotrovimab available during the COVID-19 pandemic (for more details about an EUA please see **"What is an Emergency Use Authorization?"** at the end of this document). Sotrovimab is not an FDA-approved medicine in the United States.

Read this Fact Sheet for information about sotrovimab. Talk to your healthcare provider if you have any questions. It is your choice for you or your child to receive sotrovimab or stop it at any time.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your or your child's other medical conditions to become worse. Older people and people of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, diabetes, and obesity, for example, seem to be at higher risk of being hospitalized for COVID-19.

What is sotrovimab?

Sotrovimab is an investigational medicine used for the treatment of mild-to-moderate symptoms of COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization or death. Sotrovimab is investigational because it is still being studied. There is limited information about the safety and effectiveness of using sotrovimab to treat people with mild-to-moderate COVID-19.

The FDA has authorized the emergency use of sotrovimab for the treatment of mild-to-moderate symptoms of COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization or death under an EUA. For more information on EUA, see the **"What is an Emergency Use Authorization (EUA)?"** section at the end of this fact sheet.

What should I tell my healthcare provider before I or my child receive sotrovimab?
Tell your healthcare provider about all of your or your child's medical conditions, including if you or your child:

- Have any allergies
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products).

How will I or my child receive sotrovimab?

- You or your child will receive 1 dose of sotrovimab.
- Sotrovimab will be given through a vein (intravenous or IV infusion) over 15 or 30 minutes.
- You or your child will be monitored by your healthcare provider for at least 1 hour after receiving sotrovimab.

Who should generally not receive sotrovimab?
Do not receive sotrovimab if you or your child have had a serious allergic reaction to sotrovimab or to any of the ingredients in sotrovimab. See the end of the Fact Sheet for a complete list of ingredients in sotrovimab.

What are the important possible side effects of sotrovimab?
Possible side effects of sotrovimab are:

- **Allergic reactions.** Allergic reactions can happen during and after receiving sotrovimab. Tell your healthcare provider right away if you or your child develop any of the following signs and symptoms of allergic reactions: fever; difficulty breathing; low oxygen level in your blood; chills; tiredness; fast or slow heart rate; chest discomfort or pain; weakness; confusion; nausea; headache; shortness of breath; low or high blood pressure; wheezing; swelling of your lips, face, or throat; rash including hives; itching; muscle aches; dizziness; feeling faint; and sweating.

Side effects of receiving sotrovimab intravenously may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of sotrovimab. Not many people have received sotrovimab. Serious and unexpected side effects may happen. Sotrovimab is still being studied, so it is possible that all of the risks are not known at this time.

What other treatment choices are there?

Like sotrovimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice for you or your child to be treated or not to be treated with sotrovimab. Should you decide not to receive it or your child not to receive it, it will not change you or your child's standard medical care.

What if I am pregnant or breastfeeding?

There is no experience treating pregnant women or breastfeeding mothers with sotrovimab. For a mother and unborn baby, the benefit of receiving sotrovimab may be greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

Pregnancy Registry

There is a pregnancy registry for individuals who receive sotrovimab during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how to take part in this registry. For more information visit https://covid-pr.pregistry.com or call 1-800-616-3791.

How do I report side effects with sotrovimab?

Contact your healthcare provider if you have any side effects that bother you or do not go away. Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088, or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

How can I learn more?

- Ask your healthcare provider
- Visit https://www.cdc.gov/COVID19
- Call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684)

What is an Emergency Use Authorization (EUA)?

The United States FDA has made sotrovimab available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

Sotrovimab for the treatment of mild-to-moderate symptoms of COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of SARS-CoV-2 viral testing,

and who are at high risk of progression to severe COVID-19, including hospitalization or death, has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives.

All of these criteria must be met to allow for the medicine to be used in the treatment of patients during the COVID-19 pandemic. The EUA for sotrovimab is in effect for the duration of the COVID-19 declaration justifying emergency use of sotrovimab, unless terminated or revoked (after which sotrovimab may no longer be used under the EUA).

What are the ingredients in sotrovimab?

Active ingredient: sotrovimab

Inactive ingredients: L-histidine, L-histidine monohydrochloride, L-methionine, polysorbate 80, and sucrose

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