EU RISK MANAGEMENT PLAN FOR RONAPREVE®/CASIRIVIMAB AND IMDEVIMAB

RMP version to be assessed as part of this application:

RMP Version number: 4.1

Data lock point for this RMP: 18 July 2024

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
25-Nov-2024 11:40:22	QPPV	Gellert, Birgitt (gellertb)
25-Nov-2024 12:44:28	Company Signatory (PV)	PPD

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Rationale for Submitting an Updated Risk Management Plan

The Ronapreve EU Risk Management Plan (RMP) (Version 4.1) was prepared to consolidate the EU RMP Version 4.0, which was submitted as part of the Type II variation to extend the treatment indication for patients with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen to include paediatric patients aged 2 years and older weighing at least 10 kg, with the currently approved EU RMP Version 3.0. Version 4.0 was based on Version 2.0 of the RMP because Version 3.0 was not approved at the time of Version 4.0 preparation. Therefore, Version 4.1 shows the changes proposed in Version 4.0 using Version 3.0 as a base.

Since the proposed paediatric doses have been updated since submission of EU RMP Version 4.0, EU RMP Version 4.1 includes the new paediatric doses that were modified in the response to the first request for supplementary information (response to reference safety information [RSI] submitted on 10 September 2024, EMA/CHMP/249855/2024, procedure EMEA/H/C/005814/II/0017 sequence 0083). In addition, the Sponsor is taking the opportunity to update post-marketing information based on the most recent periodic benefit-risk evaluation report (PBRER) (Report No. 1131387, data lock point [DLP] 18 July 2024).

Summary of Significant Changes in this RMP (v4.0 and v4.1 [consolidation with v3.0]):

Part I

- Product Overview: Updated to reflect the proposed indication, dosage in European Economic Area (EEA), pharmaceutical form and strength and in alignment with updates from summary of product characteristics (SmPC). Also updated the new proposed doses for paediatric patients (155 mg of casirivimab and 155 mg of imdevimab for a body weight of 10 kg to < 20 kg, 270 mg of casirivimab and 270 mg of imdevimab for a body weight of 20 kg to < 40 kg).

Part II

- Module SI.1: Addition of epidemiology data for paediatric patients and update of adult patient epidemiology since RMP Version 3.0.
- Module SIII and SIV.2: The clinical trial exposure was updated with data from Study COV-2067 Phase 3 Cohort 2 (paediatric patients).
- Module SIV.1: Updated the status of Study COV-2118.
- Module SV.1: Updated post-authorization exposure including methodology from the most recent PBRER (Report No. 1131387) with the DLP of 18 July 2024.

Annexes

- Annex 7
  - References to new literature added (Annex 7A).

  - Includes latest post-authorization exposure from PBRER (Report No. 1131387) with the DLP of 18 July 2024 (Annex 7B).
  - The methodology and summary tabulations of prospective and retrospective Individual Case Safety Reports (ICSRs) on pregnancy have been appended in Annex 7C in compliance with EMA Pregnancy and Breastfeeding Guidance (GVP P.III).
- Annex 8
  - Updated to add key changes made in this version of the RMP.

Other RMP Versions Under Evaluation

RMP Version Number: Not applicable

Submitted on: Not applicable

Procedure Number: Not applicable

Details of Currently Approved RMP

RMP Version Number: 3.0

Approved with Procedure Number: EMEA/H/C/005814/II/0015

Date of approval (opinion date): 25 April 2024

See page 1 for signature and date

Dr. Birgitt Gellert (QPPV)	Date

See page 1 for signature and date

PPD , PhD PPD	Date

PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Casirivimab and Imdevimab
Pharmacotherapeutic group(s) (ATC Code)	J06BD07
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One (combination pack) Casirivimab and imdevimab are intended to be utilized as a combination treatment and should not be used individually as monotherapy
Invented name(s) in the EEA	RONAPREVE®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Recombinant monoclonal antibodies (IgG1 isotype)
	Summary of mode of action: Casirivimab and imdevimab are a combination therapy of two recombinant human IgG1 monoclonal antibodies (mAbs), which are unmodified in the Fc regions, where each antibody targets the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Casirivimab and imdevimab exhibits neutralization activity with a concentration of 31.0pM (0.005 µg/mL) providing inhibition of 50% of viral infection in a plaque-reduction assay (PRNT50). Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor-binding domain (RBD). The blockage of the spike protein interaction with angiotensin-converting enzyme 2 (ACE2) leads to inhibition of infection of host cells.
	Important information about its composition: Casirivimab and imdevimab are recombinant proteins produced in Chinese Hamster Ovary (CHO) cells and purified with a series of chromatographic and filtration steps
Hyperlink to the Product Information	EU PI

Indication(s) in the EEA	Current: Ronapreve is indicated for: • Treatment of COVID-19 in adults and 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 adults and 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 adults and adolescents aged 12 years and older weighing at least 40 kg.
	Proposed: Ronapreve is indicated for: • Treatment of COVID-19 in adults, adolescents, and children aged 2 years and older weighing at least 10 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID 19.
Dosage in the EEA	Current: **Treatment:** The dosage in patients who do not require supplemental oxygen is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection. For these patients only, casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19. The dosage in patients who require supplemental oxygen (including low flow and high flow oxygen devices, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)) is 4 000 mg of casirivimab and 4 000 mg of imdevimab administered as a single intravenous infusion. **Prevention:** *Post-exposure prophylaxis* The dosage in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection. Casirivimab with imdevimab should be given as soon as possible after contact with a case of COVID-19.

	Pre-exposure prophylaxis The initial dose in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection. Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection may be given every 4 weeks until prophylaxis is no longer required. There are no data on repeat dosing beyond 24 weeks (6 doses).
	Proposed: **Treatment**: The dosage in adults, adolescents, and children (2 years of age and older and weighing at least 10 kg) who do not require supplemental oxygen is determined by body weight: 155 mg of casirivimab and 155 mg of imdevimab for a body weight of 10 kg to < 20 kg, 270 mg of casirivimab and 270 mg of imdevimab for a body weight of 20 kg to < 40 kg, and 600 mg of casirivimab and 600 mg of imdevimab for a body weight of at least ≥ 40 kg. In patients from 2 years of age to 11 years of age and in all patients weighing less than 40 kg, casirivimab and imdevimab are administered together as a single intravenous infusion only via pump or gravity. In patients 12 years of age and older and weighing at least 40 kg, casirivimab and imdevimab are administered as a single intravenous infusion or by subcutaneous injection. For the above patients, casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19. The dosage in adults and adolescents aged 12 years and older weighing at least 40 kg who require supplemental oxygen (including low flow and high flow oxygen devices, mechanical ventilation, or ECMO) is 4000 mg of casirivimab and 4000 mg of imdevimab administered as a single intravenous infusion.
Pharmaceutical form(s) and strengths	Current: RONAPREVE 300 mg + 300 mg Solution for injection/infusion Co-packaged 300 mg single-use vials

	Each casirivimab vial contains 300 mg of casirivimab per 2.5 mL (120 mg/mL) Each imdevimab vial contains 300 mg imdevimab per 2.5 mL (120 mg/mL) RONAPREVE 120 mg/mL + 120 mg/mL solution for injection/infusion <u>Co-packaged 1 332 mg multidose vials</u> Each casirivimab multidose vial contains 1 332 mg of casirivimab per 11.1 mL (120 mg/mL). Each imdevimab multidose vial contains 1 332 mg imdevimab per 11.1 mL (120 mg/mL).
	Proposed: <u>Co-packaged 300 mg single-use vials</u> • Each casirivimab vial contains 300 mg of casirivimab per 2.5 mL (120 mg/mL) • Each imdevimab vial contains 300 mg imdevimab per 2.5 mL (120 mg/mL) • Casirivimab and imdevimab are two IgG1 recombinant human monoclonal antibodies produced by recombinant DNA technology in Chinese hamster ovary cells Pharmaceutical Form: • solution for injection/infusion • Clear to slightly opalescent and colourless to pale yellow solution with a pH of 6.0 Osmolarity of casirivimab is 279–418 mmol/kg Osmolarity of imdevimab is 283–425 mmol/kg
Is or will the product be subject to additional monitoring in the European Union?	Yes

CHO = Chinese Hamster Ovary; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; EEA = European Economic Area;IgG1 = immunoglobulin G1; INN = International non-proprietary name; IV = intravenous; mAb = monoclonal antibody; PRNT50 = plaque-reduction assay; RBD = receptor-binding domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
aHR	adjusted hazard ratio
ARDS	acute respiratory distress syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CCU	critical care unit
CDC	Center for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
COVID-19	Coronavirus disease 2019
COVID-NET	The COVID-19-Associated Hospitalization Surveillance Network
CRP	C-reactive protein
DLP	data lock point
DSR	drug safety report
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ECG	electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU RMP	EU Risk Management Plan
FDA	The United States Food and Drug Administration
GLP	Good Laboratory Practice
HR	hazard ratio
HSR	hypersensitivity reaction
ICD	International Classification of Diseases
IgG1	immunoglobulin G1
IRR	infusion-related reaction
ISR	injection site reaction
ICU	intensive care unit
IV	intravenous
LDH	lactate dehydrogenase

Abbreviation	Definition
MAH	Marketing Authorization Holder
mAb	monoclonal antibody
mRNA	messenger RNA
NICU	neonatal intensive care unit
OR	odds ratio
PBRER	periodic benefit-risk evaluation report
PIMS	paediatric multisystem inflammatory syndrome
PSUR	periodic safety update report
RMP	risk management plan
RR	relative risk
RoW	Rest of the World
SARS CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SmPC	summary of product characteristics
WHO	World Health Organization

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 PREVENTION AND TREATMENT OF SARS-COV-2 INFECTION

Incidence and Prevalence

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the most recently discovered novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (WHO COVID-19 Pandemic). Although, most patients have mild symptoms and good prognosis, COVID-19 can cause severe illnesses including pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), multiple organ failure, or even death in some cases (Li K et al. 2020).

As of 12 October 2023, approximately 771 million confirmed cases of COVID-19 have been reported globally by the World Health Organization (WHO) with a cumulative prevalence of 10,438 cases per 100,000 population. The United States leads with approximately 103 million confirmed cases and a cumulative prevalence of 32,331 per 100,000 population, followed by China with approximately 99 million confirmed cases (prevalence: 7069 per 100,000 population), India with approximately 44 million confirmed cases (prevalence: 3438 cases per 100,000 population), France and Germany with 38 million confirmed cases each, and Brazil with approximately 37 million confirmed cases (prevalence: 18,315 cases per 100,000 population). In the WHO European region, over 276 million cases have been confirmed so far with a prevalence of 30,190 cases per 100,000 population. France and Germany are the most affected nations in Europe. In the WHO Southeast Asian region, over 61 million confirmed cases have been reported so far with a prevalence of 3177 cases per 100,000 population (WHO COVID-19 Pandemic).

Based on a systematic review and meta-analysis of 52 studies conducted between 2019 and 2022, the global prevalence of COVID-19 reinfection was estimated to be 4.2% (Ukwishaka et al. 2023). Africa had the highest prevalence of 4.7% (3 studies), whereas America and Oceania had lower estimates of 1% (7 studies) and 0.3% (1 study), respectively. The prevalence of reinfection in Asia and Europe was 3.8% (43 studies) and 1.2% (8 studies), respectively.

The incidence of COVID-19 disease in children is dramatically lower than in adults. Since the beginning of the pandemic, 1%–15% of COVID-19 cases reported from various countries are children. More than half of the paediatric patients have asymptomatic and mild disease, whereas critical disease has been reported in only 1% (Erbas et al. 2023). A prospective study in England aimed to assess the risk of SARS-CoV-2 reinfection in children up to 16 years of age and compare it with the risk in adults. In children aged 16 years and younger, 688,418 primary COVID-19 infections and 2343 reinfections were identified between January 2020 to July 2021. During this

time, the overall reinfection rate was 66.88 per 100,000 population, with the rate higher in adults (72.53 per 100,000) than in children (21.53 per 100,000). The reinfection rate after primary infection was 0.68% overall and 0.73% in adults compared with 0.18% in children aged younger than 5 years, 0.24% in those aged 5–11 years, and 0.49% in those aged 12–16 years (Mensah et al. 2022).

Hospitalized patients: Patients with severe COVID-19 may become critically ill and require hospitalization. The prevalence of COVID-19 from the European Centre for Disease Prevention and Control (ECDC) available from the European Union/European Economic Area (EU/EEA) for Week 48 (9 December 2021) depicted that the weekly hospitalization rates were 12.2 patients per 100,000 population. The rate of intensive care unit (ICU) admission due to COVID-19 was 1.9 per 100,000 population. It was estimated that the weekly hospitalization peaked at around 15 November 2020 accounting for the rate of 21.3 per 100,000 population. The ICU admission rates peaked around April 2021 with the rate of 4.0 per 100,000 population. In the United States, the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) estimates that the cumulative hospitalization rate due to COVID-19 for season 2022-2023 (as of 30 September 2023) was 249.0 per 100,000 population, while the weekly hospitalization rate was 4.6 per 100,000 population for Week 39. In children (aged 0–17 years), the overall COVID-19-associated hospitalization rate between 19 January 2023 and 18 July 2023 was estimated to be 45.9 per 100,000 population, while the weekly hospitalization rate was 0.8 per 100,000 population (as of 30 September 2023). The weekly hospitalization rate peaked in the season 2020-2021, with a weekly hospitalization rate of 35.4 per 100,000 in the first week of January 2021 (COVID-NET).

Demographics

Age: According to the Center for Disease Control and Prevention (CDC), SARS-CoV-2, infects people of all ages. Per ECDC surveillance, recent data as of 9 December 2021, indicated the overall 14-day case notification rate in the EU/EEA was 797 per 100,000 population and in people aged 65 years and older for the EU/EEA, was 423.9 per 100,000 population. As of Week 48 (9 December 2021), the overall epidemiological situation in the EU/EEA was characterized by a high and rapidly increasing overall case notification rate and a slowly increasing death rate. Increasing case notification rates and an epidemiological situation of high or very high concern are now been observed, particularly in western and northern parts of the EU/EEA. Data from the CDC COVID Data Tracker from September 2023 reported that in the United States, the highest number of cases was in the 18–29 years age group, accounting for 20% of the total cases followed by the 50–64 years (18.6%), and 30-39 years (16.4%) age groups. Among children, 6.4% of all cases were in the 5–11 years age group, 4.4% were in the 12–15 years age group, 3.7% were in the 0–4 years age group, and 2.6% were in the 16–17 years age group. However, evidence suggests that older people and those with underlying medical conditions (such as cardiovascular disease, diabetes,

chronic respiratory disease, and immunocompromised) are at a higher risk of severe COVID-19 disease (CDC Understanding Risk).

Gender: The WHO reported that globally, 52.8% of all COVID-19 patients were female and 47.2% were male. In the WHO Europe region, 53.6% of COVID-19 patients were female and 46.4% were male (WHO COVID-19 cases and deaths with age and sex). According to the September 2023 data from CDC COVID Data Tracker, in the United States, a higher proportion of females (54.0%) compared to males (46.0%) were reported to be infected with SARS-CoV-2.

Race/Ethnicity: A systematic review of 59 cohort studies, including one case-controlled study included 17,950,989 COVID-19 cases, among which 64% were Whites, 2.1% were Blacks, 5.9% were Asians, 0.086% were Hispanics, and 26% had missing ethnicity data. Evidence from CDC COVID Data Tracker revealed that in the United States, among all COVID-19 positive cases, 53.8% were White, followed by Hispanic (24.1%), Black (12.6%), and Asian (4.4%). Between February 2020 and January 2022, approximately 8.5 million children were infected with SARS-CoV-2 in the United States. The CDC data shows that the case rate per 100,000 population among American Indian/Alaska Native children has been consistently higher than other racial groups across all ages. During the peak of the Omicron surge in early 2022, children from all non-White racial groups had higher case rates when compared to White children (Vicetti Miguel et al. 2022).

Hospitalized patients: Between 19 January 2023 to 18 July 2023, among children (0–17 years), the overall hospitalization rate was estimated to be 45.3 per 100,000 population in the United States (Table 2). The highest rate of hospitalization was reported among children aged < 5 years (113.1 per 100,000), followed by 12–17 years (24.8 per 100,000) and 5–11 years (17.0 per 100,000). The overall hospitalization rate among adults (≥ 18 years) was significantly higher (305.1 per 100,000) than among children. The hospitalization rate gradually increased with advancing age and ranged from 71.7 per 100,000 (18–29 years) to 1741.5 per 100,000 (75+ years) (COVID-NET). Among children, hospitalization rates varied by race and ethnicity. The highest rate was observed for non-Hispanic American Indians (102.2 per 100,000), followed by Hispanics (64.9 per 100,000), non-Hispanic Blacks (45.2 per 100,000) and non-Hispanic Whites (32.0 per 100,000). Among adults, the highest rate was observed for non-Hispanic American Indians (365.7 per 100,000), followed by non-Hispanic Blacks (334.7 per 100,000), and non-Hispanic Whites (314.8 per 100,000) (COVID-NET).

Table 2 Hospitalization Rates due to COVID-19 Based on Different Age Groups and Gender

Age Groups (years)	Hospitalization Rate Overall (per 100,000)	Hospitalization Rate Males (per 100,000)	Hospitalization Rate Females (per 100,000)
0–17 (Children)	45.3	48.1	42.2
< 5	113.1	—	—
5–11	17.0	—	—
12–17	24.8	—	—
≥ 18 (Adults)	305.1	301.2	308.8
18–29	71.7	—	—
30–39	100.8	—	—
40–49	105.8	—	—
50–64	222.5	—	—
65–74	550.1	—	—
75+	1741.5	—	—

COVID-19 = coronavirus disease 2019.
Source: COVID-NET.
Note: Data collected 19 January 2023 through 18 July 2023.

The Main Existing Prevention and Treatment Options

Vaccination is the first line of defense in the management and control of COVID-19. However, therapeutic agents are also required to support the prevention and treatment of COVID-19. This section provides details on the prevention and potential treatments for COVID-19 that the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have approved/ authorized under emergency use provisions or have provided a scientific opinion under Article 5(3) of the EU Regulation (EC) No 726/2004.

According to the National Institute of Health (NIH) treatment guidelines for COVID–19 (updated on 10 October 2023) for the United States, patients with COVID–19 infection can experience a range of clinical manifestations, from no symptoms to critical illness. Patients who have mild illness usually recover at home, with supportive care and isolation. Patients who have moderate disease should be monitored closely and those with severe disease or critical illness should be hospitalized (NIH Treatment Guidelines).

Prevention of SARS-CoV-2 infection:

As of 12 October 2023, the EMA has authorized eight vaccines for the prevention of COVID-19 (EMA Treatments and Vaccines 2023). Table 3 shows the details of all the vaccines approved by EMA.

Table 3 Details of Vaccines Approved by European Medicine Agency

Vaccine	Type	MAH	Authorization Details	Vaccine approved per age			
				6 mo. to 4 years	≥5 years	≥12 years	≥18 years
Comirnaty	mRNA	BioNTech and Pfizer	Standard marketing authorization issued: 10/10/2023 Comirnaty Omicron XBB.1.5 (adapted) authorized: 31/8/2023	x	x	x	x
Spikevax (previously COVID-19 vaccine Moderna)	mRNA	Moderna Biotech Spain	Standard marketing authorisation issued: 3/10/2022 Spikevax XBB.1.5 (adapted) authorized: 15/9/2023	x	x	x	x
Jcovden (previously COVID-19 vaccine Janssen)	Adenoviral vector	Janssen-Cilag International NV	Standard marketing authorization issued: 10/1/2023				x
Vaxzevria (previously COVID-19 vaccine AstraZeneca)	Adenoviral vector	AstraZeneca AB	Standard marketing authorization issued: 31/10/2022				x
Valneva	Inactivated	Valneva Austria GmbH	Marketing authorization issued: 24/6/2022				x (18–50 years)
Nuvaxovid	Protein	Novavax CZ, a.s.	Standard marketing authorization issued: 4/7/23			x	x
VidPrevtyn Beta	Protein	Sanofi Pasteur	Standard marketing authorization issued: 4/7/23			x	x

Table 3 Details of Vaccines Approved by European Medicine Agency (Cont.)

Vaccine	Type	MAH	Authorization Details	Vaccine approved per age			
				6 mo. to 4 years	≥5 years	≥12 years	≥18 years
Bimervax (previously COVID-19 vaccine HIPRA)	Protein	HIPRA Human Health S.L.U.	Marketing authorization issued: 30/3/2023			(16 to 18 years)	

COVID-19=coronavirus disease 2019; EMA=European Medicine Agency; MAH=Marketing Authorization Holder; mo.=month.

Source: EMA Treatments and Vaccines 2023.

In the United States, three vaccines are authorized for the prevention of COVID-19: BNT162b2 (Pfizer-BioNTech), messenger RNA (mRNA)-1273 (Moderna), and the 2023-2024 recombinant spike protein with adjuvant vaccine NVX-CoV2373 (Novavax).

COV2.S (Johnson & Johnson/Janssen) is no longer available in the United States. COVID-19 vaccination is recommended for everyone aged ≥6 months in the United States (NIH Treatment Guidelines).

Treatment of COVID-19 disease:

The EMA has authorized drugs that may be used for people who have been hospitalized with COVID-19 or for subjects at high risk for developing severe illness, particularly older ages and those with underlying medical conditions such as diabetes, overweight, cardiovascular, kidney, and chronic respiratory diseases, immunosuppression, active cancer, neurodevelopmental disorders. According to the treatment guidelines from EMA, therapeutic management of hospitalized and non-hospitalized children and adults are discussed in Table 4 .

Table 4 Authorized COVID-19 Treatment per European Medicine Agency

Treatment	Age (years)		Recommendations	Status
	Children	Adults		
Evusheld (tixagevimab / cilgavimab)	x	x	Used in patients from 12 years of age weighing at least 40 kg, who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.	Marketing authorization granted: 25/3/2022
Kineret (anakinra)	Not used	x	Used in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor of at least 6 ng/ml.	Marketing authorization granted: 17/12/2021
Paxlovid (PF-07321332 / ritonavir)	Not used	x	Used in adults who do not require supplemental oxygen and who are at increased risk of the disease becoming severe	Conditional marketing authorization granted: 28/1/2022
Regkirona (regdanvimab)	Not used	x	Used in adults who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.	Marketing authorization granted: 12/11/2021
RoActemra (tocilizumab)	Not used	x	Used in adults with COVID-19 who are receiving treatment with corticosteroid medicines by mouth or injection and require extra oxygen or mechanical ventilation (breathing assisted by a machine).	Marketing authorization for COVID-19 indication granted: 7/12/2021
Ronapreve (casirivimab / imdevimab)	x	x	Used in adults and adolescents (from 12 years of age and weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. Used to prevent COVID-19 in people aged 12 years and older weighing at least 40 kg.	Marketing authorization granted: 8/8/2022 Conditional marketing authorization granted: 3/7/2020

Table 4 Authorized COVID-19 Treatment per European Medicine Agency (Cont.)

Veklury (remdesivir)	x	x	Used in adults and children, from 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 the start of treatment). Used 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	Marketing authorization granted: 8/8/2022 Conditional marketing authorization granted: 03/07/2020
Xevudy (sotrovimab)	x	x	From 12 years of age and weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of the disease becoming severe	Marketing authorization granted: 17/12/2021

COVID-19 = coronavirus disease 2019.
Source: EMA Treatments and Vaccines 2023.

The FDA has authorized or approved several antiviral medications used to treat mild to moderate COVID-19 in people who are at an increased risk of severe COVID-19. According to the treatment guidelines from CDC, therapeutic management of non-hospitalized children and adults are discussed in Table 5 and Table 6.

Table 5 Therapeutic Management of Non-Hospitalized Children with COVID-19

Risk of Severe COVID-19	Panel's Recommendations	
	Aged 12–17 Years	Aged < 12 Years
Symptomatic, regardless of risk factors	Provide supportive care	Provide supportive care
High Risk	Use 1 of the following options: • Ritonavir-boosted nirmatrelvir (Paxlovid) within 5 days of symptom onset • Remdesivir within 7 days of symptom onset	Ritonavir-boosted nirmatrelvir is not authorized by the FDA for use in children aged ≤ 12 years. There is insufficient evidence to recommend either for or against the routine use of remdesivir. Consider treatment based on age and other risk factors.
Intermediate Risk	There is insufficient evidence to recommend either for or against the use of any antiviral therapy. Consider treatment based on age and other risk factors.	There is insufficient evidence to recommend either for or against the routine use of remdesivir
Low Risk	Manage with supportive care alone.	Manage with supportive care alone.

COVID-19 = coronavirus disease 2019; FDA=U.S. Food and Drug Administration.
Source: NIH Treatment Guidelines.

Table 6 Therapeutic Management of Non-Hospitalized Adults with COVID-19

Patient Outcome Management	Panel's Recommendations
Patients at high risk of progressing to severe COVID-19	• Ritonavir-boosted nirmatrelvir (Paxlovid) • Remdesivir Alternative therapy (If the preferred options are not available or suitable): Molnupiravir (The panel recommends against the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated)

COVID-19 = coronavirus disease 2019.
Source: NIH Treatment Guidelines.

Several agents (i.e., baricitinib, ritonavir-boosted nirmatrelvir [Paxlovid], remdesivir, tocilizumab) are currently approved by the FDA for the treatment of COVID-19, and several other agents have received Emergency Use Authorizations.

An array of drugs that are approved for other indications and multiple investigational agents are being studied for the treatment of COVID-19 in clinical trials around the globe. According to the treatment guidelines from CDC, therapeutic management of hospitalized children and adults are discussed in the Table 7 and Table 8.

Table 7 Therapeutic Management of Hospitalized Children with COVID-19

Hospitalized for COVID-19	For children aged ≥ 12 years admitted for COVID-19, use prophylactic anticoagulation unless contraindicated.
Does not require supplemental oxygen	For children admitted for COVID-19 who are at the highest risk of progression to severe COVID-19, consider using remdesivir for children aged 12–17 years. There is insufficient evidence for using remdesivir in children aged 28 days to < 12 years.
	For children admitted for reasons other than COVID-19 who have mild to moderate COVID-19 and are at the highest risk of progression (refer to Table 5)
Requires Conventional Oxygen	Use 1 of the following options: • Remdesivir • Dexamethasone + remdesivir for children with increasing oxygen needs, particularly adolescents
Requires Oxygen Through High-Flow Device or NIV	Use 1 of the following options: • Dexamethasone • Dexamethasone plus remdesivir
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, baricitinib or tocilizumab can be considered for children aged 12–17 years and for children aged 2–11 years.
Requires mechanical ventilation or extracorporeal membrane oxygenation	Dexamethasone
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, baricitinib or tocilizumab can be considered for children aged 12–17 years and for children aged 2–11 years.

COVID-19 = coronavirus disease 2019; NIV = non-invasive ventilation.

Source: National Institute of Health 2023.

Table 8 Therapeutic management of Hospitalized Adults with COVID-19

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendation for Anticoagulant Therapy
	Clinical Scenario	**Recommendation**	
Hospitalized for reasons other than COVID-19	Mild to moderate COVID-19 patients at high risk of progressing to severe COVID-19	Use of therapeutic management of non-hospitalized adults with COVID-19.	For patients without an indication for therapeutic anticoagulation: Prophylactic dose of heparin, unless contraindicated for pregnant patients
Hospitalized patients do not require oxygen supplementation	All patients	The Panel recommends against the use of dexamethasone or other systemic corticosteroids for the treatment of COVID-19	
	Patients who are at high risk of progressing to severe COVID-19	Remdesivir (for immunocompromised patients)	
Hospitalized and requires conventional oxygen	Patients who require minimal conventional oxygen	Remdesivir	For non-pregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • Heparin For other patients: • Heparin (unless contraindicated for pregnant patients)
	Most patients	Dexamethasone + remdesivir If remdesivir cannot be obtained, use dexamethasone	
	Dexamethasone-treated patients with increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators: Preferred • PO baricitinib • IV tocilizumab Alternatives • IV abatacept • IV infliximab	

Table 8 Therapeutic management of Hospitalized Adults with COVID-19 (cont.)

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendation for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized and requires high-flow nasal cannula oxygen or non-invasive ventilation	All patients	Dexamethasone should be administered to all patients. If not already initiated, promptly add 1 of the following immunomodulators: Preferred • PO baricitinib Preferred Alternative • IV tocilizumab Additional Alternatives: • IV abatacept • IV infliximab Add remdesivir to 1 of the options above in certain patients	For patients without an indication for therapeutic anticoagulation Prophylactic dose of heparin, unless contraindicated for pregnant patients. For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a prophylactic dose of heparin, unless there is another indication for therapeutic anticoagulation
Hospitalized and mechanical ventilation or extracorporeal membrane oxygenation	All patients	Dexamethasone should be administered to all patients. If the patient has not already received a second immunomodulator, promptly add 1 of the following: • PO baricitinib • IV tocilizumab	

COVID-19 = coronavirus disease 2019; ICU = intensive care unit; IV = intravenous; PO = orally (by mouth); ULN = upper limit of normal.
Source: NIH Treatment Guidelines

Risk Factors for the Disease

Hospitalized Patients: Older adults are more likely to get severely ill from COVID-19. Severe illness refers to hospitalization, admission to ICU, use of ventilator to support breathing, or death. More than 80% of COVID-19 deaths occur in people over age 65, and more than 95% of COVID-19 deaths occur in people older than 45. Long-standing systemic health and social inequities have put various groups of people at increased risk of getting sick and dying from COVID-19, including many racial and ethnic minority groups and people with disabilities. Severity of COVID-19 is associated with increased age, male sex, and pre-existing medical conditions (Center for Disease Control and

Prevention 2023). A meta-analysis of 50 studies (42 from the United States and 8 from the United Kingdom) reported that individuals from Black (Relative Risk [RR]: 2.02; 95% CI 1.67−2.44) and Asian (RR: 1.50; 95% CI 1.24-1.83) ethnicities had a higher risk of COVID-19 infection compared to White individuals (Sze et al. 2020).

Chronic underlying health conditions or pre-existing medical conditions also place patients at increased risk for developing severe disease. These include cancer; chronic kidney disease; chronic obstructive pulmonary disease; dementia or other neurological conditions, Down Syndrome; heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies; immunocompromised state (weakened immune system); liver disease; obesity (body mass index [BMI] of 30 kg/m^2 or higher but $<$40 kg/m^2); severe obesity (BMI $\geq$ 40 kg/m^2); pregnancy; sickle cell disease; cerebrovascular disease; smoking, solid organ transplant and Type 2 diabetes mellitus (CDC Understanding Risk).

Among children hospitalized with COVID-19 in France (aged $<$ 18 years), risk factors for admission to the critical care unit (CCU) were: age younger than 7 days (odds ratio [OR]: 3.71, 95% CI [2.56–5.39]), age between 2 and 9 years (OR: 1.19, 95% CI [1.00–1.41]), paediatric multisystem inflammatory syndrome (PIMS) (OR: 7.17, 95% CI [5.97–8.6]), the respiratory form of COVID-19 based on International Classification of Diseases (ICD) codes U07.10 and U07.11 (OR: 1.26, 95% CI [1.12–1.41]), and having at least one underlying condition (OR: 2.66, 95% CI: [2.36–3.01]). Among hospitalized children younger than 2 years old, prematurity was a risk factor for CCU admission (OR: 1.89 95% CI: [1.47–2.43]). The CCU admission rate gradually decreased over the waves of COVID-19 (from 31.0% to 17.8%) (Prévost et al. 2022).

Natural History of the Indicated Condition in the Untreated Population

As of September 2023, there have been approximately 6.9 million deaths among 771 million cases worldwide due to COVID-19 resulting in the death of 94 per 100,000 population, with case fatality ranging from 1.3% (WHO Southeast Asian region) to 1.8% (WHO African Region). In the WHO European region, approximately 2.2 million deaths were reported (case fatality: 0.8%) resulting in the death of 246 per 100,000 population (WHO COVID-19 Pandemic). In the United States, data from CDC COVID Data Tracker, deaths were reported approximately negligible in children aged 0–17 years. The highest proportion of deaths among all COVID-19 deaths were reported in the 85+ years age group (27.4%) followed by the 75–84 years (26.3%), 65–74 years (22.2%), and 50–64 years (17.4%) age groups. Racial disparity was also reported among patients dying with COVID-19. Out of 1,002,986 deaths, data on Race/Ethnicity were available for 858,323 (85%) deaths, of which Non-Hispanic Whites (63.9%) were reported to be highest in mortality, followed by Hispanics (16.4%) and Non-Hispanic Blacks (13.1%) (CDC COVID Data Tracker).

A systematic review of 51 studies comprising 17,501,820 COVID-19 patients reported ethnicity-aggregated mortality data. Among patients who died from COVID-19, 63%

were White, 6.0% Asian, 2.1% Black, 0.069% Hispanic, 2.9% others, and 26% had missing ethnicity data. Compared to White ethnicity, age- and sex-adjusted all-cause mortality risks were significantly elevated for Black (hazard ratio [HR]: 1.38 [1.09–1.75]) and Asian (HR: 1.42 [1.15–1.75]), but not for Hispanic (RR: 1.14 [0.93–1.40]) (Raharja et al. 2020).

Hospitalized patients: In the United States, the in-hospital death among COVID-19 associated hospitalized patients was 3.77% for the season 2022–2023. In children (0–17 years), the in-hospital death was reported to be 0.59%, while in adults aged 18–49 years, 50–64 years, and 65+ years, the in-hospital death was 1.15%, 3.34%, and 4.78%, respectively. Among children (0–17 years) with different race and ethnicity, the in-hospital death was reported to be 0.63%, 0.54%, and 0.52% for non-Hispanic White, non-Hispanic Blacks, and Hispanics, respectively, among COVID-19 hospitalized patients (COVID-NET).

A prospective observational study in East London, in the United Kingdom, included 1737 patients aged 16 years and above admitted to hospital between 1 January 2020 and 13 May 2020. The 30-day mortality among hospitalized patients was found to be 29.2%, of whom 31% were Asian, 20% were Black, and 40% White (Apea et al. 2021).

A meta-analysis including data from 80 studies (n=25,385 patients), reported a pooled in-hospital mortality of 14% (95% CI: 12.2, 15.9) due to COVID-19. The pooled in-hospital mortality of patients with COVID-19 was 10.1%, 23.7%, and 25.4% in Asia, Europe, and North America, respectively. Older age (mean difference: 13.32), male (OR=1.66), hypertension (OR=2.67), diabetes (OR=2.14), chronic respiratory disease (OR=3.55), chronic heart disease/cardiovascular disease (OR=3.15), elevated levels of high-sensitive cardiac troponin I (mean difference=66.65), D-dimer (mean difference=4.33), C-reactive protein (mean difference=48.03), and a decreased level of albumin at admission (mean difference=−3.98) were associated with higher risk of death in patients with COVID-19 (Wu et al. 2021). However, since the meta-analysis collected information only until 26 May 2020, the mortality rates and risk factors for mortality depicted here could differ compared to the current scenario.

COVID-19 in pregnant women: Evidence from the literature suggests that pregnant women with COVID-19 are at increased risk of adverse pregnancy and neonatal outcomes such as preterm labor, preterm birth, preeclampsia, and stillbirth compared to pregnant women without COVID-19.

The impact of COVID-19 on the pregnancy rate is complex and multifaceted. There is limited information to determine the effect of COVID-19 infection on pregnancy. The pregnancy rate was however impacted largely by economic and behavioral status of individuals during the pandemic period in addition to limited access to healthcare (Aly et al. 2022). A CDC report reviewed cases from 22 January 2020 to 3 October 2020, included 461,825 reproductive age women with positive test results for

SARS-CoV-2 with data on pregnancy status and found that 6.6% were pregnant (Zambrano et al. 2020). The percentage of women of reproductive age with positive test results for SARS-CoV-2 was higher than expected given that ~5% of women aged 15 to 44 years were pregnant at any point in time during the pre-COVID-19 pandemic era (Overton et al. 2022).

A systematic review and meta-analysis of pregnancy outcomes in COVID-19 infected mothers was conducted based on 74 studies (69 cohort and five case-control studies) published up to 1 September 2022. The pooled prevalence of adverse maternal and neonatal outcomes in pregnant women with versus without COVID-19 were: 14.32% versus 5.57% preterm delivery, 0.65% versus 0.02% maternal mortality, 14.57% versus 4.53% neonatal intensive care unit (NICU) admission, and 0.65% versus 0.06% neonatal death, respectively. Thus, COVID-19 infection during pregnancy was found to increase adverse pregnancy outcomes including preterm delivery, maternal mortality, NICU admission and neonatal death (Simbar et al. 2023).

In the United States, a study identified 2326 and 11,705 pregnant women with and without COVID-19, respectively, between March 2020 and December 2020 (from 17 hospitals). In adjusted analyses (adjusted for maternal age), those with COVID-19 before 28 weeks of gestation had a subsequent increased risk of fetal or neonatal death (2.9% vs. 1.5%; adjusted RR, 1.97; 95% CI: 1.01, 3.85), preterm birth (19.6% vs. 13.8%; adjusted RR, 1.29; 95% CI: 1.02, 1.63), and hypertensive disorders of pregnancy with delivery at <37 weeks of gestation (7.2% vs. 4.1%; adjusted RR, 1.74; 95% CI: 1.19, 2.55) (Hughes et al. 2023).

A multinational prospective study recruited 8239 women who had suspected or confirmed COVID-19 infection in pregnancy between January 2020 and March 2021. The frequency of adverse pregnancy outcomes in the cohort were pre-eclampsia (4.8%), miscarriage (1.0%), intra-uterine death/stillbirth (0.4%), cesarean section (41.7%), termination of pregnancy (0.1%), and maternal death (0.2%) (Mullins et al. 2022).

A retrospective cohort study was conducted in England which identified 43,802 singleton pregnancies between 1 January 2016 and 31 January 2021. A total of 214 COVID-19 cases were matched with 214 controls (without COVID-19) who had delivered between 1 January 2019 and 16 February 2020. The incidence of adverse neonatal and maternal outcomes in COVID-19 cases versus controls reported were preterm birth (<34 weeks) (3.3% vs. 1.4%), elective cesarean section (12.6% vs. 9.8%), emergency cesarean section (21.5% vs. 19.2%), placental disruption (1.4% vs. 0.5%), stillbirth (0.5% vs. 0%), neonatal death (0.9% vs. 0.9%), pre-eclampsia (2.8% vs. 3.7%), and maternal ICU admission (1.9% vs. 0%) (Wilkinson et al. 2022).

A retrospective cohort study obtained data from Danish National registers and medical records that included 111,185 pregnancies between 1 March 2020 and 28 February 2021. SARS-CoV-2 infection was detected in 1819 (1.6%) pregnancies.

SARS-CoV-2-infected women more frequently had hypertensive disorders in pregnancy compared to non-infected pregnancies (adjusted hazard ratio [aHR] 1.31, 95% CI: 1.04, 1.64), preterm delivery before gestational age 28 (aHR 2.31, 95% CI: 1.01, 5.26), iatrogenically preterm delivery before gestational age 37 (aHR 1.49, 95% CI: 1.01, 2.19) and small-for-gestational age children (aHR 1.28, 95% CI: 1.05, 1.54) (Aabakke et al. 2023).

Important Comorbidities

A systematic review and meta-analysis included all COVID-19 studies published between 1 January 2020 and 24 July 2020 in which there were reported comorbidities. Of the 120 studies with 125,446 patients with COVID-19, the most prevalent comorbidities were hypertension (32%), obesity (25%), diabetes (18%), cardiovascular disease (16%), lung disease (9%), chronic kidney or other renal diseases (6%), cancer (5%), liver disease (5%) and cerebrovascular accident (4%) (Thakur et al 2021).

Hospitalized patients: In a study of 7485 children (age < 18 years) hospitalized for COVID-19 in France, the prevalence of common comorbidities was respiratory disease (9%), immunocompromised conditions (4.9%), neurologic disease (4.8%), metabolic disease (4.7%), cardiovascular disease (3.7%), and sickle-cell disease (2.8%) (Prévost et al. 2022). In another study of 392 children (age < 18 years) who were hospitalized with COVID-19 infection, the most common prevalent chronic underlying diseases present were obesity (5.4%), asthma (3.6%), cerebral palsy (3.6%), malignity (2.8%), epilepsy (1.8%), and congenital heart disease (1.5%) (Devrim et al. 2022).

According to the ECDC, the prevalence of preexisting medical conditions in hospitalized patients with COVID-19 were cardiac disorders (23.6%), diabetes (16.8%), cancer (9%), chronic lung disease (3.6%), hypertension (2.6%), neurological disorders (1.8%), and asthma (1.3%) (ECDC COVID-19 Surveillance Report).

In the United States , as of 30 September 2021, preliminary data from the CDC (COVID-NET) estimated that among hospitalized adults with information on underlying medical conditions, the most commonly reported were hypertension (56.8%), obesity (50.5%), metabolic disease (41.7%), and cardiovascular disease (36.7%). Other underlying conditions included chronic lung disease (20.3%), neurologic diseases (18.9%) and renal disease (16%) (COVID-NET).

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage.

TOXICITY

The in-vivo safety and toxicokinetic profiles of casirivimab and imdevimab alone and in combination were evaluated in a Good Laboratory Practice (GLP)-compliant 4-week

repeat dose toxicology study in cynomolgus monkeys with an 8-week recovery period (R10933-TX-20064). Both monoclonal antibodies (mAbs) are directed against an exogenous target; therefore, a short-term study in one species is considered appropriate to support clinical development and is consistent with the guidance "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (ICH S6 [R1], 2011). The cynomolgus monkey was chosen as the test species to allow for a robust evaluation of cardiovascular and respiratory safety pharmacology endpoints and to facilitate pharmacokinetic assessment for estimating drug exposures in humans.

Repeat dose toxicity

In Study R10933-TX-20064, once weekly intravenous (IV) injection of 50 mg/kg casirivimab alone or imdevimab alone or IV or subcutaneous (SC) injection of up to 150 mg/kg/antibody in combination for 4 weeks was well tolerated in the cynomolgus monkey. There was no mortality or adverse clinical signs evident throughout the study and there were no drug-related changes in any of the parameters evaluated.

In all groups, including control, there were transient, minimal to mild increases in C-reactive protein (CRP) on Day 2 and minimal increases in fibrinogen, with or without a minimal decrease in albumin, on Days 2 and/or 7, which returned to within normal range by Day 27. Additionally, there were transient minimal to mild increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or lactate dehydrogenase (LDH) in individual animals on Days 2 and 7 that returned within the range of control and/or baseline values by Day 27. These observed changes were considered to be transient in nature corroborated by lack of cytokine correlates (CRP), low incidence, minimal to mild magnitude of change, lack of dose response, and/or presence of similar changes in controls. As such, the observed changes are considered to be of uncertain relationship to casirivimab or imdevimab, are possibly related to study procedures, and are not considered to be adverse. On Day 27, clinical pathology changes were limited to a minimal increase in serum globulins at 150 mg/kg/antibody IV and SC. These changes are considered to be artifacts related to high doses of immunoglobulin administered during the study and are considered to be of no toxicological significance. There were no macroscopic or microscopic findings or organ-weight changes related to the administration of casirivimab and/or imdevimab at the end of the dosing or recovery period.

Based on the above, the no-observed-adverse-effect level is considered to be 50 mg/kg casirivimab and 50 mg/kg imdevimab when administered alone and 150 mg/kg/antibody for casirivimab and imdevimab, the highest doses evaluated.

Relevance to human usage: Findings from repeat –dose toxicity study has not revealed a risk for humans.

Reproductive/developmental toxicity

Reproductive and developmental toxicology studies with casirivimab and imdevimab were not performed. Given that both mAbs are directed against an exogenous target and consistent with the guidance "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (ICH S6 [R1], 2011), reproductive and developmental toxicology studies were considered not appropriate.

Furthermore, during the GLP 4-week toxicology study conducted in cynomolgus monkeys (Study R10933–TX–20064), there were no drug-related macroscopic or microscopic changes in the testes, epididymides, ovaries, uterus, or vagina. The 4-week toxicology study did not identify any potential risks to fertility.

Relevance to human usage

As casirivimab and imdevimab, are directed towards an exogenous target, and no human fetal tissue binding was detected in tissue cross-reactivity studies, effects on fetus and reproductive organs in males and females are not anticipated.

GENERAL SAFETY PHARMACOLOGY

Safety pharmacology evaluations were integrated into the ongoing GLP 4-week repeat dose toxicology study conducted in cynomolgus monkeys (Study R10933–TX-20064). There were no drug-related cardiovascular (electrocardiographic [ECG] measurements via Jacketed External Telemetry™), respiratory (pulse oximetry) or CNS (neurological examination) changes evident following the 4 once weekly doses of casirivimab or imdevimab alone (50 mg/kg) or in combination (up to 150 mg/kg/antibody).

Relevance to human usage: Findings from general safety pharmacology study (integrated into Study R10933–TX-20064) have not revealed a risk for humans.

LOCAL TOLERABILITY

Local tolerability of the IV administration of casirivimab and imdevimab alone or the IV or SC administration of casirivimab and imdevimab was evaluated in the GLP 4-week repeat dose toxicology study in cynomolgus monkeys (Study R10933 –TX-20064). There were no drug-related clinical observations at the IV or SC administration sites during the 4-week dosing period.

Relevance to human usage: Findings from local tolerability study (integrated into Study R10933–TX-20064) have not revealed a risk for humans.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

Clinical trial exposure in the target populations is based on the following six studies: R10933-10987-COV-2066, R10933-10987-COV-2067, R10933-10987-COV-2069,

R10933-10987-HV-2093, R10933-10987-COV-20145 (herein referred to as COV-2066, COV-2067, COV-2069, HV-2093, and COV-20145, respectively) and RECOVERY.

Data have been presented by route of administration (IV and SC) and indication (i.e., treatment and prevention of SARS-CoV-2 infection).

Data have been analyzed using the Safety–Analysis Set, which is defined as follows:

- Study COV-2066 (Cohorts 1, 1A, 2, and 3)

All patients randomized up to 9 April 2021 (Total: N =1473; Cohort 1: N=941; Cohort 1A: N=399; Cohort 2: N=110; Cohort 3: N=23). Data were collected up to the cutoff date of 13 September 2021.

- RECOVERY

Includes all patients exposed to treatment up to 22 May 2021 (N = 4298). Of all the randomized participants population (N = 4839), 4298 participants received casirivimab + imdevimab treatment, 495 participants who were randomized to the casirivimab + imdevimab treatment arm did not receive the assigned treatment and for 46 participants it is unknown whether they were treated due to missing data. Data were collected up to the cutoff date of 21 June 2021.

- Study COV-2067 Pooled Phase 1, 2, 3 Cohort 1 (symptomatic patients):

All patients randomized up to 17 January 2021 (N = 4206). Data were collected up to the cutoff date of 18 February 2021.

- Study COV-2067 Phase 3 Cohort 2 (paediatric)

Includes all patients exposed to treatment based on the database lock of 12 July 2022 (N = 200)

- Study COV-2067 Phase 3 Cohort 3 (pregnant at randomization)

Includes all patients exposed to treatment based on the database lock of 12 July 2022 (N = 78).

- Study COV-2069 (Cohort A and Cohort B):

All patients randomized up to 28 January 2021 (Cohort A: N = 1311; Cohort B: N = 155). Data were collected up to the cutoff date of 11 March 2021.

- Study HV-2093:

All randomized subjects (N = 729). Last subject was randomized on 10 November 2020; data were collected up to the cutoff date of 13 March 2021.

- Study COV-20145

All patients randomized up to 1 February 2021 (N =460 [IV set]; N = 228 [SC set]). Data were collected up to the cutoff date of 08 February 2021.

In the cumulative exposure tables (Table 14 to Table 29), the Safety-Analysis Set is further subdivided into:

- The IV Safety-Analysis Set for Non-Hospitalized Patients:
    - Study COV-2067 Pooled Phase 1,2,3 Cohort 1 (symptomatic patients)
    - Study COV-2067 Phase 3 Cohort 2 (paediatric patients)
    - Study COV-2067 Phase 3 Cohort 3 (pregnant at randomization)
    - Study COV-20145 (IV subset)
- The IV Safety-Analysis Set for Hospitalized Patients
    - COV-2066 Cohort 1
    - COV-2066 Cohort 1A
    - COV-2066 Cohort 2
    - COV-2066 Cohort 3
    - RECOVERY
- The SC Safety-Analysis Set:
    - The Single SC Dose Analysis Set
        - COV-2069 Cohort A
        - COV-2069 Cohort B
        - COV-20145 (SC subset)
    - The Repeat SC Dose Analysis Set
        - Study HV-2093

An overview of the studies contributing to the Safety-Analysis Sets is provided in Table 9.

Table 9 Overview of Studies Contributing to the Safety Population

Study	Study design	Primary objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set [a] (n)
COV-2066	Adaptive Phase 1/2/3 (Phase 3 not reported here), randomized, double-blinded, placebo-controlled master protocol	Safety, tolerability, virologic efficacy, clinical efficacy of casirivimab + imdevimab in hospitalized adult patients	Phase 1 and 2: Cohort 1: Oxygen saturation >93% on low-flow oxygen via nasal cannula, simple face mask or other similar device Phase 2: Cohort 1A: With COVID-19 symptoms but not requiring supplemental oxygen Cohort 2: On high–intensity oxygen therapy but not on mechanical ventilation Cohort 3: On mechanical ventilation	•Casirivimab + Imdevimab: 2.4 g (1.2 g of each mAb) IV x 1 dose • Casirivimab + Imdevimab: 8 g (4 g of each mAb) IV x 1 dose • Placebo IV x 1 dose	Cohort 1 = 941 Cohort 1A = 399 Cohort 2 = 110 Cohort 3 = 23 All Cohorts = 1473
RECOVERY	Multi-center, multi-arm, adaptive, open label, randomized controlled trial	To provide reliable estimates of the effect of study treatments on all-cause mortality for hospitalized patients within 28 days of the relevant randomization	Hospitalized patients with suspected or confirmed SARS-Cov-2 infection without medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	Casirivimab + Imdevimab: 8 g (4 g of each mAb) IV x 1 dose	N = 4298

Table 9 Overview of Studies Contributing to the Safety Population (Cont.)

Study	Study design	Primary objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set [a] (n)
COV-2067	Phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol	Safety, tolerability, virologic efficacy, clinical efficacy of casirivimab + imdevimab	Phase 1 and 2: Cohort 1: adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. Phase 3: Cohort 1: ≥ 18 years of age, not pregnant at randomization Cohort 2: < 18 years, not pregnant at randomization Cohort 3: pregnant at randomization	Phase 1 and 2: • Casirivimab + Imdevimab: 2.4 g (1.2 g of each mAb) IV x 1 dose • Casirivimab + Imdevimab: 8 g (4 g of each mAb) IV x 1 dose • Placebo IV x 1 dose Phase 3: Cohorts 1, 2, and 3: • Casirivimab + Imdevimab: 1.2 g (600 mg of each mAb) IV x 1 dose • Casirivimab + Imdevimab: 2.4 g (1.2 g of each mAb) IV x 1 dose • Placebo IV x 1 dose* *Note: Patients in Phase 3 Cohort 2 weighing <40 kg received a weight-based equivalent dose*.	Pooled Phase 1,2,3 Cohort 1 (symptomatic patients) N = 4206 Phase 3 Cohort 2 (paediatric patients) N = 200 (0 to < 12, N = 102; 12 to < 18, N = 98) Phase 3 Cohort 3 (pregnant patients) N = 78

Table 9 Overview of Studies Contributing to the Safety Population (Cont.)

Study	Study design	Primary objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set [a] (n)
COV-2069	Phase 3, randomized, double-blind, placebo-controlled study	• Efficacy of casirivimab and imdevimab in preventing asymptomatic or symptomatic SARS-CoV-2 infection • Safety and tolerability of casirivimab and imdevimab following SC administration	Asymptomatic, healthy adults, adolescents, and children who are household contacts to an individual with a diagnosis of SARS-CoV- 2 infection	Randomized in a 1:1 to the following: • Casirivimab + Imdevimab: 1.2g (600 mg of each mAb) SC x 1 dose • Placebo SC x 1 dose	Cohort A = 1311 Cohort B = 155 N = 1466
HV -2093	Phase 1, randomized, double-blind, placebo-controlled	Safety, tolerability, PK of multiple SC doses of • casirivimab and imdevimab	Adult volunteers who are healthy or have chronic but stable and well-controlled medical condition(s), and negative at screening or SARS-CoV-2 infection	Randomized in a 3:1 to the following: • Casirivimab + Imdevimab: 1.2 g (600 mg of each mAb) SC Q4W x 6 doses • Placebo SC Q4W x 6 doses *Note: Up to Protocol Amendment 2, subjects received four doses of study drug*	N = 729
COV-20145	A Phase 2, randomized, double-blind, placebo-controlled, parallel group	Virologic efficacy (antiviral effect of casirivimab and imdevimab across different IV and SC doses)	Adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2	**IV single dose**: • Casirivimab + Imdevimab: 2400 mg (1200 mg per mAb) • Casirivimab + Imdevimab: 1200 mg (600 mg per mAb)	IV = 460 SC = 228

Table 9 Overview of Studies Contributing to the Safety Population (Cont.)

Study	Study design	Primary Objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set [a] (n)
				• Casirivimab + Imdevimab: 600 mg (300 mg per mAb) • Casirivimab + Imdevimab: 300 mg (150 mg per mAb) • Placebo IV single dose **SC single dose**: • Casirivimab + Imdevimab: 1200 mg (600 mg per mAb) • Casirivimab + Imdevimab: 600 mg (300 mg per mAb) • Placebo SC single dose	

IV = intravenous ; mAb = monoclonal antibody; PK = pharmacokinetics; n = no. of patients; Q4W = every 4 weeks; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous.

* Cohort 3 did not include a placebo arm, however, pregnant participants were allowed in cohort 1 until cohort 3 was added in protocol amendment 7. Pregnant participants enrolled in Cohort 1 were reclassified such that Cohort 3 includes all participants who were pregnant at randomization.

[a] The number of patients in the Safety Analysis Sets only includes patients exposed to casirivimab and imdevimab.

DURATION OF EXPOSURE/FOLLOW-UP

All patients in the IV Safety-Analysis Set and the SC Safety-Analysis set received only one dose at baseline with the exception of subjects in Study HV-2093 (Table 9).

The IV Safety Analysis Set for non-hospitalized patients provided data from 4944 patients with 724.23 patient-years of exposure. As of the cutoff dates for COV-2067 Pooled Phase 1,2,3 Cohort 1 (18 February 2021) and COV-20145 (8 February 2021) and the database lock date for COV-2067 Phase 3 Cohorts 2 and 3 (12 July 2022), 4417 patients (4417/4944 [89.3%]) had been followed up for at least 4 weeks and 297 patients (297/4944 [6.0%]) had been followed up for at least 16 weeks (Table 10). A total of 268 patients (5.4%) had been followed up for 20 weeks or more, all of whom were from COV-2067 Phase 3 Cohorts 2 and 3.

The IV Safety Analysis Set for Hospitalized Patients provided data from 5771 patients with 502.9 patient-years of exposure. Overall, the majority of patients in COV-2066 (73.3% [1080/1473]) had been followed up for at least 8 weeks while the majority of patients in RECOVERY (81.3% [3495/4298]) had been followed up for at least 4 weeks. Data were only available for up to 4 weeks of follow-up for RECOVERY. A confirmed total of 46 patients (46/1473[3.12%]) in COV-2066 had been followed up for at least 16 weeks (Table 11).

Table 10 Duration of Follow-Up, IV Route of Administration, Non-Hospitalized Patients - Safety Analysis Set (Active Treatment Only)

Duration of Follow-Up	Number of Patients Exposed (N=4944)	Cumulative Follow-Up (Patient-Years)
≥4 weeks	4417(89.3%)	694.66
≥8 weeks	1728 (35.0%)	444.41
≥12 weeks	850 (17.2%)	276.9
≥16 weeks	297 (6.0%)	134.3
≥20 weeks	268 (5.4%)	124.9
≥24 weeks	232 (4.7%)	108.6
Cumulative total number of patients exposed to IV	4944 (100.0%)	724.23
Treatment indication (Study COV-2067 Pooled Phase 1,2,3 Cohort 1)*		
Duration of Follow-Up	**Number of Patients Exposed (N=4206)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	3947 (93.8%)	547.8
≥8 weeks	1452 (34.5%)	317.2
≥12 weeks	576 (13.7%)	150.2
≥16 weeks	25 (0.6%)	8.0
Total	4206 (100.0%)	564.0
Treatment indication (Study COV-2067 Phase 3 Cohort 2)**		
Duration of Follow-Up	**Number of Patients Exposed (N=200)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	197 (98.5%)	91.4
≥8 weeks	197 (98.5%)	91.4
≥12 weeks	197 (98.5%)	91.4
≥16 weeks	196 (98.0%)	91.2
≥20 weeks	194 (97.0%)	90.5
≥24 weeks	161 (80.5%)	75.6
Total	200 (100.0%)	91.5

Table 10 Duration of Follow-Up, IV Route of Administration, Non-Hospitalized Patients - Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2067 Phase 3 Cohort 3)**		
Duration of Follow-Up	**Number of Patients Exposed (N=78)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	78 (100.0%)	35.4
≥8 weeks	77 (98.7%)	35.3
≥12 weeks	77 (98.7%)	35.3
≥16 weeks	76 (97.4%)	35.1
≥20 weeks	74 (94.9%)	34.4
≥24 weeks	71 (91.0%)	33.0
Total	78 (100.0%)	35.4
Treatment indication (Study COV-20145)***		
Duration of Follow-Up	**Number of Patients Exposed (N=460)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	195 (42.4%)	20.06
≥8 weeks	2 (0.4%)	0.31
≥12 weeks	0	-
Total	460 (100.0%)	33.33

*Randomized patients through 17Jan2021. Data cutoff date: 18Feb2021. Patients received a single dose of study treatment.

** Database lock date: 12 July 2022. Patients received a single dose of study treatment.

*** Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021. Patients received a single dose of study treatment.

Duration of follow-up = date of patient's last available data - date of first dose

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data - date of first dose + 1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur.sas (03MAY2021 11:14 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_durexp_1_iv.sas (06MAY2021 17:05 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_c2.sas (12OCT2023 17:30 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_c3.sas (12OCT2023 17:30 SAS Linux 9.4).

Table 11 Duration of Follow-Up, IV Route of Administration for Hospitalized Patients - Safety Analysis Set (Active Treatment Only)

Duration of Follow-Up	Number of Patients Exposed (N=5771)	Cumulative Follow-Up (Patient-Years)
≥4 weeks	4302 (81.1%)	439.2
≥8 weeks	1080 (17.1%)	185.6
≥12 weeks	55 (0.8%)	23.3
≥16 weeks	46 (0.7%)	30.2
≥20 weeks	42 (0.6%)	19.7
≥24 weeks	32 (0.5%)	15.4
≥28 weeks	1 (<0.1%)	0.6
≥32 weeks	1 (<0.1%)	0.6
Cumulative total number of patients exposed to IV	5771 (100.0%)	502.9
Treatment indication (Study COV-2066 Cohort 1)*:		
Duration of Follow-Up	**Number of Patients Exposed (N=941)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	779 (82.8%)	132.4
≥8 weeks	696 (74.0%)	122.2
≥12 weeks	44 (4.7%)	19.0
≥16 weeks	37 (3.9%)	17.2
≥20 weeks	35 (3.7%)	16.5
≥24 weeks	29 (3.1%)	13.9
≥28 weeks	1 (0.1%)	0.6
≥32 weeks	1 (0.1%)	0.6
≥36 weeks	0	.
Total	941 (100.0%)	137.8

Table 11 Duration of Follow-Up, IV Route of Administration for Hospitalized Patients - Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2066 Cohort 1A)*		
Duration of Follow-Up	**Number of Patients Exposed (N=399)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	351 (88.0%)	57.0
≥8 weeks	314 (78.7%)	52.0
≥12 weeks	10 (2.5%)	3.8
≥16 weeks	8 (2.0%)	3.3
≥20 weeks	6 (1.5%)	2.7
≥24 weeks	2 (0.5%)	1.0
≥28 weeks	0	-
Total	399 (100.0%)	58.3
Treatment indication (Study COV-2066 Cohort 2)*		
Duration of Follow-Up	**Number of Patients Exposed (N=110)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	74 (67.3%)	11.4
≥8 weeks	59 (53.6%)	9.7
≥12 weeks	1 (0.9%)	0.5
≥16 weeks	1 (0.9%)	0.5
≥20 weeks	1 (0.9%)	0.5
≥24 weeks	1 (0.9%)	0.5
≥28 weeks	0	-
Total	110 (100.0%)	12.8
Treatment indication (Study COV-2066 Cohort 3*)		
Duration of Follow-Up	**Number of Patients Exposed (N=23)**	**Cumulative Follow-Up (Patient-Years)**
≥4 weeks	12 (52.2%)	1.9
≥8 weeks	11 (47.8%)	1.7
≥12 weeks	0	-
≥16 weeks	0	-
≥20 weeks	0	-
≥24 weeks	0	-
Total	23 (100.0%)	2.3

Table 11 Duration of Follow-Up, IV Route of Administration for Hospitalized Patients - Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (RECOVERY)**		
Duration of Follow-Up	**Number of Patients Exposed (N=4298)**	**Cumulative Follow-Up (Patient-Years)**
≥3 days	4258 (99.1%)	291.5
≥1 week	4028 (93.7%)	288.7
≥2 weeks	3749 (87.2%)	281.3
≥3 weeks	3589 (83.5%)	274.1
≥4 weeks	3495 (81.3%)	267.9
Total	4298 (100.0%)	291.7

*Randomized patients through 09 April 2021. Last patient follow-up visit on 13 June 2021

**Last patient follow-up visit on 21 June 2021

Patients received a single dose of study treatment.

Duration of follow-up = date of patient's last available data-date of first dose.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data-date of first dose+1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2066/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_c3.sas (13SEP2021 12:26 SAS Linux 9.4).

Program: t-ex-dur.sas (Source Dataset: ADSL, SV, DS) Version 1.0.

The Single Dose SC Safety Analysis Set provided data from 1694 patients with 459.71 patient-years of exposure. Patients in the Single Dose SC Analysis Set were followed up for up to 32 weeks. Overall, the majority of patients (91.5% [1550/1694]) had been followed up for at least 4 weeks. A total of 15 patients (15/1694 [0.9%] had been followed up for at least 32 weeks (Table 12).

The Repeat Dose SC Analysis Set (Study HV-2093) provided data from 729 subjects with 245.70 person-years of exposure. In Study HV-2093, subjects were to be followed up for up to 53 weeks. As of the cutoff date (13 March 2021), no subject had been followed up for up to 53 weeks. Overall, the majority of subjects (99.5% [725/729]) had been followed up for at least 4 weeks. A total of 41 subjects (41/729 [5.6%]) had been followed up for at least 32 weeks (Table 13).

Table 12 Duration of Follow-Up, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only)

Duration of Follow-Up	Number of Patients Exposed (N=1694)	Cumulative Follow-Up (Patient-Years)
≥4 weeks	1550 (91.5%)	452.48
≥8 weeks	1350 (79.7%)	428.94
≥12 weeks	1083 (63.9%)	378.44
≥16 weeks	689 (40.7%)	275.26
≥20 weeks	367 (21.7%)	166.39
≥24 weeks	145 (8.6%)	75.48
≥28 weeks	52 (3.1%)	29.99
≥ 32 weeks	15 (0.9%)	9.35
Cumulative total number of patients exposed to SC	1694 (100%)	459.71
Prevention indication (Study COV-2069 Cohort A*)		
Duration of Follow-Up	**Number of Patients Exposed (N=1311)**	**Cumulative Follow-Up (Patient-Years)**
≥ 4 weeks	1301 (99.2%)	397.64
≥ 8 weeks	1207 (92.1%)	385.39
≥ 12 weeks	977 (74.5%)	341.61
≥ 16 weeks	625 (47.7%)	249.42
≥ 20 weeks	333 (25.4%)	150.69
≥ 24 weeks	132 (10.1%)	68.25
≥ 28 weeks	44 (3.4%)	25.23
≥ 32 weeks	11 (0.8%)	6.83
Total	1311 (100.0%)	398.11
Treatment indication (Study COV-2069 Cohort B)**		
Duration of Follow-Up	**Number of Patients Exposed (N=155)**	**Cumulative Follow-Up (Patient-Years)**
≥ 4 weeks	155 (100.0%)	45.06
≥ 8 weeks	140 (90.3%)	43.09
≥ 12 weeks	106 (68.4%)	36.83
≥ 16 weeks	64 (41.3%)	25.84
≥ 20 weeks	34 (21.9%)	15.70
≥ 24 weeks	13 (8.4%)	7.23
≥28 weeks	8 (5.2%)	4.76

Table 12 Duration of Follow-Up, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only) (Cont.)

Duration of Follow-Up	Number of Patients Exposed (N=155)	Cumulative Follow-Up (Patient-Years)
≥32 weeks	4 (2.6%)	2.52
Total	155 (100.0%)	45.06
Treatment indication (Study COV-20145*)**		
Duration of Follow-Up	**Number of Patients Exposed (N=228)**	**Cumulative Follow-Up (Patient-Years**
≥ 4 weeks	94 (41.2%)	9.78
≥ 8 weeks	3 (1.3%)	0.46
≥ 12 weeks	0	-
≥ 16 weeks	0	-
≥ 20 weeks	0	-
≥ 24 weeks	0	-
Total	228 (100.0%)	16.54

*Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

** Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

*** Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021. Patients received a single dose of study treatment.

Duration of follow-up = date of the last available data - date of first dose

Cumulative follow-up (patient-years) = [Sum of (date of the last available data - date of first dose + 1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_durexp_1_coha.sas (06MAY2021 16:56 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_durexp_1_cohb.sas (06MAY2021 16:56 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_durexp_1_coha.sas (28MAY2021 14:17 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_durexp_1_cohb.sas (28MAY2021 14:17 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_durexp_1_sc.sas (06MAY2021 17:05 SAS Linux 9.4).

Table 13 Duration of Exposure and Follow-Up, SC Route of Administration, Repeated Dose (Study HV-2093) - Safety Analysis Set (Active Treatment Only)

Follow-Up	Duration of Follow-Up	Number of Subjects Exposed (N=729)	Cumulative Follow-Up (Person-Years)
	≥4 weeks	725 (99.5%)	336.84
	≥8 weeks	715 (98.1%)	335.84
	≥12 weeks	713 (97.8%)	335.48
	≥16 weeks	703 (96.4%)	332.90
	≥20 weeks	517 (70.9%)	266.13
	≥24 weeks	345 (47.3%)	195.05
	≥28 weeks	278 (38.1%)	161.25
	≥32 weeks	41 (5.6%)	25.59
	Total	729 (100.0%)	337.00
Exposure	**Duration of Exposure**	**Number of Subjects Exposed (N=729)**	**Cumulative Exposure (Person-Years)**
	≥4 weeks	705 (96.7%)	245.43
	≥8 weeks	688 (94.4%)	243.64
	≥12 weeks	665 (91.2%)	239.52
	≥16 weeks	613 (84.1%)	226.31
	≥20 weeks	358 (49.1%)	139.65
	Total	729 (100.0%)	245.70

Data cutoff date: 13 March 2021

Duration of follow-up in weeks = (date of last available data - date of first dose + 1)/7.

Duration of exposure in weeks = (date of last dose-date of first dose+1)/7.

Cumulative follow-up (patient-years) = [Sum of (date of last available data - date of first dose + 1)]/365.25.

Cumulative exposure (person-years) = [Sum of (date of last dose-date of first dose+1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-HV/R10933-10987-HV-2093/BLA_IA/Post_Hoc/RMP/Programs/Generated/t_durexp_1.sas (07MAY2021 09:12 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-HV/R10933-10987-HV-2093/BLA_IA/Post_Hoc/RMP/Programs/Generated/t_durexp_1.sas (28MAY2021 10:25 SAS Linux 9.4).

AGE GROUP AND GENDER

In the IV Analysis Set for non-hospitalized patients, 51.8% (n=2561) were female and 48.2% (n=2383) were male, and the majority of patients (86.1% [n=4257]) were 18 to <65 years of age. Female patients had 384.32 patient-years of exposure vs. 340.01 patient-years in male patients. The majority of patients overall were aged 18 to<65 years (4257/4944 [86.1%]). A total of 102 (2.1%) patients were<12 years of age and 99 (2.0%) patients were from 12 to <18 years of age, all of whom were from Study COV-2067 Phase 3 Cohort 2, except for one patient 12 to <18 years of age in Cohort 3 (Table 14).

In the IV Analysis Set for hospitalized patients, 39.2% (n=2261) were female and 60.8% (n=3510) were male, and the majority of patients (58.0% [n=3346]) were 18 to <65 years of age. Female patients had 206.1 patient-years of exposure vs. 297 patient-years in male patients. In the RECOVERY study, 3 male patients and 1 female patient in the age range 12 to <18 years old were enrolled (Table 15).

Table 14 Exposure by Age Group and Gender, IV Route of Administration, Non-Hospitalized Patients, Safety Analysis Set (Active Treatment Only)

	Number of Patients Exposed (N=4944)			Cumulative Follow-Up (Patient-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
0 to <12	53 (1.1%)	49 (1.0%)	102 (2.1%)	24.5	22.5	47.1
12 to <18	58 (1.2%)	41 (0.8%)	99 (2.0%)	25.7.	19.3	45.0
18 to < 65	2012 (40.7%)	2245 (45.4%)	4257 (86.1%)	253.69	309.22	562.9
65 to < 75	197 (4.0%)	155 (3.1%)	352 (7.1%)	27.7	23.8	51.5
≥ 75	63 (1.3 %)	71 (1.4%)	134 (2.7%)	8.42	9.5	17.92
Cumulative Total for IV	2383 (48.2%)	2561 (51.8%)	4944 (100%)	340.01	384.32	724.22
Treatment indication (Study COV-2067 Pooled Phase 1, 2, 3 Cohort 1* (Symptomatic Patients))						
	Number of Patients Exposed (N=4206)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	1788 (42.5%)	1933 (46.0%)	3721 (88.5%)	236.8	257.8	494.6
65 to < 75	197 (4.7%)	155 (3.7%)	352 (8.4%)	27.7	23.8	51.5
≥ 75	62 (1.5%)	71 (1.7%)	133 (3.2%)	8.4	9.5	17.9
Total	2047 (48.7%)	2159 (51.3%)	4206 (100.0%)	272.9	291.1	564.0

Table 14 Exposure by Age Group and Gender, IV Route of Administration, Non-Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2067 Phase 3 Cohort 2 [Paediatric Patients])**						
	Number of Patients Exposed (N=200)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
0 to < 12	53 (26.5%)	49 (24.5%)	102 (51.0%)	24.5	22.5	47.1
12 to < 18	58 (29.0%)	40 (20.0%)	98 (49.0%)	25.7	18.8	44.5
Cumulative total	111 (55.5%)	89 (44.5%)	200 (100.0%)	50.2	41.4	91.5
Treatment indication (Study COV-2067 Phase 3 Cohort 3)**						
	Number of Patients Exposed (N = 78)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
12 to < 18	0.	1 (1.3%)	1 (1.3%)	-	0.5	0.5
18 to < 65	0	77 (98.7%)	77 (98.7%)	-	35.0	35.0
65 to < 75	0	0 (0.0%)	0 (0.0%)	-	-	-
≥ 75	0	0 (0.0%)	0 (0.0%)	-	-	-
Total	0	78 (100%)	78 (100%)	-	35.4	35.4

Table 14 Exposure by Age Group and Gender, IV Route of Administration, Non-Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-20145***)						
	Number of Patients Exposed (N=460)			Cumulative Follow-Up (Patient-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	224 (48.7%)	235 (51.1%)	459 (99.8%)	16.89	16.42	33.30
65 to < 75	0	0	0	-	-	-
≥ 75	1 (0.2%)	0	1 (0.2%)	0.02	-	0.02
Total	225 (48.9%)	235 (51.1%)	460 (100.0%)	16.91	16.42	33.33

*Randomized patients through 17 January 2021. Data cutoff date: 18 February 2021.

** Data base lock date : 12 July 2022. Patients received a single dose of study treatment.

***Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data-date of first dose+1)]/365.25

Source:
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_age_sex.sas (03MAY2021 14:23 SAS Linux 9.
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_age_gen_iv.sas (06MAY2021 17:05 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_c2.sas (12OCT2023 17:30 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_age_sex_c3.sas (20OCT2023 14:44 SAS Linux 9.4).

Table 15 Exposure by Age group and Gender, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only)

	Number of Patients Exposed (N=5771)			Cumulative Follow-Up (Patient-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
0 to < 12	0 (0.0%)	0 (0.0%)	0	.	.	.
12 to < 18	3 (< 0.1%)	1 (< 0.1%)	4 (< 0.1%)	0.2	0.1	0.3
18 to < 65	2044 (35.4%)	1302 (22.6%)	3346 (58.0%)	184.9	125.4	310.3
65 to < 75	802 (13.9%)	461 (8.1%)	1263 (22.0%)	65.6	39.3	104.9
≥ 75	661 (11.4%)	497 (8.7%)	1158 (20.1%)	46.3	41.3	87.6
≥ 85	182 (3.2%)	167 (2.9%)	349 (6.1%)	11.3	13.1	24.4
Cumulative Total for IV	3510 (60.8%)	2261 (39.2%)	5771 (100%)	297	206.1	503.1
Treatment indication (Study COV-2066 Cohort 1*)						
	Number of Patients Exposed (N=941)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	287 (30.5%)	250 (26.6%)	537 (57.1%)	43.3	38.9	82.2
65 to < 75	108 (11.5%)	88 (9.4%)	196 (20.8%)	16.1	13.1	29.1
≥ 75	105 (11.2%)	103 (10.9%)	208 (22.1%)	12.7	13.8	26.5
≥ 85	35 (3.7%)	37 (3.9%)	72 (7.7%)	3.4	4.1	7.5
Total	500 (53.1%)	441 (46.9%)	941 (100.0%)	72.1	65.8	137.8

Table 15 Exposure by Age group and Gender, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2066 Cohort 1A*)						
	Number of Patients Exposed (N=399)			Cumulative Follow-Up (Patient-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	122 (30.6%)	110 (27.6%)	232 (58.1%)	19.1	16.1	35.2
65 to < 75	49 (12.3%)	26 (6.5%)	75 (18.8%)	6.6	3.7	10.3
≥ 75	52 (13.0%)	40 (10.0%)	92 (23.1%)	6.5	6.3	12.8
≥ 85	12 (3.0%)	17 (4.3%)	29 (7.3%)	1.3	2.6	3.9
Total	223 (55.9%)	176 (44.1%)	399 (100.0%)	32.2	26.2	58.3
Treatment indication (Study COV-2066 Cohort 2*)						
	Number of Patients Exposed (N=110)			Cumulative Follow-Up (Patient-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	35 (31.8%)	22 (20.0%)	57 (51.8%)	5.3	2.7	8.0
65 to < 75	20 (18.2%)	12 (10.9%)	32 (29.1%)	2.5	0.9	3.4
≥ 75	15 (13.6%)	6 (5.5%)	21 (19.1%)	0.9	0.5	1.4
≥ 85	2 (1.8%)	3 (2.7%)	5 (4.5%)	0.1	0.2	0.2
Total	70 (63.6%)	40 (36.4%)	110 (100.0%)	8.7	4.1	12.8

Table 15 Exposure by Age group and Gender, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2066 Cohort 3*)						
	Number of Patients Exposed (N=23)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	8 (34.8%)	3 (13.0%)	11 (47.8%)	0.9	0.4	1.3
65 to < 75	4 (17.4%)	3 (13.0%)	7 (30.4%)	0.4	0.2	0.6
≥ 75	5 (21.7%)	0 (0.0%)	5 (21.7%)	0.5	.	0.5
≥ 85	1 (4.3%)	0 (0.0%)	1 (4.3%)	0.2	.	0.2
Total	17 (73.9%)	6 (26.1%)	23 (100.0%)	1.7	0.6	2.3
Treatment indication (RECOVERY)						
	Number of Patients Exposed (N=4298)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
0 to < 12	0 (0.0%)	0 (0.0%)	0 (0.0%)			
12 to < 18	3 (0.1%)	1 (0.0%)	4 (0.1%)		0.2	0.1
18 to < 65	1592 (37.0%)	917 (21.3%)	2509 (58.4%)		116.3	67.3
65 to < 75	621 (14.4%)	332 (7.7%)	953 (22.2%)		40.0	21.4
≥ 75	484 (11.3%)	348 (8.1%)	832 (19.4%)		25.7	20.7
≥ 85	132 (3.1%)	110 (2.6%)	242 (5.6%)		6.3	6.2
Total	2700 (62.8%)	1598 (37.2%)	4298 (100.0%)		182.3	109.4

Table 15 Exposure by Age group and Gender, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

*Randomized patients through 9 April 2021. Last patient follow-up visit on 13 June 2021.

**Last patient follow-up visit on 21 June 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data-date of first dose+1)]/365.25.

sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2066/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_age_sex_c1a.sas (13SEP2021 12:26 SAS Linux 9.4).

Program: t-ex-age.sas (Source Dataset: ADSL, SV, DS) Version 1.0.

In the Single Dose SC Safety Analysis Set, 53.0% (n=1020) were female and 47.0% (n=906) were male, and the majority of patients (89.5% [n=1724]) were 18 to <65 years of age. A total of 3.4% (n=66) were paediatric patients aged 12 to <18 years. Female patients had 255.59 patient-years of exposure versus. 220.91 patient-years in male patients (Table 16).

In the Repeat Dose SC Safety Analysis Set, (Study HV-2093) 55.1% (n=402) were male and 44.9% (n = 327) were female, and the majority of subjects (87.7% [n=639]) were 18 to <65 years of age. Male subjects had 187.44 person-years of follow-up vs. 149.56 person-years in female subjects (Table 17).

No exposure data for subjects <12 years are available, as this population had not been recruited into Studies COV-2069, COV-20145, and HV-2093 at the time of data cutoffs.

Table 16 Exposure by Age Group and Gender, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only)

	Cumulative Number of Patients Exposed (N=1926)			Cumulative Follow-Up (Patient-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
12 to < 18	38 (2.0%)	28 (1.4%)	66 (3.4%)	9.15	7.44	16.58
18 to < 65	806 (41.8%)	918 (47.7%)	1724 (89.5%)	192.84	224.71	417.56
65 to < 75	51 (2.6%)	53 (2.8%)	104 (5.3%)	15.75	16.43	32.18
≥ 75	11 (0.6%)	21 (1.1%)	32 (1.7%)	3.17	7.01	10.18
Cumulative total for SC	906 (47.0%)	1020 (53.0%)	1926 (100%)	220.91	255.59	476.5
Prevention indication (Study COV-2069 Cohort A*)						
	Number of Patients Exposed (N=1311)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
12 to < 18	27 (2.1%)	18 (1.4%)	45 (3.4%)	6.51	4.96	11.47
18 to < 65	521 (39.7%)	625 (47.7%)	1146 (87.4%)	158.20	191.02	349.23
65 to < 75	45 (3.4%)	48 (3.7%)	93 (7.1%)	13.85	14.61	28.46
≥ 75	8 (0.6%)	19 (1.4%)	27 (2.1%)	2.49	6.47	8.96
Total	601 (45.8%)	710 (54.2%)	1311 (100.0%)	181.05	217.07	398.11
Treatment indication (Study COV-2069 Cohort B)**						
	Number of Patients Exposed (N=155)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
12 to < 18	11 (7.1%)	10 (6.5%)	21 (13.5%)	2.64	2.48	5.11
18 to < 65	61 (39.4%)	58 (37.4%)	119 (76.8%)	17.75	17.27	35.03

Table 16 Exposure by Age Group and Gender, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only) (Cont.)

	Number of Patients Exposed (N=155)			Cumulative Follow-Up (Patient-Years)		
65 to < 75	6 (3.9%)	5 (3.2%)	11 (7.1%)	1.90	1.82	3.72
≥ 75	2 (1.3%)	2 (1.3%)	4 (2.6%)	0.66	0.54	1.20
Total	80 (51.6%)	75 (48.4%)	155 (100.0%)	22.95	22.11	45.06
Treatment indication (Study COV-20145*)**						
	Number of Patients Exposed (N=460)			**Cumulative Follow-Up (Patient-Years)**		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	110 (48.2%)	117 (51.3%)	227 (99.6%)	7.93	8.54	16.47
65 to < 75	0	0	0	-	-	-
≥ 75	0	1 (0.4%)	1 (0.4%)	-	0.07	0.07
Total	110 (48.2%)	118 (51.8%)	228 (100.0%)	7.93	8.61	16.54

* Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

***Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of the last available data - date of first dose+1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_age_gen_coha.sas (06MAY2021 16:56 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_age_gen_cohb.sas (06MAY2021 16:56 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_age_gen_sc.sas (06MAY2021 17:05 SAS Linux 9.4).

Table 17 Exposure by Age group and Gender, SC Route of Administration, Repeated Dose, (Study HV-2093) - Safety Analysis Set (Active Treatment Only)

	Number of Subjects Exposed (N=729)			Cumulative Exposure (Person-Years)			Cumulative Follow-Up (Person-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	353 (48.4%)	286 (39.2%)	639 (87.7%)	118.09	97.54	215.63	165.28	130.46	295.74
65 to < 75	40 (5.5%)	39 (5.3%)	79 (10.8%)	13.28	13.54	26.82	18.32	18.30	36.62
≥ 75	9 (1.2%)	2 (0.3%)	11 (1.5%)	2.55	0.70	3.25	3.85	0.79	4.64
Cumulative total	402 (55.1%)	327 (44.9%)	729 (100.0%)	133.92	111.78	245.70	187.44	149.56	337.00

Data cutoff date: 13 March 2021

Cumulative follow-up (person-years) = [Sum of (date of last available data - date of first dose + 1)]/365.25.

Cumulative exposure (person-years) = [Sum of (date of last dose-date of first dose+1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-HV/R10933-10987-HV-2093/BLA_IA/Post_Hoc/RMP/Programs/Generated/t_exp_age_gen.sas (07MAY2021 09:12 SAS Linux 9.4).

EXPOSURE BY DOSE RECEIVED

In the IV Safety Analysis Set, exposure was calculated according to a patient's actual treatment received.

In the studies involving non-hospitalized patients, most patients received the 2.4 g (1.2 g of each mAb) IV dose (47.1% [n=2328]), followed by the 8.0 g (4.0 g of each mAb) IV dose (25.7% [n=1272 patients) and the 1.2 g (0.6 g of each mAb) IV dose (22.6% [n=1115]) (Table 18). Among non-hospitalized paediatric patients (< 18 years of age) in Phase 3 Cohort 2 of Study COV-2067, 129/200 (64.5%) patients received the 1.2 g IV dose (or body-weight equivalent dose) and 71/200 (35.5%) patients received the 2.4 g IV dose (or body-weight equivalent dose). The 8.0 g dose was not studied in Study COV-2067 Phase 3 Cohort 2.

For the studies involving hospitalized patients, most patients (87.2% [n=5031]) received the 8.0g (4.0g of each mAb) IV dose, followed by the 2.4 g (1.2 g of each mAb) IV dose (12.8% [n=740 patients]) (Table 19).

Table 18 Extent of Exposure by Dose Received, IV Route of Administration for Non-Hospitalized Patients, Safety Analysis Set (Active Treatment Only)

Cumulative for IV for Non-Hospitalized Populations		
Dose of exposure	**Number of Patients Exposed (N=4944)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	1272 (25.7%)	155.7
2.4 g (1.2 g each of casirivimab and imdevimab)	2328 (47.1%)	337.48
1.2 g (0.6 g each of casirivimab and imdevimab)	1115 (22.6%)	214.56
0.6 g (0.3 g each of casirivimab and imdevimab)	114 (2.3%)	8.19
0.3 g (0.15 g each of casirivimab and imdevimab)	115 (2.3%)	8.40
Cumulative total	4944 (100.0%)	724.23
Treatment indication (COV-2067 Pooled Phase 1, 2, 3 Cohort 1* [Symptomatic Patients])		
Dose of exposure	**Number of Patients Exposed (N=4206)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	1272 (30.2%)	155.7
2.4 g (1.2 g each of casirivimab and imdevimab)	2107 (50.1%)	280.8
1.2 g (0.6 g each of casirivimab and imdevimab)	827 (19.7%)	127.5
Total	4206 (100.0%)	564.0
Treatment indication (COV-2067 Phase 3 Cohort 2 [Paediatric Patients])**		
Dose of exposure	**Number of Patients Exposed (N=200)**	**Cumulative Follow-up (Patient-years)**
2.4 g (1.2 g each of casirivimab and imdevimab)	71 (35.5%)	32.3
1.2 g (0.6 g each of casirivimab and imdevimab)	129 (64.5%)	59.3
Total	200 (100.0%)	91.5
Treatment indication (Study COV-2067 Phase 3 Cohort 3)**		
Dose of exposure	**Number of Patients Exposed (N=78)**	**Cumulative Follow-up (Patient-years)**
2.4 g (1.2 g each of casirivimab and imdevimab)	35 (44.9%)	16.0
1.2 g (0.6 g each of casirivimab and imdevimab)	43 (55.1%)	19.4
Total	78 (100.0%)	35.4

Table 18 Extent of Exposure by Dose Received, IV Route of Administration for Non-Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-20145***)		
Dose of exposure	**Number of Patients Exposed (N=460)**	**Cumulative Follow-up (Patient-years)**
2.4 g (1.2 g each of casirivimab and imdevimab)	115 (25.0%)	8.38
1.2 g (0.6 g each of casirivimab and imdevimab)	116 (25.2%)	8.36
0.6 g (0.3 g each of casirivimab and imdevimab)	114 (24.8%)	8.19
0.3 g (0.15 g each of casirivimab and imdevimab)	115 (25.0%)	8.40
Total	460 (100.0%)	33.33

* Randomized patients through 17 January 2021. Data cutoff date: 18 February 2021

** Data base lock date: 12 July 2022. Patients in Phase 3 Cohort 3 received a single dose of study treatment. Patients in Phase 3 Cohort 2 weighing <40 kg received a weight based equivalent dose.

*** Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data - date of first dose+1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_trt.sas (03MAY2021 13:23 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_dose_iv.sas (06MAY2021 17:05 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_trt_c3.sas (12OCT2023 17:30 SAS Linux 9.4)

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_c2.sas (12OCT2023 17:30 SAS Linux 9.4).

Table 19 Extent of Exposure by Dose Received, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only)

Cumulative for IV for Hospitalized Populations		
Dose of exposure	**Number of Patients Exposed (N=5771)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	5031 (87.2%)	396.9
2.4 g (1.2 g each of casirivimab and imdevimab)	740 (12.8%)	106.1
Cumulative total	5771 (100.0%)	503.0
Treatment indication (COV-2066 Cohort 1*)		
Dose of exposure	**Number of Patients Exposed (N=941)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	471 (50.1%)	68.8
2.4 g (1.2 g each of casirivimab and imdevimab)	470 (49.9%)	69.0
Total	941 (100.0%)	137.8
Treatment indication (COV-2066 Cohort 1A*)		
Dose of exposure	**Number of Patients Exposed (N=399)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	197 (49.4%)	28.3
2.4 g (1.2 g each of casirivimab and imdevimab)	202 (50.6%)	30.1
Total	399 (100.0%)	58.3

Table 19 Extent of Exposure by Dose Received, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (COV-2066 Cohort 2*)		
Dose of exposure	**Number of Patients Exposed (N=110)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	54 (49.1%)	6.8
2.4 g (1.2 g each of casirivimab and imdevimab)	56 (50.9%)	6.0
Total	110 (100.0%)	12.8
Treatment indication (COV-2066 Cohort 3*)		
Dose of exposure	**Number of Patients Exposed (N=23)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	11 (47.8%)	1.3
2.4 g (1.2 g each of casirivimab and imdevimab)	12 (52.2%)	1.0
Total	23 (100.0%)	2.3
Treatment indication (RECOVERY)**		
Dose of exposure	**Number of Patients Exposed (N=4298)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	4298 (100.0%)	291.7

*Randomized patients through 9 April 2021. Last patient follow-up visit on 13 June 2021

**Last patient follow-up visit on 21 June 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data-date of first dose+1)]/365.25.

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2066/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_trt_c1.sas (13SEP2021 12:26 SAS Linux 9.4).

Program: t-ex-special.sas (Source Dataset: ADSL, SV, DS) Version 1.0.

In the Single Dose SC Safety Analysis Set, exposure data were calculated according to a patient's actual treatment received. Overall, the majority of patients (93.2% [n = 1580]) received the 1.2 g (0.6 g each of casirivimab and imdevimab) SC dose (Table 20).

An, additional 729 (100.0%) subjects received the 1.2 g (0.6 g each of casirivimab and imdevimab) SC dose in Study HV-2093 (Repeat SC Dose Safety Analysis Set; Table 21).

Table 20 Extent of Exposure by Dose Received, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only)

Cumulative for SC for all indications		
Dose of exposure	**Number of Patients Exposed (N=1694)**	**Cumulative Follow-up (Patient-years)**
1.2 g (0.6 g each of casirivimab and imdevimab)	1580 (93.2%)	451.45
0.6 g (0.3 g each of casirivimab and imdevimab)	114 (6.8%)	8.27
Cumulative total for SC	1694 (100.0%)	459.72
Prevention indication (Study COV-2069 Cohort A*)		
Dose of exposure	**Number of Patients Exposed (N=1311)**	**Cumulative Follow-up (Patient-years)**
1.2 g (0.6 g each of casirivimab and imdevimab)	1311 (100.0%)	398.11
Treatment indication (Study COV-2069 Cohort B)**		
Dose of exposure	**Number of Patients Exposed (N=155)**	**Cumulative Follow-up (Patient-years)**
1.2 g (0.6 g each of casirivimab and imdevimab)	155 (100.0%)	45.06
Treatment indication (Study COV-20145*)**		
Dose of exposure	**Number of Patients Exposed (N=228)**	**Cumulative Follow-up (Patient-years)**
1.2 g (0.6 g each of casirivimab and imdevimab)	114 (50.0%)	8.28
0.6 g (0.3 g each of casirivimab and imdevimab)	114 (50.0%)	8.27
Total	228 (100.0%)	16.54

Table 20 Extent of Exposure by Dose Received, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only)

*Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

***Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of the last available data - date of first dose+1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_dose_coha.sas (06MAY2021 16:56 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_dose_cohb.sas (06MAY2021 16:56 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_dose_sc.sas (06MAY2021 17:05 SAS Linux 9.4).

Table 21 Extent of Exposure by Dose Received, SC Route of Administration, Repeated Dose (Study HV-2093) - Safety Analysis Set (Active Treatment Only)

Dose of exposure	Number of Subjects Exposed (N=729)	Cumulative Exposure (Person-years)	Cumulative Follow-up (Person-years)
Prevention indication (Study COV-2093)			
1.2 g (0.6 g each of casirivimab and imdevimab)	729 (100.0%)	245.70	337.00

Data cutoff date: 13 March 2021.

Cumulative follow-up (person-years) = [Sum of (date of last available data - date of first dose + 1)]/365.25.

Cumulative exposure (person-years) = [Sum of (date of last dose-date of first dose+1)]/365.25.

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-HV/R10933-10987-HV-2093/BLA_IA/Post_Hoc/RMP/Programs/Generated/t_exp_dose.sas (07MAY2021 09:12 SAS Linux 9.4).

ETHNIC AND RACIAL ORIGIN

In the IV Safety Analysis Set for non-hospitalized patients, the majority of patients were Not Hispanic or Latino (61.0% [n = 3012]), followed by Hispanic or Latino (38.1%) [n=1885]) (Table 22), which was similar to the Single Dose SC Safety Analysis Set (53.8% [n=911] vs. 45.5% [n=772], respectively) (Table 24) and the Repeat Dose SC Safety Analysis Set (75.9% [n=553] vs. 23.6% [n=172], respectively) (Table 25). Among paediatric patients in COV-2067 Phase 3 Cohort 2, the reverse was true with more

Hispanic or Latino patients (62.5% [125/200 patients]) than non-Hispanic or Latino patients (36.5% [73/200 patients]) (Table 22)

In the IV Safety Analysis Set for hospitalized patients, ethnic origin data were only collected for Study COV-2066. In this study, the majority of patients were Not Hispanic or Latino (65.7% [n = 968]), followed by Hispanic or Latino (29.7% [n = 437) and Not Reported (4.6%, [n = 68]) (Table 23).

Table 22 Extent of Exposure by Ethnic Origin for Non-Hospitalized Patients, IV Route of Administration, Safety Analysis Set (Active Treatment Only)

Ethnicity	Number of Patients Exposed (N=4944)	Cumulative Follow-up (Patient-years)
Cumulative for IV		
Hispanic or Latino	1885 (38.1%)	273.82
Not Hispanic or Latino	3012 (61.0%)	444.8
Not reported	47 (1.0%)	5.61
Unknown	0 (0.0%)	-
Cumulative total for IV	4944 (100%)	724.23
Treatment indication (Study COV-2067 Pooled Phase 1, 2, 3 Cohort 1* (Symptomatic Patients)		
Ethnicity	**Number of Patients Exposed (N=4206)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	1585 (37.7%)	199.2
Not Hispanic or Latino	2588 (61.5%)	360.7
Not reported	33 (0.8%)	4.1
Unknown	0 (0.0%)	-
Total	4206 (100.0%)	564.0
Treatment indication (Study COV-2067 Phase 3 Cohort 2 (Paediatric Patients)**		
Ethnicity	**Number of Patients Exposed (N=200)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	125 (62.5%)	56.7
Not Hispanic or Latino	73 (36.5%)	33.9
Not reported	2 (1.0%)	0.9
Unknown	0 (0.0%)	-
Total	200 (100.0%)	91.5
Treatment indication (Study COV-2067 Phase 3 Cohort 3)**		
Ethnicity	**Number of Patients Exposed (N=78)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	14 (17.9%)	6.3
Not Hispanic or Latino	64 (82.1%)	29.1
Not reported	0 (0.0%)	.
Unknown	0 (0.0%)	.
Total	78 (100.0%)	35.4

Table 22 Extent of Exposure by Ethnic Origin for Non-Hospitalized Patients, IV Route of Administration, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-20145***)		
Ethnicity	**Number of Patients Exposed (N=460)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	161 (35.0%)	11.62
Not Hispanic or Latino	287 (62.4%)	21.10
Not reported	12 (2.6%)	0.61
Unknown	-	-
Total	460 (100.0%)	33.33

* Randomized patients through 17 January 2021. Data cutoff date: 18 February 2021.

** Data base lock date: 12 July 2022. Patients received a single dose of study treatment.

*** Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data - date of first dose+1)]/365.25.

Source:/home/lei.yu/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_ethnic.sas (04MAY2021 15:03 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_ethnic_iv.sas (06MAY2021 17:05 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_ethnic_c2.sas (12OCT2023 17:30 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_trt_c3.sas (12OCT2023 17:30 SAS Linux 9.4).

Table 23 Extent of Exposure by Ethnic Origin, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only)

Ethnicity	Number of Patients Exposed (N=1473)	Cumulative Follow-up (Patient-years)
Cumulative data available for IV Hospitalized Patients		
Hispanic or Latino	437 (29.7%)	62.6
Not Hispanic or Latino	968 (65.7%)	138.4
Not reported	68 (4.6%)	10
Cumulative total	1473 (100.0%)	211
Treatment indication (Study COV-2066 Cohort 1*)		
Ethnicity	**Number of Patients Exposed (N=941)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	295 (31.3%)	44.2
Not Hispanic or Latino	610 (64.8%)	88.7
Not reported	36 (3.8%)	4.9
Total	941 (100.0%)	137.8
Treatment indication (Study COV-2066 Cohort 1A*)		
Ethnicity	**Number of Patients Exposed (N=399)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	93 (23.3%)	13.3
Not Hispanic or Latino	281 (70.4%)	40.8
Not reported	25 (6.3%)	4.2
Total	399 (100.0%)	58.3
Treatment indication (Study COV-2066 Cohort 2*)		
Ethnicity	**Number of Patients Exposed (N=110)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	40 (36.4%)	4.1
Not Hispanic or Latino	63 (57.3%)	7.9
Not reported	7 (6.4%)	0.9
Total	110 (100.0%)	12.8
Treatment indication (Study COV-2066 Cohort 3*)		
Ethnicity	**Number of Patients Exposed (N=228)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	9 (39.1%)	1.0
Not Hispanic or Latino	14 (60.9%)	1.3
Not reported	0 (0.0%)	
Total	23 (100.0%)	2.3

Table 23 Extent of Exposure by Ethnic Origin, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Randomized patients through 9 April 2021. Last patient follow-up visit on 13 June 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data-date of first dose+1)]/365.25.

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2066/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_ethnic_c1a.sas (13SEP2021 12:26 SAS Linux 9.4).

Table 24 Extent of Exposure by Ethnic Origin, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only)

Ethnicity	Number of Patients Exposed (N=1694)	Cumulative Follow-up (Patient-years)
Cumulative for all indications for SC		
Hispanic or Latino	772 (45.5%)	211.88
Not Hispanic or Latino	911 (53.8%)	244.36
Not reported	11 (0.65%)	3.46
Cumulative total	1694 (100.0%)	459.7
Prevention indication (Study COV-2069 Cohort A*)		
Ethnicity	**Number of Patients Exposed (N=1311)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	616 (47.0%)	187.25
Not Hispanic or Latino	688 (52.5%)	208.12
Not reported	7 (0.5%)	2.74
Total	1311 (100.0%)	398.11
Treatment indication (Study COV-2069 Cohort B)**		
Ethnicity	**Number of Patients Exposed (N=155)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	65 (41.9%)	18.12
Not Hispanic or Latino	89 (57.4%)	26.34
Not reported	1 (0.6%)	0.59
Total	155 (100.0%)	45.06
Treatment indication (Study COV-20145*)**		
Ethnicity	**Number of Patients Exposed (N=228)**	**Cumulative Follow-up (Patient-years)**
Hispanic or Latino	91 (39.9%)	6.51
Not Hispanic or Latino	134 (58.8%)	9.90
Not reported	3 (1.3%)	0.13
Total	228 (100.0%)	16.54

*Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

***Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of the last available data - date of first dose+1)]/365.25.

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_ethnic_coha.sas (06MAY2021 16:56 SAS Linux 9.4).

Table 24 Extent of Exposure by Ethnic Origin, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only) (Cont.)

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_ethnic_cohb.sas (06MAY2021 16:56 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_ethnic_sc.sas (06MAY2021 17:05 SAS Linux 9.4).

Table 25 Extent of Exposure by Ethnic Origin, SC Route of Administration, Repeated Dose (Study HV-2093) - Safety Analysis Set (Active Treatment Only)

	Number of Subjects Exposed (N=729)	Cumulative Exposure (Person-years)	Cumulative Follow-Up (Person-years)
Prevention indication (Study HV-2093)			
Hispanic or Latino	172 (23.6%)	57.06	78.02
Not Hispanic or Latino	553 (75.9%)	187.62	257.38
Not reported	4 (0.5%)	1.01	1.60
Cumulative total	729 (100.0%)	245.70	337.00

Data cutoff date: 13 March 2021

Cumulative follow-up (person-years) = [Sum of (date of last available data - date of first dose + 1)]/365.25.

Cumulative exposure (person-years) = [Sum of (date of last dose-date of first dose+1)]/365.25.

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-HV/R10933-10987-HV-2093/BLA_IA/Post_Hoc/RMP/Programs/Generated/t_exp_ethnic.sas (07MAY2021 09:12 SAS Linux 9.4).

In the IV Safety Analysis Set for non-hospitalized patients, the majority of patients were White (84.9% [n=4198]) (Table 26). This was similar to the IV Safety Analysis Set for hospitalized patients (74.9% [n = 4319]) (Table 27), the Single SC Dose Safety Analysis Set (82.9% [n=1405]) (Table 28), and the Repeat SC Dose Safety Analysis Set (Study HV-2093; 86.7% [n=632]) (Table 29).

Table 26 Extent of Exposure by Race, IV Route of Administration, Non-Hospitalized Patients - Safety Analysis Set (Active Treatment Only)

Race	Number of Patients Exposed (N=4944)	Cumulative Follow-up (Patient-years)
Cumulative for all indications for IV		
American Indian or Alaska Native	53 (1.1%)	7.08
Asian	200 (4.0%)	28.03
Black or African American	277 (5.6%)	40.57
Native Hawaiian or other Pacific Islander	8 (0.2%)	1.63
White	4198 (84.9%)	619.71
Not Reported	99 (2.0%)	13.28
Unknown	109 (2.2%)	14.13
Cumulative total	4944 (100%)	724.43
Treatment indication (Study COV-2067 Pooled Phase 1, 2, 3 Cohort 1* [Symptomatic Patients])		
Race	**Number of Patients Exposed (N=4206)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	49 (1.2%)	6.3
Asian	179 (4.3%)	25.6
Black or African American	226 (5.4%)	28.6
Native Hawaiian or other Pacific Islander	6 (0.1%)	1.1
White	3570 (84.9%)	481.7
Not Reported	78 (1.9%)	9.8
Unknown	98 (2.3%)	11.0
Total	4206 (100.0%)	564.0

Table 26 Extent of Exposure by Race, IV Route of Administration, Non-Hospitalized Patients - Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2067 Phase 3 Cohort 2 [Paediatric Patients])**		
Race	**Number of Patients Exposed (N=200)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	0 (0.0%)	-
Asian	2 (1.0%)	0.9
Black or African American	15 (7.5%)	7 0
Native Hawaiian or other Pacific Islander	0 (0.0%)	-
White	174 (87.0%)	79.5
Not Reported	4 (2.0%)	1.8
Unknown	5 (2.5%)	2.3
Total	200 (100.0%)	91.5
Treatment indication (Study COV-2067 Phase 3 Cohort 3)**		
Race	**Number of Patients Exposed (N=78)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	1 (1.3%)	0.5
Asian	0 (0.0%)	.
Black or African American	6 (7.7%)	2.8
Native Hawaiian or other Pacific Islander	1 (1.3%)	0.5
White	67 (85.9%)	30.5
Not Reported	2 (2.6%)	0.7
Unknown	1 (1.3%)	0.5
Total	78 (100.0%)	35.4
Treatment indication (Study COV-20145*)**		
Race	**Number of Patients Exposed (N=460)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	3 (0.7%)	0.28
Asian	19 (4.1%)	1.53
Black or African American	30 (6.5%)	2.17
Native Hawaiian or other Pacific Islander	1 (0.2%)	0.03
White	387 (84.1%)	28.01
Not Reported	15 (3.3%)	0.98
Unknown	5 (1.1%)	0.33

Table 26 Extent of Exposure by Race, IV Route of Administration, Non-Hospitalized Patients - Safety Analysis Set (Active Treatment Only) (Cont.)

Race	Number of Patients Exposed (N=460)	Cumulative Follow-up (Patient-years)
Total	460 (100.0%)	33.33

*Randomized patients through 17 January 2021. Data cutoff date: 18 February 2021.

** Database lock date: 12 July 2022. Patients received a single dose of study treatment.

***Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data - date of first dose+1)]/365.25.

Source: /home/lei.yu/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_race.sas (03MAY2021 13:41 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_race_dose_iv.sas (06MAY2021 17:05 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_race_c2.sas (12OCT2023 17:30 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_race_c3.sas (12OCT2023 17:30 SAS Linux 9.4).

Table 27 Extent of Exposure by Race, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only)

Race	Number of Patients Exposed (N=5771)	Cumulative Follow-up (Patient-years)
Cumulative for all indications for IV		
American Indian or Alaska Native	25 (0.4%)	3.8
Asian	359 (6.2%)	29.2
Black or African American	310 (5.1%)	38.0
Native Hawaiian or other Pacific Islander	6 (<0.1%)	0.9
White	4319 (74.9%)	360.8
Not Reported	162 (2.6%)	24.6
Unspecified Ethnic Minority (Mixed or Other)	118 (2.7%)	8.2
Unknown	472 (8.7%)	37.7
Cumulative total	5771 (100.0%)	503.2
Treatment indication (Study COV-2066 Cohort 1*)		
Race	**Number of Patients Exposed (N=941)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	25 (2.7%)	3.8
Asian	34 (3.6%)	5.7
Black or African American	121 (12.9%)	18.9
Native Hawaiian or other Pacific Islander	4 (0.4%)	0.5
White	611 (64.9%)	87.4
Not Reported	96 (10.2%)	15.0
Unknown	50 (5.3%)	6.6
Total	941 (100.0%)	137.8

Table 27 Extent of Exposure by Race, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2066 Cohort 1A*)		
Race	**Number of Patients Exposed (N=399)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	0 (0.0%)	.
Asian	14 (3.5%)	1.8
Black or African American	57 (14.3%)	8.6
Native Hawaiian or other Pacific Islander	1 (0.3%)	0.2
White	247 (61.9%)	36.4
Not Reported	54 (13.5%)	8.1
Unknown	26 (6.5%)	3.2
Total	399 (100.0%)	58.3
Treatment indication (Study COV-2066 Cohort 2*)		
Race	**Number of Patients Exposed (N=110)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	0 (0.0%)	.
Asian	3 (2.7%)	0.5
Black or African American	15 (13.6%)	2.4
Native Hawaiian or other Pacific Islander	1 (0.9%)	0.21
White	75 (68.2%)	8.1
Not Reported	10 (9.1%)	1.2
Unknown	6 (5.5%)	0.5
Total	110 (100.0%)	12.8

Table 27 Extent of Exposure by Race, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-2066 Cohort 3*)		
Race	**Number of Patients Exposed (N=23)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	0 (0.0%)	
Asian	1 (4.3%)	0.2
Black or African American	4 (17.4%)	0.2
Native Hawaiian or other Pacific Islander	0 (0.0%)	
White	14 (60.9%)	1.4
Not Reported	2 (8.7%)	0.3
Unknown	2 (8.7%)	0.2
Total	23 (100.0%)	2.3
Treatment indication (RECOVERY)**		
Race	**Number of Patients Exposed (N=4298)**	**Cumulative Follow-up (Patient-years)**
Asian	307 (7.1%)	21.0
Black or African American	113 (2.6%)	7.9
White	3372 (78.5%)	227.5
Unspecified Ethnic Minority	118 (2.7%)	8.2
Unknown	388 (9.0%)	27.2
Total	4298 (100.0%)	291.7

*Randomized patients through 9 April 2021. Last patient follow-up visit on 13 June 2021.

**Last patient follow-up visit on 21 June 2021.

Cumulative follow-up (patient-years) = [Sum of (date of patient's last available data-date of first dose+1)]/365.25.

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2066/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_ethnic_c1a.sas (13SEP2021 12:26 SAS Linux 9.4).

Table 28 Extent of Exposure by Race, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only)

Race	Number of Patients Exposed (N=1694)	Cumulative Follow-up (Patient-years)
Cumulative total for all indications for SC		
American Indian or Alaska Native	6 (0.3%)	1.27
Asian	70 (4.1%)	15.89
Black or African American	169 (9.9%)	46.63
Native Hawaiian or other Pacific Islander	3 (0.2%)	0.90
White	1405 (82.9%)	381.22
Other	35 (2.0%)	13.38
Unknown	2 (0.9%)	0.20
Not Reported	4 (0.2%)	0.21
Cumulative total	1694 (100.0%)	459.7
Prevention indication (Study COV-2069 Cohort A*)		
Race	**Number of Patients Exposed (N=1311)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	4 (0.3%)	0.91
Asian	41 (3.1%)	11.45
Black or African American	150 (11.4%)	44.30
Native Hawaiian or other Pacific Islander	3 (0.2%)	0.90
White	1084 (82.7%)	329.24
Other	29 (2.2%)	11.30
Total	1311 (100.0%)	398.11
Treatment indication (Study COV-2069 Cohort B)**		
Race	**Number of Patients Exposed (N=155)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	1 (0.6%)	0.33
Asian	11 (7.1%)	3.11
Black or African American	8 (5.2%)	1.62
Native Hawaiian or other Pacific Islander	-	-
White	129 (83.2%)	37.92
Other	6 (3.9%)	2.08
Total	155 (100.0%)	45.06

Table 28 Extent of Exposure by Race, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only) (Cont.)

Treatment indication (Study COV-20145***)		
Race	**Number of Patients Exposed (N=228)**	**Cumulative Follow-up (Patient-years)**
American Indian or Alaska Native	1 (0.4%)	0.03
Asian	18 (7.9%)	1.33
Black or African American	11 (4.8%)	0.71
Native Hawaiian or other Pacific Islander	-	-
White	192 (84.2%)	14.06
Unknown	2 (0.9%)	0.20
Not Reported	4 (1.8%)	0.21
Total	228 (100.0%)	16.54

*Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28 January 2021. Data cutoff date: 11 March 2021. Subjects received a single dose of study treatment.

***Randomized patients through 1 February 2021. Data cutoff date: 8 February 2021.

Cumulative follow-up (patient-years) = [Sum of (date of last available data - date of first dose+1)]/365.25.

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_race_dose_coha.sas (06MAY2021 16:56 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_race_dose_cohb.sas (06MAY2021 16:56 SAS Linux 9.4).

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_race_dose_sc.sas (06MAY2021 17:05 SAS Linux 9.4).

Table 29 Extent of Exposure by Race, SC Route of Administration, Repeated Dose, Study HV-2093, Safety Analysis Set (Active Treatment Only)

	Number of Subjects Exposed (N=729)	Cumulative Exposure (Person-years)	Cumulative Follow-up (Person-years)
Prevention indication (Study HV-2093)			
American Indian or Alaska Native	8 (1.1%)	2.68	3.65
Asian	12 (1.6%)	3.57	5.28
Black or African American	73 (10.0%)	23.38	30.82
Native Hawaiian or other Pacific Islander	2 (0.3%)	0.70	0.93
White	632 (86.7%)	214.98	295.84
Unknown	2 (0.3%)	0.39	0.48
Cumulative total	729 (100.0%)	245.70	337.00

Data cutoff date: 13 March 2021

Cumulative follow-up (person-years) = [Sum of (date of last available data - date of first dose + 1)]/365.25.

Cumulative exposure (person-years) = [Sum of (date of last dose-date of first dose+1)]/365.25.

/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-HV/R10933-10987-HV-2093/BLA_IA/Post_Hoc/RMP/Programs/Generated/t_exp_race_dose.sas (07MAY2021 09:12 SAS Linux 9.4).

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

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 30 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Treatment indication (Study COV-2067):			
Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for SARS-CoV-2	CDC guidance recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody therapy to avoid interference of the treatment with vaccine induced immune responses	No	Section 4.5 of the EU SmPC states that no formal drug-drug interaction studies have been performed. Casirivimab and imdevimab are monoclonal antibodies, which are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. An interaction study (COV-2118) assessed the immunogenicity, safety, and tolerability of Moderna mRNA-1273 vaccine administered with casirivimab + imdevimab in healthy adult volunteers, the results did not impact the benefit-risk profile of casirivimab + imdevimab and no new safety signals or concerns were identified.

Table 30 Important Exclusion Criteria in Pivotal Studies in the Development Program (Cont.)

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Prevention indication (Studies COV-2069 and HV-2093)			
Has a history of significant multiple and/or severe allergies (e.g., latex gloves), or has had an anaphylactic reaction to prescription or non-prescription drugs or food	This is to avoid possible confounding of the safety analysis and not due to any presumed increased risk of these individuals to a reaction to the investigational product	No	Section 4.2 of the EU SmPC states that the administration of RONAPREVE should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored after administration according to local medical practice. Section 4.4 of the EU SmPC states that hypersensitivity reactions, including anaphylaxis, have been reported with administration of casirivimab and imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Table 30 Important Exclusion Criteria in Pivotal Studies in the Development Program (Cont.)

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Treatment and Prevention Indications (Studies RECOVERY, COV-2066, COV-2067, COV-2069, HV-2093, and COV-20145)			
Has known allergy or hypersensitivity to components of study drug (COV-2067, COV-20145, COV-2066)	Such patients cannot be treated with casirivimab and imdevimab	No	Hypersensitivity to the active substances or any of the excipients is listed as a contraindication in Section 4.3 of the EU SmPC. Section 4.2 of the EU SmPC states that the administration of RONAPREVE should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored after administration according to local medical practice.
Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for SARS-CoV-2 (COV-2067, COV-20145, COV-2069, HV-2093)	CDC guidance recommends deferral of SARS-CoV-2 vaccination for at least 90 days after administration of passive antibody therapy to avoid interference of the treatment with vaccine induced immune responses	No	Section 4.5 of the EU SmPC states that no formal drug-drug interaction studies have been performed. Casirivimab and imdevimab are monoclonal antibodies, which are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Table 30 Important Exclusion Criteria in Pivotal Studies in the Development Program (Cont.)

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			An interaction study (COV-2118) assessed the immunogenicity, safety, and tolerability of Moderna mRNA-1273 vaccine administered with casirivimab+imdevimab in healthy adult volunteers. The results did not impact the benefit-risk profile of casirivimab +imdevimab and no new safety signals or concerns were identified.
Pregnant or breastfeeding women were excluded in early versions of the protocols for Studies COV-2066, COV-2067, COV-2069, and COV-20145 (without risk factors)	There is currently limited clinical experience in the use of casirivimab, imdevimab, and casirivimab+imdevimab in female subjects who are pregnant or breastfeeding. As casirivimab and imdevimab are directed against an exogenous antigen (the S protein of SARS-CoV-2), administration casirivimab+imdevimab is not anticipated to affect endogenous pathways. Therefore, the safety profile in pregnant women is expected to be similar to that observed in adults and adolescents. Casirivimab and imdevimab should be used during pregnancy or breastfeeding only if the potential benefit justifies the potential risk for the mother and the fetus or breastfed child considering all associated health factors	No	Use in pregnancy - Refer to Section SVII.3.2. Presentation of the Missing Information for rationale. Section 4.6 of the EU SmPC sufficiently describes this risk. Section 4.6 of the EU SmPC states that it is unknown whether casirivimab and imdevimab are excreted in human milk, but maternal IgG is known to be transferred to milk during the first days after birth. As casirivimab and imdevimab directly target the spike protein of SARS-CoV-2 and in view of low systemic absorption after oral ingestion of antibodies, administration of RONAPREVE whilst breastfeeding can be considered when clinically indicated.

Table 30 Important Exclusion Criteria in Pivotal Studies in the Development Program (Cont.)

CDC = Centers for Disease Control and Prevention; COVID-19 = Coronavirus disease 2019; EU SmPC = EU Summary of product characteristics; IgG = immunoglobulin G; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical trial development program for casirivimab and imdevimab was unable to detect adverse drug reactions that are:

- **Rare adverse reactions:** The casirivimab and imdevimab safety population provides data from **13138** patients with **2023.84** patient-years of follow-up from the Phase I, Phase II, Phase III, and Phase1/2/3 studies HV-2093 (Phase 1), COV-20145 (Phase 2), COV-2069 (Phase 3), COV-2066 (Phase 1/2/3), RECOVERY and COV-2067 (Phase 1/2/3).
- **Caused by prolonged exposure**: All patients in the IV Safety Analysis Set (including hospitalized patients) and the SC Safety Analysis set received only one dose of casirivimab and imdevimab with the exception of subjects in Study HV-2093 who received up to 6 SC doses. To date, no adverse drug reactions (ADRs) caused by prolonged exposure have been observed.
- **Caused by cumulative exposure**: There have been 12409 patients who received a single IV or SC dose of casirivimab and imdevimab (see Table 10, Table 11 and Table 12) and 729 patients received repeated SC dosing (Table 13). In patients who received repeated SC dosing, cumulative exposure was 245.70 patient-years. No cumulative toxicities have been observed to date.
- **Or that have a long latency**: Overall, as of the data cutoffs, the vast majority of patients had been followed up for safety for at least 4 weeks in the non-hospitalised IV Safety Analysis Set (89.3%, Table 10), the Single Dose SC Safety Analysis Set (91.5%, Table 12), and the Repeat Dose SC Analysis Set (99.5%, Table 13). In the non-hospitalized IV Safety Analysis Set, 6.0% of patients have been followed up for at least 16 weeks (Table 11). In the IV Safety Analysis Set for hospitalized patients, 81.1% of patients have been followed up for at least 4 weeks and 0.7% of patients have been followed up for at least 16 weeks. In the Single Dose SC Safety Analysis Set and in the Repeat Dose SC Analysis Set, 0.9% of patients and 5.6% of subjects, respectively, have been followed up for at least 32 weeks. To date, no ADRs with long latency periods have been observed; however, the follow-up data available to date are not sufficient to ascertain any long latency effects.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Information available for use of casirivimab and imdevimab in populations typically under-represented in clinical development program is provided in Table 31; additional details for use in pregnancy and lactation are presented in “Use in Pregnancy and Lactation” below.

Use in Pregnancy and Lactation

Section 4.6 of the EU Summary of Product Characteristics states that there are limited data from the use of casirivimab and imdevimab in pregnant women. Data from pregnant women exposed to casirivimab+imdevimab from clinical studies as well as the registry-based cohort and post-marketing surveillance, including a total of 381 exposed pregnant women, did not identify adverse effects associated with casirivimab and imdevimab use on pregnancy or on the health of the developing fetus. Animal reproductive toxicity studies were not conducted; however, in a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, as anticipated, no binding was detected, as both mAbs bind to exogenous protein. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus (see SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP). Ronapreve should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus considering all associated health factors. If a woman becomes pregnant while taking this medicine, the individual should be informed that any potential risk to the fetus is unknown.

Section 4.6 of the EU SmPC states that it is unknown whether casirivimab and imdevimab are excreted in human milk, but maternal IgG is known to be transferred to milk during the first days after birth. As casirivimab and imdevimab directly target the spike protein of SARS-CoV-2, and in view of low systemic absorption after oral ingestion of antibodies, administration of Ronapreve while breastfeeding can be considered when clinically indicated (SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM).

A detailed evaluation of pregnancy and lactation cases with casirivimab and imdevimab available to the Marketing Authorization Holder (MAH) is present in periodic benefit-risk evaluation report (PBRER) 1131387 (19 July 2023 to 18 July 2024) in Section 15.2. Additionally, as post-authorization usage data in this population is not able to be estimated, a summary of key epidemiology data related to the incidence and outcomes of COVID-19 in pregnant women is presented in PBRER 1131387 (19 July 2023 to 18 July 2024) in Section 5.2.3. The pregnancy and lactation events will continue to be monitored as part of ongoing routine signal detection activities.

Table 31 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women*	Unless otherwise stated, the pregnancy cases were retrieved from the Roche Global Safety Database: Study COV-2067*: • 101 cases Study COV-2069: • 11 cases Study COV-20145: • 7 cases Study COV-2066: • 1 case Study COV-2118 • 1 case RECOVERY** • 15 cases
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Baseline liver disease (all degrees of impairment)	COV-2067 Pooled Phase 1,2,3 Cohort 1 • 51/4206 (1.2%) Study COV-2069 Cohort A: • 17/1311 (1.3%) Study HV-2093: • 2/729 (0.3%) RECOVERY • 63/4298 (1.5%)

Table 31 Exposure of Special Populations Included or Not in Clinical Trial Development Program (Cont.)

Type of Special Population	Exposure
Baseline kidney disease (all degrees of impairment)	COV-2067 Pooled Phase 1,2,3 Cohort 1 • 39/4206 (0.9%) Study COV-2069 Cohort A: • 11/1311 (0.8%) Study COV-2069 Cohort B: • 2/155 (1.3%) Study HV-2093: • 2/729 (0.3%) RECOVERY • 221/4298 (5.1%)
Baseline cardiovascular disease	COV-2067 Pooled Phase 1,2,3 Cohort 1 • 182/4206 (4.3%) Study COV-2069 Cohort A: • 27/1311 (2.1%) Study COV-2069 Cohort B: • 3/155 (1.9%) Study HV-2093: • 10/729 (1.4%) Study COV-20145 (IV): • 1/460 (0.2%) RECOVERY • 890/4298 (20.7%)
Baseline type 1 or type 2 diabetes	COV-2067 Pooled Phase 1,2,3 Cohort 1 • 386/4206 (9.2%) Study COV-2069 Cohort A: • 112/1311 (8.5%) Study COV-2069 Cohort B: • 8/155 (5.2%)

Table 31 Exposure of Special Populations Included or Not in Clinical Trial Development Program (Cont.)

Type of Special Population	Exposure
	Study HV-2093: • 32/729 (4.4%) Study COV-20145 (IV): • 1/460 (0.2%) RECOVERY • 1080/4298 (25.1%)
Baseline respiratory disease	COV-2067 Pooled Phase 1,2,3 Cohort 1 • 533/4206 (12.7%) Study COV-2069 Cohort A: • 87/1311 (6.6%) Study COV-2069 Cohort B: • 6/155 (3.9%) Study HV-2093: • 39/729 (5.3%) Study COV-20145 (IV): • 4/460 (0.9%) Study COV-20145 (SC): • 2/228 (0.9%) RECOVERY • 941/4298 (21.9%)
Baseline immunosuppressive disease	COV-2066 Cohort 1 • 153/941 (16.3%) COV-2066 Cohort 1A • 109/399 (27.3%) COV-2066 Cohort 2 • 15/110 (13.6%) COV-2066 Cohort 3 • 2/23 (8.7%) COV-2067 Pooled Phase 1,2,3 Cohort 1 • 264/4206 (6.3%)

Table 31 Exposure of Special Populations Included or Not in Clinical Trial Development Program (Cont.)

Type of Special Population	Exposure
	Study COV-2069 Cohort A: • 63/1311 (4.8%) Study COV-2069 Cohort B: • 13/155 (8.4%) Study HV-2093: • 51/729 (7.0%) Study COV-20145 (IV): • 7/460 (1.5%) Study COV-20145 (SC): • 5/228 (2.2%)
Population with relevant different ethnic origin	Included in the clinical development program (See Table 22, Table 24and Table 25).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Paediatric patients	Included in the clinical development program (See Table 16)
Elderly patients	Included in the clinical development program (See Table 14,Table 16 and Table 17)

* Study COV-2067 (Phase 3 Cohort 3) enrolled pregnant women. Further details in PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

** Source RECOVERY Summary of Safety Report.

Data cutoffs:

COV-2066: Randomized patients through 09Apr2021. Data cutoff date: 13Jun2021.

COV-2067 Pooled Phase 1, 2, 3 Cohort 1: Randomized patients through 17Jan2021. Data cutoff date: 18Feb2021.

COV-2067 Phase 3 Cohort 2: Database lock date: 12Jul2022. Patients received a single dose of study treatment.

RECOVERY: Data cutoff date: 21JUN2021.

Study R10933-10987-COV-2069 Cohort A): Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

Study R10933-10987-COV-2069 Cohort B): Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

Study R10933-10987-HV-2093: Data cutoff date: 13MAR2021.

Study R10933-10987-COV-20145 (IV): Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

Study R10933-10987-COV-20145 (SC): Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

Table 31 Exposure of Special Populations Included or Not in Clinical Trial Development Program (Cont.)

Source: /sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2066/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_ethnic_c1a.sas (13SEP2021 12:26 SAS Linux 9.4).
home/lei.yu/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV 2067/Phase1_2_3/Post_Hoc/RMP/Programs/Generated/t_100_dur_spop.sas (10MAY2021 09:00 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_specpop_coha.sas (07MAY2021 13:59 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2069/BLA_IA_rand28Jan/Post_Hoc/RMP/Programs/Generated/t_exp_specpop_cohb.sas (07MAY2021 13:59 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-HV/R10933-10987-HV-2093/BLA_IA/Post_Hoc/RMP/Programs/Generated/t_exp_specpop.sas (07MAY2021 19:31 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_specpop_iv.sas (07MAY2021 13:57 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-20145/IA_rand01FEB2021/Post_Hoc/RMP/Programs/Generated/t_exp_specpop_sc.sas (07MAY2021 13:57 SAS Linux 9.4).
/sasdata/Data/Production/BDM/R10933-10987/R10933-10987-COV/R10933-10987-COV-2067/Final/Post_Hoc/Type_2_EU/Programs/TFL/Generated/t_100_dur_c2.sas (12OCT2023 17:30 SAS Linux 9.4).

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

Casirivimab+imdevimab is currently approved (including Provisional Approval, Special License, Emergency Use Authorization, Special Import License, and Special Authorization License) in approximately 46 countries worldwide as of the data lock point (DLP) for the latest PBRER (1131387; DLP: 18 July 2024).

Exposure in Japan

Patient exposure in Japan was estimated from marketing data.

Exposure by age was extrapolated from the pattern of use of casirivimab+imdevimab in patients living in Tokyo. Age cohort ratios were estimated to be as follows:

- 0 to ≤18 years old: 0.9%
- >18 to <65 years old: 69.1%
- ≥65 years old: 30.0%.

For exposure by gender, the following ratios were used based on data from Suzuki et al. 2022:

- Male: 61.2%
- Female: 38.8%.

EEA and Rest of World

The patient exposure for EEA and Rest of the World (RoW) was directly received from the Roche COVID-19 team and these are estimates. Since casirivimab+imdevimab is distributed and supplied directly to governments in the EEA and RoW, it is not possible to stratify the post-marketing exposure by age or by gender.

SV.1.2 Exposure

Since the international birth date (19 July 2021) until the DLP (18 July 2024), an estimated cumulative total of 103,058patients (40,778 [Japan]+61,180 [EEA]+1100 [RoW]) have received casirivimab+imdevimab from marketing experience. Please see Annex 7B for further details.

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

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of hemoglobin levels. Casirivimab and imdevimab are directed at an exogenous antigen and do not react with mammalian tissues. Based on nonclinical studies, casirivimab and imdevimab do not penetrate into the CNS; therefore, it is unlikely that casirivimab and imdevimab will be misused for illegal purposes.

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

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

Identified Risk Considered Not Important:

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

- Systemic hypersensitivity reactions (HSRs) (including acute infusion-related reactions [IRRs] and/or injection site reactions [ISRs])

Potential Risk Considered Not Important:

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

- Immunogenic response following administration with possible consequences on safety and immunogenicity.

Other reasons for considering the risks not important:

- Viral variants and potential promotion of resistant virus
  - (assessed primarily as an efficacy concern)
- Embryo fetal toxicity (considered within the use in pregnancy missing information)

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks:

None

Important Potential Risks

None

Missing Information

None

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Use in pregnancy", previously classified as missing information, is no longer considered missing and the available data regarding exposed pregnancy has been added to this version of the EU RMP. The MAH will continue to perform routine pharmacovigilance activities (on-going signal detection) and will continue to present "Use in Pregnancy" in the PBRER. A summary of the final Clinical Study report for COVID-PR (GV44373, Category 3 post-authorization safety study) is provided in the latest PBRER (Report No. 1131387, Section 8).

Reasons for changes to the list of safety concerns:

There has been limited clinical experience with the use of casirivimab + imdevimab in patients and subjects who are pregnant (see Table 31). A cumulative analysis of the available data from all sources (clinical trials, registry based cohort and post-marketing surveillance, which included a total of 381 pregnant women exposed to casirivimab and imdevimab, did not identify adverse effects associated with casirivimab and imdevimab use on pregnancy or the health of the developing fetus (Drug safety report [DSR] 1126403). The EU SmPC has been updated accordingly. It is also important to note from epidemiology data related to incidence and outcomes of COVID-19 in pregnant women, that pregnant women with COVID-19 are at increased risk of adverse pregnancy and neonatal outcomes such as preterm labor, preterm birth, preeclampsia, and stillbirth compared to pregnant women without COVID-19.

Additionally, animal reproductive toxicity studies were not conducted; however, in a tissue cross-reactivity study with casirivimab and imdevimab using human fetal tissues, as anticipated, no binding was detected, as both mAbs bind to exogenous protein. Human IgG1 antibodies are known to cross the placental barrier; therefore, casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing fetus. Overall, the available safety data does not suggest casirivimab and imdevimab use in pregnancy is associated

with adverse effects or the health of the developing fetus. This information is included in the EU SmPC.

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

Information on Important Identified Risks

There are no important identified risks for casirivimab and imdevimab.

Information on Important Potential Risks

There are no important potential risks for casirivimab and imdevimab.

SVII.3.2. Presentation of the Missing Information

There is no missing information identified for casirivimab and imdevimab.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 32 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection

- Other forms of routine pharmacovigilance activities for pregnancy and breastfeeding:
    - The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.
    - Cumulative data will be presented in Periodic Safety Update Report (PSURs)/PBRERs.
    - Summary Tabulations of Prospective and Retrospective Individual Case Safety Reports on Pregnancy are presented in Annex 7C of the RMP.

- Other forms of routine pharmacovigilance activities for lack of efficacy:

  As part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, the Sponsor will monitor data on treatment failure due to emerging variants from all available data sources, including but not limited to:
    - Spontaneous cases (via targeted follow-up questionnaire for lack of efficacy including fields to request information on the variant)
    - Clinical trial data from MAH and development partners
    - Literature
    - Studies conducted by public health authorities

  If the review of the data leads to an impact on the benefit-risk of the product, the Sponsor will submit the data to EMA, including a benefit-risk discussion and any warranted product information updates within 1 month via appropriate variation procedure. Additionally, the cumulative data will be summarised in a dedicated section in the PSUR.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the MAH to be sufficient to obtain and analyse relevant post-marketing safety data for all risks with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

This section is not applicable because there are no agreed post-authorization efficacy studies with casirivimab and imdevimab.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

No important identified or potential risks are identified with the use of casirivimab and imdevimab, therefore this section is not applicable.

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

No important identified or potential risks are identified with the use of casirivimab and imdevimab, therefore this section is not applicable.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Not applicable.

REFERENCES

Aabakke AJM, Petersen TG, Wøjdemann K, et al. Risk factors for and pregnancy outcomes after SARS-CoV-2 in pregnancy according to disease severity: A nationwide cohort study with validation of the SARS-CoV-2 diagnosis. Acta Obstet Gynecol Scand 2023;102:282–93.

Aly J, Choi L, Christy AY. The impact of coronavirus on reproduction: contraceptive access, pregnancy rates, pregnancy delay, and the role of vaccination. F S Rev 2022;3:190-200.

Apea VJ, Wan YI, Dhairyawan R, et al. Ethnicity and outcomes in patients hospitalised with COVID-19 infection in East London: an observational cohort study. BMJ Open. 2021;11:e042140.

Center for Disease Control and Prevention (CDC). COVID data tracker. Available from https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed September 2023.

Center for Disease Control and Prevention (CDC). Understanding Risk. Available from https://www.cdc.gov/coronavirus/2019-ncov/your-health/understanding-risk.html. Accessed on 13 October 2023.

COVID-NET. Weekly Summary of COVID-19 related hospitalization. Available from: https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html. Accessed July 2023

[DSR] Drug Safety Report for casirivimab and imdevimab. Report No. 1126403 November 2023.

Devrim İ, Böncüoğlu E, Kıymet E, et al. Comparison of the pediatric hospitalizations due to COVID-19 and H1N1pdm09 virus infections during the pandemic period. J Med Virol. 2022;94:2055–59.

European Centre for Disease Prevention and Control (ECDC). Coronavirus disease 2019 (COVID-19) Surveillance Report. Available from: https://covid19-surveillance-report.ecdc.europa.eu/. Accessed on 9 December 2021.

European Medicine Agency (EMA). Treatments and Vaccine. Available from https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19. Accessed on 13 October 2023.

Erbaş İC, Keleş YE, Erdeniz EH, et al. Evaluation of possible COVID-19 reinfection in children: A multicenter clinical study. Arch Pediatr. 2023;30:187–91.

Hughes BL, Sandoval GJ, Metz TD, et al. First- or second-trimester SARS-CoV-2 infection and subsequent pregnancy outcomes. Am J Obstet Gyneco. 2023 ;228:226.e1-226.e9.

ICH S6 (R1) (2011): Addendum to ICH Guideline on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

Li K, Wu J, Wu F, et al. The Clinical and Chest CT Features Associated with Severe and Critical COVID-19 Pneumonia. Invest Radiol. 2020; 55(6):327 - 31

Mullins E, Perry A, Banerjee J, et al. Pregnancy and neonatal outcomes of COVID-19: The PAN-COVID study. Eur J Obstet Gynecol Reprod Biol. 2022 Sep;276:161–7.

Mensah AA, Campbell H, Stowe J, et al. Risk of SARS-CoV-2 reinfections in children: a prospective national surveillance study between January, 2020, and July, 2021, in England. Lancet Child Adolesc Health. 2022;6:384–92.

National Institute of Health. COVID-19 Treatment Guidelines. Available from https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed on 16 October 2023.

Overton EE, Goffman D, Friedman AM. The Epidemiology of COVID-19 in Pregnancy. Clin Obstet Gynecol 2022;65:110-22.

Periodic Benefit Risk Evaluation Report 1131387 (reporting interval, 19 July 2023 to 18 July 2024): Casirivimab + Imdevimab/Ronapreve®

Prévost B, Retbi A, Binder-Foucard F, et al. Risk factors for admission to the pediatric critical care unit among children hospitalized with COVID-19 in France. Front Pediatr. 2022;10:975826.

Raharja A, Tamara A, Kok LT. Association Between Ethnicity and Severe COVID-19 Disease: a Systematic Review and Meta-analysis. J Racial Ethn Health Disparities. 2020 Nov 12:1-10.

RECOVERY Summary of Safety Report (Randomised Evaluation of COVID-19 Therapy) Casirivimab+Imdevimab Summary of Safety Report. Data cut-off: 21 Jun 2021. Regeneron Pharmaceuticals, Inc. 20 Jan 2022

Simbar M, Nazarpour S, Sheidaei A. Evaluation of pregnancy outcomes in mothers with COVID-19 infection: a systematic review and meta-analysis. J Obstet Gynaecol 2023;43:2162867.

Suzuki Y, Shibata Y, Minemura H, et al. Real-world clinical outcomes of treatment with casirivimab-imdevimab among patients with mild-to-moderate coronavirus disease 2019 during the Delta variant pandemic. medRxiv 2022.

Sze S, Pan D, Nevill CR, et al. Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. EClinicalMedicine. 2020:100630.

Thakur B, Dubey P, Benitez J, et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Sci Rep. 2021;11:8562.

Ukwishaka J, Ndayishimiye Y, Destine E, et al. Global prevalence of coronavirus disease 2019 reinfection: a systematic review and meta-analysis. BMC Public Health. 2023;23:778.

Vicetti Miguel CP, Dasgupta-Tsinikas S, Lamb GS, et al. Ethnicity, and Health Disparities in US Children With COVID-19: A Review of the Evidence and Recommendations for the Future. J Pediatric Infect Dis Soc. 2022;11(Supplement4):S132–40.

Wilkinson M, Johnstone ED, Simcox LE, et al. The impact of COVID-19 on pregnancy outcomes in a diverse cohort in England. Sci Rep 2022;12:942.

World Health Organization. COVID-19 cases and deaths with age and sex. Available from: https://app.powerbi.com/view?r=eyJrIjoiYWRiZWVkNWUtNmM0Ni00MDAwLTljYWMtN2EwNTM3YjQzYmRmIiwidCI6ImY2MTBjMGI3LWJkMjQtNGIzOS04MTBiLTNkYzI4MGFmYjU5MCIsImMiOjh9. Accessed on 7 June 2021.

World Health Organization. Coronavirus disease (COVID-19) Pandemic. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed on 9 December 2021.

Wu Y, Li H, Zhang Z, et al. Risk factors for mortality of coronavirus disease 2019 (COVID-19) patients during the early outbreak of COVID-19: a systematic review and meta-analysis. Ann Palliat Med. 2021:apm-20-2557.

Zambrano LD, Ellington S, Strid P, et al. CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1641–7.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR RONAPREVE

Summary of Risk Management Plan for Ronapreve (casirivimab and Imdevimab)

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

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

This summary of the RMP for RONAPREVE 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 RONAPREVE's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

RONAPREVE is a combination of casirivimab and imdevimab authorized for:

- Treatment of COVID-19 in adults, adolescents and children aged 2 years and older weighing at least 10 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- Treatment of COVID-19 in adults and 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 adults and adolescents aged 12 years and older weighing at least 40 kg.

It contains casirivimab and imdevimab as the active substances, and it is given by intravenous (IV) or subcutaneous (SC) route.

Further information about the evaluation of RONAPREVE's benefits can be found in RONAPREVE's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page:

https://www.ema.europa.eu/en/medicines/human/EPAR/ronapreve

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of RONAPREVE, together with measures to minimize such risks and the proposed studies for learning more about RONAPREVE'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 as 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 events 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 casirivimab and imdevimab is not yet available, it is listed under "missing Information" below.

II.A List of Important Risks and Missing Information

Important risks of RONAPREVE 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 RONAPREVE. 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 about 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	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

There are no important identified risks, important potential risks, or missing information for RONAPREVE.

II.C Post-Authorization Development Plan

II.C.1 Studies That are Conditions of the Marketing Authorization

There are no studies that are conditional for the marketing authorization or specifically obligated for RONAPREVE.

II.C.2 Other Studies in Post-Authorization Development Plan

There are no studies required for RONAPREVE.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Ronapreve Guided Questionnaire for Lack of Effect

This questionnaire is intended to better characterize reports of 'Lack of effect' in association with Ronapreve; and to gather additional information on patients who have experienced it. By completing this questionnaire you will help us to gather important data.

Reporter Information	
Name of reporter completing this form (if other than addressee, provide contact information below):	
Health Care Provider? ☐ Yes ☐ No-Specify:	
Phone number:	Fax number:
Email address:	

Patient Information			
Patient ID/Initials:		AER No:	
Patient Gender:	☐ M ☐ F		
Patient Date of Birth (DD-MMM-YYYY):		Local Case ID:	

Drug therapy details	
Name of product:	
Route of administration: (i.e. IV, SC)	
Indication:	
Dosage and frequency:	
Treatment Date (DD/MMM/YYYY)	
Diluent used:	
Batch number:	
Was the complete dose administered?	☐ Yes ☐ No – if no, please specify the reason for not completing the administration and provide details of approximate dose administered:
Was Ronapreve stored as per guidance in the label?	☐ Yes ☐ No - if no, please provide details:
For the IV route of administration, please confirm whether the infusion bag with the antibodies was mixed by inversion	☐ Yes ☐ No, - if no please provide details of how the antibodies were prepared for infusion.
Was the antibody mix administered immediately after preparation?	☐ Yes ☐ No – if no, please provide storage details along with length of time of storage after dilution:

Details of event		
Date of first COVID-19 symptom onset (DD/MMM/YYYY):		
Date of SARS-CoV-2 test/confirmed diagnosis:		
Details of SARS-CoV-2 test performed:	☐ SARS-CoV-2 RT-PCR test Was the virology sample sequenced? ☐ No ☐ Yes – if yes, please specify strain identified:	
	☐ SARS-CoV-2 antigen test	☐ Other – please specify:
Date of diagnosis of lack of effect (DD/MMM/YYYY):		
Outcome of COVID-19 following administration of Ronapreve:	☐ Recovered ☐ Recovering ☐ No improvement	
Details of follow-up [post treatment] SARS-CoV-2 RT-PCR test:		
Was a follow-up [post treatment] RT-PCR test conducted?	☐ No ☐ Yes	
	If yes, was the virology sample sequenced? ☐ No ☐ Yes – if yes - please specify strain identified:	

Immunocompromised Status	
Is patient immunocompromised:	☐ Yes (please specify below) ☐ No
Primary Immunodeficiency (Please select applicable):	☐ B cell immunodeficiency ☐ T cell immunodeficiency (other than HIV) ☐ Severe combined immune deficiencies (SCID) ☐ Complement defects ☐ Other, please specify:
Secondary Immunodeficiency (Please select applicable):	☐ Malnutrition Chemotherapy ☐ Chemotherapy ☐ HIV ☐ Chronic infections (other than HIV) ☐ Immunosuppressive therapy after organ transplant ☐ Other concomitant immunosuppressive therapy, please specify:

Medical History ☐ **Medical history List Attached**		
Medical history	**Start date**	**Stop date**

Concomitant Medications ☐ **Medication List Attached**			
Drug Name	**Dose**	**Route**	**Frequency**

Please provide any further relevant information about the lack of effect, and indicate if there have been any significant changes from the initial report.

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail:

Thank you for completing this form!

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

Not applicable