EU RISK MANAGEMENT PLAN FOR RONAPREVE®/CASIRIVIMAB AND IMDEVIMAB

RMP version to be assessed as part of this application:

RMP Version number: 2.0

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22-Mar-2023 15:19:09	Company Signatory (PV)	PPD
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Rationale for Submitting an Updated RMP

An updated RMP is submitted with responses to the third Request for Supplementary Information within procedure EMEA/H/C/005814/II/0002.

Summary of Significant Changes in This RMP

- **Part I: Product Overview and Part VI: Summary of the Risk Management Plan –** Updated to reflect the revised indication and posology sections of the EU Summary of product characteristics. The ATC code was also added.
- **Part III.2; III.3; V.3; and Annex 2 –** The format of the study milestones due dates was amended to DD/MM/YYYY format. The actual study start date was provided.

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: 1.0

Approved with Procedure Number: EMEA/H/C/5814

Date of approval (opinion date): 11 November 2021

See page 1 for signature and date

Dr. PPD (Deputy QPPV)[1]	Date

See page 1 for signature and date

PPD , PhD (PPD)	Date

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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 binds 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 are at increased risk of progressing to severe COVID-19. • 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 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.
Dosage in the EEA	Current: **Treatment:** 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 (IV) infusion or by subcutaneous (SC) injection. Casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19 **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 IV infusion or by SC 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 IV infusion or by SC injection. Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab administered as a single IV infusion or by SC 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 (if applicable): **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).
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 Co-packaged 1 332 mg multidose vials 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 (if applicable): Not applicable
Is or will the product be subject to additional monitoring in the European Union?	Yes

CHO = Chinese Hamster Ovary; COVID-19 = coronavirus disease 2019; EEA = European Economic Area; 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
AE	adverse event
ARDS	acute respiratory distress syndrome
CDC	Center for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Coronavirus disease
COVID-NET	The COVID-19-Associated Hospitalization Surveillance Network
CRP	C-reactive protein
DSR	Drug Safety Report
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EUA	Emergency Use Authorization
EU RMP	EU Risk Management Plan
FDA	The United States Food and Drug Administration
GVP	Good Pharmacovigilance Practice
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
IRR	Infusion-related reaction
ISR	Injection site reaction
ICU	intensive care unit
MAA	Marketing Authorization Application
PV	pharmacovigilance
PI	Product Information
PIP	Pediatric Investigation Plan
RMP	Risk Management Plan
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SMQ	Standardised MedDRA Query
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 (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). As of 13 December 2021, over 267 million confirmed cases of COVID-19 have been reported globally by the World Health Organization (WHO) with the cumulative prevalence of 3626 cases per 100,000 population. In the WHO European region, over 90 million cases were confirmed so far with a prevalence of 9932 cases per 100,000 population. France and United Kingdom are the most affected nations in Europe with over 7.5 million and 10 million confirmed cases respectively (WHO COVID-19 Pandemic).

Although, most patients have mild symptoms and good prognosis, COVID-19 can develop to 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). A systematic review estimated that 33% of people with SARS-CoV-2 infection (diagnosed through Reverse Transcription Polymerase Chain Reaction (RT-PCR) tests) never develop symptoms. This estimate was based on four large population-based, cross-sectional surveys, among which the median proportion of individuals who had no symptoms at the time of a positive test was 46% (range: 43% to 77%), and on 14 longitudinal studies, among which a median of 73% of initially asymptomatic individuals remained so on follow-up (Oran and Topol 2021).

Hospitalized patients: Patients with severe COVID-19 may become critically ill and require hospitalization. The prevalence of COVID-19 from European Centre for Disease Prevention and Control (ECDC) available from 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 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 (ECDC COVID-19 Surveillance Report). In the USA, the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) estimates that the cumulative hospitalization rate due to COVID-19 on 4 December 2021 was 763.7 per 100,000 population, while the weekly hospitalization rate was 3.5 per 100,000 population. Weekly hospitalization rates peaked in January with a rate of 20.7 per 100,000 population, observed on 9 January 2021 (COVID-NET).

Demographics

Age: According to the Center for Disease Control and Prevention (CDC), SARS-CoV-2 – the cause of COVID-19, infects people of all ages. Per ECDC surveillance data for 9 December 2021, 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 is 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 (ECDC COVID-19 Surveillance Report). Data from the CDC COVID Data Tracker on 12 December 2021 reported that in the USA, the highest number of cases was in the age group of 18-29 years, accounting for 21.5% of the total cases followed by 50-64 years (19.1%), and 30-39 years (16.6%). 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 (COVID-19 CDC).

Gender: The WHO reported that globally 51% of COVID-19 patients were females and 49% were males. In the WHO Europe region, 53% of COVID-19 patients were females and 47% were males (WHO COVID-19 cases and deaths with age and sex). According to the CDC COVID Data Tracker, in the USA, a higher proportion of females (52.3%) compared to males (47.7%) 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 (Raharja et al. 2020). Evidence from the CDC COVID Tracker revealed that in the USA, among all COVID-19 positive cases, 55.4% were Whites, followed by Hispanics (24.7%), Blacks (11.6%) and Asians (3.1%).

Hospitalized patients: According to the data obtained from ECDC weekly surveillance report (week 37, dated 18 September 2021), the hospitalization rates among the COVID-19 cases for different age groups are presented in the table below.

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

Age Groups	Hospitalization rate overall (%)	Hospitalization rate males (%)	Hospitalization rate females (%)
<10	1.6	1.7	1.5
10-19	0.9	0.8	0.9
20-29	1.8	1.6	2.0
30-39	2.8	2.8	2.8
40-49	3.9	4.9	3.0
50-59	6.8	8.7	5.0
60-69	14.1	17.2	11.0
70-79	27.8	32.3	23.4

COVID-19 = Coronavirus disease

The hospitalization rate ranged between 0.8% and 44.3% among males, while among females, the rates ranged between 0.9% and 30.9% for the same age groups. However, it should be noted that the rates of hospitalization due to COVID-19 increases with the age for both sexes. In addition, the hospitalization rate doubles between the 50-59 age group and 60-69 age group and then again between the 60-69 and 70-79 age groups. The same trend has been observed in both males and females (ECDC COVID-19 Surveillance Report).

Among hospitalizations associated with laboratory-confirmed COVID-19 reported through COVID-NET in the USA, the cumulative rate of hospitalization on 4 December 2021 was reported to be 70.5 per 100,000 (for those < 18 years of age) and, 957.5 per 100,000 (for those ≥ 18 years of age). The rate of hospitalization was 1127.7 per 100,000 (for patients aged 50–64 years) and 2112 per 100,000 population for patients aged 65 years and older. Males were reported to have slightly higher rate of hospitalization compared to females (782.9 vs 745.2 per 100,000 overall population) (COVID-NET).

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 Medicines Agency (EMA) have approved/ authorized under emergency use provisions, conditional or full Marketing Authorizations, or have provided a scientific opinion under Article 5(3) of the EU Regulation (EC) No 726/2004.

According to the CDC treatment guidelines for COVID-19 (updated on 19 October 2021) for the USA, 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 (CDC Treatment Guidelines).

Prevention of SARS-CoV-2 infection:

As of 13 December 2021, the EMA has granted conditional marketing authorization to four vaccines for the prevention of COVID-19 (EMA Treatments and Vaccines 2021). The vaccines approved by EMA are:

- Comirnaty vaccine, developed by BioNTech and Pfizer, recommended in people from 5 years of age. In May 2021 the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended granting an extension of indication for Comirnaty to include use in children aged 12 to 15 and in November 2021, this was extended to children aged 5-11. The vaccine was already previously approved for use in adults and adolescents aged 16 and over. Comirnaty contains a molecule called messenger RNA (mRNA) with instructions for producing a protein from SARS-CoV-2 and does not contain the virus itself.
- Ad26.COV2-S [recombinant] developed by Janssen is made up of another virus (of the adenovirus family) that has been modified to contain the gene for making the SARS-CoV-2 spike protein. The adenovirus passes the SARS-CoV-2 gene into the vaccinated person's cells. It is recommended for people aged 18 years and older.
- Spikevax, another mRNA vaccine (nucleoside modified) developed by Moderna is the third vaccine authorized by the EMA for people aged 12 years and older.
- Vaxzevria (previously named COVID-19 Vaccine AstraZeneca), that is also made up of another virus (of the adenovirus family) which has been modified to contain the gene for making a protein from SARS-CoV-2, has also received conditional approval. The adenovirus passes the SARS-CoV-2 gene into the vaccinated person's cells. This vaccine is recommended in people aged 18 years and older.

Vaccines which are still under evaluation, are COVID-19 Vaccine (Vero Cell) Inactivated (developed by Sinovac Life Sciences), Nuvaxovid (developed by Novavax CZ AS), Sputnik V (developed by Russia's Gamaleya National Centre of Epidemiology and Microbiology),Vidprevtyn (Sanofi Pasteur) and VLA2001 (Valneva) (EMA Treatments and Vaccines 2021).

In the USA, currently, two mRNA vaccines are available. The two-dose series of the BNT162b2 (Pfizer-BioNTech) vaccine was approved by the FDA for individuals aged ≥16 years, but it can be administered to individuals aged 5 years and older under an Emergency Use Authorization (EUA). The two-dose series of the mRNA-1273 (Moderna) vaccine has an EUA for individuals aged ≥18 years. The FDA also issued an

EUA for a single dose human adenovirus type 26 (Ad26) vectored vaccine, Ad26.COV2.S (Johnson & Johnson/Janssen), for those aged ≥18 years (CDC Treatment Guidelines). As of the 19 October 2021 guidelines, the CDC recommends giving an additional dose of an mRNA COVID-19 vaccine to people who are at high risk of having suboptimal immune responses to a two-dose series. Because the effectiveness of the BNT162b2 (Pfizer-BioNTech) vaccine may wane over time, CDC recommends administering a booster dose of the vaccine to these individuals at least 6 months after they complete the primary series. EMA's human medicines committee (CHMP) has also concluded that an extra dose of the COVID-19 vaccines Comirnaty (BioNTech/Pfizer) and Spikevax (Moderna) may be given to people with severely weakened immune systems, at least 28 days after their second dose.

Treatment of COVID-19 disease:

Non-hospitalized patients: The EMA's CHMP has granted marketing authorization to the monoclonal antibodies' (mAbs) combination (casirivimab/imdevimab) and Regkirona (regdanvimab) for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe (EMA Treatments and Vaccines 2021). Casirivimab/imdevimab combination had been granted EUA from FDA and on 3 June 2021, the FDA re-issued the letter of authorization for casirivimab and imdevimab treatment for COVID-19 to authorize a dosage change from 1200 mg of casirivimab and 1200 mg of imdevimab to 600 mg of casirivimab and 600 mg of imdevimab. In addition, the FDA authorized SC injection as an alternative route of administration when IV infusion is not feasible and would lead to delay in treatment (CDC Treatment Guidelines). Bamlanivimab plus etesevimab, a mABs combination, had also been granted EUA by FDA to treat non-hospitalized patients with mild to moderate COVID-19, however EMA has ended the rolling review of bamlanivimab and etesevimab (CDC Treatment Guidelines, EMA Treatments and Vaccines 2021). EMA has started evaluating an application for marketing authorization for the monoclonal antibody Xevudy (sotrovimab) for the treatment of adults and adolescents with COVID-19 who do not require supplemental oxygen therapy. FDA also recommended sotrovimab under EUA for the treatment of mild to moderate COVID-19 in adult and pediatric patients who are at high risk for progression to severe COVID-19, including hospitalization or death (CDC Treatment Guidelines, EMA Treatments and Vaccines 2021). EMA has started evaluating an application for marketing authorization for the oral antiviral medicine Lagevrio (molnupiravir) that is intended for the treatment of COVID-19 in adults. EMA has started rolling review of Evusheld (also known as AZD7442), a combination of two monoclonal antibodies (tixagevimab and cilgavimab) for the prevention of COVID-19 in adults (EMA Treatments and Vaccines 2021). The FDA issued the EUA for Evusheld (tixagevimab with cilgavimab) for the pre-exposure prophylaxis (prevention) of COVID-19 in certain adults and pediatric individuals (FDA News Release). EMA is reviewing currently available data on the use of Paxlovid (PF-07321332/ritonavir), an oral

treatment for COVID-19 in non-hospitalized patients with mild to moderate disease (EMA Treatments and Vaccines 2021).

Hospitalized patients: As therapeutic treatment, the EMA and the FDA granted a conditional marketing authorization and full authorization, respectively, to remdesivir for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen (CDC Treatment Guidelines, EMA Treatments and Vaccines 2021). The EMA has also granted the marketing authorization to RoActemra (tocilizumab) for the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation. Tocilizumab had also been granted EUA by FDA for the treatment of hospitalized adults and pediatric COVID-19 patients. On 11 February 2021, the National Institute for Health and Care Excellence (NICE) in the UK recommended tocilizumab as a treatment option through routine commissioning for adult patients (aged 18 years and older) hospitalized with COVID-19 (NICE 2021).

The EMA has started evaluation of marketing authorizations for three drugs which include Kineret (anakinra) for treatment of COVID in adult patients with pneumonia who are at increased risk of severe respiratory failure, and Olumiant (baricitinib) for hospitalized COVID-19 patients requiring supplemental oxygen (EMA Treatments and Vaccines 2021).

In the recent update of CDC treatment guidelines for COVID-19, the panel recommended using either baricitinib or tocilizumab in combination with dexamethasone alone or dexamethasone plus remdesivir for the treatment of COVID-19 in hospitalized patients on high-flow oxygen or noninvasive ventilation. In the rare circumstance when corticosteroids cannot be used, the panel recommended using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation. The combination had already been granted EUA from FDA (CDC Treatment Guidelines). Additionally, the CDC recommends that in hospitalized patients that require invasive mechanical ventilation or extracorporeal membrane oxygenation, combination of dexamethasone plus IV tocilizumab should be used. If IV tocilizumab is not available or feasible to use, IV sarilumab can be used (CDC Treatment Guidelines) supplemental oxygen therapy (EMA Treatments and Vaccines 2021).

Risk Factors for the Disease

Older adults are more likely to get severely ill from COVID-19. 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. A meta-analysis of 50 studies (42 were from the USA 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. Asians may be at higher risk of intensive therapy unit admission and death (Sze et al. 2020).

Chronic underlying health conditions also place patients at increased risk for developing severe disease. These include cancer; chronic kidney disease; chronic obstructive pulmonary disease; 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 ≥ 40 kg/m^2); pregnancy; sickle cell disease; cerebrovascular disease; and Type 2 diabetes mellitus (ECDC High Risk Groups; CDC People at Increased Risk).

Natural History of the Indicated Condition in the (Untreated) Population

As of 13 December 2021, there have been over 5.28 million deaths among 267.8 million cases worldwide due to COVID-19, a death rate of 72 per 100,000 population, with case fatality rates ranging from 1.4% (WHO western Pacific region) to 2.4% (WHO American Region). In the WHO European region, approximately 1.59 million deaths were reported (case fatality rates: 1.8%), a death rate of 174 per 100,000 population (WHO COVID-19 Pandemic).

A systematic review of 51 studies consisting of 17,501,820 COVID-19 patients reported ethnicity-aggregated mortality data. Among patients who died from COVID-19, 63% were Whites, 6.0% Asians, 2.1% were Blacks, 0.069% Hispanics, 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 (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: According to the ECDC Country Overview report dated 9 December 2021, the 14-day COVID-19 death rate for the EU/EEA was reported to be 55.9 per 100,000 population and had been stable for two weeks (ECDC COVID-19 Surveillance Report).

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

According to the CDC COVID Data Tracker, in the USA, out of 674,231 deaths, data on Race/Ethnicity were available for 574,605 (85%) deaths, of which Non-Hispanic Whites (61.6%) were reported to be highest in mortality, followed by Hispanics (17.5%) and Non-Hispanic Blacks (13.7%).

A meta-analysis including data from 80 studies (n = 25,385), reported a pooled in-hospital mortality of 14% (95% CI: 12.2, 15.9) due to COVID-19. The pooled in-hospital mortality of COVID-19 patients was 10.1%, 23.7%, and 25.4% in Asia, Europe, and North America, respectively. Greater age (mean difference: 13.32), being male (odds ratio [OR] = 1.66), hypertension (OR = 2.67), and having 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), or 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.

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 COVID-19 patients, 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: According to the ECDC, prevalence of preexisting medical conditions in hospitalized COVID-19 patients 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 USA, 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 GLP-compliant 4-week repeat dose toxicology study in cynomolgus monkeys with an 8-week recovery period (R10933-TX-20064). Both 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 IV injection of 50 mg/kg casirivimab alone or imdevimab alone or IV or 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 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 the all 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 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-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 Nov 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 4 to Table 23), the Safety-Analysis Set is further subdivided into:

- The IV Safety-Analysis for Non-Hospitalized Patients:
    - Study COV-2067 Pooled Phase 1,2,3 Cohort 1 (Symptomatic Patients)
    - 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 3.

Table 3 Overview of Studies Contributing to the Safety Population

Study	Study design	Primary objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set (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

Study	Study design	Primary objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set (n)
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
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	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: Cohort 1: • 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	Pooled Phase 1,2,3 Cohort 1 (symptomatic patients) N = 4206

Study	Study design	Primary objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set (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

Study	Study design	Primary objectives	Population	Dosing regimen and Route of Administration	Safety-Analysis Set (n)
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) • 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 = 460 SC = 228

IV = intravenous ; mAb = monoclonal antibody; Q4W = every 4 weeks; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous

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 7).

The IV Safety Analysis Set for non-hospitalized patients provided data from 4666 patients with 597.33 patient-years of exposure. Patients in the IV Safety Analysis Set will be followed up for up to 24 weeks. As of the cutoff dates for Studies COV-2067 (18 February 2021) and COV-20145 (8 February 2021), no patients had been followed up for 20 weeks or more. Overall, the majority of patients (88.7% [4142/4666]) had been followed up for at least 4 weeks. A total of 25 patients (25/4666 [0.53%]) had been followed up for at least 16 weeks (Table 4).

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 (46/6312 [0.7%]) in COV-2066 had been followed up for at least 16 weeks (Table 5).

Table 4 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=4666)	Cumulative Follow-Up (Patient-Years)
≥4 weeks	4142 (88.7%)	567.86
≥8 weeks	1454 (31.2%)	317.51
≥12 weeks	576 (12.3%)	150.2
≥16 weeks	25 (0.53%)	8.0
Cumulative total number of patients exposed to IV	4666 (100.0%)	597.33
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 number of patients exposed	4206 (100.0%)	564.0
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 number of patients exposed	460 (100.0%)	33.33

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

**Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021. 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)

Table 5 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 number of patients exposed	941 (100.0%)	137.8

Table 5 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)
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 number of patients exposed	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 number of patients exposed	110 (100.0%)	12.8

Table 5 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)
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 number of patients exposed	23 (100.0%)	2.3
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 number of patients exposed	4298 (100.0%)	291.7

*Randomized patients through 09Apr2021. Last patient follow-up visit on 13Jun2021

**Last patient follow-up visit on 21JUN2021

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 will be 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 16 patients (16/1694 [0.9%] had been followed up for at least 32 weeks (Table 6).

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 will 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 7).

Table 6 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 patients number of patients exposed	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

Table 6 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)
≥ 28 weeks	8 (5.2%)	4.76
≥ 32 weeks	4 (2.6%)	2.52
Total patients number of patients exposed	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 patients number of patients exposed	228 (100.0%)	16.54

*Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

** Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment

*** Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021. 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 7 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 number of subjects exposed	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 number of subjects exposed	729 (100.0%)	245.70

Data cutoff date: 13MAR2021

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, 51.3% (n=2394) were female and 48.7% (n=2272) were male, and the majority of patients (89.6% [n=4180]) were 18 to <65 years of age. Female patients had 307.52 patient-years of exposure vs. 289.81 patient-years in male patients (Table 8). No exposure data for subjects <18 years are available as this population had not been recruited into Studies COV-2067 and COV-20145 at the time of data cutoffs.

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 9).

Table 8 Exposure by Age group and Gender, IV Route of Administration, Safety Analysis Set (Active Treatment Only)

	Number of Patients Exposed (N=4666)			Cumulative Follow-Up (Patient-Years)		
Age group (years)	**M**	**F**	**Total M+F**	**M**	**F**	**Total M+F**
18 to < 65	2012 (43.1%)	2168 (46.5%)	4180 (89.6%)	253.69	274.22	527.9
65 to < 75	197 (4.7%)	155 (3.7%)	352 (8.4%)	27.7	23.8	51.5
≥ 75	63 (1.3 %)	71 (1.7%)	134 (2.9%)	8.42	9.5	17.92
Cumulative Total for IV	2272 (48.7%)	2394 (51.3%)	4666 (100%)	289.81	307.52	597.32
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
Treatment indication (Study COV-20145)**						

Table 8 Exposure by Age group and Gender, IV Route of Administration, Safety Analysis Set (Active Treatment Only) (cont.)

	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 17Jan2021. Data cutoff date: 18Feb2021.

** Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

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)

Table 9 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 9 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 9 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

*Randomized patients through 09Apr2021. Last patient follow-up visit on 13Jun2021

**Last patient follow-up visit on 21Jun2021

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 pediatric patients aged 12 to < 18. Female patients had 255.59 patient-years of exposure vs. 220.91 patient-years in male patients (Table 10).

In the Repeat Dose SC Safety Analysis Set, 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 11).

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 10 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

Table 10 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)		
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
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

Table 10 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)

* Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment

***Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021

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 11 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: 13MAR2021

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 (47.6% [n = 2222]) received the 2.4 g (1.2 g of each mAb) IV dose, followed by the 8.0 g (4.0 g of each mAb) IV dose, (27.2% [n = 1272 patients)). A total of 943 (20.2%) patients received the 1.2 g (0.6 g of each mAb) IV dose (Table 12).

For the studies involving Hospitalized Patients, most patients (87.2% [n = 5031 patients]) 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 13).

Table 12 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=4666)**	**Cumulative Follow-up (Patient-years)**
8.0 g (4.0 g each of casirivimab and imdevimab)	1272 (27.2%)	155.7
2.4 g (1.2 g each of casirivimab and imdevimab)	2222 (47.6%)	289.18
1.2 g (0.6 g each of casirivimab and imdevimab)	943 (20.2%)	135.86
0.6 g (0.3 g each of casirivimab and imdevimab)	114 (2.4%)	8.19
0.3 g (0.15 g each of casirivimab and imdevimab)	115 (2.5%)	8.40
Cumulative total	4666 (100.0%)	597.33
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 (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 17Jan2021. Data cutoff date: 18Feb2021

**Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021

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

Table 12 Extent of Exposure by Dose Received, IV Route of Administration for Non-Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (cont.)

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)

Table 13 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 13 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 09Apr2021. Last patient follow-up visit on 13Jun2021

**Last patient follow-up visit on 21Jun2021

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 14).

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 15).

Table 14 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

*Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment

***Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

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)

Table 14 Extent of Exposure by Dose Received, 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_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 15 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: 13MAR2021
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 (61.6% [n = 2875]), followed by Hispanic or Latino (37.4%) [n=1746]) (Table 16), which was similar to the Single Dose SC Safety Analysis Set (53.8% [n=911]) vs. 37.4% [n=1746], respectively) (Table 18) and in the Repeat Dose SC Safety Analysis Set (75.9% [n=553] vs. 23.6% [n=172], respectively) (Table 19).

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 16 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=4666)	Cumulative Follow-up (Patient-years)
Cumulative for IV		
Hispanic or Latino	1746 (37.4%)	210.82
Not Hispanic or Latino	2875 (61.6%)	381.8
Not reported	45 (1.0%)	4.71
Unknown	0 (0.0%)	-
Cumulative total for IV	4666 (100%)	597.33
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-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 17Jan2021. Data cutoff date: 18Feb2021.

**Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

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)

Table 17 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 17 Extent of Exposure by Ethnic Origin, IV Route of Administration for Hospitalized Patients, Safety Analysis Set (Active Treatment Only) (cont.)

Randomized patients through 09Apr2021. Last patient follow-up visit on 13Jun2021.

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 18 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 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

***Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

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 18 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 19 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: 13MAR2021

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 (84.8% [n = 3957]) (Table 20). This was similar to the IV Safety Analysis Set for hospitalized patients (74.9% [n = 6312]) (Table 21), Single SC Dose Safety Analysis Set (82.9% [n = 1405]) (Table 22) and in the Repeat SC Dose Safety Analysis Set (86.7% [n = 632]) (Table 23).

Table 20 Extent of Exposure by Race, IV Route of Administration, Safety Analysis Set (Active Treatment Only)

Race	Number of Patients Exposed (N=4666)	Cumulative Follow-up (Patient-years)
Cumulative for all indications for IV		
American Indian or Alaska Native	52 (1.1%)	6.58
Asian	198 (4.2%)	27.13
Black or African American	256 (5.5%)	30.77
Native Hawaiian or other Pacific Islander	7 (0.2%)	1.13
White	3957 (84.8%)	509.71
Not Reported	93 (2.0%)	10.78
Unknown	103 (2.2%)	11.33
Cumulative total	4666	597.33
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
Treatment indication (Study COV-20145)**		

Table 20 Extent of Exposure by Race, IV Route of Administration, Safety Analysis Set (Active Treatment Only) (cont.)

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
Total	460 (100.0%)	33.33

*Randomized patients through 17Jan2021. Data cutoff date: 18Feb2021.

**Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

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)

Table 21 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 21 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 21 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 09Apr2021. Last patient follow-up visit on 13Jun2021.

**Last patient follow-up visit on 21JUN2021.

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 22 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*)		

Table 22 Extent of Exposure by Race, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only) (cont.)

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
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

Table 22 Extent of Exposure by Race, SC Route of Administration, Single Dose, Safety Analysis Set (Active Treatment Only) (cont.)

*Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

**Randomized subjects through 28Jan2021. Data cutoff date: 11Mar2021. Subjects received a single dose of study treatment.

***Randomized patients through 01FEB2021. Data cutoff date: 08FEB2021.

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 23 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: 13MAR2021

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 24 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) to assess the immunogenicity, safety, and tolerability of Moderna mRNA-1273 vaccine administered with casirivimab + imdevimab in healthy adult volunteers is ongoing.

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.
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

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			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. An interaction study (COV-2118) to assess the immunogenicity, safety, and tolerability of Moderna mRNA-1273 vaccine administered with casirivimab + imdevimab in healthy adult volunteers is ongoing.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
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	Yes (use in pregnancy only)	Use in pregnancy - not applicable (included as missing information) 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.

CDC = Centers for Disease Control and Prevention; COVID-19 = Coronavirus disease 2019; EU SmPC = EU Summary of product characteristics; 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 **12860** patients with **5586.93** 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 can receive up to 6 SC doses. To date, no ADRs caused by prolonged exposure have been observed.
- **Caused by cumulative exposure**: There have been 12131 patients who received a single dose IV or SC of casirivimab and imdevimab and 729 patients received repeated dosing with cumulative exposure of 337.00 patient-years (see Table 4, Table 5, Table 6, Table 7, respectively), and no cumulative toxicities have been observed to date.
- **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 (88.7%, 91.5%, and 99.5% in the IV Safety Analysis Set, the Single Dose SC Safety Analysis Set, and the Repeat Dose SC Analysis Set, respectively). In the non-hospitalized IV Safety Analysis Set 0.53% of patients have been followed up for at least 16 weeks. 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 up to data cutoffs, are not yet sufficient to ascertain any long latency effects.

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

Table 25 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure

Pregnant women*	• Study COV-2067:
	  • 13 cases
	• Study COV-2069:
	  • 6 cases
	Study COV-20145:
	  • 3 cases
	Study COV-2066:
	  • 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 25 Exposure of Special Populations Included or Not in Clinical Trial Development Program

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%)

Table 25 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
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%) 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%)

Table 25 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
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%) 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 16, Table 18, and Table 19).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Pediatric patients	Included in the clinical development program (See Table 10)
Elderly patients	Included in the clinical development program (See Table 8, Table 10, and Table 11)

Table 25 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure

* Pregnancy cases have been retrieved from the safety database

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.

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

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)

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

Between 21 November 2020 to 31 October 2021, Roche has supplied Ronapreve (casirivimab and imdevimab) combo packs to approximately 1,000,000 patients globally, either through EUA equivalent regulatory pathways or Marketing Approval. Accurate exposure data are not available as Ronapreve has been provided to governmental

institutions, and its distribution is under the control and responsibility of national governments or Health Agencies.

Cumulative patient exposure from marketing experience

As of 30 September 2021, only IV use of Ronapreve for treatment of COVID-19 was approved in the UK and Japan.

United Kingdom:

As of 30 September 2021, 49 patients had been exposed to Ronapreve in the UK (Table 26).

Japan

As of 30 September 2021, 30322 patients had been exposed to Ronapreve in Japan (Table 26). Based on published age and gender data, the estimated exposure is as follows:

- For patients treated with Ronapreve in Tokyo, it is estimated that of the age these patients were as follows: 27.0% were ≥ 65 years old, 73.0% were <65 years old
- There is no meaningful difference in the ratio of newly infected persons between Tokyo and Japan at the age of 65
- For the period 27 September 2021 to 05 October 2021, it is estimated that the gender of the patients was as follows:
    - Male: 53.5%, Female: 46.5%

Table 26 Cumulative Exposure from Marketing Experience

Indication	Sex			Age			Dose			Route of Administration			Region/country Country	
	Male	Female	Unk	<65	≥65	Unk	1200 mg	600 mg	Unk	IV	SC	Unk	UK	Japan
Overall	16222	14100	49	22135	8187	49	30322	-	49	30322	-	49	49	30322
Treatment	16222	14100	-	22135	8187	-	30322	-	-	30322	-	-	-	30322
Prevention	-	-	-	-	-	-	-	-	-	-	-	-	-	-

IV=intravenous; SC=subcutaneous; Unk=unknown.

Note: Rounding errors may be introduced in the total figures.

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 characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member State where the product is authorised):

- 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 of Use in Pregnancy

Risk-benefit impact:

There is currently limited clinical experience with the use of casirivimab and imdevimab in patients and subjects who are pregnant or breastfeeding (see Table 25). In addition, animal reproductive and developmental toxicity studies have not been conducted. 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.

Casirivimab and imdevimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus/baby considering all associated health factors.

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

This section is not applicable as this is the first RMP for casirivimab and imdevimab.

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

Evidence source:

Pregnancy

There are limited amount of data from the use of casirivimab and imdevimab in pregnant women (see Table 25). 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

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.

Population in need of further characterization

The available data are insufficient to characterize the use of casirivimab and imdevimab in pregnant women and there is a need to further characterize their use in these patients.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 27 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy

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 use during pregnancy:

– Presentation of periodic and cumulative data on the use in pregnancy in Periodic Benefit-Risk Evaluation Reports (PBRERs)

– Inclusion of Table P.III.2 (Table for reporting numbers of individual case safety reports in periodic safety update reports) in the PBRERs in line with the EMA draft guideline EMA/653036/2019

- 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

Table 28 COVID-PR Pregnancy Registry Summary (PASS)

Study/activity short name and title: COVid-19 International Drug Pregnancy Registry (COVID-PR)
Rationale and Study Objectives: To estimate the effect specific newly developed medications indicated for mild to severe COVID-19 have on the risk of obstetric, neonatal, and infant outcomes compared to the effects of repurposed treatments for COVID-19
Study design: An international, non-interventional, postmarketing cohort study designed to collect prospective safety data among pregnant women treated pharmacologically for mild to severe COVID-19 at any time during pregnancy. It includes maternal and offspring follow-up until the infant is one year of age
Study populations: Women 18 years of age and older who required in-hospital or ambulatory pharmacological treatment for mild to severe COVID-19 at any time during pregnancy
Milestones [a]: Study Start Date: 01/10/2021 Study Completion Date: 30/09/2026 Periodic reports: Annual report Final report: 31/12/2027

COVID-19 = Coronavirus disease 2019

[a] Study milestones are aligned with the dates available in the EU PAS Register. Fulfilment of the commitment is dependent on receipt of final report from the Sponsor.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 29 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities				
COVID-PR (COVid-19 International Drug Pregnancy Registry) Ongoing	To estimate the effect specific newly developed medications indicated for mild to severe COVID-19 have on the risk of obstetric, neonatal, and infant outcomes compared to the effects of repurposed treatments for COVID-19	Use in pregnancy	Annual report	Progress reports on enrolment and intermediate analysis results will be provided yearly
			Final report	31/12/2027

COVID-19 = Coronavirus disease 2019

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

Table 30 Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Use in pregnancy	**Routine risk communication:** EU SmPC Section 4.6: Fertility, pregnancy and lactation EU SmPC Section 5.3: Preclinical safety data PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Medicine's legal status: The combination of casirivimab and imdevimab is a prescription only medicine

EU SmPC = EU Summary of product characteristics; PL = Package Leaflet

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of casirivimab and imdevimab.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 31 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measure(s)	Pharmacovigilance Activities
Use in pregnancy	**Routine risk-minimization measures:** EU SmPC Section 4.6: Fertility, pregnancy and lactation EU SmPC Section 5.3: Preclinical safety data PL Section 2 **Other risk minimization measures beyond the Product Information:** Medicine's legal status: The combination of casirivimab and imdevimab is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Presentation of periodic and cumulative data in PBRERs **Additional pharmacovigilance activities:** COVID-PR (COVid-19 International Drug Pregnancy Registry) Final study report due date: 31/12/2027

COVID-PR = COVid-19 International Drug Pregnancy Registry; PBRER = Periodic benefit-risk evaluation report; PL = Package Leaflet

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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 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.

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	Use in pregnancy

II.B Summary of Important Risks

Use in pregnancy	
Risk minimization measures	Routine risk minimization measures: EU SmPC Section 4.6: Fertility, pregnancy and lactation EU SmPC Section 5.3: Preclinical safety data PL Section 2 Other risk minimization measures beyond the Product Information: Medicine's legal status: The combination of casirivimab and imdevimab is a prescription only medicine Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: COVID-PR (COVid-19 International Drug Pregnancy Registry) See Section II.C of this summary for an overview of the post-authorization development plan.

EU SmPC = EU Summary of product characteristics; PL = Package Leaflet

II.C Post-Authorization Development Plan

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

There are no studies that are conditions of the marketing authorization or specific obligation RONAPREVE.

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

Study short name: COVid-19 International Drug Pregnancy Registry (COVID-PR)

Purpose of the study: to estimate the effect specific newly developed medications indicated for mild to severe COVID-19 have on the risk of obstetric, neonatal, and infant outcomes compared to the effects of repurposed treatments for COVID-19.

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!