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

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	EUA 000100
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
Manufacturer, if different from Sponsor	GlaxoSmithKline, Parma.
Submission Date(s)	Part 1: March 24, 2021 Part 2: March 29, 2021
Receipt Date(s)	Part 1: March 24, 2021 Part 2: March 29, 2021
OND Division / Office	Division of Antivirals /Office of Infectious Disease

<table>
<tr><td>Reviewer Name(s)/Discipline(s)</td><td>
<table>
<tr><th colspan="2">Discipline Review Team</th></tr>
<tr><th>Discipline Reviewer</th><th>Team Lead</th></tr>
<tr><td>Clinical: Sarita Boyd</td><td>Kimberly Struble</td></tr>
<tr><td>Non-Clinical: Deacqunita Diggs</td><td>Christopher Ellis</td></tr>
<tr><td>Clinical Virology: Eric Donaldson</td><td>Julian O'Rear</td></tr>
<tr><td>Clinical Pharmacology: Tony Nicasio</td><td>Su-Young Choi</td></tr>
<tr><td>Biometrics: Scott Komo</td><td>Thamban Valappil</td></tr>
<tr><td>Associate Director of Labeling</td><td>Stacey Min</td></tr>
<tr><td>RPM: Suzanne Strayhorn</td><td>CPMS: Linda Akunne</td></tr>
<tr><th colspan="2">OPQ Team</th></tr>
<tr><td colspan="2">OBP</td></tr>
<tr><td colspan="2">RBPM (OPRO): Teshara Bouie</td></tr>
<tr><td>Review Chief: Christopher Downey</td><td>Product Quality Reviewer: Mayumi Takahashi</td></tr>
<tr><td>Lab Chief: Serge Beaucage</td><td>Labeling Assessor: Koung Lee</td></tr>
<tr><td colspan="2">OPMA Team</td></tr>
<tr><td colspan="2">Branch Chief: Candace Gomez-Broughton</td></tr>
<tr><td>Primary Reviewer: Reyes Candauchacon</td><td>Secondary Reviewer: Virginia Carroll</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>OSE/DMEPA: Melina Fanari/Sevan Kolejian</td><td>OSE/DPV: Kim Swank (SE)/Kate McCartan (MO)/ Rachna Kapoor (TL)/Ida-Lina Diak (DD)</td></tr>
<tr><td>PLT: Shawna Hutchins / Barbara Fuller</td><td>OSE/DEPI: Mingfeng Zheng/Natasha Pratt</td></tr>
<tr><td>OPDP: Nima Ossareh/Phillip Williams/Sam Skariah</td><td>OSE/DRM: Naomi Bostin (TL)</td></tr>
<tr><td>OND Policy: Andrew LeBoeuf, Acting Associate Director for Policy</td><td>OSE RPM: Danyal Chaudhry and Saharat Patanavanich
OSE CDTL: Neha Gada</td></tr>
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<tr><td>Integrated Review Completion Date</td><td>May 26, 2021</td></tr>
<tr><td>Proprietary Name</td><td>None</td></tr>
<tr><td>Established Name/Other names used during development</td><td>Sotrovimab (VIR-7831)</td></tr>
<tr><td>Dosage Forms/Strengths</td><td>Sterile solution for injection, 500mg/8 mL vial</td></tr>
<tr><td>Therapeutic Class</td><td>SARS-CoV-2 spike protein directed human IgG1κ monoclonal antibody (mAb)</td></tr>
<tr><td>Intended Use or Need for EUA</td><td>Mild-to-moderate coronavirus disease 2019 (COVID-19)</td></tr>
<tr><td>Intended Population(s)</td><td>Adults and pediatric patients (12 years of age and older and 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</td></tr>
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Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	(b) (4)

I. EUA Determination/Declaration

On February 4, 2020, the Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States (US) citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

A. Recommend EUA Issuance

The Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

The EUA will authorize 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.

B. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.

- Based on the totality of the scientific evidence available to FDA, including data from adequate and well-controlled trials, it is reasonable to believe that sotrovimab monotherapy may be effective 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; and when used under such conditions, the

known and potential benefits of sotrovimab monotherapy outweigh the known and potential risks of the product.

- There is no adequate, approved, and available alternative to the emergency use of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) 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. Sotrovimab is a recombinant human IgG1κ monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 but does not compete with human ACE2 receptor binding. Remdesivir (Veklury®) is the only drug approved by FDA to treat COVID-19 at the time of FDA's review of sotrovimab. Remdesivir is a nucleotide analog RNA polymerase inhibitor that has demonstrated antiviral activity against SARS-CoV-2. Remdesivir's approved indication is limited to the treatment of COVID-19 in adults and pediatric patients (12 years of age and weighing at least 40 kg) requiring hospitalization.

III. Proposed Use and Dosing of the Product Under the EUA

Proposed Use under EUA

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.

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 > SEE ATTACHED ADDENDUM, 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.

LIMITATIONS OF AUTHORIZED USE

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

Authorized Dosage under EUA

Adults and Pediatric Patients

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

Sotrovimab is not authorized for patients under 12 years of age or pediatric patients weighing less than 40 kg.

Pregnant or Lactating Patients

No dosage adjustment is recommended in pregnant or lactating women. Sotrovimab has not been studied in pregnant or lactating women. Sotrovimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Other Specific Populations (e.g., geriatric patients, patients with renal or hepatic impairment)

No dosage adjustment is recommended in geriatric patients. Clinical trials of sotrovimab have included patients over 65, including those over 70 years of age, but the difference in pharmacokinetics (PK) of sotrovimab in geriatric patients compared to younger patients has not been quantified.

No dosage adjustment is recommended in patients with 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.

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.

The effect of other covariates (e.g., sex, race, body weight, disease severity) on PK of sotrovimab is unknown.

Rationale for Dose

Sotrovimab 500 mg is the sole dose evaluated to date in clinical trials, including the pivotal trial, VIR-7831-5001 (COMET-ICE), that supports this EUA. Although sotrovimab was administered as an IV infusion over 60 minutes in COMET-ICE, a faster infusion time of 30 minutes is supported by safety data from the trial J2X-MC-PYAH (BLAZE-4, Arms 7 and 8). Therefore, the authorized dosage and administration is sotrovimab 500 mg administered as an IV infusion over 30 minutes. Please refer to Section XI Human Clinical Pharmacology for data to support the sotrovimab 500 mg dose against SARS-CoV-2 variants and Section XIII Nonclinical Data to Support Efficacy for data to support sotrovimab activity against SARS-CoV-2 variants.

IV. Product Information (Dose Preparation and Administration)

Preparation

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

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

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

- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.

- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and a fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.

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

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

- Discard any product remaining in the vial.

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

Administration

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

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, 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 with 0.9% Sodium Chloride Injection.

- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.

- Do not administer as an IV push or bolus.

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

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

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

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

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 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 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

Background Information on the Condition

There are many types of human coronaviruses including some that commonly cause mild upper-respiratory tract illness. The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, approximately 155.5 million

confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of May 6, 2021, including an estimated 3.2 million deaths. In the US, according to the Center for Disease Control and Prevention (CDC), as of May 5, 2021, approximately 32.3 million cases of COVID-19 have been reported with 576,238 deaths.

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report for the period of April 11, 2021 to April 24, 2021, the most common variant of concern in the US is the UK (B.1.1.7) variant, representing 66.0% (95% confidence interval (CI) [62.0-69.7%]) of circulating SARS-CoV-2. Other variants of concern are the Brazil (P.1), California (CAL.20C, or B.1.427/B.1.429), and South Africa (B.1.351) variants, which comprise 5.0% (95% CI [3.3-7.5%]), 2.3% (95% CI [1.5%-3.6%]) (B.1.427), and 0.9% (95% CI [0.6-1.4%]) of circulating SARS-CoV-2, respectively. The UK variant has most notably increased over time; for comparison, the reported prevalence of B.1.1.7 from January 17, 2021 to January 30, 2021 was 1.2% (95% CI [0.8-1.8%]). SARS-CoV-2 variants of interest currently include the New York (B.1.526) and India (B.1.617) variants. Accessed May 12, 2021 (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe and critical illness are defined as worsening pulmonary status requiring hospitalization, supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO.

The progression of SARS-CoV-2 infection to severe COVID-19 can occur in adults of any age, but the risk increases with age. Per the CDC, over 80% of COVID-19 deaths occur in adults aged 65 years and older, and more than 95% of COVID-19 deaths occur in adults aged 45 years and older. Irrespective of age, certain underlying comorbidities or conditions, including but not limited to cancer, chronic kidney disease, chronic lung disease, obesity, diabetes, pregnancy, and immunocompromised states, increase the risk for progression to severe COVID-19. People who have experienced long-standing systemic health and social inequities, such as many racial and ethnic minorities and those with disabilities, are also at increased risk of worse outcomes. Accessed May 7, 2021 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced

severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Götzinger et al., 2020).

Therapeutic Alternatives for the Disease

There is no adequate, approved, and available alternative to the emergency use of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) 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.

There is an approved drug for more severe COVID-19. Remdesivir (Veklury®) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor approved for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. This medication was initially authorized for emergency use on May 1, 2020, and was ultimately approved on October 22, 2020, under NDA 214787. At the time of this review, remdesivir remains authorized for emergency use for treating suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

There are other COVID-19 treatments authorized for emergency use. Baricitinib, an inhibitor of janus kinases, is authorized for emergency use in combination with remdesivir for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplementary oxygen, invasive mechanical ventilation, or extra-corporeal membrane oxygenation (ECMO).

Other monoclonal antibodies are currently authorized for emergency use for the same indication of 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 progressing to severe COVID-19 and/or hospitalization. Casirivimab 1200 mg and imdevimab 1200 mg were authorized to be administered together on November 21, 2020. Bamlanivimab 700 mg and etesevimab 1400 mg were authorized to be administered together on February 9, 2021. Of note, bamlanivimab 700 mg as monotherapy was authorized for emergency use on November 9, 2020 and that authorization was subsequently revoked on April 16, 2021 due to a sustained increase in variants resistant to bamlanivimab alone resulting in the increased risk for treatment failure.[1]

There are currently no approved therapies for treatment of mild-to-moderate COVID-19 in outpatients. Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html.

[1] See FDA's Letter of Revocation for EUA 090, dated April 16, 2021, on FDA's website at: https://www fda.gov/media/147629/download

VI. Related Regulatory Submission(s)

Sotrovimab 500 mg, administered as an IV infusion, has been studied under INDs 149315, 151543, and 150440 (Table 1). Vir Biotechnology, Inc. (Vir) and GlaxoSmithKline (GSK) have entered into a collaborative agreement for the development of sotrovimab monotherapy as a treatment for mild-to-moderate COVID-19 in at risk patients relative to this EUA request. GSK is the sponsor of the EUA request. Vir is the sponsor of IND 149315.

VII. Summary of Clinical Data

The data to support the authorization of sotrovimab were generated from Phase 1, 2, and 3 clinical trials (Table 1). The EUA request for the use of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) 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, was received on March 24, 2021. An EUA amendment with additional information was received on March 29, 2021. The principle efficacy and safety data in these submissions are from an interim analysis of VIR-7831-5001 (COMET-ICE). This review focuses on the interim analysis populations for efficacy and for safety, both of which are subsets of the full analysis population.

On April 30, 2021, the Applicant submitted topline efficacy results for the primary endpoint and certain secondary endpoints for the full analysis population of COMET-ICE. These results are presented in Section VIII following the interim efficacy results for the primary and available secondary endpoints. The preliminary efficacy results for the full analysis population are generally consistent with the interim efficacy results.

On May 10, 2021, the Applicant submitted preliminary topline safety results for the full analysis population; these results are not discussed in detail. The preliminary safety results available for the full analysis population are generally consistent with the interim safety results.

The safety and efficacy results from the full analysis population will not be included the Fact Sheet for Health Care Providers due to the preliminary nature of these data. The Fact Sheet for Health Care Providers may be updated once the final report on the full analysis population is submitted for review.

Table 1: All Clinical Trials

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-7831-5001, GSK-214367 (COMET-ICE) NCT04545060	IND 149315	Efficacy, Safety, PK	N=1360 Outpatient adults with early, mild/moderate COVID-19 at high risk of progression to severe disease	Phase 1/2/3 randomized (1:1), double-blind, placebo-controlled trial	Single IV infusion: Sotrovimab 500 mg or placebo Assessments to Day 29; 6-month follow-up	Active but closed to enrollment as of 11 Mar 2021 at the recommendation of the IDMC due to high efficacy Enrollment N=1057
INSIGHT-014 (ACTIV-3-TICO) NCT04501978	IND 151543	Efficacy, Safety	N=1000 (sotrovimab/placebo sub-study) Hospitalized adults with COVID-19	Phase 3 randomized, blinded, controlled platform trial that allows investigational agents to be added/dropped during the study for testing of new agents against placebo within the same trial infrastructure	Single IV infusion: Sotrovimab 500 mg or placebo Assessments to Day 5 (futility assessment) and Day 90 (primary endpoint); 18-month follow-up	Active but sotrovimab sub-study closed to enrollment at the recommendation of the DSMB on 01 Mar 2021 due to futility Enrollment N=367 Group 1 (sotrovimab): N=184 Group 2 (placebo): N=183
VIR-7831-5006, GSK-216912 (COMET-PEAK) NCT04779879	IND 149315	Safety, PK, PD	N=40 (Part A) N=150 (Part B) Outpatients with early, mild/moderate COVID-19 at high risk of progression to severe disease	Part A: Randomized (3:1), double-blind trial comparing Gen2 vs. Gen1 sotrovimab Part B: Randomized (1:1), open-label trial comparing IV to IM administration (both Gen2) and evaluating faster IV infusion (b) (4))	Part A: Single IV infusion: Sotrovimab 500 mg Part B: Sotrovimab 500 mg single IV infusion or single IM injection	Active, enrolling
J2X-MC-PYAH, VIR-7831-5007 (BLAZE-4, Arms 7 and 8) NCT04634409	IND 150440	Efficacy, Safety	N=200 (Arms 7 and 8) Outpatients with mild/moderate COVID-19 at lower risk for progression to severe disease	Phase 2 randomized, double-blind, placebo-controlled trial	Single IV infusion: • Arm 7: sotrovimab 500 mg + bamlanivimab 700 mg • Arm 8: placebo Assessments to Day 7; 6-month follow-up	Active, enrollment complete Enrollment N=202 Arm 7 (sotrovimab + bamlanivimab): N=101 Arm 8 (placebo): N=101

Sources: EUA Request Tables 2 and 3; ACTIV-3 TICO Unblinding Report VIR/GSK Study Treatment Table 3.1; and Response to FDA Information Request
PK = Pharmacokinetics

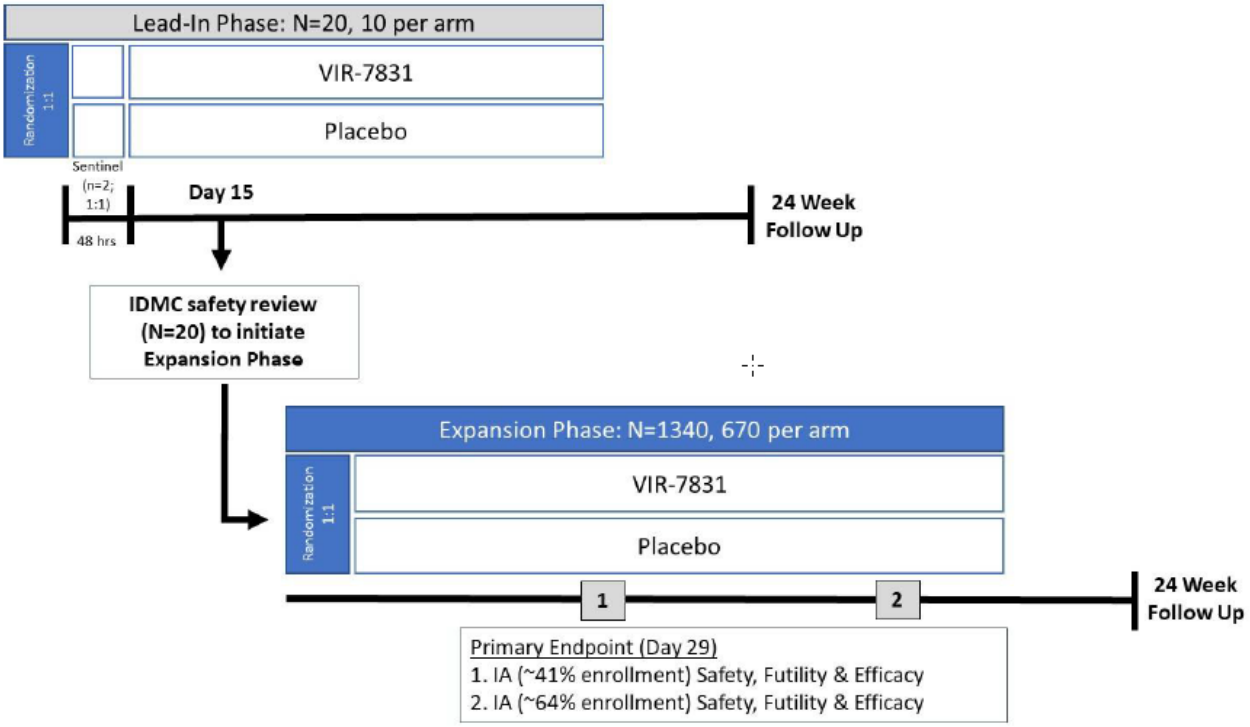
VIII. Human Clinical Efficacy

The source of clinical efficacy data to support this EUA request is the Phase 1/2/3 trial, COMET-ICE (VIR-7831-5001).

Trial Design

COMET-ICE is a randomized, double-blind, multicenter, placebo-controlled Phase 1/2/3 trial of sotrovimab for the treatment of COVID-19 in outpatients with mild-to-moderate COVID-19, who are at high risk of disease progression to severe/critical disease or death. In the trial, patients were randomized 1:1 to receive a single IV infusion of either sotrovimab (500 mg) or an equal volume of saline placebo over 1 hour. The trial was divided into two parts, a lead-in and an expansion phase.

Figure 1: Trial Schematic



Source: EUA request, Figure 1

The trial started with a lead-in phase that enrolled 21 participants with early, mild-to-moderate COVID-19 at high risk of disease progression for hospitalization or death. An independent data monitoring committee (IDMC) reviewed unblinded safety data after 20 participants completed Day 15 and recommended that the study to proceed with the expansion phase to enroll additional participants across each treatment arm (1340 additional participants in total).

The expansion phase had two planned interim analyses, at approximately 41% and 64% of participants enrolled and followed through Day 29. At the first planned interim analysis (N=583 for efficacy and N=868 for safety), the IDMC recommended that due to efficacy on the primary endpoint of reducing hospitalization >24 hours for acute management of illness or death due to any cause by Day 29, the study met the criteria for stopping enrollment. The trial has stopped enrollment, and all the randomized participants (N=1057) will continue to be followed until their Week 24 visit (end of study) or early withdrawal.

Eligibility Criteria

Inclusion criteria for enrollment in COMET-ICE specified that participants have confirmed SARS CoV-2 infection based on any validated diagnostic test (RT-PCR, antigen test), have oxygen saturation ≥94% on room air, and have one or more COVID-19 symptoms with symptom onset within five days of enrollment. The trial included only adults at high risk for progression to severe COVID-19, defined as:

- Aged 18 years or older and the presence of one or more of the following risk factors: diabetes (requiring medication), obesity (BMI >30 kg/m^2), chronic kidney disease (eGFR <60 mL/min/1.73m^2 by MDRD), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (COPD), or moderate to severe asthma
  OR
- Aged 55 years or older, irrespective of comorbidities.

Patients were excluded if they were hospitalized or had symptoms consistent with severe COVID-19, defined by shortness of breath at rest, respiratory distress, or requiring supplemental oxygen. Severely immunocompromised patients were excluded from the trial.

Enrollment in COMET-ICE began in August 2021, and the protocol-specified criteria for high risk for progression of severe COVID-19 was based on available data and thinking at that time. FDA proposes broadening the high risk criteria for the EUA compared to the enrollment criteria because a more comprehensive definition may benefit more patients. As we learn more about COVID-19, additional medical conditions and factors may place adults and adolescents at higher risk for progression to severe COVID-19. Specifically, FDA proposes expanding the proposed definition in the Fact Sheet to highlight 11 categories and adding a statement that the use of sotrovimab under the EUA would not be limited to the list. FDA also suggests providing a link to the CDC website that provides a more extensive list of medical conditions and factors that are associated with increased risk for progression to severe COVID-19, and therefore, this broader population would also be eligible to receive sotrovimab under the EUA.

FDA's proposal is based on discussions internally and with other US Government agencies regarding an optimal way of communicating this important information. Maintaining most of the currently/proposed listed high-risk conditions and adding a

link to the CDC website may be most useful for busy clinicians and would minimize updates to the Fact Sheet, should CDC's high risk criteria undergo revision in the future.

Analysis Populations

The trial included the following analysis populations:

- Full analysis Intent to Treat (ITT) population
  - N=1057; Placebo: 529; Sotrovimab: 528
  - All randomized participants, who are classified by the treatment arm they were randomized to.
- Full analysis Safety (SAF) population
  - N=1049; Placebo: 526; Sotrovimab: 523
  - All participants, who are randomized and exposed to study intervention. Participants are classified by the treatment they received. Note, 8 participants (2 placebo, 6 sotrovimab) were randomized and not dosed, so they are not included in the Safety Population. Also, 1 participant was randomized to the placebo arm but received sotrovimab.
- Intent to Treat interim analysis (ITT [IA])
  - N=583; Placebo: 292; Sotrovimab: 291
  - All randomized participants who had the opportunity to be followed to Day 29 by the time of the data cutoff for the first interim analysis.
- Safety interim analysis (SAF [IA])
  - N=868; Placebo: 438; Sotrovimab: 430
  - All randomized participants who were exposed to study intervention up to 29 days after the ITT [IA] cut-off.
- Virology interim analysis (Virology [IA])
  - N=324; Placebo: 170; Sotrovimab: 154
  - ITT (IA) analysis population participants with a central laboratory confirmed quantifiable nasopharyngeal swab at Day 1.

Interim Efficacy Results: ITT (IA) Population

Demographics and Baseline Characteristics

In the ITT (IA) population overall, slightly more than half of the participants were female (54%), and the median age was 53 years (range: 18 to 96 years). A total of 22% of participants were aged 65 years or older, and 11% were aged over 70 years. Overall, 63% of participants were Hispanic or Latino. The majority of the participants were white (87%); 7% were black or African American, and 6% were Asian. Over half of the participants (58%) had one protocol-defined risk factor for progression to severe COVID-19, while the remaining participants had more than one risk factor; 30% had two, 9% had three, and 2% had more than three. The most common protocol-defined risk factors were obesity (63%), 55 years of age or older (47%), and diabetes requiring medication (23%).

As noted above, the ITT (IA) population is a subset of the safety (IA) population. The demographics and baseline characteristics, including risk factors for progression to severe COVID-19, for the safety (IA) population were well-balanced between the sotrovimab arm and the placebo arm (Table 2) and similar to that of the ITT (IA) population and the full analysis population (Table 6).

Table 2: Demographics and Baseline Characteristics (SAF IA)

Parameter	Placebo (N=438)	Sotrovimab (N=430)
Female	226 (52%)	236 (55%)
Hispanic or Latino	280 (64%)	280 (65%)
Black or African American	33 (8%)	27 (6%)
Asian	19 (4%)	21 (5%)
Age (years), Median (Min, Max)[a]	52 (17, 88)	53 (18, 96)
Age ≥ 55 years	205 (47%)	195 (45%)
Age ≥ 65 years	88 (20%)	84 (20%)
Age ≥ 70 years	42 (10%)	42 (10%)
BMI (kg/m^2), Median (Min, Max)	32 (18, 71)	32 (17, 61)
BMI >30 kg/m^2	292 (67%)	267 (62%)
Diabetes requiring medication	88 (20%)	93 (22%)
Moderate to severe asthma	72 (16%)	69 (16%)
COPD	18 (4%)	24 (6%)
Chronic kidney disease	5 (1%)	2 (<1%)
Duration of COVID-19 symptoms ≤ 3 days	260 (59%)	254 (59%)

Source: EUA Request, Tables 7 and 9; and 5/6/2021 Response to FDA Information Request

[a.] Age is imputed from year of birth. The calculation uses 30 June as the day and month and calculates age relative to Screening date. Participant(s) designated as "17" are a result of the calculation and not a protocol deviation.

Primary Efficacy Analysis

The pre-specified primary endpoint was the proportion of participants who have progression of COVID-19, defined as hospitalization >24 hours for acute management of any illness or death due to any cause, through Day 29. The primary analysis was based on a relative risk ratio calculated using a Poisson regression model with a robust sandwich estimator, adjusted for treatment, duration of symptoms (≤3 days vs. ≥4 days), age (≤70 vs. >70 years old) and gender (female vs. male) as covariates. Missing data (4 sotrovimab; 1 placebo) in the analyses were handled using a multiple imputation model that included covariates similar to that included in the primary analysis.

At the first interim analysis, the primary endpoint, progression of COVID-19 at Day 29, was reduced by 85% with a 97.24% confidence interval (CI) of (0.04, 0.56) in recipients of sotrovimab vs. placebo (p = 0.002) (Table 3

). This result met the pre-specified efficacy stopping boundary (2-sided p-value <0.02758), and the Independent Data Monitoring Committee (IDMC) recommended stopping enrollment. The treatment effect was driven by the subcomponent of hospitalization >24 hours for acute management of any illness, as there was a single death by Day 29, and this participant was hospitalized prior to death. A supportive logistic regression analysis that included the same covariates as the primary analysis provided similar results as the primary analysis. An exploratory analysis that considered missing observations as failures reached similar conclusions. In addition, subgroup analyses by days from the onset of symptoms at baseline (≤3 days vs ≥4 days) were generally consistent with the analysis in the overall population.

Table 3: Proportion of Participants who Have Progression of COVID-19 through Day 29 (Hospitalization for >24 Hours or Death) (ITT [IA])

	Placebo (N=292)	**Sotrovimab (N=291)**	**Risk Ratio[a] Sotrovimab: Placebo (97.24 % CI)[b] p-value**
Progression Status, n (%)			
Hospitalized >24 hours for acute management of any illness or Death due to any cause	21 (7%)	3 (1%)	0.15 (0.04, 0.56) 0.002
Hospitalized >24 hours for acute management of any illness[c]	21 (7%)	3 (1%)	
Death due any cause[c]	1 (<1%)	0	
Alive and not hospitalized	270 (92%)	284 (98%)	
Missing[d]	1 (<1%)	4 (1%)	

Source: EUA Request, Table 27

[a.] Risk ratio adjusted for treatment, duration of symptoms (≤3 days vs. ≥4 days), age (≤70 vs. >70 years old) and gender (female vs. male) as covariates.

[b.] Confidence interval level adjusted for the two planned interim analyses.

[c.] Participants are counted in each subcategory of progression experienced up to the time point in question and so may be included in more than one category.

[d.] Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 3 participants randomized to sotrovimab and 1 participant randomized to placebo withdrew consent prior to dosing and 1 participant treated with sotrovimab withdrew consent by Day 8.

Based on the difference in event rates, the estimated number needed to treat is 16 [97.24% CI (20, 35)] outpatients at high risk for progression to severe COVID-19 to prevent one hospitalization or death. This level of reduction in hospitalizations or death likely represents a substantial clinical benefit.

Analysis of SARS-CoV-2 Variants

Limited sequencing data from a total of 218 participants at the time of this review indicated that nine participants (5 treated with placebo and 4 treated with sotrovimab) were infected with the CAL.20C variant (S13I, W152C, L452R), and two additional participants in the placebo arm carried the L452R variant only. One of the participants treated with sotrovimab (participant (b) (6) progressed to require hospitalization on Day 19 for COVID-19 pneumonia and hypoxia. This participant was a 96-year-old male with a history of diabetes, hypertension, and a cardiac pacemaker. He was treated with 6L of oxygen, dexamethasone, and convalescent plasma though not with remdesivir. Oxygen saturation returned to normal on room air after "a couple of days," and the participant was discharged to a rehabilitation facility after 14 days of hospitalization. The participant fully recovered.

Based on available sequencing data at the time of this review, none of the participants were infected with SARS-CoV-2 that contained the full complement of spike substitutions characteristic of the UK (B.1.1.7), South Africa (B.1.351), or Brazil (P.1) variants. One participant in the placebo arm carried the N501Y variant at baseline.

Post-baseline SARS-CoV-2 with spike protein amino acid substitutions at position E340 were detected in four participants in the sotrovimab arm (E340K ≥99.7% allele frequency). One of these participants progressed to require hospitalization (the same participant infected with CAL.20C described above). E340A (99.7%) was detected at baseline in one participant in the sotrovimab arm, and E340stop codon (6.6%) was detected at baseline in one participant in the placebo arm. E340A and E340K confer reduced susceptibility to sotrovimab (>100-fold and >297-fold change in EC_{50} value) in cell culture susceptibility assays. The clinical impact of these substitutions is currently unknown.

Please refer to Section XI Human Clinical Pharmacology for data to support the sotrovimab 500 mg dose against SARS-CoV-2 variants and Section XIII Nonclinical Data to Support Efficacy for data to support sotrovimab activity against SARS-CoV-2 variants.

Secondary Efficacy Analysis

One of the pre-specified secondary endpoints was the proportion of participants who progress to develop severe and/or critical COVID-19 based on the requirement for and method of supplemental oxygen at Day 8, Day 15, Day 22, or

Day 29. In the ITT (IA) population, a numerical reduction in the risk of severe and/or critical respiratory COVID-19 was observed for participants treated with sotrovimab compared to placebo at each of these timepoints (Table 4). No sotrovimab-treated participants required high flow oxygen, oxygen via a non-rebreather mask, or mechanical ventilation through Day 29. Two participants in the placebo arm required mechanical ventilation. No participants in either arm required extracorporeal membrane oxygenation (ECMO).

In the EUA request, the Applicant provided narratives for all SAEs, including hospitalizations and deaths irrespective of causality, that occurred in the ITT (IA) population. The narratives included baseline demographics, past medical history, COVID-19 symptoms and onset of symptoms relative to randomization, study treatment, concomitant medications, relevant laboratory assessments, description of events leading to hospitalization, and a summary of the hospital course. The narratives indicate the Sponsor or Applicant adequately followed participants who had protocol-defined progression of COVID-19 to provide a preliminary assessment of this pre-specified secondary endpoint through Day 29, which favors sotrovimab.

Table 4: Proportion of Participants who Progress to develop Severe and/or Critical Respiratory COVID-19 by Visit at Day 8, Day 15, Day 22, or Day 29 (ITT [IA])

	Day 8		Day 15		Day 22		Day 29	
	Placebo (N=292)	Sotrovimab (N=291)	Placebo (N=292)	Sotrovimab (N=291)	Placebo (N=292)	Sotrovimab (N=291)	Placebo (N=292)	Sotrovimab (N=291)
Progression Status, n (%)								
No Severe/Critical Progression[a]	278 (95%)	286 (98%)	272 (93%)	286 (98%)	272 (93%)	285 (98%)	272 (93%)	285 (98%)
Severe/Critical progression	13 (4%)	1 (<1%)	19 (7%)	1 (<1%)	19 (7%)	2 (<1%)	19 (7%)	2 (<1%)
Category 2: Low flow nasal cannulae/face mask	7 (2%)	1 (<1%)	11 (4%)	1 (<1%)	11 (4%)	2 (<1%)	11 (4%)	2 (<1%)
Category 3: Non-re-breather mask or high flow nasal cannulae/non-invasive ventilation (including continuous positive airway pressure support) (severe)	6 (2%)	0	6 (2%)	0	5 (2%)	0	5 (2%)	0
Category 4: Mechanical ventilation/extra-corporeal membrane oxygenation (critical)	0	0	2 (<1%)	0	2 (<1%)	0	2 (<1%)	0
Death	0	0	0	0	1 (<1%)	0	1 (<1%)	0
Missing	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)

Source: EUA request, Table 30

[a] All participants status at admission is Category 1: Room air.

Note: Participants with progression are counted in the worst-case progression that they have reported up to the relevant time point.

Virologic Endpoint Analysis

The virology (IA) population (N=324) is a subset of the ITT (IA) analysis set, which includes participants with a central laboratory confirmed quantifiable nasopharyngeal swab at Day 1. The Applicant stated that the subset is currently limited by the availability of baseline, Day 5, and Day 8 viral load data due to analysis turnaround times. Based on the available data, viral load was similar across treatment arms at baseline, and the changes from baseline at Day 5 and Day 8 were (marginally) numerically greater with sotrovimab compared to placebo. However, it is important to note that that the virology (IA) population represents only 56% of the ITT (IA) population, and only 37% and 35% of the ITT (IA) population had viral load measurements on Day 5 and Day 8, respectively. Because of the large magnitude of missing data, interpretation of the viral load analyses as a predictor of clinical outcome is not yet possible. Additional viral load analyses will be conducted once sufficient data are available for a larger proportion of the trial population.

Table 5: Change from Baseline in Viral Load in Nasal Secretions by qRT-PCR Through Day 8 (Virology [IA])

	Placebo (N=170)	**Sotrovimab (N=154)**
Baseline (log 10 copies/mL)		
n	170	154
Mean (standard deviation)	6.833 (1.7049)	6.682 (1.6555)
Median (Min, Max)	7.126 (3.367, 9.839)	6.853 (3.412, 9.985)
Day 5 change from baseline (log 10 copies/mL)		
n	105	109
Mean (standard deviation)	-1.803 (1.5565)	-2.210 (1.7157)
Median (Min, Max)	-1.819 (-5.941, 2.917)	-1.989 (-6.917, 3.306)
Day 8 change from baseline (log 10 copies/mL)		
n	106	98
Mean (standard deviation)	-2.878 (1.6411)	-2.996 (1.6527)
Median (Min, Max)	-2.883 (-6.685, 1.181)	-3.277 (-6.917, 0.925)

Source: EUA Request, Table 32
Note: Detectable values less than the lower limit of quantification (< 2228 copies/mL) have been imputed to 0.5 x lower limit of quantification prior to taking the log 10 value. 'Not detectable' results have been imputed to 1 prior to taking the log 10 value.

Efficacy Results: Full Analysis ITT Population

The efficacy results from the full analysis ITT population are preliminary and were submitted to the EUA in response to an FDA information request. Due to the preliminary nature of the results, this information will not be included in the Fact Sheet For Healthcare Providers at this time.

Demographics and Baseline Characteristics

The demographics and baseline characteristics for the full analysis ITT population were well-balanced between the sotrovimab arm and the placebo arm (Table 6). Slightly more than half of the participants overall were female (54%), and the median age was 53 years. A total of 20% of participants were aged 65 years or older and 11% were aged over 70 years. Overall, 65% of participants were Hispanic or Latino. The majority of the participants were white (87%); 8% were black or African American, and 4% were Asian. Geographic location of sites included the US (953 [90%]), Canada (52 [5%]), Spain (29, [3%], Brazil (22 [2%]), and Peru (1, <1%]). Over half of the participants (56%) had one protocol-defined risk factor for progression to severe COVID-19, while the remaining participants had more than one risk factor; 31% had two, 10% had three, and 2% had more than three.

Based on available information, the demographics and baseline characteristics of the full analysis ITT population were similar to the safety (IA) (Table 2) and the ITT (IA) populations and representative of patients at high risk for progression to severe COVID-19, including hospitalization and death.

Table 6. Demographics and Baseline Characteristics (Full Analysis ITT Population)

Parameter	Placebo (N=529)	Sotrovimab (N=528)
Female	273 (52%)	299 (57%)
Hispanic or Latino	346 (65%)	345 (65%)
Black or African American	42 (8%)	40 (8%)
Asian	21 (4%)	24 (5%)
Age (years), Median (Min, Max)[a]	53 (17, 88)	53 (18, 96)
Age ≥ 55 years	256 (48%)	243 (46%)
Age ≥ 65 years	108 (20%)	105 (20%)
BMI (kg/m^2), Median (Min, Max)	32 (18, 71)	32 (17, 71)
BMI >30 kg/m^2	341 (64%)	330 (63%)
Diabetes requiring medication	109 (21%)	119 (23%)
Moderate to severe asthma	88 (17%)	90 (17%)
COPD	27 (5%)	34 (6%)
Chronic kidney disease	8 (2%)	5 (<1%)
Duration of COVID-19 symptoms ≤ 3 days	310 (59%)	314 (59%)

Sources: 4/30/2021 Response to FDA Information Request, Tables 1 and 1.12

[a.] Age is imputed from year of birth. The calculation uses 30 June as the day and month and calculates age relative to Screening date. Participant(s) designated as “17” are a result of the calculation and not a protocol deviation.

Primary Efficacy Analysis

In the full analysis ITT population, the primary endpoint, progression of COVID-19 (hospitalization for >24 hours or death due to any cause) at Day 29, was reduced by 79% with a 97.24% CI of (0.08, 0.56) in recipients of sotrovimab vs. placebo (2-sided p < 0.001) (Table 7). The treatment effect was driven by the subcomponent of hospitalization

>24 hours for acute management of any disease, as it constituted the preponderance of the clinical events. There were two deaths by Day 29, and one participant was hospitalized prior to death. A supportive logistic regression analysis that included the same covariates as the interim analysis provided similar results as the primary analysis. An exploratory analysis that considered missing observations as failures reached similar conclusions.

Table 7: Proportion of Participants who Have Progression of COVID-19 through Day 29 (Hospitalization for >24 Hours or Death) (Full Analysis ITT Population)

	Placebo N=(529)	Sotrovimab (N=528)	Risk Ratio[a] Sotrovimab: Placebo (97.24 % CI)[b] p-value
Progression Status, n (%)			
Hospitalized >24 hours for acute management of any illness or Death, due to any cause	30 (6%)	6 (1%)	0.21 (0.08, 0.56) <0.001
Hospitalized >24 hours for acute management of any illness[c]	29 (5%)	6 (1%)	
Death due any cause[c,d]	2 (<1%)	0	
Alive and not hospitalized	494 (93%)	515 (98%)	
Missing[e]	5 (<1%)	7 (1%)	

Source: 4/31/2021 Response to FDA Information Request, Table 2

a. Risk ratio adjusted for treatment, duration of symptoms (≤3 days vs. ≥4 days), age (≤70 vs. >70 years old) and gender (female vs. male) as covariates.
b. Confidence interval level adjusted for the two planned interim analyses.
c. Participants are counted in each subcategory of progression experienced up to the time point in question and so may be included in more than one category.
d. One participant ((b) (6)) died at home due to COVID-19 pneumonia without hospitalization on Day 5 and one participant ((b) (6)) died at hospital due to pneumonia on Day 20.
e. Participants withdrawn prior to Day 29 for whom progression status is unknown. Includes 5 placebo participants (2 withdrew consent prior to treatment, 1 withdrew consent on Day 3, 1 withdrew consent on Day 15, 1 withdrawn due to an Adverse Event of intermittent nausea on Day 11) and 7 sotrovimab participants (4 withdrew consent prior to treatment, 2 were withdrawn due to physician decision prior to treatment and 1 withdrew consent on Day 5 due to personal reasons).

In the sotrovimab arm, three participants were hospitalized >24 hours for COVID-19 pneumonia (participants: (b) (6) on Day 19; (b) (6) on Day 6; and (b) (6) on Day 2), and three participants were hospitalized >24 hours, respectively, due to small bowel obstruction (participant (b) (6) on Day 22), non-small cell lung cancer (participant (b) (6) on Day 19), and diabetic foot ulcer (participant (b) (6) on Day 19). One additional sotrovimab recipient was hospitalized <24 hours for diabetic hyperglycemia on Day 5. In the placebo arm, 29 participants were hospitalized >24 hours due to COVID-19 (n=2), COVID-19 pneumonia (n=19), pneumonia (n=3), acute respiratory failure (n=1), respiratory distress (n=2), respiratory failure/cardio-respiratory arrest/acute kidney injury (n=1), and dehydration (n=1). One additional placebo recipient died at home of COVID-19 pneumonia without being hospitalized.

Progression of COVID-19 defined as hospitalization >24 hours for acute management of any illness or death due to any cause rather than those attributed to COVID-19 minimizes

ascertainment bias and takes into consideration potential COVID-19 complications. Nonetheless, three of the six hospitalizations >24 hours through Day 29 in the sotrovimab arm appear unlikely or less likely related to COVID-19, whereas all 29 hospitalizations or deaths in the placebo arm appear related or likely related to COVID-19. This assessment is based on the Applicant's review of CIOMS forms, the review team's assessment of available narratives (from the ITT [IA]), the nature of the events, and past medical history of these participants. The primary efficacy results which include events irrespective of causality may represent a more conservative comparison in this case and are nonetheless robust.

Overall, the pre-specified primary endpoint of progression to severe COVID-19, including hospitalization >24 hours for acute management of illness or death due to any cause, is a clinically significant endpoint, and the preliminary event rate was significantly higher in the placebo arm compared to the sotrovimab arm in the full analysis population. Based on the difference in event rates, the estimated number needed to treat is 22 [97.24% CI (14, 45)] outpatients at high risk for progression to severe COVID-19 to prevent one additional hospitalization or death. This level of reduction in hospitalizations or death in this preliminary analysis is similar to that observed in the ITT (IA) population and likely represents a substantial clinical benefit.

Analysis of SARS-CoV-2 Variants

Please refer to the interim analysis results above for available information on participants with baseline variants or treatment-emergent substitutions.

Sufficient sequencing data are not yet available to determine the precise number of participants infected with a SARS-CoV-2 variant of concern in either the interim analysis or full analysis ITT populations but particularly for those enrolled later in the trial (December 2020 onward). FDA requested the Applicant provide a best estimate of how many participants may have had a baseline variant of concern, particularly the UK variant (B.1.1.7) or the E484K substitution, based on the number of participants enrolled in each US HHS region, the dates of enrollment, and prevalence of variants of concern in those regions at the time of enrollment. The Applicant estimates that from January 17, 2021 to March 12, 2021, approximately 47 participants may have carried the UK variant (B.1.1.7) and approximately 10-11 participants may have carried the E484K substitution present in the South Africa (B.1.351), Brazil (P.1), or New York (B.1.526) variants. Additional analyses will be conducted once sufficient sequencing data are available for all or most trial participants.

Secondary Efficacy Analysis

All-cause mortality at Day 29, Day 60, and Day 90 were pre-specified secondary endpoints. As of April 27, 2021, no deaths were reported in the sotrovimab arm, whereas 4 deaths were reported in the placebo arm. Two deaths occurred before Day 29, and two deaths occurred after Day 29 but before Day 60. The deaths were attributed to COVID-19 pneumonia (participant (b) (6) on Day 5 and participant (b) (6) on Day 37), pneumonia

(participant (b) (6) on Day 20), and respiratory failure (participant (b) (6) on Day 36). Note, both participants who died after Day 29 were hospitalized before Day 29 and therefore, had an event that met the primary endpoint.

In the full analysis ITT population, for the secondary endpoint of proportion of participants who progress to develop severe and/or critical COVID-19 based on the requirement for and method of supplemental oxygen at Day 29, a numerical reduction in the risk of severe and/or critical respiratory COVID-19 was reported for participants treated with sotrovimab (1% [7/528]) compared to placebo (5% [28/529]). Similar numerical reductions were also reported at Day 8, Day 15, and Day 22. These results are similar to those seen in the ITT (IA) population (Table 4). No sotrovimab-treated participants required high flow oxygen, oxygen via a non-rebreather mask, or mechanical ventilation through Day 29. Four participants in the placebo arm required mechanical ventilation, and no participants in either arm required ECMO.

IX. Human Clinical Safety

Sotrovimab 500 mg is currently being evaluated in clinical trials in adults with confirmed COVID-19 in outpatient and hospitalized settings. Sotrovimab 500 mg is the sole dose evaluated in clinical trials to date. For the proposed EUA, the safety database consists of over 700 participants who have received an IV infusion of sotrovimab 500 mg (partial or full dose) with follow-up safety data to at least Day 15. Follow-up safety data to at least Day 29 are available in approximately 612 sotrovimab recipients. Approximately 536 sotrovimab recipients were outpatient participants with mild or moderate confirmed COVID-19, the most relevant patient population for the proposed EUA.

SEE ATTACHED ADDENDUM

Table 8 summarizes the sources for the available safety database for this review. Note: The final safety results were not available for the full analysis ITT population of COMET-

ICE (n=1057) at the time of this review, but a preliminary topline safety summary suggests that the safety results in the full population are similar to that of the interim safety population. Overall, the available safety database is sufficient to assess risk.

Table 8. Summary of sotrovimab 500 mg (IV infusion) safety database

Study	Objective	Number of participants (N)
VIR-7831-5001 (COMET-ICE) (DCO: 04 March 2021)	Primary evaluation of safety data in support of EUA Request	N=868 (sotrovimab=430)
Supportive safety information from ongoing studies		
216912 (COMET-PEAK [Part A]) (DCO: 04 March 2021)	Additional blinded safety data in mild-to-moderate COVID-19 outpatients	N~40 (sotrovimab=5)
INSIGHT-014 (ACTIV-3 TICO) (DCO: 18 March 2021)	Additional unblinded safety summary from hospitalized patients including exposure	N=360 (sotrovimab=182)
J2X-MC-PYAH (BLAZE-4, Arms 7 and 8) (DCO: 17 March 2021)	Available unblinded safety data from outpatients (combination only, no VIR-7831 monotherapy arm)	N=202 (sotrovimab + bamlanivimab=101)

Sources: EUA Request Table 2; ACTIV-3 TICO Unblinding Report VIR/GSK Study Treatment Table 3.1; and 4/19/2021 Response to FDA Information Request
DCO = data cutoff

VIR-7831-5001 (COMET-ICE) Safety Results

Exposure for Safety Analysis

The safety analysis from the pivotal trial, COMET-ICE, includes 430 sotrovimab recipients and 438 placebo recipients, each with a potential for 15 days of follow-up. Most participants have follow-up data beyond 29 days (Table 9).

Table 9. Duration of Time on Study Post-Dose (COMET-ICE)

	Placebo (N=438)	Sotrovimab (N=430)	Total (N=868)
Duration of time on study post-dose[a]			
<15 days	1 (<1%)	1 (<1%)	1 (<1%)
15 to 29 days	62 (14%)	57 (13%)	119 (14%)
>29 days	375 (86%)	372 (87%)	747 (86%)
>85 days	89 (20%)	87 (20%)	176 (20%)
Mean (SD), days	61.2 (33.13)	62.0 (32.51)	61.6 (32.81)

	Placebo (N=438)	Sotrovimab (N=430)	Total (N=868)
Median (Min, Max),days	55.0 (2, 190)	56.0 (5, 190)	55.0 (2, 190)

Source: EUA Request Table 6

a. Duration of follow-up in the study from date of infusion through to time of study completion/ withdrawal or data cutoff date if participant is still ongoing in the study.

SEE ATTACHED ADDENDUM

Safety Overview

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017) was used to grade all AEs and laboratory abnormalities in COMET-ICE. The safety review for COMET-ICE includes AEs reported as related to COVID-19 symptoms or progression. As displayed in Table 10, the occurrence of AEs assessed as related to study treatment by the investigator was similar (2%) in both treatment arms. No participants permanently discontinued sotrovimab or placebo due to an AE. Severe (≥ Grade 3) AEs and SAEs were reported in fewer participants in the sotrovimab arm compared to placebo, mostly due to a greater percentage of participants with progression to severe COVID-19 in the placebo arm. The occurrence of infusion-related reactions was relatively low and similar in each arm (1%).

Table 10. Summary of Safety (COMET-ICE)

	Placebo (N=438)	Sotrovimab (N=430)
Any AE	85 (19%)	73 (17%)
AEs related to study treatment	8 (2%)	8 (2%)
AEs leading to permanent discontinuation of study treatment[a]	0	0
AEs leading to dose interruption/delay	0	2 (<1%)[c]
Non-serious Grade 3 or 4 AEs	10 (2%)	3 (<1%)
Any SAE	26 (6%)	7 (2%)
SAEs related to study treatment	1 (<1%)	0
Fatal SAEs	2 (<1%)	0
Fatal SAEs related to study treatment	0	0
Any Infusion Related Reactions including Hypersensitivity AESI[b]	5 (1%)	6 (1%)
IRRs related to study treatment	2 (<1%)	1 (<1%)

	Placebo (N=438)	Sotrovimab (N=430)
IRRs leading to permanent discontinuation of study treatment[a]	0	0
IRRs leading to dose interruption/delay	0	0

Source: EUA Request, Table 10 and 4/26/2021 Response to FDA Information Request
AE = adverse event, SAE = serious adverse event, AESI = adverse event of special interest, IRR = infusion-related reaction

b. A participant was permanently discontinued from the completion of drug infusion if they experienced life-threatening infusion-related reactions, including severe allergic or hypersensitivity reactions during the IV infusion.
c. Infusion-related reactions (including hypersensitivity) are defined using a selection of preferred terms for AESIs that include pyrexia, chills, dizziness, dyspnea, pruritus, rash, infusion related reaction and only includes events that started within 24 hours of study treatment.
c. AEs leading to dose interruption were two events of infusion site extravasation. For both events, the infusion was able to be completed, and the time to complete the infusion was 1 h 17 min and 1 h, respectively.

Deaths

No deaths have been reported in the sotrovimab arm as of April 27, 2021. At the time of the interim analysis, two deaths had occurred in the placebo arm, both attributed to COVID-19. One participant was a 70-year-old Caucasian male with additional risk factors of chronic lung disease and obesity. This participant was hospitalized on Day 4 and died of COVID pneumonia on Day 20. The second participant was a 71-year-old Caucasian female with an additional risk factor of obesity. This participant was hospitalized on Day 8 and died of COVID pneumonitis on Day 37. At the time of preliminary analysis of the full analysis population, two additional deaths had been reported in the placebo arm.

Serious Adverse Events

A total of 38 SAEs were reported in 33 participants, 7 (2%) participants in the sotrovimab arm and 26 (6%) participants in the placebo arm (Table 10). One SAE in total was assessed as treatment-related by the investigator, which was COVID-19 pneumonia occurring in the placebo arm. SAEs reported in more than one participant in either arm (sotrovimab vs. placebo, respectively) were COVID-19 pneumonia or pneumonia (1 [<1%] vs. 19 [4%]), diverticulitis (2 [<1%]) vs. 0 [0%]), and dehydration (0 [0%] vs. 2 [<1%]).

The Applicant provided narratives for all SAEs reported for sotrovimab or placebo, irrespective of causality. All narratives were reviewed, and no safety signals for sotrovimab were identified based on available data. The assessment that none of the SAEs in the sotrovimab arm were related to study drug is reasonable. A summary of the SAEs reported in the sotrovimab arm is presented in Table 11.

Table 11. Listing of Serious Adverse Events in the Sotrovimab Arm (COMET-ICE)

Sex (M/F)/ Age (years)/ Race	Days to SAE Onset	SAE (PT)	Related to Study Drug	Related to COVID-19 (per PI)	Relevant Medical History
Sotrovimab					
F/80/Caucasian	90	Diverticulitis	No	N/S	History of diverticulitis
M/31/Caucasian	50	Diverticulitis	No	N/S	History of diverticulitis

Sex (M/F)/ Age (years)/ Race	Days to SAE Onset	SAE (PT)	Related to Study Drug	Related to COVID-19 (per PI)	Relevant Medical History
Sotrovimab					
F/31/Caucasian	5	Diabetes mellitus	No	N/S	History of diabetic ketoacidosis
F/71/Caucasian	1	COVID-19 pneumonia	No	Yes	
M/57/Caucasian	13	Hyperglycemia Non-small cell lung cancer	No	N/S	Insulin-dependent diabetes, obesity, hyperlipidemia, 120 pack-years smoking history
F/65/Caucasian	22	Small intestinal obstruction	No	N/S	History of small bowel obstruction
M/96/Caucasian	19	COVID-19	No	Yes	

Source: EUA Request, Table 13
SAE = serious adverse event, PT = preferred term, PI = principal investigator, F = female, M = male, N/S = not specified in the PI narrative

Common Adverse Events

Most AEs (irrespective of causality) were reported within the first 15 days of treatment with a small proportion occurring after Day 15 through Day 29. AEs were reported in 59 (14%) and 68 (16%) total participants in the sotrovimab arm through Day 15 and Day 29, respectively. In the placebo arm, AEs were reported in 72 (16%) and 83 (19%) total participants through Day 15 and Day 29, respectively. Infusion-related reactions, occurring within the first 24 hours after treatment, are discussed in detail in the Analysis of Submission-Specific Safety Issues section.

Table 12 and Table 13 display AEs reported by System Organ Class (SOC) and Preferred Term (PT), respectively, in at least 1% of participants in either treatment arm through Day 29, irrespective of causality. AEs more frequently reported in the sotrovimab arm compared to the placebo arm resided within the SOCs general disorders and administration site conditions, skin and subcutaneous disorders, and psychiatric disorders.

General disorders and administration site conditions more frequently reported with sotrovimab compared to placebo were feeling cold, pyrexia, chills, and infusion site extravasation, all of which appear possibly or likely associated with product infusion. Skin and subcutaneous disorders more frequently reported with sotrovimab compared to placebo were variations of rash or possible rash, including erythema, rash pruritic, and skin reaction. The psychiatric disorders more frequently reported with sotrovimab compared to placebo were depression, anxiety, delirium, and stress, each reported for 1-2 participants.

Table 12. Adverse Events by SOC ≥ 1% in Either Treatment Arm through Day 29 (COMET-ICE)

System Organ Class (SOC)	Placebo (N=438)	Sotrovimab (N=430)
Infections and infestations	27 (6%)	10 (2%)
Metabolism and nutrition disorders	17 (4%)	11 (3%)
Respiratory, thoracic and mediastinal disorders	17 (4%)	8 (2%)
Gastrointestinal disorders	12 (3%)	12 (3%)
Nervous system disorders	11 (3%)	8 (2%)
General disorders and administration site conditions	**6 (1%)**	**12 (3%)**
Skin and subcutaneous tissue disorders	**6 (1%)**	**9 (2%)**
Investigations	7 (2%)	6 (1%)
Musculoskeletal and connective tissue disorders	7 (2%)	3 (<1%)
Psychiatric disorders	**3 (<1%)**	**6 (1%)**

Source: EUA Request, IDMC Table 3.4

With respect to specific events, diarrhea and rash were reported more frequently with sotrovimab compared to placebo (Table 13).

Table 13. Adverse Events by PT ≥ 1% in Either Treatment Arm through Day 29 (COMET-ICE)

Preferred Term (PT)	Placebo (N=438)	Sotrovimab (N=430)
Rash[1]	3 (<1%)	7 (2%)
Diarrhea	3 (<1%)	6 (1%)
COVID-19 pneumonia	14 (3%)	4 (<1%)
Nausea	5 (1%)	4 (<1%)
Headache	9 (2%)	3 (<1%)
Dyspnea	5 (1%)	2 (<1%)
Pneumonia	7 (2%)	0
Dehydration	5 (1%)	0

Sources: EUA Request, Table 11 and IDMC Table 3.4
[1] Combined terms: Rash, Erythema, Palmer erythema, Pruritus, Rash pruritic, Skin reaction

The majority of non-serious AEs in either arm were Grade 1 or 2, with fewer non-serious Grade 3 or 4 AEs reported in the sotrovimab arm compared to the placebo arm (<1% vs. 2%, respectively). None of the non-serious Grade 3 or 4 AEs were reported in more than one participant, irrespective of treatment arm. These events included dyspnea, COVID-19 pneumonia, and cardiovascular deconditioning in the sotrovimab arm (3 total participants); and asthma, hiccups, pneumothorax, respiratory distress, COVID-19 pneumonia, pneumonia, arthralgia, back pain, pain in extremity, pain, dehydration, and headache in the placebo arm (10 total participants). No significant safety signals were identified for sotrovimab.

The majority of non-serious AEs of any grade were not related to study treatment per investigator assessment. Overall, a total of 20 adverse drug reactions (ADRs; AEs related to study treatment) were reported in 16 participants, 8 in each arm. All ADRs reported in

the sotrovimab arm were Grade 1 or 2. Similar ADRs reported in more than one participant were skin or subcutaneous disorders (2 sotrovimab recipients and 3 placebo recipients). In the sotrovimab arm, rash and skin reaction were reported on Day 2 and Day 4, respectively. In the placebo arm, rash, pruritus, and infusion site erythema/swelling were reported in 2 participants approximately 2-7 hours after treatment. An assessment of ADRs raised no significant safety concerns for sotrovimab.

Laboratory Findings

Safety laboratory testing was conducted weekly through Day 29 in COMET-ICE, with additional testing on Day 2 and Day 5 during the lead-in phase. As displayed in Table 14, more participants in the sotrovimab arm (21 [4.8%]) compared to the placebo arm (9 [2%]) had Grade 3 or higher abnormalities for clinical chemistry parameters, driven by increased creatinine. Overall, laboratory abnormalities did not appear to correlate with clinical AEs based on available information.

Table 14. Worsening Laboratory Abnormalities (COMET-ICE)

	Placebo (N=438)		Sotrovimab (N=430)	
Laboratory Parameter	**Any grade shift, n (%)**	**Grade 3/4 shift, n (%)**	**Any grade shift, n (%)**	**Grade 3/4 shift, n (%)**
Creatinine/Creatinine, high	39 (11%)	9 (2%)	50 (13%)	20 (5%)
ALT/ALT or SGPT, high	32 (9%)	0	29 (8%)	1 (<1%)[a]
AST/AST or SGOT, high	18 (5%)	0	9 (2%)	1 (<1%)[a]
Total Bilirubin/Total Bilirubin, high	3 (<1%)	0	4 (1%)	0

Source: EUA Request, Table 17

a. Both ALT and AST grade shifts were reported in the same participant.

In response to an FDA information request, the Applicant stated that an additional 4 participants within the safety analysis population had Grade 3 or 4 increases in creatinine, bringing the cumulative total to 21/430 (5%) participants in the sotrovimab arm compared to 12/438 (3%) participants in the placebo arm but retaining an imbalance between arms. Approximately half of these participants had an improvement or return to normal/near normal creatinine levels, whereas 10 sotrovimab recipients and 6 placebo recipients had an undulating pattern that overall worsened at Day 29 or the last study visit. The Applicant is requesting follow-up information on these 16 participants.

Notably, renal events were reported at a low and similar rate in the sotrovimab arm (2 [<1%]) compared to the placebo arm (3 [<1%]). Renal events were defined as a 50% decline in eGFR from baseline or urine albumin creatinine ratio > 500 mg/g and only for participants without end-stage renal failure at baseline. In addition, no AEs within the SOC renal and urinary disorders have been reported in the sotrovimab arm, whereas two have been reported in the placebo arm (PTs acute kidney injury and stress urinary incontinence). The lack of reported clinical manifestations of increased creatinine associated with sotrovimab is reassuring, but the potential signal of increased creatinine will be reassessed in the full analysis set when available.

As displayed in Table 14, one participant in the sotrovimab arm had Grade 3 ALT and AST elevations (>5x ULN) beginning on Day 22, which represented an increase from Grade 1 ALT and AST elevations (>2x ULN) at baseline. Both values remained elevated at Grade 3 (>5x ULN) at Day 29. Grade 1 AEs of fever, chills, and diarrhea were reported on Day 1; however, no additional AEs and no SAEs were reported, and no treatment was provided. In response to an FDA information request, the Applicant stated that the participant's ALT and AST decreased to near-baseline levels on Day 58. The presence of other external risk factors (e.g., OTC or herbal medications or alcohol) is unknown. Overall, one AE within the SOC hepatobiliary disorders was reported for one participant in each treatment arm (PT hepatitis alcoholic in the sotrovimab arm), which is reassuring at this time.

For hematology parameters, one participant in the sotrovimab arm had a Grade 3 or higher abnormality (low hemoglobin, Grade 3) compared to three participants in the placebo arm (all low lymphocytes/absolute lymphocyte count, all Grade 3). The participant in the sotrovimab arm who experienced a Grade 3 decrease in hemoglobin had a baseline value of 9.2 g/dL (normal range 12.7-18.1 g/dL) and an ongoing history of gout, obesity, diabetes mellitus, and hypertension. Overall, more participants in the placebo arm (19 [6%)] than the sotrovimab arm (11 [3%]) had a Grade 1-2 decline in hemoglobin. No hematologic safety signals are apparent at this time.

ECG Findings

No formal (thorough) QTc studies have been performed in humans. Interaction with ion channels is not expected due to the size of sotrovimab, restricting its ability to cross the plasma membrane and reach the site of action required for functional block. In the lead-in phase of COMET-ICE (n=21), 12-lead ECGs were obtained at baseline and daily through Day 8. In the expansion phase, ECGs were scheduled only pre-dose; however, post-baseline ECGs were obtained in 9 participants, either post-dose on Day 1 or as an unscheduled assessment. ECG intervals including PR, QRS, and QT were not routinely collected.

Post-baseline abnormalities (worst case) occurred in fewer participants in the sotrovimab arm (4/15) compared to the placebo arm (10/15). None of the abnormalities were deemed clinically significant by the Investigator. In the systematic assessment of the lead-in phase, no clinically significant changes from baseline at Day 8 were noted in either arm. Overall, no safety concerns were identified from this assessment; and although the assessment is based on a limited sample size, significant ECG changes are not expected.

Analysis of Submission-Specific Safety Issues

Infusion-related Reactions including Immediate Hypersensitivity Reactions

In COMET-ICE, infusion-related reactions (IRR) including hypersensitivity reactions were defined as those occurring within 24 hours of infusion. Participants were monitored for at least 2 hours after the end of the infusion and then at least once daily for 7 days (by telephone or in person). As displayed in Table 15, IRRs were reported at a similar rate in the sotrovimab and placebo arms, respectively. All IRRs were Grade 1 or 2 in severity, with one Grade 2 event reported in the sotrovimab arm. None of the events were serious or resulted in interruption or discontinuation of the infusion. The events reported for participants in the sotrovimab arm include pyrexia (n=3), chills (n=2), dizziness (n=1), infusion related reaction (n=1), and dyspnea (n=1). Participants in the placebo arm also experienced pyrexia (n=1), dizziness (n=2), and dyspnea (n=1) as well as pruritus (n=1) and rash (n=1).

A notable difference was the number of fully recovered/resolved IRRs initially reported in each arm: 5 of 5 participants in the placebo arm compared to only 3 of 6 participants in the sotrovimab arm. Based on the response to an FDA information request regarding the unresolved IRRs, one participant experienced Grade 1 fever that was entered erroneously as “resolved with sequelae” when instead it was fully resolved. The Applicant confirmed the other two participants had ongoing IRRs as of the data cutoff date and provided additional information on these events (summarized below). The nature of both events is reassuring and does not raise any safety concerns; both events resolved and neither was considered related to sotrovimab.

> One participant experienced chills and fever, both Grade 1, approximately 21 hours after receiving the sotrovimab infusion. No treatment was given, and both events resolved (after the data cutoff date). The Investigator considered these events unrelated to sotrovimab.
>
> Another participant, with a history of obesity and home oxygen use via nasal cannula for shortness of breath due to nocturnal orthopnea, experienced intermittent Grade 2 increased shortness of breath approximately 2 days after receiving the sotrovimab infusion. Although this event started more than 24 hours after the infusion, the event was included as an IRR because the start time of shortness of breath was unavailable. The participant was treated with 2 liters of oxygen via low-flow nasal cannula/prongs, and the event resolved (after the data cutoff date). The Investigator considered the event unrelated to sotrovimab.

Table 15. Summary of Infusion-Related Reactions including Hypersensitivity Reactions (COMET-ICE)

	Placebo (N=438)	**Sotrovimab (N=430)**
Number of Participants with an IRR	5 (1%)	6 (1%)
Number of Events	6	8
Event Characteristics[a]		
Serious	0	0
Resulting in Hospitalization	0	0
Related to study treatment	2/5	1/6

	Placebo (N=438)	Sotrovimab (N=430)
Withdrawal from study	0	0
Number of occurrences of IRR[a]		
One	4/5	4/6
Two	1/5	2/6
Outcome of IRR		
Recovered/resolved	5/5	6/6[b]
Maximum Grade		
Grade 1	3/5	5/6
Grade 2	2/5	1/6
Grade 3, 4, or 5	0	0
Action Taken		
Dose interrupted	0	0
Infusion stopped	0	0

Sources: EUA Request, Table 15 and 4/19/2021 Response to FDA Information Request
IRR = infusion-related reaction

a. Participant may be included in more than one category for 'Event Characteristics'
b. Updated based on Response to FDA Information Request. See text for details.

In the BLAZE-4 trial on the day of study treatment administration, no IRRs or hypersensitivity reactions were reported in the sotrovimab (plus bamlanivimab) arm, whereas one hypersensitivity reaction was reported in the placebo arm.

In the ACTIV-3 trial, which enrolled a hospitalized population, IRRs were collected via a checklist and defined as those occurring within 2 hours of infusion. IRRs were reported at a numerically higher rate in the sotrovimab arm (18/182 [10%]) compared to the placebo arm (14/178 [8%]). The imbalance was driven by Grade 1 IRRs, as the rate of Grade 2 or higher IRRs was similar in both arms: sotrovimab (7/182 [4%]) and placebo (8/178 [4%]).

In ACTIV-3, Grade 4 IRRs were reported in two sotrovimab recipients, one of which was anaphylaxis (see below for more details) and one of which was Grade 4 shortness of breath described as respiratory failure. One additional sotrovimab recipient experienced Grade 3 shortness of breath and Grade 2 bronchospasm. Both severe or life-threatening non-anaphylactic respiratory events were possibly related to sotrovimab use or COVID-19 progression.

In the placebo arm of ACTIV-3, one participant experienced Grade 3 shortness of breath and Grade 3 bronchospasm; and one participant experienced Grade 4 delirium. All other IRRs in the sotrovimab arm were Grade 1 or 2. IRRs in the sotrovimab arm of ACTIV-3 that were not reported in the placebo arm of ACTIV-3 or in COMET-ICE included paresthesia, oral hypoesthesia, myalgia, headache, and hyperhidrosis.

Anaphylaxis

While no anaphylaxis events have occurred in the outpatient trials COMET-ICE, BLAZE-4 (Arms 7 and 8), or COMET-PEAK to date, one participant in the hospitalized trial, ACTIV-3, experienced anaphylaxis associated with sotrovimab.

> A 92-year-old hospitalized female, requiring low-flow oxygen (2 L) at randomization, developed anaphylaxis approximately 20 minutes after the start of infusion (planned infusion time of 60 minutes). The infusion was immediately and permanently discontinued. Symptoms consisted of chest tightness (assessed as 10/10), shortness of breath, and dizziness accompanied by expiratory wheezing, poor air movement, flushing, and a new punctate rash on the face and neck. The participant became tachypneic and required increased oxygen (4 L). She denied difficulty swallowing, had no signs of angioedema or stridor, and did not experience significant hypotension. Treatment included diphenhydramine, epinephrine, famotidine, and methylprednisolone. Wheezing and chest tightness subsequently resolved, and air movement, flushing, and rash improved. However, dizziness persisted as well as the increased oxygen requirement (4 L). Almost two hours after sotrovimab discontinuation, chest tightness (assessed as 6/10) and shortness of breath accompanied by expiratory wheezing reoccurred, which was assessed as a recurrent infusion reaction. The participant received an additional dose of diphenhydramine and epinephrine along with albuterol, and symptoms and exam improved within minutes. No additional reactions occurred. The participant continued to receive daily corticosteroids (dexamethasone).

Given the serious nature of anaphylaxis and potential hypersensitivity reactions observed with sotrovimab in the hospitalized trial, the review team agrees with the Applicant's inclusion of a warning statement in the Fact Sheet to communicate this potential risk along with appropriate management, should such reactions occur. In addition, a more comprehensive list of potential signs and symptoms of these reactions was added to the warning, consistent with the Fact Sheets for other SARS-CoV-2 monoclonal antibodies.

Delayed Hypersensitivity Reactions

In COMET-ICE, rash or other skin reactions were not reported in the sotrovimab arm in the IRR analysis above (within 24 hours of infusion) but were reported in 7 participants in the sotrovimab arm through Day 29. None of these events were Grade 3 or higher or serious. Based on the overall analysis of AEs and SAEs in COMET-ICE, no serious delayed hypersensitivity reactions are apparent at this time.

In BLAZE-4 (Arms 7 and 8), none of the AEs reported in participants who received sotrovimab (plus bamlanivimab) through Day 29 were suggestive of delayed hypersensitivity.

Based on the information provided for ACTIV-3 along with the presence of severe disease in hospitalized participants, an assessment of delayed hypersensitivity in this trial cannot be made at this time.

Anti-Drug Antibodies

SEE ATTACHED ADDENDUM

Sotrovimab is a human IgG1κ monoclonal antibody targeting an exogenous target (spike protein RBD of SARS-CoV-2), which is intended to be used as a single-dose treatment under the EUA. The incidence and impact of anti-drug antibodies (ADA) after a single dose of sotrovimab are currently unknown.

Validation of ADA assays (screening, confirmatory, and titer assays) are underway. Overall, the ADA assay validation plan appear adequate, and the proposed immunogenicity testing strategy is acceptable. Once the assays are available, stored samples from participants in COMET-ICE will be analyzed.

Assays to characterize the activity of potentially neutralizing antibody (NAb) in participant serum samples are under development. Method qualification and validation are not yet available. Once available, the validated assay will be used for NAb analysis on stored serum samples.

Antibody-Dependent Enhancement of Infection

To date, there are no compelling data to support the occurrence of antibody-dependent enhancement (ADE) of infection following sotrovimab administration in outpatients with mild-to-moderate disease. However, follow-up data in most clinical trial participants for at least 5 half-lives following sotrovimab administration is not yet available. The risk of ADE was addressed by the Applicant in completed non-clinical cell culture and animal model studies (Please see Section XIII, Nonclinical Data to Support Efficacy for more information related to ADE). The applicability of the findings from these nonclinical studies to the clinical setting is not known. While there was no evidence of enhanced disease in participants treated with sotrovimab in COMET-ICE, there is still a theoretical possibility of increased incidence of reinfection or enhanced disease if infected again once mAb concentrations have waned to sub-neutralizing concentrations in sotrovimab-treated patients. Longer-term data (6 months post-dose) from COMET-ICE and other outpatient clinical trials are being collected.

Supporting Safety Data from Other Outpatient Trials

In BLAZE-4, 198 of the 202 participants enrolled and treated with sotrovimab (plus bamlanivimab) or placebo had completed Day 29 as of the data cutoff date. Notably, the infusion time for sotrovimab was 30 minutes in this trial (compared to 60 minutes in COMET-ICE and ACTIV-3). No deaths, SAEs, or discontinuation of study treatment due to an AE were reported in either arm. The rate of AEs was comparable with sotrovimab (plus bamlanivimab) (5%) versus placebo (6%). All AEs were mild or moderate, except one severe AE in the placebo arm. Laboratory data are not currently available. Overall, no safety signals have been identified for sotrovimab (plus bamlanivimab) in this trial, and sotrovimab infusion over a 30-minute period appears reasonably safe.

In COMET-PEAK, five participants have received an IV infusion of sotrovimab. Minimal safety data are available; however, no SAEs have been reported.

Experience in Hospitalized Patients

Sotrovimab is being evaluated in a hospitalized population in a substudy of the master protocol ACTIV-3, entitled: A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19. The master protocol allows for evaluation of multiple investigational agents compared to placebo. On March 1, 2021, the ACTIV-3 sponsor halted enrollment in the sotrovimab substudy as recommended by an independent Data Safety and Monitoring Board (DSMB) following an interim review of unblinded data from 344 participants. The DSMB analysis initially indicated that sotrovimab met the pre-specified criteria for continuation. However, once data were adjusted to account for the presence of more advanced illness in the placebo arm compared to the sotrovimab arm, the DSMB recommended stopping enrollment due to futility. The DSMB found no safety concerns or indication of harm with sotrovimab compared to placebo in the interim analysis. Although enrollment in the sotrovimab substudy has ceased, participants will continue to be followed for 18 months per protocol.

The primary safety outcome for ACTIV-3 is based on a composite of deaths, SAEs, Grade 3/4 clinical adverse events, and clinical organ failure or serious infections through Day 5 (Table 16). According to the most recent ACTIV-3 report for the sotrovimab substudy, there was no evidence of a difference between treatment arms for this outcome (p=). The number of deaths increased in both arms through Day 28 (Table 16).

SEE ATTACHED ADDENDUM

Table 16. Summary of Safety through Day 5 (ACTIV-3)

	Placebo (N=178)	**Sotrovimab (N=182)**
Events through Day 5		
Death	1 (<1%)	0
Death or SAE	5 (3%)	5 (3%)
Death, SAE, or Grade 3/4 AE	35 (20%)	25 (14%)
Death, SAE, Grade 3/4 AE, Organ Failure, or Serious Infection	44 (25%)	35 (19%)
Events through Day 28		
Death	7 (4%)	9 (5%)

Source: ACTIV-3 Unblinding Report VIR/GSK Study Treatment, March 19, 2021, Table 5.1

Notably, the sotrovimab substudy was limited to hospitalized participants not requiring high-flow oxygen or mechanical ventilation due to safety concerns identified in these populations from clinical trials for other SARS-CoV-2 monoclonal antibodies. In addition, evaluation of other similar products in hospitalized patients has been halted due to futility. The following information is publicly available.

- The ACTIV-3 sponsor halted enrollment in the bamlanivimab substudy on October 26, 2020, based on recommendation from the independent DSMB. The recommendation was based on a low likelihood of benefit in hospitalized

participants without end-stage organ failure. Ultimately, bamlanivimab was not found to be more effective than placebo in this population.

- The sponsor for casirivimab and imdevimab halted enrollment of hospitalized patients requiring high-flow oxygen or mechanical ventilation in a clinical trial based on the recommendation from an independent Data Monitoring Committee (IDMC) on October 30, 2020. The recommendation was based on a potential safety signal and an unfavorable benefit/risk profile in these populations.

- The ACTIV-3 sponsor halted enrollment in the BRII-196 and BRII-198 substudy when it halted enrollment in the sotrovimab substudy, also based on recommendation from the independent DSMB and also due to futility. The DSMB reported no evidence of harm with BRII-196 and BRII-198 compared to placebo.

Based on the totality of data in hospitalized patients, including a study with sotrovimab, the review team agrees with the Applicant's inclusion of a Limitations of Authorized Use statement specifying that sotrovimab is not authorized in patients hospitalized due to COVID-19. The review team also recommends adding a statement about the safety concerns in a more severe hospitalized population.

LIMITATIONS OF AUTHORIZED USE

- Sotrovimab is not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

X. Specific Populations

Rationale for Inclusion of Adolescent Patients under EUA

As of April 22, 2021, over 3.7 million cases of COVID-19 have been reported in children in the United States, Puerto Rico, and Guam (https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/). While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020). Given that COVID-19 can be a serious and life-threatening disease in adolescent patients (particularly in those with risk

factors for the development of severe illness and hospitalization), the similarities in physiology to adults, the expected similar PK in pediatric patients weighing ≥40 kg, and the safety profile, there is a prospect of benefit for this patient population. Based on the totality of evidence to support the prospect of benefit and that it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of sotrovimab includes pediatric patients who are 12 years of age and older and who weigh at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. To date, sotrovimab has not been administered in pediatric patients.

Dose Considerations for Specific Populations

- Safety and pharmacokinetic (PK) data are not available in children, pregnant or lactating individuals, or patients with hepatic insufficiency. No dosage adjustment is recommended based on renal impairment, during pregnancy or while lactating. The effect of other covariates (e.g., age, sex, race, body weight, disease severity) on PK of sotrovimab is unknown.
- Nonclinical reproductive toxicology studies with sotrovimab have not been conducted.
- No binding of clinical concern was observed with sotrovimab in tissue-cross reactivity studies in select human and monkey tissues.
- No binding of clinical concern was observed with sotrovimab in a protein microarray study using human embryofetal proteins.
- No specific risks to pregnant or lactating individuals have been identified based on the nonclinical safety data.

XI. Human Clinical Pharmacology

Pharmacokinetics

- From the COMET-ICE study, the Applicant submitted partial intense serum PK data through Day 57 from the lead-in phase (n=9). The analysis showed that the mean maximum concentration (C_{max}) of a single sotrovimab 500 mg dose was 218.8 µg/mL following a 1-hour IV infusion. The mean serum concentration level on Day 29 (C_{29}) was 37.2 µg/mL. PK parameters (i.e., area under the curve, clearance, volume distribution, half-life) of sotrovimab could not be determined due to insufficient serum sampling in the terminal phase.
- It is expected that the half-life of sotrovimab is longer than Fc-unmodified IgG monoclonal antibodies due to the LS modification. In LS modified IgG monoclonals, the half-life ranges from 30-90 days.
- Sparse PK through Day 29 from the expansion phase (n=144) of COMET-ICE was acquired and showed a mean C_{max} of 145.1 µg/mL and mean C_{29} of 34.6 µg/mL.
- PK serum samples were analyzed using a validated electrochemiluminescence immunoassay method.

Rationale for dosing recommendations

- The Applicant stated that a 500 mg sotrovimab dose is predicted to achieve lung concentrations above the *in vitro* geometric mean EC_{90} values of sotrovimab for live virus neutralization of the wild-type virus (0.186 µg/mL) and virus variants (B.1.1.7 [1.247 µg/mL], B.1.351 [0.385 µg/mL], and P.1 [0.336 µg/mL]), for at least 28 days after administration, assuming a lung to serum concentration ratio of 15%. Following a 500 mg sotrovimab dose, the geometric mean sotrovimab serum concentration at Day 29 was 34.1 µg/mL (95% CI geo: 21.8, 53.3 µg/mL). It should be noted that there are uncertainties in the EC_{90} values and the prediction of a lung to serum ratio of 15%, which was based on one publication (Magyarics, 2019). However, when using a more conservative estimate for the lung to serum concentration ratio based on lung penetration data from the literature (e.g., 1% partition), it is still predicted to achieve concentrations above *in vitro* EC_{90} of live wild-type virus and P.1 virus variant and EC_{50} of live B.1.1.7 and B.1.351 virus variants for several weeks.

Rationale for dosing recommendations in pediatric patients and other specific populations

- Pediatric patients: The PK of sotrovimab in pediatric patients have not been evaluated. The recommended dosing regimen is expected to result in comparable serum exposures of sotrovimab in pediatric patients 12 years of age and older and weighing at least 40 kg as those observed in adults, because adults with similar body weight have been included in trial COMET-ICE.
- Patients with renal impairment: sotrovimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of sotrovimab
- Patients with hepatic impairment: The effect of hepatic impairment on PK of sotrovimab is unknown.
- Other specific populations: The effect of other covariates (e.g., age, sex, race, body weight, disease severity) on PK of sotrovimab is unknown.

XII. Nonclinical Data to Support Safety

- Sotrovimab was evaluated in a GLP 2-week repeat dose toxicology study in cynomolgus monkeys with a 105-day recovery period using intravenous dosing.
    - Non-adverse findings included injection site reactions consisting of minimal perivascular fibroplasia; a decrease in lymphocytes in male animals that correlated with a decrease in thymus weight and thymic involution; an increase in heart weights in females without correlative gross or histopathology findings and the presence of anti-drug antibodies. No adverse, drug-related findings were observed up to the highest dose tested (500 mg/kg/week). Safety factors at the NOAEL of 500 mg/kg are approximately 40 and 60 at the authorized pediatric (weighing at least 40 kg) and adult dose, respectively.

- GLP tissue cross-reactivity studies were conducted with sotrovimab using adult human and cynomolgus monkey tissues. No binding of clinical concern was observed with sotrovimab in either species in these studies.
- A non-GLP protein microarray study evaluating the potential for sotrovimab binding to 66 human embryofetal proteins was conducted. The proteins evaluated were secreted or membrane bound proteins expressed in embryofetal tissue that had little or no expression in adult tissues.
    - No binding of clinical concern was observed with sotrovimab.

XIII. Nonclinical Data to Support Efficacy

Mechanism of Action

Sotrovimab (VIR-7831; GSK4182136) is a recombinant human IgG1κ mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant of 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 does not impact wild-type Fc-mediated effector functions in cell culture.

Summary of Data Reviewed for Nonclinical Virology Studies

- Sotrovimab bound to recombinant SARS-CoV-2 spike monomer protein with an IC_{50} value of 0.14 nM (20.4 ng/mL) as assessed by ELISA
- Sotrovimab bound to the recombinant RBD domain of the SARS-CoV-2 spike protein with an equilibrium constant (K_D) of 0.21 nM as measured by surface plasmon resonance
- Sotrovimab bound efficiently to surface expressed spike protein with an IC_{50} value of ~0.8 nM (~120 ng/mL)

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- Sotrovimab) did not compete with ACE2 for binding to either the RBD or to the spike ectodomain trimer (IC_{50} value >33.6 nM [5 µg/mL])
- The sotrovimab epitope in SARS-CoV-2 RBD includes amino acids 332-337, 339-340, 343-346, 354, 356-361, 440-441, and 509 as defined using single-particle cryo-EM and X-ray crystallography (Pinto et al., 2020)
- Evaluation of >116,000 SARS-CoV-2 spike protein sequences from the global initiative on sharing all influenza data (GISAID; download October 7, 2020) database showed >99.9% conservation of the amino acids comprising the epitope.
- Polymorphisms in the spike protein and in the sotrovimab epitope (as assessed by looking at conservation in sequences from public databases) did not impact binding to sotrovimab (as assessed by flow cytometry) or neutralization in a SARS-CoV-2 pseudotyped virus-like particle neutralization assay. Notably, sotrovimab bound to the single variant D614G and to haplotypes including D614G, indicating the highly prevalent D614G variant does not impact sotrovimab binding in biochemical based experiments.
- The neutralizing capacity of sotrovimab was assessed against SARS-CoV-2 virus in VeroE6 cells with an average EC_{50} value of 0.67 nM (100.1 ng/mL; range: 0.51 – 0.88 nM) and an average EC_{90} value of 1.2 nM (186.3 ng/mL; range: 0.84 – 2.2 nM).
- The mechanism by which sotrovimab ( ) binding to the spike protein leads to neutralization is unclear. In pseudotyped virus-like particle experiments using sotrovimab ( ) IgG, IgG-mediated neutralization reached 100%, whereas neutralization plateaued at about 80% in the presence of sotrovimab (S309) Fab

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(Pinto et al., 2020). These data indicate that one or more IgG-specific bivalent mechanisms—such as S-glycoprotein trimer cross-linking, steric hindrance or aggregation of virions—may contribute to the ability of the antibody to neutralize SARS-CoV-2.

- Cell culture combination assessments indicated that the drug combination effects of sotrovimab and remdesivir were not antagonistic across drug concentration ranges that comprised the EC_{50} values of both drugs.
- Passaging of SARS-CoV-2 for >1 month in the presence of fixed concentrations of an antibody with an identical Fab domain to sotrovimab demonstrated no emergence of viral escape substitutions even at the minimum antibody concentration tested (10x EC_{50} value). Passaging of virus in the presence of increased concentrations of sotrovimab resulted in a >10-fold shift in EC_{50} value which correlated with an E340A substitution that confers a >100-fold reduction in susceptibility to sotrovimab. The E340 amino acid position is >99.9% conserved based on identity among available SARS-CoV-2 sequences.
- Amino acids comprising the sotrovimab epitope are conserved, with ≥99.93% conservation based on identity among >750,000 currently available sequences (as of March 26, 2021 in the GISAID database) for all positions including 17/23 amino acid positions that are ≥99.99 conserved (PC-7831-0129 and PC-7831-0124). Sotrovimab neutralized epitope variants at most sotrovimab epitope amino acid positions except for variants with substitutions at two positions, E340 and P337, which resulted in significant increases in the EC_{50} value indicating reduced susceptibility to sotrovimab. SARS-CoV-2 spike protein substitutions of concern for sotrovimab based on observed fold-shifts in EC_{50} value shown in parentheses are: E340K (>297), P337R (>276), P337L (>180), E340A (>100; also selected for in cell culture selection experiments), and E340G (>27). These data indicate that substitutions at positions P337 and E340 are likely sotrovimab resistance-associated substitutions (PC-7831-0124).
- In Study Report PC-7831-0131, >1,000,000 full-length human SARS-CoV-2 sequences in the GISAID database were examined at the amino acid positions comprising the sotrovimab epitope, and as of April 16, 2021 ≥99.89% conservation was observed among currently available sequences for all sotrovimab epitope positions including 17/23 amino acid positions that were ≥99.99 conserved. sotrovimab retains neutralization activity against epitope variants at positions 333, 339, 344, 346, 354, 356, 357, 358, 359, 440, and 441 in a pseudotyped VLP assay.
- Sotrovimab neutralized pseudotyped virus-like particles expressing SARS-CoV-2 spike RAS that conferred reduced susceptibility to bamlanivimab, casirivimab, and/or imdevimab with 15/19 RAS exhibiting <2-fold shifts in EC_{50} values (PC-7831-0123). Four RAS exhibited increases in EC_{50} values between 2-fold and 3.38-fold, including the following RAS (fold-shift): V445A (3.38), G476S (2.94), S494P+D614G (2.5) and G261D+Y453F (2.19). L452R (0.70) and E484K (0.33) did not shift the susceptibility of sotrovimab.
- Sotrovimab neutralization was not impacted by pseudotyped virus-like particles expressing SARS-CoV-2 spike protein variants of the B.1.351, P.1, or CAL.20C lineages where fold-changes in EC_{50} value ranged from 0.35- to 0.70-fold (PC-7831-

0123). Sotrovimab neutralization was impacted with a 2.3-fold increase in the EC_{50} value against pseudotyped virus-like particles expressing SARS-CoV-2 spike protein variants of the B.1.1.7 lineage that included deletions at spike positions 69, 70, and 144 and substitutions N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H.

- Sotrovimab neutralization was not impacted by pseudotyped virus-like particles expressing SARS-CoV-2 spike protein variants of the B.1.617 (India) lineage where the fold-change in EC_{50} value was 0.70 (PC-7831-0132).
- Study report PC-7831-0126 reported that sotrovimab neutralized authentic SARS-CoV-2 South African and Brazil variants in a microneutralization assay with geometric means EC_{50} values of 482.5 pM (71.89 ng/mL) and 490.7 pM (73.11 ng/mL), respectively (1.2- and 1.6-fold change in EC_{50} value versus wild-type, respectively) and geometric mean EC_{90} values of 2,580 pM (385.01 ng/mL) and 2,250 pM (335.79 ng/mL), respectively (1.3- and 1.4-fold changes in EC_{90} value versus wild-type, respectively). A shift in activity was observed for the UK variant in this assay with a geometric mean EC_{50} value of 1,260 pM (187.15 ng/mL) (3.0-fold shift versus wild-type) and EC_{90} value of 8,370 pM (1246.86 ng/mL) (4.1-fold shift versus wild-type).
- Sotrovimab provided protection against weight loss in B.1.1.7-infected hamsters receiving prophylactic sotrovimab one day before challenge with SARS-CoV-2 of the B.1.1.7 lineage based on significant differences in body weight at Day 4 post-infection in animals receiving 30 mg/kg and 5 mg/kg sotrovimab compared to animals treated with isotype control antibody.
- In Study Report PC-7831-0127, sotrovimab exhibited neutralization activity against SARS-CoV-2 variants in an authentic SARS-CoV-2 microneutralization assay and in a pseudotyped VLP assay with a 3.3-fold difference or less in EC_{50} value compared to wild-type.
- Sotrovimab retains Fc effector function activities comparable to the parental S309-LS and binds to complement component 1q (C1q).
- In primary human cells, sotrovimab induces NK-cell mediated killing (ADCC) of target cells expressing SARS-CoV-2 spike protein and induces monocyte-mediated phagocytosis (ADCP) of target cells expressing SARS-CoV-2 spike.
- There were no signals for antibody dependent enhancement (ADE) of disease in several cell culture-based assays assessing concentrations of sotrovimab at 1X to 0.001X times the EC_{50} value.
- An assessment of ADE in the Golden Syrian hamster model of SARS-CoV-2 infection indicated that the risk of ADE is low for sotrovimab and a recombinant mAb containing a hamster Fc domain (GHS309) carrying the N297A substitution. However, the assessment did not investigate mAb concentrations that have previously been associated with ADE in other viral systems (≥100-fold below the EC_{50} value).
- In the Syrian Golden Hamster model of SARS-CoV-2 infection, there was a significant dose-dependent decrease in total viral shedding observed for prophylactic doses ≥0.5 mg/kg compared to negative control as assessed by RT-qPCR and a $TCID_{50}$ assay and no evidence of ADE was observed based on changes in weight, total viral RNA in

the lungs, or SARS-CoV-2 levels based on $TCID_{50}$ measurements for any of the animals receiving sotrovimab as compared to controls at the doses assessed (PC-7831-0130). Of note, a greater log_{10} reduction was detected by $TCID_{50}$ compared to quantitative RT-PCR which is consistent with the RT-PCR assay detecting both infectious viral particles and viral particles that are neutralized by bound antibody.

XIV. Supply Information

One vial of sotrovimab (500 mg/8 mL) represents one treatment course per patient for the proposed EUA indication. The Applicant has (b) (4) vials, or treatment courses, available in Parma Italy, that could be available for US distribution within approximately (b) (4) of EUA issuance. The Applicant states that the (b) (4) period covers labeling, packing, release, and shipment of the vials as well as finalization of distributor arrangements.

In addition, the following treatment courses are expected to be available for a total of (b) (4) doses for 2021. The Applicant notes that these estimates are correct as of April 29, 2021 and depend on purchases by other jurisdictions.

- June: (b) (4)
- July: (b) (4)
- August: (b) (4)
- December: (b) (4)

XV. Chemistry, Manufacturing, and Controls Information

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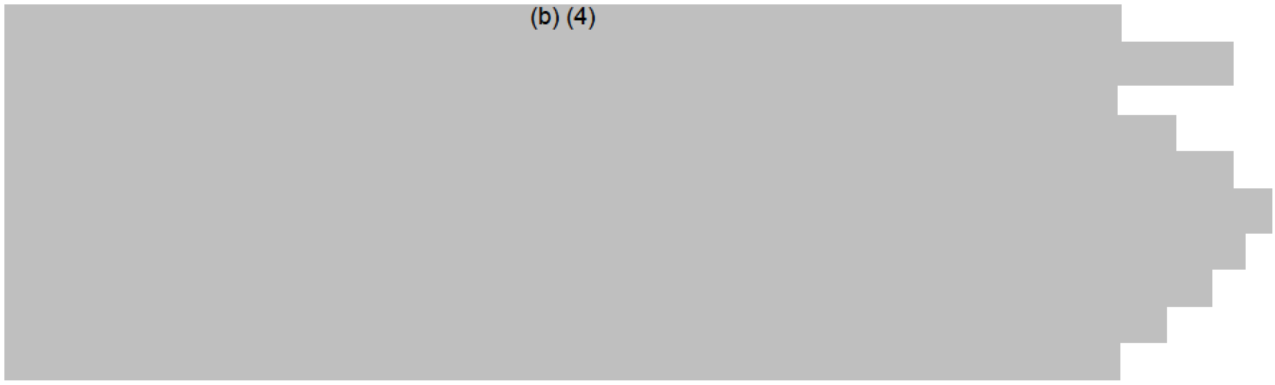
Sotrovimab (GSK4182136, VIR-7831) is a human immunoglobulin G (IgG1) monoclonal antibody consisting of two heavy chains (HC) and two light chains (LC) with 12 intrachain disulfide bonds. The HC contains the Asn-Ser-Thr (NST) consensus glycosylation site at N307 (numbered from the N-terminus). The main N-glycans are G0F, G1F, Man5, G0, and G0F-GN. The theoretical molecular mass of intact sotrovimab with the most common glycosylation pattern, (G0F/G0F), is 149 kDa when expressed without heavy chain C-terminal lysine.

The sotrovimab drug product (DP) intended to supply the EUA is a sterile solution for intravenous infusion. Each single-use (b) (4) glass vial is filled with (b) (4) mL DP to enable 8 mL extractable volume. The DP is a liquid solution of 62.5 mg/mL sotrovimab in (b) (4) containing (b) (4) L-methionine, (b) (4) % (w/v) sucrose and (b) (4) % (w/v) polysorbate 80 at pH (b) (4).

Sotrovimab is expressed in Chinese Hamster Ovary (CHO) cells while employing a standard monoclonal antibody manufacturing process. The sotrovimab drug substance (DS) is manufactured at (b) (4) at a scale of (b) (4) DS). The DP is manufactured at GSK, Parma, Italy ((b) (4) GSK Parma DP). The DS manufacturing process consists of (b) (4) The

formulated DS is (b) (4) . The DP manufacturing process consists of (b) (4) .

(b) (4)



The DS/DP manufacturing processes are appropriately controlled through monitoring critical process parameters and critical performance attributes; process- and product-related impurities are monitored either during the manufacturing process or as part of release testing. The overall process control strategy is adequate to support consistent manufacturing process and ensure quality of the materials intended to be used as EUA supply.

Identity, strength, purity and potency of sotrovimab DS/DP lots were appropriately assessed through batch analyses. Extended characterization studies addressed primary- and high-order structures, size and charge heterogeneity, glycans profiles and biological activity of sotrovimab. A high level of consistency in Gen1 and Gen2 manufacturing processes and product quality is demonstrated by comparing extended characterization data in addition to release and stability data obtained from Gen1 non-clinical/clinical materials and Gen2 clinical/EUA materials.

The proposed initial shelf-life of sotrovimab DP for use under EUA is 12 months at 5 ± 3°C with possible extension. The proposed shelf-life is supported by the totality of information provided, which include: (i) available stability data including up to 6 months for Gen1 DP and 3 months for Gen2 (b) (4) DP stored under long-term (5°C ± 3°C), accelerated (25 ± 2°C / 60 ± 5% RH), and stressed (40 ± 2°C / 75 ± 5% RH) conditions, (ii) comparability assessments of stability data and trends; (iii) risk assessment based on the stability data provided and; (iv) justification as to why the proposed shelf-life is needed to meet patient supply. The given information supports the proposed initial shelf-life of 12 months for the material to be used as the EUA supply. The Applicant continues to monitor and evaluate stability data in accordance with the proposed stability protocols. If any lot fails to conform to the stability specifications or

there are unexpected stability issues or an adverse trend is confirmed during the study, the Applicant commits to notify the FDA, evaluate the implications associated with the stability data and propose corrective actions. Shelf-life extensions are dependent on all test results complying with the proposed specifications defined in the stability protocols; detection of no significant changes; maintenance of the storage conditions; and analysis of any trends.

XVI. Manufacturing Site Inspections

Table 17: Manufacturing Sites

Manufac-turing Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant*	Inspection Dates	GMP Status (if known)
(b) (4) FEI: (b) (4)	DS manufacturing DS testing	(b) (4)	IND 149315	Vir Biotechnology, Inc.	FDA: (b) (4) FDA: (b) (4) (b) (4)	Acceptable
GSK Manufacturing S.p.A. FEI: 3002807114	DP manufacturing DP testing, packaging, labeling	Parma, Italy	IND 149315	Vir Biotechnology, Inc.	FDA: Feb 17-21, 2020 MRA: April 25-29, 2017 (AIFA) Apr 17-19, 2019 (AIFA)	Acceptable
(b) (4)	DS testing DP testing	(b) (4)	IND 149315	Vir Biotechnology, Inc.	FDA: (b) (4)	Acceptable

FEI: (b) (4)						
(b) (4) . FEI: (b) (4)	(b) (4)	(b) (4)	IND 149315	Vir Biotechnology, Inc.	FDA: (b) (4)	Acceptable

*GSK is the sponsor of the EUA request. Vir Biotechnology, Inc. is the sponsor of the IND and has provided a Letter of Authorization and Right of Reference to GSK.

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following condition(s) to the authorization as necessary to protect the public health[2]:

- GlaxoSmithKline will manufacture sotrovimab to meet all quality standards and per the manufacturing process and control strategy as detailed in the GlaxoSmithKline EUA request. GlaxoSmithKline will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without prior notification to and concurrence by the Agency as described in the corresponding condition detailing the process by which GlaxoSmithKline may request changes to the authorization (i.e., condition D).
- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).
- GSK will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of sotrovimab injection that includes the following:
    i. Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
    ii. Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

  If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information should be submitted for all potentially impacted lots.

[2] See the evaluation documented in OMQ's EUA Recommendation Memo in CMS Case# 614523 dated May 26, 2021, OPMA's Facility Assessment Memo associated with EUA 0100 dated May 26, 2021, and OPQ's Office of Pharmaceutical Quality Chemistry, Manufacturing, and Controls EUA Targeting COVID-19 Review memo dated May 7, 2021.

GSK will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, GSK must recall them.

If not included in its initial notification, GSK must submit information confirming that GSK has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. GSK must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- GSK will list sotrovimab injection with a unique product NDC under the marketing category of Unapproved Drug- Other. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

XVII. Clinical Trial Site Inspections

Clinical site inspections were not conducted for this EUA.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA.

XIX. Recommendations From Treatment Guidelines and Other Sources

The following COVID-19 treatment guidelines panels recommend or suggest using bamlanivimab plus etesevimab or casirivimab plus imdevimab for treatment of patients with mild-to-moderate COVID-19 who are at high risk of clinical progression.

- The National Institutes of Health (NIH) COVID-19 Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/outpatient-management/; updated April 21, 2021). The rating of the recommendation is strong. The rating of evidence is IIa, other randomized trials or subgroup analyses of randomized trials.

- The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/; updated April 14, 2021). The strength of recommendation is rated weak or conditional. The certainty of evidence is rated low.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

Sotrovimab is a recombinant human IgG1κ monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. The Fc domain of sotrovimab includes amino acid substitutions (LS modification) that extend antibody half-life but do not impact wild-type Fc-mediated effector functions in cell culture.

Sotrovimab has demonstrated activity in cell culture and animal models against SARS-CoV-2 and is currently being evaluated in clinical trials for treatment of COVID-19.

Based on FDA's review of the totality of scientific evidence available, including data from VIR-7831-5001, also called COMET-ICE (NCT04545060), a randomized, double-blind, placebo-controlled, Phase 1/2/3 trial in outpatients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, it is reasonable to believe that sotrovimab monotherapy may be effective 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. FDA has also determined that the known and potential benefits of sotrovimab monotherapy, when used for the treatment of COVID-19 as described in this memorandum, outweigh the known and potential risks of the product.

The primary endpoint for COMET-ICE was the proportion of participants with progression of COVID-19, defined as hospitalization >24 hours for acute management of any illness or death due to any cause, through Day 29. Event rates for the primary endpoint in the planned interim analysis ITT population were 7% in the placebo arm versus 1% in the sotrovimab arm, corresponding to an 85% relative reduction in hospitalization or deaths with sotrovimab versus placebo and an estimated number needed to treat of 16 high risk outpatients to prevent one hospitalization or death event. The difference was highly statistically significant and met the pre-specified efficacy stopping boundary leading to the Independent Data Monitoring Committee (IDMC)'s recommendation to stop enrollment.

Topline efficacy data for the full analysis ITT population became available during the EUA review. Event rates for the primary endpoint in the full analysis ITT population were 6% in the placebo arm versus 1% in the sotrovimab arm, corresponding to a 79% relative reduction in hospitalization or deaths with sotrovimab versus placebo and an estimated number needed to treat of 22 high risk outpatients to prevent one hospitalization or death event. The difference was highly statistically significant and similar to the interim analysis results.

Clinically meaningful secondary endpoints of all-cause mortality through Day 29 and Day 60 and the requirement for and method of supplemental oxygen through Day 29 in the interim analysis and full analysis ITT populations numerically favored sotrovimab compared to placebo. The impact of sotrovimab versus placebo on viral load endpoints could not be sufficiently assessed or correlated with clinical outcomes because of the large magnitude of missing viral load data in the EUA submission. Overall, the primary and available secondary outcome data from COMET-ICE provide convincing evidence of benefit to both individual patients and the public health system.

Regarding assessment of the known and potential risks, the overall safety database for sotrovimab is comprised of over 700 participants who have received an IV infusion of sotrovimab 500 mg, the only dose evaluated to date, with follow-up safety data to at least Day 15. The major adverse events of concern were infusion-related reactions including

hypersensitivity reactions. Serious or severe hypersensitivity reactions including anaphylaxis were observed in a hospitalized trial but have not been reported in any outpatient trials. Infusion-related reactions reported in COMET-ICE were mild or moderate, and none resulted in discontinuation of the infusion. To mitigate the risk of significant infusion-related reactions including hypersensitivity reactions, patients receiving sotrovimab should be clinically monitored during the infusion and for at least 1 hour after the infusion is complete. Sotrovimab should be administered in settings where healthcare providers would 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.

Sotrovimab is expected to retain activity against the current circulating SARS-CoV-2 variants of concern or interest, including the UK (B.1.1.7), South Africa (B.1.351), Brazil (P.1), California (CAL.20C), New York (B.1.526) and India (B.1.617) 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-ICE participants is unknown at this time, but the Applicant is continuing to obtain this information.

With respect to treatment emergent substitutions, E340K (≥99.7%), which was identified as a potential resistance-associated substitution in cell culture, was detected post-baseline in four participants in the sotrovimab arm. E340A (99.7%) was detected at baseline in one participant in the sotrovimab arm, and E340stop codon (6.6%) was detected at baseline in a participant in the placebo arm. The presence of substitutions at position E340 did not appear to impact clinical outcomes. However, the Applicant is continuing to obtain sequencing data in all COMET-ICE participants to better assess the presence and clinical relevance of substitutions at position E340.

The FDA carefully considered findings available or reported from trials of hospitalized patients treated with sotrovimab or other similar monoclonal antibodies. As the benefit of sotrovimab has not been observed in patients hospitalized due to COVID-19 and the use of SARS-CoV-2 monoclonal antibodies may be associated with risk of worse clinical outcomes in patients with severe or critical COVID-19, limitations of use in the Fact Sheet will specify that sotrovimab is not authorized for patients who are hospitalized due to COVID-19, or who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 (in individuals with an underlying non-COVID-19 related comorbidity that requires chronic oxygen therapy).

Based on the totality of scientific evidence available, including data from adequate and well-control trials, it is reasonable to believe that sotrovimab monotherapy may be effective 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; and when used under such conditions, the known and potential benefits of sotrovimab monotherapy outweigh the known and potential risks of the product. Therefore, the Review Division and the Office of Infectious Diseases

conclude that the statutory criteria under section 564(c) of the Federal Food, Drug and Cosmetic Act are met and recommend authorization of an EUA for sotrovimab 500 mg for the treatment of mild-to-moderate COVID-19 as described above.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will be used either in clinical trials under IND or in clinical practice under EUA. In clinical trials, FDA IND safety reporting regulations will apply.

In clinical practice, EUA-labeled product will be made available. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system. The prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all serious adverse events occurring during sotrovimab use and considered potentially related to sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)."

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheets for Health Care Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

Fact sheets will be available to health care providers and patients through hard copy and electronic links.

The Applicant's plan for distribution of the Fact Sheet for Health Care Providers (HCP) and Fact Sheet for Patients, Parents, and Caregivers is as follows:

- Each carton contains one vial of sotrovimab 500 mg and a hard copy of the HCP and Patient Fact Sheets.
    - The Fact Sheets will also include the Global URL www.sotrovimabinfo.com.
    - The carton has a QR code on it which directs users to the Global URL www.sotrovimabinfo.com. The Global labeling site www.sotrovimabinfo.com will allow users to select their country for country-specific information.
    - US users will be redirected via geolocation tools to the US website www.sotrovimab.com where they may access the HCP and Patient Fact Sheets, the Letter of Authorization and additional US-specific information.
- GSK has established a dedicated team for support called the GSK COVID Contact Center (https://contactus.gsk.com/callback/covid.html or 866-GSK-COVID (866-475-2684)) that can provide answers to questions from the Fact Sheets and copies of the Fact Sheets upon request.

FDA agrees with the plan for implementation for dissemination of the Fact Sheets.

- Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Fact Sheet for Patients, Parents, and Caregivers (See Section XXVI. Appendices)

XXIV. Outstanding Issues/Data Gaps

The EUA for sotrovimab is primarily based on efficacy and safety results from a planned interim analysis of COMET-ICE. The topline efficacy and safety results for the full analysis population received to date are similar to the interim analysis data and therefore, are supportive of the EUA. However, final results for the full analysis population remain critical to confirm the initial benefit-risk assessment for sotrovimab. Furthermore, if COMET-ICE included participants infected with confirmed variants of concern, clinical efficacy of sotrovimab against these variants may be better discerned. Obtaining this information is important because of the increasing prevalence of global SARS-CoV-2 variants in the US. As such, we are requesting the Applicant submit the following information for the full analysis population of COMET-ICE.

- All sequencing data assessing sotrovimab including sequencing of any participant samples that have not been completed to date by September 30, 2021. Provide a frequency table reporting all substitutions detected for all participants at all available timepoints at a frequency >1%.
- All SARS-CoV-2 viral shedding and viral load data including quantitation of viral shedding and viral load for any participant samples that have not been completed to date by June 30, 2021.

XXV. References

Götzinger F, Santiago-Garcia B, Noguera-Julian A, *et al*. COVID-19 in children and adolescents in Europe: a multinational, multicenter cohort study. *Lancet Child Adolesc Health* 4(9), 653-661 (2020). doi: 10.1016/S2352-4642(20)30177-2

Magyarics Z, Leslie F, Bartko J, *et al*. Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study of the Penetration of a Monoclonal Antibody Combination (ASN100) Targeting *Staphylococcus aureus* Cytotoxins in the Lung Epithelial Lining Fluid of Healthy Volunteers. *Antimicrob Agents Chemother* 63(8):e00350-19 (2019). doi: 10.1128/AAC.00350-19.

Pinto D, Park YJ, Beltramello M, *et al.* Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature* **583,** 290–295 (2020). https://doi.org/10.1038/s41586-020-2349-y

Additional references are included in the relevant sections of this review, where applicable.

XXVI. Appendices

1. Fact Sheet for Health Care Providers
2. Fact Sheet for Patients, Parents, and Caregivers

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

Sotrovimab 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.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Healthcare providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

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.

Sotrovimab must be administered after dilution by intravenous (IV) infusion.

Healthcare providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to sotrovimab. See Sections 8 and 9 of the Full EUA

Prescribing Information for reporting instructions below.

- See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.
- The authorized dosage for sotrovimab is one single IV infusion of 500 mg administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 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 administration.
- Administer 500 mg of sotrovimab by IV infusion over 30 minutes.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
- 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

None.

Dosing

Patient Selection and Treatment Initiation

This section provides essential information on 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.

Dosage

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

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on renal impairment, during pregnancy or while lactating *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration

Preparation

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

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

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled infusion bag. Choose one of the following sizes: prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, and
  - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and a fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.
- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**
- Withdraw 8 mL of sotrovimab from one vial and inject into the prefilled infusion bag containing 0.9% Sodium Chloride Injection.
- Discard any product remaining in the vial.
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

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

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, 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 with 0.9% Sodium Chloride Injection.
- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other

medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.

- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

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 use of sotrovimab.

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.

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

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

Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (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 patients *[see Limitations of Authorized Use]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

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 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 medication errors and serious adverse events* potentially related to sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.
    - Submit adverse event reports to FDA MedWatch using one of the following methods:
        - Complete and submit the report online at 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.
- Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)."

*Serious Adverse Events are defined as:

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

5. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of sotrovimab.
6. OTHER REPORTING REQUIREMENTS
   - In addition, please provide a copy of all FDA MedWatch forms to:

     GlaxoSmithKline, Global Safety
     Fax: 919-287-2902
     Email: WW.GSKAEReportingUS@gsk.com

     Or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684) to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Additional information on COVID-19 treatments can be found at 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.[1] 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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[1] 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 use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).
- Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[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 10 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 of sotrovimab in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is a single IV infusion of 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single intravenous infusion over 30 minutes.

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 administration.

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

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyolefin (PO), sterile prefilled infusion bag. Choose one of the following sizes: prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, and
  - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and 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 containing 0.9% Sodium Chloride Injection.
- Discard any product remaining in the vial.
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

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

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, 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 with 0.9% Sodium Chloride Injection.
- Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Storage

This product is preservative-free; therefore, the diluted infusion solution should be administered

immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

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 for intravenous infusion after dilution.

4 CONTRAINDICATIONS

None.

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.

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

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

Authorization.

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, arrythmia (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 patients *[see Limitations of Authorized Use]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The ongoing Phase 1/2/3 double-blind, placebo-controlled, randomized study enrolled 1,057 non-hospitalized patients with COVID-19 (COMET-ICE). The safety of sotrovimab is primarily based on an interim analysis from 868 patients through Day 15 *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

All patients received a single 500-mg infusion of sotrovimab (n = 430) or placebo (n = 438). Two patients experienced treatment interruptions due to infusion site extravasation; infusion was completed for each.

Infusion-related reactions, including immediate hypersensitivity reactions, have been observed in 1% of patients treated with sotrovimab and 1% of patients treated with placebo in COMET-ICE. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate).

One case of anaphylaxis was reported following sotrovimab infusion in a study in hospitalized patients; the infusion was immediately discontinued, and the patient received epinephrine. The event resolved but recurred within 2 hours; the patient received another dose of epinephrine and

improved with no additional reactions. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following sotrovimab infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. Sotrovimab is not authorized for use in patients hospitalized due to COVID-19 *[see Warnings and Precautions (5.1, 5.3)]*.

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

7 PATIENT MONITORING RECOMMENDATIONS

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

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

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

Completion of an FDA MedWatch Form to report all medication errors and serious adverse events* occurring during sotrovimab use and considered to be potentially related to sotrovimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*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;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of sotrovimab, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA 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.

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 should 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:

1. In Section A, Box 1, provide the patient's initials in the Patient Identifier.
2. In Section A, Box 2, provide the patient's date of birth.
3. In Section B, Box 5, description of the event:
   a. Write "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line.
   b. 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.
4. In Section G, Box 1, name and address:
   a. Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
   b. Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

- In addition, please provide a copy of all FDA MedWatch forms to:

  GlaxoSmithKline, Global Safety
  Fax: 919-287-2902
  Email: WW.GSKAEReportingUS@gsk.com
  Or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684) to report adverse events.

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

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.

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 an Fc-enhanced human immunoglobulin G (IgG), 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.

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 based on an allometric scaling approach (which accounted for effect of body weight changes associated with age on clearance and volume of distribution).

11.4 Geriatric Use

Of the 430 patients receiving sotrovimab in COMET-ICE, 20% were 65 years of age and older and 10% were over 70 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 intravenous 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

It is expected that the half-life of sotrovimab is longer than Fc-unmodified IgG due to the LS modification, but data are not available. Based on noncompartmental analysis, the mean (geomean) C_{max} following a 1 hour IV infusion was 137 µg/mL (N = 129, CV% 40), and the mean (geomean) Day 29 concentration was 34 µg/mL (N = 78, CV% 23) from all subjects with an available Day 29 sample.

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, lung 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 consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

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

Table 1: Authentic SARS-CoV-2 and Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Sotrovimab

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

[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

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

[d] Not determined.

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

In COMET-ICE, post-baseline epitope variants were detected in eight participants in the cohort receiving sotrovimab (spike protein substitutions E340K [4 subjects: ≥99.7% allele frequency]; A344V [6.2%]; K356R [7.5%]; S359G [2 subjects: 12.2% and 8.3%]). Of the variants detected at baseline and post-baseline, L335F, G339C, E340A, E340K, R346I, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. E340A and E340K substitutions confer reduced susceptibility to sotrovimab (>100-fold and >297-fold changes in EC_{50} value, respectively). Sotrovimab retains susceptibility against L335F (0.8-fold change in EC_{50} value), G339C (1.2-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 variants is not yet known. Data collection and analysis is still ongoing.

Immune Response Attenuation

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

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.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

Clinical data supporting this EUA are based on an interim analysis from the Phase 1/2/3 COMET-ICE trial (NCT #04545060) that occurred after 583 randomized subjects had the opportunity to complete at least Day 29 of the trial. COMET-ICE is an ongoing, randomized, double-blind, placebo-controlled trial studying sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma, or were 55 years of age and older regardless of comorbidities. The study included symptomatic patients with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 5 days of

enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization and severely immunocompromised patients were excluded from the trial. Subjects were treated with a single 500-mg infusion of sotrovimab (n = 291) or placebo (n = 292) over 1 hour (Intent to Treat [ITT] population at interim analysis 1).

At baseline, the median age was 53 years (range:18 to 96); 22% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 7% Black or African American, 6% Asian, 63% Hispanic or Latino. Fifty-eight percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 42% within 4 to 5 days. The three most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), and diabetes requiring medication (23%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 85% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo (p = 0.002). Table 2 provides the results of the primary endpoint and a key secondary endpoint of COMET-ICE.

Table 2. Interim Efficacy Results in Adults with Mild-to-Moderate COVID-19

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

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

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 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 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

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".

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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Research Triangle Park, NC 27709

STR:1FS-HCP

Issued: May 2021

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 a medicine called **sotrovimab** for the treatment of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking sotrovimab, which you may receive.

Receiving sotrovimab may benefit certain people with COVID-19.

Read this Fact Sheet for information about sotrovimab. Talk to your healthcare provider if you have any questions. It is your choice 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 other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, diabetes, for example, and other conditions including obesity, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?

The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness, including breathing problems, can occur and may cause your other medical conditions to become worse.

What is sotrovimab?

Sotrovimab is an investigational medicine used to treat 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. 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 U.S. Food & Drug Administration (FDA) has authorized the emergency use of sotrovimab for the treatment of COVID-19 under an Emergency Use Authorization (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 receive sotrovimab?
Tell your healthcare provider about all of your medical conditions, including if you:

- 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 receive sotrovimab?

- You will receive 1 dose of sotrovimab.
- Sotrovimab will be given to you through a vein (intravenous or IV infusion) over 30 minutes.
- You will be observed by your healthcare provider for at least 1 hour after you receive 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 infusion with sotrovimab. Tell your healthcare provider right away if you get 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.

The side effects of getting any medicine through a vein 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 been given 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.

It is possible that sotrovimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, sotrovimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

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 not approved 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 to be treated or not to be treated with sotrovimab. Should you decide not to receive sotrovimab, or stop it at any time, it will not change your 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.

How do I report side effects with sotrovimab?

Tell your healthcare provider right away 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 www.sotrovimabinfo.com
- Call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684)
- Visit https://www.covid19treatmentguidelines.nih.gov/
- Visit https://combatcovid.hhs.gov/i-have-covid-19-now/available-covid-19-treatment-options
- Contact your local or state public health department

What is an Emergency Use Authorization (EUA)?

The FDA has made sotrovimab available under an emergency access mechanism called an 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 has not undergone the same type of review as an FDA-approved medicine. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality 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 these medicines, unless terminated or revoked (after which the products may no longer be used).

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Issued: May 2021

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/s/

SUZANNE K STRAYHORN
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KIMBERLY A STRUBLE
05/26/2021 03:56:12 PM

DEBRA B BIRNKRANT
05/26/2021 03:57:35 PM

JOHN J FARLEY
05/26/2021 04:00:48 PM

EMERGENCY USE AUTHORIZATION REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS
ADDENDUM

EUA:	000100
Product:	Sotrovimab
Sponsor:	GlaxoSmithKline Research & Development Limited
Intended Population:	Adults and pediatric patients (12 years of age and older and 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

This addendum references the summary EUA review for sotrovimab for the treatment of mild-to-moderate COVID-19, dated May 26, 2021.

On page 4 of the summary EUA review Section III, Proposed Use and Dosing of the Product Under the EUA, the example provided for obesity or being overweight, one of the medical conditions or factors that may place patients at higher risk for progression to severe COVID-19, was BMI > 30 kg/m^2. However, the intended high risk population, as defined in the sotrovimab Fact Sheet for Healthcare Providers, is BMI > 25 kg/m^2. The corrected example BMI (> 25 kg/m^2) replaces the example BMI provided in the May 26, 2021 summary EUA review.

On page 17 of the summary EUA review Section VIII, Human Clinical Efficacy, the first instance of Table 3 was unintentional and should be removed. The second Table 3 is the correct placement for this table. This correction clarifies the duplication of Table 3, a formatting error, in the May 26, 2021 summary EUA review.

The table on page 25 of the summary EUA review Section IX, Human Clinical Safety, was unintentional and should be removed. Table 8 on page 26, a duplication of the table on page 25, is the correct placement for this table. This correction clarifies the duplication of Table 8, a formatting error, in the May 26, 2021 summary EUA review.

The first paragraph on Page 27 of the summary EUA review Section IX, Human Clinical Safety, may be confusing as written. The corrected text below replaces the paragraph contained in the May 26, 2021 summary EUA review.

Of note, one participant in COMET-ICE was randomized to placebo but received

sotrovimab. This subject is included in the efficacy analysis for the placebo arm and in the safety analysis for the sotrovimab arm. Additionally, due to a data entry error, the Applicant incorrectly included this participant in the placebo arm for the safety analysis (who had been randomized to and received sotrovimab) in the EUA request, resulting in 438 participants in the placebo arm and 430 participants in the sotrovimab arm. This participant was randomized after the data cut-off date for the interim efficacy analysis but in time for the safety analysis. Therefore, this participant incorrectly remains in the placebo arm in the safety review for the EUA**,** but reportedly had no AEs, hospitalizations, or abnormal laboratory or vital signs of concern.

In the summary EUA review, on Page 36 in the Anti-Drug Antibodies subsection and on page 45 in Section XV, Chemistry, Manufacturing and Controls Information, sotrovimab was described as a fully human IgGκ monoclonal antibody. The term “fully” should be removed. This correction replaces the description of sotrovimab in the May 26, 2021 summary EUA review.

On Page 42 of the summary EUA review in the Summary of Data Reviewed for Nonclinical Virology Studies subsection, sotrovimab (S309) should instead be noted as sotrovimab (derived from S309). This correction replaces the notation in all three instances in the May 26, 2021 summary EUA review.

None of these corrections alter the conclusion of the review or alter the information presented in the authorized Facts Sheets for Healthcare Providers or for Patients, Providers, and Caregivers.

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KIMBERLY A STRUBLE
06/15/2021 09:41:22 AM

DEBRA B BIRNKRANT
06/15/2021 11:28:10 AM

JOHN J FARLEY
06/15/2021 11:42:44 AM

EMERGENCY USE AUTHORIZATION REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS
ADDENDUM

EUA:	000100
Product:	Sotrovimab
Sponsor:	GlaxoSmithKline Research & Development Limited
Intended Population:	Adults and pediatric patients (12 years of age and older and 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

This addendum references the summary EUA review for sotrovimab for the treatment of mild-to-moderate COVID-19, dated May 26, 2021.

On page 37 of the summary EUA review Section IX, Human Clinical Safety (Experience in Hospitalized Patients), the p-value provided for the difference between sotrovimab and placebo for the composite safety outcome through Day 5 was 0.42. However, the p-value for this difference is actually 0.22. A p-value of 0.42 instead describes the difference between treatment arms for this outcome through Day 28. This correction replaces the error made in the May 26, 2021 summary EUA review.

This correction does not alter the conclusion of the review or alter the information presented in the authorized Facts Sheets for Healthcare Providers or for Patients, Providers, and Caregivers.

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KIMBERLY A STRUBLE
06/23/2021 09:57:49 AM

DEBRA B BIRNKRANT
06/23/2021 10:04:56 AM

JOHN J FARLEY
06/23/2021 10:11:23 AM