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	1.1
Data lock point for this RMP	19 August 2023
Date of final sign off	06 November 2023

Rationale for submitting an updated RMP

This EU RMP update is to propose to:

- remove Use in children ≥12 to <18 years old as missing information (supporting data provided in Part II Module SVII.2)
- remove COMET PACE study as an interventional PASS – study terminated early (see Part II Module SVII.2)
- discontinue use of sotrovimab specific Targeted Follow up Questionnaire to collect additional information for reports of potential lack of efficacy including information on virus lineage; this proposal is supported by review of information collected and summarized in each 6-monthly PBRER/EU PSUR for sotrovimab since implementation of TFuQ in December 2021; based on the limited data received via TFuQ no new information has been received to what is being acquired from ongoing in vitro testing and literature review

Summary of significant changes in this RMP:

PART	MODULE	Changes made in EU-RMP version 1.1
II	SI	Relevant epidemiology information updated to reflect current information for the target population
II	SIII	Updated clinical exposures
II	SV	Updated with estimated post authorization exposures
II	SVII1.1, 1.2 and 3.2	Updated to remove Use in children ≥12 to <18 years old as missing information
II	SVII.2	Updated to provide supporting data for removal of Use in children ≥12 to <18 years old as missing information
II	SVIII	Updated to remove Use in children ≥12 to <18 years old as missing information
III	III.1.1	Updated to remove use of TFuQ to collect additional information for reports of potential lack of efficacy including information on virus lineage

III	III.2 and III.3	Updated to remove COMET-PACE study
V	V.1 and V.3	Updated to remove Use in children ≥12 to <18 years old as safety concern
VI	II.A, II.B and II.C	Updated to align with changes in the 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)
1.1	EMEA/H/C/005676/II/0026	7 March 2024

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic Signature on File

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
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
COVID-PR	COVID-19 International Drug Pregnancy Registry
CSI	Core Safety Information
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
ED	Emergency department
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUA	Emergency Use Authorization
EV	EudraVigilance
GISAID	Global Initiative on Sharing All Influenza Data
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HSR	Hypersensitivity reactions
ICH	International Conference of Harmonization
IDMC	Independent Data Monitoring Committee
IgG1	Immunoglobulin G1
IM	Intramuscular
IRR	Infusion related reactions
IV	Intravenous
MAA	Marketing Authorization Application
mAb	Monoclonal Antibody
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	Multisystem Inflammatory Syndrome in Children
NYHA	New York Heart Association
PASS	Post authorization safety study
PBRER	Periodic Benefit Risk Evaluation Report
PIP	Pediatric Investigation Plan

PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PT	Preferred term
RMM	Risk Minimization Measure
RMP	Risk Management Plan
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard deviation
SmPC	Summary of product Characteristics
SMQ	Standard MedDRA Query
TESSy	The European Surveillance System
ULN	Upper limit of normal
US	United States
Vir	Vir Biotechnology, Inc.
VLP	Virus-like particle
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Xevudy

Trademarks not owned by the GlaxoSmithKline group of companies
REGEN-COV
Evusheld
Kineret
Paxlovid
Regkirona
RoActemra
Ronapreve
Veklury
Bimervax
Comirnaty
Valneva
Jcovden
Spikevax
Vaxzevria

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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)	J06BD05
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 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	Please refer to the product information in the Module 1.3.1 of the eCTD
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. The use of Xevudy should take into account information on the activity of sotrovimab against viral variants of concern.

	Proposed: No change
Dosage in the EEA	**Current:** The recommended dose is a single 500 mg intravenous infusion administered following dilution. **Proposed:** No change
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, colorless, or yellow to brown solution free from visible particles, with a pH of approximately 6 and an osmolality of approximately 290 mOsm/kg. **Proposed:** No change
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

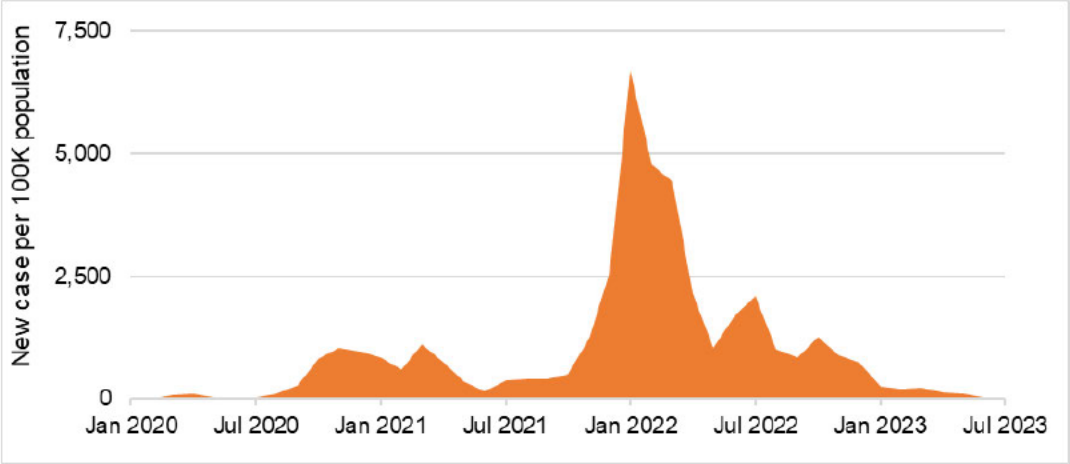
SI.1 Indication

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

From 1 January 2020 to 27 July 2023, there were a total of 41,415 cases of COVID-19 infections per 100,000 people in European Economic Area (EAA) / European Union (EU) over a span of 42.5 months. The highest number of cases of COVID-19 infections per 100,000 people were reported in January 2022 (6,699 cases per 100,000 people), followed by February and March 2022 (4,761 and 4,419 cases per 100,000 people, respectively) [Figure 1] [ECDC, 2023a]

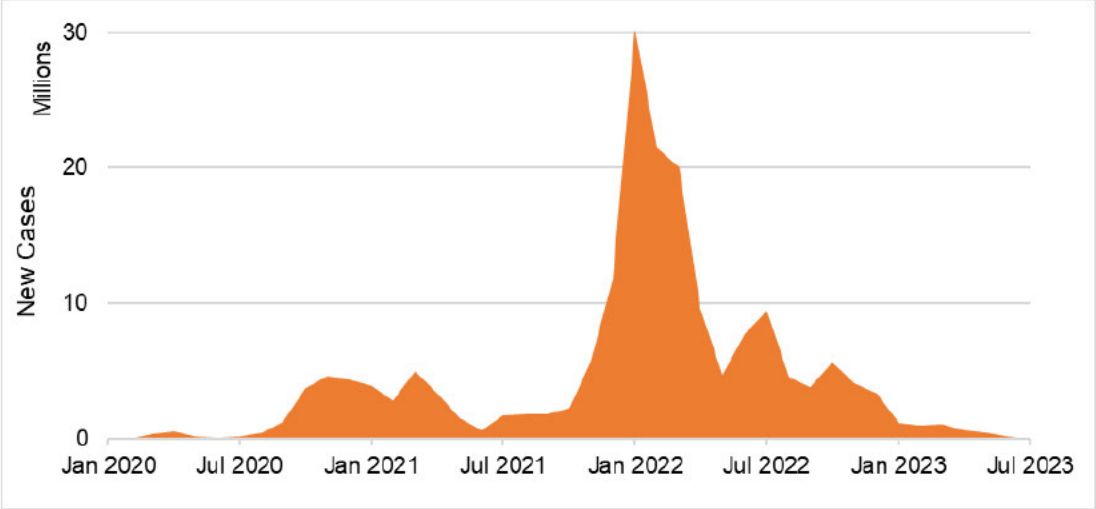
Figure 1 New confirmed COVID-19 cases per 100,000 population in EU/EAA



EAA: European Economic Area, EU: European Union Calculated based on the ECDC, 2023a.

In the first quarter of 2022, an increase was observed in EU/EAA in terms of new COVID-19 cases. In January, 30,318,898 new COVID-19 cases were reported, followed by 21,545,047 new COVID-19 cases in February and 19,999,847 in March 2022 [Figure 2] [ECDC, 2023a].

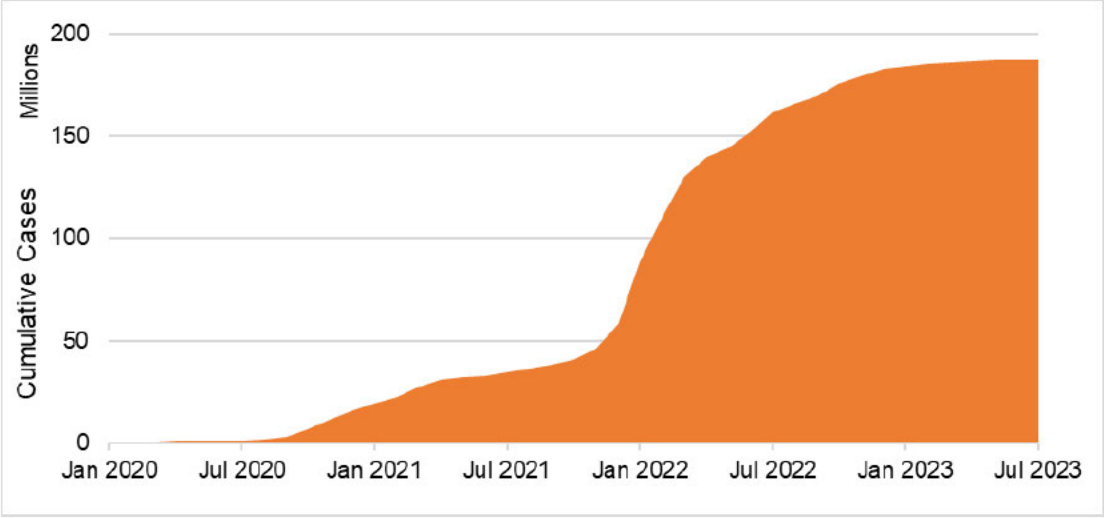
Figure 2 New confirmed COVID-19 cases in EU/EAA



EAA: European Economic Area, EU: European Union Calculated based on the ECDC, 2023a.

European Centre for Disease Prevention and Control (ECDC)'s reports for EU/EAA from 27 July 2023, revealed that there had been a total of 187,436,630 confirmed cases of COVID-19 in EU/EAA [Figure 3] [ECDC, 2023a].

Figure 3 Cumulative confirmed COVID-19 cases in EU/EAA



EAA: European Economic Area, EU: European Union Calculated based on the ECDC, 2023a.

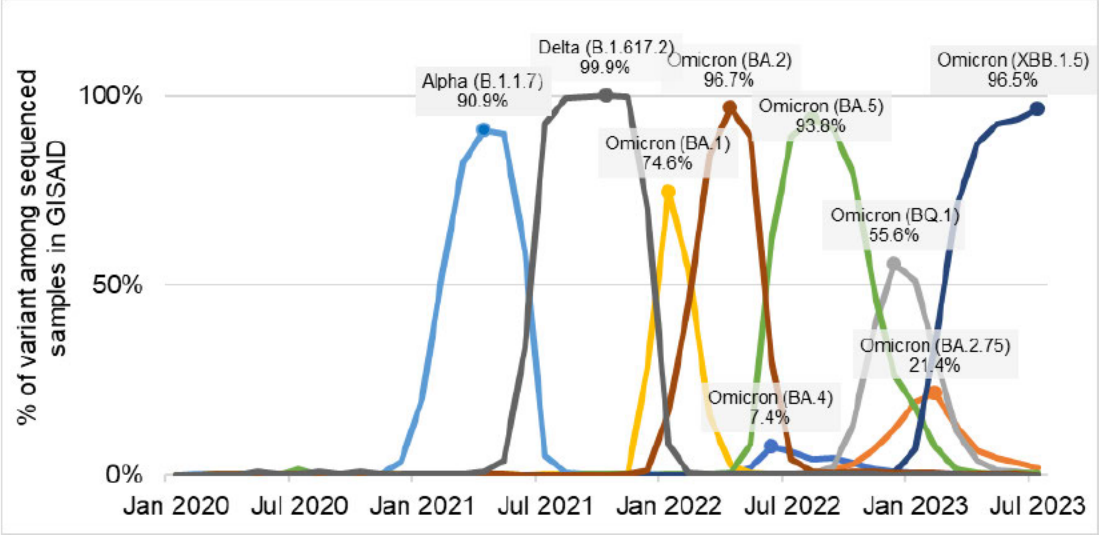
SARS-CoV-2 Variants

The virus responsible for causing COVID-19, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has undergone mutations over time, as is

common with many viruses. While most of these mutations have not had a significant impact on the virus, some mutations affected the virus's virulence, disease severity, or the effectiveness of vaccines, and medicines.

Global Initiative on Sharing All Influenza Data (GISAID) has facilitated the exchange of outbreak genome data during the COVID-19 pandemic [GISAID 2023]. Based on EU/EAA data recorded in the GISAID repository, the Alpha (B.1.1.7) variant peaked in April 2021, whereas Delta (B.1.617.2) in October 2021. Omicron BA.1 subvariant peaked in January 2022, followed by Omicron BA.2 subvariant in April 2022, Omicron BA.4 subvariant in June 2022, Omicron BA.5 subvariant in August 2022, Omicron BQ.1 subvariant in December 2022, Omicron BA.2.75 subvariant in February 2023 and Omicron XBB.1.5 subvariant in July 2023 [Figure 4] [ECDC, 2023b].

Figure 4 SARS-CoV-2 variants over time in GISAID

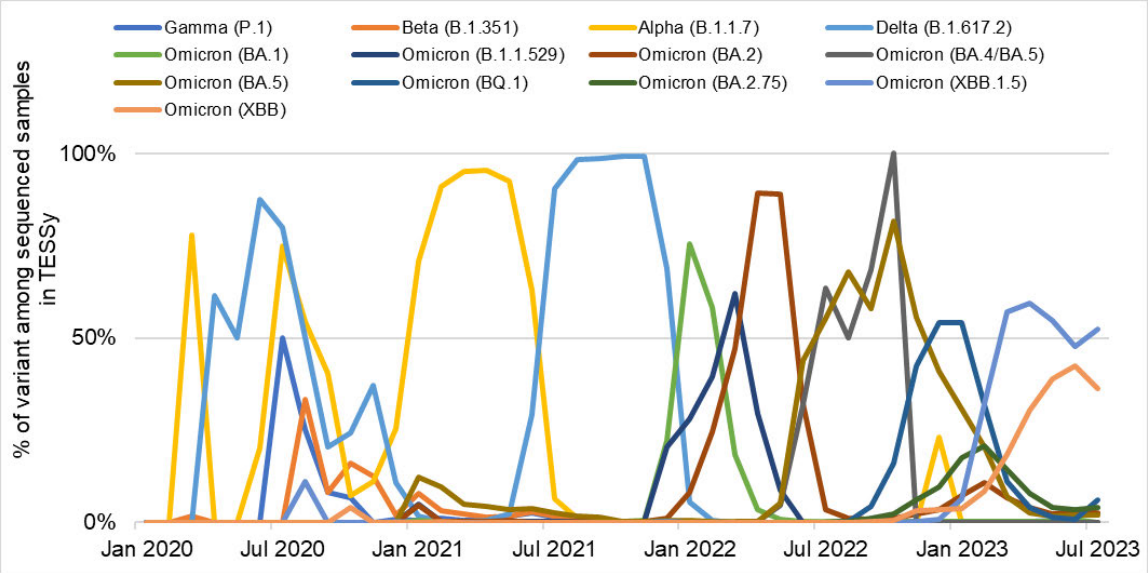


Percentage of variants among sequenced samples in GISAID repository with a peak percentage of less than 7% were omitted from the graph to increase the readability of the graph. Calculated based on the ECDC, 2023b.

The ECDC also shares information about COVID-19 variants through the European Surveillance System (TESSy) repository. While the data provided by TESSy were more detailed and provided more details for the first year of the pandemic, it was based on a smaller number of samples compared to GISAID [ECDC, 2023b].

The sequencing results from TESSy repository revealed that Gamma (P.1) variant peaked in July 2020, followed by Beta (B.1.351) variant in August 2020, Alpha (B.1.1.7) variant in April 2021 and Delta (B.1.617.2) variant in October 2021. An Omicron subvariant (BA.1) first reached its peak in January 2022, and since then, many other Omicron subvariants reached their peak [Figure 5][ECDC, 2023b].

Figure 5 SARS-CoV-2 variants over time in TESSy



Percentage of variants among sequenced samples in TESSy repository Variants with peak percentage less than 10% were omitted from the graph and monthly results based on less than 25 sequencings were omitted from the graph to increase readability of the graph. Calculated based on the ECDC, 2023b.

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

Gender and Age

The COVID-19 detailed surveillance dashboard by the World Health Organization (WHO) reports gender and age-related information regarding COVID-19 patients, which is based on the data reported by countries.

As of 24 July 2023, gender information was available for 793,514,917 cases, out of which 53.3% were female. [WHO 2023b].

Up until 24 July 2023, the majority of COVID-19 cases (67.2%) were aged between 20 to 59 years old, while 16.0% were under 20 years old. The remaining 16.8% were aged over 60 years old. [WHO 2023b].

Non-hospitalized cases tend to be females and are younger than those who are hospitalized or hospitalized with severe disease. In a European multi-center 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].

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. 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) have been identified for both progression to severe disease and mortality [ECDC, 2021; Gold, 2020; Jordan, 2020; Weiss, 2020; Zheng, 2020].

SI.1.2 The main existing treatment options

Prior to the development of effective vaccines and medical treatments for SARS-CoV-2, precautionary measures such as social distancing, isolation, wearing face masks, limiting mobility, and travel restrictions were put in place to help slow the spread of the virus.

As of 27 July 2023, eight treatments have been authorized for use in the EU. The first authorization was issued in July 2020, followed by 7 marketing authorizations in 2021 and 2022. [Table 3] [EMA, 2023a].

Table 3 Treatments authorized for use in the European Union

Treatment	Status
Evusheld (tixagevimab / cilgavimab)	Marketing authorization granted: 25/03/2022
Kineret (anakinra)	Marketing authorization granted: 17/12/2021
Paxlovid (nirmatrelvir / ritonavir)	Conditional marketing authorization granted: 28/01/2022
Regkirona (regdanvimab)	Marketing authorization granted: 12/11/2021
RoActemra (tocilizumab)	Marketing authorization for COVID-19 indication granted: 07/12/2021
Ronapreve (casirivimab / imdevimab)	Marketing authorization granted: 12/11/2021
Veklury (remdesivir)	Marketing authorization granted: 08/08/2022 Conditional marketing authorization granted: 03/07/2020
Xevudy (sotrovimab)	Marketing authorization granted: 17/12/2021

Table was created based on publicly available information on EMA website (EMA, 2023a)

Xevudy (sotrovimab) is a monoclonal antibody with activity against the SARS-CoV-2 virus. Xevudy was approved in the EU for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of the disease becoming severe. It is recommended to be given as an IV infusion within 5 days of the patient developing symptoms of COVID-19 [EMA. 2023a]. The summary of product characteristics has been updated three times in 2022 to indicate that Xevudy showed a decrease in in-vitro neutralization against Omicron subvariants, and the clinical relevance of the observed decrease in in-vitro neutralization against Omicron subvariants is not known. Finally, the SmPC was updated to indicate that it is unlikely that sotrovimab might be expected to provide clinical benefit against certain Omicron lineages currently driving the COVID-19 pandemic [EMA, 2023e].

Evusheld consists of two monoclonal antibodies, tixagevimab and cilgavimab. European Medicines Agency (EMA) has approved Evusheld for the prevention of COVID-19 in

adults and adolescents from 12 years of age who weigh at least 40 kg and who may be at risk of exposure to the virus, and it should be given intramuscularly as soon as possible after a positive test for SARS CoV-2 and within 7 days of the start of symptoms of COVID-19 [EMA, 2023a]. In the first quarter of 2023, the Food and Drug Administration (FDA) in the US withdrew their authorization for the use of Evusheld. This was due to the medication considered being likely ineffective against the subvariant of Omicron that was circulating at the time of the decision. In the United Kingdom, while Evusheld was still authorized, the National Institute for Health and Care Excellence (NICE) stop recommending its use for same reason [Mahase, 2023].

Regkirona (regdanvimab) is a monoclonal antibody with activity against the SARS-CoV-2 virus. EMA approved Regkirona for the prevention of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe and it should be given as a single iv infusion within 7 days of the start of COVID-19 symptoms [EMA, 2023a]. In May 2022, the summary of product characteristics was updated by indicating that the Omicron variant showed reduced susceptibility against Regkirona in in-vitro evaluations [EMA, 2023b]

Ronapreve consists of two monoclonal antibodies - casirivimab and imdevimab. It has been approved by the EMA for use in treating COVID-19 in adults and adolescents who are at a higher risk of developing severe symptoms and who do not require oxygen supplementation. Ronapreve can also be used to prevent COVID-19 in people aged 12 years and older who weigh at least 40 kg. It can be administered as an IV infusion or subcutaneously. If Ronapreve is being used for treatment, it should be given within 7 days of the onset of COVID-19 symptoms. If it is being used for prevention after contact with someone who has COVID-19, Ronapreve should be administered as soon as possible after the contact occurs [EMA, 2023a]. In March 2022, the summary of product characteristics was updated by indicating that the Omicron variants showed reduced susceptibility against Ronapreve in in-vitro evaluations [EMA, 2023c].

Paxlovid is a combination of 2 anti-virals, nirmatrelvir / ritonavir, as separate tablets, and EMA has approved Paxlovid for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19, and it should be given orally twice a day for 5 days. Paxlovid should be started as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of the start of symptoms [EMA, 2023a]. The opinion/ notification issued in the summary of product characteristics in January 2023 indicated that nirmatrelvir showed antiviral activity against the Omicron sub-variants B.1.1.529/BA.1, BA.2, BA.2.12.1, BA.4, and BA.5 based on in vitro assays [EMA, 2023e].

Veklury (remdesivir) is an antiviral approved in the EU for treatment of COVID-19 in adults and children, from at least 4 weeks of age and weighing at least 3 kg, with pneumonia requiring supplemental oxygen and also in adults and children (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19. It should be given as an IV infusion [EMA, 2023a]. In May 2023, EMA updated the summary of product characteristics by indicating that Veklury showed no relevant decrease in susceptibility, demonstrating full potency against all Omicron subvariants tested to date [EMA 2023f].

RoActemra (tocilizumab) is a monoclonal antibody which has been used for the treatment of rheumatic diseases, and RoActemra indication was expanded to include treatment of

COVID-19 patients who are receiving treatment with corticosteroid medicines by mouth or injection and require extra oxygen or mechanical ventilation [EMA, 2023a].

Kineret, anakinra, is a human interleukin-1 (IL-1) receptor antagonist. It is currently approved for use in the EU to treat different types of inflammatory conditions. The indication of Kineret was expanded in the EU to include the treatment of COVID-19 in adult patients who have pneumonia and require extra oxygen support and are at risk of experiencing severe respiratory failure [EMA, 2023a]. However, a recent meta-analysis conducted by Dahms in 2023 suggested that Kineret may not have any beneficial effect on the mortality rate or clinical improvement in adult patients who are hospitalized with SARS-CoV-2 infection [Dahms, 2023].

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

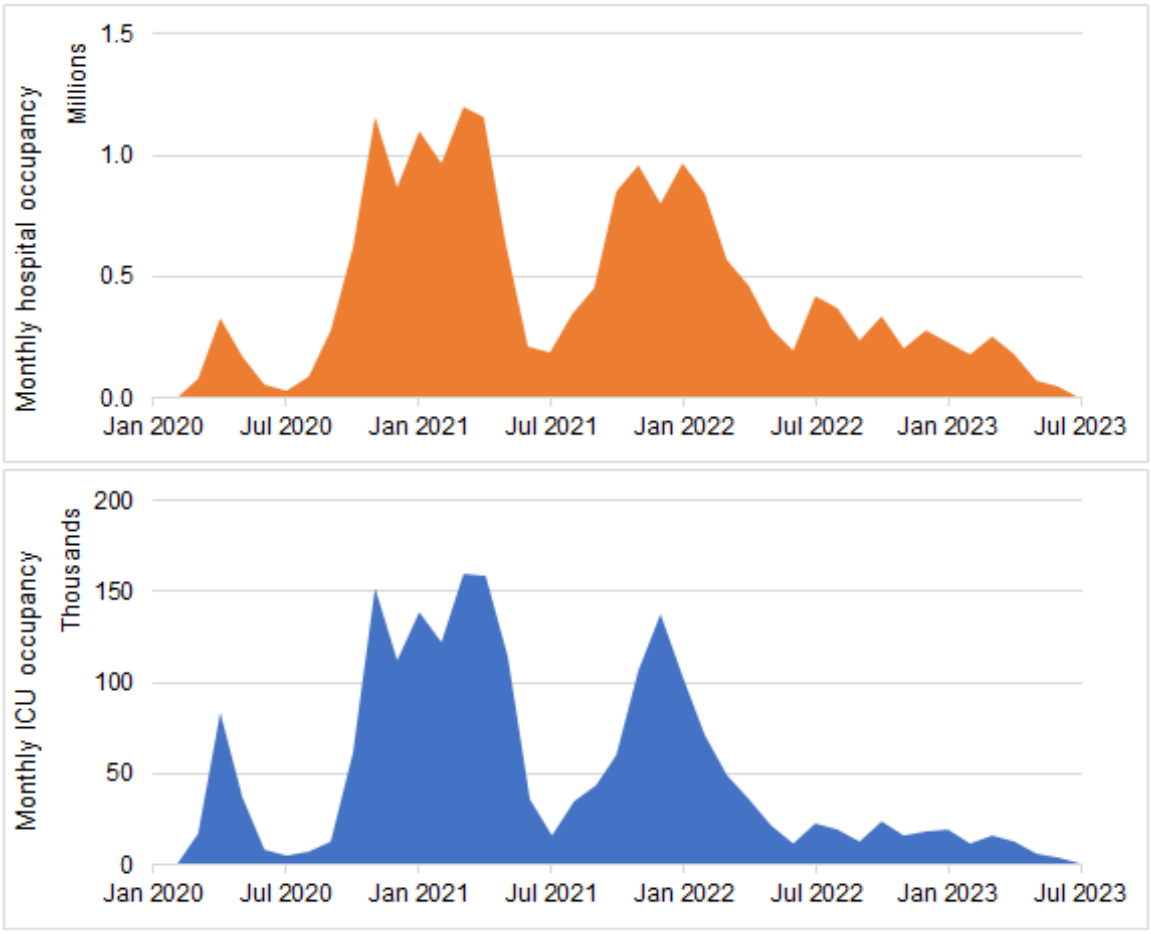
The clinical presentation and natural history of COVID-19 depends on the age and the comorbidities of the patient. Children and young adults tend to experience mild or no symptoms, while older adults may experience severe symptoms such as acute respiratory distress syndrome and even death. COVID-19 patients can experience a range of symptoms, from mild to critical illness. Typically, symptoms start with influenza -like symptoms such as high fever, dry cough, and fatigue, and progress to breathing difficulties [Khan 2020].

It has been shown that older age, being male and having pre-existing comorbidities were the main risk factors for the severity and mortality of COVID-19 disease progression. Sustained low level of immunity status due to older age, pre-existing comorbidities or autoimmune disease or using immunosuppressive treatment results in lower immune response to virus and cause more severe disease [Zhang, 2023].

Hospitalization and Intensive care admission attributed to COVID-19

Between 1 January 2020, and 27 July 2023, hospitals in the EU reported a total 18,737,194 daily occupancy attributed to COVID-19, while intensive care units reported a total 2,109,422 daily occupancy attributed to COVID-19 for the same period. The data from ECDC indicates that the biggest surge in hospital occupancy was recorded between November 2020 and April 2021. During this six-month period, around a total of 6.5 million daily hospital occupancy and around 0.84 million daily intensive care unit occupancy were reported, with the highest of 1.2 million hospital occupancy and 0.16 million intensive care unit occupancy in March 2021. Following this period, from October 2021 to February 2022, approximately a total of 4.4 million daily hospital occupancy and 0.48 million daily intensive care unit occupancy were reported, with the highest of 0.96 million hospital occupancy in January 2022 and 0.14 million intensive care unit occupancy in December 2021 [Figure 6] [ECDC, 2023c].

Figure 6 Hospitalizations and intensive care occupancy attributed to COVID-19 in EU/EAA

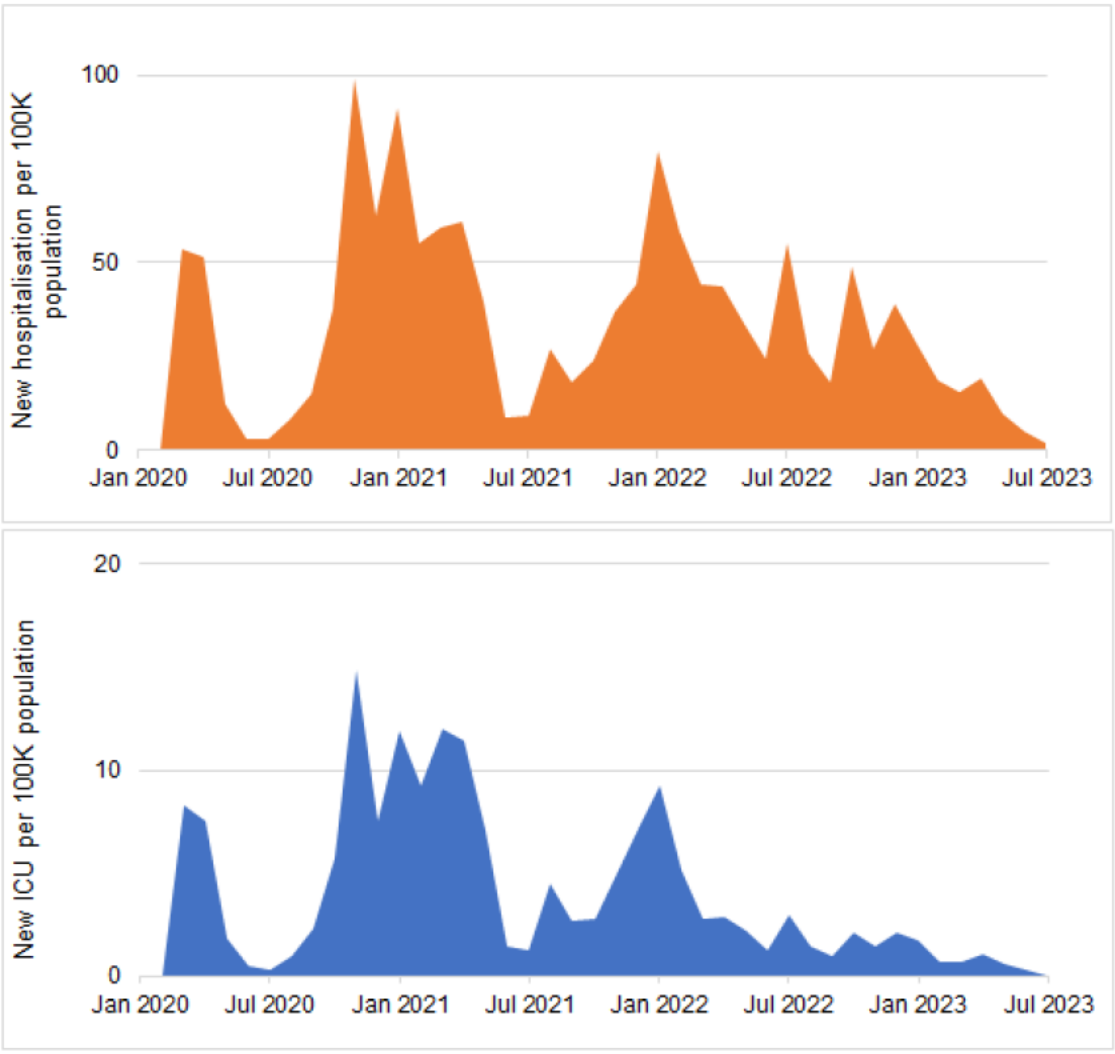


a. hospital occupancy attributed to COVID-19 in EU/EAA
b. intensive care occupancy attributed to COVID-19 in EU/EAA
EAA: European Economic Area, EU: European Union Calculated based on daily occupancy number from ECDC, 2023c.

From 1 January 2020 to 27 July 2023, there were several peaks in monthly new hospitalizations and intensive care unit admission attributed to COVID-19 per 100,000 population.

The highest rate of new hospitalizations per 100,000 population occurred in November 2022 (99.1/100,000), followed by January 2021 (91.1/100,000) and January 2022 (79.9/100,000). The pattern was similar for new intensive care unit admissions, with the highest rate of new admissions per 100,000 population occurring in November 2022 (14.9/100,000), followed by March 2021 (12.0/100,000) and January 2021 (11.9/100,000) [Figure 7] [ECDC,2023c].

Figure 7 **New hospitalizations and intensive care admissions per 100,000 population**



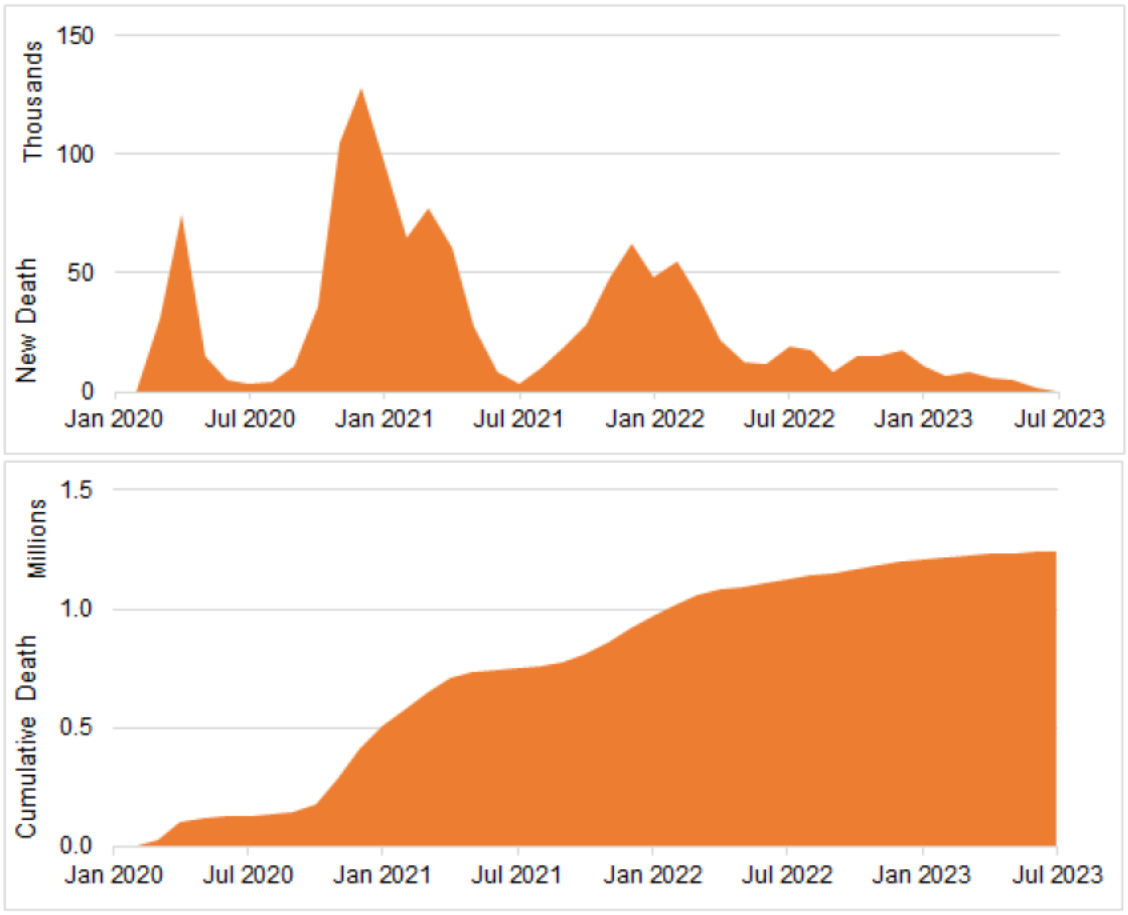
a. new hospitalization attributed to COVID-19 per 100,000 population in EU
b. new intensive care unit admission attributed to COVID-19 per 100,000 population in EU
EU: European Union Calculated based on weekly new case number from ECDC, 2023c.
Population size of countries were based on the ECDC, 2023a.

Mortality

As of 27 July 2023, the number of deaths attributed to COVID-19 stands at 1,238,895 in EU/EAA. Almost 86% of the deaths were reported within two years after the World Health Organization declared a global pandemic of COVID-19 (from March 2020 to March 2022) [Figure 8] [ECDC2023a].

A surge was observed in EU/EAA in terms of deaths attributed to COVID-19 during late 2020 and early 2021. In December 2020, 128,194 deaths attributed to COVID-19 were reported, followed by 104,499 deaths attributed to COVID-19 in November 2020 and 95,552 in January 2021 [Figure 8] [ECDC, 2023a].

Figure 8 New and cumulative deaths attributed to COVID in EU/EAA



a. New deaths attributed to COVID in EU/EAA
b. Cumulative death attributed to COVID-19 in EU/EAA
EAA: European Economic Area, EU: European Union Calculated based on the ECDC, 2023a.

Vaccination

As of 27 July 2023, eight vaccines have been authorized for use in the EU. The first marketing authorization was issued in December 2020, followed by four authorizations in 2021. So far seven vaccines had received standard marketing authorization in the EU [Table 4] [EMA, 2023a].

Table 4 Vaccines have been authorized for use in the European Union

Vaccine	Key milestones
Bimervax (previously COVID-19 Vaccine HIPRA)	Marketing authorization issued: 30/03/2023
Comirnaty (developed by BioNTech and Pfizer)	Conditional marketing authorization issued: 21/12/2020 Annual renewal issued: 03/11/2021 Comirnaty Original/Omicron BA.1 (adapted) authorized: 01/09/2022 Comirnaty Original/Omicron BA.4-5 (adapted) authorised: 12/09/2022 Full marketing authorization issued: 10/10/2022
Valneva COVID-19 Vaccine (inactivated, adjuvanted)	Marketing authorization issued: 24/06/2022
Jcovden (previously COVID-19 Vaccine Janssen)	Conditional marketing authorization issued: 11/03/2021 Annual renewal issued: 03/01/2022 Full marketing authorization issued: 10/01/2023
Nuvaxovid	Conditional marketing authorization issued: 20/12/2021 Annual renewal issued: 03/10/2022
Spikevax (previously COVID-19 Vaccine Moderna)	Conditional marketing authorization issued: 06/01/2021 Annual renewal issued: 04/10/2021 Spikevax bivalent Original/Omicron BA.1 (adapted) authorized: 01/09/2022 Standard marketing authorization issued: 03/10/2022 Spikevax bivalent Original/Omicron BA.4-5 (adapted) authorized: 20/10/2022
Vaxzevria (previously COVID-19 Vaccine AstraZeneca)	Conditional marketing authorization issued: 29/01/2021 Annual renewal issued: 09/11/2021 Standard marketing authorization issued: 31/10/2022
VidPrevtyn Beta	Marketing authorization issued: 10/11/2022

Table was created based on the information provided in EMA, 2023a

SI.1.4 Important co-morbidities

It has been shown that older age, being male and having pre-existing comorbidities were the main risk factors for severe COVID-19 symptoms, hospitalization, admission to an intensive care unit, intubation, and mortality.

Sustained low level of immunity status due to older age, pre-existing comorbidities or autoimmune disease or using immunosuppressive treatment results in lower immune response to virus and cause more severe disease [Zhang, 2023].

A recent meta-analysis synthesized the results from observational studies to describe the common comorbidities among COVID-19 patients [Chenchula, 2023].

Among COVID-19 patients globally, hypertension was the most commonly observed comorbidity, affecting nearly 39% of them. Following closely were diabetes mellitus and obesity, both affecting around 27% of patients whereas asthma was observed in 8% of patients. Moreover, around 15% of COVID-19 patients worldwide had a history of smoking [Table 5][Chenchula 2023].

In Europe, hypertension was the most common comorbidity as well, affecting 43% of patients, followed by obesity at 23%, and diabetes mellitus at 20%. Asthma was observed in 9% of patients in Europe, while 16% of them reported a smoking history [Table 5] [Chenchula 2023].

Table 5 Pooled percentage of patients with comorbidities at the global level and continental Europe

	Global*	Continental Europe*
Comorbidity; % (95% CI of %)		
Hypertension	39 (36 - 42)	43 (39 - 47)
Diabetes Mellitus	27 (25 - 30)	20 (17 - 23)
Obesity	27 (25 - 30)	23 (20 - 26)
Asthma	8 (7 - 9)	9 (8 - 11)
Clinical characteristics; % (95% CI of %)		
Smoking	15 (12 - 18)	16 (11 - 22)

CI: lower and upper bounds of confidence interval
Table was created based on results in Chenchula, 2023
* Authors calculated the pooled percentage estimates of comorbidities by using regional / country population size weights

PEDIATRIC POPULATION

Incidence

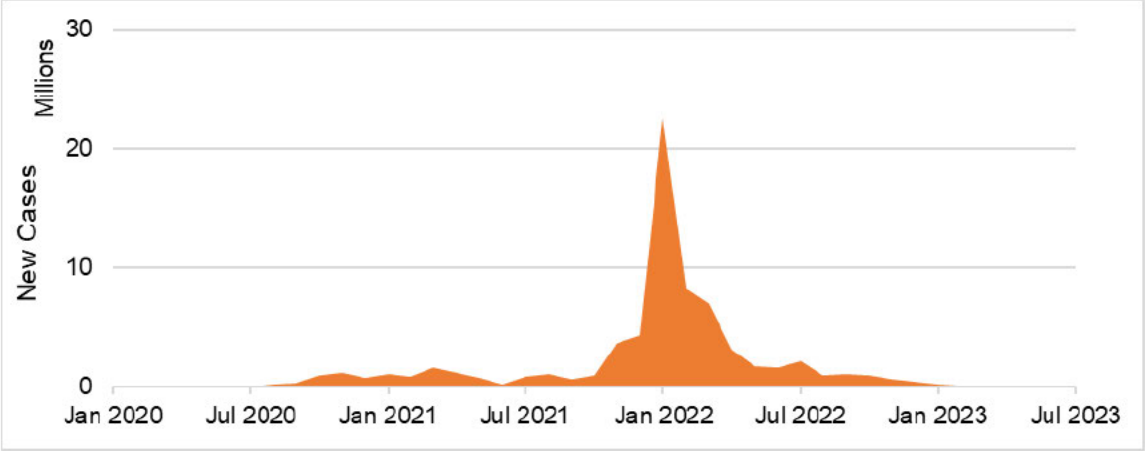
There are no recent data from ECDC resources on pediatric COVID-19 cases in the EU. Therefore, the data from WHO datasets were analyzed to calculate pediatric COVID-19 cases in 27 European Union countries (data on file).

WHO datasets record age groups of <2 years, 2-4 years <5 years, 5-9 years, 10-14 years, 15-19 years and 15-24 years. The age groups <2 years, 2-4 years were included to the calculation if no data reported for <5 years in the same country during the same time period. The age groups of 15-24 years were excluded from the case calculation which represented 24703 cases from Hungary in 2020 and 335 cases from Latvia in 2020.

Due to definition of WHO data; following results represented 0-19 years.

From 1 January 2020 to 27 July 2023 a major increase of new cases aged 0-19 years was observed in first quarter of 2022 in 27 countries in the European Union. In January, 22,583,030 new COVID-19 cases aged 0-19 years were reported, followed by 8,307,684 new COVID-19 cases in February and 6,960,664 in March 2022 [Figure 9] [data on file based on WHO, 2023a].

Figure 9 : New confirmed COVID-19 cases age 0-19 years in 27 countries in the European Union

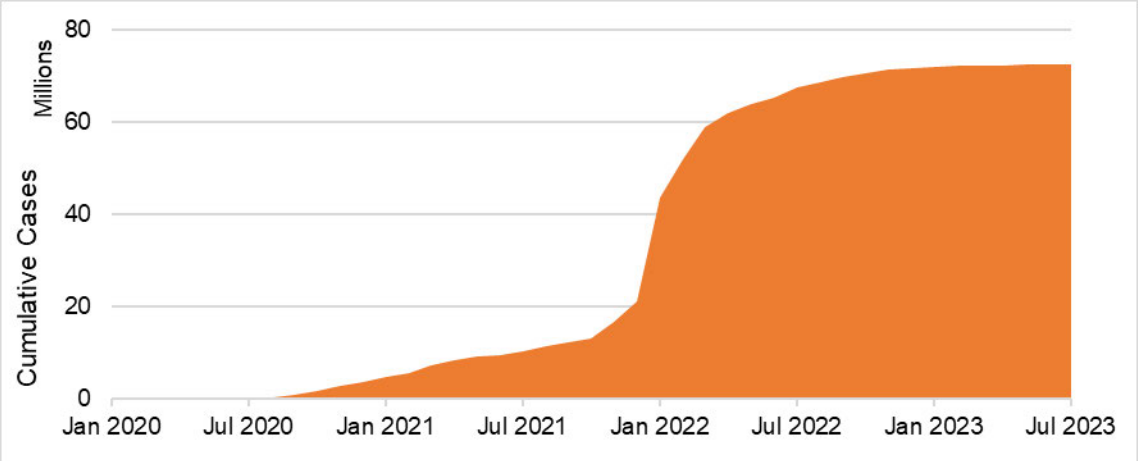


Calculated based on the WHO, 2023a (data on file).

Prevalence

WHO data up to 17 July 2023 revealed that there had been a total of 72,498,734 confirmed COVID-19 cases aged 0-19 years in 27 countries in the European union [Figure 10] [data on file based on WHO, 2023a].

Figure 10 Cumulative confirmed COVID-19 cases age 0-19 years in 27 countries in the European Union



Calculated based on the WHO, 2023a (data on file).

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

Mortality

WHO data up to 17 July 2023 revealed that there had been a total of 1,434 deaths reported for confirmed COVID-19 cases aged 0-19 years in 27 countries in the European union. In 2020, 232 deaths were reported followed by 512 deaths in 2021, 628 deaths in 2022 and 62 deaths in 2023 (until July) [data on file based on WHO, 2023a].

Important co-morbidities

Children infected with COVID-19 typically exhibit milder symptoms compared to adult patients. Moreover, their prognosis is generally positive and many children may even be asymptomatic [Zimmermann, 2020]

According to a systematic review of 41 observational studies from various countries, including the US, Europe, and China, published before March 2021, pediatric patients with comorbidities had higher likelihood of experiencing severe COVID-19 (odds ratio 4.1, 95% CI 2.3-7.2) compared to those without comorbidities. Children with severe COVID-19 often have hematologic and immune disorders, malignancies, respiratory disease, cardiovascular disease, neurological disease, obesity, or genetic syndromes [Widjanarko,2022].

The main existing treatment options

As of 27 July 2023, eight treatments have been authorized for use in the EU in the pediatric population. Of these treatments:

- Evusheld, Ronapreve and Xevudy can be used in adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19

- Veklury can be used in pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen or in pediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- Evusheld and Ronapreve can also be used as prevention of COVID-19 in adolescents aged 12 years and older weighing at least 40 kg [Table 6] [EMA, 2023a].

The recent updates on these treatments are provided in Section SI.1.2 The main existing treatment options.

Table 6 Treatments authorized for use in the pediatric population in the European Union

Treatment	Pediatric use
Evusheld (tixagevimab / cilgavimab)	Pre-exposure prophylaxis of COVID-19 in adolescents aged 12 years and older weighing at least 40 kg treatment of adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19
Kineret (anakinra)	Not authorized for using in pediatric population
Paxlovid (nirmatrelvir / ritonavir)	Not authorized for using in pediatric population
Regkirona (regdanvimab)	Not authorized for using in pediatric population
RoActemra (tocilizumab)	Not authorized for using in pediatric population
Ronapreve (casirivimab / imdevimab)	Treatment of COVID-19 in adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. Treatment of COVID-19 in adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result. Prevention of COVID-19 in adolescents aged 12 years and older weighing at least 40 kg
Veklury (remdesivir)	Pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)

Treatment	**Pediatric use**
	Pediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19
Xevudy (sotrovimab)	treatment of 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

Table was created based on the information provided in EMA, 2023a

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 Harmonization (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 7 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 embryofetal 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.

Key Safety findings (from non-clinical studies)	Relevance to human usage
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 (including QTc), neurobehavioral, or respiratory findings.	Since sotrovimab is directed against an exogenous viral target and there was no off-target binding identified in cross-reactivity 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	As of 12 April 2023, the conservation for the sotrovimab epitope at amino acid positions:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Pseudotyped VLP assessments in cell culture were performed using Wuhan-Hu-1, Omicron BA.1, and Omicron BA.2 spike proteins. The epitope sequence polymorphisms K356T, P337H/K/L/N/R/T, E340A/K/G/I/Q/S/V, T345P, and L441N in the Wuhan-Hu-1 spike, conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC50 value shown in parentheses: P337K (>304), E340K (>297), T345P (225), E340V (>200), P337R (>192), P337L (>192), E340I (>190), E340A (>100), L441N (72), E340S (68), E340Q (>50), E340G (18.21), P337T (10.62), K356T (5.90), P337N (5.57) and P337H (5.13). Epitope substitutions P337H (>631), K356T (>631), P337S (>609), E340D (>609), and V341F (5.89) in the Omicron BA.1 spike variant, and P337H (>117), P337S (>117), P337T (>117), E340D (>117), E340G (>117), K356T (>117), and K440D (5.13) in the Omicron BA.2 spike variant conferred reduced susceptibility to sotrovimab based on the observed fold-increase in EC50 value shown in parenthesis relative to each spike viral variant.	337, 340, 345, 356 and 441 in the spike protein of SARS-CoV-2 is >99.47%. 440 in the spike protein was 53.65%. The epitope conservation observed for position 440 is impacted by the N440K change that is part of the characteristic changes in the spike protein associated with the SARS-CoV-2 Omicron lineages and does not reflect the emergence of resistance to sotrovimab. Characterization of potential risk of emergence of sotrovimab-resistant variants is ongoing.

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 may be further assessed during the clinical development program, as applicable.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Since completion of the pivotal COMET-ICE study, several more Vir/GSK- sponsored clinical trials have also been conducted with sotrovimab that evaluated sotrovimab doses up to 3000mg IV as well as the IM route of administration with doses up to 500mg. The following is a brief summary of the studies included in the exposure tables below:

COMET-ICE (pivotal) study that evaluated sotrovimab 500mg IV dose in adult participants with mild to moderate COVID 19 and high risk of disease progression (sotrovimab N=523; placebo N=526)

- COMET-TAIL:
    - main study that evaluated sotrovimab 500mg IV dose (N=393), 500mg IM dose (N=385) and 250mg IM dose (N=195) in adult and adolescent participants with mild to moderate COVID-19 and high risk of disease progression

  - sub study that evaluated sotrovimab 2000mg IV dose (N=81) in adult participants with mild to moderate COVID-19 and high risk of disease progression

- COMET-PEAK was a 3-part study (Parts A, B, C) that evaluated sotrovimab in non-hospitalized adult participants with mild to moderate COVID-19. Part A was double-blind to evaluate single dose of 500 mg IV infusion of sotrovimab Generation 2 (Gen2 [commercial product], N=22) or 500mg IV Generation 1 (Gen1[clinical trial material]; N=8). Part B was open label to evaluate single dose of sotrovimab Gen2 500 mg administered by IV infusion (N=84) or IM injection (N=82). Part C was open label, to evaluate single dose of sotrovimab Gen2 500 mg administered by IV infusion (N=79) or 250 mg IM injection (N=78)
- COMET-PACE study that evaluated 500mg IV dose (weight adjusted) in 8 pediatric participants (6 - <18 years old)
- Japan PK was a 2-part study; Part 1 evaluated a single dose of sotrovimab 500 mg IV (N=18) or placebo (N=6) and Part 2 evaluated a single dose of sotrovimab 500 mg IM (N=20) or placebo (N=4) in healthy Japanese and Caucasian participants
- COSMIC was a Phase 1 study that evaluated sotrovimab 500mg IM (N=215) and sotrovimab 3000mg IV dose (N=98) in healthy adult participants

Cumulatively in all clinical trials, 2289 of clinical trial participants were exposed to sotrovimab.

Table 8 Duration of exposure

Duration of time on study post-dose [1]	Sotrovimab
All Indications	
<5 days	3
5-10 days	9
11-14 days	5
15-29 days	18
>29 days	2254
>85 days	2114
>141 days	1938
>169 days	1426
>197 days	1121
>253 days	184
Mean (SD), days	197.1 (60.90)
Median (Min, Max), days	183.0 (3,286)
Non-Hospitalized Symptomatic Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)	

Duration of time on study post-dose [1]	Sotrovimab
<5 days	3
5-10 days	9
11-14 days	5
15-29 days	12
>29 days	1909
>85 days	1892
>141 days	1870
>169 days	1418
>197 days	1121
>253 days	184
Mean (SD), days	212.7 (50.58)
Median (Min, Max), days	247.0 (3,286)
Healthy Volunteers	
<5 days	0
5-10 days	0
11-14 days	0
15-29 days	6
>29 days	345
>85 days	222
>141 days	68
>169 days	8
>197 days	0
>253 days	0
Mean (SD), days	110.7 (35.19)
Median (Min, Max), days	91.0 (16,186)

[1] Duration from date of dosing through to time of study completion/death/withdrawal, or the data cut-off date within a study's last reported data if subject is still ongoing in the study.
Note: Subjects can be counted in more than one category from >29 days onwards.
Note: 214367 (COMET-ICE), 215226 (COMET-PACE), 216912 (COMET-PEAK), 217114 (COMET-TAIL), 217653 (Japan PK), 218128 (COSMIC) are included in analysis.

Table 9 Age group and gender

	-Sotrovimab-	
	-Gender-	
Age Group	**Male**	**Female**
All Indications		
Children (2 to 11 years)	2	1
Adolescents (12 to 17 years)	3	5
Adults (18 to 64 years)	869	1046
Elderly >=65	155	208
65-74 years	102	150
75-84 years	46	46
>=85 years	7	12
Total	1029	1260
Non-Hospitalized Symptomatic Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)		
Children (2 to 11 years)	2	1
Adolescents (12 to 17 years)	3	5
Adults (18 to 64 years)	714	851
Elderly >=65	155	207
65-74 years	102	149
75-84 years	46	46
>=85 years	7	12
Total	874	1064
Healthy Volunteers		
Children (2 to 11 years)	0	0
Adolescents (12 to 17 years)	0	0
Adults (18 to 64 years)	155	195
Elderly >=65	0	1
65-74 years	0	1
75-84 years	0	0
>=85 years	0	0
Total	155	196

Note: 214367 (COMET-ICE), 215226 (COMET-PACE), 216912 (COMET-PEAK), 217114 (COMET-TAIL), 217653 (Japan PK), 218128 (COSMIC) are included in analysis.

Table 10 Dose

Dose of Exposure	Sotrovimab
All Indications	
IV route of administration	
250mg IV	2
500mg IV	1133
2000mg IV	81
3000mg IV	98
Total IV	1314
IM route of administration	
250mg IM	273
500mg IM	702
Total IM	975
All routes of administration	
Total	2289
Non-Hospitalized Symptomatic Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)	
IV route of administration	
250mg IV	2
500mg IV	1115
2000mg IV	81
3000mg IV	0
Total IV	1198
IM route of administration	
250mg IM	273
500mg IM	467
Total IM	740
All routes of administration	
Total	1938
Healthy Volunteers	
IV route of administration	
250mg IV	0
500mg IV	18

Dose of Exposure	Sotrovimab
2000mg IV	0
3000mg IV	98
Total IV	116
IM route of administration	
250mg IM	0
500mg IM	235
Total IM	235
All routes of administration	
Total	351

Note: 214367 (COMET-ICE), 215226 (COMET-PACE), 216912 (COMET-PEAK), 217114 (COMET-TAIL), 217653 (Japan PK), 218128 (COSMIC) are included in analysis.

Table 11 Ethnic origin

Ethnic Origin and Race	Sotrovimab
Ethnicity	
All Indications	
Hispanic or Latino	1532
Not Hispanic or Latino	754
Unknown	3
Total	2289
Non-Hospitalized Symptomatic Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)	
Hispanic or Latino	1462
Not Hispanic or Latino	476
Unknown	0
Total	1938
Healthy Volunteers	
Hispanic or Latino	70
Not Hispanic or Latino	278
Unknown	3
Total	351
High Level Race	

Ethnic Origin and Race	Sotrovimab
All Indications	
American Indian or Alaska Native	5
Asian	105
Black or African American	144
Native Hawaiian or Other Pacific Islander	3
White	2007
Multiple	12
Other	4
Unknown	9
Total	2289
Non-Hospitalized Symptomatic Participants with Mild to Moderate Coronavirus Disease 2019 (COVID-19)	
American Indian or Alaska Native	2
Asian	59
Black or African American	113
Native Hawaiian or Other Pacific Islander	1
White	1748
Multiple	7
Other	4
Unknown	4
Total	1938
Healthy Volunteers	
American Indian or Alaska Native	3
Asian	46
Black or African American	31
Native Hawaiian or Other Pacific Islander	2
White	259
Multiple	5
Other	0
Unknown	5
Total	351

Note: 214367 (COMET-ICE), 215226 (COMET-PACE), 216912 (COMET-PEAK), 217114 (COMET-TAIL), 217653 (Japan PK), 218128 (COSMIC) are included in analysis.

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

Sotrovimab received first marketing authorization on 20 August 2021 in Australia for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk of progression to hospitalization or death, at a dose of 500 mg of sotrovimab administered via intravenous infusion.

There were no trials conducted specifically in special patient populations (i.e., pregnant or lactating women, patients 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 pediatric patients is subject to a Pediatric Investigation Plan (PIP) in the EU	No	No patients <18 years old were enrolled and received sotrovimab in COMET-ICE study The indication includes 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

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			at increased risk of progressing to severe COVID-19. COMET-TAIL study enrolled 3 adolescents (12-<18 years old) with mild to moderate COVID-19 at high risk of disease progression who received sotrovimab. COMET-PACE study in pediatric 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 has been recently terminated early; this study enrolled 8 participants who received sotrovimab. No new safety issues have been identified in these studies. Considering the accumulated clinical data supported by available post marketing data, use in children ≥12 to <18 years old is no longer considered missing information.
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.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
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. COMET-TAIL study enrolled 27 patients with immunocompromised status at baseline. No new safety issues have been identified in this subgroup of participants.
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-19; a total of 182 participants received sotrovimab in this study. Following review of safety and efficacy data, 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. University of Oxford sponsored RECOVERY trial in hospitalized patients with COVID-19 is ongoing with 777 patients randomized by August 2023 to receive sotrovimab 1g IV dose. DMB review of the data as of

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			March 2023 has not identified any safety concerns.
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 fetus is not known. Sotrovimab exposure in pregnancy is being 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 program 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 12 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.	Female participants were excluded from the clinical trial program if they were pregnant or breastfeeding. Women of childbearing potential were required to use acceptable contraceptive measures as specified in the study protocol.

Type of special population	Exposure
The SmPC states that sotrovimab should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.	As of the RMP cut-off date 4 reports of exposure during pregnancy in clinical studies have been received. Three in Vir/GSK-sponsored studies: two in COMET-TAIL study evaluating sotrovimab for treatment of mild to moderate COVID-19 in patients with high risk of disease progression; the third one from COSMIC study in the healthy volunteer population. The 4th report was from Vir/GSK supported study evaluating sotrovimab for pre-exposure prophylaxis. The previously described one pregnancy in ACTIV-3 TICO study in hospitalized patients with COVID-19 was wrongly diagnosed and patient was later confirmed as not being pregnant.
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. • <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 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. In COMET-ICE study, 22 patients on sotrovimab had hepatobiliary disorders reported as current medical condition at baseline. 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
• Patients with cardiovascular impairment	No specific exclusion criteria have been implemented in the clinical program. 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. Severely immunocompromised participants were not included in the clinical development program in patients with COVID-19.
• 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.	COMET-TAIL study enrolled 27 patients with immunocompromised status at baseline. In addition, sotrovimab is also being evaluated as pre-exposure prophylaxis in patients with immunocompromised status in Vir/GSK-supported studies.
• 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 Vir/GSK-supported ACTIV-3-TICO trial in participants with COVID-19 requiring hospitalization; a total of 182 participants received sotrovimab in this study. DSMB review of the safety and efficacy data did not raise any specific safety issues. 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. Sotrovimab is being evaluated in Vir/GSK-supported RECOVERY trial with 777 participants enrolled by August 2023 to receive sotrovimab 1g IV dose. Following DMB review in March 2023 no safety issues have been identified.
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Type of special population	Exposure
Other: • Children <18 years old Patients <18 years old were excluded from clinical program. The pharmacokinetics of sotrovimab in pediatrics under the age of 18 years have not been evaluated. However, the recommended dosing regimen in pediatrics 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 changes associated with age on clearance and volume of distribution.	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. In the completed COMET-TAIL study 3 adolescents (12-<18 years old) with mild to moderate COVID-19 at high risk of disease progression were enrolled and received 250m mg IM dose (one participant) and 500 mg IV dose (2 participants). COMET-PACE study i to evaluate pharmacokinetics, pharmacodynamics (viral load) and safety of sotrovimab in pediatric patients (birth to <18 years old) with mild to moderate COVID-19 at high risk of progression was terminated early with 8 participants enrolled: 6 received 500 mg IV dose and 2 received weight based 250 mg IV dose.
• 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. As of July 2023, a total of 363 elderly participants (age ≥65) were enrolled in Vir/GSK sponsored studies; of these 226 received sotrovimab administered IV.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

The cumulative post-marketing exposure do not alter considerations on the risk evaluation for sotrovimab.

SV.1.1 Method used to calculate exposure

The algorithm used to derive post marketing exposure data is absolute number of vials sold (each patient gets a single dose, which is 1 vial).

Sotrovimab is administered via infusion in a hospital or clinic setting, IQVIA sales data are not considered sufficient at this time for calculation of estimated exposure for sotrovimab. Additionally, the unique distribution during the COVID-19 pandemic and the diverse distribution processes within each country that authorized the use of sotrovimab are also beyond the scope of sales data that IQVIA can provide. Therefore, internal GSK sales data has been utilized to estimate post-marketing exposure for sotrovimab.

SV.1.2 Exposure

Based on internal GSK sources, as of 19 August 2023 cumulative post marketing exposure to sotrovimab is estimated to be approximately 865 000 patients treated and of this approximately 98 000 patients in the EU.

IQVIA's "Prescribing Insights data" is not appropriate (or has significant limitations) to represent exposure to sotrovimab due to data not being suitable for product like sotrovimab that is primarily hospital or clinic based, and due to the unique distribution during the COVID-19 pandemic as explained above. Therefore, this data (exposure by indication, gender, age group and region) is not presented.

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 13 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 titer values near the sensitivity limit of the assay (titers ≤160). Available results from approximately 75% of the participants up to Day 29 are provided in Table 14. In this study, 17 participants confirmed positive at Day 1 (baseline) for ADAs with no increase in titer 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 titer 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 analyzed. 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 titers 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 14 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 dependent 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 FcγR-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 15 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 16 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-7831 500mg 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 17 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-7831 500mg 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 PPD participant was hospitalized for COVID-19 pneumonia and had concurrent anemia 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 Pediatric Investigation Plan (PIP) has been received and a pediatric 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

GSK considers use in children ≥12 to <18 years old (adolescents) to be sufficiently characterized based on the available safety data from clinical studies (8 adolescent participants), post marketing data and/or literature (over 100 adolescent patients) and that there is no supposition based on available data that the safety profile in adolescents is likely to differ from the one in adults. Therefore, missing information: use in children ≥12 to <18 years old is proposed to be removed as safety concern from the RMP. Summary of the supporting available data from clinical studies, literature and/or post marketing reports received in GSK Safety database is provided below.

As stated above, based on the accumulated safety data from clinical studies and post marketing, the safety profile in adolescent is considered similar to the one identified in the adults with no new safety issues identified. Therefore, following termination of COMET-PACE study, no additional PV activities are proposed and the study is also proposed to be removed as an interventional PASS. Considering that the use in children ≥12 to <18 years old (adolescents) is sufficiently characterized, the relatively low usage of sotrovimab including in pediatric population, as well as the level of burden on healthcare systems and patients, a new observational study is not considered needed or a viable option to collect further information on this patient population.

Clinical trial data

A total of 11 participants <18 years old were enrolled in sotrovimab clinical studies. Of these 11 participants, 3 participants (age 12 to <18 years) were enrolled in COMET-TAIL (2 received sotrovimab 500mg IV, and one 250mg IM), and 8 participants were enrolled in COMET-PACE study. Of the 8 participants in COMET-PACE study, 5 participants were enrolled in the 12 to <18 years age band and 3 participants were enrolled in the 6 to <12 years age band. Two participants (6 to <12 years) received 250 mg IV sotrovimab and remaining 6 participants (5 in 12 to <18-year group, 1 in 6 to <12 year group) received 500 mg IV sotrovimab.

None of the 3 adolescents participants enrolled in COMET-TAIL study reported adverse events. One participant who received 500mg IV dose reported disease related event: vomiting of Grade 2 in severity, which started on the day of dosing and resolved in 9 days. There were no laboratory values outside of normal range or clinically significant changes post baseline observed.

Of the 8 participants enrolled in COMET-PACE, 5 (63%) experienced any AE. None of the AEs were considered related to study intervention by the investigator and none led to withdrawal from the study. All the AEs were non serious and of Grade 1 or Grade 2 severity. There were no SAEs or deaths reported. Of the 4 participants who reported AEs after dosing, the preferred terms of the AEs were:

- 6 to <12-year age group: graft versus host disease (worsening); polyomavirus viraemia, aspartate aminotransferase increase, alanine aminotransferase increase and blood creatinine increase (all in 1 participant with complex medical history that included leukemia, anemia, GVHD involving skin, mouth, eye, liver and cytopenias, hypokalemia, neutropenia, hypo-gammaglobulinemia, thrombocytopenia, thrombotic microangiopathy, hypertension, immunocompromised state, seizure disorder, and obesity)

- 12 to <18 years age group: contusion (1 participant), gastroenteritis viral (1 participant), hypoplastic left heart syndrome (worsening) and hepatic fibrosis (1 participant with complex medical history including hypoplastic left heart syndrome and Fontan surgery; diagnosis of hepatic fibrosis was made during a multidisciplinary review as part of his routine follow-up care following the historical Fontan surgery, that included a liver core biopsy as part of standard protocol at the institution participant was followed).

No other significant AEs were reported including adverse events of special interest such as IRR within 24 hours post dose, HSR at any time post dose, events suggestive of antibody dependent enhancement (ADE) or immunogenicity related adverse events. There were no reports of MIS-C in this study.

Grade shifts in laboratory parameters, including increases to Grade 3 and 4, were noted for post-baseline versus baseline values in hematology and clinical chemistry parameters and reflected complex medical history or participants' comorbidities.

No evidence of treatment affected changes in vital signs were observed. There were no baseline or post baseline changes in ECG considered clinically significant by the investigator.

None of the participants reported progression of COVID-19 through Day 29.

Post marketing data

Cumulatively, by 19 August 2023, 57 post marketing reports have been received in GSK safety database for use of sotrovimab in children (<18 years old). Of these, 21 cases were from literature, 35 were spontaneous cases and the remaining one was a PMS case.

Of these 57 reports, 45 cases had age provided and the remaining 12 cases indicate that report is for a child but age is not specified. For these 12 cases, 11 cases did not have any adverse events reported (the PTs include off label use and product prescribing issue). The remaining case was for a child who received sotrovimab off label (hypoxic COVID-19 with symptoms onset more than 5 days). Concurrent comorbidities included acute renal failure, methemoglobinemia and the patient was receiving continuous veno-venous hemofiltration. Concomitant medications included anakinra, dexamethasone, anidulafungin, posaconazole, vancomycin, meropenem and methylthioninium chloride. The patient deteriorated, experienced hypotension requiring inotropic support, and hyperlactacidemia, had to be admitted to ICU, suffered pulmonary hemorrhage and eventually died. It was unknown if an autopsy was performed.

Of the 45 cases with age provided, 13 cases were for adolescents (12 to <18 years old) and 32 cases were for children <12 years old (range 2 months to 11 years).

For cases received for adolescent patients, majority of the adverse events reported are consistent with known safety profile of sotrovimab and include PTs of drug hypersensitivity, lip oedema, rash, urticaria, pruritus, erythema, hypersensitivity and swelling (one event each). The remaining adverse events reported included PTs of paresthesia, vertigo, vomiting, hyperglycemia and alopecia (one event each).

Of the 32 cases received for children <12 years old, 30 cases did not have any adverse events reported (the PTs include off label use, product use issue, or product prescribing issue). The remaining two cases described non serious event of infusion related reaction and urticaria in PPD with outcome resolved and serious event of encephalopathy in PPD with significant comorbidities (ruptured spleen and T cell acute leukemia) and the following other medications that were initiated as early as day after sotrovimab infusion: cytarabine, methotrexate, vincristine sulfate, Oncaspar, nelarabine, mitoxantrone hydrochloride and venetoclax.

In addition, published data on use of sotrovimab in children have been reviewed. There were 13 articles identified which are listed in the Table 18 below. In summary, these publications describe use of sotrovimab in approximately 200 pediatric patients and of these approximately 90 patients were less than 12 years old. Where dosing of sotrovimab was specified, it was either at approved dose of 500mg or weight adjusted for weight below 40kg. Overall, the data reported provides evidence that sotrovimab treatment was well tolerated in these pediatric patients.

Table 18 Published data of sotrovimab use in pediatric patients with COVID-19

Lead author / Country	Title	Population on sotrovimab	Treatments	Safety summary
Bahakel H et al US	Single Site Experience of the use of Monoclonal Antibodies for the Treatment of COVID-19 in High-risk Paediatric and Young Adult Patients	26 patients – includes young adults (≥18 years) but not specified how many of the total 26	Sotrovimab and other mAb in class	On sotrovimab one patient had IRR reported but grade was not specified. Overall, all IRRs resolved with cessation of treatment. No deaths or life threatening events were reported.
Blind JE et al US	Implementation and Patient Outcomes of a Pediatric COVID-19 Monoclonal Antibody Program	12 – 17 years: 35 patients	Sotrovimab and other mAb in class	The article states that no suspected drug adverse reactions reported on sotrovimab; rash in one participant <1 day post infusion reported via phone call
Tanaka H et al Japan	Safe administration of sotrovimab to a COVID-19 patient with acute phase type 1 diabetes mellitus	12-yearr-old patient	Sotrovimab 500mg	Patient was treated with sotrovimab for COVID-19 immediately after treatment for diabetic ketoacidosis (DKA) due to new-onset T1DM hyperglycemia post infusion that remained for 7 days; no other events reported
Vora SB et al US	Monoclonal antibody and antiviral therapy for treatment of mild-to-moderate COVID-19 in pediatric patients	12-19 years: 16 patients	sotrovimab and other mAb in class	One participant on sotrovimab reported: chest pain during infusion and for 2 days afterwards, leading to ED visit
Weber SC et al Germany	Sotrovimab in pediatric cardiac transplant recipients with SARS-CoV2 infection	<12 years: 6 patients 12 - <18 years: 3 patients	Sotrovimab ≥20kg full dose <20 kg 250mg	The article states that no adverse reactions or side effects, such as allergic symptoms or anaphylaxis

Lead author / Country	Title	Population on sotrovimab	Treatments	Safety summary
Butzer SK et al Germany	Use of Sotrovimab in 14 Children with COVID-19: A Single-center Experience	0–4 years: 1 patient 5–11 years: 5 patients 12 - <18 years: 7 patients	Sotrovimab The median dose/ kg was 12.5 mg if patients were <40 kg, Patients ≥40 kg received 500mg	The article states that infusion was tolerated very well, and no infusion-related reactions were reported
Minotti C et al Italy	Early Treatments of Fragile Children with COVID-19—Results of CLEVER (Children COVID Early Treatment), a Retrospective, Observational Study	≤2 years: 3 patients old >2 years: 16 patients	Sotrovimab Patients ≥40 kg received 500mg weight adjusted dose for <40kg and other mAb in class and antiviral treatments	The article states that no severe adverse drug reactions reported
White E et al Australia	Sotrovimab Use in Young Pediatric Patients at High Risk of Progression to Severe COVID-19 Disease	≥2 - <6 years: 2 patients ≥6 - <12 years: 8 patients 12 to <18 years: 22 patients	Sotrovimab 500mg – ≥40 kg 250mg – 15- <40 kg 125mg – 5-<15 kg	The article states that no documented adverse reactions, infusion-related reactions, hypersensitivity reactions, or side effects to the sotrovimab infusion in this patient cohort.
Chiara CD et al Italy	Early Use of Sotrovimab in Children: A Case Report of an 11-Year-Old Kidney Transplant Recipient Infected with SARS-CoV-2	11-year-old patient	Sotrovimab 450mg (weight adjusted)	The article states that no adverse reactions were reported
Pruccoli G et al Italy	A Single-center Experience in Treating Young Children at High Risk For Severe COVID-19 With Sotrovimab	<5 years: 4 patients 5 to <12 years: 1 patient	Sotrovimab 12.5 mg/kg	The article states that no significant adverse events and reactions that required the cessation of infusion.

Lead author / Country	Title	Population on sotrovimab	Treatments	Safety summary
Rau C et al Austria, Denmark Germany	Treatment of Infants and Children With SARS-CoV-2 Monoclonal Antibodies: A European Case Series	<12 years: 42 patients	Sotrovimab median dose of 12.5 mg/kg (7–30.5) other mAb in class and other treatments	The article states that no treatment discontinuation due to adverse event Safety data reported for all 53 patients and therefore not known which occurred on sotrovimab. The most frequently reported potential side effects were neutropenia (11%), lymphopenia (6%), nausea or vomiting (4%), rise of alanine transaminase over 3 times the upper limit of normal (2%) and hypotonia (2%). Pre-existing conditions for these 53 patients included immunodeficiency, malignancy, hematologic disease, cardiac disease, chronic lung disease, chronic liver disease, kidney disease and diabetes.
Romani L et al Italy	Safety of Monoclonal Antibodies in Children Affected by SARS-CoV-2 Infection	< 12 years: 4 patients	Sotrovimab 125 mg for <20 kg 250mg for ≥20 to <40 kg and other mAb in class	The article states that infusion was well tolerated, no significant adverse effects or reactions that required the cessation of the infusion, such as anaphylaxis, hypotension or dyspnea
Scutari et al Italy	A case of SARS-CoV-2 Omicron reinfection resulting in a significant immunity boost in a paediatric patient affected by B-cell acute lymphoblastic leukemia	5-year-old patient	Sotrovimab – dose weight adjusted	No reference in the article to tolerability of sotrovimab infusion

In summary, there is an established benefit of sotrovimab 500mg administered IV in adult and adolescent patients with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19. Available clinical data, although limited (8 adolescent participants), together with additional supporting post marketing data (over 100 adolescent patients) provides sufficient evidence that treatment of adolescents with 500mg IV dose of sotrovimab is well tolerated and the safety profile appears to be similar to the safety profile established in adults. Therefore, use in children ≥12 to <18 years old is no longer considered to meet the criteria for inclusion as a missing information.

GSK considers that routine risk minimization measures via sotrovimab labelling (SmPC Section 4.2, 4.8 and 5.2) are sufficient. Routine PV through routine signal detection activities and PSUR assessments of use of sotrovimab in children is also considered sufficient.

Owing to the obligation to fulfil pediatric regulatory requirements, the COMET-PACE study remained on pause since 28 March 2022 due to a decrease in in vitro neutralization of sotrovimab against circulating Omicron BA.2 SARS-CoV-2 variants and awaiting a permissive change in the variant landscape. However, as no significant change in the variant landscape was forthcoming since the study pause, GSK took the decision to close the study early on 14 June 2023. Since current usage of sotrovimab in general and including the pediatric population is relatively low, an observational study is not considered a viable option to collect further information on this patient population. Moreover, since use in children ≥12 to <18 years old is no longer considered to meet the criteria for inclusion as a missing information no additional PV is proposed.

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.3.2Presentation 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 embryofetal 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 fetus. The potential treatment benefit or risk from placental transfer of sotrovimab to the developing fetus 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.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 19 Summary of safety concerns

Summary of Safety Concerns	
Missing Information	Use in pregnancy

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.

   Sotrovimab is not in scope of the pilot.

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 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 enroll 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	31/03/2027

III.3 Summary Table of additional Pharmacovigilance activities

Table 20 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 authorization under exceptional circumstances				
NA				
Category 3- Required additional pharmacovigilance activities				
COVID-19 International Drug Pregnancy Registry (COVID-PR) Ongoing	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	31/03/2027

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None

Table 21 Planned and on-going post-authorization efficacy studies that are conditions of the marketing authorization 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 authorization or a marketing authorization 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 22 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization 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

V.2. Additional Risk Minimisation Measures

Routine risk minimization 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 23 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety concern 1 Use in pregnancy	**Routine risk minimization 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 minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** COVID-19 International Drug Pregnancy Registry (COVID-PR)

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 minimized, 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 minimize such risks and the proposed studies for learning more about Xevudy 's risks, are outlined below.

Measures to minimize 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 authorized 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 minimize its risks

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed 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 minimize 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

II.B Summary of important risks

Missing Information: Use in pregnancy	
Risk minimization measures	**Routine risk minimization 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 minimization 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-authorization 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 authorization 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 is one of the medications monitored in the COVID-PR.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.