FACT SHEET FOR HEALTHCARE PROVIDERS
INTERIM AUTHORIZATION OF SOTROVIMAB

AUTHORIZED USE

The Health Sciences Authority (HSA) has granted an Interim Authorization to permit the emergency use of the therapeutic product sotrovimab for the treatment of adult patients 18 years of age and above with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. The risk factors include age ≥55 years, diabetes, obesity (BMI >30 kg/m^2), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and/or moderate to severe asthma.

Contraindications

Hypersensitivity to sotrovimab or to any of the excipients [see *Prescribing Information, Product Description (13)*].

Dosing

Dosage

The dosage of sotrovimab is 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of symptom onset. Sotrovimab must be diluted and administered as a single IV infusion over 30 minutes.

Specific Populations

Sotrovimab has not been studied in pediatrics less than 18 years of age, patients with renal impairment, hepatic impairment, pregnant and lactating women [see *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 or 5% Dextrose Injection, and
  - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.

- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and 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.
- Discard any product remaining in the vial.
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 6 hours at room temperature (up to 25°C [up to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

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

- 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.
- 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 and 5% Dextrose Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride or 5% Dextrose to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- 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.

- 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 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.

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.

Side Effects

Adverse events have been reported with sotrovimab *[see 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 their caregiver, information consistent with the "Fact Sheet for Patients and Caregivers" (and provide a copy of the Fact Sheet**)** prior to the patient receiving sotrovimab, including:

- HSA has granted an interim authorization for the use of sotrovimab for the treatment of adult patients 18 years of age and above with COVID-19 who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19.
- The patient or their 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).

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 INTERIM AUTHORIZATION

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

1. Treatment of adult patients 18 years of age and above with COVID-19 who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19.

2. As the healthcare provider, communicate to your patient or their caregiver information consistent with the "Fact Sheet for Patients and Caregivers" prior to the patient receiving sotrovimab.
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. The reports should include the words "Sotrovimab use for COVID-19 under Interim Authorization" in the description section of the report.

   *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;
   - an important medical event that based on appropriate medical judgement may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.
5. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from HSA for information about adverse events and medication errors following receipt of sotrovimab.
6. ADVERSE EVENT REPORING TO GSK SINGAPORE

   Healthcare providers may report adverse events by contacting GSK Singapore at **+65 6232 8338** or sending an email to **sg.drugsafety@gsk.com**

APPROVED AVAILABLE ALTERNATIVES

There is currently no adequate, approved and available alternative to sotrovimab for the treatment of adult patients 18 years of age and above with COVID-19 who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. There may be clinical trials or availability under Interim Authorization of other alternatives.

AUTHORITY FOR ISSUANCE OF THE INTERIM AUTHORIZATION

The Interim Authorization for the abovementioned emergency therapeutic product by the Health Sciences Authority (HSA) of Singapore is made under Regulations 60A(4) and (5)(b) of the

Health Product (Therapeutic Products) Regulations. HSA issued this Interim Authorization based on GlaxoSmithKline's request and submitted data.

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 adults with COVID-19 who do not require oxygen supplementation in certain at-risk patients as specified in this Fact Sheet.

CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

END SHORT VERSION FACT SHEET

Long Version Prescribing Information Begins on Next Page

PRESCRIBING INFORMATION

PRESCRIBING INFORMATION: CONTENTS*

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

1 AUTHORIZED USE

Sotrovimab is authorized for use under Interim Authorization for the treatment of adult patients 18 years of age and above with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. The risk factors include age ≥55 years, diabetes, obesity (BMI >30 kg/m^2), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and/or moderate to severe asthma *[see Clinical Trial Results and Supporting Data for Interim Authorization (18)]*.

- 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 Dosage

The dosage of sotrovimab is 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 5 days of symptom onset. Sotrovimab must be diluted and administered as a single IV infusion over 30 minutes.

2.2 Specific Populations

Pregnancy or Lactation

Sotrovimab has not been studied in pregnant and lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use

Sotrovimab has not been studied in pediatrics less than 18 years of age *[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)]*.

Hepatic Impairment

No dosage adjustment is expected to be required in patients with hepatic impairment *[see Use in Specific Populations (11.6)]*.

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 or 5% Dextrose Injection, and
  - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.
- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**
- Withdraw 8 mL of sotrovimab from one vial and inject into the prefilled infusion bag.
- Discard any product remaining in the vial.
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 6 hours at room temperature (up to 25°C [up to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

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

- 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.

- 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 and 5% Dextrose Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride or 5% Dextrose to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- 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.
- 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 6 hours at room temperature (up to 25°C [up to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

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 IV infusion after dilution.

4 CONTRAINDICATIONS

Hypersensitivity to sotrovimab or to any of the excipients [see *Prescribing Information, Product Description (13)*].

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.

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.

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 based on an analysis from 1049 patients *[see Clinical Trial Results and Supporting Data for Interim Authorization (18)]*.

All patients received a single 500-mg infusion of sotrovimab (n = 523) or placebo (n = 526). 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).

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received sotrovimab at the authorized dose *[see Warnings and Precautions (5.1)]*:

- hypersensitivity reactions (n = 9, 2%)

In COMET-ICE, hypersensitivity reactions of Grade 1 (mild) or Grade 2 (moderate) were reported (9 patients treated with sotrovimab; 5 patients treated with placebo). None of the reactions in either arm led to pausing or discontinuation of the infusions.

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.

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

6.2 Post-Authorization Experience

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

Immune System Disorders

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

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during 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)]*.

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.

*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.

9 ADVERSE EVENT REPORTING TO GSK SINGAPORE

Healthcare providers may report adverse events by contacting GSK Singapore at +65 6232 8338 or sending an email to sg.drugsafety@gsk.com

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. Concomitant administration of sotrovimab with COVID-19 vaccines has not been studied.

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.

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 engineered 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.

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.

11.3 Pediatric Use

The safety and effectiveness of sotrovimab have not been assessed in pediatric patients.

11.4 Geriatric Use

Of the 528 patients receiving sotrovimab in COMET-ICE, 20% were 65 years of age and older and 11% were over 70 years of age. Based on preliminary population pharmacokinetic (PK) analyses, there was no difference in the PK of sotrovimab in geriatric patients compared to younger patients.

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. Furthermore, based on preliminary population PK analyses, there was no difference in PK of sotrovimab in patients with mild, moderate, or severe renal impairment.

11.6 Hepatic Impairment

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. Sotrovimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, therefore changes in hepatic function are not expected to have any effect on the elimination. Based on preliminary population PK analyses, there was no difference in PK of sotrovimab in patients with mild-to-moderate elevations in alanine aminotransferase (1.25 to <5 x ULN).

12 OVERDOSAGE

There is no human experience of acute overdosage with sotrovimab.

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

13 PRODUCT DESCRIPTION

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

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

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

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

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

14.2 Pharmacokinetics

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. The geometric mean C_{max} following a 1 hour IV infusion was 117.6 µg/mL (N = 290, CV% 46.5), and the geometric mean Day 29 concentration was 24.5 µg/mL (N = 372, CV% 42.4) from all subjects with an available Day 29 sample.

Distribution

Based on noncompartmental analysis, the mean steady-state volume of distribution of sotrovimab was 8.1 L.

Metabolism

Sotrovimab is an engineered human IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Based on noncompartmental analysis, the mean systemic clearance (CL) was 125 mL/day with a median terminal half-life of approximately 49 days.

Specific Populations

Based on preliminary population PK analyses, the PK of sotrovimab were not affected by age, sex, or renal impairment; body weight and BMI were significant covariates.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

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

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

Antibody Dependent Enhancement (ADE) of Infection

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

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, total viral RNA in the lungs, or infectious virus levels based on $TCID_{50}$ measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab. Prescribing healthcare providers should 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 K356T, 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), K356T (5.90), 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 B.1.1.7 (Alpha, UK origin: H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H; 2.3-fold change in EC_{50} value), B.1.351 (Beta, South Africa origin: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V; 0.6-fold change in EC_{50} value), P.1 (Gamma, Brazil origin: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F; 0.35-fold change in EC_{50} value), B.1.427/B.1.429 (Epsilon, California origin: S13I, W152C, L452R, D614G; 0.7-fold change in EC_{50} value), B.1.526 (Iota, New York origin: L5F, T95I, D253G, E484K, D614G, A701V; 0.6-fold change in EC_{50} value), B.1.617.1 (Kappa, India origin: T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H; 0.7-fold change in EC_{50} value), B.1.617.2 (Delta, India origin: T19R, G142D, E156G, F157-, R158-, L452R, T478K, D614G, P681R, D950N; 1-fold change in EC_{50} value), AY.1 (Delta Plus, India origin: T19R, T95I, G142D, E156G, F157-, R158-, W258L, K417N, L452R, T478K, D614G, P681R, D950N; 1.1-fold change in EC_{50} value), AY.2 (Delta Plus, India origin: T19R, V70F, G142D, E156G, F157-, R158-, A222V, K417N, L452R, T478K, D614G, P681R, D950N; 1.3-fold change in EC_{50} value), C.37 (Lambda, Peru origin: G75V, T76I, del246-252, L452Q, F490S, T859N; 1.5-fold change in EC_{50} value), and B.1.621 (Mu, Colombia origin: T95I, Y144T, Y145S, ins146N, R346K, E484K, N501Y, D614G, P681H, D950N; 1.3-fold change in EC_{50} value) variant spike proteins (Table 1). Microneutralization data using authentic SARS-CoV-2 variant virus indicate that sotrovimab retains activity against the B.1.1.7 (Alpha, UK origin: 3-fold change in EC_{50} value), B.1.351 (Beta, South Africa origin: 1.2-fold change in EC_{50} value), P.1 (Gamma, Brazil origin: 1.6-fold change in EC_{50} value), B.1.617.1 (Kappa, India origin; 0.9-fold change in EC_{50} value), and B.1.617.2 (Delta, India origin; 0.4-fold change in EC_{50} value) variants (Table 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 (Alpha, UK origin)	N501Y	No change[b]	No change[b]
B.1.351 (Beta, South Africa origin)	K417N + E484K + N501Y	No change[b]	No change[b]
P.1 (Gamma, Brazil origin)	K417T + E484K + N501Y	No change[b]	No change[b]
B.1.427/B.1.429 (Epsilon, California origin)	L452R	No change[b]	nd[c]
B.1.526 (Iota, New York origin)[d]	E484K	No change[b]	nd[c]
B.1.617.1 (Kappa, India origin)	L452R + E484Q	No change[b]	No change[b]
B.1.617.2 (Delta, India origin)	L452R + T478K	No change[b]	No change[b]
AY.1 (Delta Plus, India origin)	L452R + T478K + K417N	No change[b]	nd[c]
AY.2 (Delta Plus, India origin)	L452R + T478K + K417N	No change[b]	nd[c]
C.37 (Lambda, Peru origin)	G75V, T76I, del246-252, L452Q, F490S, T859N	No change[b]	nd[c]
B.1.621 (Mu, Colombia origin)	T95I, Y144T, Y145S, ins146N, R346K, E484K, N501Y, D614G, P681H, D950N	No change[b]	nd[c]

[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 determined.

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

Limited nucleotide sequencing data from a total of 539 COMET-ICE participants indicated that 36 participants (16 treated with placebo and 20 treated with sotrovimab) carried the B.1.1.7 (Alpha, UK origin) variant. Four participants (2 treated with placebo and 2 treated with sotrovimab) carried the N501Y substitution. Thirty-one participants (19 treated with placebo and 12 treated with sotrovimab) carried the B.1.427/B.1.429 (Epsilon, California origin) variant. Eight additional participants carried the L452R substitution (6 treated with placebo and 2 treated with sotrovimab). Eleven participants carried the P.1 (Gamma, Brazil origin) variant (3 treated with placebo and 8 treated with sotrovimab). Three participants carried the B.1.526 (Iota, New York origin) variant with the E484K substitution (2 treated with placebo and 1 treated with sotrovimab), while 9 participants (4 treated with placebo and 5 treated with sotrovimab) carried the S477N substitution that has been associated with the B.1.526 (Iota, New York origin) variant. Additionally, 10 participants carried the E484K substitution (4 treated with placebo and 6 treated with sotrovimab), 2 carried the S494P substitution (1 treated with placebo and 1 treated with sotrovimab), and 3 carried the S494P substitution with the N501Y substitution (2 treated with placebo and 1 treated with sotrovimab). Two participants in the group receiving sotrovimab (1carrying the B.1.427/B.1.429 [Epsilon, California origin] variant and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. Four participants in the placebo group (2 carrying the E484K substitution, 1 carrying the P.1 [Gamma, Brazil origin] variant, and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. None of the participants with currently available baseline sequences carried the full complement of mutations characteristic of the B.1.351 (Beta, South Africa origin) or B.1.617 (Delta, India origin) variants. In COMET-ICE, post-baseline epitope substitutions were detected in 20 participants in the cohort receiving sotrovimab (spike protein substitutions E340K [5 subjects: 8.0% to 99.9% allele frequency]; A344V [6.2%]; R346G [5.2%]; K356R [7.5%]; E340A [99.0%]; E340V [73.1%]; P337L/E340K [49.4%/54.8%]; S359G [2 subjects: 12.2% and 8.3%]); C361T [7 subjects, 5.0% to 15.7%]. Of the substitutions detected at baseline and post-baseline, L335F, L335S, P337L, G339C, E340A, A344V, E340K, R346I, R346G, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. P337L, E340A and E340K substitutions confer reduced susceptibility to sotrovimab (>180-fold, >100-fold, and >297-fold changes in EC_{50} value, respectively). Sotrovimab retains activity against L335F (0.8-fold change in EC_{50} value), L335S (0.9-fold change in EC_{50} value), G339C (1.2-fold change in EC_{50} value), A344V (1.1-fold change in EC_{50} value), R346I (1.7-fold change in EC_{50} value), R346G (0.9-fold change in EC_{50} value), K356N (1.1-fold change in EC_{50} value), K356R (0.8-fold change in EC_{50} value), R357I (1-fold change in EC_{50} value), I358V (0.7-fold change in EC_{50} value), and S359G (0.8-fold change in EC_{50} value) substitutions. The clinical impact of these substitutions is not yet known. Data collection and analysis is still ongoing.

Immune Response Attenuation

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

16 NONCLINICAL TOXICOLOGY

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

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

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

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

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

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

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

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR INTERIM AUTHORIZATION

Clinical data supporting this Interim Authorization are based on an analysis of 1057 randomized subjects from the Phase 1/2/3 COMET-ICE trial (NCT #04545060). 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 randomized to receive a single 500-mg infusion of sotrovimab (n = 528) or placebo (n = 529) over 1 hour (Intent to Treat [ITT] population at Day 29).

At baseline, the median age was 53 years (range: 17 to 96); 20% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 8% Black or African American, 4% Asian, 65% Hispanic or Latino. Fifty-nine percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 41% within 4 to 5 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medication (22%), and moderate-to-severe asthma (17%).

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 79% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo ($p < 0.001$). Tables 2 and 3 provide the results of the primary endpoint and key secondary endpoints of COMET-ICE.

Table 2. Efficacy Results in Adults with Mild-to-Moderate COVID-19 at Day 29

	Sotrovimab n = 528	**Placebo n = 529**
Primary Endpoint[a]		
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, %)	6 (1%)	30 (6%)
Adjusted Relative Risk Reduction (95% CI)	79% (50%, 91%)	
p-value	<0.001	
Secondary Endpoints		
Progression of COVID-19 as defined by visit to a hospital emergency room for management of illness or hospitalization for acute management of illness or death from any cause (Day 29)		
Proportion (n, %)	13 (2%)	39 (7%)
Adjusted Relative Risk Reduction (95% CI)	66% (37%, 81%)	
p-value	<0.001	
Progression to develop Severe and/or Critical Respiratory COVID-19 (Day 29)[b]		
Proportion (n, %)[c]	7 (1%)	28 (5%)
Adjusted Relative Risk Reduction (95% CI)	74% (41%, 88%)	
p-value	0.002	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	2 (<1%)
Mean Change in FLU-PRO Plus[d] total score (AUC through Day 7)		
n	412	399
Mean (95% CI)	-3.05 (-3.27, -2.83)	-1.98 (-2.20, -1.76)
Difference (95% CI)	-1.07 (-1.38, -0.76)	
p-value	<0.001	

[a] No subjects required an intensive care unit (ICU) stay in the group receiving sotrovimab versus 9 subjects in the group receiving placebo.

[b] Defined as the requirement for supplemental oxygen (low flow nasal cannula/face mask, high flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]).

[c] No subjects required use of high flow oxygen, non-rebreather mask, or mechanical ventilation in the group receiving sotrovimab versus 14 subjects in the group receiving placebo.

[d] FLU-PRO: COVID-19 adapted influenza patient-reported outcomes questionnaire.

Table 3. Summary of SARS-CoV-2 Viral Load in Nasal Secretions by qRT-PCR on Day 8 (Virology Population)

	Sotrovimab	Placebo
Baseline (log 10 copies/mL)		
n	369	385
Mean (standard deviation)	6.535 (1.6331)	6.645 (1.6632)
Day 8 (log 10 copies/mL)		
n[a]	316	323
Least Squares Mean (standard error)	3.968 (0.0593)	4.219 (0.0589)
Day 8 Change from Baseline (log 10 copies/mL)		
Least Squares Mean (standard error)	-2.610 (0.0593)	-2.358 (0.0589)
95% CI	-2.726, -2.493	-2.474, -2.243
Least Squares Mean Difference (standard error)	-0.251 (0.0835)	
95% CI	-0.415, -0.087	
p-value	0.003	

[a] Number of participants with available data at Day 8.

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.

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

20 PATIENT COUNSELING INFORMATION

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

21 CONTACT INFORMATION

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