ANNEX I

CONDITIONS OF USE, CONDITIONS FOR DISTRIBUTION AND PATIENTS TARGETED AND CONDITIONS FOR SAFETY MONITORING ADRESSED TO MEMBER STATES

FOR

UNAUTHORISED PRODUCT SOTROVIMAB

AVAILABLE FOR USE

1. MEDICINAL PRODUCT FOR USE

- **Name of the medicinal product for Use: Sotrovimab**
- **Active substance(s): Sotrovimab**
- **Pharmaceutical form: Concentrate for solution for infusion**
- **Route of administration: Intravenous infusion**
- **Strength: 500 mg (each vial contains sotrovimab in 8 mL (62.5 mg/mL)).**

2. NAME AND CONTACT DETAILS OF THE COMPANY

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3. TARGET POPULATION

For the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19.

Risk factors may include but are not limited to:
• Advanced age
• Obesity
• Cardiovascular disease, including hypertension
• Chronic lung disease, including asthma
• Type 1 or type 2 diabetes mellitus
• Chronic kidney disease, including those on dialysis
• Chronic liver disease
• Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, and prolonged use of immune-weakening medications.

4. CONDITIONS FOR DISTRIBUTION

Medicinal product subject to medical prescription.

5. CONDITIONS OF USE

5.1 Posology

- **Dosing recommendations**

The recommended dose in adults and adolescents (aged 12 years and over and weighing at least 40 kg) is a single 500 mg intravenous (IV) diluted infusion.

- **Treatment duration and monitoring**

Single dose.

Patients should be monitored during and for at least 1 hour after infusion is complete.

- **Specific populations**

Paediatric Use
No dose adjustment is recommended in patients who are 12 years of age and older and weighing at least 40 kg.

No data are available in children aged less than 12 years old and weighing less than 40 kg.

Geriatric use
The pharmacokinetics of sotrovimab have not been quantified in patients aged 65 years or older. However, a dose adjustment is not considered necessary.

Renal impairment
Sotrovimab has not been studied in patients with renal impairment. However, no dose adjustment is considered necessary.

Hepatic impairment
It is unknown whether a dose adjustment is needed in patients with hepatic impairment. No formal studies have been conducted.

- **Method of administration**

For intravenous use.
Sotrovimab must be diluted prior to administration.
Sotrovimab should be administered as a single intravenous (IV) infusion over 30 minutes. Patients should be monitored during and for at least 1 hour after infusion is complete.
Sotrovimab must not be administered as an intravenous push or bolus.
Sotrovimab should be prepared by a qualified healthcare professional using aseptic technique.

Preparation for Dilution
1. Remove one vial of sotrovimab from the refrigerator (2°C to 8°C). Allow the vial to equilibrate to ambient room temperature, protected from light, for approximately 15 minutes.
2. Visually inspect the vial to ensure it is free from particulate matter and that there is no visible damage to the vial. If the vial is identified to be unusable, discard and restart the preparation with a new vial.
3. Gently swirl the vial several times before use without creating air bubbles. Do not shake or vigorously agitate the vial.

Dilution Instructions
1. Withdraw 8 mL from an infusion bag containing 50 mL or 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.
2. Withdraw 8 mL from the vial of sotrovimab.
3. Inject the 8 mL of sotrovimab into the infusion bag via the septum.
4. Discard any unused portion left in the vial as the product contains no preservative. The vial is single-use only and should only be used for one patient.
5. Prior to the infusion, gently rock the infusion bag back and forth 3 to 5 times. Do not invert the infusion bag. Avoid forming air bubbles.

The diluted solution of sotrovimab is intended to be used immediately. If immediate administration is not possible, the diluted solution may be stored for up to 4 hours at room temperature (20°C to 25°C) or refrigerated up to 24 hours (2°C to 8°C).

Administration Instructions
1. Attach an infusion set to the infusion bag using standard bore tubing. The intravenous dosing solution is recommended to be administered with a 0.2 µm in-line filter.
2. Prime the infusion set with sodium chloride 9 mg/mL (0.9%) solution for injection.
3. Administer as an IV infusion for 30 minutes at room temperature.

5.2 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 5.11).

Previous anaphylaxis to a monoclonal antibody.

5.3 Special warnings and precautions for use

Hypersensitivity
Anaphylaxis has been reported following infusion of sotrovimab in a study in hospitalised patients. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration and initiate appropriate therapy.

Infusion-related reactions (IRRs)
IRRs have been reported with sotrovimab in the COMET-ICE study (see section 6), and across the ongoing clinical program. All IRRs from the COMET-ICE study were mild to moderate. If an IRR occurs, consider slowing or stopping the infusion along with appropriate supportive care.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

5.4 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have 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.

5.5 Pregnancy and lactation

- **Pregnancy**

There are no or limited amount of data from the use of sotrovimab in pregnant women. Animal studies with respect to reproductive toxicity have not been performed. In a cross-reactive binding assay using a protein array enriched for human embryofoetal proteins, no off-target binding was detected. Since sotrovimab is a human immunoglobulin G (IgG), it has the potential for placental transfer from the mother to the developing foetus. The potential treatment benefit or risk from placental transfer of sotrovimab to the developing foetus is not known.

Sotrovimab should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

- **Lactation**

There is no available data on the excretion of sotrovimab in human milk. A risk to the newborns/infants cannot be excluded. Human IgGs are known to be excreted in breast milk.

A decision must be made whether to discontinue breast-feeding or to abstain from sotrovimab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

- **Fertility**

No fertility studies have been performed.

5.6 Incompatibilities

This medicinal product must not be mixed or administered simultaneously with other medicinal products in the same dedicated line except those mentioned in section 5.1

5.7 Overdose

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

5.8 Shelf life

Unopened vials
1 year

Diluted solution for infusion
The diluted solution is intended to be used immediately. If immediate administration is not possible, the diluted solution may be stored for up to 4 hours at room temperature (20°C to 25°C) or refrigerated up to 24 hours (2°C to 8°C).

5.9 Storage conditions

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 5.8.

5.10 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

5.11 List of excipients

Histidine
Histidine monohydrochloride
Sucrose
Polysorbate 80
Methionine

6. OTHER INFORMATION

- **Undesirable effects**

Summary of the safety profile
The safety of sotrovimab was evaluated in an interim analysis from an ongoing placebo-controlled randomised study in 868 non-hospitalised patients with COVID-19 (COMET-ICE) (see section 6). All patients received one IV infusion of sotrovimab 500 mg or matching placebo. Adverse events reported in COMET-ICE are presented in table 1 below (≥1% in either arm). Two patients experienced treatment interruptions, both due to infusion site extravasation; infusion was completed for each. All IRRs including hypersensitivity reactions were mild and moderate (see section 5.3). No events consistent with antibody dependent enhancement (ADE) were observed. The only event to occur with a frequency of ≥1% in the sotrovimab arm was diarrhoea (<1% in placebo group). All other adverse events with a frequency of ≥1% occurred in the placebo arm.

Table 1 Incidence of Adverse Events as Reported in at Least 1% of Patients in Either Treatment Group in the COMET-ICE Trial

	Sotrovimab 500 mg (N=430)	**Placebo (N=438)**
COVID-19 pneumonia[a]	4 (<1%)	14 (3%)
Headache	3 (<1%)	9 (2%)
Pneumonia	0	7 (2%)
Dehydration	0	5 (1%)
Dyspnoea	2 (<1%)	5 (1%)
Nausea	4 (<1%)	5 (1%)
Diarrhoea	6 (1%)	3 (<1%)

[a]As recorded by the investigator.

In COMET-ICE, hospitalisations including those due to progression of COVID-19 were included as serious adverse events (SAEs). SAEs were reported in 7/430 (2%) in the group receiving sotrovimab and in 26/438 (6%) in the group receiving placebo. Diverticulitis was reported in 2 subjects in the group receiving sotrovimab, each with a prior history of diverticulitis and obesity. COVID-19 pneumonia, pneumonia and/or dehydration were reported in 2 or more subjects in the group receiving placebo. Single reports of the following in the sotrovimab arm included: non-small cell lung cancer, small intestinal obstruction, hyperglycemia, and diabetes mellitus. Single reports of the following were noted in the placebo arm: hypovolemia, acute respiratory failure, dyspnea, hypoxia, pulmonary embolism, respiratory distress, obstructive pancreatitis, oxygen saturation decreased, and acute kidney injury. There was one SAE considered to be possibly related to study drug by the investigator, which was an event of COVID-19 pneumonia occurring in the group receiving placebo.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

- **Summary of relevant pharmacological properties**

Mechanism of action
Sotrovimab is a recombinant engineered human IgG1 monoclonal antibody that binds to a highly conserved epitope on the spike (S) protein receptor binding domain (RBD) of SARS-CoV-2 with high affinity (dissociation constant Kd = 0.21 nM), but does not compete with human angiotensin-converting enzyme 2 receptor binding. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extends antibody half-life, but does not impact wild-type Fc-mediated effector functions in cell culture.

Antiviral activity
Sotrovimab neutralized SARS-CoV-2 virus *in vitro* (EC_{50} 100.1 ng/mL), and *in vivo* (≥5 mg/kg in SARS-CoV-2 infected hamsters) and effectively neutralized pseudo-typed virus containing the SARS-CoV-2 spike.

Sotrovimab demonstrated *in vitro* 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 ADCC and ADCP in cell-based assays.

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 substitution emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay.

A pseudotyped VPL assessment in cell culture showed that the epitope 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 (7.50), and P337T (5.438). The presence of the highly prevalent D614G variant, either alone or in combination, did not alter neutralization of sotrovimab. Pseudotyped VLP *in vitro* assessments indicate that sotrovimab retains activity against the UK (B.1.1.7; 2.30-fold change in EC_{50} value); South Africa (B.1.351; 0.60-fold change in EC_{50} value); Brazil (P.1; 0.35-fold change in EC_{50} value); and California (B.1.427/B.1.429; 0.70-fold change in EC_{50} value) variant spike proteins. Microneutralization data from authentic SARS-CoV-2 variant virus also 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 (1.4-fold change in EC_{50} value) variants.

In the COMET-ICE clinical trial, post-baseline epitope variants were detected in eight participants in the sotrovimab arm. The clinical impact of these variants is not yet known. Data collection and analysis are still ongoing.

- **Summary of relevant Clinical properties**

Clinical efficacy
Study 214367 (COMET-ICE) was a Phase II/III randomised, double-blind, placebo-controlled study which evaluated sotrovimab as treatment for COVID-19 in non-hospitalised patients at high risk of medical complications of the disease. Patients included were aged 18 years and older with at least 1 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 aged 55 years and older. The study included patients with symptoms for ≤ 5 days, oxygen saturation in room air ≥94% and SARS-CoV-2 infection, as confirmed by local laboratory tests and/or point of care tests. Patients with severe COVID-19 requiring supplemental oxygen or hospitalisation were excluded from the trial. Patients 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).

A total of 46% of randomised participants were male. The median age of the overall randomised population was 53 years (range: 18-96). A total of 22% of participants were aged 65 years or older and 11% were over 70. The majority of participants were of White race (87%); 7% were Black or African American and 6% were Asian. The ethnicity of the majority of subjects was Hispanic or Latino (63%). 58% of participants received the sotrovimab or placebo within 3 days of COVID-19 symptoms onset and 42% within 4-5 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 treatment arms.

The efficacy of sotrovimab was evaluated in an interim analysis of the ongoing COMET-ICE study. The primary endpoint, progression of COVID-19 at Day 29, was reduced by 85% compared with placebo (adjusted relative risk reduction) in recipients of sotrovimab vs placebo (p=0.002). Table 2 below,

provides the results of the primary endpoint and key secondary endpoints of COMET-ICE.

Table 2: Results of interim analysis of primary and secondary endpoints in the ITT population (COMET-ICE)

	Sotrovimab (500 mg IV infusion) N=291	Placebo N=292
Primary endpoint		
Progression of COVID-19 as defined by hospitalisation for >24 hours for acute management of any illness or death from any cause (Day 29)		
Proportion (n, %) [b]	3 (1%)	21 (7%)
Adjusted relative risk reduction (97.24% CI)	85% (44%, 96%)	
p-value	0.002	
Secondary endpoints		
Progression of COVID-19 as defined by visit to a hospital emergency room for management of illness or hospitalisation for acute management of illness or death from any cause (Day 29)		
Proportion (n, %)	6 (2%)	28 (10%)
Progression to develop Severe and/or Critical Respiratory COVID-19 (Day 29) [a]		
Proportion (n, %) [c]	2 (<1%)	19 (7%)
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	1 (<1%)

[a] Progression to develop severe and/or critical respiratory COVID-19 defined as the requirement for supplemental oxygen (low flow nasal cannulae/face mask, high flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)).
[b] No participants required intensive care unit (ICU) stay in the sotrovimab arm versus five participants in the placebo arm.
[c] No participants required use of high flow oxygen, non-rebreather mask or mechanical ventilation in the sotrovimab arm versus seven participants in the placebo arm.

7. CONDITIONS FOR SAFETY MONITORING

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 6 for how to report adverse reactions.

8. DATE OF CHMP OPINION