Module 1.8.2
European Union Risk Management Plan (EU-RMP) for Xevudy (Sotrovimab)

RMP version to be assessed as part of this application	
RMP Version number	1.0
Data lock point for this RMP	27-April-2021
Date of final sign off	10 December 2021

Rationale for submitting an updated RMP

This is an initial EU RMP in support of first marketing authorization application for Sotrovimab.

Summary of significant changes in this RMP:

Not applicable-Initial RMP

PART	MODULE	Changes made in EU-RMP

Other RMP versions under evaluation: Not applicable

RMP Version number	Submitted on	Procedure number

Details of the currently approved RMP

Version number	Approved with procedure	Date of approval (opinion date)
1.0	EMEA/H/C/005676	16 December 2021

QPPV Name	Dr. Jens-Ulrich Stegmann, MD
QPPV Signature	

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) (INN or common name)	Sotrovimab
Pharmacotherapeutic group(s) (ATC Code)	TBD
Marketing Authorisation Holder	GlaxoSmithKline Trading Services Ltd 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Xevudy
Marketing authorisation procedure	Centralized Procedure
Brief description of the product	Sotrovimab is a human monoclonal antibody (mAb) (IgG1, kappa) which binds to a highly conserved epitope on the spike protein receptor binding domain (RBD) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Sotrovimab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.
Reference to the Product Information	The product information is located in the Module 1.3.1
Indication(s) in the EEA	Current: 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 increased risk of progressing to severe COVID-19.

Dosage in the EEA	Current: The recommended dose is a single 500 mg intravenous infusion administered following dilution.
Pharmaceutical form(s) and strengths	Current: Concentrate for solution for infusion Each vial contains 500 mg of Sotrovimab in 8 mL (62.5 mg/mL). A clear, colourless or yellow to brown solution free from visible particles, with a pH of approximately 6 and an osmolality of approximately 290 mOsm/kg.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations

ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	adverse events of special interest
ARDS	Acute respiratory distress syndrome
AE	Adverse Event
BMI	Body Mass Index
CFR	Case fatality rates
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Coronavirus Disease 2019
COVID-PR	COVID-19 International Drug Pregnancy Registry
CSI	Core Safety Information
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUA	Emergency Use Authorization
EV	EudraVigilance
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HSR	Hypersensitivity reactions
HIV	Human immunodeficiency virus
ICH	International Conference of Harmonization
IDMC	Independent Data Monitoring Committee
IgG1	Immunoglobulin G1
IM	Intramuscular
IRR	Infusion related reactions
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
IV	Intravenous
KD	Kawasaki disease
MAA	Marketing Authorization Application
mAb	Monoclonal Antibody
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MIS-A	Multisystem Inflammatory Syndrome in Adults
MIS-C	Multisystem Inflammatory Syndrome in Children
NPIs	Non-pharmaceutical interventions
NYHA	New York Heart Association
PBRER	Periodic Benefit Risk Evaluation Report
PHEIC	Public Health Emergency of International Concern
PIL	Patient Leaflet
PIP	Paediatric Investigation Plan

PK	Pharmacokinetic
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
PT	Preferred term
RMM	Risk Minimization Measure
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of product Characteristics
SMQ	Standard MedDRA Query
TSS	Toxic Shock Syndrome
VLP	Virus-like particle
VOCs	Variants of concern
WHO	World Health Organization

Trademark Information

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Xevudy

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PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

SI.1 Indication

Sotrovimab is indicated 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 increased risk of progressing to severe COVID-19.

Incidence and Prevalence

On the 31st December 2019 a cluster of 'pneumonia of unknown cause', centred on the city of Wuhan in the Hubei province of China, was reported to the China Country Office of the World Health Organisation (WHO) (ProMed 2019). The aetiological agent, a novel coronavirus, was subsequently named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease it caused termed coronavirus disease 2019 (COVID-19). Infection spread rapidly around the globe, facilitated by air travel and a high level of transmissibility, and the WHO declared a public health emergency of international concern (PHEIC) on 30th January 2020 and a global pandemic on 11th March 2020. In late 2020, it was identified that viral variants had emerged. Variants of concern (VOCs) are those where there is clear evidence indicating a significant impact on transmissibility, severity and/or immunity. As of June 2021, circulating VOCs in the EU/EAA region include the Alpha [UK] (B.1.1.7), Beta [South Africa] (B.1.351), Gamma [Brazil] (P.1), and Delta [India] (B.1.617) [ECDC, 2021].

As of 01 June 2021, approximately 173 million cases and 3.7 million deaths from COVID 19 were reported globally [Johns Hopkins, 2021]. Approximately 32 801 529 cases and 729 953 deaths (as of 11 June 2021) were reported in the European Union (EU)/European Economic Area (EEA) [ECDC, 2021]. Initially, incidence data were focused in Asia, with the index country of China accounting for the majority (93%) of the 88,000 cases reported in January & February 2020 [ECDC, 2021]. By March, however, the infection had spread to Europe and North America. From mid-March 2020, the incidence in the EU/EAA region started to rise (Figure 1), and non-pharmaceutical interventions (NPIs) such as lockdowns were implemented [ECDC, 2021]. By the end of April 2020, the initial wave had exceeded its peak and a decreasing incidence was generally reported over the northern hemisphere summer. However, from the end of August, an increasingly substantial rise in COVID-19 cases was observed until November (peak incidence: 581 per 100,000 persons) [ECDC, 2021]. A third wave set in around March 2021, reaching its peak in mid-April and has been since declining. As of 30 May 2021, the 14-day case notification rate for the EU/EEA was 111 (country range: 10–312) per 100 000 population (based on data collected by ECDC from official national sources in 28 countries) [ECDC, 2021]. The incidence in the first versus the subsequent peaks are likely heavily influenced by the change in testing strategies over the course of the pandemic.

Figure 1 14-Day COVID-19 Case and Death Notification Rates in the EU/EAA

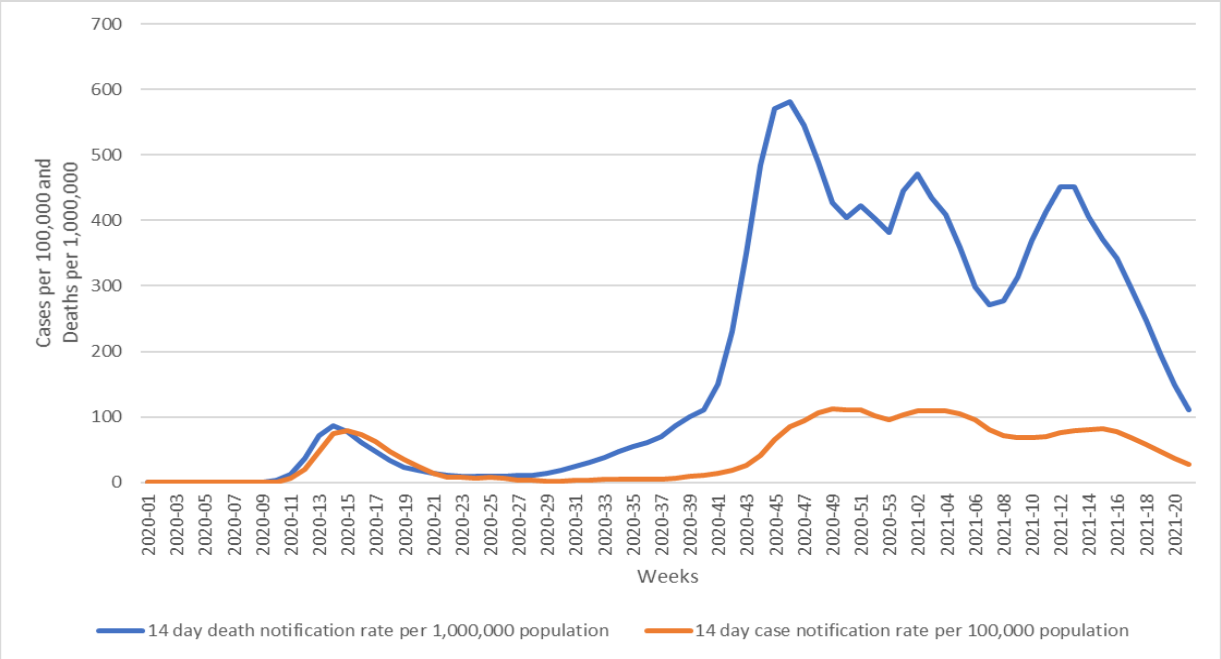

Figure 1 is from ECDC, 2021. Figure produced 30 May 2021. Source: Epidemic Intelligence, national weekly data

SI.1.1 Demographics of the population in the authorised indication and risk factors for the disease:

Non-Hospitalized Patients

Age & Sex

Age-sex distributions of cases in the EU/EAA region reported for non-hospitalized (mild severity) hospitalized and severely hospitalized cases are shown in Figure 2 [ECDC, 2021]. Non-hospitalized cases tend to be females and are younger than those who are hospitalized or hospitalized with severe disease. In a European multi-centre study by Lechien, 2020, the mean age of patients with mild-to-moderate COVID-19 (consisting of non-hospitalized [92%] and hospitalized without intensive care [8%] patients) was 37 years, which is in line with estimates from the literature in US and China non-hospitalized populations [Hsu, 2020; Lechien, 2020; Tenforde, 2020; van Gerwen, 2020; Xu, 2020]. In the same study, Lechien, 2020 reported that 67% of patients with mild-to-moderate COVID-19 were female. Similarly, other studies in the US and China have also observed a higher proportion of females to males in the outpatient setting [Bergquist, 2020; Hsu, 2020; Tenforde, 2020; van Gerwen, 2020; Xu, 2020].

Figure 2 Age-sex distribution of COVID-19 Cases at different levels of severity and by time period, pooled data for EU/EAA

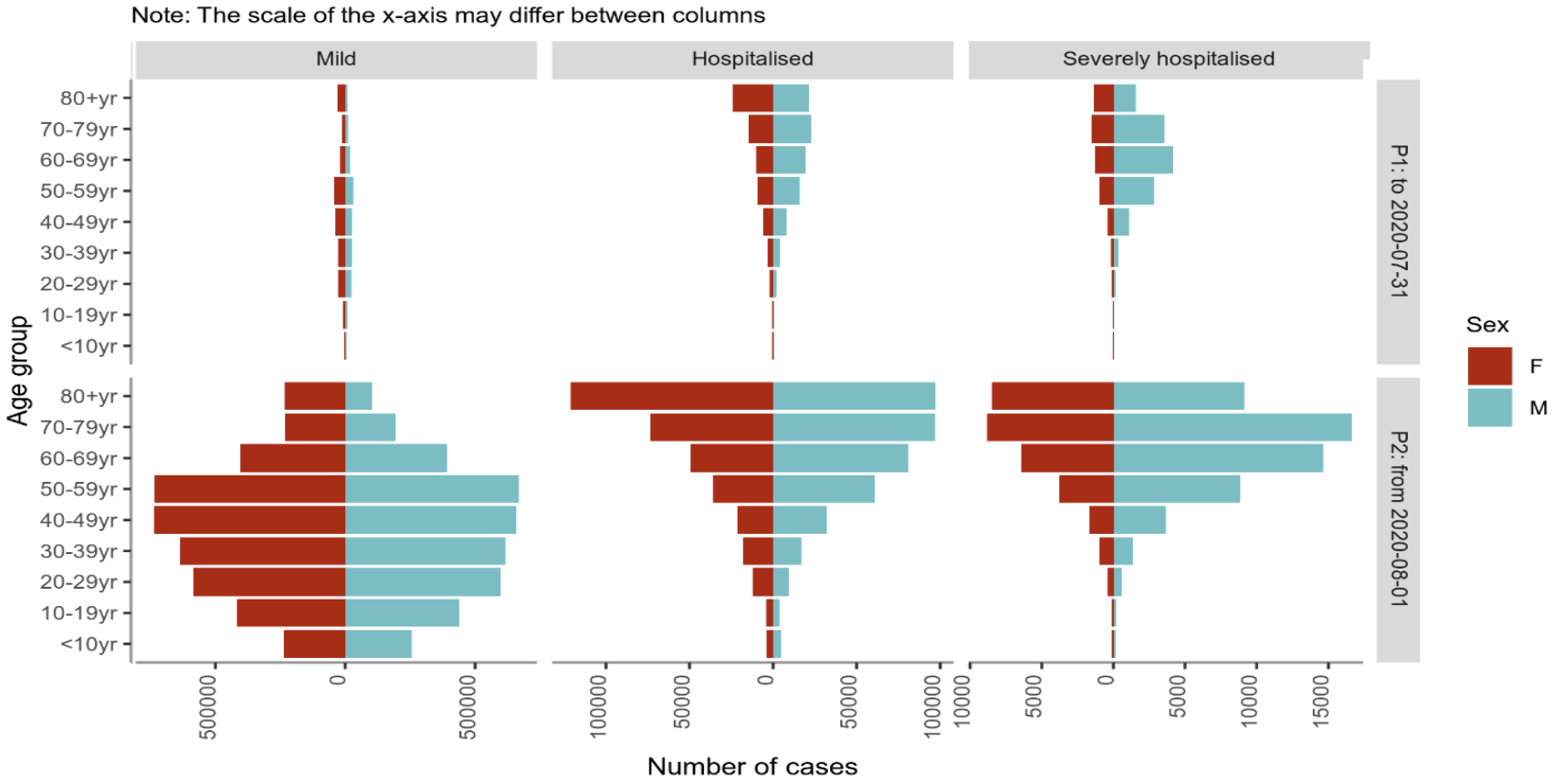

Figure 2 is adapted from ECDC, 2021. Data as of 6 June 2021.

Race/Ethnicity

Data on the racial and ethnic characteristics among non-hospitalized and hospitalized patients remain limited. It has been suggested that among adult patients with COVID-19, underrepresented racial and ethnic groups are disproportionately affected, perhaps related to underlying health conditions and economic and social conditions [Razai, 2021]. Racialized populations tend to have less access to testing, higher rates of severe disease, higher mortality rates and worse sequalae when they survive the infection [Melchior, 2021]. The current evidence suggests that race/ethnicity differences tend to exist between hospitalized and non-hospitalized patients, though data are mostly based on US studies [Lechien, 2020; Tenforde, 2020; van Gerwen, 2020] (Table 2).

Table 2 Racial and Ethnic Characteristics of Non-hospitalized and Hospitalized Patients

Author (Year)	Country/ Continent	Race/Ethnicity	Non-Hospitalized Patients (n/N[%])	Hospitalized Patients (n/N[%])	p-value
Lechien, 2020*	Europe	European/Caucasian	1298/1,420 (91.4)	NR	NR
		Asian	11/1,420 (0.8)	NR	
		Black African	25/1,420 (1.8)	NR	
		North African	41/1,420 (2.9)	NR	
		North American	2 /1,420 (<0.1)	NR	
		South American	37/1,420 (2.6)	NR	
		Oceanian	1/1,420 (<0.1)	NR	
		Mixed	5/1,420 (0.4)	NR	
van Gerwen, 2020	US	Non-Hispanic White	490/1,688 (29.0)	523/2,015 (26.0)	<0.001
		Non-Hispanic Black	459/1,688 (27.2)	533/2,015 (26.4)	
		Other	621/1,688 (37.8)	868/2,015 (43.1)	
		Unknown	118/1,688 (7.0)	91/2,015 (4.5)	
Tenforde, 2020	US	White, non-Hispanic	101/271 (37)	15/79 (19)	0.008
		Black, non-Hispanic	51/271 (19)	22/79 (28)	
		Hispanic	82/271 (30)	34/79 (43)	
		Other, non-Hispanic	35/271 (13)	8/79 (10)	
		Unknown	2/271 (1)	0/79 (0)	

NR = not reported; US = United States.
*Population consists of non-hospitalized [92%] and hospitalized without intensive care [8%] patients

Risk factors for the disease

There is increasing breadth of literature describing factors associated with increased risk of infection, severe disease, and mortality. Those at greatest risk of infection include healthcare and other essential workers, household contacts of infected individuals, persons with prolonged close contact (within 6 feet for at least 15 minutes) with an infected person, members of minority ethnic/racial groups, and populations living in high-density neighbourhoods [Ahrenfeldt, 2021; Allen, 2020; Chou, 2020; Li, 2020; Moore, 2020; Wiersinga, 2020].

Similar risk factors have been identified for both progression to severe disease and mortality, including lifestyle (current smoking and higher body mass index [BMI]),

demographic factors (age over 65, male gender, minority race/ethnicity), and presence of pre-existing comorbidities (hypertension, diabetes, cardiovascular disease, obesity, history of heart failure, ischemic heart disease, chronic obstructive pulmonary disease, solid organ tumours, chronic kidney disease, chronic respiratory disease, immune compromised status, neurologic conditions) [ECDC, 2021; Gold, 2020; Jordan, 2020; Weiss, 2020; Zheng, 2020].

SI.1.2 The main existing treatment options

Monoclonal antibodies have been proposed as a potential early treatment modality in patients at risk for progression of COVID-19 as manifested by the requirement for hospitalization and oxygen support. Additionally, treatment with a mAb has the potential to both reduce symptoms and reduce disease duration of COVID-19, leading to a decrease in the risk of transmission.

As of June 2021, no mAb treatment of COVID-19 has been granted a marketing authorisation in the EU. The CHMP reached a positive scientific opinion following a referral under Article 5(3) of Regulation 726/2004 for regdanvimab (adults only), casirivimab-imdevimab; and bamlanivimab alone or in combination with etesevimab, for the indication of *"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."*

While data on these mAbs have demonstrated proof-of-principle that these products are capable of reducing the need for hospitalization, some, such as Lilly mAb bamlanivimab, have limited activity against several viral variants (including the California [B.1.427/B.1.429], South Africa [B.1.351], Brazil [P.1], and New York [B.1.256] variants).For the casirivimab and imdevimab combination only one of the two mAbs in the combination retains efficacy for certain variants, such as the South Africa [B.1.351] variant.

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Natural history of the indicated condition in the untreated population, including morbidity and mortality

The natural history of SARS-CoV-2 infection, and the associated clinical manifestations, vary widely, ranging from asymptomatic infection to severe disease that may include acute respiratory distress syndrome (ARDS), septic shock, Multisystem Inflammatory Syndrome in Children (MIS-C), multi-organ failure and death [Feng, 2020; Kaur, 2020]. The WHO Clinical Progression Scale measures patient illness by tracking progress through the health-care system. Clinical manifestations are categorized into 'uninfected', 'ambulatory (mild disease)', 'hospitalized (moderate disease)', 'hospitalized (severe disease)', and 'dead' and provides a measure of illness severity across a range from 0 (not infected) to 10 (dead). [WHO, 2020a] Approximately 80% of infections present asymptomatically or as mild disease, 15% result in severe disease requiring oxygen therapy, and 5% are critical cases requiring ventilation [Lauretani, 2020].

Asymptomatic persons seem to account for approximately one third of all cases [Oran, 2020], whilst individual study estimates range from 18% to 81% [Nikolai, 2020]. Age appears to strongly dictate asymptomatic carriage: in a study of index case contacts in Italy asymptomatic rates of 81.9%, 70.5% and 35.5% were observed in 0-19, 40-59, and 80+ year old age groups respectively [Poletti, 2020]. Both asymptomatic and symptomatic persons are capable of transmitting disease, and notwithstanding a limited understanding of the role of asymptomatic spread, the risk of transmission is likely higher among symptomatic persons [WHO, 2020b].

The incubation period for symptomatic infection ranges from 0-24 days, with shorter periods (5-7 or 14 days) most commonly reported [Feng, 2020; Shi, 2020; Siordia, 2020].

In the first phase of the infection, patients most often experience mild symptoms (e.g. fever, cough, malaise) which persist for approximately eight days, and progressive lung lesions can be observed approximately a week after onset [Asokan, 2020; Sheervalilou, 2020]. Among adults, symptoms including fever (98%), cough (76%), dyspnoea (55%), and myalgia (44%) predominate during this time [Lauretani, 2020; Tang, 2020] and a loss of taste and/or smell helps differentiate SARS-CoV-2 infection from other infectious aetiologies [Zhou, 2020]. When present, the most common symptoms experienced by children include fever (59.1%), cough (55.9%), and rhinorrhoea/nasal congestion (20.0%), while myalgia/fatigue (18.7%), sore throat (18.2%), shortness of breath/dyspnoea (11.7%), abdominal pain/diarrhoea (6.5%), vomiting/nausea (5.4%), headache/dizziness (4.3%), pharyngeal erythema (3.3%), decreased oral intake (1.7%), and rash (0.25%) were also reported [Hoang, 2020].

A progression to lung involvement, which comprises the second phase of infection, occurs 7-10 days after the development of initial symptoms [Kowalik, 2020]. Patients experiencing this phase of disease generally require hospitalization and supportive care. According to data collected on 340,312 cases across 54 countries (including several EU/EAA countries and the United Kingdom) from and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), the symptoms most commonly reported upon admission to hospital include shortness of breath, cough, history of fever, fatigue/malaise, and altered consciousness/confusion [ISARIC Consortium, 2021]. Laboratory results may indicate lymphopenia and elevated transaminases, and chest imaging reveal bilateral pulmonary infiltrates [Gouveia, 2020]. Progression to ARDS occurs between 8-14 days following symptom onset and the median time to requiring mechanical ventilation and ICU admission is 10 days [Asokan, 2020; Tang, 2020]. The third and most severe phase of infection is largely extra-pulmonary and occurs within 2-3 weeks of initial symptom presentation. Notable features include extra-pulmonary systemic hyperinflammatory syndrome, severe pneumonia, septic shock, respiratory failure, cardiac arrest, and multiple organ failure. [Gouveia, 2020; Malik, 2020]. Irregular reticular opacities mixed with ground glass opacities can be identified by chest CT in the fourth week [Sheervalilou, 2020]. Paediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 (MIS-C) has emerged as a late-stage complication of SARS-CoV-2 infection observed in children and recently a similar syndrome in adults Multisystem Inflammatory Syndrome Adults (MIS A) has been observed [Feldstein, 2020; Morris, 2020]. MIS-C is similar in presentation to Kawasaki disease (KD) or Toxic Shock Syndrome (TSS)]. The condition is characterized

by a severe auto-inflammatory disorder involving two or more multiple organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) [Malik, 2020].

Data suggests that some patients experience persistent symptoms or prolonged organ dysfunction up to 6 months after their original COVID-19 illness has resolved. This has, generally, been referred to as post-acute COVID-19 and can occur even after relatively mild acute illness. Depending on the definitions, population studied, setting, and the study design, between 13%-87% of patients report ≥1 persistent symptom(s) 3 or more weeks following initial symptoms [Nalbandian, 2021; Sudre, 2021]. The most commonly reported symptoms of post-acute COVID-19 include fatigue, dyspnoea, continued loss of smell or taste, and cognitive issues such as "brain fog" [Carfi, 2020; Garrigues, 2020; Logue, 2021; Sudre, 2021]. Clinical sequelae such as acute kidney injury, new or worsening control of existing diabetes mellitus, increased cardiometabolic demand and others have also been noted [Nalbandian, 2021]. Approximately 14% of patients with COVID-19 experienced new clinical sequalae 3 or more weeks after the acute phase of the illness [Daugherty, 2021].

Morbidity

COVID-Related Complications

COVID-related complications include atypical pneumonia, respiratory failure, ARDS, liver injury, acute myocardial injury, acute injury, septic shock, and multiple organ failure [Baek, 2020; Cavallo, 2020; Shi, 2020]. Lung damage is most commonly associated with SARS-CoV-2 infection; however, the virus can also cause damage to the heart, liver, kidney, brain and intestines [Tang, 2020]. Accumulated data suggest that more than one-third of patients hospitalized due to COVID-19 infection might have impaired liver function [Cichoż-Lach, 2021]. Hypokalaemia has been documented among COVID-19 patients and is likely to increase the risk of dysfunction among the lungs, heart, and other organs [Sheervalilou, 2020].

Older age, male sex, and comorbidities including hypertension, diabetes, cardiovascular and respiratory tract diseases (asthma and COPD), chronic renal failure, hypercholesterolemia, cancer, smoking, and obesity are associated with increased risk of complications [Asokan, 2020; Godri, 2020; Gouveia, 2020; Lauretani, 2020]. Cytokine storm syndrome is more common among patients with obesity, hypertension, diabetes, history of smoking, and lung disease [Gasparyan, 2020].

Children generally have good prognosis and recover within 1-2 weeks after symptom onset [Cavallo, 2020; Ludvigsson, 2020]; however, complications among critically ill children can include septic shock, toxic encephalopathy, multiple organ dysfunction syndrome, disseminated intravascular coagulation, and status epilepticus [Sun, 2020].

Severe Disease/Hospitalizations

Rates of hospitalization for COVID-19 patients are also dependent on a number of factors including age, geography, underlying comorbidities, and VOCs. As demonstrated in Figure 3, rates of hospitalization and severe hospitalization among the EU/EEA countries are also age dependent with increasing risk associated with increased age [ECDC, 2021]. The reduced risk of severe hospitalization among the oldest age groups may reflect clinical decisions about the use of limited ICU or ventilator capacity and is a pattern that is observed in many countries [ECDC, 2021].

Figure 3 Age-specific rates of hospitalization (a), severe hospitalization (b, d), and case-fatality (c, e) of all cases and hospitalized cases from the EU/EEA countries, to 30 May 2021

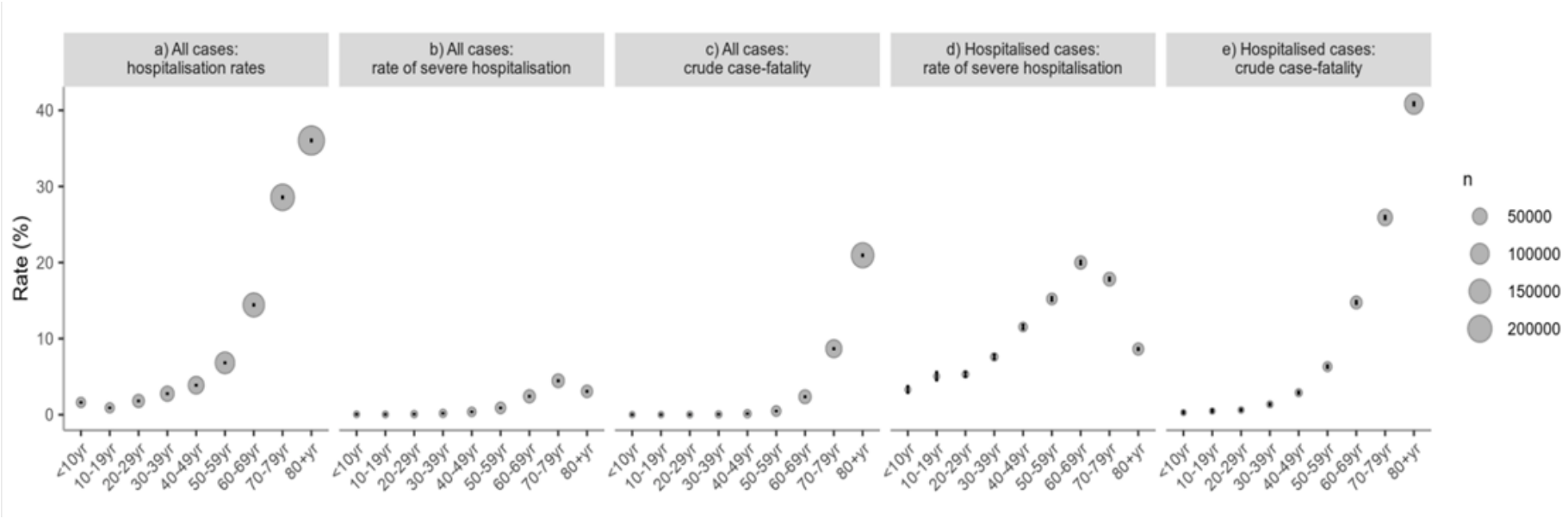

Figure 3 is from ECDC, 2021. Note: Severe hospitalizations refer to those where the patient was admitted to intensive care and/or required respiratory support

Hospitalization for COVID-19 has been associated with diabetes, heart failure, COPD, renal disease, obesity, and ischaemic heart disease in the community setting [ECDC, 2021]. In addition, recent data from 7 EU/EAA countries suggests that viral VOCs Alpha [UK] B.1.1.7, Beta [South Africa] (B.1.351), and Gamma [Brazil] (P.1) are associated with a higher risk for hospitalisation, and also for ICU admission in age groups < 60 years [Funk, 2021]. A larger proportion of VOC cases were admitted to hospital (Alpha 11.0%; Beta 19.3%, and Gamma 20.0%; $p < 0.001$ for all VOC) and ICU (Alpha 1.4%, $p = 0.002$; Beta 2.3%, $p = 0.001$ and Gamma 2.1%, $p = 0.005$) compared with non-VOC cases (7.5%, hospitalized and 0.6% requiring ICU) [Funk, 2021].

Mortality

Over the course of the pandemic, reported case fatality rates (CFR) have varied markedly by country, reflecting heterogeneity in underlying risk, ascertainment, definitions and reporting. As of 11 June 2021, estimates of CFR in the EU/EAA region range from 0.4% in Iceland to 4.3% in Bulgaria, with incidence of death ranging from 8 per 100,000 persons in Iceland to 306 per 100,000 persons in Hungary [Johns Hopkins, 2021a]. COVID-19 age-specific mortality varies as well, reported to be 0%-0.1% among patients <19 years, 4.3%-10.5% among adults aged 75-84 years, and rising to as high as 17% (range 10.4% - 27.3%) among older adults aged >85 years and those with multiple comorbidities [Atzrodt, 2020; Feng, 2020]. When asymptomatic and mildly symptomatic disease is included, age-specific COVID-19 infection fatality rates were estimated to increase exponentially with age from 0.004% (95% CI: 0.003%-0.005%) for 0-34 year old to 28.3% (95% CI: 21.8%-36.6%) for ≥85 year old [Levin, 2020].

Mortality among cases detected in the community setting is associated with a history of heart failure, stroke, diabetes, and end-stage renal disease [ECDC, 2021]. Estimates of mortality among hospitalized COVID-19 patients range between 14.5% to 40.7% [Hansrivijit, 2020; Lala, 2020; Lewnard, 2020; Nimkar, 2020; Tian, 2020; Yan, 2020]. Mortality among COVID-19 patients in the ICU is approximately 40% [Shi, 2020]. Importantly, CFR estimates will vary over time given improvements in detection of SARS-CoV-2 infections and treatment regimens [Kadkhoda, 2020].

The spread of new circulating viral variants has had a significant impact on mortality compared to previously circulating variants, particularly during the second wave of the pandemic in Europe [Challen, 2021; Davies, 2021; Jabłońska, 2021]. In the UK, the 28-day risk of death for the Alpha [UK] B.1.1.7 variant was 64% higher in the community than for previously circulating strains in people older than 30 years [Challen, 2021]. Mortality risk from the B.1.1.7 variant increases with age [Davies, 2021].

Predictors of mortality include older age, male sex, immunosuppression (including cancer), diabetes, cardiovascular disease, hypertension, pre-existing respiratory disease and/or infection, abnormal kidney function, increased time from onset of disease to hospitalization, and elevated procalcitonin levels [Ahrenfeldt, 2021; Asokan, 2020; Lauretani, 2020; Shi, 2020; Venter, 2020].

The literature includes CFR estimates among COVID-19 patients with cardiovascular disease (10.5%), cancer (5.6%-7.6%), diabetes (7.3%), chronic lung disease (6.3%), and hypertension (6.0%) [Asokan, 2020; Siordia, 2020].

SI.1.4 Important co-morbidities

Comorbidities

Evidence suggests that outpatients have a lower number of health conditions than inpatients and that specific individual health conditions are less common in outpatients than inpatients (Table 3) [ECDC, 2021]. Studies from the US support this finding, with the study by van Gerwen, 2020 concluding that patients who were hospitalized were more likely to have 2 or more underlying health conditions compared with those not hospitalized (P<0.001) [van Gerwen, 2020; Hsu, 2020; Tenforde, 2020].

Table 3 Distribution of Comorbidities among COVID-19 cases by severity in the EU/EAA region

Comorbidities	Outpatients	Inpatients	
	Non-Hospitalized [Mild] (%) n=1,757,394	Hospitalized (%) n=289,481	Severely Hospitalized (%) n=48,861
Cardiac disorder excluding hypertension	6	18	20.1
Diabetes	4	13.9	18.7
Cancer, malignancy	2	6.8	9.3
Chronic lung disease excluding asthma	1.7	4.5	5.1
Hypertension	1	4.2	4.4
Neuromuscular disorder, chronic neurological	0.6	2.2	1.4
Asthma	0.6	1.6	1.8
other endocrine disorder, excluding Diabetes	0.3	0.2	0.1
Kidney-related condition renal disease	0.3	2.2	2.1
Liver-related condition liver disease	0.2	0.7	0.7
Obesity	0.2	0.2	0.5
HIV / other immune deficiency	0.1	0.9	1

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

Sotrovimab has undergone a targeted program of nonclinical toxicology studies. The nonclinical program was designed and accelerated due to urgency to find effective medicines for COVID-19 in accordance with the guidance provided in International Conference on Harmonisation (ICH) S6(R1) and other applicable guidances as pertaining to a non-human antiviral target. Consequently, only studies directly and immediately relevant to support clinical development were conducted.

Table 4 Key Safety Findings from Non-Clinical Studies and their Relevance to Human Usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including:	
General Toxicity In a 2-week repeat dose (once weekly) IV infusion (10 mL/kg/hr infusion rate) monkey toxicology study at doses up to 500 mg/kg with 105-day recovery period, no toxicity was observed.	Toxicology studies conducted with sotrovimab in monkeys did not identify any safety findings of clinical concern.
Reproductive and Developmental toxicity Animal reproductive and developmental toxicology studies were not conducted. No toxicity was identified in male or female reproductive organs in young (adolescent) male or female monkeys in the repeat-dose toxicity study (all males were sexually mature except one high dose male was peripubertal). In addition, no off-target binding was detected human reproductive tissue, including placenta, in a tissue cross-reactivity study, or in a non-GLP human embryofoetal protein array.	Since sotrovimab is directed against an exogenous viral target, there is no mechanism-based concern for reproductive or developmental toxicity. In addition, no elevated clinical concern was identified from evaluation of reproductive tissues in the general toxicology study or in cross-reactive binding studies.
Genotoxicity and carcinogenicity Genotoxicity and carcinogenicity studies were not conducted	Due to their molecular structure and molecular weight, mAbs are unlikely to diffuse into cells or to interact with DNA. Therefore, mAbs are not likely to be genotoxic. Furthermore, there is not a mechanism-based theoretical concern for carcinogenicity since sotrovimab targets an exogenous viral target and is administered as a single dose for short term use.
Safety pharmacology:	
Safety pharmacology endpoints were evaluated in the 2-week monkey toxicology study at doses up to 500 mg/kg (5/sex/group). There were no cardiovascular	Since sotrovimab is directed against an exogenous viral target and there was no off-target binding identified in cross-reactivity

(including QTc), neurobehavioral, or respiratory findings.	studies, there is a low likelihood for safety effects on CV, CNS or respiratory function.
Other toxicity-related information or data:	
Infusion-related reactions and immunogenicity In the 2-week monkey IV toxicology study, there was no evidence of systemic infusion reactions. Anti-drug antibodies (ADA) were detected in 12 of 40 monkeys. There were no apparent ADA-related effects on TK or toxicity.	No elevated clinical concern for infusion-related reactions was identified in the monkey toxicology study. ADA in animals are not considered predictive of immunogenicity in humans because human antibodies, like sotrovimab, are immunologically foreign in monkeys. Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to sotrovimab following treatment.
Local tolerance In the 2-week monkey IV toxicology study, local infusion site reactions were not observed. In a single dose IM local tolerance study in minipig at a dose of 250 mg (4 mL, 62.5 mg/L), no injection site reactions were observed.	No elevated clinical concern was identified for IV or IM local injection site reactions in toxicology studies.
Cross reactivity No off-target binding was detected in an in vitro immunohistochemistry human tissue cross reactivity study.	No elevated clinical concern was identified in off-target tissue binding studies.
Antibody-dependent enhancement The potential for antibody-dependent enhancement (ADE) of disease was evaluated in non-GLP in vitro and in vivo studies. Sotrovimab did not enhance viral uptake or replication, or cytokine production in peripheral blood mononuclear cells, monocyte-derived dendritic cells and the U937 monocytic cell line. In a hamster SARS-CoV-2 model, sotrovimab showed a dose-dependent improvement in all measured outcomes, with no evidence of disease exacerbation at any dose tested, including sub-neutralizing doses.	Nonclinical in vitro and in vivo data did not identify an elevated clinical concern for ADE of disease.
Viral Resistance An E340A amino acid substitution in the virus spike protein emerged in a SARS-Cov-2 cell culture assay designed to select mAb resistant virus mutants. This substitution is in the conserved epitope that is recognized by sotrovimab. In a pseudotyped virus-like particle (VLP) assessment in cell culture, reduced susceptibility to sotrovimab neutralization was observed for amino acid sequence polymorphisms P337H/L/R/T (7.5X, 180X, >276X, 5.4X, respectively, of wild-type EC_{50}) and E340A/K/G (>100X, >297X, 27X, respectively). The presence of the highly prevalent D614G variant, either alone or in	The nonclinical studies did not identify an elevated clinical risk for treatment failure for currently prevalent SARS-CoV-2 variants. The clinical significance of resistance related to substitutions at amino acid positions E340 or P337 is unknown at this time. Notably, E340 and P337 are ≥99.99% conserved among available SARS-CoV-2 sequences. Characterization of potential risk of emergence of sotrovimab-resistant variants is ongoing.

combination, did not alter neutralization of sotrovimab. Pseudotyped VLP assessments indicate that sotrovimab retains activity against 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) variant spike proteins. Microneutralization data using authentic SARS-CoV-2 variant virus indicate that sotrovimab retains activity against the UK, South Africa and Brazil variants. In addition, sotrovimab demonstrated protection in a hamster model of SARS-CoV-2 infection using the UK B.1.1.7 variant based on improvements in disease-related body weight changes.	

In conclusion, there are no important identified risks from the non-clinical data. The potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab or potential risks associated with biologic therapies including mAbs will be further assessed during the clinical development program.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The exposure data provided below are from one pivotal clinical study COMET-ICE.

Table 5 Duration of exposure

Duration of time on study post-dose[a]	SOTROVIMAB 500 mg, n (%) (N=523)
<5 days	0 (0.0)
5 to 10 days	1 (<1)
11 to 14 days	0 (0.0)
15 to 29 days	2 (<1)
>29 days	520 (>99)
>85 days	360 (69)
>141 days	78 (15)
Mean (SD), days	103.7
Median (Min, Max), days	103.0 (5, 178)

a. Duration of follow-up in the study from date of infusion through to time of study completion/withdrawal or data cut-off date (27 April 2021) if participant still ongoing in the study.

Table 6 Age group and gender

Age group	SOTROVIMAB 500 mg, n (%) (N=523)	
	Patients	
	Male	Female
Adults (18 to 64 years)	177 (34)	242 (46)
Elderly people (≥ 65 years)	51 (10)	53 (10)
65-74 years	35 (7)	41 (8)
75-84 years	13 (2)	10 (2)
85 + years	3 (1)	2 (<1)
Total	228 (44)	295 (56)

Table 7 Ethnic origin

Race and Ethnic origin	SOTROVIMAB 500mg, n (%) (N=523)
Ethnicity	
Hispanic or Latino	340 (65)
Not Hispanic or Latino	183 (35)
Total	523
High Level Race	
American Indian or Alaska Native	1 (<1)
Asian	25 (5)
Black or African American	40 (8)
Native Hawaiian or Other Pacific Islander	0
White	453 (87)
Mixed Race	3 (<1)
Not Collected	1 (<1)
Total	523

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Sotrovimab is not approved in any country.

There were no trials conducted specifically in special patient populations (i.e. pregnant or lactating women, patient with renal, hepatic or cardiac disorders) as part of the development program for sotrovimab.

Missing information relevant for the indication is included in module SVII.

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Known hypersensitivity to any constituent present in the investigational product	To minimize risk to the patient and to minimize confounding of the assessment of both safety and efficacy data in the study population.	No	Hypersensitivity to the active substance or to any of the excipients is included as a contraindication in the sotrovimab SmPC
Previous anaphylaxis or hypersensitivity to a monoclonal antibody	To minimize risk to the patient and to minimize confounding of the assessment of both safety and efficacy data in the study population.	No	Hypersensitivity reactions are listed in Warnings and precautions for use section and under adverse drug reactions section in the sotrovimab SmPC
Children <18 years old	COMET-ICE was first study conducted in humans and safety and efficacy has not been established. Evaluation of safety and efficacy in paediatric patients is subject to a Paediatric Investigation Plan (PIP) in the EU	Yes	No patients <18 years old were enrolled and received sotrovimab in COMET-ICE study In the ongoing COMET-TAIL study adolescents (12-<18 years old) with mild to moderate COVID-19 at high risk of disease progression are included. The indication includes adolescents (aged 12 years and over and weighing at least 40 kg) with coronavirus disease

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 and therefore, use in children ≥12 to <18 years old is considered missing information. COMET-PACE study is planned in paediatric patients (birth to <18 years old) with mild to moderate COVID-19 at high risk of progression to evaluate pharmacokinetics, pharmacodynamics (viral load) and safety of sotrovimab; study is planned to start in 4Q 2021.
Patients receiving or who had received convalescent plasma from a recovered COVID-19 patient or had received an anti-SARS-CoV-2 mAb within 3 months of study enrolment	To minimize confounding of the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.
Patients who are severely immunocompromised	COMET-ICE was first study conducted in humans and safety and efficacy of sotrovimab is not established in patients actively receiving immunosuppressive chemotherapy or immunotherapy.	No	No anticipated impact on safety for the indicated population.
Patients with symptoms of severe COVID-19 manifested by the need for hospitalization and/or supplemental oxygen therapy	COMET-ICE was first study conducted in humans that included non-hospitalized patients with mild or moderate COVID-19.	No	No anticipated impact on safety for the indicated population. NIH-sponsored ACTIV-3 trial was conducted to evaluate safety and efficacy of sotrovimab as an add on therapy to standard of care in hospitalized adults with COVID-

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			19. Following review of safety and efficacy data for 300 patients enrolled, the Independent Data and Safety Monitoring Board (DSMB) recommended to close enrolment due to concerns about the magnitude of potential benefit. DSMB did not indicate any safety concerns in this patient population.
Patients who have been vaccinated for COVID-19	At the time COMET-ICE study was initiated SARS-COV2 vaccines were under investigation and therefore patients enrolled in these trials were excluded.	No	No anticipated impact on safety for the indicated population.
Pregnant/lactating females	COMET-ICE was first study conducted in humans and vulnerable populations were excluded.	Yes	The potential treatment benefit or risk from placental transfer of sotrovimab to the developing foetus is not known. Sotrovimab exposure in pregnancy will be evaluated in the COVID-19 International Drug Pregnancy Registry (COVID-PR).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 8 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women There are no or limited amount of data from the use of sotrovimab in pregnant women. The SmPC states that sotrovimab should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.	Female participants were excluded from the clinical trial programme if they were pregnant or breastfeeding. Women of childbearing potential were required to use acceptable contraceptive measures as specified in the study protocol. As of the RMP cut-off date one pregnancy was reported in ACTIV-3 TICO study in hospitalized patients with COVID-19. No additional information is available.
Breastfeeding women There is insufficient information on the excretion of sotrovimab in human milk. A risk to the new-borns/infants cannot be excluded. 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.	Breast feeding women were excluded from clinical studies with sotrovimab.
Patients with relevant comorbidities: • <u>Patients with hepatic impairment</u> Sotrovimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, therefore changes in hepatic function are unlikely to have any effect on the elimination of sotrovimab. Furthermore, based on population pharmacokinetic analyses there is no difference in sotrovimab pharmacokinetics in patients with mild to moderate elevations in alanine aminotransferase (1.25 to < 5 x ULN). No dose adjustment is expected to be required in patients with hepatic impairment.	No specific exclusion criteria have been implemented in the clinical program. In COMET-ICE study, 22 patients on sotrovimab had hepatobiliary disorders reported as current medical condition at baseline.
• <u>Patients with renal impairment</u> Sotrovimab, like other immunoglobulins, is too large to be excreted renally, thus renal impairment is not expected to have any effect on the elimination of sotrovimab. Furthermore, based on population pharmacokinetic analyses there was no difference in sotrovimab pharmacokinetics in patients with mild, moderate or severe renal impairment (creatinine clearance < 30	No specific exclusion criteria have been implemented in the clinical program. In COMET-ICE study, 22 patients on sotrovimab had renal and urinary disorders reported as current medical condition at baseline and 5 patients had chronic kidney disease (eGFR <60 by MDRD) reported as risk factor for COVID-19 progression.

Type of special population	Exposure
mL/min/1.73m2). No dose adjustment is required in patients with renal impairment	No specific exclusion criteria have been implemented in the clinical program.
• Patients with cardiovascular impairment	In COMET-ICE study, 51 patients on sotrovimab had cardiac disorders reported as current medical condition at baseline and 4 patients had congestive heart failure (NYHA class II or more) reported as risk factor for COVID-19 progression.
• Immunocompromised patients Severely immunocompromised participants, including but not limited to cancer patients actively receiving immunosuppressive chemotherapy or immunotherapy, those with a solid organ transplant or allogeneic stem cell transplant within the last 3 months, or those having conditions requiring the use of systemic corticosteroids equivalent to ≥ 0.5 mg/kg of body weight per day of prednisone within 6 weeks of randomization were excluded from clinical program.	Severely immunocompromised participants were not included in the clinical development programme in patients with COVID-19.
• Patients with a disease severity different from inclusion criteria in clinical trials Patients with COVID-19 requiring hospitalization were excluded from COMET-ICE study	Sotrovimab was evaluated in ACTIV-3-TICO trial with 300 participants with COVID-19 requiring hospitalization; of these approximately 150 participants received sotrovimab. Following DSMB review of the unblinded data no specific safety issues were raised. The DSMB recommended that the trial be closed to future enrolment based on sensitivity analyses of the available data that raised concerns about the magnitude of potential benefit.
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other: • Children <18 years old Patients <18 years old were excluded from clinical program. The pharmacokinetics of sotrovimab in paediatrics under the age of 18 years have not been evaluated. However, the recommended dosing regimen in paediatrics aged 12 years and older 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	Sotrovimab is indicated 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. No patients <18 years old were enrolled and received sotrovimab in COMET-ICE study.

Type of special population	Exposure
changes associated with age on clearance and volume of distribution.	In the ongoing COMET-TAIL study adolescents (12-<18 years old) with mild to moderate COVID-19 at high risk of disease progression are included. COMET-PACE study is planned to evaluate pharmacokinetics, pharmacodynamics (viral load) and safety of sotrovimab in paediatric patients (birth to <18 years old) with mild to moderate COVID-19 at high risk of progression
• Elderly Based on population PK analyses, there was no difference in sotrovimab pharmacokinetics in elderly patients. No dose adjustment is required in elderly patients. In clinical trials, no dosage adjustment was made for patients over 65 years of age.	In COMET-ICE study a total of 105 sotrovimab treated subjects ≥65-year-old were included of which 56 subjects were > 70years old and 6 were ≥85 years old.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

There are no data for this section as sotrovimab has not been marketed in any country.

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

A potential for misuse for illegal purposes or abuse has not been identified for sotrovimab and is considered unlikely from the knowledge of sotrovimab.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not all potential or identified risks are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Identified risk of hypersensitivity reactions:

Incidence of hypersensitivity reactions from frequently used mAbs (e.g. infliximab, rituximab, cetuximab, tocilizumab) was generally low but ranges widely (<1% to 27%) [Santos, 2017].

Serious hypersensitivity reactions have been reported with monoclonal antibodies for treatment of SARS-Cov2 infection (bamlanivimab [both as monotherapy and in combination with etesevimab] and the casirivimab-imdevimab [REGN-COV2] combination) including anaphylaxis reported for REGN-COV2 (REGN-COV2 Conditions of Use and Bamlanivimab/ bamlanivimab + etesevimab Conditions of Use).

Hypersensitivity reactions reported in COMET-ICE study include all events that matched preferred terms under MedDRA Hypersensitivity SMQ (narrow) and occurred at any time after the dose.

Table 9 Summary of Hypersensitivity Reactions in COMET-ICE Study

Hypersensitivity SMQ Narrow **Preferred Term**	**Placebo (N=526) N (%)**	**Sotrovimab 500mg IV (N=523) N (%)**	**Relative Risk[1] 95 % CI Unadjusted p-value[2]**
Any event	5 (<1)	9 (2)	1.810 (0.611,5.366) 0.2973
Rash	4 (<1)	3 (<1)	
Dermatitis	1 (<1)	0	
Dermatitis contact	0	1 (<1)	
Skin reaction	0	1 (<1)	
Hypersensitivity	0	1 (<1)	
Multiple allergies	0	1 (<1)	
Infusion related reaction	0	1 (<1)	
Bronchospasm	0	1 (<1)	

[1] Risk Proportion of Vir-7831 500mg vs. Placebo.
[2] Fishers Exact p-value.

In COMET-ICE study, none of the hypersensitivity reactions across both treatment groups were serious and majority were of Grade 1. One event in each treatment arm was of Grade 2 severity: rash in the placebo group that occurred 7 days and 21 hours after the dose and skin reaction in the sotrovimab group that occurred 4 days after the dose. All events across both treatment groups were reported as resolved (two on sotrovimab resolved with sequalae-events of skin reaction and rash [verbatim skin rash]) except one event on sotrovimab arm (PT dermatitis contact) that was reported as resolving at the time of data cut off. None of these events in either the sotrovimab or the placebo arm led to premature pausing or discontinuation of the infusions. One event of rash (verbatim facial rash) in the placebo group that occurred 5 hours and 57 minutes after the dose was considered related to study treatment by the investigator. Two events in the sotrovimab group: skin reaction described above and rash (verbatim skin rash that occurred 2 days and 13 hours after the dose) were considered related to study treatment by the investigator. The event of bronchospasm in the sotrovimab group that occurred 12 days after the dose was reported for patient with history of asthma. The event of hypersensitivity (verbatim allergic reaction over face and forearms) in the sotrovimab group occurred 14 days after the dose and was treated with topical steroids.

No anaphylaxis events were reported in COMET-ICE study in patients with mild to moderate COVID-19 not requiring hospitalization at study entry.

A potentially life-threatening allergic reaction (anaphylaxis) was observed in one participant, who received sotrovimab in the study of individuals hospitalized with COVID-19 (the ACTIV-3-TICO study). This participant reported Grade 4 anaphylaxis and bronchospasm, Grade 3 shortness of breath, Grade 2 rash, and Grade 1 dizziness and flushing 21 minutes after the start of the infusion. All events were considered serious and related to study treatment by the

investigator. The infusion was recorded as paused but never resumed. The participant was treated with epinephrine and recovered.

Risks with minimal and temporary clinical impact on patients (in relation to the severity of the indication treated):

Potential risk of infusion related reactions

While sotrovimab is a human Immunoglobulin G1 (IgG1) mAb, infusion related reactions (IRRs) are a potential general risk associated with the mAb class of therapeutics administered via intravenous infusion.

IRRs, including hypersensitivity reactions were listed in the COMET-ICE protocol as adverse events of special interest (AESI). Systemic IRRs were defined as events with preferred terms (PTs) matching the custom list of PTs and occurring within 24 hours of initiation of infusion. This custom list of PTs was pre-specified at the beginning of the study and derived from the MedDRA Anaphylactic standard MedDRA query (SMQ) and Hypersensitivity SMQ as well as IRRs from other approved monoclonal antibodies. These included PTs such as pyrexia, chills, hypersensitivity, angioedema, anaphylaxis, and allergic reactions. In COMET-ICE study, participants were observed for 2 hours after infusion for immediate IRRs.

Systemic IRRs that started within 24 hours of study treatment were observed with similar frequency in participants treated with either sotrovimab (6 of 523 [1%]) or placebo (6 of 526 [1%]). AEs reported in the participants captured as IRRs include pyrexia, chills, dizziness, dyspnoea, pruritus, rash, and IRR. Pyrexia was the most frequent IRR in the sotrovimab arm (3 of 523 [<1%] and in placebo 1 of 526 [<1%]), whilst dizziness was the most frequent in the placebo arm (3 of 526 [<1%] and in sotrovimab 1 of 523 [<1%]). All IRRs were non-serious, low grade (Grade 1 or 2) and clinically manageable with no life-threatening reactions. None of them lead to treatment discontinuation and all patients received full dose. In the sotrovimab arm all of the cases of IRRs were considered resolved and none were considered related to study treatment by the investigator. In the placebo arm, one participant had event considered not resolved at the time of data cut off and 3 had events considered related to study treatment by the investigator.

Potential risk of immunogenicity

During clinical development, immunogenicity was assessed using a risk-based bioanalytical strategy to understand whether ADA responses against sotrovimab impact safety or efficacy. Based on the low immunogenicity risk for sotrovimab, a validated, multi-tiered approach to evaluating anti-sotrovimab antibodies, consisting of screening, confirmation, and titration assays were implemented.

Currently, in the COMET-ICE study, the observed incidence of post-treatment ADAs has been low, with all titre values near the sensitivity limit of the assay (titres ≤160). Available results from approximately 75% of the participants up to Day 29 are provided in Table 10 . In this study, 17 participants confirmed positive at Day 1 (baseline) for ADAs with no increase in titre values in subsequent timepoints and, therefore, are not considered to have treatment-induced ADAs. Ten participants confirmed positive for anti-sotrovimab antibodies at Day 29.

Four of the 10 participants were positive at baseline with no boosting in titre values at Day 29 and therefore are not considered to have treatment-induced ADAs. The other 6 participants with positive responses are currently considered to have treatment-induced ADAs: 2 participants were negative at baseline and 4 participants have not yet had a baseline sample analysed. There were no apparent clinical consequences related to the presence of anti-sotrovimab antibodies.

To date, the incidence of treatment-induced anti-sotrovimab antibody responses has remained low with relatively low titres and with no detectable impact on safety or efficacy. This clinical evidence aligns with the low immunogenicity risk profile of the molecule. Immunogenicity will continue to be assessed in this study and in the clinical program.

Table 10 Number of Participants with Confirmed Positive Immunogenicity Results for Sotrovimab Through Day 29 (ITT [Day 29])

Visit	Sotrovimab 500 mg IV (N=528)
Day 1	17/375 (5%)
Day 29	10/391 (3%)

Note: Summary presents the number of confirmed positive out of the total number of confirmatory results.

Other reasons for considering the risks not important:

Potential risk of antibody depended enhancement of the disease

ADE is a theoretical risk with vaccines and antiviral antibodies and has been best described in association with some vaccine development programs. ADE can occur via one of three previously described mechanisms:

1. By facilitating viral entry into host cells and enhancing viral replication in these cells

2. By increasing viral fusion with target host cells, enhancing viral replication in these cells

3. By enhancing disease pathology from viral antigen-antibody related immune complex deposition or complement activation and immune cell recruitment in target organs

The first two mechanisms are hypothesized to occur at sub-neutralizing antibody concentrations. The third mechanism is hypothesized to occur at high levels of antigen (i.e., viral load) and antibody potentially leading to immune complex deposition and complement activation in tissue sites of high viral replication. If these were to occur, they may manifest as increased severity or duration of illness in sotrovimab-treated participants compared to what would be clinically expected.

Sotrovimab shows potent binding as well as neutralization of pseudovirus and live virus in vitro, thus this risk is deemed to be low. No enhanced viral uptake or enhanced replication in the presence of sotrovimab was noted in in human cells that express FcγRs: moDCs, PBMCs

and U937 cells. No enhancement of cytokine or chemokine production detected in PBMC, DC or U937 cells treated with sotrovimab. The impact of sotrovimab on SARS-CoV-2 replication indicated comparable levels of replication in the presence or absence of sotrovimab. The in vitro data to date show no evidence of Fcγ/R-dependent or independent mechanisms of ADE of infection. In addition, an intraperitoneal ADE evaluation in Syrian golden hamsters also did not identify an elevated concern for ADE in the clinical setting.

To identify any potential events which might be suggestive of ADE, specific renal, cardiac, and pulmonary events were reviewed including review by the Independent Data Monitoring Committee (IDMC). Renal events were defined as 50% decline in eGFR from baseline (lab identified event), urine albumin creatinine ratio > 500mg/g. Only for subjects without end-stage renal failure at baseline. Cardiac events were defined as a selection of sub-SMQs and selected preferred terms. Pulmonary events were defined as any change from baseline in requirement for respiratory support.

Table 11 Summary of Potential ADE Events Based on IDMC defined Safety Criteria

Event Type	Placebo (N=526) N (%)	Sotrovimab 500mg IV (N=523) N (%)
All-cause Mortality	4 (<1)	0
Any SAE	32 (6)	11 (2)
Renal Events	3 (<1)	4 (<1)
Cardiac Events	0	1 (<1)
Pulmonary Events	28 (5)	7 (1)

Upon the review of the data no evidence was noted suggestive of potential ADE associated with sotrovimab. Review of the data by the IDMC resulted in same conclusions with no evidence of treatment emergent ADE.

To further characterize potential ADE events, COVID-19 related events as well as respiratory related events were evaluated. Upon the review of the data no evidence was noted suggestive of potential ADE associated with sotrovimab.

Table 12 Summary of Potential ADE Events Based on COVID-19 Adverse Events

Preferred term	Placebo (N=526) N (%)	Sotrovimab 500mg IV (N=523) N (%)	Relative Risk[1] 95 % CI Unadjusted p-value[2]
Any Event	30 (6)	6 (1)	0.201 (0.084,0.479) 0.0001
COVID-19 pneumonia	22 (4)	5 (<1)	
COVID-19	5 (<1)	0	
Pneumonia	5 (<1)	0	
Pneumonia bacterial	0	1 (<1)	

[1] Risk Proportion of Vir-7831500mg vs. Placebo.
[2] Fishers Exact p-value.

In the sotrovimab group COVID-19 events were Grade 2-3 severity and 3 events were considered serious. One event was reported as not resolved (PT of pneumonia bacterial) at the time of data cut off and none were fatal.

In the placebo group COVID-19 events were Grade 1-5 severity and 25 events were considered serious. Two events were reported as not resolved (PTs of pneumonia and COVID 19 pneumonia) at the time of data cut off and 3 events were fatal (PTs of pneumonia [1 patient], and COVID 19 pneumonia [2 patients]).

Table 13 Summary of Potential ADE Events Based on Respiratory Adverse Events

Preferred term	Placebo (N=526) N (%)	Sotrovimab 500mg IV (N=523) N (%)	Relative Risk[1] 95 % CI Unadjusted p-value[2]
Any Event	14 (3)	5 (<1)	0.359 (0.130, 0.990) 0.0612
Dyspnoea	4 (<1)	2 (<1)	
Respiratory distress	2 (<1)	0	
Hypoxia	2 (<1)	1 (<1)	
Respiratory failure	1 (<1)	1 (<1)	
Acute respiratory failure	1 (<1)	0	
Pneumothorax	1 (<1)	0	
Pneumonia	5 (<1)	0	
Pneumonia bacterial	0	1 (<1)	

[1] Risk Proportion of Vir-7831500mg vs. Placebo.
[2] Fishers Exact p-value

In the sotrovimab group respiratory events were Grade 1-3 severity and none were considered serious. One event (PT Pneumonia bacterial) was reported as not resolved at the time of data cut off and none were fatal.

In the placebo group respiratory events were Grade 1-5 severity and 6 were considered serious. Two events were reported as not resolved (PTs of dyspnoea and pneumonia) at the time of data cut off and 2 events were fatal (PTs of respiratory failure and pneumonia).

In addition, to identify any potential events that might be suggestive of ADE, a broad array of PTs was reviewed within the renal, cardiac, and pulmonary SOCs. This comprehensive review did not identify any trends suggestive of ADE associated with sotrovimab. Summaries are provided below.

The incidence of the potential pulmonary ADE events was 6% (30/526) in the placebo arm and 1% (6/523) in the sotrovimab arm and there were more severe events in the placebo arm (4 Grade 4 events and 3 Grade 5 events) compared to the sotrovimab arm (3 Grade 3 events).

All potential renal ADE events occurred in the placebo arm 5/526 (<1%) with 3 events of Grade 4 severity.

The incidence of the potential cardiac ADE events was <1% (2/526) in the placebo arm and <1% (5/523) in the sotrovimab arm. The events reported are in different MedDRA higher-level term groups, indicating that the events are in different cardiac pathophysiological conditions. Thus, there is no indication of an emerging immune type effect reminiscent of ADE.

Medical review of the events in the sotrovimab arm show baseline risk factors for each of these events:

- Tachycardia: concurrent with anxiety
- Palpitations (verbatim: worsening of palpitations): participant had baseline palpitations
- Cardiovascular deconditioning (verbatim: deconditioning): Occurred after participant was hospitalized for COVID-19 pneumonia and had concurrent anaemia of chronic disease which may have complicated participant's recovery.
- Cardiomegaly: participant had history of heart disorder and congestive heart failure with baseline Electrocardiogram (ECG) showing left ventricular hypertrophy.
- Myocardial ischemia: participant with history of hypertension, heart failure and baseline ECG showing chamber hypertrophy.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Missing information #1: Use in pregnancy

Risk-benefit impact:

The safety profile of sotrovimab in pregnant and breastfeeding women is not known since they were excluded from the clinical program. Sotrovimab exposure in pregnancy will be monitored in the COVID-19 International Drug Pregnancy Registry (COVID-PR), a non-interventional, post-marketing cohort study, designed to collect prospective safety data among pregnant women treated for COVID-19 at any time during pregnancy and in their offspring until one year of age.

Missing information #2: Use in children ≥12 to <18 years old

Risk-benefit impact:

Only adult patients were included in sotrovimab clinical program to date. Although, the indication includes patients 12 years old whose weight is at least 40kg, it was based on adult PK data extrapolation. A positive opinion for the Paediatric Investigation Plan (PIP) has been received and a paediatric study in patients from birth to <18 years of age to evaluate pharmacokinetics, pharmacodynamics and safety is planned.

SVII.2 New safety concerns and reclassification with a submission of in updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

None

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Use in pregnancy:

Evidence Source:

The safety profile of sotrovimab in pregnant and breastfeeding women is not known since they were excluded from the clinical program. Animal studies are insufficient with respect to reproductive toxicity. 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. There is insufficient information on the excretion of sotrovimab in human milk. A risk to the new-borns/infants cannot be excluded.

Population in need of further characterisation:

Pregnant and breast-feeding women were excluded from clinical studies with sotrovimab. Women of childbearing potential participating in the studies were required to commit to use of a contraceptive method, as specified in the protocol. Sotrovimab exposure in pregnancy will be monitored in the COVID-PR, a non-interventional, post-marketing cohort study, designed to collect prospective safety data among pregnant women treated for COVID-19 at any time during pregnancy and in their offspring until one year of age. Other data, including sales, spontaneous or electronic healthcare data may be utilized to identify and characterize women exposed to Sotrovimab and contextualize the observed sample size and population of COVID-PR.

SVII.3.2.2 Use in children ≥12 to <18 years old:

Evidence Source:

Only adult patients were included in sotrovimab clinical program to date. Although, the indication includes patients 12 years old whose weight is at least 40kg, it was based on adult PK data extrapolation.

Population in need of further characterisation:

Patients <18 years of age were excluded from studies with sotrovimab to date. A positive opinion was received for the PIP and a study in children (from birth to <18 years of age) is planned. In this study, the pharmacokinetics, pharmacodynamics and safety of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of progression will be evaluated.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of safety concerns

Summary of Safety Concerns	
Missing Information	Use in pregnancy Use in children ≥12 to <18 years old

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

The safety of patients is of paramount importance to GSK, and to reflect this commitment, GSK has implemented routine pharmacovigilance practices which are:

- Established processes for the collection and, as required, notification of any AEs occurring anywhere in the world;
- Established processes for the regular and systematic review of ongoing safety data relating to its pharmaceutical products.

This employs a routine, pro-active process for identifying safety signals with four main components:

1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and, qualitative and quantitative methodologies to detect safety signals.
3. Systematic, regular review of the literature.
4. Regular review of data from EudraVigilance (EV), the pharmacovigilance database of the European Medicines Agency (EMA), for products included in EMA's list of medicines under additional monitoring as of 25 October 2017. The Global Safety Database contains information on AEs received from spontaneous sources, literature, regulatory agencies, post-marketing surveillance studies as well as SAEs from clinical studies. AEs and Serious AE reports are actively followed up to obtain relevant clinical information for evaluation.

Potential safety issues identified from non-clinical studies, clinical studies, individual case reviews, signal detection and data mining activities, Periodic Benefit Risk Evaluation Report PBRER)/ Periodic Safety Update Report (PSUR), from regulatory queries or other sources are carefully evaluated. Adverse drug reactions identified during these reviews are incorporated into the Core Safety Information (CSI) for Sotrovimab and subsequently reflected in local country labelling.

Traceability

The SmPC Section 4.4 includes the following instructions to healthcare providers:

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

III.1.1 Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Treatment failure due to emerging variants

Data monitoring, including systematic, and proactive review of the emerging data will be done from all available data sources including but not limited to the following:

- evaluation of new and cumulative non-clinical data (antiviral activity and viral resistance) on new variants found in the sotrovimab epitope
- evaluation of new and cumulative post-baseline epitope variants detected in clinical studies among patients who received sotrovimab, when possible
- evaluation of spontaneous reports via targeted follow up questionnaire for lack of efficacy including information for variant lineage
- evaluation of literature reports
- evaluation of studies conducted by public health authorities

Cumulative data from the reviews will be summarized in a dedicated section of the PSUR. If the review of data leads to an impact on the benefit risk profile of sotrovimab appropriate variation (including the data, a benefit-risk discussion and any warranted product information updates) will be submitted to the agency within one month.

III.2 Additional pharmacovigilance activities

Study short name and title:

COVID-19 International Drug Pregnancy Registry (COVID-PR)

Rationale and study objectives:

The overall objective of the COVID-PR is to evaluate obstetric, neonatal, and infant outcomes among women who required at least one in-hospital or ambulatory medication for mild to severe COVID-19 at any time during pregnancy. Sotrovimab exposure in pregnancy will be one of the medications monitored in the COVID-PR.

Study design:

The COVID-PR is an international, non-interventional, post-marketing cohort study designed to collect prospective safety data among pregnant women treated pharmacologically for mild to severe COVID-19 at any time during pregnancy. It includes maternal and offspring follow-up until the infant's one year of age. Registration and participation, via a website especially developed for the COVID-PR, are voluntary. Eligible women can enrol at any time during pregnancy and up to 30 days after the end of pregnancy. Postpartum mothers and their live offspring are followed-up to the infant's one year of age. In addition to self-reported

information, the web data collection system requests participants upload their de-identified medical records.

Study population:

The study population includes women 18 years of age and older who required in-hospital or ambulatory pharmacological treatment, including Sotrovimab, for mild to severe COVID-19 at any time during pregnancy. The actual study population will depend on medication utilization, the recruitment into the Pregnancy Registry, the retention during follow up and, for livebirth outcomes, on the observed percentage of live births among the study pregnancies. Other data, including sales, spontaneous or electronic healthcare data may be utilized to identify and characterize women exposed to Sotrovimab and contextualize the observed sample size and population of COVID-PR.

Milestones:

Sotrovimab utilization within COVID-PR will be examined on a yearly basis to determine the futility of the study for Sotrovimab. The total duration of the overall COVID-PR study will be 5 years. Obstetric, neonatal, and infant outcomes will be assessed on an ongoing basis as data become available. The first two years will include, primarily, enrolment of pregnancies; the third and fourth years will involve follow-up of pregnancies and new-borns; and, the final year, will be for data analyses and publications. A final report will be prepared at the end of the study.

Milestone	Planned date
Start of data collection	31/12/2021
End of data collection	31/12/2025
Final report of study results	31/12/2026

Study short name and title:

COMET-PACE is an open-label study to evaluate pharmacokinetics, pharmacodynamics and safety following single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of progression.

Rationale and study objectives:

There is an urgent medical need for treatments of coronavirus disease 2019 (COVID-19). While children are more likely than adults to have asymptomatic or mild infection, those that are young or have a history of obesity, gastrointestinal conditions, heart disease since birth, genetic or metabolic conditions, neurologic disease, diabetes mellitus, asthma or chronic lung disease, immunosuppression, Sickle Cell Disease, or baseline medical complexity are more likely to be hospitalized with severe disease or die.

In the sotrovimab clinical development program to date patients <18 years of age were excluded. Therefore, there is a need to evaluate sotrovimab in children (age <18).

In this planned study the main objectives are:

- to assess pharmacokinetics and pharmacodynamics of sotrovimab
- to evaluate safety and tolerability of sotrovimab

Study design:

This study includes 2 cohorts (Cohort A and Cohort B). Participants in Cohort A will receive IV sotrovimab and participants in Cohort B will receive sotrovimab via IM injections.

Cohort A and Cohort B will each enrol approximately 36 participants to be evaluated for the primary analysis divided into the following age groups:

- adolescents 12-<18 years of age – at least 6
- children 6 to <12 years of age – at least 12
- children 2 to <6 years of age – at least 12
- infants and toddlers from birth to <2 years of age (including premature infants born at least at 32 weeks) – at least 6

Each patient will receive single dose of sotrovimab and will be followed for up to 36 weeks post dose. Dosing will be based on weight in each age band.

Study population:

Male and female infants, children and adolescents from birth to <18 years of age (including premature infants born at least at 32 weeks of gestation) with mild to moderate COVID-19 with high risk of progression.

Milestones: Study is planned

Milestone	Planned Date
Final protocol approved (amendment 1)	01 October 2021
Registration in the EU PAS register	TBD
Planned start date	31/12/2021
Final study report	30/06/2024

III.3 Summary Table of additional Pharmacovigilance activities

Table 15 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorisation under exceptional circumstances				
NA				
Category 3- Required additional pharmacovigilance activities				
COVID-19 International Drug Pregnancy Registry (COVID-PR) Planned	To evaluate obstetric, neonatal, and infant outcomes among women who required at least one in-hospital or ambulatory medication for mild to severe COVID-19 at any time during pregnancy and received sotrovimab.	Use in pregnancy	Final study report	31/12/2026
COMET-PACE an open-label study to evaluate pharmacokinetics, pharmacodynamics and safety following a single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of disease progression Planned	To evaluate pharmacokinetics, pharmacodynamics and safety in children with mild to moderate COVID-19 with high risk of progression	Use in children ≥12 to <18 years old	Final study report	30/06/2024

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None

Table 16 Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 17 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Safety concern 1 Use in pregnancy	**Routine risk communication:** SmPC includes appropriate information in Section 4.6, Fertility, Pregnancy and Lactation, and Section 5.3 Preclinical Safety Data. Equivalent wording is included in the patient leaflet Section 2
Safety concern 2 Use in children ≥12 to <18 years old	**Routine risk communication:** The SmPC includes appropriate information in Section 4.2, Posology and method of Administration, Section 5.1, Pharmacodynamic properties, and Section 5.2, Pharmacokinetic properties. Equivalent wording is included in the patient leaflet Section 2

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 18 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety concern 1 Use in pregnancy	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.6, Fertility, Pregnancy and Lactation and Section 5.3 Preclinical Safety Data Equivalent wording is included in the patient leaflet Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** COVID-19 International Drug Pregnancy Registry (COVID-PR) Final study report – 31/12/2026
Safety concern 2 Use in children ≥12 to <18 years old	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.2, Posology and method of Administration, Section 5.1, Pharmacodynamic properties, and Section 5.2, Pharmacokinetic properties. Equivalent wording is included in the patient leaflet Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Planned open-label study (COMET-PACE) to evaluate pharmacokinetics, pharmacodynamics and safety following single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of progression. Final study report – 30/06/2024

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Xevudy (Sotrovimab)

This is a summary of the risk management plan (RMP) for Xevudy. The RMP details important risks of Xevudy, how these risks can be minimised, and how more information will be obtained about Xevudy 's risks and uncertainties (missing information).

Xevudy 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Xevudy should be used.

This summary of the RMP for Xevudy should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xevudy's RMP.

I. The medicine and what it is used for

Xevudy is authorized for the treatment of patients with coronavirus disease 2019 (COVID-19) who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 (see SmPC for the full indication). It contains sotrovimab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Xevudy's benefits can be found in Xevudy's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/xevudy

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Xevudy, together with measures to minimise such risks and the proposed studies for learning more about Xevudy 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Xevudy is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Xevudy are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xevudy. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Missing information	Use in pregnancy Use in children ≥12 to <18 years old

II.B Summary of important risks

Missing Information: Use in pregnancy	
Risk minimisation measures	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.6, Fertility, Pregnancy and Lactation, and Section 5.3 Preclinical Safety Data Equivalent wording is included in the patient leaflet Section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** *Short study name:* COVID-19 International Drug Pregnancy Registry (COVID-PR) *See section* II.C *of this summary for an overview of the post-authorisation development plan.*

Missing Information: Use in children ≥12 to <18 years old	
Risk minimisation measures	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.2, Posology and method of Administration, Section 5.1, Pharmacodynamic properties, and Section 5.2, Pharmacokinetic properties. Equivalent wording is included in the patient leaflet Section 2 **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** *Short study name:* Planned open-label COMET-PACE study to evaluate pharmacokinetics, pharmacodynamics and safety following single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of progression. *See section* II.C *of this summary for an overview of the post-authorisation development plan.*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of sotrovimab.

II.C.2 Other studies in post-authorisation development plan

Study Short Name:

COVID-19 International Drug Pregnancy Registry (COVID-PR)

Purpose of the Study:

The overall objective of the COVID-19 International Multi-Drug Pregnancy Registry (COVID-PR) is to evaluate obstetric, neonatal, and infant outcomes among women who required at least one in-hospital or ambulatory medication for mild to severe COVID-19 at any time during pregnancy. Sotrovimab exposure in pregnancy will be one of the medications monitored in the COVID-PR.

Study Short Name:

Planned COMET-PACE study to evaluate pharmacokinetics, pharmacodynamics and safety following single dose of sotrovimab in paediatric patients with mild to moderate COVID-19 at high risk of progression

Purpose of the Study:

There is an urgent medical need for treatments of coronavirus disease 2019 (COVID-19). While children are more likely than adults to have asymptomatic or mild infection, those that are young or have a history of obesity, gastrointestinal conditions, heart disease since birth, genetic or metabolic conditions, neurologic disease, diabetes mellitus, asthma or chronic lung disease, immunosuppression, Sickle Cell Disease, or baseline medical complexity are more likely to be hospitalised with severe disease or die.

In the sotrovimab clinical development program to date patents <18 years of age were excluded. Therefore, there is a need to evaluate sotrovimab in children (age <18).

In this planned study the main objectives are:

- to assess pharmacokinetics and pharmacodynamics of sotrovimab
- to evaluate safety and tolerability of sotrovimab

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

GlaxoSmithKline

Targeted Follow Up Questionnaire

Sotrovimab

Lack of Efficacy – SARS-CoV2 Variant Information

Date of Birth: GSK CASE No:

Patient Information and Testing for SARS-CoV-2 Infection

Date (DD/MMM/YYYY) of COVID-19 diagnosis:

Indicate how COVID-19 was diagnosed:

☐ Clinical ☐ PCR ☐ Antigen (e.g. lateral flow test) ☐ Other, please specify:

Duration of COVID-19 symptoms (days) prior to receiving sotrovimab:

Was supplemental oxygen required prior to onset of COVID-19 symptoms? ☐ Yes ☐ No

If Yes, indicate the following:

☐ supplemental oxygen (not high flow) ☐ non-invasive ventilation or high-flow

☐ invasive ventilation or ECMO

Was supplemental oxygen required due to COVID-19 prior to sotrovimab? ☐ Yes ☐ No

If Yes, indicate the following:

☐ supplemental oxygen (not high flow) ☐ non-invasive ventilation or high-flow

☐ invasive ventilation or ECMO

Was the patient's serostatus assessed? ☐ Yes ☐ No

If Yes, please indicate if assessed by:

☐ antibodies to spike protein ☐ antibodies to nucleocapsid

☐ Other, please specify name of test used:

Result:

Product number of test used: Or Product lot/batch number:

Age range (years): ☐ <12 ☐ ≥12 - <18 ☐ ≥18 - <60 ☐ ≥ 60 - <85 ☐ ≥85

BMI (kg/m^2): ☐ <18.5 ☐ 18.5-24.9 ☐ 25-29.9 ☐ 30-34.9 ☐ 35-39.9 ☐ >40

If height not available, please provide weight (kg):

Does the patient have any of the following risk factors? Mark all that apply

☐ Cardiovascular disease (including congenital heart disease) or hypertension

☐ Chronic kidney disease

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

☐ Diabetes

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

☐ Pregnancy

☐ Sickle cell disease

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

☐ Any other ongoing comorbidities you might consider as a risk factor, please specify:

Is the patient considered to be immunocompromised? ☐ Yes ☐ No

If yes, please state if:

☐ **Primary (PIDs):**

☐ B cell immunodeficiencies ☐ T cell immunodeficiencies (*other than HIV*)

☐ Severe combined immune deficiencies (SCID) ☐ Complement defects

☐ other, please specify:

☐ **Secondary (SIDs):**

☐ Malnutrition ☐ Chemotherapy ☐ HIV ☐ Chronic infections (other than HIV)

☐ Immunosuppressive therapy after organ transplant

☐ Other concomitant immunosuppressive therapy, please specify:

Vaccination Status

COVID-19 vaccination status (select one):

☐ Not vaccinated
☐ Partial vaccinated (one dose of the two-dose regimen)
☐ Fully vaccinated (one dose of a one dose regimen or at least two doses of the two-dose regimen)
☐ Unknown

If vaccinated, please specify:

First vaccine: Brand: Date (DD/MM/YYYY):

Second vaccine: Brand: Date (DD/MM/YYYY):

Third vaccine*: Brand: Date (DD/MM/YYYY):

Additional (e.g. booster) vaccine: Brand: Date (DD/MM/YYYY):

*complete for standard 3 dose vaccine regimen, i.e. for severely immunocompromised patients

Lack of Efficacy Assessment

Is this event considered lack of efficacy? ☐ Yes ☐ No

If yes, please select criteria used to determine this; Mark all that apply

☐ Progression to severe COVID-19* ☐ Required oxygenation for COVID-19

☐ Required hospitalization for COVID-19 ☐ Death due to COVID-19

☐ Other, please specify:

If supplemental oxygenation required, indicate the following:

☐ supplemental oxygen (not high flow) ☐ non-invasive ventilation or high-flow

☐ invasive ventilation or ECMO

* for example individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, lung infiltrates >50%, respiratory failure, septic shock, and/or multiple organ dysfunction (NIH COVID-19 treatment guidelines, 2021).

Virus Variant Detection

Was sequencing for SARS-COV2 virus variant identification performed? ☐ Yes ☐ No

If Yes, please attach a copy of the report or complete the below

If more than one test was performed please append all reports or complete the below for each test separately

Was the sample collected: Before sotrovimab ☐ After sotrovimab ☐

Date (DD/MMM/YYYY) of sample collection for testing:

Virus variant sequencing results obtained:

☐ Yes ☐ No - the viral load is too low to perform variant sequencing

If Yes, select WHO variant of interest or variant of concern detected:

☐ Alpha B.1.1.7 UK ☐ Iota B.1.526 USA (New York)

☐ Beta B.1.351 South Africa ☐ Kappa B.1.617.1 India

☐ Delta B.1.617.2 India ☐ Lambda C.37 Peru

☐ Delta [+K417N] AY.1/AY.2 India ☐ Mu B.1.621 Colombia

☐ Gamma P.1. Brazil ☐ Omicron B.1.1.529

☐ Other, please specify virus lineage:

List specific spike amino acid substitutions detected:

E340 substitutions:

☐ E340A ☐ E340K ☐ E340V ☐ Other E340 substitution, please specify:

P337 substitutions:

☐ P337L ☐ P337K ☐ P337R ☐ Other P337 substitution, please specify:

Other substitutions:

☐ Other, please specify:

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