11 November 2021
EMA/680189/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ronapreve

International non-proprietary name: casirivimab / imdevimab

Procedure No. EMEA/H/C/005814/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted and personal data anonymised.

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Administrative information

Name of the medicinal product:	Ronapreve
Applicant:	Roche Registration GmbH
Active substance:	casirivimab / imdevimab
International Non-proprietary Name/Common Name:	casirivimab / imdevimab
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indications:	-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. -Prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.
Pharmaceutical form:	Solution for injection/infusion
Strength(s):	6 mL single-use vials: 300 mg + 300 mg 20 mL multi-dose vials: 120 mg/mL + 120 mg/mL
Route(s) of administration:	Subcutaneous injection Infusion
Packaging:	1 vial (6 mL) + 1 vial (6 mL) 1 vial (20 mL) + 1 vial (20 mL)
Package size(s):	1 vial + 1 vial

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List of abbreviations

ACE2	Angiotensin converting enzyme 2
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
AEX	Anion-exchange chromatography
ALP	Alkaline phosphatase
ALT	Alkaline aminotransferase
AST	Aspartate aminotransferase
AU	Absorbance unit
CDC	Complement-dependent cytotoxicity
CFU	Colony-forming unit
CHO	Chinese hamster ovary
Cmax	Maximum concentration
CoA	Certificate of Analysis
COVID-19	Coronavirus disease 2019
CPP	Critical process parameter
CQA	Critical quality attribute
CV	Column volume
DO	Dissolved oxygen
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FDS	Formulated Active substance
FcG	Fragment crystallizable, IgG
FFU	Fluorescent focus units
FIJ	First in human
GCP	Good clinical practice
HCCF	Harvested cell culture fluid
HCP	Host cell protein
hFc	Human fragment crystallizable
his	Histidine
HIC	Hydrophobic interaction chromatography
HMW	High molecular weight
HRP	Horseradish peroxidase

ICF	Informed consent form
ICH	International council for harmonisation
iCIEF	Imaged capillary isoelectric focusing
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IN	Intranasal
IPC	In-process control
IT	Intratracheal
IV	Intravenous
*k*a	Association rate constant
KD	Equilibrium dissociation constant
*k*d	Dissociation rate constant
LLOQ	Lower limit of quantification
LMW	Low molecular weight
mAb	Monoclonal antibody
MAV	Medically attended visit
MCE	Microchip capillary electrophoresis
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mFc	Mouse FcG domain
MW	Molecular weight
NA	Not applicable
NB	No detectable binding observed under the assay conditions used
NP	Nasopharyngeal
NR	Not recorded
OD_{450}	Absorbance at 450 nm
PBS	Phosphate-buffered saline
PD	Pharmacodynamic
PFU	Plaque-forming unit
PK	Pharmacokinetic
PT	Preferred term
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
RBD	Receptor binding domain
RNAseq	RNA sequencing
RU	Resonance units
S protein	Spike glycoprotein
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SOC	System Organ Class
SPR	Surface plasmon resonance
t½	Dissociative half-life
TE	Treatment emergent
TEAE	Treatment emergent adverse event
TFF	Tangential flow filter
Tmax	Time to maximum plasma levels
UFDF	Ultrafiltration and diafiltration
VI	Viral inactivation
VRF	Virus-retentive filtration
Vss	Volume of distribution at steady state
VSV	Vesicular stomatitis virus
WCB	Working cell bank
WFI	Water for injection
WHO	World health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 8 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Ronapreve through the centralised procedure falling within the Article 3(1) and point 1 Annex of Regulation (EC) No 726/2004.

A combination pack request was submitted to the Agency on 13th November 2020. In accordance with Eudralex, Notice to Applicants, Volume 2A, Chapter 1, Section 5.5, "In very exceptional circumstances, which must be considered on a case by case basis, the marketing of distinct medicinal products in the same package may be indispensable for public health reasons. Such reasons cannot be related to convenience or commercial purposes". Further to consultation with ETF on 18th December 2020, the CHMP endorsed via written procedure, the outcome of the review process that the proposed combination pack was considered indispensable for public health, in order to facilitate patient access to the medicinal product in the current pandemic situation. The European Commission has been informed of this outcome and endorsed the acceptance of the combination pack in the context of the Covid-19 emergency situation, stressing that the studies to support co-formulation shall be accelerated, and the progress of these ongoing studies must be reported to the EMA.

The applicant applied for the following indications:

- Treatment of COVID-19 in patients aged 12 years and older who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

- Prevention of COVID-19 in individuals aged 12 years and older.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included the EMA Decisions P/0347/2021 and P/0348/2021 on the agreement of paediatric investigation plans (PIPs).

At the time of submission of the application, the PIPs P/0347/2021 and P/0348/2021 were not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substances casirivimab and imdevimab contained in the above medicinal product to be considered as new active substances, as the applicant claims that they are not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference
06/05/2020	EMEA/H/SA/4486/1/2020/I
05/06/2020	EMEA/H/SA/4486/2/2020/III
30/11/2020	EMA/SA/0000048369
05/02/2021	EMA/SA/0000052696
28/05/2021	EMA/SA/0000061655

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Strategy regarding cell lines and cell banks
- Potency testing
- Viral clearance
- In Use Compatibility strategy
- Shelf-Life strategy
- Comparability strategy
- CMC data package to support rolling submission

- Preclinical data requirements for FIH and MAA
- Preclinical assessment of the risk of antibody-dependent enhancement of disease
- Data requirement and timelines for initiation of the different clinical studies
- Concurrence on the clinical study protocol in hospitalised patients
- Concurrence on the clinical study protocol in outpatients
- Concurrence on the clinical study protocol in the prophylaxis setting

- Inclusion of paediatric patients, dosing strategy, sample size and endpoints
- Concurrence on the proposal for monitoring potential treatment emergent viral variants
- Data package to support approval in the COVID-19 treatment (in patients that do not require supplemental oxygen) and prevention indications
- Questions on the RMP
- Content and data presentation to be provided in Module 2.7.4, Summary of Clinical Safety
- Posology for IV and SC formulations for the treatment (in patients that do not require supplemental oxygen) and prevention of COVID-19

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Jayne Crowe

The CHMP confirmed eligibility to the centralised procedure on	12 November 2020
The ETF recommended to start the rolling review procedure on	18 December 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	29 January 2021
The procedure (Rolling Review 1) started on	1 February 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	1 March 2021
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	8 March 2021
ETF discussions took place on	9 March 2021
Adoption of first Interim Opinion (Rolling Review 1 [non-clinical]) via written procedure on	12 March 2021
The applicant submitted documentation as part of a rolling review on quality data to support the marketing authorisation application	31 March 2021
The procedure (Rolling Review 2) started on	1 April 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	30 April 2021
BWP discussions took place on	5 May 2021
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	6 May 2021
ETF discussions took place on	7 May 2021

Adoption of second Interim Opinion (Rolling Review 2 [quality]) via written procedure on	11 May 2021
The applicant submitted documentation as part of a rolling review on quality and non-clinical data (2nd package) to support the marketing authorisation application	30 April 2021
The procedure (Rolling Review 3) started on	3 May 2021
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	26 May 2021
BWP discussions took place on	31 May 2021
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	1 June 2021
ETF discussions took place on	4 June 2021
Adoption of third Interim Opinion (Rolling Review 3 [quality and non-clinical]) via written procedure on	8 June 2021
The applicant submitted documentation as part of a rolling review on clinical, non-clinical and RMP data to support the marketing authorisation application	27 July 2021
The procedure (Rolling Review 4) started on	28 July 2021
The PRAC Rapporteur's Assessment Report was circulated to all CHMP and PRAC on	31 August 2021
The Rapporteur's Assessment Report on quality part only was circulated on	3 September 2021
The Rapporteur's Assessment Report on clinical part and overviews were circulated to all CHMP and ETF on	7 September 2021
BWP discussions took place on	8 September 2021
The Rapporteurs circulated joint draft overview and LoQ to all CHMP and ETF on	10 September 2021
ETF discussions took place on	14 September 2021
PRAC discussions took place on	16 September 2021
Adoption of forth Interim Opinion (Rolling Review 4 [clinical, non-clinical and RMP]) via written procedure on	16 September 2021
The application for the marketing authorisation was formally received by the EMA on	8 October 2021
The procedure started on	11 October 2021
The PRAC Rapporteur's first Assessment Report on revised RMP and responses to LoQ was circulated to all CHMP, PRAC and ETF on	18 October 2021
The CHMP rapporteur's and co-rapporteurs joint Assessment Reports	25 October 2021

were circulated to all CHMP, PRAC, BWP and ETF on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary PRAC meeting on	28 October 2021
The PRAC Rapporteur's updated Assessment Report on revised RMP and responses to LoQ was circulated to all CHMP, PRAC, BWP and ETF on	28 October 2021
The CHMP rapporteur's and co-rapporteurs updated Assessment Reports were circulated to all CHMP, PRAC, BWP and ETF on	3 November 2021
ETF discussions took place on	5 November 2021
BWP discussions took place on	5 November 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ronapreve on	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In December 2019, pneumonia of unknown cause was identified in clusters of patients in the city of Wuhan, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the disease caused by SARS-CoV-2 infection was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) (WHO, 2020) (Zhu, 2020). Millions of SARS-CoV-2 infections have been confirmed worldwide, and the rapidly spreading, worldwide outbreak has prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern.

2.1.2. Epidemiology and risk factors

As of 7 June 2021, over 172 million confirmed cases of COVID-19 have been reported globally by the WHO with the cumulative prevalence of 2331 cases per 100,000 population.

In the WHO European region, over 54.5 million cases were confirmed so far with a prevalence of 5963 cases per 100,000 population.

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 (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 with Certain Medical Conditions).

2.1.3. Aetiology and pathogenesis

Coronaviruses (CoV) are enveloped RNA viruses and are important human and animal pathogens. Two coronaviruses have previously been identified as zoonotic infections which have adapted to humans and caused severe respiratory illnesses with high fatality: Severe Acute Respiratory Syndrome coronavirus 1 (SARS-CoV-1) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV).

SARS-CoV-2 spike glycoprotein (S protein) is a class I transmembrane envelope protein that forms a homo-trimer and mediates binding, fusion, and viral entry into host cells. The S protein is essential for virus infectivity and is the main target of the humoral immune response, as demonstrated by serology analysis of recovered COVID-19 patients (Long, 2020). The S protein mediates binding to the host receptor angiotensin converting enzyme 2 (ACE2), resulting in membrane fusion and entry of the virus into susceptible cells (Hoffmann, 2020).

Transmission of SARS-CoV-2 occurs primarily through person-to-person contact and respiratory droplet transmission (Lai, 2020) (Lewis, 2020). A high background rate of lateral transmission has been observed in households with a documented SARS-CoV-2 infected individual quarantining alongside other household members (Madewell, 2020). Compared to other betacoronavirus infections, the incubation period of SARS-CoV-2 infection (i.e., time before symptoms occur) has features that complicate the control of virus transmission: the period is highly variable (range 2 to 14 days) and it is often characterized by high viral loads and viral shedding (Ellington, 2020).

2.1.4. Clinical presentation and prognosis

The majority of patients with SARS-CoV-2 infection exhibit relatively mild symptoms or are asymptomatic (Hu, 2020) (Oran, 2020), suggesting that most cases can be managed in an outpatient setting. However, a subset of infections leads to hypoxemia and other serious respiratory conditions that require hospitalization or can be fatal (Guan, 2020) (Richardson, 2020) (Wu, 2020). Infection is more likely to lead to hospitalization among patients with pre-existing risk factors or comorbidities, such as older age, obesity, diabetes mellitus, cardiovascular disease, or chronic lung disease (CDC, 2021) (Lighter, 2020). Such risk factors also increase the likelihood of death following hospitalization (Wu, 2020). There is also a subset of patients, approximately 10% to 35%, who recover from the acute SARS-CoV-2 infection but experience persistent symptoms, which occur beyond 4 weeks from the initial SARS-CoV-2 infection and are not explained by an alternative diagnosis (Greenhalgh, 2020) (Tenforde, 2020).

Studies among hospitalized patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby, 2020) (Westblade, 2020). Community-based studies in non-hospitalized patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung, 2021).

2.1.5. Management

Currently, there is no approved outpatient treatment for COVID-19 in the EU. The mainstay for COVID-19 prevention is vaccination, but no therapeutic is approved for acute prevention of unvaccinated or partly vaccinated individuals with a known or likely exposure and there is no non-vaccine-based intervention for acute and chronic prevention of COVID-19 in populations unlikely to respond to or be protected by vaccination, i.e., those with altered immunocompetence such as due to primary or secondary immunodeficiencies.

Clinical management of COVID-19 consists of supportive care, which may include inpatient management, supplemental oxygen and mechanical ventilatory support as required. Prevention measures include infection control consisting of widespread vaccination efforts, and non-therapeutic-based approaches such as quarantining, social distancing, and wearing masks. Veklury (remdesivir) is conditionally approved in the European Union (EU) for the treatment of COVID-19 in adults and adolescents ≥12 years old and weighing ≥40 kg with pneumonia requiring supplemental oxygen.

About the product

Casirivimab and imdevimab are human, IgG1 mAbs that bind simultaneously to the S protein receptor binding domain (RBD) and block its interaction with the host receptor, angiotensin-converting enzyme 2 (ACE2). When co-administered as combination therapy, casirivimab and imdevimab treatment is anticipated to potently neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. Co-administered casirivimab+imdevimab combination therapy ("casirivimab+imdevimab," also referred to as "REGN10933+REGN10987" or "REGN-COV2" throughout this report) is intended to

substitute or augment for the endogenous antibody response, especially in patients in whom this response is delayed or inadequate.

The combination pack has been considered indispensable for public health by the CHMP and the European Commission, in order to facilitate patient access to the medicinal product in the current pandemic situation.

The applicant applied for the following indications:

- Treatment of COVID-19 in patients aged 12 years and older who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.
- Prevention of COVID-19 in individuals aged 12 years and older.

For the treatment and post-exposure prophylaxis of COVID-19, the proposed 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.

For pre-exposure prophylaxis, the proposed initial (loading) 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, administered every 4 weeks, are 300 mg of casirivimab and 300 mg of imdevimab by intravenous infusion or subcutaneous injection until prophylaxis is no longer required.

2.2. Quality aspects

2.2.1. Introduction

Ronapreve, also referred to as REGN-COV2, is a combination pack containing two monoclonal antibodies as active substances, casirivimab (REGN10933) and imdevimab (REGN10987).

Casirivimab and imdevimab are two recombinant human monoclonal antibodies (IgG1κ and IgG1λ respectively) with unmodified Fc regions and produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike (S) protein receptor binding domain (RBD) of SARS-CoV 2. This prevents RBD binding to the human angiotensin converting enzyme 2 (ACE2) receptor, thereby preventing virus entry into cells. Casirivimab and imdevimab were developed for co-administration to minimise the likelihood of virus escape.

Ronapreve is presented as a solution for injection or infusion in vials:

- Presentation EU/1/21/1601/001: Two co-packaged single-use vials of 6 mL containing 300 mg of each antibody in 2.5 mL (1 vial per antibody). This corresponds to a 300 mg strength and 120 mg/mL concentration for each antibody;

- Presentation EU/1/21/1601/002: Two co-packaged multi-dose vials of 20 mL containing 1332 mg of each antibody in 11.1 mL (1 vial per antibody). This corresponds to a 120 mg/mL strength and concentration for each antibody.

The vials for these two presentations can be used for both intravenous route (concomitant administration) and subcutaneous route (consecutive administration). For intravenous use, the syringe and needle required for vial withdrawal and the infusion set are provided separately. For subcutaneous use, the syringes for administration, the 21-gauge transfer needle (for vial withdrawal) and the 25- or 27-gauge administration needle are provided separately.

Casirivimab and imdevimab are formulated with commonly used excipients: L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injections. Ronapreve is preservative-free.

2.2.2. Active Substance

General Information

REGN10933 and REGN10987 are recombinant monoclonal antibodies (IgG1 isotype) consisting each of two disulfide-linked human gamma heavy chains, each covalently linked through a disulfide bond to a human kappa light chain (REGN10933) or lambda light chain (REGN10987). Based on the primary structure (in the absence of N-linked glycosylation), REGN10933 and REGN10987 possess a molecular weight of 145.23 kDa and 144.14 kDa, respectively, taking into account the formation of 16 disulfide bonds. There is a single N-linked glycosylation site (Asn^{300}) on each heavy chain, located within the constant region in the Fc domain of REGN10933 and REGN10987 molecules.

The complementarity-determining regions (CDRs) within the heavy chain and light chain variable domains of REGN10933 and REGN10987 combine to form the binding sites for its target, the receptor binding domain of SARS-CoV-2 spike protein.

REGN10933 and REGN10987 mediate antibody-dependent cellular cytotoxicity (ADCC) of target cells expressing SARS-CoV-2 S protein, but do not mediate complement-dependent cytotoxicity (CDC).

The biological and physico-chemical properties have been described in detail.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Manufacture of REGN10933 and REGN10987 formulated active substances is conducted at the following locations:

- Regeneron Pharmaceuticals (RNS), Inc., 81 Columbia Turnpike, Rensselaer, NY 12144, USA;

- Roche/Genentech, Inc., 1000 New Horizons Way, Vacaville (VV), CA 95688, USA.

Both manufacturing sites are multi-product facilities located in the US and are regularly inspected by competent authorities.

EU GMP compliance has been documented for all sites involved.

The manufacture of the active substances represents a standard manufacturing process for monoclonal antibodies. Each antibody is manufactured and formulated independently to produce the formulated active substance. In general, the manufacturing processes for the two individual antibodies consist of an identical platform seed train, production, and purification process (i.e. identical equipment, same cell culture media and chromatography resins).

The active pharmaceutical ingredients are initially produced in a suspension culture of recombinant CHO cells that express either REGN10933 or REGN10987 protein molecules.

The production process begins with thawing a frozen vial of the REGN10933 or REGN10987 WCB and transferring the cells into a shake flask. The cell culture is expanded through a series of seed train bioreactors that increase in volume. The contents of the final seed train bioreactor are transferred to the production bioreactor containing conditioned medium where the recombinant product is produced and secreted into the culture medium. The culture is harvested by a centrifugal separator followed by depth and polish filtration. The protein is then purified using a series of packed bed chromatographic and

membrane filtration techniques. Finally, dilution and excipient solutions are added to prepare the formulated active substances.

The formulated active substances produced will be filtered and stored in cryovessels whereas the formulated active substance is dispensed and stored in biotainers. Shipping conditions are briefly outlined.

All successive steps including relevant process parameters and in-process-testing are provided for both manufacturing sites. The purpose of each step is clearly stated and detailed description are provided for both sites in the respective dossier sections.

Process parameters were categorised as non-critical (non-CPPs) and critical (CPPs) by assessing their impact on critical quality attributes (CQAs). If a parameter is considered to affect a CQA but has little or no effect on the CQA within the normal operating range (NOR), and the magnitude of impact on the attribute is not significant over the characterised range, the parameter is not considered critical. At both sites, CPPs have been identified.

The Applicant confirmed that any changes to the classifications or control criteria detailed in Section 3.2.S.2.2, and Section 3.2.S.2.4 will be submitted in post-approval submission variation applications.

Reprocessing is currently indicated for both manufacturing sites. The Applicant states this is performed according to the protocol. Validation has not been performed yet and would be conducted as concurrent validation. Upon the first instance during production of an active substance batch, the respective batch will be used for verification at manufacturing scale; product quality and stability will be evaluated according to a protocol. The protocol was provided and amended as requested. Conditions are sufficiently described and considered acceptable.

In-process pools may be held for specified times at specified temperatures prior to further processing. The acceptable in-process hold conditions are the maximum validated hold times and temperatures supported by both biochemical in-process pool hold stability and microbial hold validation. This is acceptable.

Chromatography resins and ultrafiltration/diafiltration (UF/DF) membranes used in the purification steps are dedicated to REGN10933 and REGN10987. Chromatography skids, virus-retentive filtration, and tangential flow filtration (TFF) systems are automated. Details on the post-use cleaning and storage of the chromatography columns and the tangential flow filters are described. Cleaning and sanitisation procedures are sufficiently summarised for both sites.

A combination of development, prior knowledge, clinical manufacturing experience and process validation was used to define the proposed commercial manufacturing process and process controls described in Module 3.2.S.2.2. A summary of the prior knowledge and manufacturing experience supporting the IPCs for REGN10933 and REGN10987 is provided. Considering the substantial experience of both manufacturing sites in manufacturing monoclonal antibodies, the approach is accepted. The proposed ranges (proven acceptable ranges (PARs)) and set points for commercial manufacturing as proposed are considered appropriate. The Applicant is recommended to provide results of the remaining ongoing small-scale process characterisation studies conducted to support PARs and update the relevant CTD sections following the review of the corresponding data (see Recommendation 1).

Control of materials

Raw materials

Raw materials used in the manufacture of REGN10933 and REGN10987 formulated active substances are listed. There are no raw materials of human origin used during REGN10933 and REGN10987 manufacturing.

Non-compendial materials used in the manufacture of REGN10933 and REGN10987 are tested by the material manufacturer.

Source, history and generation of cell substrate

A detailed description of the source history and generation of the cell substrate is provided giving no reason for concern.

The REGN10933, REGN10987 expression cell lines were generated. The selected cell lines were used for production of REGN10933, REGN10987, respectively, for toxicological and clinical studies.

The cell banking system employed for REGN10933 and REGN10987 is a standard two-tiered system. Identity of MCB and WCB was confirmed via nucleotide sequencing and no evidence of viral or microbial contamination was observed. MCB and WCB were further characterised by sequencing, gene copy number, heavy chain and light chain gene integration sites, and integrity of the REGN10933 and REGN10987 transcripts. Cell line stability has been sufficiently demonstrated. The test results are provided and indicate the suitability of the MCB and WCB. In addition, the underlying raw data were provided with the original study reports.

A qualification protocol for implementation of future WCBs is described in the dossier. This is accepted.

Overall, the MCB, WCB, end-of-production and limit-of-in-vitro-cell-age cell banks have been appropriately characterised, in line with ICH guidelines. Cell line stability has been sufficiently demonstrated.

Control of critical steps and intermediates

IPC tests and limits applied to the cell culture process and purification are summarised for each active substance manufacturing site. Depending on criticality, IPCs are tested against defined action limits or acceptance criteria.

Bioburden and bacterial endotoxins sampling is performed throughout the process as IPCs. In addition, further IPCs have been defined for each step of the manufacturing process. For the upstream process, the maximum total expansion time for the production bioreactor is considered critical at both sites.

The Applicant states that revisions to the IPC program may occur during the lifecycle of a product in accordance with the quality system. Revisions may be prompted by increased process knowledge.

The Applicant confirmed that any changes to the classifications or control criteria detailed in Section 3.2.S.2.2, and Section 3.2.S.2.4 will be submitted in post-approval submission variation applications. Excursions from acceptance criteria and action limits are addressed within manufacturing site quality system. The deviation management system documents quality events and, when required, determines the level of investigation based on risk. The deviation management system is used assess product impact, and determine root cause assessments, and corrective/preventive actions.

Process validation

Process validation was performed individually at the two proposed active substance manufacturing sites. The validation of the REGN10933 and REGN10987 formulated active substance manufacturing process included process performance qualification (PPQ) batches, extended hold times validation, limit of *in vitro* cell age, column and filter (lifetime, cleaning and storage) validation, medium, feed and buffer validation, shipping validation and ongoing process verification. Consecutive PPQ batches were manufactured and extended holds were performed for all PPQ batches. All validation criteria were met. Extended hold times during manufacturing steps were validated. Shipping validation of the FDS was performed.

Manufacturing process development

REGN10933 and REGN10987 are manufactured using process for IgG molecules (i.e., identical equipment, same cell culture media and chromatography resins). The REGN10933 and REGN10987 materials were used in animal pharmacokinetics and toxicology studies.

Initial production occurred in a bioreactor. This material was used during clinical development and preclinical studies.

Phase-appropriate comparability of REGN10933 and REGN10987 lots was evaluated. These studies found that the quality attributes, potency, and stability of the REGN10933 and REGN10987 material are comparable.

In order to increase the production capacity, the formulated active substance manufacturing processes for REGN10933 and REGN10987 were transferred and scaled up. This process uses the same cell line at scale. The manufacturing process follows the same overall process flow. A comparison of the formulated active substances manufacturing processes is provided in the dossier. The changes implemented are generally considered related to the upscale and additional facility fits. The process was used for emergency use procedures.

Briefly, a scale-appropriate seed train is implemented to support inoculation and protein production in a fed batch suspension production bioreactor. A centrifugation step is used to clarify the harvest culture fluid. Downstream purification includes chromatography, viral inactivation steps and filtration.

A comprehensive comparability program has been performed. Preliminary data has been provided during previous Rolling Review cycles. With the present submission, the section has been updated with completed comparability data and summary of results (e.g. comparison of accelerated stability data, stressed study, completed active substance extended characterisation). The comparability assessment is summarised in Module 3.2.S.2.6 Manufacturing Process Development.

In-process, release, and extended characterisation testing were performed on REGN10933 and REGN10987 active substances. The results of the in-process testing were compared to acceptance criteria and predefined evaluation limits generated from historical data, as defined in the process validation protocol. The results from the release testing were evaluated against predefined limits derived from historical data from REGN10933 and REGN10987.

Extended comparative characterisation defined in the comparability plan are summarised in the dossier section and the data supporting comparability is provided.

The Applicant concluded that the quality of the REGN10933 and REGN10987 samples produced from the two manufacturing sites is comparable.

Comparative stability studies under the stress storage condition of 45 °C for 35 days have been conducted. Side-by-side stress stability studies demonstrate that the formulated active substance are highly similar.

Long-term and accelerated stability data are provided.

Comparability in the context of manufacturing process development for REGN10933 and REGN10987 is considered acceptable.

Characterisation

Elucidation of structure

Extensive analytical characterisation was performed to provide a detailed understanding of the physicochemical properties of each anti-SARS-CoV-2 S protein (REGN10933 and REGN10987). Quality attributes were all assessed. Post-translational modifications were also examined.

Binding of REGN10933 and REGN10987 to SARS-COV2-S protein was evaluated using surface plasmon resonance (SPR) technology (binding to SARS-CoV2 S protein). Results demonstrated that both antibodies bind with high affinity to SARS-CoV2 S protein. Binding to human FcRn was also assessed for both antibodies. Detailed method descriptions of methods used for characterisation are provided in the dossier.

Analysis revealed that one of the two heavy chains of REGN10933 and REGN10987 contains N-linked glycans predominantly composed of a complex, fucosylated bi-antennary core structure, with 0, 1, or 2 galactose residues at the glycan chain termini.

Information on biological characterisation is currently limited to binding to target via SPR technology and a high-level summary on Fc mediated biological activity of REGN10933 and REGN10987. Both antibodies mediate concentration-dependent ADCC antibody-dependent cellular phagocytosis (ADCP) activity but no CDC activity.

Characterisation data (including representative curves) on neutralisation activity of REGN10933 and REGN10987 against wild type and currently circulating variants of SARS-CoV2 are provided.

Results from these analytical, biochemical, and biophysical characterisation assays were also used to assess comparability of the toxicology and clinical formulated active substance samples for each anti-SARS-CoV-2 S protein. Overall, the quality of the toxicology and clinical formulated active substance lot samples for each anti-SARS-CoV-2 S protein appeared highly similar with respect to all quality attributes examined.

Impurities

Known potential impurities arising from raw materials, the manufacturing process and degradation products were assessed.

All process-related impurities of REGN10933 and REGN10987 formulated active substance manufacturing process were demonstrated to either be sufficiently cleared or reduced to quantities that do not exceed acceptable daily exposure levels.

Product-related impurities include forms, and species. Through manufacturing data and characterisation studies, it was demonstrated for both antibodies that product-related impurities are sufficiently controlled by the manufacturing process. Additionally, a comprehensive control strategy is in place through the release and stability testing programs to ensure product consistency.

Overall, impurities are well controlled by IPCs, release criteria and removal capacities of the manufacturing process.

Characterisation of REGN10933 and REGN10987 and evaluation of impurities is considered acceptable.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

The specifications for REGN10933 and REGN10987 include control of identity, purity and impurities, potency and other general tests.

Analytical Procedures

Sufficient information on analytical procedures is provided. Validation data for methods was also provided and are considered appropriate, demonstrating suitability for their intended purpose.

Batch Analyses

Batch information and release data on multiple lots of REGN10933 and REGN10987 are provided. Batch release data indicate robust reproducible manufacturing processes. All pre-defined acceptance criteria were met.

In addition, information on preclinical batches is provided. The preclinical lots were used to create the initial reference standard for REGN10933 and REGN10987, respectively.

Reference standard

REGN10933 and REGN10987 reference standards are used in all routine in-process, release, and stability testing. In principle, candidate reference standard material for qualification may originate from any batch of GMP produced formulated active substance.

A history of the reference standard used during development is provided. The initial reference standard for REGN10933 and REGN10987 were derived from tox batches. Based on data provided, process development material as reference standard for both sites is accepted.

The current primary reference standards were tested according to the specification in place at the time of reference standard qualification, against the respective previous reference standard.

Results for qualification of the primary and working reference material for REGN10933 and REGN10987 are considered acceptable.

Overall, the primary reference standards are considered appropriately characterised in-house primary reference materials for REGN10933 and REGN10987.

Container closure system.

The material meets Ph. Eur. requirements. Physicochemical testing is performed on the bottle and cap in accordance with Ph. Eur. *3.2.2.1, Plastic Containers for Aqueous Solutions for Infusion*. The material met all required testing acceptance criteria.

Based on acceptable biocompatibility and physicochemical testing, demonstrated lack of solvent loss and gas permeation, acceptable extractable and leachable evaluations, and demonstrated temperature and procedural control conducted using the same container closure, the container closure system has been demonstrated to be suitable.

Different container closure systems for the formulated active substances are used at each site but both are commonly known from other monoclonal antibody products. This is acceptable.

Stability

Stability summary and conclusion

The proposed shelf life for REGN10933 and REGN10987 active substances manufactured at both sites is based on product-specific data, in conjunction with the Applicant's extensive platform manufacturing experience and product knowledge, as well as long-term stability data from other IgG1 antibodies from the Applicant.

Post-approval stability protocol and stability commitments

A post-approval stability protocol and commitment are provided.

Stability data

Currently, real-time, real temperature stability data is provided for the active substances.

Little to no degradation is expected in REGN10933 and REGN10987 finished products; therefore, REGN10933 and REGN10987 active substances are expected to be stable at the long-term storage conditions, and the same shelf life is proposed for the active substances as for the finished products.

Given the ongoing COVID-19 pandemic situation, the proposed approach to justify REGN10933 and REGN10987 active substances shelf life, as well as long-term stability data from other IgG1 antibodies from the Applicant, are considered acceptable.

Shelf life for REGN10933 and REGN10987 active substances is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the finished product

REGN10933 and REGN10987 finished products are in an aqueous buffered solution, pH 6.0, containing the following compendial excipients: L-histidine and L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injections (WFI). The qualitative and quantitative composition in excipients is identical for REGN 10933 and REGN10987. Ronapreve formulation does not contain preservatives.

The solution for each vial should be clear to slightly opalescent, colourless to pale yellow.

There are two finished product presentations (see above) corresponding to 1332 mg of each antibody in 20 mL multidose vial (11.1 mL withdrawable volume) and 300 mg of each antibody in 6 mL single-use vial (2.5 mL withdrawable volume). The same vial can be used for both infusion and SC routes.

The two finished product presentations use the same Type I clear glass vial equipped with an elastomeric butyl rubber stopper and aluminium seal cap with flip-off button.

Formulation development

REGN10933 and REGN10987, used in the preclinical toxicology studies to assess safety and tolerability in non-human primates following IV infusion and SC injection, were formulated at 120 mg/mL.

Based on experience gained during previous product development activities, a platform formulation approach was used to identify a formulation.

The results from the accelerated and stress stability studies demonstrated the same main degradation pathways for the REGN10933 and REGN10987 formulation.

In addition, the formulation is compatible with the glass vials and the stoppers; and the formulation stability profile indicates acceptable long-term storage stability at 2°C to 8°C.

There are no overages included in the formula. An overfill is required to ensure that there is adequate volume in the vial to provide the required dose.

Physico-chemical properties are provided.

The rationale to select the final composition/formulation is sufficiently described and accepted. The presented overview of the formulation development is acceptable. The formulation is considered robust.

Manufacturing process development

Initial supplies for Phase I and Phase I/II/III (pivotal) clinical studies were manufactured by filling formulated active substances into fluorinated ethylene propylene (FEP) bags. Two vial presentations were used to supply pivotal clinical studies. There are no differences between the glass vials used to

supply clinical studies and the intended commercial glass vials. The same formulation was used throughout all finished product manufacturing processes.

An overview of the clinical and commercial finished product manufacturing processes is provided. Information regarding the compatibility of the primary container closure system with the finished product solution is provided.

The finished product manufacturing processes have been designed to ensure adequate product quality. No major changes were made between clinical and commercial processes. Acceptance criteria and/or action limits of IPCs were based on data acquired throughout development studies and clinical manufacturing. All major equipment used in clinical manufacturing remains the same for commercial manufacturing.

Details of the development leading to the commercial finished product manufacturing process and process controls, as well as information about single-use (disposable) materials and sterilising filters are provided.

Extractable and leachable studies were performed.

The extractables identified were chemically similar to compounds that are detectable by the analytical methods used to assess potential leachables. Results of the confirmative finished product leachable study demonstrate that there are no leachables of toxicological concern associated with the manufacturing process.

In order to expand production capacity for REGN10933 and REGN10987 the finished product manufacturing process was transferred to an additional manufacturing site, Roche. Both sites will manufacture both presentations of each antibody i.e. 300 mg and 1332 mg. The filling line is a multi-product filling line previously validated and approved for other monoclonal antibodies. The fill/finish processes for REGN10933 and REGN10987 follow the same overall process flow. Differences in the processes due to facility fit are summarised in the dossier.

The manufacturing process consists of thawing, pooling/mixing, bioburden reduction filtration, sterile filtration, aseptic filling, stoppering, capping, tray loading and 100% inspection of filled vials. The filled vials are transferred a facility where labelling and secondary packaging takes place. Each monoclonal antibody is independently filled into separate vials. Target withdrawable volumes of 2.5 mL or 11.1 mL of sterile-filtered finished products are filled into 6 mL or 20 mL vials. The finished product vials are stored at 2–8°C.

Comparability evaluation

The analytical comparability exercise comprises of in-process, release and stability testing. Extended characterisation is not planned for the finished products comparison as attributes tested by extended characterisation are not anticipated to be impacted by differences in filling operations. Given the comprehensive comparability study performed at the active substance level, the approach for demonstrating comparability of REGN10933 and REGN10987 finished products is considered acceptable.

Post-change finished product lots of REGN10933 and REGN10987 are evaluated for comparability.

Results for the initial comparability assessment of in-process and release data are submitted. Comparative stability is ongoing.

Results for in-process testing for all finished product lots met the established limits demonstrating that the REGN10933 and REGN10987 processes operated as intended. In addition, release results for the REGN10933 and REGN10987 finished products lots met all acceptance criteria.

The side-by-side stress (45°C) stability studies indicated that the finished product lots have highly similar degradation profiles.

Overall, comparability evaluation to support the use of REGN10933 and REGN10987 finished product is considered satisfactory.

Container Closure System

The finished product primary container closure system used at the initial fill site consists of a Type I glass vial and a 20 mm elastomeric stopper. Finished product primary container closure system used at the second fill site consists of a Type I glass vial and a 20 mm fluororesin-laminated rubber stopper with a 20 mm aluminum seal with plastic flip-off cap. The primary packaging components (vial and stopper) for the finished product were selected from standard, pharmaceutical-grade components. Compatibility of the vial and stopper with the finished product is demonstrated by long-term finished product stability data (refer to Section P.8.1 *Stability Summary and Conclusion*). Integrity of the container closure system to ensure sterility of the finished product has been demonstrated through process validation, manufacturing controls, and regular testing as outlined in Section P.2.5 *Microbiological Attributes*.

The container closure systems are suitable for its intended use, as demonstrated by protection of the product from physicochemical degradation, the safety of the container closure components, and compatibility with the dosage form. There were no leachable compounds of toxicological concern originating from the glass vials or elastomeric stoppers to date. Evaluation of the container closure systems are performed at pre-determined time points according to the leachable study protocol through at least the end of shelf life.

In principle, it is agreed that the primary container and closure systems used at each site are considered equivalent and will provide the same withdrawable volumes. Overall, the information submitted for the container closure systems is considered sufficient and acceptable.

Microbiological attributes

REGN10933 and REGN10987 finished products are intended for either intravenous infusion following dilution or subcutaneous injection. The microbiological quality and sterility of REGN10933 and REGN10987 finished products are controlled and assessed during routine manufacturing, process validation and stability testing.

Compatibility

Overall, information provided to support compatibility is considered acceptable.

Manufacture of the product and process controls

Manufacturer(s)

Manufacturing sites are multi-product facilities are regularly inspected by competent authorities.

Roche Pharma AG, Emil Barrell Strasse 1, 79639 Grenzach-Wyhlen, Germany is responsible for EU batch release of Ronapreve.

Compliance with EU GMP for all sites involved in manufacture, in-process control testing, quality control/release testing was confirmed.

Batch formula

The validated batch size ranges for REGN10933 and REGN10987 are provided and include both the 300 mg and 1332 mg presentations.

Description of manufacturing process and process controls

The manufacturing process for REGN10933 and REGN10987 finished products is a standard fill and finish process for monoclonal antibodies including following principle steps: thawing of formulated active substances, pooling and mixing, bioburden reduction filtration, sterile filtration, aseptic filling and stoppering of vials, capping and crimping, 100% vial inspection.

Differences in the finished product manufacturing process conducted at each site due to site-specific adaptions are detailed in section P.2.3 Manufacturing Process Development.

Overall, the information provided in for manufacturing process and process controls are acceptable

Process validation

A series of studies was conducted to prospectively evaluate and validate the REGN10933 and REGN10987 300 mg and 1332 mg finished product commercial manufacturing processes.

Mixing studies and processing time limits were included.

Media fills (aseptic filling) and environmental particle monitoring were established, as part of the comprehensive overall process validation.

Overall, REGN10933 and REGN10987 finished product manufacturing processes are considered successfully validated.

Product specification, analytical procedures, batch analysis

Specifications

The release specifications for REGN10933 and REGN10987 finished product include control of identity, purity and impurities, potency and other general tests.

Justification for the acceptance criteria for the quality attributes tested for REGN10933 and REGN10987 finished products, as well as at end-of-shelf-life are provided.

The specifications for REGN10933 and REGN10987 finished products are in line with ICH Q6B and are considered acceptable.

Analytical procedures

For analytical procedures performed for in-process, release, or stability testing of finished product that are the same as those used for testing formulated active substances, the Applicant is referring to Module S.4.2 Analytical Procedures.

Analytical procedures specific to finished product testing manufactured at all sites are sufficiently described in the section.

Validation of analytical procedures

Analytical procedures used for finished product testing are validated. Compendial methods were qualified.

The information provided is considered acceptable.

Batch analyses

Batch analyses from several lots for each site have been provided and the results confirm compliance with the specifications. Overall, the results comply well with the acceptance criteria and demonstrate a satisfactory batch to batch consistency within and between sites.

Batch-specific manufacturing, study usage, and lot genealogy information for REGN10933 and REGN10987 manufactured and filled into vials is summarised.

In addition, release data for historical finished product forms filled into FEP bags for clinical use are provided.

Characterisation of impurities

The known potential impurities that may arise during the manufacture and storage of the finished products are categorised into process- and product-related impurities.

A summary of each potential finished product impurity and details of the control strategies are outlined in this section. The identified impurities and control strategies are essentially the same for both sites.

Potential elemental impurities may be introduced during the finished manufacturing process and as a result of product contact with the container closure.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been provided. No additional control measures are deemed necessary.

The information provided in this section is considered sufficient and acceptable.

Reference standards

Please refer to active substance part.

Container closure system

The primary container closure system for REGN10933 and REGN10987 finished products consists of a Type I glass vial, 20 mm elastomeric stopper, and a 20 mm aluminium seal cap with a flip-off button. Details of the primary packaging components used at each manufacturing site are provided. Differences in the container closure system used at each site are indicated. Discussion of the suitability and rationale for selection of the finished product container closure system is provided.

Stability of the product

An overview of the currently available product-specific data and the overall approach for determination of shelf life is provided.

In general, the finished product shelf life should be determined in accordance with ICH Q5C guideline "Stability testing of biotechnological/biological products". However, given the current COVID-19 pandemic situation, the approach of the Applicant to define a shelf life for REGN10933 and REGN10987 finished products is considered appropriately justified and thus, accepted. In addition, the Applicant's approach relates to the draft CHMP toolbox guidance on "scientific elements and regulatory tools to support quality data packages for PRIME marketing authorisation applications".

The proposed shelf life of 24 months at 2-8°C for REGN10933 and REGN10987 finished products is acceptable.

Photostability studies conducted in accordance with ICH Q1B confirm that the vials should be kept in the original carton protected from light.

In-use stability

After initial puncture:

- The medicinal product in the single-use 6 mL vial should be used immediately, any remaining product should be discarded.

- The medicinal product in the multi-dose 20 mL vial, if not used immediately after initial puncture, can be stored for 16 hours at room temperature up to 25°C or for no more than 48 hours in a refrigerator (2°C to 8°C).

For IV administration, the solution in vial requires dilution prior to administration, using 0.9% sodium chloride injection or 5% dextrose injection. The prepared infusion solution is intended to be used immediately. The chemical and physical in-use stability data has been demonstrated for 20 hours at room temperature (up to 25°C) and 72 hours at 2°C to 8°C. From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, the intravenous infusion bag should be allowed to equilibrate to room temperature for approximately 30 minutes prior to administration.

For SC administration, the prepared syringes should be administered immediately. The chemical and physical in-use stability data has been demonstrated for 24 hours at room temperature (up to 25°C) and 72 hours at 2°C to 8°C. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless preparation has taken place in controlled and validated aseptic conditions. If refrigerated, the syringes should be allowed to equilibrate to room temperature for approximately 10 - 15 minutes prior to administration.

Adventitious agents

TSE compliance

No TSE-risk materials have been identified. Compliance with TSE-Guideline EMEA 410/01 rev03 has been demonstrated.

Virus safety

Bulk harvests are routinely tested for adventitious viruses according to ICH Q5A.
The purification process includes several chromatography steps, a low-pH treatment step and virus filtration. These steps have been validated in small scale studies for virus reduction using model viruses. Effective inactivation was demonstrated. It was shown that the chromatography step and the virus retentive filtration step are both capable of effective removal of viruses. The results from the validation of the virus reduction studies at the loads are provided in Module A.2 Adventitious Agents Safety Evaluation. A retrovirus risk assessment was performed demonstrating sufficient clearance for the CHO cell-derived RVLP.

In summary, virus safety is appropriate and the validation of virus reduction has been completed using a panel of model viruses according to ICH Q5A guideline.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the quality of Ronapreve is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation generally comply with existing ICH/CHMP guidelines.

The manufacturing processes of the active substances and finished products are adequately described, controlled and validated. Active substance and finished product batch release data indicate robust reproducible manufacturing processes within and between manufacturing sites. All pre-defined

acceptance criteria were met. The active substance and finished product manufacturing history is described in sufficient detail and the outcome of the comparability evaluations of different processes used is satisfactory.

The active substances have been extensively characterised with regard to their physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. Process- and product-related impurities have been evaluated and are sufficiently cleared during the process and/or controlled at release.

The quality of the active substances and finished products is controlled by adequate test methods and specifications.

In the context of the COVID-19 pandemic, the Applicant's approach to set the finished product shelf life in addition to the currently available product-specific stability data, is considered appropriately justified. The Applicant is recommended to provide the Arrhenius plots illustrating the behaviour of stability.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

Overall, the quality of the active substances and finished products has been well evaluated and presented by the Applicant, also considering the accelerated development due to the COVID-19 pandemic situation.

No major objection in the Quality dossier was identified during the Rolling Reviews and with the present marketing authorisation application.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Ronapreve is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Ronapreve is considered approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, CHMP recommends the following points for investigation:

1. The Applicant is recommended to provide results of the ongoing small-scale process characterisation studies.
2. The Applicant is recommended to the re-evaluate and tighten the acceptance criteria in the specifications.

3. The assessment of the finished product stability.

2.3. Non-clinical aspects

2.3.1. Introduction

SARS-CoV-2 spike glycoprotein (S protein) is a class I transmembrane envelope protein that forms a homo-trimer and mediates binding, fusion, and viral entry into host cells. The S protein is essential for virus infectivity and is the main target of the humoral immune response, as demonstrated by serology analysis of recovered COVID-19 patients (Long, 2020). The S protein mediates binding to the host receptor angiotensin converting enzyme 2 (ACE2), resulting in membrane fusion and entry of the virus into susceptible cells (Hoffmann, 2020). The S protein is composed of 2 functional subunits: the S1 subunit that contains the receptor binding domain (RBD), which binds to ACE2 on host cells, and the S2 subunit, which mediates fusion of the viral and cellular membranes (Walls, 2020). Structural studies have mapped the interface between human ACE2 and SARS-CoV-2 RBD, and results suggest simultaneous binding of 2 individual S protein trimers to a single ACE2 dimer (Yan, 2020).

As the S protein is required for viral entry, blockade of its interaction with the ACE2 receptor may offer a powerful way to block viral infectivity and spread. Indeed, a vaccine study utilizing the S protein as an immunogen has shown prophylactic efficacy in the rhesus macaque model of COVID-19, with a several log-fold decrease in viral load versus naïve animals (Yu, 2020).

The Applicant is developing the high-affinity human IgG1 anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies (mAbs), casirivimab and imdevimab (hereafter referred to as REGN10933 and REGN10987, which bind specifically to the receptor binding domain of the spike glycoprotein (S protein) of SARS-CoV-2, and neutralize virus infectivity by blocking binding to angiotensin converting enzyme 2 (ACE2). REGN10933 and REGN10987 were developed for co-administration (referred to as REGN-COV2) to minimize the likelihood of virus escape. REGN10933 was isolated from Regeneron's VelocImmune® human antibody mouse platform (Macdonald, 2014) (Murphy, 2014). REGN10987 was isolated from B cells of human donors previously infected with SARS-CoV-2.

Please note that besides REGN10933 and REGN10987 additional individual mAbs directed against SARS-CoV-2 S protein were used throughout the non-clinical program (REGN10989, REGN10993 and REGN10943). Results and data presented for these additional mAbs are noted and are partially included in the non-clinical assessment report, however, are not evaluated by the assessor for the present rolling review procedure for REGN-COV2 (REGN10933 and REGN10987).

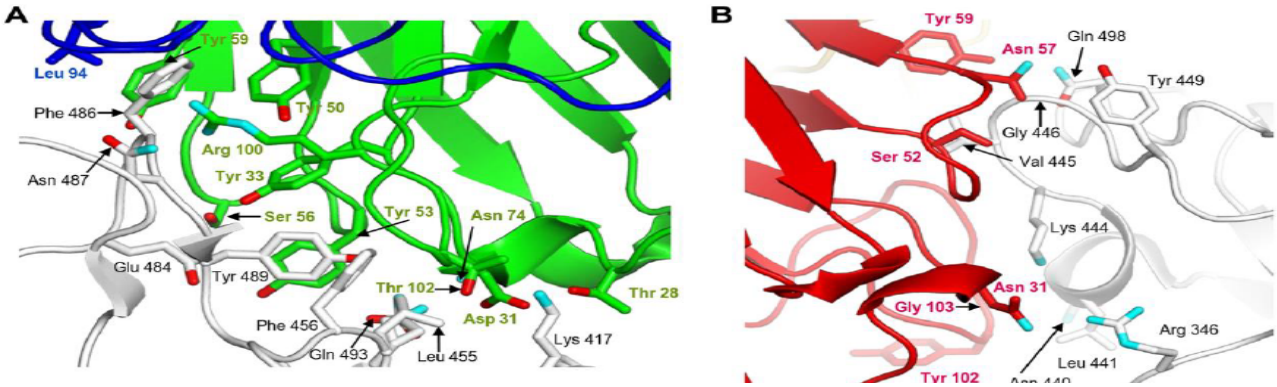
2.3.2. Pharmacology

Primary pharmacodynamic studies

***In vitro* binding and primary mode of action** (R10933-PH-20155-SR-01V1 R10933-PH-20088-SR-01V1, R10933-PH-20089-SR-01V1)

The structural basis for REGN10933 and REGN10987 binding to the target SARS-CoV-2 receptor binding domain (RBD) was assessed using cryogenic electron microscopy. Single-particle cryo-EM of the complex of SARS-CoV-2 spike RBD bound to Fab fragments of REGN10933 and REGN10987 showed that the two antibodies can simultaneously bind to distinct regions of the RBD (Figure 1).

Figure 1. REGN10933 and REGN10987 bind discrete residues on SARS-COV-2 RBD



Ribbon structure of the SARS-COV-2 S protein(gray) epitopes for (A) REGN 10933 and (B) REGN 10987 depicting the RBD residues that interact directly with residues of the REGN 10933 heavy chain (green), REGN 10933 light chain (blue) and REGN 10987 heavy chain (red): no RBD residues interact with the light chain of REGN 10987. Contact residues are represented as sticks, where red colouring represents oxygen and aqua colouring represents nitrogen atoms.

Results from cross-competition studies using SPR technology further confirmed that REGN10933 and REGN10987 bind non-overlapping epitopes on SARS-CoV-2 RBD. Moreover, sequence analysis using publicly available SARS-CoV-2 genomes identified through mid-August 2020 revealed that the RBD residues bound by REGN10933 and REGN10987 are highly conserved regions (i.e.≥99.96% and ≥99.98%, respectively, at each position across 58,728 SARS-CoV-2 S protein variants that were of sufficient quality for the analysis). In addition, the Applicant provided and update with more recent data demonstrating that the epitopes are highly conserved in currently (as of March 2021) circulating variants.

The kinetic binding parameters for the interaction of anti-SARS-CoV-2 S protein mAbs with monomeric and dimeric SARS-CoV-2 RBD as well as with stabilised, trimerized SARS-CoV-2 S protein were determined using surface plasmon resonance (SPR) technology. Results at 25ºC are presented in Table 1.

Table 1. Summary of kinetic binding parameters for the interaction of REGN10933 and REGN10987 with SAR-CoV2-2 RBD proteins or stabilised, trimerized SARS-COV-2 S protein at 25ºC and pH 7.4

anti-SARS-CoV-2 S Protein mAbs	Protein Injected Over Surface-Captured mAbs	Kinetic Binding Parameters			
		k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (M)	$t_{½}$ (min)
REGN10933	Monomeric SARS-CoV-2 RBD.mmH	1.70E06	3.10E-03	1.83E-09	3.7
	Dimeric SARS-CoV-2 RBD.mFc	4.65E06	8.71E-05	1.87E-11	132.6
	Stabilized, trimerized SARS-CoV-2 S protein	1.32E06	6.05E-05	4.58E-11	190.9
REGN10987	Monomeric SARS-CoV-2 RBD.mmH	5.34E05	1.68E-02	3.15E-08	0.7
	Dimeric SARS-CoV-2 RBD.mFc	1.89E06	1.86E-04	9.85E-11	62.1
	Stabilized, trimerized SARS-CoV-2 S protein	8.92E05	4.16 E-05	4.67E-11	277.6

k_a: association rate constant, k_d: dissociation rate constant, K_D: equilibrium dissociation constant, $t_{½}$: dissociative half-life

In addition, concentration-dependent binding to immobilized monomeric SARS-CoV-2 RBD protein (Figure 2) as well as concentration-dependent blocking of binding of dimeric SARS-CoV2 RBD to human ACE2 (summarized in Table 2) was demonstrated for REGN10933, REGN10987 and REGN-COV2 using different ELISA formats.

Figure 2. REGN10933, REGN10987, REGN10989 and REGN-COV2 display concentration dependant binding to SARS-COV-2 RBD

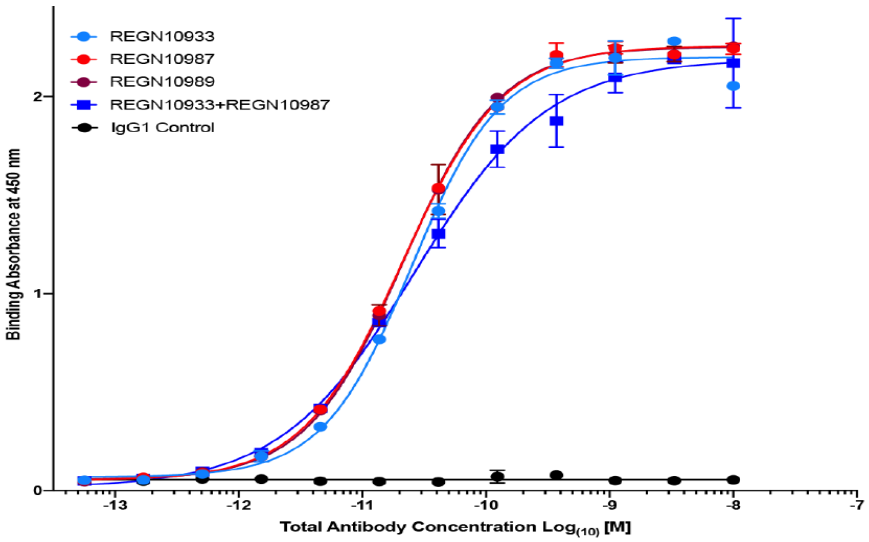


Table 2. Summary of IC_{50} and maximum percent blocking of SARS-CoV-2 RBD binding to human ACE-2 by REGN10933, REGN10987, REGN10989 and REGN-COV-2

Blockade of 100pM SARS-CoV-2 RBD Binding to Human ACE2		
Antibody	**IC_{50} [M]**	**Maximum % Blockade***
REGN10933	5.64E-11	101
REGN10987	1.65E-10	101
REGN10989	5.00E-11	96
REGN-COV2 (REGN10933+REGN10987)	8.18E-11	100
IgG1 Control	ND	4

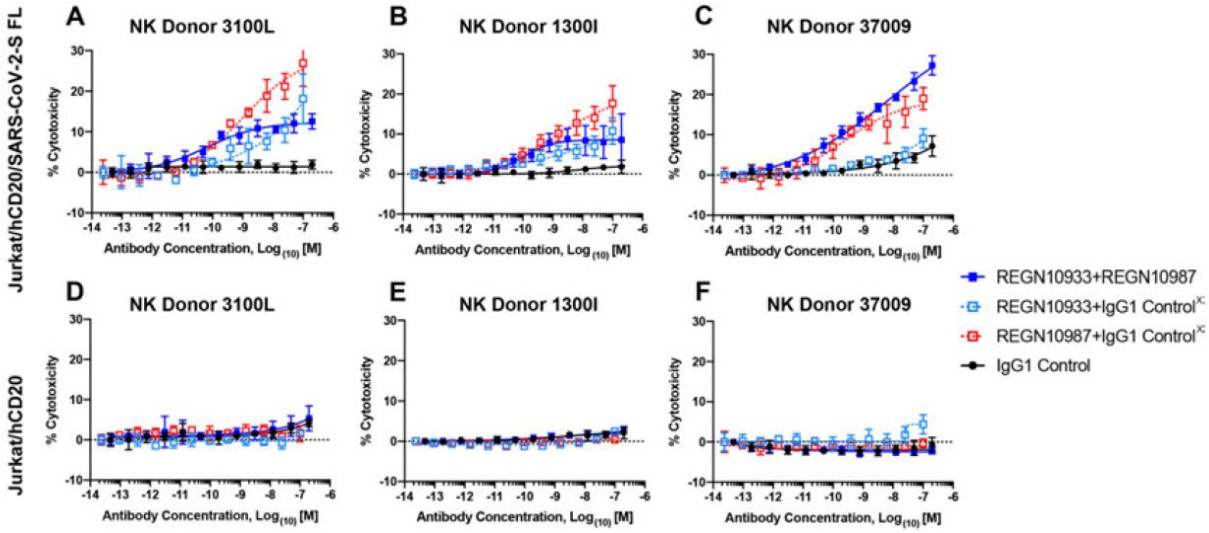
*Maximum % blockade is defined as 100 minus the average binding signal observed at the highest antibody concentration tested (100nM) with buffer control subtracted, divided by the binding signal observed at constant concentration of RBD.hFc (100pM) with buffer control subtracted, multiplied by 100.
Abbreviation(s): ND, not determined because concentration-dependent blockade was not observed

***In vitro* functional characterisation** (R10933-PH-20090-SR-01V1, R10933-PH-20091-SR-01V4, R10933-PH-20100-SR-01V1)

Fc functions

To understand whether REGN10933, REGN10987 and REGN-COV2 are capable of mediating effector function, ADCP activity and ADCC in primary human cell bioassays were assessed utilizing monocyte-derived phagocytes and natural killer (NK) cells (3 independent donors). Results for the experiments with the NK cells are presented in Figure 3.

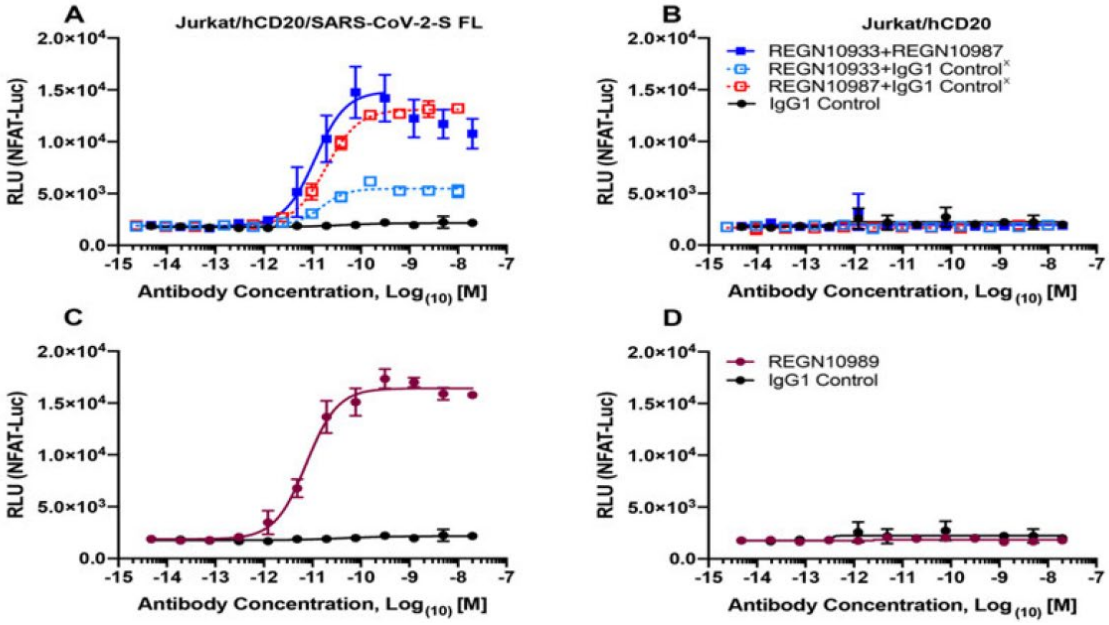
Figure 3. REGN10933, REGN10987 and REGN10989 medicate ADCC of target cells expressing SAR-CoV2 S Protein



In addition, an ADCC-surrogate reporter assay using activation of FCGR3A receptor signalling as a read-out in the presence of target cells was performed (Figure 4).

Figure 4. REGN10933, REGN10987 and REGN10989 enhance NFAT activity in Jurkat/NFAT-Luc/FCGR3A reporter cells

Figure 3: REGN10933, REGN10987, REGN-COV2, and REGN10989 Enhance NFAT Activity in Jurkat/NFAT-Luc/FCGR3A Reporter Cells



Furthermore, the ability to mediate CDC of target cells in presence of normal human serum was investigated. Results demonstrate that REGN10933, REGN10987, REGN-COV2, and REGN10989 do not mediate CDC against Jurkat/hCD20/SARS-CoV-2-S FL or Jurkat/hCD20 cells (data not shown).

Neutralisation activity(R10933-PH-20091-SR-01V4)

REGN10933, REGN10987 and REGN-COV2 neutralisation activity against SARS-CoV2 virus and Vesicular Stomatitis Virus (VSV) pseudotyped with SARS-CoV-2-Spike Protein was evaluated using cell-based assay formats. Briefly, non-replicating pseudoparticles (pVSV-SARS-CoV-2-S, aa 14-1255) or virus (VSV-SARS-CoV-2-S, aa 1-1255 or SARS-CoV-2, USA-WA1/2020 isolate) were pre-incubated with either REGN10933, REGN10987, REGN-COV2 or an IgG1 isotype control mAb and added to Vero (VSVs) or Vero E6 (SARS-CoV-2) cells to assess neutralisation. Vero cell infectivity was detected by utilizing expression of fluorescent mNeon reporter (pseudoparticles) or immunostaining with anti-VSV polyclonal antibody (virus). Vero E6 cell infectivity by SARS-CoV-2 was detected by a plaque assay.

REGN-COV2 and the individual mAbs mediate concentration-dependent neutralisation of pVSV-SARS-CoV-2-S, VSV-SARS-CoV-2-S virus, and SARS-CoV-2 entry into Vero or Vero E6 cells, with IC50 and IC90 values in the picomolar range (Table 3).

Table 3. Summary of values for REGN10933, REGN10987, REGN-COV2 and REGN-10989 mediating neutralisation of viral entry into Vero or Vero E6 cells

	pVSV-SARS-CoV-2-S Pseudoparticles			VSV-SARS-CoV-2-S Virus		SARS-CoV-2 Virus		
Antibody Treatment	IC_{50} [M]	IC_{90} [M]	IC_{99} [M]	IC_{50} [M]	IC_{90} [M]	IC_{50} [M]	IC_{90} [M]	IC_{99} [M]
REGN10933	6.24E-11	4.36E-10	3.63E-09	4.31E-11	1.71E-10	3.74E-11	1.78E-10	9.78E-10
REGN10987	4.30E-11	2.53E-10	1.75E-09	3.13E-11	1.38E-10	4.21E-11	4.30E-10	5.43E-09
REGN10933+REGN10987	4.89E-11	2.60E-10	1.61E-09	2.70E-11	7.70E-11	3.10E-11	1.73E-10	1.14E-09
REGN10989	1.18E-11	2.60E-10	4.83E-10	4.79E-12	2.32E-11	7.38E-12	2.38E-11	8.55E-11
IgG1 Control	ND							

Abbreviations: ND, not determined because a dose-dependent response was not observed

Neutralisation of SARS-CoV-2 S RBD variants

Additional in vitro studies were performed using pVSV-SARS-CoV-2-S pseudoparticles to evaluate the ability of REGN10933, REGN10987, REGN-COV2, and REGN10989 to neutralize putative escape mutants identified in vitro under antibody pressure with anti-S protein mAbs (R10933-PH-20100), as well as S protein variants identified from preclinical animal studies, clinical trials, and publicly available sources of SARS-CoV-2 virus in circulation. WT SARS-CoV-2 or the S protein variant, D614G, the predominant globally circulating SARS-CoV-2 virus (Yurkovetskiy, 2020), was used as the reference virus to calculate fold changes for each variant tested in these assays. Variants located outside the RBD were not evaluated. This is acceptable as they will likely not influence the binding and neutralisation activity of REGN-COV2.

Non-replicating VSV pseudoparticles pseudotyped with SARS-CoV-2 S protein variants were incubated with REGN10933, REGN10987, REGN-COV2, or REGN10989 to assess the capacity of anti-S protein antibodies to block pseudoparticle entry into Vero cells. WT SARS-CoV-2 or the S protein variant, D614G, was used as the reference virus for these assays.

Results demonstrate that REGN10933, REGN10987, REGN-COV2, and REGN10989 mediate neutralization in a concentration-dependent manner (Table 4, R10933-PH-20091-SR-01V4).

Table 4. Summary of IC50 and IC90 values for REGN-10933, REGN10987 and REGN-COV2 mediated neutralisation of pSV-SAR-COV-2 pseudotyped with variants into Vero cells

SARS-CoV-2 S Protein Variant	REGN10933			REGN10987			REGN10933+REGN10987		
	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
Full Sequences or Key Residues of Variants of Interest/Concern[b]									
B.1.351	1.90E-09	7.67E-09	44.66	7.06E-12	1.26E-10	0.18	1.91E-11	1.08E-10	0.60
B.1.1.7	4.52E-11	5.22E-10	1.16	1.75E-11	1.13E-10	0.73	3.00E-11	1.42E-10	0.87
P.1‡	1.31E-08	1.16E-07	417.60	5.39E-12	5.66E-11	0.11	2.91E-11	1.64E-10	1.16
H69del/V70del‡ (B.1.1.7)	4.77E-11	2.87E-10	1.44	4.11E-11	2.04E-10	1.24	4.16E-11	1.49E-10	1.66
K417T/E484K (P.1)	6.07E-09	1.71E-08	142.85	2.53E-11	1.42E-10	0.66	4.54E-11	3.27E-10	1.43
L452R/T478K‡ (B.1.617.2)	2.65E-11	2.01E-10	0.65	4.45E-11	3.90E-10	0.88	2.82E-11	1.18E-10	0.80
L452R/E484Q‡ (B.1.617.1)	2.00E-10	4.90E-09	7.16	1.85E-11	5.97E-10	0.63	3.57E-11	2.78E-10	1.42
All Single-Mutation Variants									
L18F	4.27E-11	2.35E-10	1.00	3.58E-11	1.59E-10	0.93	3.62E-11	1.19E-10	1.14
W152C‡	2.40E-11	1.98E-10	0.72	3.13E-11	1.59E-10	0.94	2.73E-11	9.95E-11	1.09
A222V	1.52E-11	9.35E-11	0.70	1.85E-11	1.39E-10	0.61	1.29E-11	6.02E-11	0.92
Q321L	7.03E-11	3.51E-10	1.56	5.20E-11	3.78E-10	1.11	NT	NT	NA
P322A	3.76E-11	2.20E-10	0.76	1.73E-11	1.80E-10	0.65	2.42E-11	3.29E-10	0.70
T323I	5.49E-11	4.00E-10	1.18	2.10E-11	1.26E-10	1.12	3.08E-11	1.59E-10	1.11
P330S	5.00E-11	4.05E-10	1.09	1.73E-11	1.10E-10	0.48	3.13E-11	1.48E-10	0.95
P337L‡	4.03E-11	1.07E-09	1.26	3.51E-11	5.72E-09	5.02	2.08E-11	1.37E-08	0.98
E340A‡	2.39E-11	1.48E-10	0.44	3.05E-11	1.70E-10	0.96	1.53E-11	1.13E-10	0.47

Single mutations that reduced neutralization potency (IC50) of either REGN10933 or REGN10987 individually (e.g., 51-fold decrease with E406D for REGN10933 and 463-fold decrease with N439K for REGN10987) did not reduce neutralization potency of REGN-COV2. Notably, REGN-COV2 combination did not demonstrate reduction in neutralization potency >6-fold with any of the variants tested.

Further neutralization studies were performed using authentic SARS-CoV-2 isolates of the various variants of interest/concern (Table 5), with IC50s and IC90s calculated for the gamma and delta variants (Table 5, lower panel).

Table 5. Neutralisation of authentic SARS-COV-2 isolates of variants of interest/concern

SARS-CoV-2 Lineage	REGN10933		REGN10987		REGN10933+REGN10987	
	IC_{50} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	Fold Change in IC_{50} over Ref Virus
B.1.351	3.86E-09	5.49	9.68E-11	0.12	2.64E-10	0.32
B.1.1.7	1.30E-10	0.18	2.13E-10	0.25	1.03E-10	0.12
B.1.617.1	4.10E-09	5.84	1.33E-10	0.16	6.83E-10	0.82
WT	7.02E-10	Ref Virus	8.38E-10	Ref Virus	8.35E-10	Ref Virus

REGN10933, REGN10987, REGN-COV2 (REGN10933+REGN10987), and IgG1 isotype control were tested at concentrations ranging from approximately 11.29fM-2nM. Fold change over reference (ref) virus was calculated by dividing the IC_{50} value generated by the antibody(ies) in the presence of a particular variant, by the IC_{50} value generated by the antibody(ies) in the presence of reference virus (WT [Washington-1 isolate]) from the same assay. A numerical value is not provided for fold change of WT since this row contains neutralization data generated with the reference virus itself. IC_{50} and fold change for each virus incubated with IgG1 isotype control are not shown in table, as a concentration-dependent response was not observed (B.1.351, B.1.1.7, and B.1.617.1) or because the curve did not reach saturation over the concentration range (WT).

SARS-CoV-2 Lineage	Casirivimab			Imdevimab			RONAPREVE		
	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus	IC_{50} [M]	IC_{90} [M]	Fold Change in IC_{50} over Ref Virus
P.1 (Gamma)	NC	NC	371.06[a]	1.40E-11	2.92E-10	0.78	3.17E-11	2.34E-10	2.19
B.1.617.2 (Delta)	1.43E-11	2.10E-10	0.27	3.64E-11	3.36E-09	2.03	2.10E-11	2.63E-10	1.45
WA-1	5.39E-11	2.45E-10	Ref Virus	1.79E-11	1.15E-10	Ref Virus	1.45E-11	2.87E-11	Ref Virus

[a] As an IC_{50} value could not be accurately calculated, the change in mAb potency in the presence of the P.1 (Gamma) isolate was calculated by dividing the maximum antibody concentration tested (2nM) by the IC_{50} value calculated for casirivimab in the presence of reference virus (WA-1).
NC, not calculated due to poor neutralization
Casirivimab, imdevimab, and RONAPREVE (casirivimab+imdevimab) were tested at concentrations ranging from approximately 11.29fM-2nM. Fold change over reference (ref) virus (Washington [WA]-1 isolate) was calculated by dividing the IC_{50} value generated by the antibody(ies) in the presence of a particular variant, by the IC_{50} value generated by the antibody(ies) in the presence of reference virus from the same assay. A numerical value is not provided for fold change of WA-1 since this row contains neutralization data generated with the reference virus itself.

Development of viral escape mutants (*in vitro*)

The Applicant performed *in vitro* viral escape mutant studies to evaluate the selection of SARS-CoV-2 S protein escape mutant due to presence of a range of concentrations of anti-S protein mAbs (REGN10933, REGN10987 and REGN-COV2). Treatment of VSV-SARS-CoV-2-S virus with REGN10933 and REGN10987 resulted in rapid virus escape, defined as ≥20% CPE, within 2 passages; whereas for REGN-COV2, mutations that impacted sensitivity to both antibodies were not identified in the population until passage 6. Putative escape mutations were identified through sequencing analysis.

In subsequent *in vitro* neutralisation studies using pVSV-SARS-CoV-2-S pseudoparticles pseudotyped with RBD-encoding putative escape mutations from passaged virus, mutations that impacted REGN10933 or REGN10987 potency were neutralized by combination. REGN-COV2 demonstrated potency against all tested escape mutants and wild-type pVSV-SARS-CoV-2-S pseudoparticles in the picomolar range, with IC50 values differing no more than 10-fold based on assay variability. A double mutant (K417R/K444Q) was required to see reduction in neutralisation potency by combination REGN-COV2, which impacted the IC50 by 89-fold.

***In vivo* PoC studies** (R10933-PH-20093, R10933-PH-20160, R10933-PH-20161-PD-01V1, R10933-PH-20192)

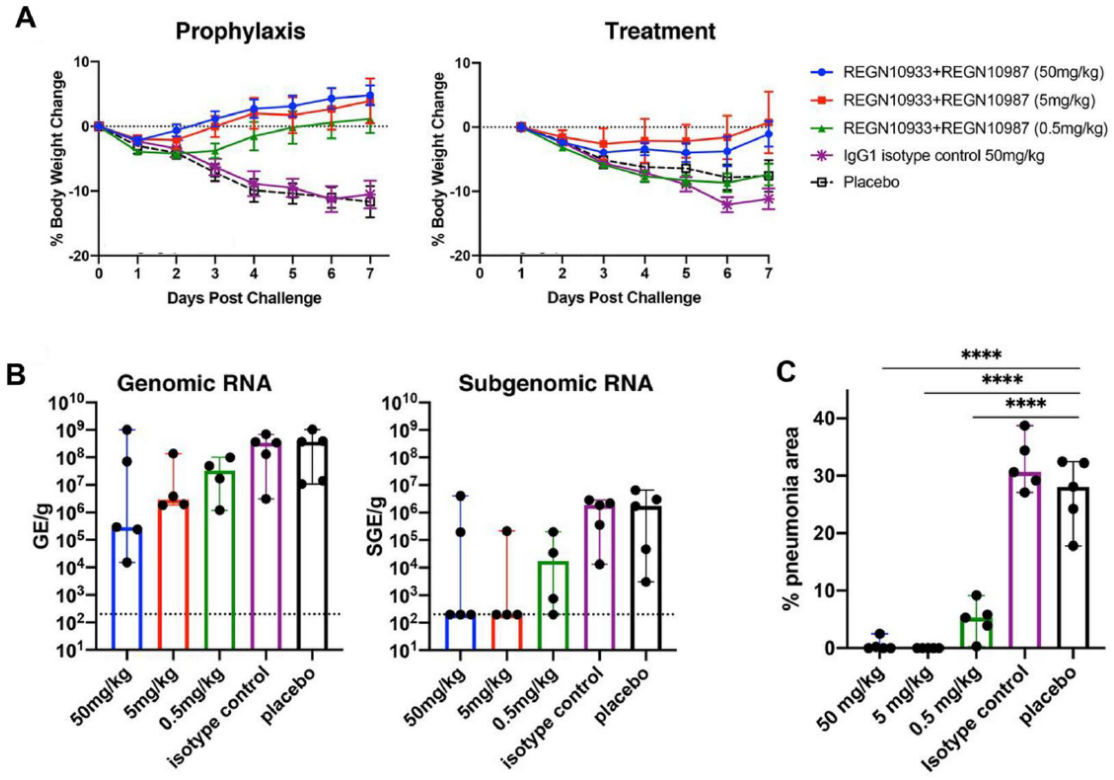
In vitro binding and cell-based functional studies were complemented by *in vivo* studies conducted in NHP rhesus macaque monkeys and Syrian Golden hamsters. SARS-CoV-2 infection of the rhesus macaque results in mild disease with none or limited clinical signs, multifocal lung lesions with mild to moderate, interstitial pneumonia. The virus replicates in the upper and lower respiratory tract and virus quantitation at these sites therefore serves as the primary study endpoint for evaluating efficacy of COVID-19 vaccine /treatment candidates in this species. The Syrian Golden Hamster model manifests a more severe disease phenotype than rhesus macaques, characterized by rapid weight loss and severe lung pathology. Both animal models are considered established SARS-CoV-2 infection models. In an *in vivo* non-GLP study the Applicant evaluated REGN-COV2 for the treatment and prevention of SARS-CoV-2 infection in the rhesus macaque model, using a mucosal route of exposure (R10933-PH-20093). The study evaluated intravenous dose administration three days prior to exposure (prophylactic arm) and 1 day after exposure (therapeutic arm) at different dose levels. There were no unscheduled deaths during the course of this study. Histopathological findings in the lungs, when present, were consistent with reported lesions for SARS-CoV-2 in rhesus macaques. Oral and nasal swab samples were collected throughout the study and analysed via qRT-PCR to quantify viral load. Results from qRT-PCR suggest that high dose prophylactic treatment (50mg/kg) and therapeutic treatments (25mg/kg and 150mg/kg) effectively decreased viral burden. Viral loads declined more rapidly in treated animals than placebo control animals. Viral replication and viral shedding appeared to decrease more quickly in treated animals. Furthermore, RNAseq analysis was performed to assess for putative viral escape mutants in SARS-CoV-2 S protein in rhesus monkeys following prophylactic or therapeutic administration of REGN-COV2. All variants identified in the REGN-COV2 treated animals were also present in the placebo group, with approximately half of these variants already being present in the inoculum.

A subsequent *in vivo* study was conducted to further evaluate the prophylactic efficacy of REGN-COV2 for prevention of SARS-CoV-2 infection in rhesus macaques (10933-PH-20160). Briefly, Rhesus monkeys were given a single IV injection of 50 mg/kg REGN-COV2 (25 mg/kg/antibody) or placebo 3 days prior to challenge with a total inoculum of 1.1E05 PFU of SARS-CoV-2 via combined IT/IN inoculation (Day 0). Results for both nasopharyngeal swabs and bronchoalveolar lavage (BAL) fluid show that monkeys given REGN-COV2 prophylactically demonstrate a reduction of gRNA and nearly complete ablation of viral sgRNA (reflecting newly replicating virus) when compared with animals receiving placebo. In summary, a single 50 mg/kg IV dose of REGN-COV2 administered prophylactically 3 days prior to challenge with SARS-CoV-2 reduces viral load in the upper and lower airways. These results confirmed the prophylactic treatment effect of REGN-COV2 indicated in the previous nonclinical study performed in rhesus macaque (R10933-PH-20093).

In addition, based on the pathology summary report provided, REGN-COV2 prophylactic treatment slightly reduced the severity of SARS-CoV-2 induced lung inflammation as well the incidence of number of lung lobes affected, suggesting possible efficacy in this rhesus macaque model of COVID-19. Furthermore, the Applicant studied the therapeutic and prophylactic effect of REGN-COV2 on SARS-CoV-2 infection using Syrian Golden Hamster as a model (R10933-PH-20161-PD-01V1) which is characterized by rapid weight

loss and severe lung pathology. Briefly, fifty 6-8-week-old male and female hamsters were randomized to dosing groups and given a single intraperitoneal (IP) injection of REGN-COV2 (0.5, 5, or 50 mg/kg), IgG1 isotype control (50 mg/kg), or placebo 2 days prior to SARS-CoV-2 challenge (prophylactic) or 1 day post-SARS-CoV-2 challenge (therapeutic). In both study arms, hamsters were intranasally challenged on Day 0 with 2.3x104 PFU of SARS-CoV-2. Study endpoints included body weights, clinical signs, and viral loads in the upper (oral swabs) and lower (lungs) respiratory tract of the animals and results are summarized in Figure 5.

Figure 5. Prophylactic and therapeutic efficacy of REGN-COV-2 in the Syrian Golden Hamster model of SARS-COV-2 infection



Male and female Syrian golden hamsters (n=5/group) were given a single IP injection of REGN-COV2 (0.5, 5, or 50 mg/kg [0.25, 2.5, or 25 mg/kg/antibody, respectively]), IgG1 isotype control (50 mg/kg), or placebo prophylactically 2 days prior to SARS-CoV-2 challenge or therapeutically 1 day post-SARS-CoV-2 challenge. In both study arms, all hamsters were IN challenged on Day 0 with SARS-CoV-2. Body weight was measured daily throughout the prophylactic (A, left panel) and therapeutic (A, right panel) study periods and was reported as percentage body-weight change from baseline (Day 0 for prophylaxis and Day 1 for treatment). At the end of the study period (Day 7), lungs were harvested from hamsters in the prophylactic arm to measure levels of SARS-CoV-2 gRNA (B, left panel) and sgRNA (B, right panel) by qRT-PCR. Data in (B) is presented as genomic equivalents (GE) and subgenomic equivalents (SGE) per gram of tissue. Histopathology was performed on lung tissues and the percentage area exhibiting pathology typical of pneumonia was quantified (C). Asterisks '*' in (C) indicate statistically significant differences ($p<0.0001$).

Furthermore, the potential for a sub-neutralizing dose (0.0005 mg/kg) of REGN-COV2 to mediate ADE of SARS-CoV-2 infection was assessed in Syrian golden hamsters (R10933-PH-20192-SR). Hamsters (n=5 to 7) were given a single IP injection of REGN-COV2 (0.0005, 0.005, 0.05, 0.5, or 5 mg/kg [0.00025, 0.0025, 0.025, 0.25, or 2.5 mg/kg/antibody, respectively]) the same doses of the REGN10993+REGN10943 IgG4P-GG isotype mAbs, or placebo 2 days prior to IN challenge with 1.00E04 PFU SARS-CoV-2 (USA-WA1/2020).

Body weight was assessed daily as an indicator of morbidity, with the percentage change in body weight from baseline (day of challenge) graphed. Lung tissue was harvested at the end of the study to assess viral load (log10 copies/g), measured by qRT-PCR, and pathology, assessed using a 5-point scale of

inflammation severity. Details are outlined in R10933-PH-20192-SR. As seen in the previous hamster study, prophylactic administration of REGN-COV2 protected against weight loss and reduced the severity of lung inflammation in a dose-dependent manner. The high dose (5 mg/kg) also reduced the incidences of lung inflammation and secondary changes such as type II pneumocyte hyperplasia (R10933-PH-20192-SR Appendix). Viral load in lungs was also reduced at 5 mg/kg REGN-COV2 relative to placebo. Importantly, ADE of infection was not observed at a sub-neutralizing dose of REGN-COV2, as indicated by a lack of more severe weight loss, increased inflammation, or enhanced viral load relative to placebo. Likewise, no clear differences in efficacy between the IgG1 and IgG4P-GG isotype versions of REGN10933 and REGN10987 were determined, further supporting lack of FCGR-mediated ADE.

Secondary pharmacodynamic studies

Antibody-dependent enhancement (ADE) of viral infectivity can lead to enhanced viral replication, increased inflammation, or more severe disease as a result of the antibody Fc domain simultaneously binding virus particles and cell-surface Fc gamma receptors.

The potential of REGN10933, REGN10987 and REGN-COV2 to mediate ADE of virus infection was also investigated *in vitro*. Briefly, Fcgamma receptor positive (FCGR+) U937, THP1, IM9, K562, and Raji cells were co-incubated with pVSV-SARS-CoV-2-S pseudoparticles and a range of concentrations of REGN10933, REGN10987 and REGN-COV2, and assessed by flow cytometry to determine the percentage of cells containing pseudoparticles. Ramos cells, which were determined to be FCGR-negative, served as a negative control. Results are summarized in Table 6.

Table 6. Summary of Maximum Percentage of Viral Entry into Cell Lines in the Presence of REGN10933, REGN10987, or REGN-COV2

	Maximum Infection (%mNeon+ in Total Cells)					
Antibody Treatment	Ramos	U937	THP1	IM9	K562	Raji
REGN10933+IgG1 Control	0.00	0.00	0.01	0.00	0.01	0.02
REGN10987+IgG1 Control	0.01	0.02	0.24	0.00	0.00	1.34
REGN10933+REGN10987	0.00	0.01	0.06	0.00	0.01	0.69
IgG1 Control	0.00	0.00	0.02	0.00	0.00	0.25

Maximum percentage of viral entry is defined as the highest mean percentage of mNeon+ cells within live/singlets across the tested antibody dose range (3.05pM to 200nM).

To assess the likelihood of ADE in a more physiologically relevant in vitro system, a study using SARS-CoV-2 virus and FCGR-positive primary monocyte-derived macrophages (MDMs) from 2 human donors was conducted (R10933-PH-21015). Neither REGN10933, REGN10987, nor REGN-COV2 demonstrated any evidence of mediating ADE, as evidenced by very low (<1.4%) viral antigen-positive MDMs, independent of whether the cells were untreated or incubated with anti-S protein mAbs or isotype control. Furthermore, the percentage of viral antigen-positive cells did not correlate with the concentration of anti-S protein mAbs. Therefore, in contrast to studies with pseudoparticles and immortalized cell lines, studies with authentic SARS-CoV-2 and primary human monocytic cells did not show enhancement of viral uptake in the presence of the anti-S protein mAbs.

Safety pharmacology programme

Safety pharmacology endpoints (e.g. cardiovascular, respiratory or neurobiological endpoints) were evaluated as part of the repeat-dose toxicity study conducted in Cynomolgus Monkeys (R10933-TX-20064). There was no mortality or adverse clinical signs evident throughout the dosing period, and there were no drug-related changes in any of the parameters evaluated. There were no macroscopic or microscopic findings or organ-weight changes related to the administration of REGN10933 and/or REGN10987.

Pharmacodynamic drug interactions

No studies of pharmacodynamic drug interactions have been submitted. Considering the nature of the product this is acceptable.

2.3.3. Pharmacokinetics

To support clinical development, the intravenous (IV) and subcutaneous (SC) pharmacokinetics (PK) and toxicokinetics (as part of the GLP- repeat dose tox study) of REGN10933 and REGN10987 given alone and in combination as REGN-COV2 were characterized following individual or combined administration to cynomolgus monkeys. It is noted that IV and SC administration was evaluated for PK.

Females were not included in the PK studies, but TK data from both males and females do not indicate sex differences.

Methods of Analysis

Drug concentrations in serum were determined using an enzyme-linked immunosorbent assay (ELISA) for human IgG. The results for method validation demonstrate that the assay accurately measures levels of total anti-SARS-CoV-2 antibodies, separately or in combination.

Pharmacokinetic parameters were estimated by noncompartmental analysis (NCA).

PK studies (R10933-PK-20071 (pilot), R10933-PK-20074)

The PK of total REGN10933 and total REGN10987 when administered individually or in combination as REGN-COV2 is described as linear, as would be expected for mAbs directed against an exogenous target. Following a single IV or SC administration of REGN10933 and REGN10987 administered individually or in combination to cynomolgus monkeys, concentration-time profiles were characterized by an initial brief distribution phase (IV) or an absorption phase (SC), followed by a single linear elimination phase. Following SC administration of 10 mg/kg/antibody (total dose of 20 mg/kg REGN-COV2), mean time to peak concentration (tmax) in serum was observed approximately 4 days postdose, and the estimated bioavailability was 81.6%. Pharmacokinetic results are summarised in Table 7.

Table 7. Summary of mean pharmacokinetic parameters of total REGN10933, total REGN10989 and total REGN-COV2 in Cynomolgus monkey serum following a single intravenous or subcutaneous injection of REGN10933 or REGN10989 individually or REGN-COV2.

Study No. (Compliance)	Species/Route	Administered mAb (Measured)	Dose (mg/kg)	N/Sex	t_{max} (h/day)	C_{max} (µg/mL)	C_{max}/Dose ((µg/mL)/(mg/kg))	Elimination $t_{1/2}$ (day)	AUC_{inf} (day•(µg/mL)/(mg/kg))	V_{ss} (mL/kg)	CL or CLF[a] (mL/day/kg)	F[b] (%)
R10933-PK-20074 (non-GLP)	Monkey/ IV	REGN10933 (total Hu IgG)	1	2M	0.0833	24.3	24.3	17.0	304	77.6	3.36	NA
	Monkey/ IV	REGN10987 (total Hu IgG)	1	2M	0.0833	31.9	31.9	7.78	196	53.6	5.19	NA
	Monkey/SC	REGN10933 (total Hu IgG	1	2M	5.00	9.57	9.57	15.9	260	NA	3.87	85.5
	Monkey/SC	REGN10987 (total Hu IgG)	1	2M	2.50	11.7	11.7	10.3	195	NA	5.21	99.5
R10933-PK-20071 (non-GLP)	Monkey/ IV	REGN10933 (total Hu IgG)	10	4M	0.0833	310	31.0	16.8	3670	68.2	3.00	NA
	Monkey/ IV	REGN10987 (total Hu IgG)	10	4M	0.0833	272	27.2	13.1	2710	71.3	3.93	NA
	Monkey/ IV	REGN-COV2 (total Hu IgG)	10/10	4M	0.0833	639	31.9	18.0	7080	68.4	2.82	NA
	Monkey/ IV	REGN-COV2 (total Hu IgG)	50/50	4M	0.0833	2960	29.6	16.8	27700	63.3	3.62	NA
	Monkey/SC	REGN-COV2 (total Hu IgG)	10/10	4M	3.75	206	10.3	16.3	5780	NA	3.53	81.6

*Concentration values considered to be ADA impacted were excluded from 1 animal (2002) in the 1 mg/kg REGN10987 IV group (R10933-PK-20074-PP Table 18).

[a] CL applies to IV dose groups and CL_F applies to the SC dose groups.

[b] Bioavailability was calculated as (SC mean AUC_{inf}/mean AUC_{inf} at the respective IV dose level) x 100%.

ADA, Anti-drug antibody; AUC_{inf}, Area under the concentration-time curve from time zero extrapolated to infinity; C_{max}, Peak concentration; CL, Total body clearance; CL_F, Apparent total body clearance; ELISA, Enzyme-linked immunosorbent assay; F, Bioavailability; GLP, Good Laboratory Practice; h, Hours; Hu, Human; IV, Intravenous; M, Male; mAb, Monoclonal antibody; N, Number of animals; NA, Not applicable; SC, Subcutaneous; $t_{1/2}$, Elimination half-life; t_{max}, Time to C_{max}; V_{ss}, Volume of distribution at steady state

Notes: t_{max} is represented in hours for the IV dose groups and in days for the SC dose groups.

ELISA measures total REGN10933 and total REGN10987 as total Hu IgG.

Dose-normalized parameters for REGN10933+REGN10987 (REGN-COV2) combination groups are normalized by total human mAb dose.

No studies on tissue distribution, metabolism and excretion have been conducted for REGN10933, REGN10987, or REGN-COV2. Considering the nature of the product this is accepted and in accordance with ICH S6(R1).

2.3.4. Toxicology

A short-term safety study was conducted in a single species, consistent with ICH S6(R1) as REGN10933 and REGN10987 are directed against an exogenous target. 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.

In addition, *ex vivo* GLP-tissue cross-reactivity studies were conducted using panels of normal human and cynomolgus monkey tissues and selected human fetal tissues.

Single dose toxicity

Not applicable.

Repeat dose toxicity

In a 4-week GLP study in male and female Cynomolgus monkeys aged 2.2-4 years (study R10933-TX-20064), weekly IV injections of 50 mg/kg REGN10933 alone or REGN10987 alone, or weekly IV or SC injections of up to 150 mg/kg/antibody REGN-COV2 were well tolerated. Incidences of increased ALT, lens opacity and injection site abrasions were considered unlikely related to treatment, due to slight severity, single incidences, and (except for skin abrasion) similar findings in non-treated animals.

Cytokine levels measured for 5 days following first dose were either below LLOQ (IL-2, IL-4, IL-5, and IFN-γ), or not considered treatment-related (IL-6, IL-10, TNF-α, and IL-8) due to low magnitude (within predose or control ranges) and sporadic findings. In addition, sporadic increases in plasma MCP-1 concentrations above control levels were observed in 4 animals on Day 1, considered of uncertain relation to REGN10933 and/or REGN10987 administration.

Based on the lack of adverse effects, the NOAEL is considered to be 50 mg/kg REGN10933 and 50 mg/kg REGN10987 when administered alone and 150 mg/kg/antibody (total dose of 300 mg/kg) for REGN-COV2, the highest doses evaluated.

Based on exposure levels at NOAEL and predicted human exposure based on population PK models for REGN10933 and REGN10987, generated by interim data from clinical studies COV-2067, COV-20145 and COV-2069, the estimated margins were ≥38 at single therapeutic or prophylactic doses and ≥ and ≥17 at repeated prophylactic doses

Genotoxicity

No genotoxicity studies were conducted for REGN-COV2. This is acceptable for an exogenous target and in line with ICH S6(R1).

Carcinogenicity

No carcinogenicity studies were conducted for REGN-COV2. This is acceptable for an exogenous target and in line with ICH S6(R1).

Reproduction Toxicity

During the GLP 4-week repeat-dose toxicology study conducted in cynomolgus monkeys (2.2 to 4.0 years old) (R10933-TX-20064), there were no drug-related macroscopic or microscopic changes in the testes, epididymides, ovaries, uterus, or vagina. The study did not identify any potential risks to fertility. Because REGN10933 and REGN10987 are directed against an exogenous target (SARS-CoV-2), dedicated reproductive and developmental toxicology studies or studies in juvenile animals were not conducted, consistent with the ICH S6(R1). This is also supported by the lack of cross reactivity with reproductive or foetal tissues in the tissue cross reactivity studies (see further below).

Toxicokinetic data

In the GLP 4-week repeat-dose toxicology study, continuous exposure to total REGN10933, total REGN10987, or total REGN-COV2 was maintained in all drug-treated animals throughout the treatment period with detectable concentrations observed in all drug-treated animals through the end of the recovery period. Dose-proportional increases in exposure were observed across the individual mAb and combination dose groups during the treatment and the recovery periods, indicating that linearity in PK was maintained throughout the study and there was no impact on the TK of the individual REGN10933 or REGN10987 mAbs when given in combination. Results are summarised in Table 8.

Table 8. Summary of toxicology study design and toxicokinetics of total REGN10933, total REGN10987 and total REGN-COV2 in the Cynomolgus monkey (Study R10933-TX-20064)

Study No.	Module 2.6.7 Cross-Reference	Administered mAb (Measured)	Description (Compliance)	Dosing Route	N/Sex	Dose Level/Frequency (Total Number of Doses)	Accumulation Ratio	Approximate Number of Doses to Reach Steady State	Sex-Related Effect
Repeat-Dose Toxicology									
R10933-TX-20064	2.6.7.7	REGN10933 (total Hu IgG)	4-week study with an 8-week recovery period (GLP)	IV	5M/5F	50 mg/kg/week (total of 4 doses)	2.7	4	None
		REGN10987 (total Hu IgG)		IV	5M/5F	50 mg/kg/week (total of 4 doses)	2.6	4	
		REGN-COV2 (total Hu IgG)		IV	5M/5F	50/50 mg/kg/week[a] (total of 4 doses)	2.4	4	
		REGN-COV2 (total Hu IgG)		IV	5M/5F	150/150 mg/kg/week[a] (total of 4 doses)	1.8	4	
		REGN-COV2 (total Hu IgG)		SC	5M/5F	150/150 mg/kg/week[a] (total of 4 doses)	1.9	4	

[a] Administration of REGN10933 and REGN10987 were sequentially dosed, with REGN10933 dosed first. Any timed collection(s) were based off completion of the second administration.

C_{trough}, Last concentration in a dosing interval; GLP, Good Laboratory Practice; Hu, Human; IV, Intravenous; F, Female; M, Male; mAb; Monoclonal antibody; N, Number of animals; SC, Subcutaneous; TK, Toxicokinetics

Notes: Accumulation ratio was calculated as: Mean C_{trough} at Dose 4/mean C_{trough} at Dose 1.

REGN10933 or REGN10987 was administered via a bolus IV injection or a slow bolus SC injection at a volume of 2 mL/kg.

No apparent impact of ADA on total REGN10933 and total REGN10987 concentration-time profiles was observed in the definitive PK study or in the toxicology study. However, in the pilot PK study, 1 animal that received 1 mg/kg REGN10987 via IV injection exhibited a precipitous decline in serum concentrations of REGN10987 after dosing. Concentrations considered to be impacted by ADA were excluded from mean concentration calculations and NCA.

Local Tolerance

Local tolerability of the IV administration of REGN10933 and REGN10987 alone or the IV or SC administration of REGN-COV2 was evaluated in the GLP 4-week repeat-dose toxicology study in cynomolgus monkeys (R10933-TX-20064). There were no drug-related macroscopic or microscopic findings at the IV or SC administration sites.

Other toxicity studies

Antigenicity

Serum samples were not analysed for potential ADA formation/ This was assessed by visual inspection of individual concentration-time profiles in the single-dose pilot PK study (R10933-PK-20074), the single-dose definitive PK study (R10933-PK-20071), and the 4-week repeat-dose toxicology study (R10933-TX-20064). The overall impact of ADA was low and generally dose independent. The observed potential ADA responses in monkeys are not necessarily predictive of immunogenicity in humans and did not affect the ability to characterize the PK or safety profiles of REGN10933, REGN10987, or REGN-COV2 in the monkey studies. It is however not clear whether the method used to quantitate REGN-COV2 in monkey serum actually will report a reduction in REGN-COV2 exposure as a result of neutralizing ADAs.

Immunotoxicity

No drug-related hematologic changes or changes in plasma cytokine concentrations observed during the GLP 4-week repeat-dose toxicology study in cynomolgus monkeys. In addition, no drug-related macroscopic or microscopic findings were noted in the bone marrow, thymus, spleen, lymph nodes, or liver. *GLP-Tissue Cross reactivity studies (R10933-TX-20129, R10933-TX-20065)*

In the *ex vivo* tissue cross-reactivity studies, there was no off-target binding of REGN10933 or REGN10987 in any of the human or monkey tissues or human fetal tissues evaluated, which was anticipated as both mAbs bind an exogenous protein.

2.3.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) was submitted including an acceptable justification for not providing ERA studies. Considering the nature of Ronapreve, which consists of large proteins, these are not expected to be stable or remain biologically active in the environment and unlikely to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The applicant applied a comprehensive set of *in vitro* studies to analyse binding sites, structural analysis of the REGN-COV2-target-complex, binding affinities and concentration-dependent blocking of SARS-CoV-2 RBD to human ACE2. Results demonstrated that REGN10933 and REGN10987 (casirivimab and imdevimab) bind specifically to non-overlapping epitopes of the RBD of the spike glycoprotein of SARS-CoV-2, thereby neutralizing virus infectivity by blocking binding to human angiotensin converting enzyme 2 (ACE2). As no RBD residues are shared by REGN10933 and REGN10987, a single point mutation is unlikely to affect both epitopes, supporting the rationale for co-development (REGN-COV2) of the two mAbs. The results support the development of the combinational treatment using REGN10933 and REGN10987 (REGN-COV2), aiming to decrease the potential for loss of efficacy caused by (naturally) evolving variants during Covid-19 pandemic.

Sequence analysis revealed that the epitopes bound by REGN-COV2 are conserved in (as of March 2021) circulating variants.

Functional *in vitro* characterisation demonstrated that ADCP and ADCC, but not CDC activity are part of the mode of action of REGN-COV2. In addition, REGN-COV2 and the individual mAbs were shown to neutralise SARS-CoV-2 virus infectivity in a dose dependent-manner *in vitro*. It is understood that these effector functions are anticipated and contribute to the mode of action. Based on current literature, the role of antibody effector function in protection against SARS-CoV-2 is unknown, however, it has been well established that it plays an important role in mAb therapeutic efficacy against other viruses. In addition, effector cells including macrophages and monocytes have also been shown to be important for antibody-mediated protection from SARS-CoV-1 infection (Yasui et al., 2014).

Overall, the anticipated biological activity for REGN-COV2 is considered demonstrated.

Moreover, the development of viral escape mutants affecting the potency of anti-SARS-CoV-2 mAbs appear to be minimised due to the combinational treatment (REGN-COV2) as demonstrated by *in vitro* and *in vivo* macaque data.

Notably, REGN-COV2 retained neutralisation activity *in vitro* against different RBD (aa R319-F541) variants of SARS-CoV-2 S protein in circulation as of October 2021.

The variants/mutants were identified *in vitro* under antibody pressure with anti-S protein mAbs (R10933-PH-20100), as well as S protein variants identified from preclinical animal studies, clinical trials, and publicly available sources of SARS-CoV-2 virus in circulation. WT SARS-CoV-2 or the S protein variant, D614G, the predominant globally circulating SARS-CoV-2 virus (Yurkovetskiy, 2020), was used as the reference virus to calculate fold changes for each variant tested in these assays.

Importantly, REGN-COV2 retained neutralization potency against the full sequences or key residues of the B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.1/2 (Delta) variants of interest/concern as defined by the CDC (CDC, 2021). Likewise, REGN-COV2 neutralized the L452R and E484K mutations, which have been identified in multiple variants of interest/concern such as B.1.427/9 (Espilon) and B.1.526 (Iota), respectively, and have been flagged by the CDC as substitutions of therapeutic concern (CDC, 2021). None of the variants of interest/concern resulted in complete loss of neutralization of REGN10933 or showed any impact on REGN10987.

Further neutralization studies were performed using authentic SARS-CoV-2 isolates of the B.1.617.1, B.1.1.7, and B.1.351 variants of interest/concern. In alignment with neutralization data using pseudo-particles, REGN10933, REGN10987, and REGN-COV2 mediated neutralisation of authentic SARS-CoV-2 isolates from the B.1.617.1, B.1.1.7, and B.1.351 lineages in a concentration-dependent manner. Notably, REGN-COV2 retained neutralization potency against all tested authentic isolates of variants of interest/concern compared with reference virus (Washington-1 isolate).

In summary, assessment of the REGN-COV2 combination for neutralization potency against full sequences or key residues identified in the S protein of variants of interest/concern (CDC, 2021) (McCormick, 2021) has demonstrated that the combination retains potency against all of these variants. The applicant will continuously monitor emergent variants and inform the Agency on REGN-COV2 neutralization activity against circulating SARS-COV2 RBD variants, once available.

Monotherapy with individual anti-S protein mAbs, but not combination REGN-COV2, results in the rapid selection of viral escape mutants *in vitro* and a functional impact on neutralisation potency of the individual mAbs, whereas the potency of REGN-COV2 was retained within 10-fold. These results further support the development of the combinational anti-SARS-CoV-2 S mAbs as the development of escape mutants, appear to be minimised due to the combination of REGN10933 and REGN10987.

In vitro studies conducted to assess the potential risk for ADE of viral infection indicate that REGN10987 alone or in combination with REGN10933 (REGN-COV2) mediates entry of pVSV-SARS-CoV-2-S pseudoparticles into two out of five FCGR+ cell lines. REGN10933 alone did not mediate entry of pVSV-SARS-CoV-2-S pseudoparticles into any of the tested cell lines. The clinical translation of these results and their relevance is however currently unclear.

To assess the likelihood of ADE in a more physiologically relevant *in vitro* system, a study using SARS-CoV-2 virus and FCGR-positive primary monocyte-derived macrophages (MDMs) from 2 human donors was conducted. Neither REGN10933, REGN10987, nor REGN-COV2 demonstrated any evidence of mediating ADE, as evidenced by very low (<1.4%) viral antigen-positive MDMs, independent of whether the cells were untreated or incubated with anti-S protein mAbs or isotype control. Lack of ADE is currently supported by *in vivo* studies data from the SARS-CoV-2 infection rhesus macaque and the Syrian Golden Hamster model (see *in vivo* primary pharmacology section). There was no evidence of ADE *in vivo* using the Syrian Golden Hamster model, as prophylactic REGN-COV2 administration at all tested dose levels (including low and sub-neutralizing dosing) did not result in enhanced body-weight loss, increased viral load, or more severe lung pathology. The applicant concluded that these data indicate a lack of evidence for ADE of viral infectivity. Overall, based on the data provided it is agreed that the REGN-COV2 itself does not trigger/mediate ADE in the model system used.

In vivo PoC studies (therapeutic and prophylactic administration) were conducted in NHP rhesus macaque monkeys and Syrian Golden Hamsters. The use of two animal models to capture the diverse pathology of SARS-CoV-2 infection is acknowledged and accepted.

Therapeutic administration of REGN-COV2 at 25 mg/kg or 150 mg/kg in rhesus macaques infected with SARS CoV-2 resulted in accelerated viral clearance in nasopharyngeal swabs and oral swabs, as well as

reduced lung pathology, relative to placebo-treated animals. Prophylactic administration (50 mg/kg IV) 3 days prior to challenge with SARS-CoV2 reduces viral load in the upper and lower airways.

Therapeutic administration of REGN-COV2 at 5 mg/kg and 50 mg/kg doses in SARS-CoV-2 infected hamsters provided a therapeutic benefit as demonstrated by limited weight loss relative to placebo treated animals. Additionally, the prophylactic administration of REGN-COV2 at doses ≥0.5 mg/kg resulted in less severe lung pathology.

Overall, based on the comprehensive *in vitro* and *in vivo* studies currently presented the proof-of-concept is considered established and the data provided support the development of the combinational treatment of REGN10933 and REGN10987. REGN-COV2 reduces viral load and replication of SARS-CoV-2 in airways of animals, and thereby reduce infection mediated lung pathology in these models.

Pharmacokinetics

To support clinical development, the intravenous (IV) and subcutaneous (SC) pharmacokinetics (PK) and toxicokinetics (TK) of REGN10933 and REGN10987 given alone and in combination as REGN-COV2 were characterized following individual or combined administration to cynomolgus monkeys.

Serum samples were not analysed for potential ADAs. No apparent reductions in exposure were seen on individual concentration-time profiles from the definitive PK study or the toxicity study.

Overall, the nonclinical PK data obtained for REGN-COV2 were as predicted for mAbs directed against an exogenous target, with linear kinetics demonstrated for both REGN10933 and REGN10987 when administered alone as well as in combination across all studies, and no impact on the PK and TK of the individual REGN10933 and REGN10987 mAbs was observed when given in combination.

Toxicology

A short-term safety study was conducted in a single species (cynomolgus monkey) as REGN10933 and REGN10987 are directed against an exogenous target. This is consistent with ICH S6(R1) and CHMP Scientific Advice.

Once weekly administrations of REGN10933 alone, REGN10987 alone, and REGN-COV2, were well tolerated at all dose levels, with no drug-related or adverse effects evident. In addition, there were no drug-related macroscopic or microscopic findings at the IV or SC administration sites. Based on the lack of adverse effects, the NOAEL is considered to be 50 mg/kg REGN10933 and 50 mg/kg REGN10987 when administered alone and 150 mg/kg/antibody (total dose of 300 mg/kg) for REGN-COV2, the highest doses evaluated. The absence of adverse findings in the repeat-dose toxicity study was anticipated, given that REGN-COV2 binds to an exogenous viral target.

Based on exposure levels at NOAEL and the human exposure levels calculated from population PK models for REGN10933 and REGN10987, generated by interim data from clinical studies COV-2067, COV-20145 and COV-2069. the provided data support substantial exposure margins between NOAEL in repeat-dose toxicity studies in monkeys and intended clinical use of REGN-COV2.

Based on the exogenous binding targets of the product, and the lack of other findings in non-infected animals, an immunotoxic potential of REGN-COV2 is not expected

In the *ex vivo* tissue cross-reactivity studies, there was no off-target binding of REGN10933 or REGN10987 in any of the human or monkey tissues or human fetal tissues evaluated, which was anticipated as both mAbs bind an exogenous protein.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, Ronapreve (casirivimab and imdevimab) is recommended for marketing authorisation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Study Population	Dosage and Dosage Regimen	Study Status/ Cut-off date/Data included in application
Treatment Studies			
COV-2067 Phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol.	**Phase 1 and 2:** Adult, non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. **Phase 3:** Non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. Cohort 1: ≥18 years of age Cohort 2: 0 to <18 years of age Cohort 3: Pregnant at randomization	**Phase 1 and 2:** Casirivimab+imdevimab IV single dose: • 8000 mg (4000 mg per mAb) • 2400 mg (1200 mg per mAb) Placebo IV single dose **Phase 3:** Cohort 1 and cohort 3 patients ≥18 years: • Casirivimab+imdevimab 1200 mg (600 mg per mAb) IV single dose • Casirivimab+imdevimab 2400 mg (1200 mg per mAb) IV single dose Cohort 2 and cohort 3 patients <18 years: Casirivimab+imdevimab lower-dose and higher-dose treatment arms tiered according to body weight. Cohort 1 and cohort 2[a] • Placebo IV single dose	Phase 1 and 2 complete. Phase 3 cohort 1: Primary analysis complete; follow-up ongoing. Phase 3 cohorts 2 and 3: enrollment ongoing; unblinded data not included in this application. **Cut-off:** 18 Feb 2021[b] **Data included in this application:** • Primary analysis of efficacy data from phase 3 cohort 1 (patients ≥18 years). • Integrated safety data from phase 1/phase 2 symptomatic patients/phase 3 cohort 1 up to the cut-off date. • Blinded safety data from phase 2 asymptomatic patients, phase 3 cohort 2 and phase 3 cohort 3 up to the cut-off date.
COV-20145 Phase 2, randomized, double-blind, placebo-controlled, parallel group study.	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) • 1200 mg (600 mg per mAb) • 600 mg (300 mg per mAb) • 300 mg (150 mg per mAb) Placebo IV *SC Single Dose:* Casirivimab+imdevimab: • 1200 mg (600 mg per mAb) • 600 mg (300 mg per mAb) Placebo SC single dose	Primary analysis complete; follow-up ongoing. **Cut-off:** 08 Feb 2021[b] **Data included in this application:** • Efficacy data from all patients randomized by 01 Feb 2021 and who completed primary efficacy endpoint visit on study day 7. All safety data from these patients up to the cut-off date.

Study	Study Population	Dosage and Dosage Regimen	Study Status/ Cut-off date/Data included in application
COV-2066 Phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol.	Hospitalized patients who have a positive diagnostic test for SARS-CoV-2 • **Cohort 1A**: hospitalized patients not requiring oxygen • **Cohort 1**: hospitalized patients requiring low-flow oxygen • **Cohort 2**: hospitalized patients requiring high-flow oxygen • **Cohort 3**: hospitalized patients requiring mechanical ventilation	• Casirivimab+imdevimab: 2400 mg (1200 mg per mAb) IV x 1 dose • Casirivimab+imdevimab: 8000 mg (4000 mg per mAb) IV x 1 dose • Placebo IV x 1 dose	Phase 1, 2 and 3 complete. **Data included in this application:** • Safety data for patients in cohort 1, (phase 1 and 2), cohort 2 (phase 2) and cohort 3 (phase 2). • Efficacy data from cohort 1 (phase 1 and 2).
Prevention Studies			
COV-2069 Phase 3, randomized, double-blind, placebo-controlled study.	Asymptomatic, healthy adults (≥18 years), adolescents (≥12 years to <18 years), and children (<12 years) who are household contacts to the first known household member with a diagnosis of SARS-CoV-2 infection. **Cohort A**: ≥12 years who are SARS-CoV-2 RT-qPCR negative at baseline. **Cohort A1**: <12 years who are SARS-CoV-2 RT-qPCR negative at baseline. **Cohort B**: ≥12 years who are SARS-CoV-2 RT-qPCR positive at baseline. **Cohort B1**: <12 years who are SARS-CoV-2 RT-qPCR positive at baseline	Participants ≥12 years: • Casirivimab+imdevimab: 600 mg of each mAb SC x 1 dose on day 1 • Placebo SC x 1 dose on day 1	Primary analysis of cohort A and cohort B complete; follow-up ongoing. **Data cut-off:** 11 Mar 2021[b] **Data included in this application:** • Efficacy and safety data from subjects randomized by 28 Jan 2021 in cohort A up to the cut-off date. • Blinded safety data from subjects randomized by 28 Jan 2021 in cohort A1 up to the cut-off date. No adolescents were enrolled into cohorts A or B at the time of the data cut off.
HV-2093 Phase 1, randomized, double-blind, placebo-controlled study.	Adult volunteers who are healthy or have chronic but stable and well-controlled medical condition(s), and negative at screening for SARS-CoV-2 infection	• Casirivimab+imdevimab: 1200 mg (600 mg per mAb) SC Q4W x 6 doses • Placebo SC Q4W x 6 doses	Interim analysis complete; study ongoing. **Data cut-off:** 13 Mar 2021[b] **Data included in this application:** • Safety data from all subjects up to the cut-off date

a) Per Independent Data Monitoring Committee (IDMC) recommendation, as of February 25, 2021, patients will no longer be randomized to placebo

2.4.2. Pharmacokinetics

PK data have been generated after intravenous (IV) and subcutaneous (SC) dosing with Ronapreve, i.e. with IV or SC co-administration of casirivimab and imdevimab. The total doses of Ronapreve stated in this report reflect co-administration of equal amounts of the two components (e.g. 1200 mg Ronapreve equates with co-administration of 600 mg of each component).

All submitted clinical studies collected some PK data as summarised below.

COV-2069 Cohort A provided PK data after a single SC dose of 1200 mg in generally healthy adults not infected with SARS-CoV-2.

COV-2069 Cohort B provided PK data after a single SC dose of 1200 mg in generally healthy and asymptomatic adults infected with SARS-CoV-2.

HV-2093 enrolled generally healthy volunteers adults not infected with SARS-CoV-2, with or without underlying stable conditions. This study involved SC dosing every 4 weeks for 6 months with 1200 mg.

COV-2067 provided PK data from infected and non-hospitalised symptomatic subjects who received single IV doses of Ronapreve (1200 mg, 2400 mg or 8000 mg) for treatment of COVID-19.

COV-2066 provided PK data from hospitalised subjects who received single IV doses of Ronapreve (2400 mg or 8000 mg) for treatment of COVID-19.

COV-20145 compared IV and SC dosing in parallel groups of infected adults, with or without COVID-19 symptoms.

Data have been analysed by non-compartmental and population PK analyses.

Pharmacokinetic data from studies COV-2067, COV-20145, and COV-2069 (A and B) were included in the population PK dataset for the estimation of pop PK models for casirivimab and imdevimab. As the observed data indicated comparable PK of both mAbs, the final population PK models for casirivimab

and imdevimab have the same 2-compartmental structure with identical statistically significant covariates and similar PK parameter estimates. The parameters for casirivimab are listed in Table 9.

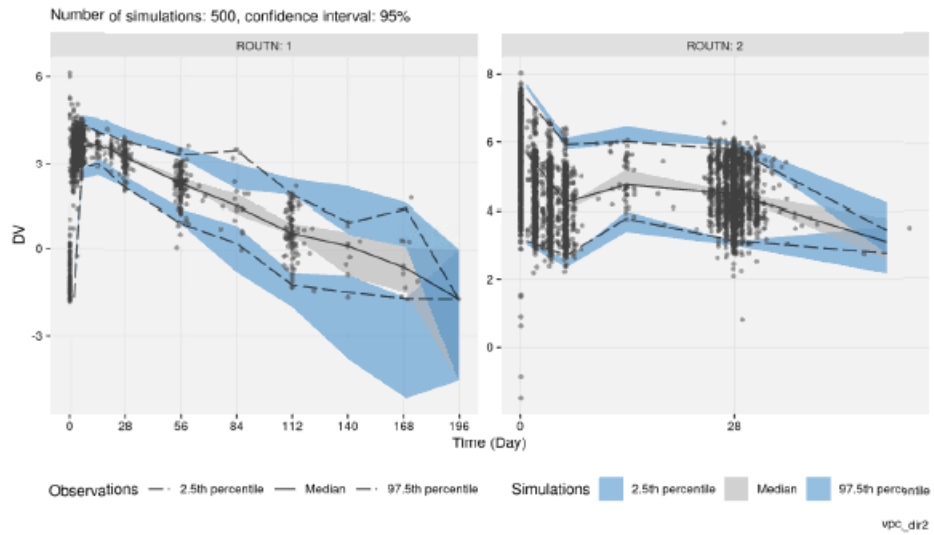
Table 9. Population PK parameter estimates and bootstrap confidence intervals for the final model for casirivimab

CL: Clearance (L/day)	0.182	2.21	0.182 (0.174,0.19)
Vc: Central Volume of Distribution (L)	3.875	1.52	3.881 (3.762,3.994)
Q: Intercompartmental Clearance (L/day)	0.583	7.09	0.581 (0.512,0.684)
Vp: Peripheral Volume of Distribution (L)	3.286	3.97	3.303 (3.046,3.553)
Ka: Absorption Rate Constant (1/day)	0.220	7.73	0.219 (0.19,0.254)
F1: Bioavailability	0.718	2.77	0.721 (0.678,0.762)
Weight on CL	0.900	4.48	0.898 (0.823,0.982)
Weight on Vc	0.579	6.77	0.575 (0.5,0.647)
Albumin on CL	-0.999	11.00	-1.004 (-1.22,-0.776)
Female on CL	-0.084	20.33	-0.084 (-0.115,-0.051)
Black Race on CL	0.122	26.54	0.123 (0.061,0.183)
Mild Hepatic Impairment on CL	0.081	25.56	0.08 (0.042,0.12)
Albumin on Vc	-0.553	21.78	-0.559 (-0.795,-0.326)
Female on Vc	-0.117	16.01	-0.118 (-0.155,-0.08)
Viral Load on CL	-0.011	35.68	-0.011 (-0.018,-0.004)
IIV in CL	0.048	25.00	0.048 (0.023,0.071)
IIV in Vc	0.152	17.87	0.15 (0.102,0.208)
Residual Variability	0.093	13.85	0.091 (0.071,0.119)
Objective Function	-6192.108		

Visual predictive check plots

The predictive performance of the final models for casirivimab and imdevimab was evaluated through an internal visual predictive check (VPC). From 500 simulated datasets conditioned upon the observed study designs, 90% confidence intervals (CIs) were calculated for the median, and the 5th and 95th percentiles of Mab concentration-time profiles. The simulated 90% CIs of the median, and VPC plots imdevimab stratified by route of administration are presented in Figure 6.

Figure 6. Visual predictive check plots for the final model of imdevimab.



DV = Log-transformed casirivimab concentration
Note: ROUTN:1 represents SC administration; ROUTN:2 represents IV administration.

Absorption

Casirivimab+imdevimab administered as a single dose of 1200 mg (600 mg each mAb) IV as a 1-hour infusion results in peak concentrations at the end of the infusion (100% bioavailability).

Following casirivimab+imdevimab administered as a single dose of 1200 mg SC (600 mg each mAb), casirivimab and imdevimab were absorbed with a population PK estimated bioavailability of 71.8% for casirivimab and 71.7% for imdevimab. Estimated tmax was 6.7 days (5th and 95th percentile: 4.4, 9.3) for casirivimab and 6.6 days (5th and 95th percentile: 4.4, 9.1) for imdevimab.

Mean Cmax (SD) reached after 600 mg SC single dose of casirivimab was 52.2 (12.15) mg/L, mean Cmax (SD) reached after 600 mg SC single dose of imdevimab was calculated to 49.2 (11.01) mg/L.

Absorption rate constants ka have been estimated by pop PK analyses to 0.220 (1/day) for casirivimab and to 0.197 (1/day) for imdevimab.

Population PK predicted exposure metrics (i.e., Cmax, AUC0-28, and AUC0-inf) for casirivimab and imdevimab were comparable after either a single 1200 mg (600 mg per mAb) IV dose, or a single 1200 mg (600 mg per mAb) SC dose (Table 10).

Table 10. Population PK exposure predictions for casirivimab and imdevimab following single dose of 1200 mg (600 mg per mAb) SC or IV

		600 mg Single Dose SC				600 mg Single Dose IV			
	Exposure Metrics	Median	Mean	SD	5th, 95th percentiles	Median	Mean	SD	5th, 95th percentiles
Casirivimab	$AUC_{0\text{-}28}$ (mg*day/L)	1102.4	1121.7	243.12	751, 1545.5	1721.5	1754.9	380.50	1184.3, 2414.3
	AUC_{inf} (mg*day/L)	2390.0	2559.5	890.35	1416.9, 4236.1	3327.0	3563.6	1239.61	1973.9, 5898.1
	C_{28} (mg/L)[1]	29.6	30.5	7.55	19.4, 44.1	36.8	37.9	10.33	22.4, 56.6
	C_{max} (mg/L)[2]	51.6	52.2	12.15	33.1, 72.6	166.9	182.7	81.45	81.4, 333.8
Imdevimab	$AUC_{0\text{-}28}$ (mg*day/L)	1001.4	1016.9	203.92	708.3, 1370.2	1573.8	1600.8	320.88	1119, 2152.6
	AUC_{inf} (mg*day/L)	1957.5	2073.3	628.60	1235, 3227.1	2729.0	2890.5	876.31	1722, 4498.9
	C_{28} (mg/L)[1]	25.2	25.9	6.07	16.9, 36.7	30.3	31.0	8.24	18.5, 45.8
	C_{max} (mg/L)	48.7	49.2	11.01	31.8, 67.6	166.9	181.7	77.78	83.7, 324.8

$AUC_{0\text{-}28}$ = Area under the concentration time curve from time 0 to day 28; AUC_{inf} = Area under the concentration time curve from time 0 to infinity; C_{28} = Concentration on day 28 following single dose; C_{max} = Maximum (peak) concentration; IV = Intravenous; SC = Subcutaneous; SD = Standard deviation

As expected, serum levels of casirivimab and imdevimab in the initial days after dosing are higher with IV vs. SC dosing. SC administration gives a much lower Cmax and longer Tmax (about 6.5 days) for casirivimab and imdevimab. Lower AUCs for each of casirivimab and imdevimab when the same dose is given SC vs. IV but by Day 28 the serum levels (C28) are similar for the two dosing routes.

Data from COV-20145 show the effect of the longer Tmax and reduced bioavailability on serum concentrations after a 1200 mg SC dose vs. a 1200 mg IV dose. On day 2, the mean serum casirivimab and imdevimab concentrations were ~115 mg/L for both components after 1200 mg IV compared to ~42 mg/L for each after 1200 mg SC. Similarly, the day 6 serum concentrations were in the range 80-90 mg/L after 1200 mg IV vs. ~55 mg/L after 1200 mg SC.

Distribution

As is typical for a mAb, the distribution of casirivimab and imdevimab is primarily restricted to the vascular compartment. Based on population PK analysis, the central volume of distribution (Vc) and the peripheral volume of distribution (Vp) for casirivimab are estimated to 3.9 L and 3.3 L and for imdevimab to 3.9 L and 3.6 L, respectively. The total volume of distribution (calculated as the sum of Vc + Vp) of casirivimab is 7.161 L while that of imdevimab is 7.425 L.

Elimination

Consistent with other antibodies, the metabolism of casirivimab and imdevimab is expected to be limited to proteolytic catabolism to small peptides and individual amino acids by the endoplasmic reticulum system.
Based on population PK analysis, mean clearance (SD) and mean terminal elimination half-life of casirivimab (0.188 (0.054) L/day; 29.8 (8.14) days) and imdevimab (0.277 (0.0636) L/day; 26.2 (5.67) days) were comparable.

Dose proportionality and time dependencies

Dose ranging PK data following single IV (300 mg to 8000 mg) and SC (600 mg and 1200 mg) doses of casirivimab and imdevimab indicate overall a dose-proportional increase in exposure across the dose range studied (study COV-2067 and COV-20145). No dose-ranging PK data following multiple dosing are available to characterize dose-proportionality in steady state.

The observed concentration-time profiles of casirivimab and imdevimab in uninfected adult subjects (study HV-2093) and outpatients with COVID-19 (studies COV-2067, COV-20145) exhibited concentration-time profiles with a terminal elimination phase described by mono-exponential decline.

Multiple doses of 1200 mg SC were investigated in Study HV-2093 in healthy subjects. In non-infected adult subjects, based on the observed concentration versus time profiles, steady state was achieved following the third casirivimab+imdevimab 1200 mg SC Q4W dose (week 12) and was maintained throughout the remainder of the 24-week treatment period. After six 1200 mg SC Q4W doses, observed Cmax,ss and Ctrough,ss were 105 (37.9) mg/mL and 72.4 (31.3) mg/mL for casirivimab, and 83.0 (31.7) mg/mL and 50.5 (23.2) mg/mL for imdevimab, respectively. This results in serum accumulated approximately 2.2-fold and 2-fold based on Ctrough over the duration of treatment compared to the Ctrough after the first dose.

Special populations

None of the statistically significant covariates identified by the population PK models (body weight, albumin, viral load (log10 copies/mL), Black (race), mild hepatic impairment, or gender) indicate a meaningful impact on exposures of casirivimab and imdevimab. No dose adjustment based on these covariates is deemed warranted.

Elderly

The population PK analysis included data from subjects from 18 to 96 years and advancing age was not identified as a significant covariate on PK for casirivimab or imdevimab. Exposures to casirivimab and

imdevimab were similar in subjects aged <65, 65-74 and ≥ 75 years after IV or SC administration (data not shown).

The number of subjects above 65 years for each clinical trial are summarised in Table 11.

Table 11. Patients/Subjects by Study and Age Group (PK Analysis Set)

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
COV-2066	297/1373	202/1373	85/1373
COV-2067	223/2926	69/2926	11/2926
COV-2069	8/169	6/169	1/169
COV-20145	0/685	2/685	0/685
HV-2093	79/724	11/724	0/724
ALL TRIAL SUBJECTS	607/5877	290/5877	97/5877

Paediatric population

For study COV-2067, concentration results for casirivimab and imdevimab for the paediatric dose equivalent to the adult 1200 mg IV dose are available for a total of 24 paediatric patients (N=19 at weight ≥ 40 kg), and in 26 paediatric subjects (N=22 at weight ≥ 40 kg) for the paediatric dose equivalent to the adult 2400 mg IV dose. For study COV-2069, casirivimab and imdevimab concentration results for the paediatric dose equivalent to the adult 1200 mg SC dose are available for a total of 65 paediatric subjects (N=64 at weight ≥ 40 kg).

The observed casirivimab and imdevimab Ceoi and C28 values for paediatric subjects in the ≥40 kg body weight tiers (COV-2067) were similar to those values observed in adult outpatients following the 1200 and 2400 mg IV doses, Concentrations of casirivimab and imdevimab in serum in adolescents following SC administration in the ≥40 kg body weight tiers at both 28 and 112 days after dosing were similar to observed values in adults following a single 1200 mg SC dose (COV-2069).

Observed concentrations were consistent with population PK predicted values as shown by external validation.

The expected exposure for casirivimab and imdevimab in adolescents is listed in Tables 12, 13 and 14.

Table 12. Exposure predictions for casirivimab in adolescents (age 12-18 years) following dose equivalent to 1200 mg (600 mg per mAb) IV or SC single does by weight categories

Casirivimab Dose	Weight Group		Median	Mean	SD	5th Percentile	95th Percentile
600 mg IV	≥40 kg	$AUC_{0\text{-}28}$ (mg*day/L)	1867.4	1945.4	534.0	1199.8	2949.8
		AUC_{inf} (mg*day/L)	3844.0	4006.7	1145.9	2394.4	6155.9
		C_{max} (mg/L)	171.3	190.2	91.3	80.8	367.0
		C1 (mg/L)	142.6	151.9	59.5	73.7	267.7
		C2 (mg/L)	119.8	125.5	41.6	66.3	200.0
		C4 (mg/L)	92.7	95.7	26.5	57.3	144.9
		C7 (mg/L)	73.8	76.3	20.0	48.2	114.1
		C28 (mg/L)	41.4	43.0	11.6	26.6	65.9

600 mg SC	≥40 kg	AUC_{0-28} (mg*day/L)	1210.3	1258.2	355.1	758.6	1921.3
		AUC_{inf}(mg*day/L)	2788.0	2918.9	860.5	1735.6	4524.6
		C_{max} (mg/L)	54.7	57.6	17.6	33.0	90.3
		C1 (mg/L)	22.4	24.4	10.9	11.0	43.7
		C2 (mg/L)	36.7	39.3	15.8	18.6	67.1
		C4 (mg/L)	50.6	53.1	18.3	27.7	85.9
		C7 (mg/L)	54.2	56.8	17.0	32.2	87.8
		C28 (mg/L)	33.7	35.0	9.5	21.8	52.5

Table 13. Exposure predictions for casirivimab in adolescents (age 12-18 years) following dose equivalent to 600 mg (300 mg per mAb) IV or SCQ4W maintenance with 1200mg (600 mg per mAb) IV or SC loading dose by weight categories

Casirivimab Dose	Weight Group		Median	Mean	SD	5th Percentile	95th Percentile
300 mg IV Q4W with 600 mg IV Loading Dose	≥40 kg	$AUC_{tau,ss}$ (mg*day/L)	1894.8	1983.3	564.62	1197.2	2980.1
		$C_{max,ss}$ (mg/L)	134.1	144.2	52.12	79.1	234.3
		$C_{min,ss}$ (mg/L)	45.7	48.0	16.78	24.7	77.7

Table 14. Exposure predictions for imdevimab in adolescents (age 12-18 years) following dose equivalent to 600 mg (300 mg per mAb) IV or SCQ4W maintenance with 1200mg (600 mg per mAb) IV or SC loading dose by weight categories

Imdevimab Dose	Weight Group		Median	Mean	SD	5th Percentile	95th Percentile
300 mg IV Q4W with 600 mg IV Loading Dose	≥40 kg	$AUC_{tau,ss}$ (mg*day/L)	1580.0	1643.2	430.95	1024.4	2421.9
		$C_{max,ss}$ (mg/L)	123.2	133.1	48.68	73.0	218.9
		$C_{min,ss}$ (mg/L)	34.9	36.6	12.03	19.9	58.5

Target population

In the target population, at the recommended clinical dose of 1200 mg SC (600 mg per mAb) IV and SC, concentration-time profiles for casirivimab and imdevimab were comparable between studies COV-2067 and COV-20145 (IV), across studies COV-2069A, COV-2069B, and COV-20145 (SC) and consistent with the population PK model simulated concentrations, respectively, including external validation of PK data from healthy subjects (Study HV-2093).

No differences in concentration-time profiles for casirivimab and imdevimab were observed in SARS-CoV-2 infected and uninfected subjects. PK results indicate that COVID-19 disease severity, baseline viral load and serostatus did not affect the PK of either casirivimab or imdevimab for the IV and SC dose groups.

Pharmacokinetic interaction studies

No formal PK interaction studies have been performed with casirivimab and imdevimab.

2.4.3. Pharmacodynamics

The pharmacodynamics (PD) of casirivimab+imdevimab was evaluated in multiple studies comprised of different participant populations across the COVID-19 disease spectrum, including study COV-2067 phase 1/2 and phase 3, study COV-20145 and study COV-2069 cohort B.

The PD effect of casirivimab+imdevimab was assessed by measuring SARS-CoV-2 viral load reduction (as measured by RT-qPCR), which is a direct effect of the mechanism of action to block viral entry and prevent infection of host cells.

Mechanism of action

Casirivimab+imdevimab (REGN10933+REGN10987) is a cocktail of two human immunoglobulin G1 (IgG1) monoclonal antibodies (mAbs) directed against different, non-overlapping epitopes in the spike (S) protein receptor binding domain (RBD) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The antibodies are developed for the treatment or prevention (acute and chronic) of SARS-CoV-2 infection in adults and paediatric individuals (≥40 kg).

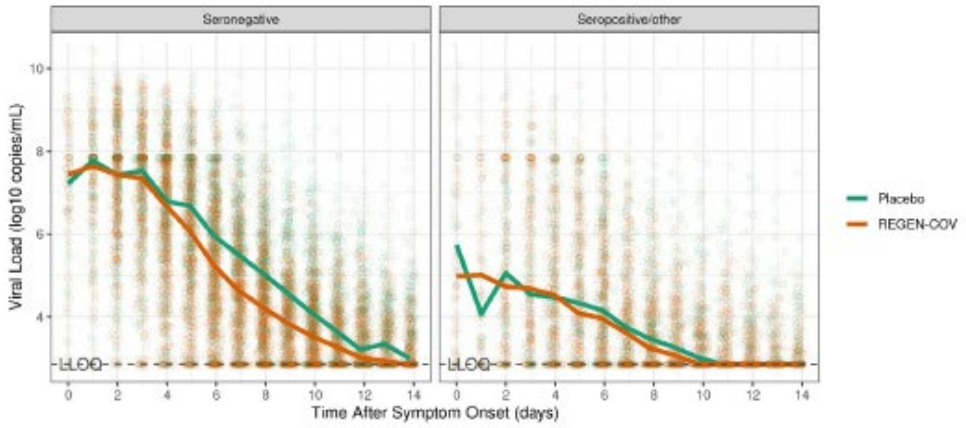
Primary and Secondary pharmacology

A population PK/PD model for viral dynamics was developed to describe the relationship between the PD response of SARS-CoV-2 viral load measured in NP swabs collected in patients from the 3 studies, COV-2067, COV-20145, COV-2069B, and casirivimab and imdevimab. Based upon the assumption that a reduction in viral load is related to improved clinical outcomes, the overall goal of these population exposure-response analyses was to identify the casirivimab+imdevimab doses that are expected to provide near-maximal antiviral activity. The model was used to simulate the viral load-time profile, predict the total viral load versus infectious viral load time profile, and predict the viral load-time profile for different treatment start dates relative to onset of symptoms. The predicted individual exposure metrics for casirivimab and imdevimab from the final population PK models were used as inputs for this population PK/PD modelling.

Descriptive dose-response analyses investigating the relationship between viral load (PD biomarker) reduction and exposure metrics were conducted for clinical studies COV-2067 and COV-20145 in SARS-CoV-2-infected individuals.

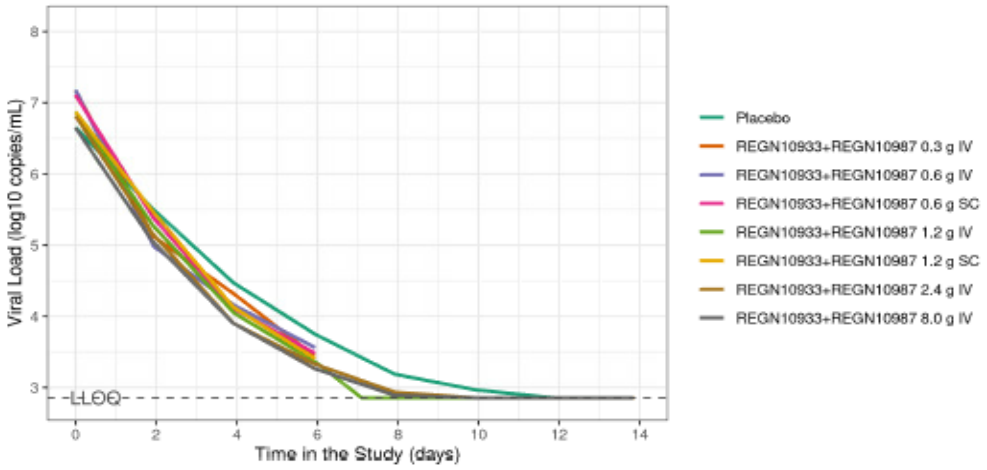
A summary and visualisation of the data is provided in Figures 7 and 8.

Figure 7. Viral load over time grouped by placebo versus casirivimab+imdevimab treatment and stratified by SARS-CoV-2 serology status



Note: Open circles are horizontally jittered observed data, lines are median of observed dataset, LLOQ is lower limit of quantification of the assay.

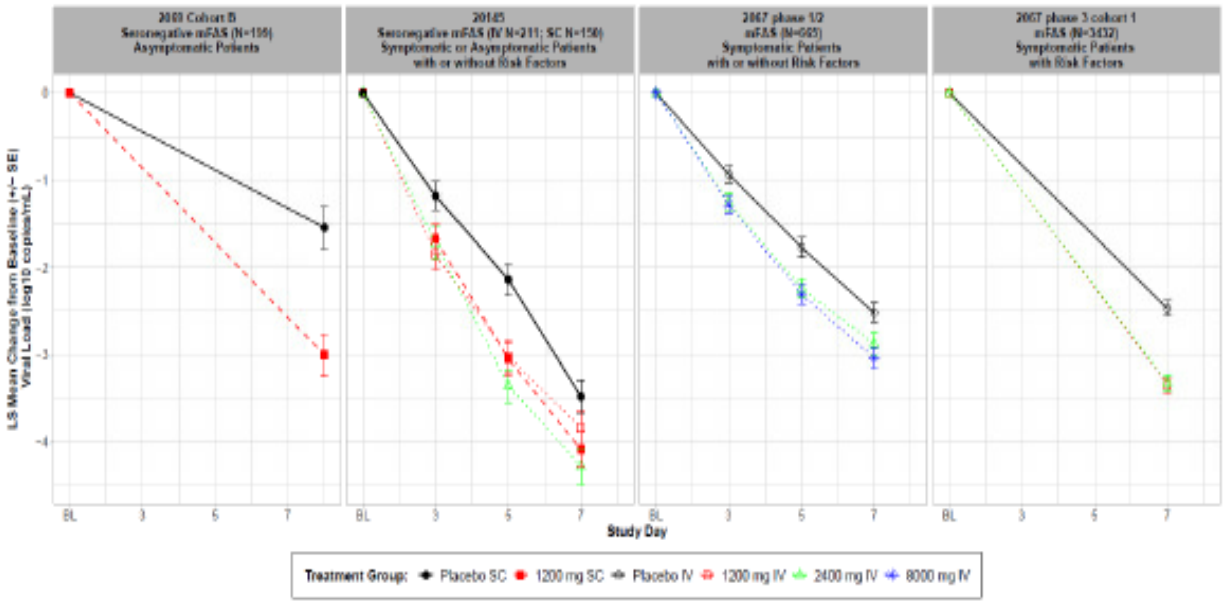
Figure 8. Viral load over time grouped by placebo versus casirivimab+ imdevimab dose regimens



Note: Lines are median of observed dataset, LLOQ is lower limit of quantification of the assay.

Viral load reduction for all casirivimab+imdevimab IV (1200, 2400, and 8000 mg) and SC (1200 mg) dose regimens was greater than placebo and similar in magnitude (Figure 9).

Figure 9. Mean (±SE) viral load (log_{10} copies/mL) over time for studies supporting the treatment indication



N/treatment group	2069 cohort B	20145	2067 phase 1/2	2067 phase 3 cohort 1
placebo	97	73-77	208-231	1234-1334
1200 mg SC	95	73-77	NA	NA
1200 mg IV	NA	67-72	NA	691-734
2400 mg IV	NA	6-62	198-215	1277-1353
8000 mg IV	NA	NA	199-219	NA

mFAS, modified full analysis set

The change from baseline in SARS-CoV-2 viral load or time-weighted average change from baseline in SARS-CoV-2 viral load exhibited flat concentration-response relationship over the dose range studied, for either IV or SC dosing, in the overall and seronegative populations (Table 15).

Table 15. Time-weighted average daily change from baseline in viral load in NP samples from day 1 to day 7 (Study COV-20145, Seronegative mFAS)

Hierarchy Number	Casirivimab+Imdevimab Treatment Group (Versus Pooled Placebo)	Difference (log_{10} copies/mL)[1]	95% CI[1]	p-value[1]
1	**2400 mg IV vs Pooled Placebo** (n=61 vs n=74)	-0.71	(-1.05, -0.38)	<0.0001
2	**1200 mg IV vs Pooled Placebo** (n=67 vs n=74)	-0.56	(-0.89, -0.24)	0.0007
3	**1200 mg SC vs Pooled Placebo** (n=71 vs n=74)	-0.56	(-0.87, -0.24)	0.0007
4	**600 mg IV vs Pooled Placebo** (n=66 vs n=74)	-0.66	(-0.99, -0.34)	<0.0001
5	**600 mg SC vs Pooled Placebo** (n=71 vs n=74)	-0.56	(-0.88, -0.24)	0.0006
6	**300 mg IV vs Pooled Placebo** (n=76 vs n=74)	-0.57	(-0.88, -0.25)	0.0004

1. LS Means difference, 95% CI, and p-value for change from baseline is based on the ANCOVA model with terms for treatment, baseline, and baseline-by-treatment interaction.

As both therapeutic mAbs are targeting an external target, no secondary PD effects are expected.

Model-based results

The presence of a high-risk factor for severe COVID-19 illness was associated with a 4.81% decrease in the elimination rate of productively infected cells while seropositive/other status at baseline was associated with a 110% increase in elimination rate of productively infected cells.

Exploratory PK/PD analyses across studies and doses (COV-2067, COV-20145, COV-2069) indicate no dose- and exposure response relationship with respect to dose- or exposure-related effects on viral load data (change from baseline at day 7). This is in line with results from population PK/PD analysis of viral dynamics also suggesting that all studied doses result in maximum effect on the PD marker. All doses regardless of route of administration and dose strength increased the decline in viral load compared to placebo to the same extent.

Concentrations of Casirivimab and Imdevimab in Serum Required to Neutralize SARS-CoV-2 Reference Viruses and VOI/VOCs

Concentrations of casirivimab+imdevimab in serum required to achieve IC90 for different virus strains are provided in the Tables 16 and 17.

Table 16. Concentrations of casirivimab+imdevimab combined in serum at various times relative to concentrations in serum required to achieve in vitro neutralisation (IC_{90}) in respiratory tract fluids for SARS-CoV-2 variants for 1200 IV mg dose

SARS-CoV-2 Variant[1]			1200 mg IV[3] Casirivimab+Imdevimab			
Pango Lineage	WHO Label	$C_{s,target}$[2] (mg/L)	Ratio C_{eoi} / $C_{s,target}$	Ratio C_2 / $C_{s,target}$	Ratio C_6 / $C_{s,target}$	Ratio C_{28} / $C_{s,target}$
Reference Viruses						
Wild-type (Wuhan)	reference	3.76	88.7	61.6	37.8	17.8
D614G	reference	1.63	204	142	87.0	41.0
Variants of Concern/Interest						
B.1.351	Beta	1.56	214	148	91.1	42.9
B.1.1.7	Alpha	2.05	162	113	69.3	32.7
P.1	Gamma	2.37	141	97.6	60.0	28.3
L452R/T478K (B.1.617.2)	Delta	1.71	196	136	83.4	39.3
L452R/E484Q (B.1.617.1)	Kappa	4.02	83.0	57.6	35.4	16.7
Substitutions of Therapeutic Concern						
L452R	N/A	6.00	55.63	38.62	23.72	11.18
E484K	N/A	119.09	2.80	1.95	1.19	0.56

[1] Source: Appendix Section 7.2.1
[2] Concentration in serum required to achieve IC_{90} in respiratory tract fluid ($C_{s,target}$) = IC_{90}/Pc, where Pc = 0.01
[3] Population PK predicted median concentration of casirivimab+imdevimab combined at end of infusion (C_{eoi}) 333.8 mg/L; 2 days after dosing (C_2) 231.7 mg/L; 6 days after dosing (C_6) 142.3 mg/L; and 28 days after dosing (C_{28}) 67.1 mg/L

Table 17. Concentrations of casirivimab+imdevimab combined in serum at various times relative to concentrations in serum required to achieve in vitro neutralisation (IC_{90}) in respiratory tract fluids for SARS-CoV-2 variants for 1200 mg SC dose

SARS-CoV-2 Variant[1]			1200 mg SC[3] Casirivimab+Imdevimab			
Pango Lineage	WHO Label	$C_{s,target}$[2] (mg/L)	Ratio $C_{0.2}$ / $C_{s,target}$	Ratio C_2 / $C_{s,target}$	Ratio C_6 / $C_{s,target}$	Ratio C_{28} / $C_{s,target}$
Reference Viruses						
Wild-type (Wuhan)	reference	3.76	2.56	17.8	26.5	14.6
D614G	reference	1.63	5.90	40.9	61.0	33.5
Variants of Concern/Interest						
B.1.351	Beta	1.56	6.17	42.8	63.9	35.1
B.1.1.7	Alpha	2.05	4.69	32.6	48.6	26.7
P.1	Gamma	2.37	4.06	28.2	42.1	23.1
L452R/T478K (B.1.617.2)	Delta	1.71	5.65	39.2	58.5	32.1
L452R/E484Q (B.1.617.1)	Kappa	4.02	2.40	16.6	24.8	13.6
Substitutions of Therapeutic Concern						
L452R	N/A	2.72	3.54	24.60	36.69	20.15
E484K	N/A	7.54	1.28	8.87	13.24	7.27

[1] Source: Appendix Section 7.2.2
[2] Concentration in serum required to achieve IC_{90} in respiratory tract fluid ($C_{s,target}$) = IC_{90}/Pc, where Pc = 0.01
[3] Population PK predicted median concentration of casirivimab+imdevimab combined 0.2 days after dosing ($C_{0.2}$) 9.64 mg/L; 2 days after dosing (C_2) 66.9 mg/L; 6 days after dosing (C_7) 99.8 mg/L; and 28 days after dosing (C_{28}) 54.8 mg/L

Immunogenicity

Study COV-2067:

The immunogenicity analyses in this study are summarised in Table 18.

Table 18. Summary of ADA status by treatment group in ambulatory patients with COVID-19 (Study COV-2067, ADA analysis set).

Analyte ADA Status and Category	Placebo n (%)	R10933+R10987 1.2g IV n (%)	R10933+R10987 2.4g IV n (%)	R10933+R10987 8.0g IV n (%)	All Active Doses n (%)	Overall n (%)
R10933						
Total ADA Subjects	795 (100%)	124 (100%)	1238 (100%)	1122 (100%)	2484 (100%)	3279 (100%)
Negative at all Times	769 (96.7%)	122 (98.4%)	1201 (97.0%)	1091 (97.2%)	2414 (97.2%)	3183 (97.1%)
Positive at any time	21 (2.6%)	2 (1.6%)	12 (1.0%)	3 (0.3%)	17 (0.7%)	38 (1.2%)
Positive at baseline only	5 (0.6%)	0	25 (2.0%)	28 (2.5%)	53 (2.1%)	58 (1.8%)
R10987						
Total ADA Subjects	787 (100%)	123 (100%)	1204 (100%)	1090 (100%)	2417 (100%)	3204 (100%)
Negative at all Times	734 (93.3%)	119 (96.7%)	1146 (95.2%)	1027 (94.2%)	2292 (94.8%)	3026 (94.4%)
Positive at any time	45 (5.7%)	3 (2.4%)	20 (1.7%)	7 (0.6%)	30 (1.2%)	75 (2.3%)
Positive at baseline only	8 (1.0%)	1 (0.8%)	38 (3.2%)	56 (5.1%)	95 (3.9%)	103 (3.2%)

n = Number of patients.
Notes: Positive at any time: At least one positive result post 1st dose disregard of baseline ADA status. A phase 2 patient 840077027 received R10987 2.4 g IV is not presented. Only cohort 1 subjects in phase 3 were included in this analysis.

Although ADA titers have not yet been determined in the titer assay, the low intensity signals observed in the ADA screening assay suggested that titers in ADA positive samples were low. Comparison of drug concentrations between ADA positive and negative patients showed no difference between these 2 groups.

Study COV-2069:

The casirivimab and imdevimab ADA status by treatment group for the ADA analysis set are summarized in Tables 19 and 20 respectively.

Table 19. Summary of casirivimab ADA status by treatment group in subjects with household contact exposure to individuals with SARS-CoV-2 infection (Study COV-2069, AAS)

ADA Status	Placebo n (%)	R10933+R10987 1200 mg SC n (%)	Overall n (%)
ADA Analysis Set	447 (100%)	960 (100%)	1407 (100%)
Negative at all time	440 (98.4%)	920 (95.8%)	1360 (96.7%)
Positive at any time	7 (1.6%)	17 (1.8%)	24 (1.7%)
Positive at Baseline	0	23 (2.4%)	23 (1.6%)

n = Number of subjects
Note: Positive at any time: at least 1 post first dose positive result regardless of baseline ADA status.

Table 20. Summary of imdevimab ADA status by treatment group in subjects with household contact exposure to individuals with SARS-CoV-2 infection (Study COV-2069, AAS)

ADA Status	Placebo n (%)	R10933+R10987 1200 mg SC n (%)	Overall n (%)
ADA Analysis Set	441 (100%)	957 (100%)	1398 (100%)
Negative at all time	425 (96.4%)	909 (95.0%)	1334 (95.4%)
Positive at any time	14 (3.2%)	24 (2.5%)	38 (2.7%)
Positive at Baseline	2 (0.5%)	24 (2.5%)	26 (1.9%)

n = Number of subjects
Note: Positive at any time: at least 1 post first dose positive result regardless of baseline ADA status.

The presence of ADA did not affect concentration-time profiles of casirivimab or imdevimab, as the concentrations of casirivimab or imdevimab in subjects positive for ADA at any time were within the range of concentrations in subjects who were ADA negative at all times or ADA positive only at baseline.

Study HV-2093:

One (0.1%) and 14 (2.0%) subjects who received casirivimab+imdevimab experienced treatment-emergent ADA to casirivimab and imdevimab, respectively; the subject who had treatment-emergent ADA to casirivimab also had treatment-emergent ADA to imdevimab.

The incidence of treatment emergent immunoreactivity in subjects receiving placebo was 0% in the anti-casirivimab assay and 2.6% in the anti-imdevimab assay. The ADA titer was low (<1000) for all subjects with pre-existing or treatment-emergent immunoreactivity. The concentrations of casirivimab and imdevimab in subjects positive for ADA were within the range of concentrations for subjects without immunogenicity.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In COV-20145, casirivimab and imdevimab exhibited linear and dose-proportional PK after single IV doses from 300 mg (i.e. 150 mg casirivimab and 150 mg imdevimab) to 8,000 mg (4,000 mg of each).

As expected, SC administration gives a much lower Cmax and longer Tmax (about 6.5 days) for casirivimab and imdevimab. After a 1200 mg SC dose, the POPPK analysis estimated the bioavailability of casirivimab and imdevimab to be 71.8% and 71.7%, respectively. In turn, this leads to lower AUCs for each of casirivimab and imdevimab when the same dose is given SC vs. IV but by Day 28 the serum levels (C_{28}) are similar for the two dosing routes.

Data from COV-20145 show the effect of the longer Tmax and reduced bioavailability on serum concentrations after a 1200 mg SC dose vs. a 1200 mg IV dose. On day 2, the mean serum casirivimab and imdevimab concentrations were ~115 mg/L for both components after 1200 mg IV compared to ~42 mg/L for each after 1200 mg SC. Similarly, the day 6 serum concentrations were in the range 80-90 mg/L after 1200 mg IV vs. ~55 mg/L after 1200 mg SC.

Once casirivimab and imdevimab reach the blood, their distribution and elimination are the same regardless of the route of administration. The total volume of distribution estimated via POPPK analysis is ~7.2 L and ~7.4 L for casirivimab and imdevimab, respectively. As human monoclonal IgG1

antibodies, casirivimab and imdevimab are expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. For these reasons, no drug-drug interactions are expected. The terminal elimination half-life approximates to 26-30 days for casirivimab and imdevimab, reflecting slightly higher clearance for imdevimab.

Inter-individual variability is comparable between both mAbs and in an acceptable range. However, between-subject-variability of reference exposure (AUCd28, Cd28 and Cmax) are identical for casirivimab (21.8%) and imdevimab (18.1%).

No dose-ranging PK data following multiple dosing are available to characterize dose-proportionality and time-dependency at steady state. This is acceptable as the mAb combination is intended for single dose use, except for chronic prevention in certain subgroups. Exposure is reliably predicted based on the derived pop PK models.

Special populations

The POPPK analysis included data from subjects from 18 to 96 years and advancing age was not identified as a significant covariate on PK for casirivimab or imdevimab. Exposures to casirivimab and imdevimab were similar in subjects aged <65, 65-74 and ≥ 75 years after IV or SC administration. Furthermore, casirivimab and imdevimab do not undergo significant renal elimination due to their molecular weight (> 69 kDa) and are not expected to undergo significant hepatic elimination.

Exposure predictions based on the established pop PK model indicated that despite the lower concentrations/exposure metrics of casirivimab and imdevimab in the higher weight groups (100-120 kg and 120-140 kg), the concentrations/exposure metrics following a single 1200 mg IV or SC dose, and during a dosing interval at steady-state, are expected to maintain maximal antiviral activity. The 5th percentile of casirivimab+imdevimab combined concentrations in serum exceed Cs, target for all currently circulating VOC/VOIs. Exposures simulations do not indicate a need for adaptation of dose recommendations based on weight. There is no objection to inclusion of adolescents from 12 years and 40 kg in the indication statement and no objection to recommending the adult dose for this age and weight range.

Posology

Although no clinical PK or efficacy data are available for the proposed maintenance prophylaxis regimen (600 mg -300 mg each mAb) administered Q4W and no definitive efficacy data were available to support a 1200 mg SC monthly dosing regimen since this is an exploratory endpoint in HV-2093, expected mean exposure predicted based on population PK models for casirivimab and imdevimab indicated that target concentrations (IC90) will be reached even at the end of the 4-week interval. However, exposure achieved following 600 mg SC is predicted to be below that reached after 1200 mg Q4W, which was studied in COV-20145. There was concern that the 600 mg maintenance dose may be suboptimal especially for less susceptible variants. Since the safety of 1200 mg SC Q4W appears acceptable and this is a more secure dose from the PK point of view, it was recommended that this is used for Q4W follow-on dosing. Therefore, the maintenance dosing using the 600 mg dose IV or SC Q4W was asked to be further justified. In addition, these concerns applied to patients at high weight.

The Applicant summarised the data and provided arguments, which could be followed, to justify the planned posology for chronic prevention: A loading dose of 1200 mg SC/IV will be followed by a 600 mg SC/IV Q4W maintenance dose. This regimen would lead to maintain therapeutic levels over the entire

monthly maintenance-dosing interval comparable with those levels reached by a single dose of 1200 mg SC (or IV) by day 28, which is sufficient to maintain efficacy in the acute prevention setting. In support, pop PK predicted exposure (at steady state), including that expected in patients at higher weight (120 kg -140 kg), has been provided, and was related to the concentration needed to achieve maximum antiviral activity against VOC/VOI strains. Population PK simulations show that the median predicted trough concentration at steady state of casirivimab and imdevimab in serum for different combinations of IV and/or SC, repeat-dose regimens (including 600mg maintenance dosing) is similar (3% lower to 6% higher) to the observed median day 28 concentrations in serum for the single 1200 mg SC dose in study COV-2069.

It is agreed that exposure predictions based on pop PK will reach a comparable Ctrough ss following 600 mg Q4W SC and IV after the 1200 mg loading dose. The derived pop PK model is deemed fit for the purpose of robust exposure predictions. Thus, exposure matching for the prevention stetting (C28) with Ctrough ss reached is assumed a valuable basis for extrapolation of efficacy. It is plausible that the exposure reached is in the range of 1200 mg SC or IV Single dose for all weight categories. The totality of evidence is thus deemed sufficient to recommend the 600 mg dose for the maintenance phase. Further, given that no definite exposure- and dose response relationship could be established for the prevention settings with respect to efficacy and safety, the Applicant's proposal for reducing the maintenance dose is supported by the available evidence.

The SC route of administration was not used in the pivotal study for treatment (COV-2067) therefore there are no efficacy data to support use of 1200 mg SC as an alternative to the 1200 mg IV dose that was studied. In the absence of convincing dose-response and exposure-response data, the extrapolation of efficacy from the 1200 mg IV dose to the proposed alternative 1200 mg SC dose in the treatment setting based on PK bridging was not considered acceptable. There was concern that 1200 mg SC will not provide the necessary concentrations of casirivimab and imdevimab required for efficient neutralisation in the early phase of the disease that is likely critical for prevention of progression to severe disease.

The applicant argued that the SC administration in the treatment indication is supported from Study COV-2069 Cohort B in which 1200 mg SC demonstrates clinical efficacy on prevention of SARS-CoV-2 infection and COVID-19 through early treatment of infected, but asymptomatic individuals) and from the exploratory analyses from HV-2093, showing that repeat dose administration of 1200 mg SC monthly was highly effective in preventing symptomatic COVID-19 infections.

In addition, both modes of administration provided comparable reduction of viral load including at the earliest time points measured in infected patients, even in individuals with high viral load at baseline in COV-20145 and who received the lowest IV dose of 300 mg studied; however, how this PD effect translates into clinical efficacy remains uncertain.

Furthermore, pop PK simulations indicate – despite the delay due to absorption – a relative fast increase within 5 hours to reach exposure expected to be sufficient for maximal antiviral activity.

Finally, the applicant emphasised the benefit from a public health perspective through the easier access for treatment of outpatients via the SC route of administration. To further support this, preliminary data on the primary endpoint in clinical trial COV-2067 in relation to days from onset of symptoms to randomisation were presented. This analysis showed that patients treated earlier after symptom onset appeared to have a lower risk of COVID-19-related hospitalization or all-cause death than those treated later after symptom onset with a greater reduction observed the earlier treatment was initiated.

The CHMP considered that the pharmacokinetics of casirivimab and imdevimab in the first 48 hours after subcutaneous administration of 600 mg of each monoclonal antibody indicate lower serum exposures compared to intravenous administration of the same dose. It is unknown whether differences in initial systemic exposure result in differences in clinical efficacy. It is therefore recommended that the

subcutaneous route of administration is used only if intravenous administration is not feasible and would lead to a delay in treatment.

Pharmacodynamics

The two monoclonal antibodies do not act synergistically based on in-vitro activity. However, by binding to non-overlapping regions in the RBD, the combination product has the potential to be effective against SARS-Cov-2 even if the virus being treated has mutational resistance to one of the components. Studies with some of the currently known variants indicate that reduced susceptibility to casirivimab occurs more often than reduced susceptibility to imdevimab.

Authentic virus neutralization data have been generated for a few variants (see also non-clinical section). Ronapreve retained neutralization potency against all tested authentic isolates of variants of interest/concern compared with reference virus (Washington-1 isolate), including the predominant in EU delta variant.

An interim analysis of 31,102 clinical samples found no evidence that the clinical use of casirivimab and imdevimab has led to the selection of viral variants with alterations in the RBD, in casirivimab and imdevimab binding epitopes, or other S protein variation. Findings suggest that the overall mutation rate is not substantially different between Ronapreve and placebo groups. Of those mutations found at baseline or post-baseline in clinical treatment studies, the minority occurred in the RBD. Also, few potentially treatment-emergent variants have been detected thus far. Sequencing and analysis of additional samples is ongoing for all clinical studies which were submitted with this application. The timeline for the updated analyses for the remaining studies is dependent on the final database locks for those trials it is thus recommended that the applicant submits updated reports as soon as these become available.

The ADA analyses are currently incomplete but indicate that ≤3% of subjects develop ADA to casirivimab and ≤5% to imdevimab after a single dose. The effect of developing ADA to either component on their serum concentrations was assessed within COV-2067. While the applicant claimed no appreciable effect of ADA on PK, the graphs do not provide convincing evidence to support a conclusion on the effect of ADA on serum levels.

The population PK/PD modelling which was conducted (viral dynamical modelling) based on viral load data did not provide no additional insights in the mechanism of action but was consistent in showing the lack of any dose and exposure response relationship. Thus, viral load data as PD biomarker is not considered suitable for quantitative conclusion regarding dose selection.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of casirivimab and imdevimab have been well characterized in healthy volunteers and in the target population. Due to the possibility of reduced efficacy with subcutaneous administration when used for the treatment of COVID-19, in this setting the subcutaneous route of administration is used only if intravenous administration is not feasible and would lead to a delay in treatment.

The mechanism of action of Ronapreve is well established and despite the lack of clinical data on variants of concern, non-clinical data suggest that it retains activity against these, importantly including the delta variant.

2.5. Clinical efficacy

2.5.1. Dose response study

Study COV-20145

Study COV-20145 is a randomised, double-blind, placebo-controlled, parallel group study to assess the dose response profile of single IV or single SC doses of casirivimab+imdevimab in outpatients with SARS-CoV-2 infection. The study was conducted with adults who had either asymptomatic SARS-CoV-2 infection or had COVID-19 but no risk factors for severe COVID-19. Participants were randomized equally to receive a single dose of casirivimab+imdevimab or placebo by either SC injection or IV infusion

COV-20145 was designed to provide an understanding of the virologic dose response relationship for a range of intravenous and subcutaneous doses, including lower intravenous doses than previously tested in the COV-2067 study. An additional aim was to assess the role of SC dosing of casirivimab+imdevimab in the treatment of outpatients with SARS-CoV-2 infection. This dose ranging study helps establish the virologic efficacy of lower IV doses and SC doses that may provide clinical efficacy and broaden the ability to provide therapeutic doses of casirivimab+imdevimab.

The following treatment arms were included in the study: casirivimab+imdevimab 2400 mg IV, 1200 mg IV, 1200 mg SC, 600 mg IV, 600 mg SC, 300 mg IV, placebo IV, and placebo SC. Randomization occurred within 72 hours of obtaining a positive SARS-CoV-2 diagnostic test sample.

NP swab samples were collected every other day for the first week of the study to measure viral load, and once weekly for 2 more weeks to assess potential persistence of viral load. After the first month, participants had visits approximately once monthly for 4 additional months for safety follow-up. Additionally, participants were asked to notify study personnel as soon as possible about any MAVs.

The primary objective was to assess the virologic efficacy of casirivimab+imdevimab across different IV and SC doses compared to placebo. For viral load, AUC for change from baseline at a given time point was calculated using the linear trapezoidal rule and TWA was then calculated.

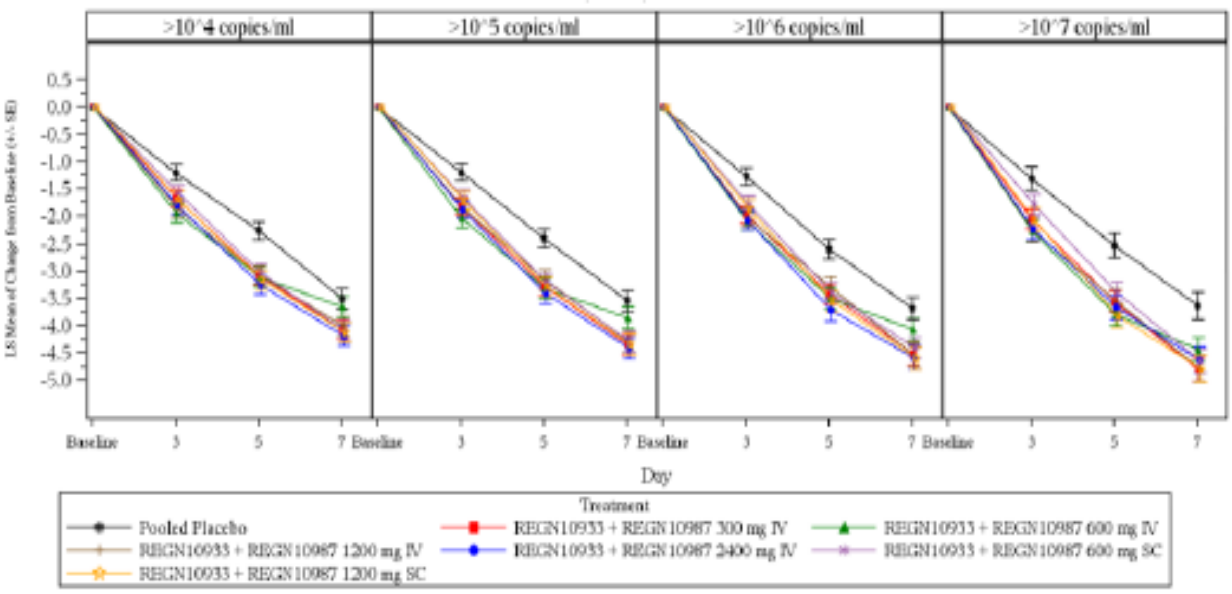
The primary efficacy variable was tested hierarchically at an $\alpha=0.05$, two-sided. If a test was insignificant, then the formal testing procedure stopped at that step. The primary analysis of the virologic variable demonstrated statistical significance for each of the 6 comparisons tested.

Single doses of casirivimab+imdevimab of various doses showed significant and comparable virologic reduction at all doses assessed (IV: 2400 mg, 1200 mg, 600 mg and 300 mg; SC: 1200 mg and 600 mg). Similar virologic efficacy was observed at the same dose level (600 mg or 1200 mg) whether administered through IV or SC routes (see Table 24).

Of note, the 600 mg dose (300 mg casirivimab and 300 mg of imdevimab) is sought for repeated prevention once every 4 weeks. Short term PK data are provided, and simulation data are available and are discussed in the Clinical Pharmacology section of this report.

Effects on the time course of viral load through day 7 by baseline load groups are shown in Figure 10.

Figure 10. LS Mean (±SE) change from baseline in viral load (Log_{10} copies/mL) for different viral loads for all casirivimab+imdevimab treatments (IV and SC) (Overall mFAS, study COV-20145)



2.5.2. Main studies

- **R10987-10933-COV-2067**: A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19 (Study COV-2067)

Methods

This was an adaptive study which was conducted in three parts/phases with the 3rd part including 3 cohorts depicted in Figures 11, 12, 13 and 14.

Figure 11. Study COV-2067 flow diagram Phase 1.

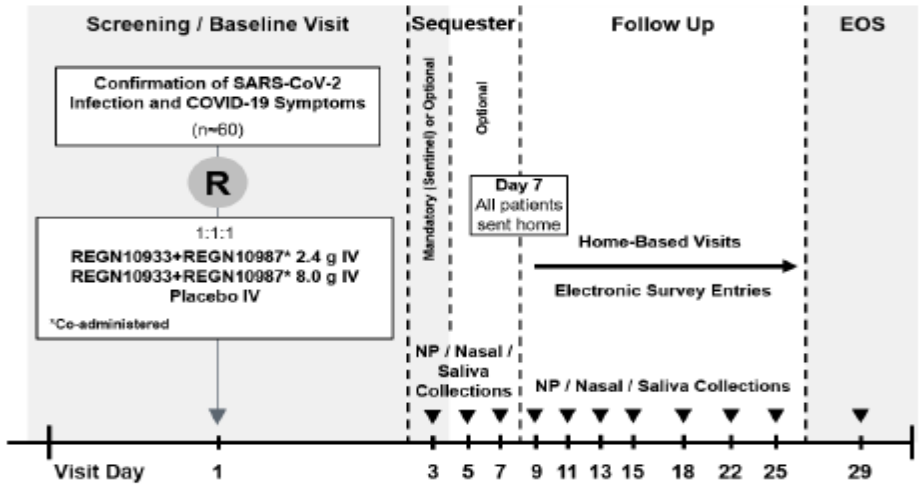


Figure 12. Study COV-2067 flow diagram Phase 2 (and Phase 3 prior to amendment 6)

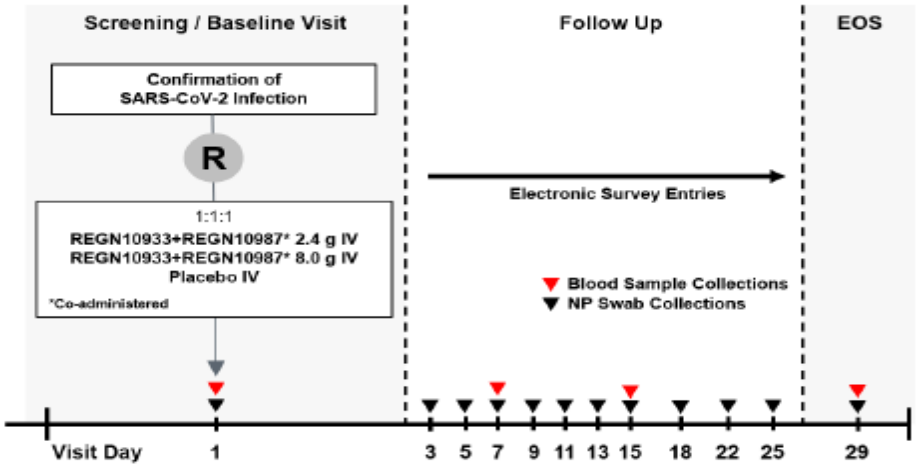


Figure 13. Study COV-2067 flow diagram Phase 3 Cohort 1 patients; Cohort 3 patients ≥18 years

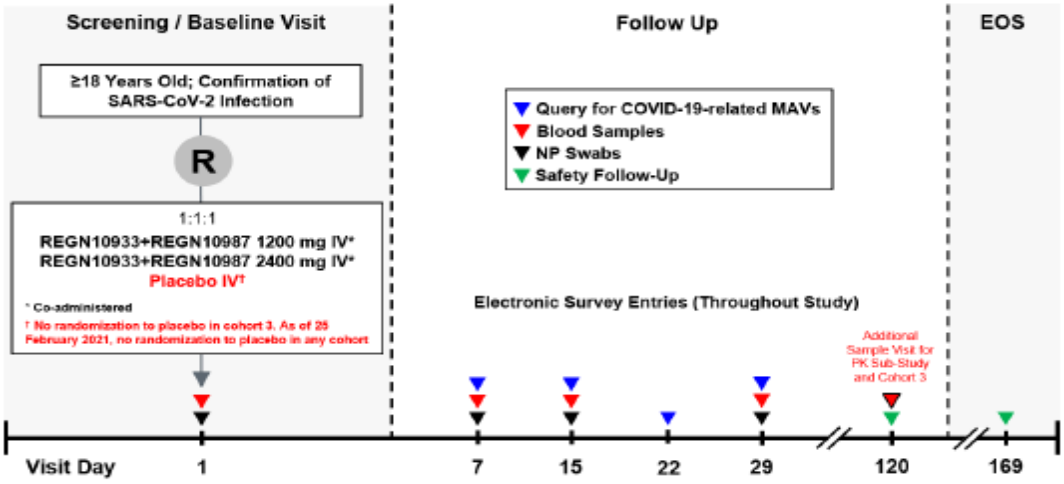
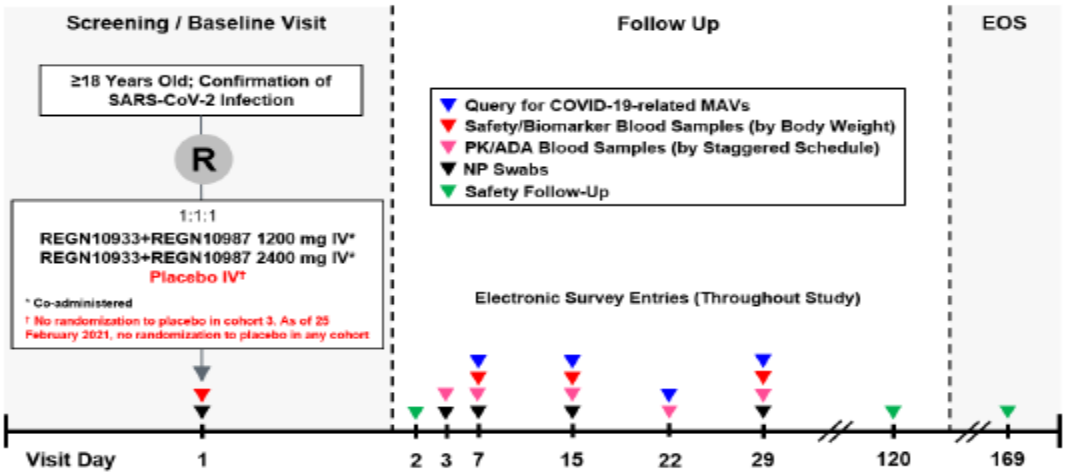


Figure 14. Study COV-2067 flow diagram Phase 3 Cohort 2 patients; Cohort 3 patients <18 years)



Study Participants

The study population in all 3 phases comprised non-hospitalised patients who have a positive diagnostic test for SARS-CoV-2. Subjects in Phases 1 and 3 were to be symptomatic. Phase 2 subjects could be symptomatic or asymptomatic.

Key inclusion criteria for Phase 3 cohorts were:

- a. Cohort 1: ≥18 years of age and not pregnant at randomization
- b. Cohort 2: <18 years of age and not pregnant at randomization
- c. Cohort 3: Pregnant at randomization

Note: cohort 2 and cohort 3 will only be enrolled where permitted by local requirements

- SARS-CoV-2-positive diagnostic test from a sample collected ≤72 hours prior to randomisation, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay and an appropriate sample such as nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva (historical record of positive result is acceptable, as long as the sample was collected ≤72 hours prior to randomization).
- Symptoms consistent with COVID-19, as determined by the investigator, with onset ≤7 days before randomisation
- Maintains O2 saturation ≥93% on room air
- Cohort 1 and cohort 2: Has ≥1 risk factor for severe COVID-19.

Only cohort 1 is relevant for the current submission. Cohort 2 and 3 are not addressed in this submission.

Risk factors were defined as follows:

Phase 2 Risk Factor Definitions (Stratification)	Phase 3 Risk Factor Definitions (Eligibility)
Age ≥50 years	Age ≥50 years
Obesity, defined as BMI ≥30 kg/m^2	Obesity, defined as BMI ≥30 kg/m^2
Cardiovascular disease, including hypertension	Cardiovascular disease, including hypertension
Chronic lung disease, including asthma	Chronic lung disease, including asthma
Chronic metabolic disease, including diabetes	Type 1 or type 2 diabetes mellitus
Chronic kidney disease, including those on dialysis	Chronic kidney disease, including those on dialysis
Chronic liver disease	Chronic liver disease
Immunocompromised	Immunocompromised

Key exclusion criteria

- Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (e.g., bamlanivimab), IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational).
- Has a known positive SARS-CoV-2 serologic test

- Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization
- 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 COVID-19.

The inclusion and exclusion criteria were subject to modifications, additions, and deletions, across each of the study phases as well as within each study phase.

The most salient change was that with amendment 6 (dated 14 November 2020), subjects enrolled into Cohort 1 and Cohort 2 were to have ≥1 risk factor for severe COVID-19, being any of age ≥50 years (cohort 1 only); BMI ≥30 kg/m2 (cohort 1 only), BMI ≥95th percentile for age and sex based on CDC growth charts (cohort 2 ≥2 years only); cardiovascular disease, chronic lung disease, diabetes mellitus, chronic kidney or liver disease, immunocompromised (based on investigator assessment); underlying genetic, neurologic, metabolic or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19 (cohort 2 only). The protocol amendment 6 notes that some subjects were enrolled into Phase 3 before the requirement for at least one risk factor was implemented.

Treatments

Phase 1
Randomisation (1:1:1) was not stratified and was to one of the following:
• 2400 mg IV single dose (1200 mg each of REGN10933 and REGN10987)
• 8000 mg IV single dose (4000 mg each of REGN10933 and REGN10987)
• Placebo IV single dose

Phase 2 (and Phase 3 Prior to Protocol Amendment 6)
Randomisation (1:1:1) was to one of the following:
• 2400 mg IV single dose (1200 mg each of REGN10933 and REGN10987)
• 8000 mg IV single dose (4000 mg each of REGN10933 and REGN10987)
• Placebo IV single dose
Randomisation was stratified by:
• Presence/absence of COVID-19 symptoms (symptomatic versus asymptomatic cohort)
• Country
• Risk factors for hospitalisation due to COVID-19 (none vs. ≥1; see above)

Phase 3

Cohort 1 (Prior to 25 February 2021) subjects were randomised (1:1:1) to one of the following:
• 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
• 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
• Placebo IV single dose
Randomisation was stratified by country.

Cohort 1 (after 25 February 2021; amendment 8) subjects were randomised (1:1) to the following:
• 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
• 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
Randomisation was stratified by country.

Objectives

Phase 1:
• To evaluate safety and tolerability compared to placebo
• To evaluate virologic efficacy compared to placebo based on reducing viral load

Phase 2:
To evaluate virologic efficacy compared to placebo based on reducing viral load

Phase 3:

Primary

- To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo as measured by COVID-19- related hospitalizations or all cause death.

Secondary (Key)

- To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo as measured by COVID-19- related hospitalizations or all cause death
- To evaluate the impact of casirivimab+imdevimab on the resolution of self-reported COVID- 19 symptoms compared to placebo.

Secondary (Other)

- To evaluate the clinical efficacy of casirivimab+imdevimab compared to placebo using various measures of COVID-19-related medically attended visits, including COVID-19 related hospitalisations, emergency room visits or all-cause death.
- To describe the virologic effects of casirivimab+imdevimab compared to placebo.

Outcomes/endpoints

Phase 1
• Proportion with SAEs through day 29
• Proportion with infusion-related reactions (grade ≥2) through day 4
• Proportion with hypersensitivity reactions (grade ≥2) through day 29
• Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.

Phase 2
Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.

Phase 3
Cohort 1

Primary

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29.

Secondary (Key)

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29.
- Time to COVID-19 symptoms resolution.

Secondary (Other)

- Proportion of patients with ≥1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29.
- Proportion of patients with ≥1 COVID-19-related medical attended visit or all-cause death through day 29.

Sample size (Phase 3)

Based on data from the phase 2 analysis involving the first 799 symptomatic patients enrolled and blinded phase 3 data, the sponsor assumes an event rate of 3.4% for COVID-19-related hospitalization or all-cause death among patients on placebo in the mFAS (patients with at least 1 risk factor for severe COVID-19 and a positive SARS-CoV-2 RTqPCR test at baseline), and that 83% of all randomized patients (FAS) will have a positive SARSCoV- 2 RT-qPCR test at baseline.

Table 21 presents estimated number of randomized patients with at least 1 risk factor for severe COVID-19 at each analysis time point for cohort 1 efficacy analysis.

Table 21. Estimated sample sizes at each analysis time point for Phase 3 patients with at least 1 risk factor for severe COVID-19

	Placebo FAS[1] (mFAS)	1200 mg FAS[1] (mFAS)	2400 mg FAS[1] (mFAS)	8000 mg FAS[1] (mFAS)	Total FAS[1] (mFAS)
Pre-Amendment 6 patients	662 (550)	Not applicable	662 (550)	662 (550)	1986 (1650)
Amendment 6/7 patients randomized by 17 January 2021	841 (698)	841 (698)	841 (698)	Not applicable	2523 (2094)
Final analysis for 2400 mg vs. placebo (patients randomized by 17 January 2021)	1503 (1248)		1503 (1248)		
Interim analysis for 1200 mg vs. placebo (patients randomized by 17 January 2021)	841 (698)	841 (698)			
Amendment 6/7 patients randomized by 24 February 2021	1352 (1122)	1352 (1122)	1352 (1122)	Not applicable	4056 (3366)
Final analysis for 1200 mg vs. placebo (patients randomized by 24 February 2021)	1352 (1122)	1352 (1122)			

[1] FAS estimates only include those in FAS with ≥1 risk factor for severe COVID-19.

Randomisation

Patients in cohort 1 were planned to be randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered casirivimab+imdevimab combination therapy, 1200 mg (600 mg each of casirivimab+imdevimab) IV single dose
- Co-administered casirivimab+imdevimab combination therapy, 2400 mg (1200 mg each of casirivimab+imdevimab) IV single dose
- Placebo IV single dose

In phase 3 cohort 1, randomisation was planned to be stratified by country.

A permuted block randomisation with fixed block length was used for randomization. During the course of the study, the initial randomisation list was replaced by a new one in order to introduce the 1200mg arm.

Blinding (masking)

This was a double-blinded study.

Statistical methods

Analysis sets

The Phase 1/2 portion of the study included all symptomatic subjects up to the 799th individual randomised into the study. The full analysis set (FAS) included all randomised subjects. The mFAS included all randomised with a positive RT-qPCR result from a NP swab obtained at baseline. The seronegative FAS and seronegative mFAS were the subsets with documented seronegative status at baseline. The mFAS was to be used for the analysis of all efficacy endpoints. Some additional analyses were to be conducted in the seronegative mFAS.

For the Phase 2 (asymptomatic) subset, the analysis populations were defined as above.

For Phase 3 (Cohort 1), the primary analysis was planned to be performed based on mFAS, defined as all randomized participants in phase 3 (from the 800th randomized patient) with both of the following:

- A qualitatively positive RT-qPCR (via central laboratory) from NP swab samples taken at randomization or collected within 2 hours after study drug infusion was initiated
- At least one risk factor for severe COVID-19 at baseline; based on the treatment allocated (as randomized).

Variable and analysis model

The primary efficacy endpoint for phase 3 cohort 1 was planned to be the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29, which was planned to be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor.

P-values from the stratified CMH test and 95% confidence intervals for the risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method were planned to be presented. Exact method for p-values and confidence intervals were planned to be used if the expected frequencies in all cells are not at least 5.

Prior to amendment 8 a stratified logrank test was planned for the analysis of the primary endpoint, which was defined as time to first COVID-19 related medically attended visit (MAV) through day 29 in amendment 6, and time to MAV or death through day 29 in amendment 7.

Significance level and multiplicity

The final analysis of the primary efficacy endpoint was planned at the α level of 0.05.

The primary endpoint and key secondary endpoints were planned to be tested hierarchically as described in Table 22.

Table 22. Statistical testing hierarchy, Phase 3 Cohort 1 analysis, Study COV-2067

Hierarchy Number	Description
1	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
2	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
3	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 2400 mg group versus placebo
4	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 2400 mg group versus placebo
5	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 1200 mg group versus placebo
6	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 1200 mg group versus placebo
7	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
8	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
9	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
10	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo

Prior to amendment 8 a slightly different hierarchy was planned, in which the previously defined primary endpoint of MAVs was also included in the hierarchy.

Interim analyses

In amendment 8 an interim analysis of the 1200mg vs placebo comparison was introduced. The 2400 mg group versus placebo comparison for the primary endpoint was conducted after recruitment to the placebo arm was closed upon recommendation by the iDMC. If this comparison was positive, an interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison was planned to be performed at α level of 0.01 based on patients randomized on or before 17 January 2021 in the mFAS. Final analysis of the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison (2 in Table 31) was planned to be performed based on all patients randomized on or before 24 February 2021.

Multiplicity control of the interim analysis

The Gamma family alpha spending function based on the primary endpoint of proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg versus placebo comparison was planned to be used to control for type I error for the planned interim and final analyses. The parameter for the Gamma family spending function was planned to be calculated based on the information fraction of the interim analysis, such that the alpha level at the interim analysis is equal to 0.01 and the remaining alpha level is calculated based on the gamma parameter.

The information fraction was planned to be determined based on the sample size in the mFAS at the interim analysis and at the final analysis of the primary endpoint for the 1200 mg group versus placebo comparison.

In case of a statistically significant result for this comparison (at interim or final analysis), key endpoints for comparisons 3 to 10 were then planned to be performed based on the same subset of patients (i.e. patients randomized on or before 17 January 2021 or randomized on or before 24 February 2021) in the mFAS in the hierarchical order above at α level of 0.05.

Non-concurrency of the treatment arms

The comparison of 1200 mg dose group to placebo was planned to include only the subset of placebo patients concurrently randomized with 1200 mg dose group.

Results- Phase 1 and 2

The results reflect the first 799 subjects enrolled into the study, of which 758 completed and 671 met criteria for inclusion in the mFAS (positive RT-PCR for SARS-CoV-2 at central laboratory). The baseline demographic and disease factors, including baseline serostatus, are summarised in Tables 23, 24 and 25.

Table 23. Demographics and baseline characteristics, excluding virology and serostatus (Phase 1/2, Combined Phase 1 and Phase 2, mFAS, Study COV-2067)

	Placebo (N=232)	REGN10933+REGN10987 2400 mg IV (N=219)	REGN10933+REGN10987 8000 mg IV (N=220)	REGN10933+REGN10987 Combined (N=439)	Total (N=671)
Age (Years)					
n	232	219	220	439	671
Mean (SD)	42.5 (15.21)	42.0 (15.61)	41.9 (14.08)	42.0 (14.85)	42.2 (14.96)
Median	41.0	42.0	42.0	42.0	42.0
Q1 : Q3	32.0 : 53.0	29.0 : 52.0	30.0 : 52.0	30.0 : 52.0	30.0 : 52.0
Min : Max	18 : 89	18 : 85	19 : 80	18 : 85	18 : 89
Age Group (Years), n (%)					
18 - 44	137 (59.1%)	123 (56.2%)	123 (55.9%)	246 (56.0%)	383 (57.1%)
45 - 64	78 (33.6%)	81 (37.0%)	84 (38.2%)	165 (37.6%)	243 (36.2%)
65 - 84	16 (6.9%)	14 (6.4%)	13 (5.9%)	27 (6.2%)	43 (6.4%)
≥85	1 (0.4%)	1 (0.5%)	0	1 (0.2%)	2 (0.3%)
≥50	73 (31.5%)	67 (30.6%)	67 (30.5%)	134 (30.5%)	207 (30.8%)
≥65	17 (7.3%)	15 (6.8%)	13 (5.9%)	28 (6.4%)	45 (6.7%)
≥75	4 (1.7%)	8 (3.7%)	3 (1.4%)	11 (2.5%)	15 (2.2%)
Sex, n (%)					
Male	122 (52.6%)	96 (43.8%)	101 (45.9%)	197 (44.9%)	319 (47.5%)
Female	110 (47.4%)	123 (56.2%)	119 (54.1%)	242 (55.1%)	352 (52.5%)
Time from symptom onset to randomization (days)					
n	230	217	216	433	663
Mean (SD)	3.4 (1.87)	3.6 (2.19)	3.4 (1.86)	3.5 (2.03)	3.5 (1.98)
Median	3.0	3.0	3.0	3.0	3.0
Q1 : Q3	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0
Min : Max	0 : 7	0 : 20	0 : 8	0 : 20	0 : 20

Table 24. Baseline virology (Phase 1/2, Combined Phase 1 and Phase 2, mFAS, Study COV-2067)

	Placebo	REGN10933+REGN10987 2400 mg IV	REGN10933+REGN10987 8000 mg IV	REGN10933+REGN10987 Combined
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS				
n	231	218	219	437
Mean (SD)	5.84 (1.838)	5.90 (1.657)	5.76 (1.802)	5.83 (1.730)
Median	5.95	6.15	5.94	6.05
Q1 : Q3	4.18 : 7.85	4.53 : 7.46	4.09 : 7.60	4.41 : 7.53
Min : Max	2.6 : 7.9	2.6 : 7.9	2.6 : 7.9	2.6 : 7.9
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS, baseline viral load >10^6 copies/mL				
n	114	111	108	219
Mean (SD)	7.49 (0.516)	7.34 (0.556)	7.37 (0.565)	7.36 (0.559)
Median	7.85	7.43	7.61	7.53
Q1 : Q3	7.17 : 7.85	6.95 : 7.85	7.01 : 7.85	7.00 : 7.85
Min : Max	6.1 : 7.9	6.1 : 7.9	6.0 : 7.9	6.0 : 7.9
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS, baseline viral load ≤10^6 copies/mL				
n	117	107	111	218
Mean (SD)	4.23 (1.063)	4.41 (0.930)	4.20 (1.053)	4.30 (0.998)
Median	4.19	4.52	4.10	4.40
Q1 : Q3	3.48 : 5.21	3.73 : 5.16	3.28 : 5.21	3.49 : 5.16
Min : Max	2.6 : 6.0	2.6 : 6.0	2.6 : 6.0	2.6 : 6.0
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS, baseline viral load >10^7 copies/mL				
n	93	83	81	164
Mean (SD)	7.70 (0.259)	7.62 (0.288)	7.66 (0.265)	7.64 (0.277)
Median	7.85	7.84	7.85	7.85
Q1 : Q3	7.68 : 7.85	7.37 : 7.85	7.49 : 7.85	7.41 : 7.85
Min : Max	7.0 : 7.9	7.0 : 7.9	7.0 : 7.9	7.0 : 7.9
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): Seronegative mFAS				
n	121	124	117	241
Mean (SD)	6.93 (1.242)	6.65 (1.215)	6.77 (1.265)	6.71 (1.238)
Median	7.61	7.10	7.36	7.18
Q1 : Q3	6.23 : 7.85	5.47 : 7.85	6.06 : 7.85	5.85 : 7.85
Min : Max	3.2 : 7.9	3.6 : 7.9	3.2 : 7.9	3.2 : 7.9
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS, seropositive at baseline				
n	84	73	79	152
Mean (SD)	4.34 (1.417)	4.46 (1.433)	4.16 (1.318)	4.30 (1.378)
Median	3.98	4.28	3.87	4.04
Q1 : Q3	3.32 : 5.35	3.41 : 5.07	3.21 : 5.08	3.28 : 5.07
Min : Max	2.6 : 7.9	2.6 : 7.9	2.6 : 7.9	2.6 : 7.9

Table 25. Baseline serostatus (Phase 1/2, Combined Phase 1 and Phase 2, mFAS, Study COV-2067)

	Placebo	REGN10933+REGN10987			Total
		2400 mg IV	8000 mg IV	Combined	
Baseline Serology Status: mFAS					
Negative[1]	122 (52.6%)	124 (56.6%)	118 (53.6%)	242 (55.1%)	364 (54.2%)
Positive[1]	84 (36.2%)	73 (33.3%)	79 (35.9%)	152 (34.6%)	236 (35.2%)
Other[1]	26 (11.2%)	22 (10.0%)	23 (10.5%)	45 (10.3%)	71 (10.6%)
Baseline Serology Status: mFAS, baseline viral load >10^6 copies/mL					
Negative	94 (82.5%)	85 (76.6%)	89 (82.4%)	174 (79.5%)	268 (80.5%)
Positive	9 (7.9%)	12 (10.8%)	7 (6.5%)	19 (8.7%)	28 (8.4%)
Other	11 (9.6%)	14 (12.6%)	12 (11.1%)	26 (11.9%)	37 (11.1%)
Baseline Serology Status: mFAS, baseline viral load ≤10^6 copies/mL					
Negative	27 (23.1%)	39 (36.4%)	28 (25.2%)	67 (30.7%)	94 (28.1%)
Positive	75 (64.1%)	61 (57.0%)	72 (64.9%)	133 (61.0%)	208 (62.1%)
Other	15 (12.8%)	7 (6.5%)	11 (9.9%)	18 (8.3%)	33 (9.9%)
Baseline Serology Status: mFAS, baseline viral load >10^7 copies/mL					
Negative	77 (82.8%)	66 (79.5%)	69 (85.2%)	135 (82.3%)	212 (82.5%)
Positive	6 (6.5%)	7 (8.4%)	3 (3.7%)	10 (6.1%)	16 (6.2%)
Other	10 (10.8%)	10 (12.0%)	9 (11.1%)	19 (11.6%)	29 (11.3%)

[1] serostatus was considered positive if any available anti-SARS-CoV-2 antibody test utilized (eg, anti-SARS-CoV-2 IgA or IgG) was positive, negative if all available tests were negative, and 'other' if serostatus was neither positive or negative (eg, borderline result) or was unknown.

At baseline, 62.3% had at least one risk factor for severe COVID-19/hospitalisation due to COVID-19. The most common risk factor was obesity (39.5% with BMI ≥ 30 kg/m^2), followed by age ≥ 50 years (30.8%) and cardiovascular disease (21%; mainly hypertension). Less than 2% had chronic renal or hepatic disease or were immunosuppressed for any reason.

An initial descriptive virologic efficacy analysis was conducted on the first 275 symptomatic subjects randomised into Phases 1 and 2. The prospective virologic (primary) analysis included the subsequent 524 subjects randomised into Phase 2 (Next Phase 2 population). Clinical efficacy was not assessed during the initial descriptive virology analysis. Thus, the prospective clinical analysis included all 799 randomised into Phase 1 and 2 (Combined Phase 1 and Phase 2 population).

Virologic efficacy data

Analyses of virologic endpoints were conducted using mFAS of Next Phase 2 subjects (n=442) based on serial NP swabs collected every other day for 14 days and then twice weekly. The RT-qPCR had a LLOQ of 2.87 $\log_{10}$ copies/mL.

Treatment with Ronapreve significantly reduced viral load, with statistical significance for the 8 endpoints tested (Table 26).

Table 26. Summary of hierarchical results for Phase 2 primary analysis (mFAS, Next Phase 2 participants, Study COV-2067)

No.	Variable	Analysis Population	Active Treatment Group	Difference vs Placebo	P-value
1	TWA daily change from baseline in viral load from day 1 through day 7	mFAS with baseline viral load >10^7 copies/mL	Combined (2400 mg IV and 8000 mg IV)	-0.60 (log_{10} copies/mL)	<0.0001
2		mFAS with baseline viral load >10^6 copies/mL	Combined (2400 mg IV and 8000 mg IV)	-0.60 (log_{10} copies/mL)	<0.0001
3		Seronegative mFAS	Combined (2400 mg IV and 8000 mg IV)	-0.68 (log_{10} copies/mL)	<0.0001
4		mFAS	Combined (2400 mg IV and 8000 mg IV)	-0.35 (log_{10} copies/mL)	0.0005
5		mFAS with baseline viral load >10^7 copies/mL	8000 mg IV	-0.63 (log_{10} copies/mL)	0.0002
6		mFAS with baseline viral load >10^7 copies/mL	2400 mg IV	-0.58 (log_{10} copies/mL)	0.0005
7		mFAS with baseline viral load >10^6 copies/mL	8000 mg IV	-0.56 (log_{10} copies/mL)	0.0001
8		mFAS with baseline viral load >10^6 copies/mL	2400 mg IV	-0.65 (log_{10} copies/mL)	<0.0001
9	Proportion of participants with ≥1 COVID-19-related MAV through day 29*	mFAS	Combined (2400 mg IV and 8000 mg IV)	-4.8%	0.0065
10	Proportion of participants with ≥1 COVID-19-related hospitalization, ER visit, or UC visit through day 29*	mFAS	Combined (2400 mg IV and 8000 mg IV)	-2.2%	0.1695

* Secondary endpoint

Greater reductions in viral load were observed in those with higher viral load at baseline and in those that were seronegative at baseline.

In those with a baseline viral load >7 log_{10} copies/mL, for each dose there was a -0.68 log_{10} copies/mL difference from placebo in the LSM time-weighted-average daily change from baseline through Day 7. In those with a baseline viral load >4 log_{10} copies/mL, for each dose there was a -0.47 log_{10} copies/mL difference from placebo in the LSM time-weighted-average daily change from baseline through Day 7.

The benefit of Ronapreve was almost exclusively in subjects who had not yet developed effective immunity to SARS-COV-2, such that:

- In those seronegative at baseline, there was a -0.74 log_{10} copies/mL and -0.71 log_{10} copies/mL difference vs. placebo with 2400 mg and 8000 mg, respectively.
- In those seropositive at baseline, the LSM time-weighted-average daily change from baseline in viral load through Day 7 was very similar between active and placebo arms.

In subjects with baseline viral load >7 log_{10} copies/mL, both doses of Ronapreve gave statistically significant reductions at each time point up to study day 11, by which time the
in the active treatment groups was <LLOQ.

Analyses of Medically Attended Visits

Ronapreve significantly reduced the risk for Medically Attended Visits (MAVs) for COVID-19 compared to placebo. Using a narrower definition of MAVs, there was a numerical but not statistically significant difference (Table 27).

Table 27. Proportion of participants with ⩾COVID-19 related MAV through day 29 (mFAS, combined Phase 1 and 2 participants, Study COV-2067)

		REGN10933+REGN10987		
	Placebo (N=232) n/N1 (%)	2400 mg IV (N=219) n/N1 (%)	8000 mg IV (N=220) n/N1 (%)	Combined (N=439) n/N1 (%)
Patients with ≥1 COVID-19 Related Medically-attended Visit through Day 29	18/232 (7.8%)	7/219 (3.2%)	6/220 (2.7%)	13/439 (3.0%)
95% CI	(4.7%, 12.0%)	(1.3%, 6.5%)	(1.0%, 5.8%)	(1.6%, 5.0%)
Proportion Difference vs Placebo		-4.6%	-5.0%	-4.8%
95% CI		(-9.2%, -0.3%)	(-9.6%, -0.8%)	(-9.2%, -1.0%)
p-value		0.0397	0.0203	0.0065
Hospitalization or ER or Urgent Care	11/232 (4.7%)	6/219 (2.7%)	5/220 (2.3%)	11/439 (2.5%)
95% CI	(2.4%, 8.3%)	(1.0%, 5.9%)	(0.7%, 5.2%)	(1.3%, 4.4%)
Proportion Difference vs Placebo		-2.0%	-2.5%	-2.2%
95% CI		(-6.0%, 1.7%)	(-6.3%, 1.1%)	(-6.0%, 0.8%)
p-value		0.3265	0.2045	0.1695

Data cutoff 18 Feb 2021

COVID-19 related medically-attended visit: 1. Hospitalizations 2. ER visits 3. Urgent Care Clinic visits 4. Outpatient/physician office/telemedicine visits. Note: N = number of patients in each treatment group; N1 = number of patients in each treatment group - number of on-going patients who haven't completed study; n = number of patients with at least 1 COVID-19 related medically-attended visit through day 29; % = n/N1. 95% CI and p-value are based on exact method.

The benefit of Ronapreve was most apparent in those with at least one of the listed risk factors at baseline and in those who were seronegative at baseline (Table 28).

Table 28. Proportion of participants with ≥COVID-19 related MAV through day 29 (mFAS, combined Phase 1 and 2 participants with ≥1 risk factor for severe COVID-19, Study COV-2067)

		REGN10933+REGN10987		
	Placebo (N=145) n/N1 (%)	2400 mg IV (N=138) n/N1 (%)	8000 mg IV (N=135) n/N1 (%)	Combined (N=273) n/N1 (%)
Patients with ≥1 COVID-19 Related Medically-attended Visit through Day 29	15/145 (10.3%)	4/138 (2.9%)	4/135 (3.0%)	8/273 (2.9%)
95% CI	(5.9%, 16.5%)	(0.8%, 7.3%)	(0.8%, 7.4%)	(1.3%, 5.7%)
Proportion Difference vs Placebo		-7.4%	-7.4%	-7.4%
95% CI		(-14.0%, -1.6%)	(-14.0%, -1.3%)	(-13.8%, -2.0%)
P-Value		0.0161	0.0167	0.0027
Hospitalization or ER or Urgent Care	10/145 (6.9%)	3/138 (2.2%)	4/135 (3.0%)	7/273 (2.6%)
95% CI	(3.4%, 12.3%)	(0.5%, 6.2%)	(0.8%, 7.4%)	(1.0%, 5.2%)
Proportion Difference vs Placebo		-4.7%	-3.9%	-4.3%
95% CI		(-10.5%, 0.2%)	(-9.7%, 1.4%)	(-9.9%, -0.2%)
P-Value		0.0862	0.1725	0.0394

COVID-19 Related Medically-attended Visit: 1. Hospitalizations 2. ER visits 3. Urgent Care Clinic visits 4. Outpatient/physician office/telemedicine visits. Note: N = number of patients in each treatment group; N1 = number of patients in each treatment group - number of on-going patients who haven't completed study; n = number of patients with at least 1 COVID-19 related medically-attended visit through day 29; % = n/N1. 95% CI and p-value are based on exact method.

Results-Phase 3

Participant flow

Table 29. Summary of disposition (Phase 3, FAS with ≥1 risk factor for severe COVID-19, Study COV-2067

	Placebo (N=1869)	REGN10933+REGN10987			Total (N=5607)
		1200 mg IV (N=838)	2400 mg IV (N=1873)	8000 mg IV (N=1027)	
Randomized patients	1869 (100%)	838 (100%)	1873 (100%)	1027 (100%)	5607 (100%)
Randomized patients but not treated	26 (1.4%)	11 (1.3%)	24 (1.3%)	15 (1.5%)	76 (1.4%)
Patients who completed the study	659 (35.3%)	0	690 (36.8%)	670 (65.2%)	2019 (36.0%)
Patients ongoing in the study	1125 (60.2%)	817 (97.7%)	1118 (59.7%)	311 (30.3%)	3371 (60.0%)
Patients who discontinued the study	85 (5.4%)	19 (2.3%)	64 (3.4%)	46 (4.5%)	214 (3.8%)
Reasons for study discontinuation					
Adverse Event	4 (0.3%)	0	1 (<0.1%)	1 (0.1%)	6 (0.1%)
Pregnancy	0	0	0	0	0
Lack of Efficacy	1 (<0.1%)	0	0	0	1 (<0.1%)
Physician Decision	4 (0.3%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	8 (0.2%)
Sponsor Request	8 (0.4%)	4 (0.5%)	7 (0.4%)	8 (0.8%)	27 (0.5%)
Death	3 (0.2%)	1 (0.1%)	1 (<0.1%)	0	5 (0.1%)
Lost To Follow-Up	28 (1.5%)	1 (0.1%)	23 (1.2%)	15 (1.5%)	67 (1.2%)
Subject Decision	37 (2.0%)	12 (1.4%)	30 (1.6%)	21 (2.0%)	100 (1.8%)

Randomized patients through 17Jan2021. Data cutoff date is 18Feb2021.

Recruitment

Study Initiation (first patient first visit): 16 June 2020

Database lock (primary analysis): 15 March 2021

Conduct of the study

The study was conducted using an adaptive master protocol design, to allow for flexible adaptation and seamless enrolment with the intent to maximize identification of early signs of efficacy, allow for the potential to study multiple therapeutic combinations, and avoid the use of ineffective dose levels. Correspondingly, several significant adaptations were made to the study design over the duration of the study (Table 30).

Table 30. Summary of key changes in conduct of study COV-2067

Amendment	Nature of Change	Change and Rationale[1]
PA1	Safety Assessment	In response to health authority feedback, increased safety monitoring (additional vital sign assessment) was included for the phase 1 sentinel safety group.
PA2	Safety Assessment	In response to health authority feedback, collection of grade ≥3 TEAEs was added to phase 1, to provide a broader assessment of safety for the FIH study phase.
PA3 and PA4	Efficacy Assessment	In phase 1, NP swabs, nasal swabs, and saliva samples were collected to measure virologic efficacy. Nasal swabs and saliva samples were collected with the intent to assess the reliability of relatively non-invasive collection methods. Beginning with phase 2, only NP swabs were collected, based on subsequent evidence that NP swabs were the most reliable sample method for quantitative measurement of SARS-CoV-2 viral load.
PA5	Target Population	Phase 2 eligibility was broadened, including allowance for antigen screen testing for SARS-CoV-2 and removal of the requirement for specific COVID-19 symptoms at screening,
PA6	Safety Assessment	In response to health authority feedback on study design adaptations made for phase 3, safety collection was broadened to all TEAEs that led to a medically-attended visit, regardless of relatedness to COVID-19
	Efficacy Assessment	Prior to unblinding for analysis of phase 1/2 data, the cutoff date of the primary virologic endpoint was pre-specified in the SAP (Appendix 16.1.9.1 Primary Phase 1/2 Statistical Analysis Plan) as day 7, instead of day 22 as was originally indicated in the protocol. This was done as the result of blinded analysis of interim phase 1/2 data suggesting that the majority of viral clearance had occurred prior to day 7.
	Treatment Groups	The initially planned dosing of REGN10989 monotherapy did not occur during this study, owing to the theoretical concern that a single anti-SARS-CoV-2 mAb may promote the emergence of treatment-resistant variants. Phase 1, part B (REGN10989 compared to placebo), did not open for enrollment, and REGN10989 was therefore not cleared for use in subsequent study phases. All reference to REGN10989 was removed from the protocol. For more information on phase 1 part B, refer to Appendix 16.1.1 Amendment 5 Section 3.2.1.1 and Section 6.1.1.
PA7	Efficacy Assessment	Per health authority request, all-cause death was added to the phase 3 cohort 1 primary endpoint.
PA8	Treatment Groups	Following IDMC recommendation, placebo randomization in phase 3 was discontinued on 25 February 2021
	Clinical Efficacy Assessment	The primary endpoint for phase 3 cohort 1 was modified per health authority feedback as described below: • **Original endpoint**: cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29 • **Modified endpoint**: proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29

[1] For more information on study conduct changes for each amendment, refer to Appendix 16.1.1 Amendment 1 to Appendix 16.1.1 Amendment 8.

Protocol deviations

During the phase 3 portion of the study, 579 important protocol deviations occurred in 340 patients (7.4%) in the FAS. The most common deviation was receipt of an excluded concomitant medication, which occurred in 188 patients, and a procedure not performed, which occurred in 130 patients. Receipt of excluded concomitant medication occurred more frequently among patients who received placebo compared to active drug. Twenty-three patients who did not satisfy eligibility criteria entered the study.

Procedures not performed included screening/baseline visit collection of NP swab samples, pregnancy test for women of childbearing potential, and haematology, blood chemistry, and/or coagulation tests

Baseline data

In general, demographic characteristics were well balanced between the groups (summarised in Tables-31-34).

Table 31. Frequency of baseline risk factors for severe COVID-19 (Phase 3, mFAS, Study COV-2067)

	Placebo		REGN10933+REGN10987			Total (N=4057)
	Pooled for 1200 mg IV analysis[1] (N=748)	Pooled for 2400 mg IV analysis[1] (N=1341)	1200 mg IV (N=736)	2400 mg IV (N=1355)	8000 mg IV (N=625)	
Risk factor for Severe COVID-19						
Age ≥50 years	356 (47.6%)	678 (50.6%)	357 (48.5%)	715 (52.8%)	351 (56.2%)	2101 (51.8%)
Obesity, defined as BMI ≥30 kg/m^2	427 (57.1%)	772 (57.6%)	410 (55.7%)	787 (58.1%)	384 (61.4%)	2353 (58.0%)
Cardiovascular disease, including hypertension	266 (35.6%)	473 (35.3%)	282 (38.3%)	520 (38.4%)	196 (31.4%)	1471 (36.3%)
Chronic lung disease, including asthma	139 (18.6%)	219 (16.3%)	139 (18.9%)	216 (15.9%)	92 (14.7%)	666 (16.4%)
Type 1 or type 2 diabetes mellitus	100 (13.4%)	210 (15.7%)	94 (12.8%)	202 (14.9%)	97 (15.5%)	603 (14.9%)
Chronic kidney disease, including those on dialysis	4 (0.5%)	9 (0.7%)	8 (1.1%)	19 (1.4%)	9 (1.4%)	45 (1.1%)
Chronic liver disease	4 (0.5%)	8 (0.6%)	3 (0.4%)	14 (1.0%)	11 (1.8%)	36 (0.9%)
Immunocompromised	10 (1.3%)	34 (2.5%)	24 (3.3%)	46 (3.4%)	16 (2.6%)	120 (3.0%)
Immunosuppressed	10 (1.3%)	31 (2.3%)	24 (3.3%)	46 (3.4%)	15 (2.4%)	116 (2.9%)
Taking Immunosuppressants	0	11 (0.8%)	0	10 (0.7%)	6 (1.0%)	27 (0.7%)

Table 32. Demographics and baseline characteristics, excluding virology and serostatus (Phase 3, mFAS, Study COV-2067)

	Placebo		REGN10933+REGN10987			Total (N=4057)
	Pooled for 1200 mg IV analysis[1] (N=748)	Pooled for 2400 mg IV analysis[1] (N=1341)	1200 mg IV (N=736)	2400 mg IV (N=1355)	8000 mg IV (N=625)	
Age (Years)						
n	748	1341	736	1355	625	4057
Mean (SD)	47.1 (14.80)	47.8 (14.39)	47.6 (14.73)	49.3 (15.14)	49.7 (14.32)	48.5 (14.72)
Median	48.0	50.0	48.5	50.0	51.0	50.0
Q1 : Q3	35.0 : 57.0	37.0 : 58.0	37.0 : 57.5	39.0 : 60.0	40.0 : 59.0	38.0 : 59.0
Min : Max	18 : 89	18 : 92	18 : 90	18 : 96	18 : 90	18 : 96
Age Group (Years), n (%)						
18 - 44	300 (40.1%)	519 (38.7%)	303 (41.2%)	498 (36.8%)	219 (35.0%)	1539 (37.9%)
45 - 64	360 (48.1%)	678 (50.6%)	340 (46.2%)	643 (47.5%)	309 (49.4%)	1970 (48.6%)
65 - 84	85 (11.4%)	138 (10.3%)	90 (12.2%)	202 (14.9%)	95 (15.2%)	525 (12.9%)
≥85	3 (0.4%)	6 (0.4%)	3 (0.4%)	12 (0.9%)	2 (0.3%)	23 (0.6%)
≥50	356 (47.6%)	678 (50.6%)	357 (48.5%)	715 (52.8%)	351 (56.2%)	2101 (51.8%)
≥65	88 (11.8%)	144 (10.7%)	93 (12.6%)	214 (15.8%)	97 (15.5%)	548 (13.5%)
≥75	20 (2.7%)	37 (2.8%)	31 (4.2%)	59 (4.4%)	23 (3.7%)	150 (3.7%)
Sex, n (%)						
Male	352 (47.1%)	633 (47.2%)	364 (49.5%)	656 (48.4%)	324 (51.8%)	1977 (48.7%)
Female	396 (52.9%)	708 (52.8%)	372 (50.5%)	699 (51.6%)	301 (48.2%)	2080 (51.3%)
Time from symptom onset to randomization (days)						
n	743	1319	727	1334	610	3990
Mean (SD)	3.6 (13.66)	3.5 (10.32)	3.2 (1.84)	6.1 (100.13)	3.4 (1.83)	4.3 (58.21)
Median	3.0	3.0	3.0	3.0	3.0	3.0
Q1 : Q3	2.0 : 4.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0	2.0 : 5.0
Min : Max	0 : 372	0 : 372	0 : 7	-1 : 3660	0 : 7	-1 : 3660

Table 33. Baseline virology (Phase 3, mFAS, Study COV-2067

	Placebo		REGN10933+REGN10987			Total
	Pooled for 1200 mg IV analysis[1]	Pooled for 2400 mg IV analysis[1]	1200 mg IV	2400 mg IV	8000 mg IV	
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS						
n	744	1333	734	1353	625	4045[2]
Mean (SD)	6.63 (1.823)	6.66 (1.754)	6.73 (1.863)	6.72 (1.707)	6.64 (1.671)	6.69 (1.746)
Median	6.85	6.95	6.92	7.01	7.00	6.98
Q1 : Q3	5.35 : 8.10	5.43 : 7.85	5.31 : 8.33	5.54 : 7.85	5.48 : 7.85	5.45 : 7.85
Min : Max	2.6 : 10.2	2.6 : 10.2	2.6 : 10.5	2.6 : 10.0	2.6 : 9.8	2.6 : 10.5
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS, baseline viral load >10^6 copies/mL						
n	471	876	482	924	428	2710
Mean (SD)	7.79 (1.008)	7.72 (0.948)	7.86 (1.033)	7.69 (0.933)	7.60 (0.862)	7.72 (0.949)
Median	7.73	7.70	7.80	7.69	7.73	7.73
Q1 : Q3	6.96 : 8.58	6.98 : 8.45	7.01 : 8.72	6.95 : 8.38	6.94 : 8.12	6.97 : 8.43
Min : Max	6.0 : 10.2	6.0 : 10.2	6.0 : 10.5	6.0 : 10.0	6.0 : 9.8	6.0 : 10.5
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): Seronegative mFAS						
n	517	925	498	940	412	2775
Mean (SD)	7.18 (1.550)	7.18 (1.473)	7.27 (1.611)	7.17 (1.469)	7.20 (1.337)	7.20 (1.478)
Median	7.41	7.45	7.47	7.38	7.51	7.44
Q1 : Q3	6.12 : 8.40	6.25 : 8.29	6.28 : 8.63	6.28 : 8.24	6.42 : 7.85	6.29 : 8.30
Min : Max	2.6 : 10.2	2.6 : 10.2	2.6 : 10.5	2.6 : 10.0	2.6 : 9.8	2.6 : 10.5
SARS-CoV-2 results from central lab - NP Swab (log_{10} copies/mL): mFAS, Seropositive at Baseline						
n	162	295	177	322	162	956
Mean (SD)	5.07 (1.671)	5.12 (1.652)	5.27 (1.728)	5.34 (1.675)	5.30 (1.696)	5.25 (1.681)
Median	4.94	4.96	4.97	5.19	5.23	5.06
Q1 : Q3	3.69 : 6.10	3.73 : 6.39	4.01 : 6.18	4.05 : 6.64	3.81 : 6.55	3.84 : 6.49
Min : Max	2.6 : 9.6	2.6 : 9.6	2.6 : 10.2	2.6 : 9.6	2.6 : 9.3	2.6 : 10.2
SARS-CoV-2 results from central lab - NP Swab (log10 copies/mL): FAS, Positive RT-qPCR at Baseline and No Risk Factors for Severe COVID-19						
n	N/A	325	N/A	304	290	919
Mean (SD)	N/A	6.35 (1.721)	N/A	6.56 (1.676)	6.44 (1.639)	6.45 (1.681)
Median	N/A	6.56	N/A	6.89	6.65	6.68
Q1 : Q3	N/A	4.93 : 7.80	N/A	5.33 : 7.85	5.39 : 7.85	5.23 : 7.85
Min : Max	N/A	2.6 : 10.1	N/A	2.6 : 9.6	2.6 : 9.7	2.6 : 10.1

Table 34. Baseline serostatus (Phase 3, mFAS, Study COV-2067)

	Placebo		REGN10933+REGN10987			Total
	Pooled for 1200 mg IV analysis[1]	Pooled for 2400 mg IV analysis[1]	1200 mg IV	2400 mg IV	8000 mg IV	
Baseline serology status: mFAS						
Negative[2]	519 (69.4%)	930 (69.4%)	500 (67.9%)	940 (69.4%)	412 (65.9%)	2782 (68.6%)
Positive[2]	164 (21.9%)	297 (22.1%)	177 (24.0%)	323 (23.8%)	162 (25.9%)	959 (23.6%)
Other[2]	65 (8.7%)	114 (8.5%)	59 (8.0%)	92 (6.8%)	51 (8.2%)	316 (7.8%)
Baseline serology status: mFAS, baseline viral load >10^6 copies/mL						
Negative	393 (83.4%)	722 (82.4%)	395 (82.0%)	748 (81.0%)	341 (79.7%)	2206 (81.4%)
Positive	46 (9.8%)	89 (10.2%)	49 (10.2%)	114 (12.3%)	56 (13.1%)	308 (11.4%)
Other	32 (6.8%)	65 (7.4%)	38 (7.9%)	62 (6.7%)	31 (7.2%)	196 (7.2%)
Baseline serology status: FAS, Positive RT-qPCR at Baseline and No Risk Factors for Severe COVID-19						
Negative	N/A	226 (69.5%)	208 (68.4%)	200 (69.0%)	408 (68.7%)	634 (69.0%)
Positive	N/A	69 (21.2%)	78 (25.7%)	67 (23.1%)	145 (24.4%)	214 (23.3%)
Other	N/A	30 (9.2%)	18 (5.9%)	23 (7.9%)	41 (6.9%)	71 (7.7%)

Prior to protocol amendment 6, 66.3% of randomized patients (n=2048/3088; 660/1029 placebo, 688/1034 2400 mg, 700/1027 8000 mg) had ≥1 risk factor for severe COVID-19.

After protocol amendment 6, all randomized patients (n=2519) were required to have at least 1 risk factor for severe disease. As such, across all phase 3, cohort 1 treatment groups, 81.5% (not 68.6%) of randomized patients (n=4567/5607) had ≥1 risk factor for severe COVID-19.

Data on the frequency of risk factors for the phase 3 patients in the mFAS were provided. The different treatment groups were balanced with respect to the risk factors. The most common risk factors for severe COVID-19 at baseline were obesity, defined as BMI ≥30 kg/m^2, age ≥50 years, and cardiovascular disease including hypertension.

Chronic lung disease (including asthma) and type 1 or type 2 diabetes mellitus were less common (16.4% and 14.9% respectively). Chronic kidney disease, chronic liver disease, and immunocompromised state were uncommon (≤3% frequency).

Numbers analysed

Table 35. Summary of populations in each analysis set (Phase 3, ≥1 risk factor for severe COVID-19, Study COV-2067)

	Placebo (N=1500)	REGN10933+REGN10987			Total (N=4567)
		1200 mg IV (N=838)	2400 mg IV (N=1529)	8000 mg IV (N=700)	
Patients randomized	1500 (100%)	838 (100%)	1529 (100%)	700 (100%)	4567 (100%)
Patients in full analysis set (FAS), n(%)	1500 (100%)	838 (100%)	1529 (100%)	700 (100%)	4567 (100%)
Patients in modified full analysis set (mFAS), n(%)	1341 (89.4%)	736 (87.8%)	1355 (88.6%)	625 (89.3%)	4057 (88.8%)

Randomized patients through 17 Jan 2021. Data cutoff date is 18 Feb 2021.

Outcomes and estimation

Table 36. Statistical hierarchy and summary of hierarchical results for Phase 3, Study COV-2067

No.	Variable	Analysis Population	Active Treatment Group	Relative Risk Reduction (%); Events	95% CI; p-value
1	Proportion of participants with ≥1 COVID-19-related hospitalization or all-cause death through day 29	mFAS	2400 mg IV	**71.3% reduction**; 18/1355 (1.3%) vs 62/1341 (4.6%)	95% CI (51.7%, 82.9%); p<0.0001
2			1200 mg IV	**70.4% reduction**; 7/736 (1.0%) vs 24/748 (3.2%)	95% CI (31.6%, 87.1%); p=0.0024
3		mFAS with baseline viral load >10^6 copies/mL	2400 mg IV	**77.6% reduction**; 13/924 (1.4%) vs 55/876 (6.3%)	95% CI (59.3%, 87.7%); p<0.0001
4		Seronegative mFAS	2400 mg IV	**75.8% reduction**; 12/940 (1.3%) vs 49/930 (5.3%)	95% CI (54.7%, 87.0%); p<0.0001
5		mFAS with baseline viral load >10^6 copies/mL	1200 mg IV	**70.7% reduction**; 6/482 (1.2%) vs 20/471 (4.2%)	95% CI (27.6%, 88.1%); p=0.0045
6		Seronegative mFAS	1200 mg IV	**82.7% reduction**; 3/500 (0.6%) vs 18/519 (3.5%)	95% CI (41.6%, 94.9%); p=0.0014
7	Proportion of participants with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29*	mFAS	2400 mg IV	**89.2% reduction**; 5/1351 (0.4%) vs 46/1340 (3.4%)	95% CI (73.0%, 95.7%); p<0.0001
8			1200 mg IV	**71.7% reduction**; 5/735 (0.7%) vs 18/748 (2.4%)	95% CI (24.3%, 89.4%), p=0.0101
9	Time to COVID-19 symptoms resolution*	mFAS	2400 mg IV	Median 10 days vs 14 days	p<0.0001
10	Time to COVID-19 symptoms resolution*		1200 mg IV	Median 10 days vs 14 days	p<0.0001

*Key secondary endpoint.

Differences between the Ronapreve 1200 mg and 2400 mg and placebo groups for the primary endpoint were observed beginning about 2 days after treatment as shown in Figures 15 and 16, respectively.

Figure 15. Kaplan-Meier curve for time to COVID-19 hospitalisation or all-cause death through Day 29 for REGN-COV2 1200 mg IV, Phase 3, ≥1 risk factor for severe COVID-19, mFAS, Study COV-2067

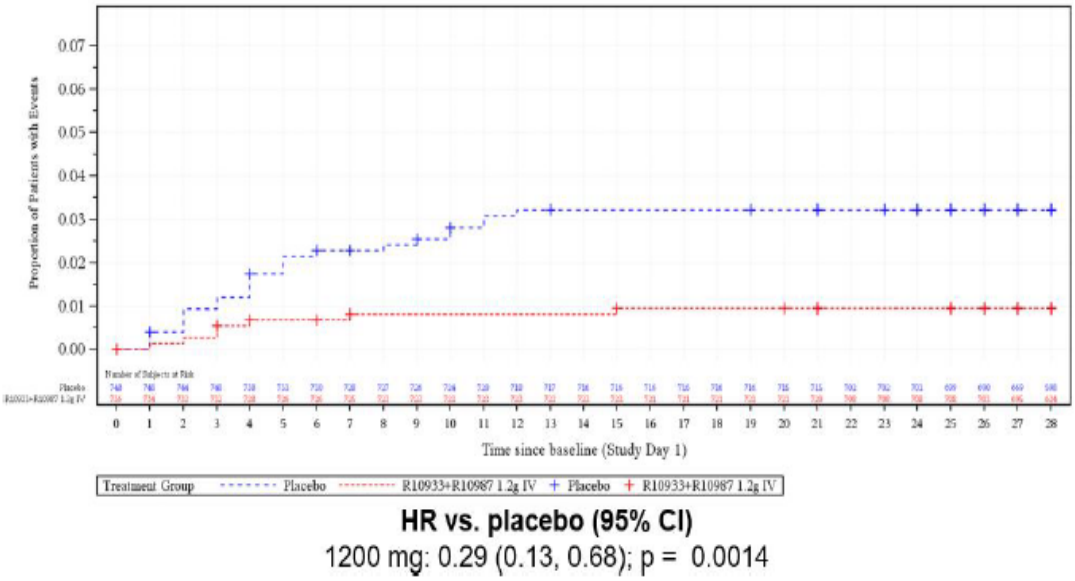
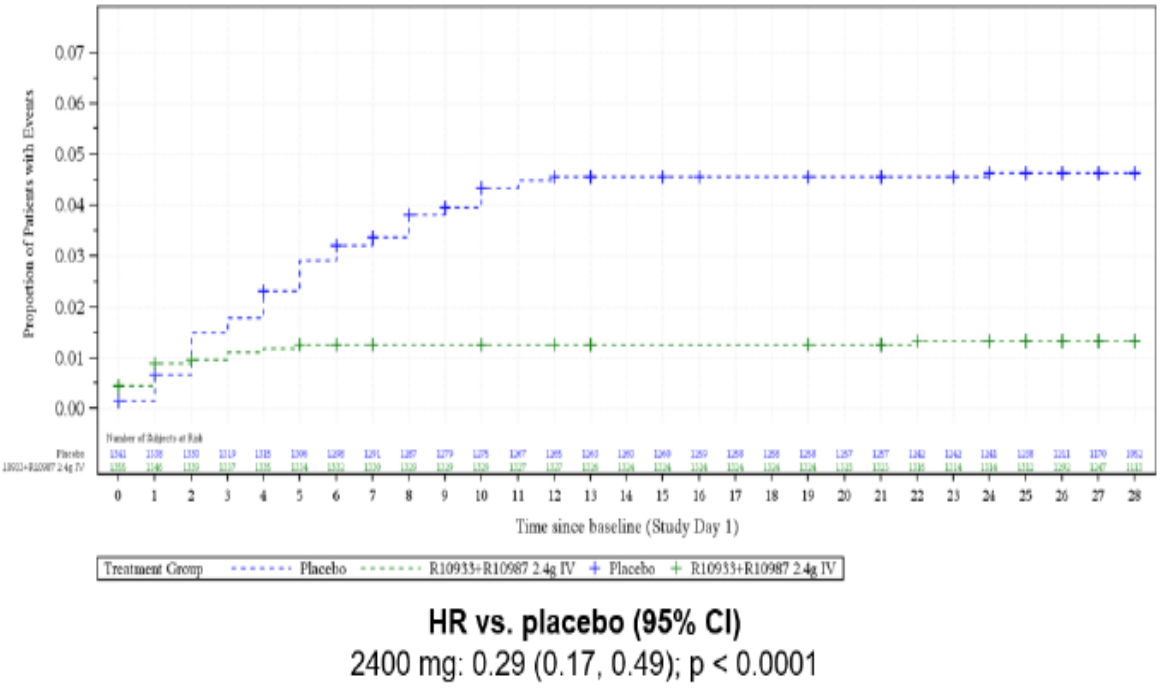


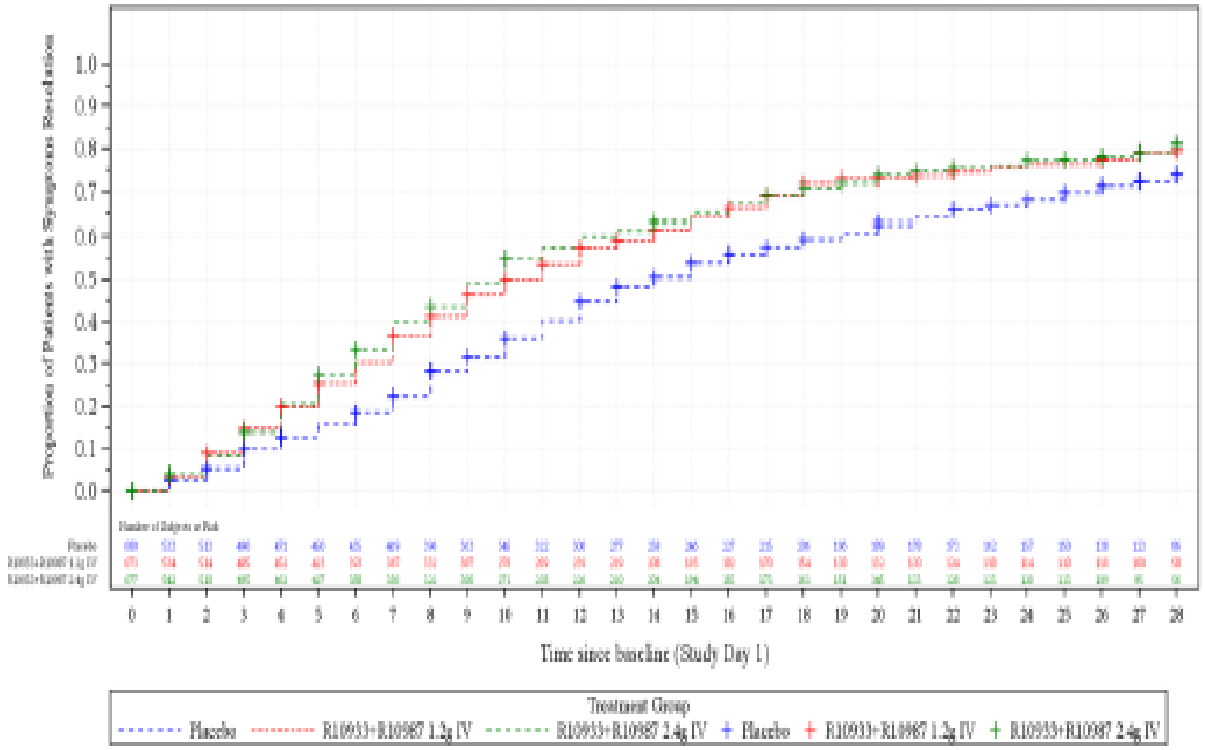
Figure 16. Kaplan-Meier curve for time to COVID-19 hospitalisation or all-cause death through Day 29 for REGN-COV2 1200 mg IV, Phase 3, ≥1 risk factor for severe COVID-19, mFAS, Study COV-2067



Ancillary analyses

Subject-reported COVID-19 symptoms were collected daily using the SE-C19 instrument developed by Regeneron, in which subjects recorded 23 symptoms daily and by severity. The time from randomisation to the first day on which the score was 0 for 19 symptoms (exceptions being cough, fatigue and headache, which could have been mild/moderate (score of 1), was statistically significantly reduced with Ronapreve vs. placebo, with a similar result for the 1200 mg and 2400 mg doses (Figure 17) .

Figure 17. Time to COVID-19 symptoms resolution for participants with ≥1 risk factor for severe COVID-19 (mFAS, Study COV-2067)



For those with no risk factors, the median time to resolution was 3 days shorter with 2400 mg vs. placebo (data not shown).

There were also benefits in terms of prevention of any MAV, as summarised in Table 37.

Table 37. Proportion of participants with COVID-19 related MAVs (by type or all all-cause death (mFAS-Study COV-2067)

	REGN10933+REGN10987 2400 mg (N=1355) 1200 mg (N=736)	Placebo (N= 1341) (N=748)	Relative Risk Reduction	Nominal P-value
≥1 COVID-19-related hospitalization, ER visit, or all-cause death				
2400 mg IV	27/1355 (2.0%)	78/1341 (5.8%)	65.7%	p<0.0001
1200 mg IV	9/736 (1.2%)	34/748 (4.5%)	73.1%	p=0.0001
≥1 COVID-19-related MAV or all-cause death				
2400 mg IV	43/1355 (3.2%)	109/1341 (8.1%)	61%	p<0.0001
1200 mg IV	20/736 (2.7%)	51/748 (6.8%)	60.1%	p=0.0002
≥1 COVID-19-related hospitalization				
2400 mg IV	17/1355 (1.3%)	59/1341 (4.4%)	71.5%	p<0.0001
1200 mg IV	6/736 (0.8%)	23/748 (3.1%)	73.5%	p=0.0017
≥1 COVID-19-related ER visit				
2400 mg IV	9/1355 (0.7%)	16/1341 (1.2%)	44.3%	p=0.1478
1200 mg IV	2/736 (0.3%)	10/748 (1.3%)	79.7%	p=0.0379
≥1 COVID-19-related Urgent care center visit				
2400 mg IV	3/1355 (0.2%)	7/1341 (0.5%)	57.6%	p=0.2234
1200 mg IV	1/736 (0.1%)	5/748 (0.7%)	79.7%	p=0.2179
≥1 COVID-19-related Physician Office/Telemedicine visit				
2400 mg IV	13/1355 (1.0%)	24/1341 (1.8%)	46.4%	p=0.0614
1200 mg IV	10/736 (1.4%)	12/748 (1.6%)	15.3%	p=0.6961
≥2 COVID-19-related MAV or all-cause death				
2400 mg IV	1/1355 (<0.1%)	15/1341 (1.1%)	93.4%	p=0.0002
1200 mg IV	3/736 (0.4%)	4/748 (0.5%)	23.8%	p=1.000

There were too few subjects who required mechanical ventilation to draw any conclusions, with rates of <0.1% for 2400 mg vs. 0.4% placebo and 0.1% for 1200 mg vs. 0.3% placebo.

An updated analysis, based on the latest data cut-off date of 19 August 2021, inclusive of patients randomized from 18 January 2021 through 24 February 2021 is summarised in Table 38.

Table 38. Summary of primary endpoint phase 3 results from study COV-2067, data cut-off August 2021

	1 200 mg IV	Placebo	2 400 mg IV	Placebo
	n = 1 192	n = 1 193	n = 1 812	n = 1 790
Patients in the mFAS with ≥1 COVID-19-related hospitalisation or death through day 29				
Risk reduction	72.5% (p <0.0001)		70.9% (p < 0.0001)	
Number of patients with events	11 (0.9%)	40 (3.4%)	23 (1.3%)	78 (4.4%)

mFAS: modified full analysis set included those subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization, and with at least one risk factor for severe COVID-19.

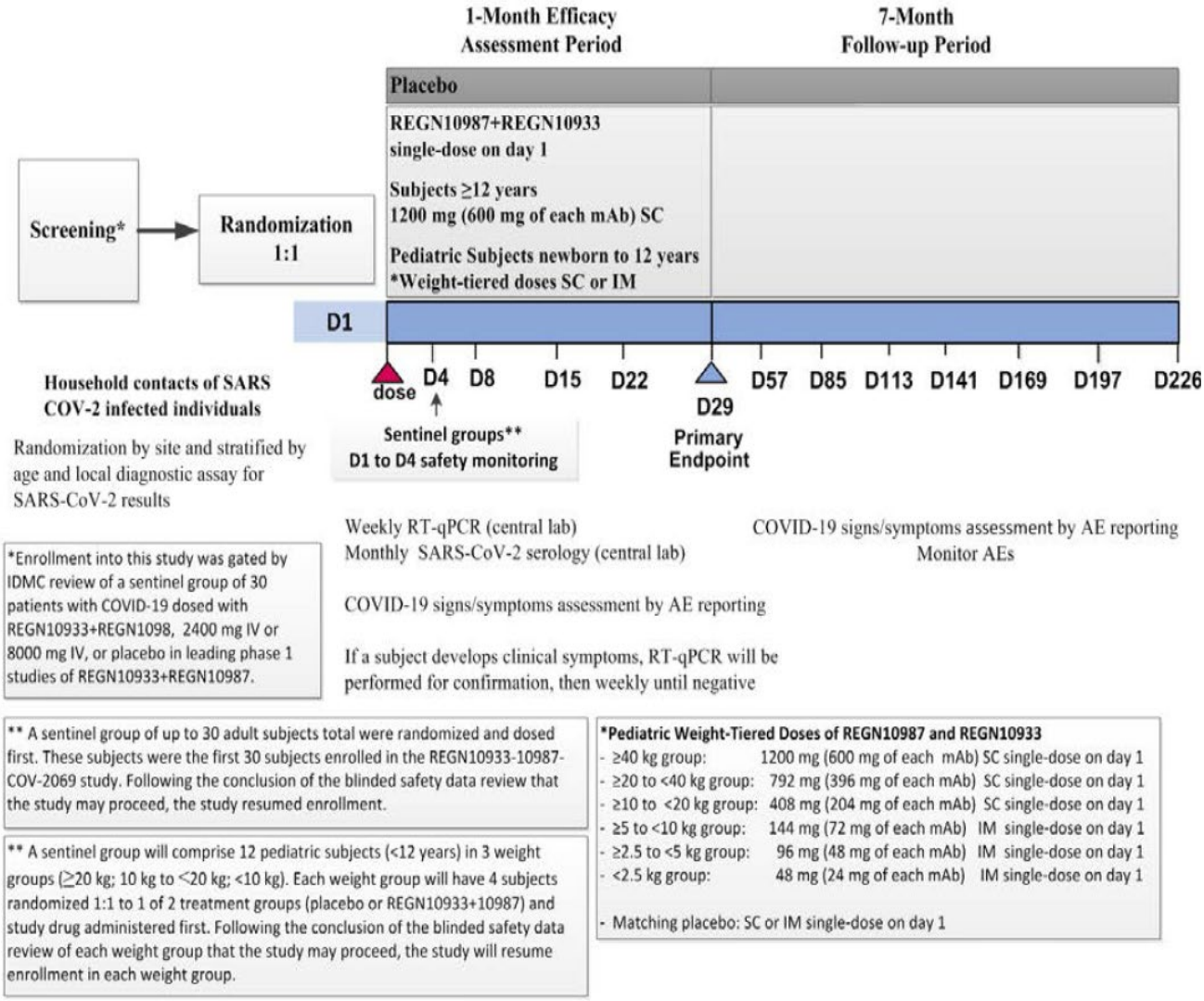
In this updated analysis, time to resolution of COVI-19 symptoms was 13 days in the REGN-COV2 treated patients for both dose groups compared to 10 days for the placebo treated patients.

- **R10987-10933-COV-2069**: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARSCoV- 2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

Methods

The study design is depicted in Figure 18.

Figure 18. Study COV-2069 flow diagram



Study Participants

Study participants were asymptomatic, healthy adults and children (including those with a chronic, stable medical condition) who were household contacts to the first known household member with a diagnosis of SARS-CoV-2 infection (index case). Participants themselves could have been positive or negative for SARS-CoV-2 at screening.

Study participants included adults and adolescents (age ≥12 years) and paediatric participants (age <12 years).

To be included in the study, subjects must be randomized within 96 hours of collection of the index cases' positive SARS-COV-2 diagnostic test sample anticipates living in the same household with the index case until study day 29.

The most salient exclusion criteria were:

- Subject-reported history of prior positive SARS-CoV-2 RT-PCR test or positive SARS-CoV-2 serology test at any time before the screening
- Subject has lived with individuals who have had previous SARS-CoV-2 infection or currently lives with individuals who have SARS-CoV-2 infection, with the exception of the index case(s), the first individual(s) known to be infected in the household
- Current hospitalization or was hospitalized (i.e., >24 hours) for any reason within 30 days of the screening visit
- Received an investigational or approved SARS-CoV-2 vaccine
- Received investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (e.g., convalescent plasma or sera, monoclonal antibodies, hyperimmuneglobulin)
- Use of hydroxychloroquine/chloroquine for prophylaxis/treatment of SARS-CoV-2 or anti-SARS-viral agents, e.g., remdesivir, within 60 days of screening NOTE: hydroxychloroquine/chloroquine for other uses, e.g., for use in autoimmune diseases is allowed

Patients were allocated to 4 different cohorts

Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline- adult and adolescent subjects

Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline- paediatric subjects (<12 years)

Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline- adult and adolescent subjects will be enrolled

Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline- paediatric subjects (<12 years)

No paediatric participants were enrolled at the time of the randomization cut-off for this CSR. Cohort A1 and B1 are not included in this report.

Treatments

Treatment was to be administered within 96 h of the index case sample in which the presence of SARS-CoV-2 was confirmed.
The REGN10987 and REGN10933 dose is 1200 mg (600 mg of each mAb) SC single dose on day 1. The two components of Ronapreve were provided as 120 mg/mL solutions for SC or IM injection. All adult or adolescent subjects will receive 4 SC injections of study drug on day 1, each injection containing 2.5 mL of active study drug or placebo.

Objectives/Outcomes/Endpoints

Cohort A

Primary and key secondary objectives/endpoints were defined for participants who were negative for SARS-CoV-2 (i.e., uninfected) and seronegative at baseline.

Cohort A Primary Efficacy Objective	Cohort A Primary Efficacy Endpoint
• To evaluate the efficacy of casirivimab+imdevimab compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR	• Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
Cohort A Primary Safety Objective	Cohort A Primary Safety Endpoint
• To evaluate the safety and tolerability of casirivimab+imdevimab following SC administration compared to placebo	• Proportion of subjects with TEAEs and severity of TEAEs
Cohort A Secondary Efficacy Objectives	Cohort A Key Secondary Efficacy Endpoints
• To evaluate the efficacy of casirivimab+imdevimab compared to placebo in preventing a SARS-CoV-2 infection with a high viral load (ie, viral load >4 $\log_{10}$ copies/mL) • To evaluate the impact of casirivimab+imdevimab compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS CoV-2 infection (broad-term) confirmed by RT-qPCR • To evaluate the impact of casirivimab+imdevimab compared to placebo on the duration of SARS-CoV-2 infection with a high viral load (ie, viral load >4 $\log_{10}$ copies/mL) • To evaluate the impact of casirivimab+imdevimab compared to placebo on the duration of SARS-CoV-2 infection • To evaluate the efficacy of casirivimab+imdevimab compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR • To evaluate the impact of treating the index case with casirivimab+imdevimab on the incidence of SARS-CoV-2 infection among household contacts in the placebo group (This is a cross-study analysis based on only subjects in placebo group of study R10933-10987-COV-2069 whose index cases participated in study R10933-10987-COV-2067)	• Proportion of subjects with viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP • Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP • Number of weeks of high-viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP • Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP • Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP • Proportion of subjects in the placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases received casirivimab+imdevimab versus placebo in study R1033-10987-COV-2067)

CDC, US Centers for Disease Control and Prevention; EAP, efficacy assessment period; REGN10933, casirivimab; REGN10987, imdevimab; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; TEAE, treatment-emergent adverse event

Cohort B

Primary and key secondary objectives/endpoints were defined for participants who were positive for SARS-CoV-2 (i.e., with asymptomatic infection) and seronegative at baseline.

Cohort B Primary Efficacy Objective	Cohort B Primary Efficacy Endpoint
• To evaluate the efficacy of casirivimab+imdevimab compared to placebo in preventing COVID-19 symptoms (broad-term)	• Proportion of participants who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
Cohort B Primary Safety Objective	Cohort B Secondary Safety Endpoint
• To evaluate the safety and tolerability of casirivimab+imdevimab following SC administration compared to placebo	• Proportion of participants with TEAEs and severity of TEAEs
Cohort B Secondary Efficacy Objective	Cohort B Key Secondary Efficacy Endpoints
• To evaluate the impact of casirivimab+imdevimab compared to placebo on the duration of signs and symptoms in participants with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR	• Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP • Number of weeks of high viral load >4 (log_{10} copies/mL) in NP swab samples during the EAP

EAP, efficacy assessment period; REGN10933, casirivimab; REGN10987, imdevimab; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, subcutaneous; TEAE, treatment-emergent adverse event

Sample size

It was estimated that the total enrolment may reach approximately 3500 adult and adolescent subjects and 250 paediatric subjects. The rationale for the overall expected sample size of 3500 adult/adolescent subjects was not presented, but further considerations were made for cohorts A and B.

Cohort A

To detect a relative risk of 0.5 (i.e., 50% reduction of the assumed 10% attack rate in the placebo arm), equivalent to an odds ratio of 0.47, power was calculated compared to the p-value of 0.05 based on 2000 simulations in 1248 subjects from 430 households (i.e., assuming an average household size of 2.9 seronegative subjects). Based on simulation, at least 1980 subjects were planned to be enrolled in cohort A to have a minimum of 1248 seronegative subjects, assuming that 10% of subjects drop out and 30% of subjects are seropositive at baseline. This was expected to provide >90% power using a generalized linear model with the generalized estimation equation (GEE) approach and assuming a compound symmetry covariance matrix.

Cohort B

The sample size consideration of cohort B was based on the frequency of finding positive subjects while enrolling cohort A and assumed that approximately 10% of subjects in a household would be already positive for SARS-CoV-2 by RT-qPCR at baseline. Among approximately 3500 adult and adolescent subjects that were anticipated to be enrolled in cohort A or cohort B, the number of subjects expected in cohort B was approximately 220, including 200 seronegative subjects. Assuming that 50% of infected placebo subjects at baseline would develop symptoms, 200 seronegative subjects in cohort B was expected to provide >90% power to detect a relative risk of 0.5 using a 2-sided Fisher's exact test at an alpha level of 0.05.

The sample size was amended through protocol amendments, and assumptions were verified through an unplanned unblinded interim analysis, called "administrative assessment".

Randomisation

Subjects were planned to be randomized in a 1:1 ratio to receive REGN10987+ REGN10933 or placebo according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization was planned to be performed by individual study subjects, not by households.

In addition to a randomization number, all subjects randomized were planned to be given a household identification number in the case that multiple members of the same household are enrolled and receive study drug. This was planned to ensure that any correlation among subjects within the same household may be considered in the statistical analysis.

Randomization was stratified as follows:

- Site
- Local diagnostic assay for SARS-CoV-2 from appropriate samples (positive, negative, or undetermined)
- Age and/or weight:
  - <12 years and <10 kg,
  - <12 years and ≥10 kg to <20 kg,
  - <12 years and ≥20 kg
  - ≥12 years and <18 years
  - ≥18 years and <50 years
  - ≥50 years

Note that the cohorts used in the analysis are defined by the baseline central lab SARS-CoV-2 RT-qPCR results, not by the local diagnostic assay.

Blinding (masking)

This was a double-blinded study.

Statistical methods

Analysis sets

Efficacy analyses were planned to be conducted on the seronegative modified full analysis set (seronegative mFAS). The seronegative mFAS was defined as follows for each of the cohorts:

Seronegative Modified Full Analysis Set (Seronegative mFAS-A) - Cohort A

The seronegative modified full analysis set for cohort A (seronegative mFAS-A) was planned to include all randomized subjects aged 12 years and older who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects included in the administrative assessment analysis were planned to be excluded from the seronegative mFAS-A population.

Subjects were planned to be analysed based on the randomized treatment assignment. The seronegative mFAS-A population was planned to be the primary analysis population for the primary and secondary endpoints for cohort A of this study unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B) - Cohort B

The seronegative modified full analysis set for cohort B (seronegative mFAS-B) was planned to include all randomized subjects aged 12 years and older who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) and are asymptomatic at baseline.

Subjects were planned to be analysed based on the randomized treatment assignment. The primary and secondary endpoints for cohort B were planned to be analysed using the seronegative mFAS-B unless otherwise specified.

The primary analysis was restricted to subjects who did not have evidence of previous or ongoing infection because this was thought to be the most vulnerable population who were likely to get infected. Inclusion of patients with prior immunity would not meaningfully contribute to an assessment of RONAPREVE treatment effects versus placebo and would merely inflate the sample size required to have enough events (asymptomatic or symptomatic SARS-CoV-2 infections) necessary to complete the trial.

Nevertheless, a small number of prior infected patients (seropositive patients) and serostatus undermined patients were enrolled. The sample size is also small for the seropositive patients and patients with undetermined serostatus. The data suggested that the treatment effect was not driven by the asymptomatic early infected population, regardless of serostatus

Cohorts (and thereby analysis sets) were defined by means of central laboratory assessment for both PCR as well as serology testing, whereas randomization was planned to be stratified by Local diagnostic assay for SARS-CoV-2 from appropriate samples (positive, negative, or undetermined).

Variable and analysis model

The primary efficacy variable for Cohort A was planned to be the Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP.

A mixed model was planned as primary analysis with a fixed effect model as fall-back strategy:

In order to account for the correlation among subjects within a household and control the associated type 1 error inflation, a generalized linear model was planned to be used to estimate the odds ratio between the treatment groups by using the GEE approach. This model estimates a single within-household correlation coefficient. The model was planned to include the fixed category effects of treatment group (placebo versus REGN10933+REGN10987), region (US versus ex-US), and age (≥12 to <50, ≥50 years). The model was planned to use a compound symmetry covariance matrix and estimate the odds ratio between the treatment groups and corresponding 95% CI and p-value.

Fall-back strategies: If the GEE model fails to converge due to most households containing only a single study subject in seronegative mFAS-A or the percentage of households in cohort A with only a single study subject is 70% or more, then a logistic regression model was planned to be used, with treatment, region, and age group as fixed effects. The threshold of 70% was based on simulations of within-household correlation which suggest that the type I error rate is inflated, and the power is decreased when the proportion of single-subject households is high (further information in the SAP).

If the logistic regression model does not converge, an exact logistic regression was planned to be used. The estimates of odds ratio, the corresponding 95% CI and p-value were then planned to be provided

from logistic regression (or exact logistic regression) for comparison of REGN10933+REGN10987 against placebo group.

The primary efficacy variable for Cohort B was planned to be the Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP.

The same statistical methods as described for cohort A were planned to be used to obtain the estimate of odds ratio and p-value for comparison between the treatment groups.

Missing values

Subjects with COVID-19 symptoms that are missing a central lab-determined RT-qPCR test during the EAP (e.g., are too sick to go to the study site) but have a positive SARS-COV-2 test from a local lab (e.g., in the hospital) were planned to be considered as having a symptomatic infection if any of the symptoms occurred within 14 days of the positive SARS-COV-2 test(s).

Significance level and multiplicity

The overall type I error was planned to be controlled in each of seronegative mFAS-A and seronegative mFAS-B independently at 2-sided 5% significance level. The applicant argued that cohorts A and B could be interpreted as independent studies. This was not fully agreed, mainly due to practicalities in prospectively identifying the cohorts. In consequence, there are uncertainties in the interpretation of statistical significance.

If the primary efficacy endpoint in cohort A or cohort B is statistically significant, the alpha level of 0.05 was planned to be released for the key secondary endpoints in cohort A or cohort B respectively. The hierarchical testing sequence for key secondary efficacy endpoints is presented in Table 39 (cohort A) and Table 40 (cohort B).

Table 39. Hierarchy testing of key secondary efficacy endpoints in Seronegative mFAS-A, Study COV-2069

Key Secondary Efficacy Endpoints
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP
Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in R1033-10987-COV-2067)

Table 40. Hierarchy testing of key secondary efficacy endpoints in Seronegative mFAS-B, Study COV-2069

Key Secondary Efficacy Variables
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
Number of weeks of high viral load (log10 copies/mL) >4 in NP swab samples during the EAP

This hierarchical testing approach was defined in amendment 6.

Interim analyses

Previously planned interim analyses were removed in protocol amendment 6.

An initially unplanned unblinded "administrative assessment" was conducted with data of all 554 subjects in cohort A randomized on or before 16 Oct 2020, based on a database snapshot on 19 Jan 2021. None of the data from these 554 subjects were to be included in the primary efficacy analysis for the study.

Results

Participant flow

Table 41. Overview of participant disposition by cohort (all randomised participants, Study COV-2069)

	Cohort A (N=2621)	Cohort B (N=314)	SARS-CoV-2 Undetermined[1] (N=94)	Total (N=3029)
Randomized subjects	2621 (100%)	314 (100%)	94 (100%)	3029 (100%)
Randomized but not treated	4 (0.2%)	3 (1.0%)	20 (21.3%)	27 (0.9%)
Randomized and treated	2617 (99.8%)	311 (99.0%)	74 (78.7%)	3002 (99.1%)
Complete the efficacy assessment period (EAP) (as derived)[2]	2601 (99.4%)	310 (99.7%)	72 (97.3%)	2983 (99.4%)
Complete the end of study follow-up visit (as per CRF)	15 (0.6%)	3 (1.0%)	0	18 (0.6%)
Did not complete the end of study follow-up visit	2602 (99.4%)	308 (99.0%)	74 (100%)	2984 (99.4%)
Subjects discontinued from the study during EAP	16 (0.6%)	1 (0.3%)	2 (2.7%)	19 (0.6%)
Reason for subjects discontinuing from the study during EAP				
Adverse event	0	0	0	0
Pregnancy	0	0	0	0
Lack of efficacy	0	0	0	0
Physician decision	0	0	0	0
Sponsor request	0	0	0	0
Death	0	0	0	0
Lost to follow-up	7 (0.3%)	0	0	7 (0.2%)
Subject decision	9 (0.3%)	1 (0.3%)	2 (2.1%)	12 (0.4%)

Note: For the first step analysis, all subjects randomized by 28Jan2021 are included. The data cutoff date is 11Mar2021.

1. Cohort allocation for analysis was based on centrally assessed RT-qPCR test result from NP swab sample collected at baseline.
2. Subjects who completed day 29 visit or skipped day 29 visit but still are in the follow-up period were considered as completing the EAP

Recruitment

Study Initiation Date: 13 July 2020 (first participant first visit)

Primary completion date: 11 Mar 2021 (last participant last visit in the Efficacy Assessment Period).

The analyses presented in this report are based on a database lock date of 30 Mar 2021.

Conduct of the study

Table 42. Summary of key changes in conduct of study COV-2069

Protocol Amendment	Change(s) and Rationale
Appendix 16.1.1 Amendment 1	From protocol amendment 1 onward, only NP swabs were collected for the baseline SARS-CoV-2 RT-qPCR test. Previously, nasal swabs and saliva samples were also collected.
Appendix 16.1.1 Amendment 2	Protocol amendment 2 eased operational constraints by removing the requirement for participants to have sustained exposure to the index case for at least 48 hours (participants were to be living in the same household with the index case) and allowed flexibility in local diagnostic assays for SARS-CoV-2 used for randomization (data analysis was based on screening samples collected for RT-qPCR testing by the central laboratory).
Appendix 16.1.1 Amendment 3	From protocol amendment 3 onward, adolescent participants (age 12 to 17 years) were allowed to participate in the study.
Appendix 16.1.1 Amendment 4	From protocol amendment 4 onward, women who were pregnant or breastfeeding and men who were unwilling to use contraception were allowed to participate in the study. Previously, these populations were excluded.
Appendix 16.1.1 Amendment 5	Protocol amendment 5 introduced an administrative assessment of the sample size estimation based on updated literature on infection rates; the sample size was increased in protocol amendment 5 from 2200 to 3500 participants (Appendix 16.1.1 Amendment 6 Section 11.2). The amendment also allowed the use of COVID-19 vaccines in participants who have completed the EAP.
Appendix 16.1.1 Amendment 6	Protocol amendment 6 introduced separate primary, key secondary, other secondary, and exploratory endpoints for cohort A and cohort B. Separate analyses, each with its own alpha allocation and testing hierarchy, were to be conducted in these 2 study populations.

Protocol deviations

Approximately 3% of participants in cohort A and 6% in cohort B had important protocol deviations during the study, and incidences were comparable between treatment groups.

In the baseline seronegative subgroup in Cohort B, 3/207 (1.4%) participants were randomized despite having symptomatic infection and were subsequently removed from the efficacy population.

Baseline data

Cohort A:

In general, demographic characteristics are well balanced between the groups (Table 43).

Table 43. Demographics (Seronegative, mFAS-A, Study COV-2069)

Baseline-seronegative	Placebo (N=752)	REGN10933+ REGN10987 (N=753)	Total (N=1505)
Age (years)			
n	752	753	1505
Mean (SD)	42.7 (15.58)	43.2 (16.32)	42.9 (15.95)
Median	44.0	44.0	44.0
Q1 : Q3	31.0 : 54.0	30.0 : 55.0	30.0 : 55.0
Min : Max	12 : 92	12 : 87	12 : 92
Age Group (Years), n (%)			
>=12 to <18	34 (4.5%)	34 (4.5%)	68 (4.5%)
>=18 to <45	346 (46.0%)	346 (45.9%)	692 (46.0%)
>=45 to <65	317 (42.2%)	297 (39.4%)	614 (40.8%)
>=65 to <80	51 (6.8%)	73 (9.7%)	124 (8.2%)
>=80	4 (0.5%)	3 (0.4%)	7 (0.5%)
Sex, n (%)			
Male	358 (47.6%)	333 (44.2%)	691 (45.9%)
Female	394 (52.4%)	420 (55.8%)	814 (54.1%)
BMI group (kg/m^2)			
BMI < 30 kg/m^2	501 (66.6%)	487 (64.7%)	988 (65.6%)
BMI >= 30 kg/m^2	250 (33.2%)	261 (34.7%)	511 (34.0%)
Missing	1	5	6

Approximately 30% of baseline-seronegative participants in cohort A had risk factors at baseline for severe COVID-19 if they were to become infected (as defined in the SAP) and risk factors were generally balanced between treatment groups. Risk factors present in more than 10% of participants were BMI ≥35 kg/m2 and age ≥65 years with cardiovascular disease (CVD), hypertension, or chronic obstructive pulmonary disease (COPD). Fewer than 2% of participants were immunosuppressed (due to disease or to immunosuppressive treatment).

Based on information collected during an interview with study participants at baseline, the characteristics of participants' interaction with their index case were similar between the treatment groups. Approximately 30% in both treatment groups shared a bedroom with the index case at baseline, and approximately 95% shared a common room.

Cohort B

The Applicant decided to include only the data of a subset of Cohort B, namely Cohort B seronegative, in the main efficacy analysis.

In general, demographic characteristics were well balanced between the groups beside some imbalances regarding the risk factors (Table 44).

Table 44. Demographics (Seronegative, Randomised Subjects in Cohort B, Study COV-2069)

Baseline-seronegative	Placebo (N=106)	REGN10933+ REGN10987 (N=101)	Total (N=207)
Age (years)			
n	106	101	207
Mean (SD)	42.5 (18.26)	39.2 (17.65)	40.9 (18.00)
Median	42.5	39.0	40.0
Q1 : Q3	25.0 : 58.0	24.0 : 51.0	24.0 : 55.0
Min : Max	12 : 87	12 : 87	12 : 87
Age Group (Years), n (%)			
>=12 to <18	11 (10.4%)	15 (14.9%)	26 (12.6%)
>=18 to <45	46 (43.4%)	44 (43.6%)	90 (43.5%)
>=45 to <65	35 (33.0%)	33 (32.7%)	68 (32.9%)
>=65 to <80	12 (11.3%)	8 (7.9%)	20 (9.7%)
>=80	2 (1.9%)	1 (1.0%)	3 (1.4%)
Sex, n (%)			
Male	43 (40.6%)	51 (50.5%)	94 (45.4%)
Female	63 (59.4%)	50 (49.5%)	113 (54.6%)
BMI group (kg/m²)			
BMI < 30 kg/m²	74 (69.8%)	63 (62.4%)	137 (66.2%)
BMI >= 30 kg/m²	30 (28.3%)	37 (36.6%)	67 (32.4%)
Missing	2	1	3

More than 30% of participants had baseline risk factors for severe COVID-19 if they were to become infected groups. Risk factors present in more than 10% of participants were age ≥65 years, BMI ≥35 kg/m2 and age ≥55 years with CVD, hypertension, or COPD. In each treatment group, ≤3% of participants were immunosuppressed (due to disease or to immunosuppressive treatment). More participants in the casirivimab+imdevimab group had a BMI ≥35 kg/m2 (16.0% vs 10.6% in the placebo group). More participants in the placebo group had diabetes (10.6% vs 5.0% in the casirivimab+imdevimab group). Other risk factors were generally balanced between the treatment groups, with a difference in incidence <5%.

Numbers analysed

Table 45. Safety and efficacy analysis sets, randomised population Study COV-2069)

	Placebo (N=1522)	REGN10933+REGN10987 (N=1507)	Total (N=3029)
Efficacy analysis sets			
Seronegative mFAS-A	752 (49.4%)	753 (50.0%)	1505 (49.7%)
Seronegative mFAS-B	104 (6.8%)	100 (6.6%)	204 (6.7%)
Safety analysis sets			
Cohort A	1306 (85.8%)	1311 (87.0%)	2617 (86.4%)
Cohort B	156 (10.2%)	155 (10.3%)	311 (10.3%)
Cohort Undetermined	47 (3.1%)	27 (1.8%)	74 (2.4%)

Note: For the first step analysis, all subjects randomized by 28Jan2021 are included. The data cutoff date is 11Mar2021. For efficacy analysis, 554 subjects in cohort A who were in the administrative assessment are excluded.

Outcomes and estimation

Cohort A: Negative SARS-CoV-2 RT-qPCR status at baseline

Effect on symptomatic SARS-CoV-2 infection

In mFAS-A, there was an 81.4% relative risk reduction for symptomatic, RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) in the REGN-COV2 group vs. placebo (Table 46).

Table 46. Proportion of participants with symptomatic SARS-CoV-2 infection (broad-term) during the EAP (Seronegative mFAS-A, Study COV-2069)

Criteria: Symptomatic Infection (By Broad-term Definition)	Placebo (N=752)	REGN10933+ REGN10987 (N=753)
Proportion of subjects meeting the criteria based on the central lab or local confirmatory positive RT-qPCR test	59/752 (7.8%)	11/753 (1.5%)
Risk reduction vs Placebo		81.4%
Odds ratio estimate (drug vs placebo) [1]		0.17
95% CI		(0.090 to 0.332)
p-value vs placebo		<0.0001

Note: For the first step analysis, the data cutoff date is 11Mar2021.

1. The CI with p-value is based on the odds ratio (casirivimab+imdevimab group vs placebo group) using a logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).

The hierarchical results for the primary efficacy analysis for Cohort A are summarised in Table 47.

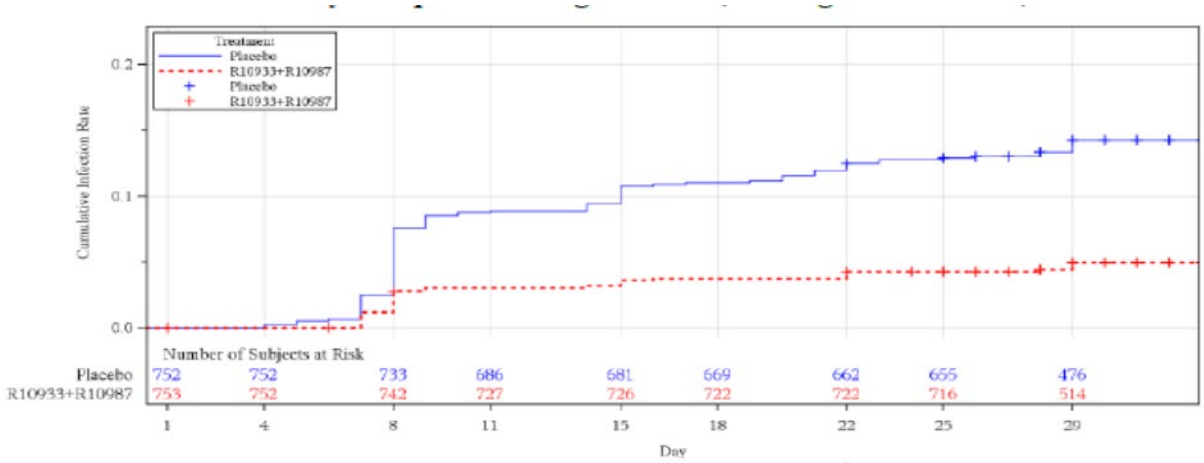
Table 47. Summary of hierarchical results for the primary efficacy analysis for Cohort A, Study COV-2069

No.	Endpoint	Treatment Effect; OR (95% CI)	P-value
1	Proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP	81.4% risk reduction; OR: 0.17 (0.090, 0.332)	<0.0001[1]
2	Proportion of subjects with viral load >4 (log_{10} copies/mL) during the EAP	85.8% risk reduction; OR: 0.13 (0.069, 0.236)	<0.0001[1]
3	Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP	93.1% reduction; 17.1 vs 249.6 weeks per 1000 subjects	<0.0001[2]
4	Number of weeks of high-viral load >4 (log_{10} copies/mL) during the EAP	89.6% reduction; 18.8 vs 181.6 weeks per 1000 subjects	<0.0001[2]
5	Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	82.3% reduction; 54.4 vs 307.2 weeks per 1000 subjects	<0.0001[2]
6	Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	66.4% risk reduction; OR: 0.31 (0.208, 0.456)	<0.0001[3]
7	Proportion of placebo subjects with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP living with a household member receiving the active treatment in R10933-10987-COV-2067 compared to placebo subjects not living with any household members receiving the active treatment in R10933-10987-COV-2067	No reduction; 19.8% vs 19.6% (index case receiving active treatment vs placebo in Study COV-2067 who were linked to a placebo-treated subject in this study)	1.0000[4]

1. The CI with p-value is based on the odds ratio (casirivimab+imdevimab group vs placebo group) using a logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).
2. The p-value is based on a stratified Wilcoxon rank sum test (Van Elteren Test) with the strata region (US vs ex-US) and age group (age in years:>=12 to<50 and >=50).
3. Based on multiple imputations using fully conditional specification followed by a logistic regression model including the treatment group, region (US vs ex-US) and age group (12 to <50 vs ≥50 years).

The cumulative incidence of SARS-CoV-2 infection diverged between the treatment groups by day 8 (i.e., the first post-baseline NP swab sample collection), and a reduced incidence compared to placebo was maintained in the casirivimab+imdevimab group through day 29 (Figure 19).

Figure 19. Kaplan-Meier cumulative incidence of time to first positive SAR-CoV-2 infection by RT-qPCR during the EAP, Seronegative mFAS-A, Study COV-2069



Note: For the first step analysis, the data cutoff date is 11Mar2021.

Ancillary analyses

Seropositive subjects at baseline

In the overall group regardless of baseline serostatus, REGN-COV2 gave a statistically significant reduction in symptomatic infections. In the subset that was seropositive at baseline, REGN-COV2 numerically reduced the risk of symptomatic infections by 81% based on a total of 6 cases (5 on placebo).

Effect on viral load

There was an 86% relative risk reduction in the proportion of subjects with high SARS-CoV-2 viral load (>10^4 copies/ml) infection for REGN-COV2 vs. placebo (Table 48).

Table 48. Proportion of participants with high viral load (>4 $\log_{10}$ copies/mL) in NP swab samples during the EAP (Seronegative mFAS-A, Study COV-2069)

Symptomatic Infection	Placebo (N=749)	REGN10933+ REGN10987 (N=745)
Proportion of subjects with high viral load (>4 $\log_{10}$ copies/mL)	85/749 (11.3%)	12/745 (1.6%)
Risk reduction vs Placebo		85.8%
Odds ratio estimate (drug vs placebo) [1]		0.13
95% CI		(0.069 to 0.236)
p-value vs placebo		<0.0001

Consistent with this finding, there was a 90% reduction in the number of weeks of high viral load for REGN-COV2 vs. placebo.

In those who became infected with SARS-CoV-2, REGN-COV2 treatment prevented high viral load in symptomatic and asymptomatic subjects. Furthermore, REGN-COV2-treated subjects exhibited decreased peak viral load vs. placebo and a shorter duration of viral shedding (Table 49).

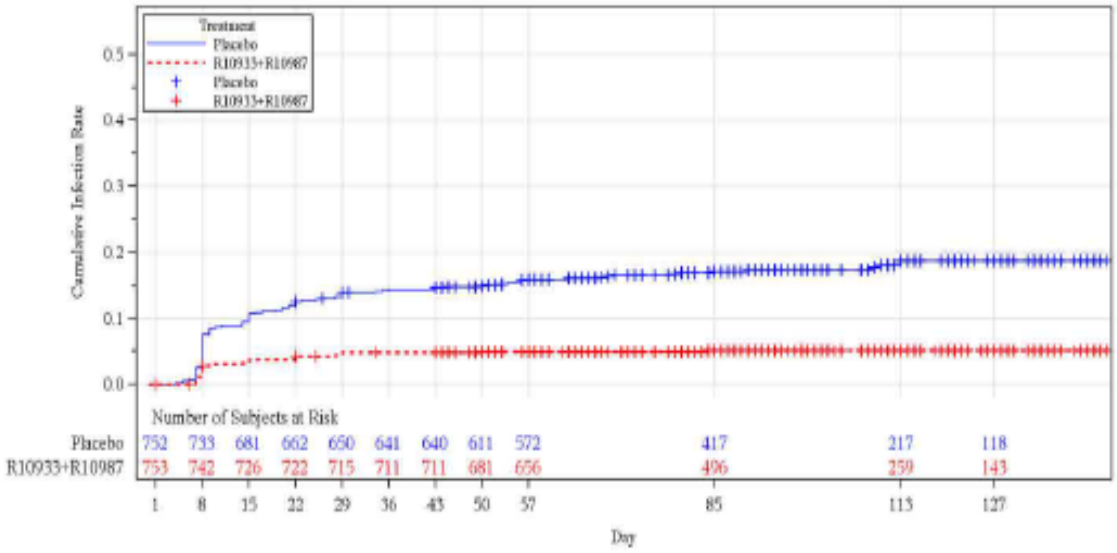
Table 49. Summary of viral endpoints (Seronegative mFAS-A, Study COV-2069)

Endpoint Mean (SD)	Placebo (N=107)	REGN10933+ REGN10987 (N=36)	LS mean difference (SE) [95% CI][1]	Nominal P-value[1]
Number of participants analyzed	98	33		
Time-weighted average of viral load (log_{10} copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the second weekly visit after the first positive test	3.789 (1.8775)	1.337 (0.9253)	-2.483 (0.342) [-3.161 to -1.806]	<0.0001
Time-weighted average of viral load (log_{10} copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the third weekly visit after the first positive test	3.070 (1.6477)	0.986 (0.6300)	-2.123 (0.295) [-2.707 to -1.539]	<0.0001
Number of participants analyzed	107	36		
Maximum SARS-CoV-2 RT-qPCR viral load (log_{10} copies/mL) in NP swab samples among individuals with ≥1 positive RT-qPCR that has an onset during the EAP	6.414 (2.2020)	3.990 (1.2606)	-2.428 (0.389) [-3.196 to -1.659]	<0.0001
Number of participants analyzed	104	36		
SARS-CoV-2 RT-qPCR viral load (log_{10} copies/mL) in NP swab samples corresponding to the onset of first positive RT-qPCR during the EAP	6.389 (2.1487)	3.964 (1.2807)	-2.441 (0.381) [-3.194 to -1.688]	<0.0001
Number of participants analyzed	81	33		
Area under the curve in viral load (log_{10} copies/mL·day) from the first positive SARS-CoV-2 RT-qPCR NP swab samples detected during the EAP until the first confirmed negative test[2]	65.982 (47.6933)	19.700 (14.8257)	-47.676 (8.650) [-64.818 to -30.534]	<0.0001

Summary of events after Day 29

There were more infections (symptomatic and asymptomatic) in the placebo group compared to the REGN-COV2 group after Day 29.
A first onset of any RT-qPCR-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) from Day 29 occurred in 2/753 (0.3%) in the REGN-COV2 group vs. 25/752 (3.3%) in the placebo group (Figure 20).

Figure 20. Kaplan-Meier cumulative incidence curve of time to first positive RT=PCR during Study COV-2069A



Cohort B (positive SARS-CoV-2 RT-qPCR status at baseline)

Effect on progression to symptomatic infection

Efficacy analyses for cohort B were conducted using the seronegative modified full analysis set (mFAS-B), which consisted of randomised participants with asymptomatic infection (i.e., positive for SARS-CoV-2 per central lab RT-qPCR test) and who did not test positive for antibodies for SARS-CoV-2 at baseline (per central lab serology testing), during the EAP.

In the mFAS-B, there was a statistically significant risk reduction in development of symptomatic disease (broad-term) with REGN-COV2 treatment vs. placebo (Table 50). at the nominal level of α=0.05.

Table 50. Proportion of participants who subsequently develop signs and symptoms (broad-term) with and onset within 14 days of a positive RT-qPCR at baseline or during the EAP (Seronegative mFAS-B, Study COV-2069)

Symptomatic Infection	Placebo (N=104)	REGN10933+ REGN10987 (N=100)
Broad-term definition, central RT-qPCR test (primary)	44/104 (42.3%)	29/100 (29.0%)
Risk reduction vs Placebo		31.5%
Odds ratio estimate (drug vs placebo) [1]		0.54
95% CI		(0.298 to 0.966)
p-value vs placebo		0.0380

Note: For the first step analysis, the data cutoff date is 11Mar2021.
If a visit with a missing central lab RT-qPCR result had a local confirmatory positive RT-qPCR for a subject with a COVID-19 symptom occurring within 14 days, that visit was considered to have a positive RT-qPCR result.
1. The CI with p-value is based on the odds ratio (casirivimab+imdevimab group vs placebo group) using a logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to <50 and >=50), and region (US vs ex-US).

The hierarchical results for the primary efficacy analysis for Cohort bare summarised in Table 51.

Table 51. Summary of hierarchical results for the first-step efficacy analysis for Cohort B, Study COV-2069

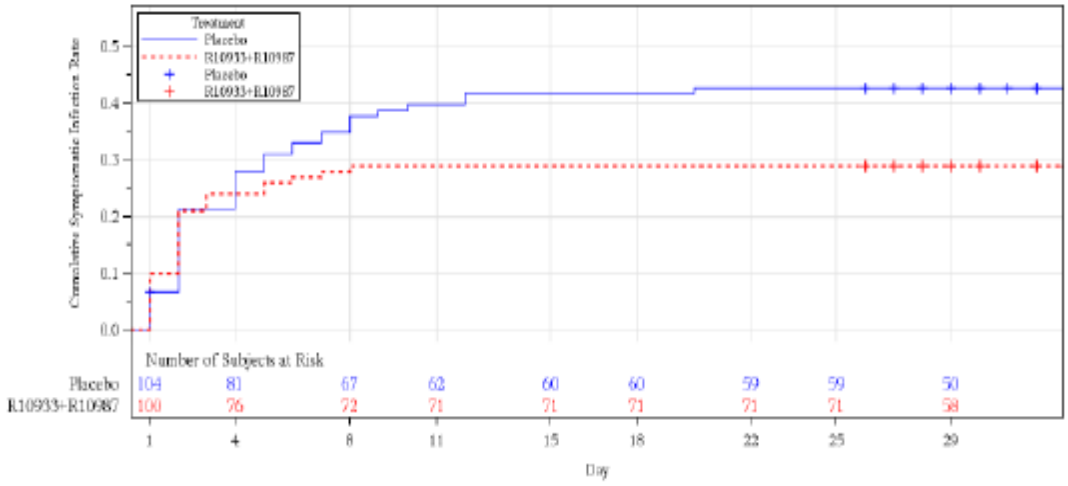
No.	Endpoint	Treatment Effect; OR (95% CI)	P-value
1	Proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP	31.5% risk reduction; OR: 0.54 (0.298, 0.966)	0.0380[1]
2	Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR during the EAP	45.3% reduction; 895.7 vs 1637.4 weeks per 1000 subjects	0.0273[2]
3	Number of weeks of high viral load (log_{10} copies/mL) >4 during the EAP	39.7% reduction; 489.8 vs 811.9 weeks per 1000 subjects	0.0010[2]

Note: For the first step analysis, the data cutoff date is 11Mar2021.

1. The CI with p-value is based on the odds ratio (casirivimab+imdevimab group vs placebo group) using a logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).
2. The p-value is based on a stratified Wilcoxon rank sum test (Van Elteren Test) with the strata region (Us vs ex-US) and age group (age in years:>=12 to<50 and >=50).

The reduction in progression to symptomatic infection was most apparent after Day 3. Also, risk reduction increased from 72% in the first week to 93% from weeks 2-4 (Figure 21).

Figure 21. Kaplan-Meier cumulative incidence of time to first symptom within 14 days of a positive RT-qPCR, Seronegative mFAS-B, Study COV-2069



Ancillary analyses

Seropositive subjects at baseline

For all subjects regardless of baseline serostatus, Ronapreve reduced the risk of symptomatic infections by 35%, which reached statistical significance. In the seropositive subset of Cohort B based on 9 cases, Ronapreve reduced the risk of symptomatic infections by 34%. Baseline seropositive subjects had a

lower rate of development of symptomatic infection compared to baseline seronegative subjects (44/104; 42.3% vs. 5/38; 13.2%).

Effect on viral load

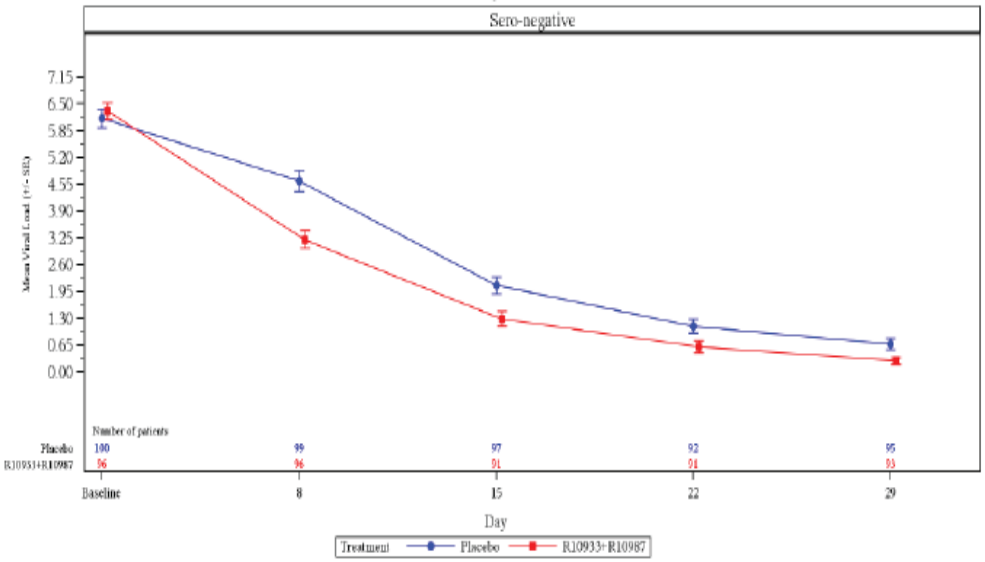
In the mFAS-B, there was a 40% reduction in the number of weeks (based on mean per subject and cumulative across all subjects in each group) of high viral load infection for Ronapreve vs. placebo (Table 52).

Table 52. Number of weeks of high viral load (>4 $\log_{10}$ copies/mL) in NP swab samples during the EAP (Seronegative mFAS-B, Study COV-2069)

	Placebo (N=101)	REGN10933+ REGN10987 (N=98)
Total number of weeks of high viral load	82	48
Total duration (weeks) of high viral load per 1000 subjects	811.9	489.8
Reduction vs Placebo		39.7%
Number of weeks of high viral load (among all subjects in seronegative mFAS-B)		
n	101	98
Mean (SD)	0.81 (0.758)	0.49 (0.677)
Median	1.00	0.00
Q1 : Q3	0.00 : 1.00	0.00 : 1.00
Min : Max	0.0 : 3.0	0.0 : 3.0
p-value vs placebo		0.0010
Proportion of subjects with high viral load by duration		
0 week	38 (37.6%)	58 (59.2%)
1 week	46 (45.5%)	34 (34.7%)
2 weeks	15 (14.9%)	4 (4.1%)
3 weeks	2 (2.0%)	2 (2.0%)
4 weeks	0	0
Subjects with a high viral load during the EAP		
Number of weeks of high viral load		
n	63	40
Mean (SD)	1.30 (0.528)	1.20 (0.516)
Median	1.00	1.00
Q1:Q3	1.00 : 2.00	1.00 : 1.00
Min: Max	1.0 : 3.0	1.0 : 3.0

Moreover, Ronapreve reduced the viral load faster than placebo, as summarised in Table 53.

Table 53. Mean viral load high viral load (log_{10} copies/mL) in NP swab samples over time during the EAP (randomised participants in Seronegative mFAS-B, Study COV-2069)



Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 54. Summary of RONAPREVE (casirivimab and imdevimab) efficacy for trial R10933-10987-COV-2067 (COV-2067)

Title: **A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19**		
Global Study identifier	NCT04425629 IND 148069 EudraCT 2020-003690-21 Sponsor's code R10933-10987-COV-2067 Short code COV-2067	
Design	This is an adaptive, seamless, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of casirivimab+imdevimab combination therapy in ambulatory patients (i.e., outpatients) with COVID-19. Phase 1 and phase 2 have completed, while phase 3 is ongoing (for safety assessment only).	
	8 months duration first patient, first visit: 16 June 2020	In phase 3, details of COVID-19-related medically attended visits are collected throughout the study up to day 29, with collection occurring minimally on a weekly basis. The trial is still ongoing because the assessment of safety continues to Day 169.
Hypothesis	Superiority	

Treatments groups	1200mg (Amendment 6 onwards)	600mg casirivimab + 600mg imdevimab single dose; IV (intravenous) 838 randomized
	2400mg	1200mg casirivimab + 1200mg imdevimab single dose; IV (intravenous) 1529 randomized
	8000mg (Through Amendment 5 only)	4000mg casirivimab + 4000mg imdevimab single dose; IV (intravenous) 700 randomized
	Placebo (Through to 25 February 2021)	Placebo single dose; IV (intravenous) 1500 randomized
Phases and protocol amendments	**Seamless design**. This is an adaptive seamless phase 1/2/3 study. A number of patients were initially enrolled in phase 3 prior to completion of the phase 1/2 analysis and subsequent phase 3 design adaptations. As a result, patients in cohort 1 of phase 3 initially continued the randomization scheme designed in phase 2, and were thus randomized 1:1:1 to a single IV dose of placebo, or to a single IV dose of RONAPREVE 2400 mg or 8000 mg. **Randomisation Dose Groups.** Based on the results of the primary efficacy analysis in phase 1/2, phase 3 was amended (protocol amendment 6) such that subsequent patients in cohort 1 were randomized 1:1:1 to a single IV dose of placebo, or to a RONAPREVE single IV dose of 1200 mg, or, 2400 mg. As of 25 Feb 2021, per IDMC recommendation, patients were randomized 1:1 to single IV dose of RONAPREVE 2400mg or 8000mg (no placebo). **Risk Factor.** The amended portion of phase 3 also required, as a condition of enrolment, that patients have symptomatic COVID-19 at baseline and at least 1 risk factor for developing severe COVID-19. The risk factor requirements are reflected in the primary efficacy analysis set. **Swab Sampling Schedule.** Prior to the amended portion of phase 3, NP swabs were collected according to the dense sampling schedule employed in phase 2. After phase 3 was amended, NP swab sample collection was reduced to approximately once weekly. Cohort 2 and cohort 3 were added to phase 3 in the amended portion. **Cohorts.** This tabular summary only includes patients randomized to cohort 1 on or prior to 17 Jan 2021. Cohort 1 is adult outpatients (≥18 years). Cohorts 2 and 3 were excluded from this efficacy analysis: cohort 2 were adolescent outpatients (<18 years at randomisation) and cohort 3 were outpatients (pregnant at randomisation).	

Phase 3 PRIMARY ENDPOINT	**ABBREVIATION**	**Phase 3 OBJECTIVE**
Proportion of patients with ≥1 COVID-19-related hospitalization or all cause death through day 29	**D1-29 hospitalisation or death**	To evaluate the clinical efficacy of RONAPREVE compared to placebo as measured by COVID-19-related hospitalizations or all cause death
Phase 3 KEY 2º ENDPOINTS	**ABBREVIATION**	**Phase 3 KEY 2º OBJECTIVES**
Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29	**D4-29 hospitalisation or death**	To evaluate the clinical efficacy of RONAPREVE compared to placebo as measured by COVID-19-related hospitalizations or all cause death
Time to COVID-19 symptoms resolution (defined as time from randomization to first day when patient scored 0 on all 19 analysed symptoms except Cough, Fatigue, and Headache, for which the patient	**Time to Symptom Resolution**	To evaluate the impact of RONAPREVE on the resolution of self-reported COVID-19 symptoms compared to placebo

could have a score of 1/2 (mild/moderate symptom) or 0 (no symptom). 0 = no symptom 1 = mild symptom 2 = moderate symptom 3 = severe symptom			
Database lock (primary analysis)	15 March 2021	Data cut-off: 18 February 2021 (efficacy and safety) Phase 3 efficacy analysis includes all participants randomized through 17 January 2021.	
Results and Analysis **FAS = Full Analysis Set** **mFAS = modified Full Analysis Set** **Seronegative mFAS = patients in mFAS with no positive antibody result from available testing**		**The number of patients included in each analysis population is provided here for patients with ≥1 risk factor for severe COVID-19.** **A total of 4567 randomized patients had ≥1 risk factor for severe COVID-19, and 4057 (88.8%) met the criteria for the mFAS.** **In addition, 1040 randomized patients had no risk factors.**	

PRIMARY EFFICACY ENDPOINT ANALYSIS

DAY 29 Efficacy

Proportion of Patients with COVID-19-related Hospitalization or All-cause Death Through Day 29 for RONAPREVE 2400 mg IV (mFAS)

	placebo	**2400mg**
N (number of patients)	1341	1355
Proportion of patients with events	62/1341 (4.6%)	18/1355 (1.3%)
95% CI Clopper-Pearson method	3.6%, 5.9%	0.8%, 2.1%
Relative Risk versus placebo		0.287
95% CI Farrington-Manning method		0.171, 0.483
Relative risk reduction versus placebo		71.3%
95% CI Farrington-Manning method		51.7%, 82.9%
p-Value Cochran-Mantel-Haenszel (CMH) test		<0.0001

PRIMARY EFFICACY ENDPOINT ANALYSIS

DAY 29 Efficacy

Proportion of Patients with COVID-19-related Hospitalization or All-cause Death Through Day 29 for RONAPREVE 1200 mg IV (mFAS)

	placebo	**1200mg**
N (number of patients)	748	736
Proportion of patients with events	24/748 (3.2%)	7/736 (1.0%)
95% CI Clopper-Pearson method	2.1%, 4.7%	0.4%, 1.9%

Relative Risk versus placebo	0.296
95% CI **Farrington-Manning method**	0.129, 0.684
Relative risk reduction versus placebo	70.4%
95% CI **Farrington-Manning method**	31.6%, 87.1%
p-Value **Cochran-Mantel-Haenszel (CMH) test**	0.0024

The phase 3 efficacy analysis used a pre-specified hierarchical testing strategy to control for multiplicity for testing the primary and key secondary endpoints. In the table below the analysis of all clinical endpoints in the statistical hierarchy has demonstrated statistical significance in COV-2067 vs placebo.

Endpoint Analysis	Primary Analysis Population	Treatment Groups	Relative Risk Reduction (%); events	Confidence Interval
D1-29 hospitalisation or death	mFAS	2400mg	71.3% (18/1355 vs 62/1341)	95% CI 51.7%, 82.9%; P<0.0001
	mFAS	1200mg	70.4% (7/736 vs 24/748)	95% CI 31.6%, 81.7% P=0.0024
D1-29 hospitalisation or death	mFAS with baseline viral load >10^6 copies/mL	2400mg	77.6% (13/924 vs 55/876)	95% CI 59.3%, 87.7% P<0.0001
D1-29 hospitalisation or death	Seronegative mFAS	2400mg	75.8% (12/940 vs 49/930)	95% CI 54.7%, 87.0% P<0.0001
D1-29 hospitalisation or death	mFAS with baseline viral load >10^6 copies/mL	1200mg	70.7% (6/482 vs 20/471)	95% CI 27.6%, 88.1% P=0.0045
D1-29 hospitalisation or death	Seronegative mFAS	1200mg	82.7% (3/500 vs 18/519)	95% CI 41.6%, 94.9% P=0.0014
D4-29 hospitalisation or death	mFAS	2400mg	89.2% (5/1351 vs 46/1340)	95% CI 73.0%, 95.7% P<0.0001
	mFAS	1200mg	71.7% (5/735 vs 18/748)	95% CI 24.3%, 89.4% P=0.0101
Time to Symptom Resolution	mFAS	2400mg	Median 10 days vs 14 days	P<0.0001
Time to Symptom Resolution	mFAS	1200mg	Median 10 days vs 14 days	P<0.0001

OTHER PHASE 3 SECONDARY ENDPOINT		ABBREVIATION	OBJECTIVE	
Secondary Efficacy Endpoint: VIROLOGIC Time-weighted average daily change from baseline in viral load (log10 copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal (NP) swab samples (participants enrolled prior to the adapted portion of phase 3, protocol amendment 6)		**TWA anti-viral**	To evaluate the virologic efficacy of RONAPREVE compared to placebo in reducing viral load of SARS-CoV-2	
	Placebo	**2400mg**	**8000mg**	**2400mg + 8000mg Combined TOTAL**
mFAS	593	619	625	1244
N	571	603	608	1211
Mean	-1.32	-1.91	-1.92	-1.91
95% CI	-1.49, -1.16	-2.07, -1.74	-2.09, -1.76	-2.07, -1.76
Difference versus placebo	Mean	-0.58	-0.6	-0.59
	95% CI	-0.70, -0.46	-0.72, -0.48	-0.69, -0.49
	p-Value	<0.0001	<0.0001	<0.0001

Table 55. Summary of RONAPREVE (casirivimab and imdevimab) efficacy for trial R10933-10987-COV-2069 (COV-2069)

Title: **A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2**		
Study identifier	NCT 04452318 EudraCT 2020-003654-71 IND 148069 R10933-10987-COV-2069 Short code COV-2069	
Design	This randomized, double-blind, placebo-controlled master protocol assessed the safety, tolerability, and efficacy of RONAPREVE in adult subjects and paediatric subjects who are household contacts of the first known household member infected with SARS-CoV-2 (index case).	
	First subject first visit Last subject last visit Efficacy phase duration Database lock (efficacy) Data cut-off (efficacy)	13 July 2020 11 March 2021 (efficacy assessment) 241 calendar days (approximately 34 weeks) 30 March 2021 11 March 2021

<table>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td rowspan="4">Treatments groups</td><td rowspan="2">SINGLE DOSE 1200mg</td><td>Cohort A</td><td rowspan="4">Cohort A was negative for SARS-CoV-2 Infection at Baseline (by RT-qPCR on Nasopharyngeal (NP) swab)
Cohort B was positive for SARS-CoV-2 Infection at Baseline (by RT-qPCR on NP swab)</td></tr>
<tr><td>Cohort B</td></tr>
<tr><td rowspan="2">SINGLE DOSE Placebo</td><td>Cohort A</td></tr>
<tr><td>Cohort B</td></tr>
<tr><td>Phases and populations and protocol amendments</td><td colspan="3">Cohorts of trial subjects. Two distinct study populations were analysed. Cohort A analyses evaluated infection prevention in participants who were uninfected at baseline, and cohort B evaluated early treatment to prevent symptomatic progression in participants with asymptomatic infection at baseline. For efficacy analysis, cohort allocation was based on results from the central laboratory assessment of SARS-CoV-2 RT-qPCR status at baseline: participants who were negative for SARS-CoV-2 (i.e., uninfected) were allocated to cohort A, and participants who were positive for SARS-CoV-2 (i.e., with asymptomatic infection) were allocated to cohort B. Cohort A and B had separate efficacy analyses, each with its own alpha allocation and testing hierarchy. During trial conduct, subjects were randomised according to local laboratory testing.

Administrative Assessment. In the absence of a phase 2 clinical trial, protocol amendment 5 (19 January 2021) introduced an administrative assessment of unblinded trial results. The data from 554 cohort A subjects (who were randomised up to 16 October 2020) were used to verify assumptions about infection rates and adequacy of sample size. Consequently, the sample size was increased from 2000 subjects to 3500 subjects (adults and adolescents) to accommodate the observed higher non-seronegativity rate and the unblinded administrative assessment. The planned total study population comprised ~3150 subjects in cohort A and ~350 subjects in cohort B, including the 554 subjects in the administrative assessment and approximately 250 paediatric subjects <12 years old (~225 subjects in cohort A1 and 25 subjects in cohort B1), with household contact exposure to an individual with a confirmed SARS-CoV-2 infection. The rationales for the primary and secondary objectives and endpoints were revised after the administrative assessment. The subjects who were included in the administrative assessment are excluded from the phase 3 efficacy analysis. In 409 out of 554 participants without prior infection (i.e., baseline-seronegative), the proportion of participants with symptomatic events in the RONAPREVE group was 0% (0/186) compared to 3.6% (8/223) in the placebo group. The 554 cohort A participants were excluded from the efficacy analysis population (i.e. seronegative mFAS) presented below (but were included in the safety analysis for cohort A). The administrative assessment did not include cohort B.</td></tr>
<tr><td colspan="4"></td></tr>
<tr><td colspan="4">COHORT A EFFICACY ANALYSIS</td></tr>
<tr><td>Primary Efficacy Endpoint</td><td colspan="2">Abbreviation</td><td>Primary Efficacy Objective</td></tr>
<tr><td>Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during efficacy assessment period</td><td colspan="2">Proportion symptomatic infection</td><td>To evaluate the efficacy of RONAPREVE compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR</td></tr>
</table>

Key Secondary Endpoints	Abbreviation	Key Secondary Objectives
Proportion of subjects with viral load >4 (log10 copies/mL) in NP (nasopharyngeal) swab samples in efficacy assessment	**Proportion High Viral Load**	To evaluate the efficacy of RONAPREVE compared to placebo in preventing a SARS-CoV-2 infection with a high viral load (i.e., viral load >4 log10 copies/mL)
Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) in efficacy assessment	**Symptom Duration**	To evaluate the impact of RONAPREVE compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS CoV-2 infection (broad-term) confirmed by RT-qPCR
Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples in efficacy assessment	**High viral Load Duration**	To evaluate the impact of RONAPREVE compared to placebo on the duration of SARS-CoV-2 infection with a high viral load (i.e., viral load >4 log10 copies/mL)
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) in efficacy assessment	**Duration Infection**	To evaluate the impact of RONAPREVE compared to placebo on the duration of SARS-CoV-2 infection
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) in efficacy assessment	**Proportion Infected**	To evaluate the efficacy of RONAPREVE compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
Proportion of subjects in the placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study COV-2067 (comparison of those whose index cases received RONAPREVE versus placebo in study COV-2067)	**Proportion Placebo Index**	To evaluate the impact of treating the index case with RONAPREVE on the incidence of SARS-CoV-2 infection among household contacts in the placebo group (This is a cross-study analysis based on only subjects in placebo group of study COV-2069 whose index cases participated in study COV-2067)

Results and Analysis

EAP: Efficacy assessment period

mFAS = modified Full Analysis Set: randomized asymptomatic subjects with negative RT-qPCR at baseline excluding 554 randomized Cohort A subjects in the administrative assessment

Seronegative mFAS = asymptomatic subjects in mFAS with negative antibody result at baseline from available testing

PRIMARY EFFICACY ENDPOINT ANALYSIS
COHORT A

Proportion of Participants with Symptomatic SARS-CoV-2 Infection (Broad-Term) During the Efficacy Assessment Period (Seronegative mFAS-A) (Proportion symptomatic infection)

	placebo	1200mg
Seronegative mFAS-A	752	753
Proportion of subjects meeting criteria (central lab, or, local RT-qPCR)	59/752 (7.8%)	11/753 (1.5%)
Relative Risk reduction versus placebo		81.4%
Odds ratio estimate (logistic regression with fixed effects of treatment group, age group (age in years:>=12 to <50 and >=50), and region (US versus ex-US)		0.17

95% CI	0.090, 0.332
P Value	<0.0001

PROPORTION PLACEBO INDEX **Proportion of Participants in Placebo Group with a RT-qPCR Confirmed SARS-CoV-2 Infection with an Index Case Participating in Outpatient Treatment Study R10933-10987-COV-2067**	
Analyses were conducted to determine whether treatment of an index case with RONAPREVE had any impact on the incidence of SARS-CoV-2 infection in household contacts. Of the participants who developed SARS-CoV-2 infection following exposure to an index case who was participating in Study COV-2067, the proportion of index cases who received treatment	No interaction was observed as the proportion of infected participants in the placebo group in COV-2069 was similar regardless of whether the index case received product or placebo in Study COV-2067 (10/51 [19.6%] vs 23/116 [19.8%] participants, respectively; p=1.0000). Treatment of the index case with product in Study COV-2067 therefore did not reduce infections in the household contact participants in the placebo group in cohort A.

COHORT B EFFICACY ANALYSIS		
Primary Efficacy Endpoint	**Abbreviation**	**Primary Efficacy Objective**
Proportion of participants who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	**Proportion symptomatic infection D14**	To evaluate the efficacy of RONAPREVE compared to placebo in preventing COVID-19 symptoms (broad-term)
Key Secondary Efficacy Endpoint	**Abbreviation**	**Key Secondary Efficacy Objective**
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	**Symptom Duration**	To evaluate the impact of RONAPREVE compared to placebo on the duration of signs and symptoms in participants with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
Number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples during the EAP	**High viral Load Duration**	

PRIMARY EFFICACY ENDPOINT ANALYSIS **COHORT B**		
Proportion of participants who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP (% symptomatic infection D14)		
	placebo	**1200mg**
Subjects in seronegative mFAS-B	104	100
Broad term definition, central RT-qPCR	44/104 (42.3%)	29/100 (29.0%)
Relative Risk reduction versus placebo		31.5%
Odds ratio estimate. Logistic regression model with the fixed categorical effects of treatment		0.54

group, age group (age in years:>=12 to <50 and >=50), and region (US vs ex-US).	
95% CI	0.298, 0.966
P Value	0.0380
The efficacy analysis for cohort B met the primary endpoint and all key secondary endpoints in the pre-specified statistical testing hierarchy (see table below)	

COHORT B– Efficacy analysis of seronegative mFAS-B

#	Type	Endpoint	Treatment effect 95% CI	P Value
1	**Primary**	**Proportion symptomatic infection D14**	31.5% relative risk reduction 0.54 (0.298, 0.966)	0.0380
2	**Secondary**	**Symptom Duration**	45.3% reduction 895.7 vs 1637.4 weeks per 1000 subjects	0.0273
3	**Secondary**	**High viral Load Duration**	39.7% reduction 489.8 vs 811.9 weeks per 1000 subjects	0.0010

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No studies in special populations were submitted.

Supportive studies

HV-2093

This randomised and placebo-controlled study assesses the safety and PK of repeat subcutaneous (SC) administrations of Ronapreve at 4-week intervals. Eligible subjects were adults up to age 90 years who were healthy or had stable underlying medical conditions.

During the screening period, subjects were to have a negative result for SARS-CoV-2 RT-PCR by a central laboratory test applied to a NP swab obtained within 72 h of randomisation. Alternatively, screening assessment for SARS-CoV-2 infection could be based on a local test using an approved diagnostic assay. If the local test was negative and the subject was enrolled but the central laboratory result for the screening swab was subsequently reported as positive, subjects were to be discontinued. Serological testing for SARS-CoV-2 was conducted at baseline and was then to be repeated at weeks 25 (end of treatment period - EOTP) and week 53 (end of study – EOS). Subjects were discontinued if a symptomatic SARS-CoV-2 infection occurred.

Subjects were randomised in a 3:1 ratio to receive six SC doses of 1200 mg Ronapreve or placebo.

The primary endpoints are:

• Incidence of AESIs that occur within 4 days of SC administration of REGN10933+REGN10987 or placebo at baseline and days 29, 57, 85, 113 and 141
• Concentration of REGN10933 and REGN10987 in serum over time

All analyses of safety, immunogenicity and efficacy were descriptive.

According to protocol amendment 4, the treatment assignment of individual subjects could be unblinded on consideration by the investigator to allow the individual to receive vaccination against COVID-19 with a 90-day minimum interval from last receipt of Ronapreve.

Subjects who were unblinded were discontinued, whether they went on to receive vaccination.

Results

The applicant provided an interim analysis with a data cut off on 13 March 2021 and a lock date of 13 April 2021 based on 974 randomised subjects, of which 969 received at least one dose of assigned study treatment. One subject randomised to placebo received a dose of 1200 mg Ronapreve and is counted in the Ronapreve group.

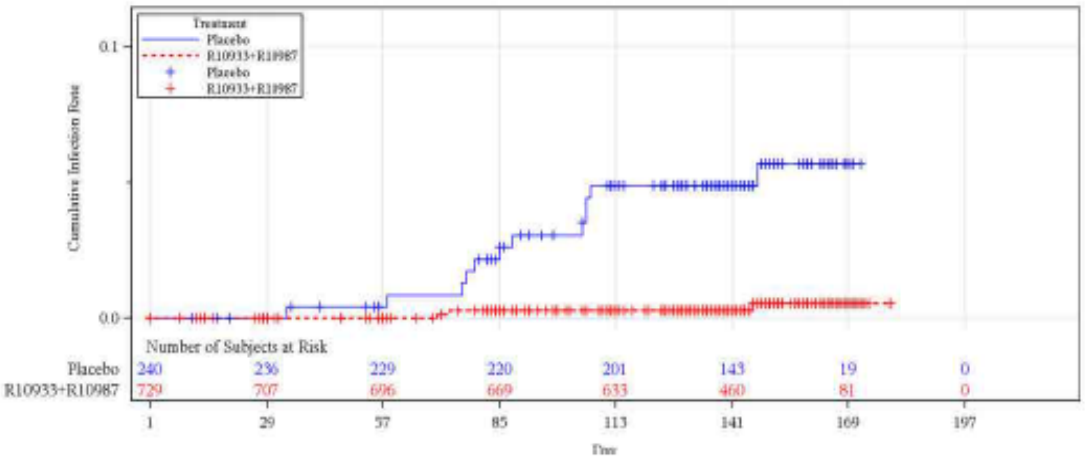
At the time of the data cut off, no subjects had reached end of study (day 28 after the week 24 dose). There had been 111 discontinuations from treatment, of which 53 discontinued from study. Of the total, 13 discontinued due to COVID-19 (10 placebo and 3 Ronapreve; see further below). The mean age for the population was 47 years, with 13% aged ≥65 years, and 55% were of male gender.

At baseline, 6 subjects (0.6%) were found to be positive for SARS-CoV-2 based on the central laboratory RT-PCR and 85 (8.8%) had positive serology (at least one of anti-spike IgA or IgG or anti-N IgG). The subjects who were RT-PCR positive for the virus were discontinued from further study doses but were followed for safety. The seropositive subjects continued in the study.

At the data cut off, ~60% had received all 6 doses of assigned treatment and >80% had received 5 doses. Study drug adherence was high (>96%) in both groups.

Since the assessment of efficacy was exploratory, cases of symptomatic COVID-19 (not necessarily RT-PCR confirmed) were captured as AEs. During the 6-month treatment period, there was a 91.8% relative risk reduction for symptomatic COVID-19 in the Ronapreve group vs. placebo group. This was based on 15 cases (3 on active and 12 on placebo).

Figure 22. Kaplan Meier cumulative incidence curve of time to symptomatic SARS-CoV-2 infection during the treatment period in Study HV-2093.



Nine of 12 cases in the placebo group had a positive SARS-CoV-2 RT-PCR result or seroconverted whereas 0/3 subjects in the REGN-COV2 group were RT-PCR positive or seroconverted by the end of the treatment period.

A similar estimate of efficacy applied when counting all cases since there was only one additional case during follow-up and that occurred in the placebo group.

At baseline, ~67% per group were seronegative as defined above. By the time of cut off, 8/162 (4.9%) in the placebo group but none in the Ronapreve group had seroconverted. 5/238 (2.1%) in the placebo group who were RT-PCR negative at baseline subsequently had a positive result vs. none of 719 in the Ronapreve group. Since routine RT-PCR testing was not conducted post-baseline in this study, it is presumed that these 5 placebo subjects were among those who had symptomatic COVID-19.

COV-2066

This is an adaptive Phase 1/2/3 study to evaluate the safety and efficacy of Ronapreve in adults hospitalised for ≤72 hours prior to randomisation due to COVID-19. Eligible subjects were to have a SARS-CoV-2-positive antigen or molecular diagnostic test using an appropriate sample obtained ≤72 hours prior to randomisation and no alternative explanation for their clinical condition. Symptoms at baseline were to be consistent with COVID-19 as determined by investigator with onset ≤10 days before randomization.

Subjects were to be enrolled into four cohorts based on disease severity at randomisation. Those who met >1 criterion were to be included in the most severely affected category:

Cohort 1A: With COVID-19 symptoms but not requiring supplemental oxygen
Cohort 1: Maintains O2 saturation >93% on low-flow oxygen via nasal cannula, simple face mask or other similar device (saturation was corrected for altitude above sea level)
Cohort 2: High-intensity oxygen therapy without mechanical ventilation, defined as supplemental oxygen via:
– Non-rebreather mask (with SpO2 ≤96% on oxygen flow rate of at least 10 L/min)
– High-flow device (e.g. AIRVO™ or Optiflow™) with at least 50% FiO2

– Non-invasive ventilator, including CPAP
Cohort 3: On mechanical ventilation

Due to IDMC recommendations, enrolment into cohorts 2 and cohort 3 is on hold.

Subjects were randomised (1:1:1) to receive single IV doses of Ronapreve 2400 mg or 8000 mg or placebo. Randomisation was stratified by country (Phase 2 only) and the type of background standard-of-care being administered for COVID-19 at randomisation (Phase 1 and 2) as follows:
• Antiviral therapies only (e.g. remdesivir)
• Non-antiviral therapies: Immune-based therapies, both antiviral and immune-based therapies or no COVID-19-specific treatment.

The primary objectives of the phase 1/2 **(Cohort 1)** of the study was to exclude futility of Ronapreve vs. placebo based on rates of death or mechanical ventilation

Serial NP swabs were collected every other day for the first 2 weeks and then twice weekly to determine viral load by SARS-CoV-2 RT-qPCR and changes over time.

Analyses and sample size

The sample size for Cohort 1 assumed accrual of 35 events (death or mechanical ventilation) and a cumulative incidence of death or mechanical ventilation in the placebo group of 25% at day 29 (derived from the sarilumab study in COVID-19 subjects receiving low flow oxygen supplementation at baseline, with an assumption of twice this rate in the seronegative mFAS). Applying a futility threshold of α=0.3 (1-sided), the minimum HR between Ronapreve (pooled dose groups) vs. placebo that excludes futility is 0.827 (i.e. minimum risk reduction 17.3%). If the observed risk reduction is ~17% or lower, the assessment of efficacy would be declared futile.

It was estimated that 43 total events in the seronegative mFAS were needed to achieve 80% power to detect a risk reduction of 50% (HR=0.5) between Ronapreve group vs. placebo, at α=0.1 (one sided) level of significance. Assuming patients are followed through day 29, accrual takes 90 days and 30% of the FAS are eligible for the seronegative mFAS, 250 subjects were required across 3 arms.

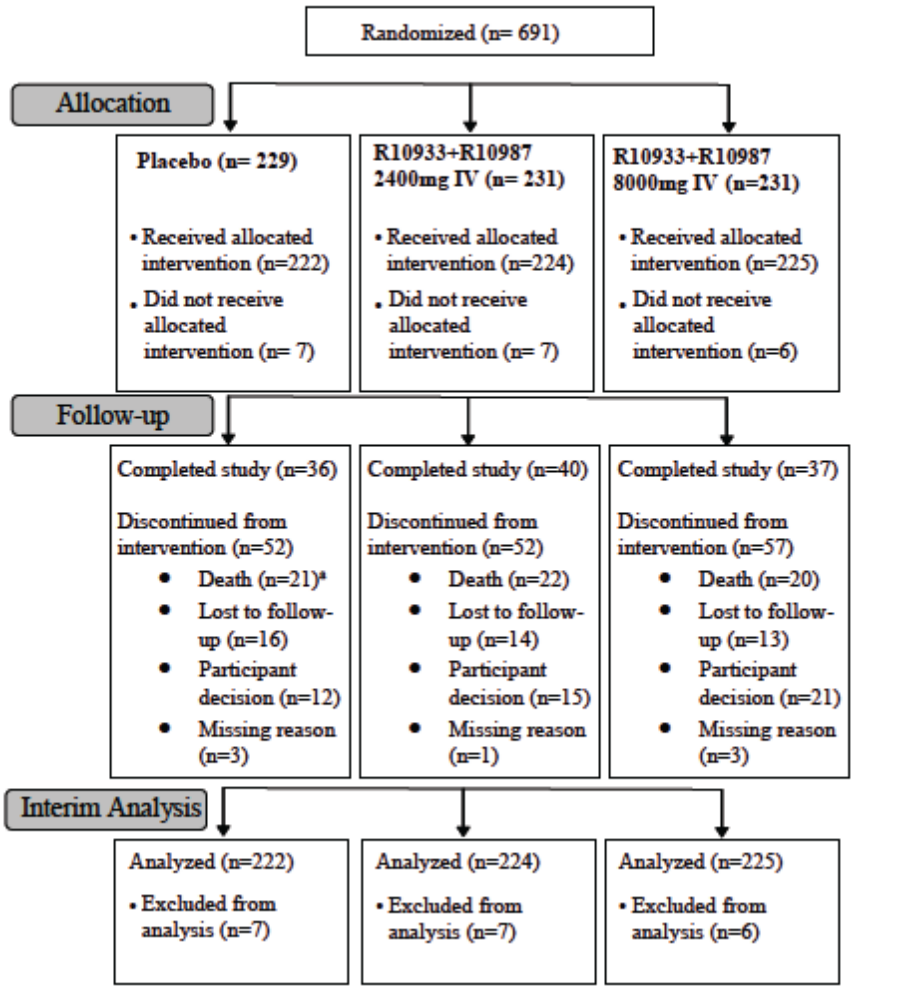
Results

The analysis submitted by the applicant is based on the study population enrolled by 01 Dec 2020.

The Phase 1/2 portion consisted of the first 671 subjects randomised and treated in Cohort 1 and all subjects randomised and treated in Cohort 2 (n=161) and Cohort 3 (n=35). While efficacy is reported for the subjects in Cohort 1, safety is reported for Cohorts 1, 2 and 3 up to the data cut off.

Subject disposition in Cohort 1 is summarised in Figure 28.

Figure 8. Cohort 1, Phase 1 and 2-Participant disposition, Study COV-2066



a: One participant in the cohort 1 placebo group died after end of study and is not captured in this diagram

Demographic characteristics and baseline virology and disease characteristics in the Cohort 1 FAS population (n=671) were generally comparable across the treatment groups.

The same pattern applied to the mFAS population (n=533), defined as patients that were central lab confirmed SARS-CoV-2 RT-qPCR positive at baseline from NP swab sample. However, there was a significantly higher viral load in the seronegative subsets vs. the seropositive subsets.

The initial futility analysis was conducted on a 09 Dec 2020 data cut, by which time all subjects had a minimum of 8 days of follow-up and 487 patients had at least 28 days of follow-up. Based on this data cut, futility was excluded in seronegative hospitalised patients on low flow oxygen, with a 22% reduction in the risk of death or mechanical ventilation for the pooled Ronapreve dose groups vs. placebo ($p = 0.23$, which was below the pre-specified $\alpha = 0.3$ [1-sided]). There was a 26.3% relative risk reduction in the proportion progressing to death or ventilation.

Using a data cut of 19 Jan 2021, by which time all subjects had achieved at least 28 days of follow-up, there was a 29% reduction in the risk of death or mechanical ventilation in baseline seronegatives for pooled Ronapreve groups vs. placebo ($p = 0.14$, which was also below the pre-specified $\alpha = 0.3$ [1-sided]).

A post-hoc proportions analysis applied to the second data cut revealed a 31.5% relative risk reduction for pooled Ronapreve dose groups vs. placebo in the proportion of baseline seronegatives who died or went on mechanical ventilation (p=0.095).

There was no apparent advantage for the higher Ronapreve dose group when each was compared to placebo in the baseline seronegative subsets. There were trends for risk reduction for death or mechanical ventilation for pooled Ronapreve dose groups vs. placebo in subsets of the mFAS with high baseline viral load ($>10^6$ and $>10^7$ copies/mL). Also, the trend to treatment benefit was observed regardless of the background concomitant COVID-19 therapies used, such as remdesivir or dexamethasone.

Using the second data cut, the benefit (on clinical endpoints) with Ronapreve seemed to start approximately 8 days after treatment. Additional analyses were done to evaluate the effect of Ronapreve from day 9 to 29, which showed a risk reduction of 69% (p = 0.006) in death or mechanical ventilation for baseline seronegative subjects.

In the placebo group 26.9% of seronegative vs. 11.6% of seropositive subjects progressed to death or mechanical ventilation. There was no appreciable benefit of Ronapreve in the baseline seropositive subsets although there was also no excess risk of progression to ventilation or death.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study COV-2067 is the pivotal study supporting the claimed indication of "treatment of confirmed COVID-19 in patients aged 12 years and older and weighing at least 40 kg that do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19".

Non-hospitalised patients with symptoms consistent with COVID-19, as determined by the investigator, with onset ≤7 days before randomisation who have a positive diagnostic test for SARSCoV-2 were enrolled in the study. SARS-CoV-2-positive diagnostic test from a sample collected ≤72 hours prior to randomisation, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay is an inclusion criterion. With amendment 6 phase 3 of the study was amended; patients in cohort 1 were enrolled if they had ≥1 risk factor for severe COVID-19

In Phase 1/2 two doses, namely 2400 mg and 8000 mg of casirivimab+imdevimab were explored. After completion of the Phase 1/2 a lower dose of 1200 mg of casirivimab+imdevimab was introduced in the ongoing Phase 3 study via amendment. The applicant was asked to clarify and to discuss how the late addition of a third dose arm (1200mg) might have impacted the balancing properties, and it was agreed that the impact was minor.

It is evident through the changes to the ongoing study that uncertainty was high at the initial planning stage and the trial underwent repeated refinement in light of accumulating information in an adaptive design approach. This is understood and acceptable in the pandemic situation, however some uncertainty remains and warrants discussion.

There was some uncertainty around the stopping criteria and the decision to unblind the data before the event-driven criteria, which had been used for the power calculations, were reached. The applicant confirmed that these rules were not considered, as the decision to stop enrolment was entirely based on

the recommendation by the DMC. However, the applicant also confirmed that the information from the ongoing phase 3 part of the study on observed events, was not used in amendments to the sample size or analysis of phase 3 cohort 1. Enrolment to the placebo arm in phase 3 was also stopped upon recommendation by the independent data monitoring committee. Following this decision, an interim analysis for the 1200 mg vs placebo arm was introduced in amendment 8. The applicant was asked to discuss the expected timing of the "final analysis" as compared to the timing of the "interim analysis" and justify the need for the interim analysis of 1200 mg vs placebo. Whilst the motivation around the late introduction of the interim analysis could not be verified, in view of the positive results it was agreed that this was unlikely to have a significant impact on the outcomes of the study.

The analysis of interim data was submitted, in which overrunning data were considered relevant. The applicant was asked to update the primary and key secondary results, including all concurrent patients in the comparisons of 2400mg vs placebo and 1200mg vs placebo, respectively. This analysis was consistent with the initial interim analysis.

The primary outcome variable of COVID-19-related hospitalization or all-cause death was analysed by means of a stratified CMH test for country. The approach to the primary analysis is considered reasonable. Changes were made to the primary endpoint and analysis model (previously a logrank-test for time to medically attended visits), but due to the rather short follow-up of 29 days for the primary endpoint, the dichotomous analysis seems more reasonable than the initially planned time-to-event endpoint.

Analyses of the primary and key secondary efficacy endpoints in these studies were conducted at a two-sided significance level of α=0.05 utilizing a hierarchical testing strategy to control for type I error (Table 22).

The primary analysis in phase 3 was conducted only in patients with ≥1 risk factor (introduced via Amendment 6 to the protocol) which was influenced by the results of the phase 1/2 results. This raised some uncertainty on whether the analysis sets optimally reflect clinical practise. However, the applicant provided results in the FAS with ≥1 risk factor, including subjects without confirmation of SARS-CoV-2 infection by PCR test which was consistent with the results from the primary analysis

The Applicant also provided a comparison of the demographics and baseline characteristics, excluding Virology and serostatus between Phase 3 mFAS overall, Phase 3 mFAS pre-amendment 6, Phase 3 mFAS post and Phase 3 Phase (all ≥1 risk factor, PCR positive) and Phase 3 FAS (no risk factors, PCR positive).Demographics and baseline characteristics were similar were similar between the 4 risk factor populations.

Prevention

Study COV-2069

Study COV-2069 is an ongoing, global, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study conducted in individuals at high-risk for SARS-CoV-2 infection and COVID-19 due to living with a known SARS-CoV-2-infected household member. Participants were randomized 1:1 to receive a single SC dose of casirivimab+imdevimab 1200 mg or placebo.

Study participants were asymptomatic, healthy adults and children (including those with a chronic, stable medical condition) who were household contacts to the first known household member with a diagnosis of SARS-CoV-2 infection (index case). Several members of the same household could be

included in the study. Participants themselves could have been negative (cohort A) or positive (B) for SARS-CoV-2 at screening.

An initially unplanned unblinded analysis, called administrative assessment was conducted for which there was concern that it could have affected the integrity of the study.

The applicant explained that there was some uncertainty despite blinded reassessment of some of the parameters and that this was the reason to conduct the administrative assessment. The applicant asserted that measures were taken to preserve integrity of the ongoing study and that the subjects analysed in the administrative assessment were excluded from further analyses of efficacy. This is supported, to avoid further inflation of type-I-error despite the fact the results of the administrative assessment were known to study personnel.

The study was planned to include approximately 3500 subjects, in order to have sufficient power to show a treatment effect in Cohorts A and B. There were uncertainties at the planning stage about household sizes and correlations, distribution of subjects across the cohorts and the distribution of the outcome variable. Accordingly, the sample size was reassessed during the ongoing study. The applicant asserted that assessment of the relevant parameters proportion of subjects with symptomatic/asymptomatic infections and the sero-positivity rate at baseline and household size was done without breaking the blind (except for the unblinded administrative assessment). The applicant confirmed that measures were taken to preserve integrity of the study.

Subjects were randomly assigned to casirivimab+imdevimab 1200 mg or placebo. The applicant stated that randomization was stratified for study site as well as local diagnostic assay for SARS-CoV-2 and age which is supported,

Analyses of the primary and key secondary endpoints were conducted at a two-sided $\alpha=0.05$ utilizing a hierarchical testing strategy to control for type I error. This was specified separately for each of the cohorts A and B. No strong control of type I error on the study level was implemented. The applicant argued that cohorts A and B should be interpreted as two independent studies, but this was not agreed by CHMP, mainly because of practicalities of identifying the cohorts. In consequence there were uncertainties around the interpretation of statistical significance.

The primary efficacy variable, the proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the 28 day efficacy assessment period, was planned to be analysed by means of a generalized linear model to estimate the odds ratio using a GEE approach to account for household correlation. The model was planned to be adjusted for region and age. The applicant presented in the SAP a simulation study discussing the impact of household correlation and household size on the statistical properties of this model and concluded that type-I-error is inflated if the proportion of households with only one study participant is large. Accordingly, the applicant defined a fall-back-strategy by means of a logistic regression adjusted for region and age and ignoring household. This fall-back method was in the end applied. Although households may play a role (within cohorts, and across cohorts A and B), this is not considered critical, and the fall-back strategy is endorsed.

The applicant confirmed that amendment 6, dated 25 March 2021 was finalized prior to the database lock and unblinding of the treatment assignment on 30 March 2021. Although the timing is not optimal and the late changes may have carried a risk to the integrity of the study, the applicant's response is considered sufficiently convincing and there is currently no reason to believe that decisions were data driven.

As of the cut-off dates for this CSR, 3096 participants were screened for the study. A total of 3029 participants were randomised, of whom 3002 were treated and were presented by cohort. Upon request the Applicant stated that in study COV-2069, of the 3096 subjects who were screened, 83 subjects

discontinued during the screening phase. The majority (65/83) of the subjects who discontinued during the screening phase were screen failed due to reasons related to inclusion/exclusion criteria. An additional 18 subjects discontinued during the screening period, most commonly due to subject decision to not participate in the study.

In general, demographic characteristics are well balanced between the groups (both cohorts). Of note, the Applicant decided to include only the data of a subset of Cohort B, namely Cohort B seronegative, in the main efficacy analysis.

Efficacy data and additional analyses

Treatment

Study COV-2067

The primary and key secondary endpoints tested hierarchically and reached nominal statistical significance at the level of 5%. The updated analysis which included overrunning information is the one considered most relevant to assess the treatment effect of casirivimab+imdevimab.

In patients with at least 1 risk factor for severe COVID-19 (phase 3 portion of COV-2067), treatment with casirivimab+imdevimab reduced the proportion of patients with COVID-19-related hospitalization or all-cause death by approximately 70% across all dose groups (1200 mg, 2400 mg, and 8000 mg) compared to placebo. The primary endpoint hospitalization for COVID-19 or all-case death is a composite endpoint, however results are driven by the incidence of hospitalization, and the data currently do not allow any conclusion on an effect of treatment (neither positive nor negative) on the occurrence of death. Of note, the incidence of death was low. There were 7 deaths reported as of the data cut; 5 in the placebo group, 1 in the casirivimab+imdevimab 1200 mg group and 1 in the casirivimab+imdevimab 2400 mg group). All considered related to advanced and progressive COVID-19 disease.

Post-hoc analysis across risk factor subgroups for severe COVID-10 disease showed similar clinical benefit in reduction in COVID-19-related hospitalization or all-cause death across all groups.

No dose dependent effect was observed. However, for some groups / events the number were low and do not allow a firm conclusion e.g. immunocompromised patient.

Casirivimab+imdevimab 1200 mg and 2400 mg both shortened the median time to symptom resolution by 3 day (median 10 days vs. 13 days for placebo). This finding lends support to the utility of treatment.

Single IV doses of casirivimab+imdevimab resulted in a statistically significant reduction in the LS mean viral load (log10 copies/mL) from baseline to day 7 compared to placebo (-0.71 log10 copies/mL for 1200 mg and -0.86 log10 copies/mL for 2400 mg; nominal $p<0.0001$ for both comparisons).

Reductions were observed in the overall mFAS population. Similar trends were observed in other subgroups, including by baseline viral load and serologic status, with greater reductions in those with higher viral load and baseline seronegative status.

For Study COV-2067 the data of Phase 3 in patients with > 1 risk factor (main efficacy population) as well as data in patients with no risk factor and in addition the Phase 1/2 data in patients with or without

risk factors were provided. The data of the Phase 1/2 part in patients with or without risk factors are consistent with the Phase 3 in patients with > 1 risk factor, a significant reduction of MAVs was observed. However, in Phase 3, in patients without risk factors the effect was smaller, and not significant. This suggest that the result of Phase 1 was driven by the patients with >risk factors.

Study COV-20145

In Study COV-20145 similar effect of reduction of MAVs was seen in all dose groups (2400 mg IV, 1200 mg IV, 1200 mg SC, 600 mg IV, 600 mg SC, 300 mg IV), however the numbers are small to draw a robust conclusion.

Prevention

Study COV-2069

Cohort A

The primary and key secondary endpoints tested hierarchically and reached statistical significance at the level of 5% except the last in the pre-specified statistical testing hierarchy.

Treatment with casirivimab+imdevimab significantly reduced the risk of symptomatic infection by 81.4% compared to placebo in uninfected participants (cohort A) who were seronegative at baseline ($p<0.0001$). Subgroup analyses were provided for the primary endpoint in cohort A to assess the consistency of results in participants with different demographic or other baseline characteristics. In general results demonstrated a consistent treatment effect across subpopulations, including subgroups based on age); race and ethnicity); gender, BMI, and region risk factors as defined in the SAP and household size

The risk of developing a high viral load infection (>4 log10 copies/mL) was reduced by 85.8% in the treatment group compared to placebo ($p<0.0001$)

The data indicate that active treatment of the index case in Study COV-2067 did not reduce the risk of symptomatic infection in the household contact compared to placebo. The outcome is not unexpected. Given the natural course of disease, participants in Study COV-2067 could have passed the infection to household contacts prior to treatment.

Cohort B

Efficacy analyses for cohort B were conducted using the seronegative modified full analysis set (mFAS-B), which consisted of randomised participants with asymptomatic infection (i.e., positive for SARS-CoV-2 per central lab RT-qPCR test) and who did not test positive for antibodies for SARS-CoV-2 at baseline (per central lab serology testing), during the EAP.

The primary and key secondary endpoints tested hierarchically and reached nominal statistical significance at the two-sided level of 5%. Statistical significance was considered uncertain due to lack of strong type I error control over the two cohorts A and B.

Treatment with casirivimab+imdevimab reduced the risk of progression to symptomatic disease seronegative participants with asymptomatic RT-qPCR-confirmed SARS-CoV-2 infection at baseline by 31.5% compared to placebo (nominal $p=0.0380$). A consistent, but no longer significant effect was observed (relative risk reduction 25.3%, $p=0.2329$) when using a different laboratory assay to determine SARS-CoV-2 infection status. A consistent treatment effect was observed in participants regardless of baseline serology, with a 35.4% risk reduction compared to placebo (OR 0.54 [0.325, 0.894], nominal $p=0.0166$). A comparable level of reduction was also shown when the analysis included

only baseline-positive participants (33.9% risk reduction vs placebo, OR 0.62 [0.147, 2.587], nominal p=0.5079), however not statistically significant (post hoc analysis).

Subgroup analyses were conducted for the primary endpoint in cohort B. While event numbers were small in some of the subgroups, results generally showed a consistent treatment effect of casirivimab+imdevimab across subpopulations with different baseline characteristics, including age, race and ethnicity, gender, BMI, and region; risk factors as defined in the SAP and household size.

Treatment with casirivimab+imdevimab reduced the duration of symptomatic infection (by broad term definition) by 45.3% compared to placebo (p=0.0273) (Table 38).

The cumulative duration of high viral load infection was shorter by 39.7% after treatment with casirivimab+imdevimab compared to placebo (p=0.0010)

In the ≥12 to <18 years of age uninfected subpopulation of COV-2069A, no participant (0/34) treated with casirivimab+imdevimab had symptomatic RT-qPCR-confirmed SARS-CoV-2 infection during the EAP compared to 4/34 (11.8%) of placebo participants, corresponding to a 100% relative risk reduction in symptomatic infection compared to placebo.

Data from COV-2069B showed that in the ≥12 to <18 years of age subpopulation, the proportion of participants with asymptomatic RT-qPCR-confirmed SARS-CoV-2 infection at baseline who subsequently developed broad term signs and symptoms of COVID-19 was lower in the group that received a single SC dose of casirivimab+imdevimab (n=2/15, 13.3%) compared to placebo (n=5/11, 45.5%), corresponding to a 70.7% reduction in the risk of progression to symptomatic disease.

Overall Study Population

Upon request, the applicant provided effect estimates in the overall population, comprising all randomised subjects. Results indicate that treatment with casirivimab+imdevimab reduced the risk of progression to symptomatic RT-qPCR confirmed SARS-CoV-2 infection by 65.0% compared to placebo (nominal p<0.0001).

HV-2093

Study HV-2093 is an ongoing, phase 1, randomized, double-blind, placebo-controlled study, designed to assess the safety and tolerability of multiple doses casirivimab+imdevimab SC given at monthly intervals in adult healthy volunteers who are SARS-CoV-2 negative at baseline.

Participants were randomized in a 3:1 ratio to receive up to 6 doses of casirivimab+imdevimab (600 mg+600 mg) or placebo over 24 weeks. The treatment period lasted for up to 24 weeks (shorter if a participant developed a symptomatic SARS-CoV-2 infection or permanently discontinued from study drug), and there was a follow-up period of 28 weeks.

While a positive SARS-CoV-2 RT-PCR result excluded participants from the study, serology results were not part of the inclusion or exclusion criteria. This study also did not require that participants be withdrawn from study drug following positive serology results, which were made available by the central lab during the study. For the purpose of a PEP study it is adequate to exclude patients with a positive SARS-CoV-2 RT-PCR at baseline from the efficacy analysis. However, patients with a positive of anti-SARS-CoV-2 antibody are included in the study. This is understandable for the COVID-19 vaccine interaction sub-study (immunogenicity results not reported in the current submission).

Across all trials and regardless of the patient's baseline serostatus the dose of 1200 mg of casirivimab+imdevimab reduced the relative risk of symptomatic COVID-19 infection. The interim data of Study HV-2093 are consistent with the data of Study COV-2069.

2.5.4. Conclusions on the clinical efficacy

Primary and key secondary results support a treatment effect in reducing risk of hospitalization for COVID-19, especially in those patients with high viral load, and in reducing the time to symptom resolution.

In patients negative for SARS-CoV-2 at screening and asymptomatic the primary and key secondary endpoints support an effect of reducing the risk of symptomatic infection and of SARS-CoV-2 infection with or without symptom and duration of infection. The risk of developing a high viral load infection was also reduced in the treatment group compared to placebo.

In patients known to be infected with SARS-CoV-2 who were determined to be positive for SARS-CoV-2 at screening but asymptomatic for COVID-19 the primary and key secondary endpoints suggest that treatment with casirivimab+imdevimab reduced the risk of progression to symptomatic disease in seronegative participants. These findings are considered supportive of the prevention indication despite uncertainties of statistical significance in asymptomatic SARS-CoV-2 positive subjects.

A consistent treatment effect was observed in participants regardless of baseline serology. A comparable level of reduction was also shown when the analysis included only baseline-positive participants however not statistically significant.

Post-hoc analyses indicate that casirivimab+imdevimab reduces the risk of progression to symptomatic RT-qPCR confirmed SARS-CoV-2 infection, irrespective of whether subjects are already infected or not before initiation of prophylaxis.

2.6. Clinical safety

Patient exposure

The safety evaluation is based on 7671 participants who received casirivimab+imdevimab either IV or SC in the randomized clinical studies contributing safety data to this application (Table 56). Of these participants:

- 5248 received a single dose casirivimab+imdevimab IV
- 1694 received a single dose casirivimab+imdevimab SC
- 729 received repeated administration of casirivimab+imdevimab SC Q4W x 6 doses.

Table 56. Duration of observation in individuals receiving casirivimab+imdevimab in clinical studies

Indication Study	Dose Regimen	Data Cut-off Date	Duration of Observation[a]			
			Any Duration	4 weeks	12 weeks	24 weeks
Outpatient Treatment						
COV-2067	1200 mg IV x 1 dose	18-Feb-2021	827	822	26	0
	2400 mg IV x 1 dose		2107	1976	278	0
	8000 mg IV x 1 dose		1272	1152	272	0
COV-20145	300 mg IV x 1 dose	8-Feb-2021	115	44	0	0
	600 mg IV x 1 dose		114	42	0	0
	600 mg SC x 1 dose		114	44	0	0
	1200 mg IV x 1 dose		116	41	0	0
	1200 mg SC x 1 dose		114	44	0	0
	2400 mg IV x 1 dose		115	44	0	0
Prevention						
COV-2069	1200 mg SC x 1 dose	24-Feb-2021	1466	1456	1347	145
HV-2093	1200 mg SC Q4W x 6 doses	13-Mar-2021	729	729 (≥1 dose)	694 (≥3 doses)	454 (6 doses)
Supportive Data (Hospitalized Treatment)						
COV-2066	2400 mg IV x 1 dose	09-Dec-2020	292	171	12	3
	8000 mg IV x 1 dose		290	182	13	3

a. Duration of observation numbers presented in this table show actual duration of observation for various IV and SC doses of casirivimab+imdevimab for unblinded studies and estimated duration of observation for blinded studies. The numbers exclude subjects randomized to placebo.

Under the CU program, from 13 Aug 2020 through 16 Apr 2021, a total of 236 patients (from multiple countries) were treated with casirivimab+imdevimab. Of these patients, 169 were treated under the physicians' emergency INDs in US and 8 treated in other countries (5 in United Kingdom and 3 in Italy) under respective health authority approval, and 59 were Regeneron employees or their immediate family members who were treated under the Regeneron IND (Compassionate Use Tracker).

Safety data in the abbreviated COV-2066 CSR submitted as part of the MAA are presented for the following cohorts:

- Cohort 1 (hypoxic requiring low flow oxygen - phase 1 and 2)
- Cohort 2 (hypoxic requiring non-invasive high flow oxygen - phase 2)
- Cohort 3 (requiring mechanical ventilation - phase 2)

Data from cohorts 1, 2, and 3 are each presented separately within the abbreviated CSR and within the corresponding tables and figures since each cohort represents a different hospitalized patient population with regards to disease severity.

Adverse events

Outpatients (Study COV-2067 and Study COV-20145)

Casirivimab+imdevimab was well tolerated in adult outpatients with COVID-19 (pooled phase 1/2/3 safety data from COV-2067 and COV-21045). No dose-dependent pattern of AEs was observed, and no specific safety signal was identified in either study.

In Study COV-2067 higher percentage of participants in the placebo group than in any casirivimab+imdevimab group experienced a grade 3 or 4 TEAE, treatment emergent SAE, or TEAE leading to a medically attended event regardless of COVID-19 relatedness (see Table 68).

Across the IV dose groups in Study COV-20145 from day 1 through day 169, the highest percentage of participants experiencing a TEAE in any dose group was 19.0%, experienced by participants in the casirivimab+imdevimab 1200 mg IV group, while the lowest was 7.8%, experienced by participants in the casirivimab+imdevimab 2400 mg IV group. In comparison, 17.5% of participants in the placebo IV group experienced at least 1 TEAE. Across the SC dose groups from day 1 through day 169, the highest percentage of participants experiencing a TEAE in any dose group was 10.5%, experienced by participants in the casirivimab+imdevimab 1200 mg SC group, while the lowest was 4.4%, experienced by participants in the casirivimab+imdevimab 600 mg SC group. In comparison, 10.3% of participants in the placebo SC group experienced at least 1 TEAE.

Prevention (Study COV-2069 and Study HV-2093)

- **Study COV-2069 Cohort A**

With a cut-off date of July 01 2021, in **Cohort A** there were lower AE reporting rates in the casirivimab+imdevimab group during the overall study period. (Table 57).

Table 57. Study COV-2069: Overview of TEAEs during the overall study period (SAF-A)

	Primary Analysis N = 2617 (11Mar2021 data cutoff)		Addendum Analysis N = 2867 (01Jul2021 data cutoff)	
	Placebo (N=1306)	R10933+ R10987 (N=1311)	Placebo (N=1428)	R10933+ R10987 (N=1439)
Number of TEAEs	709	556	1006	932
Number of non-COVID-19 TEAEs	481	483	740	839
Number of TEAEs with grade >= 3	25	21	32	40
Number of serious TEAEs	17	14	27	31
Number of AESIs	0	0	0	0
Number of TEAEs resulting in study drug withdrawn	0	0	0	0
Number of TEAEs resulting in death	2	2	2	3
Subjects with at least one TEAE	379 (29.0%)	265 (20.2%)	494 (34.6%)	387 (26.9%)
Subjects with at least one non-COVID-19 TEAE	215 (16.5%)	210 (16.0%)	315 (22.1%)	329 (22.9%)
Subjects with at least one TEAE with grade >= 3	22 (1.7%)	11 (0.8%)	28 (2.0%)	22 (1.5%)
Subjects with at least one serious TEAE	15 (1.1%)	10 (0.8%)	22 (1.5%)	20 (1.4%)
Subjects with at least one AESI	0	0	0	0
Subjects with at least one TEAE resulting in study drug withdrawn	0	0	0	0
Subjects with any TEAE resulting in death	2 (0.2%)	2 (0.2%)	2 (0.1%)	3 (0.2%)

Note: Data from all treated participants by the 01Jul2021cutoff date are included.
AESI, adverse event of special interest; COVID-19, Coronavirus Disease 2019; REGN10933, casirivimab; REGN10987, imdevimab; SAF-A, safety analysis set for cohort A; TEAE, treatment-emergent adverse event

The proportion of participants reporting non-COVID-19 TEAEs were comparable between the placebo and casirivimab+imdevimab groups. The majority of TEAEs was mild or moderate in severity (grade 1 or grade 2) and < 2% of participants in either treatment group experienced SAEs or severe (grade 3 or grade 4) TEAEs.

Five participants (2 [0.1%] in the placebo group and 3 [0.2%] in the casirivimab+imdevimab group) died during the study, all of which occurred during the follow-up period and all were considered unrelated to assigned treatment.

Compared to the placebo group, more cohort A participants in the casirivimab+imdevimab group reported treatment-related TEAE during the overall study period, consistent with a higher incidence of ISR in this treatment arm. Injection site reaction was also the most frequently reported treatment-related TEAE in both treatment groups but none was grade ≥3. No other treatment-related TEAE was experienced by more than 3 participants in either treatment group.

In the SOC of Skin or subcutaneous tissue disorder, 4 (0.3%) participants experienced treatment-related TEAEs in the placebo group (PTs of Rash, Rash erythematous, and Drug eruption) and 1 (<0.1%) participant in the casirivimab+imdevimab group (PT of Pruritis). With the exception of COVID-19 and COVID-19 pneumonia, no other SAE was experienced by more than 2 participants in each treatment group. No participant in the casirivimab+imdevimab group experienced a COVID-19-related SAE.

- **Study COV-2069 Cohort B**

Fewer participants in the casirivimab+imdevimab group reported TEAEs during the study period, and the number and proportion of participants reporting non-COVID-19 TEAEs were also smaller in the casirivimab+imdevimab group compared to the placebo (Table 58).

Table 58. Study COV-2069: Overview of TEAEs during the overall study period (SAF-B)

	Primary Analysis N = 311 (11Mar2021 data cutoff)		Addendum Analysis N = 335 (01Jul2021 data cutoff)	
	Placebo (N=156)	R10933+ R10987 (N=155)	Placebo (N=170)	R10933+ R10987 (N=165)
Number of TEAEs	109	67	151	101
Number of non-COVID-19 TEAEs	42	26	78	58
Number of TEAEs with grade >= 3	5	1	6	4
Number of serious TEAEs	4	0	5	1
Number of AESIs	0	0	0	0
Number of TEAEs resulting in study drug withdrawn	0	0	0	0
Number of TEAEs resulting in death	0	0	0	0
Subjects with at least one TEAE	75 (48.1%)	52 (33.5%)	88 (51.8%)	58 (35.2%)

Subjects with at least one non-COVID-19 TEAE	25 (16.0%)	17 (11.0%)	42 (24.7%)	26 (15.8%)
Subjects with at least one TEAE with grade ≥3	4 (2.6%)	1 (0.6%)	5 (2.9%)	1 (0.6%)
Subjects with at least one serious TEAE	4 (2.6%)	0	5 (2.9%)	1 (0.6%)
Subjects with at least one AESI	0	0	0	0
Subjects with at least one TEAE resulting in study drug withdrawn	0	0	0	0
Subjects with any TEAE resulting in death	0	0	0	0

AESI, adverse event of special interest; COVID-19, Coronavirus Disease 2019; REGN10933, casirivimab; REGN10987, imdevimab; SAF-B, safety analysis set for cohort B; TEAE, treatment-emergent adverse event
Note: Data from all treated participants by the 01Jul2021cutoff date are included

There were no deaths, AESIs or TEAEs resulting in study drug withdrawal. The majority of TEAEs were mild or moderate in severity (grade 1 or 2). Treatment-emergent SAEs occurred in 5 (2.9%) participants in the placebo group and 1 (0.6%) in the casirivimab+imdevimab group.

The most often reported treatment-related TEAE was ISR in both treatment groups. No other treatment-related TEAE was experienced by more than 2 participants in either treatment group. In the SOC of Skin or subcutaneous tissue disorder, 2 (1.3%) participants experienced treatment-related TEAEs in the placebo group (PTs of Skin lesion and Rash erythematous). No treatment-related TEAEs in this SOC were reported in the casirivimab+imdevimab group. No SAE was considered related to study treatment by the investigator, and all SAEs were resolved.

- **Study COV-2069 Cohort Undetermined**

A greater proportion of placebo-treated participants reported TEAEs overall, but the incidence of non-COVID-19-related TEAEs was similar between the treatment groups (8.5% [4/47] in placebo group vs 7.4% [2/27] in casirivimab+imdevimab group). There were no deaths, SAEs, AESIs, or TEAEs resulting in study drug withdrawal among participants with undetermined baseline SARS-CoV-2 status. All TEAEs were mild or moderate in severity (grade <3).

- **Study HV-2093**

A greater proportion of participants experienced at least 1 TEAE during the entire study period in the casirivimab+imdevimab 1200 mg group (52.7%) than in the placebo group (46.3%). This imbalance was mainly due to the higher incidence of ISRs experienced by participants treated with casirivimab+imdevimab 1200 mg (34.7%) compared to placebo (15.5%). More participants in the placebo group experienced (12 (5%) a TEAE leading to study drug withdrawal than in the casirivimab+imdevimab 1200 mg SC group 9 (1.2%).

Hospitalized Participants Study COV-2066

- **Study COV-2066 Cohort 1 (Phases 1 and 2)**

Only select TEAEs were required to be collected in this study (cohort 1, phase 1 only: all grade ≥3 TEAEs; all cohorts, all phases: treatment-emergent SAEs, treatment-emergent grade ≥2 hypersensitivity reactions and grade ≥2 infusion-related reactions). In cohort 1 (phases 1 and 2), which consisted of hospitalized participants on low flow oxygen, a higher percentage of participants in the placebo group experienced grade 3 and 4 TEAEs and SAEs, compared to the casirivimab+imdevimab

2400 mg and 8000 mg dose groups (Table 22). The percentage of participants who experienced TEAEs leading to death was similar across all treatment groups.

Overall, the incidence of infusion-related reactions (grade ≥2) and hypersensitivity reactions (grade ≥2 through day 29) was low in all treatment groups. A higher percentage of participants in the casirivimab+imdevimab 8000 mg dose group experienced an infusion-related reaction (grade ≥2) through day 4 than in the placebo group or in the casirivimab+imdevimab 2400 mg dose group.

Overall, the incidence of TEAEs leading to study withdrawal or leading to interruption of study drug infusion was low. Two participants in the casirivimab+imdevimab 8000 mg group withdrew from study due to TEAEs (Infusion related reaction and Hypoxia, PTs), and 1 participant in the casirivimab+imdevimab 8000 mg group experienced a TEAE (Anxiety, PT) leading to infusion interruption.

- **Study COV-2066 Cohort 2 (Phase 2)**

In COV-2066 cohort 2 (phase 2), which consisted of hospitalized patients on high-intensity oxygen therapy but not on mechanical ventilation, a greater percentage of patients receiving casirivimab+imdevimab than placebo experienced grade 3 or 4 TEAEs (30.9% vs. 23.5%), SAEs (50.9% vs. 39.2%), and TEAEs leading to death (39.1% vs. 25.5%). The IDMC recommended to pause further enrolment based on a potential safety signal and an unfavourable risk-benefit profile in cohorts 2 and 3 at the time. A review of complete follow-up data by the sponsor for Cohort 2 show that these imbalances were related to advanced and progressive COVID-19 with associated concurrent medical conditions resulting in the events. Despite the imbalance between the combined casirivimab+imdevimab group compared to the placebo group for these events, there was no clear dose-dependence between the casirivimab+imdevimab 2400 mg and 8000 mg treatment groups. No imbalance was observed in the recently published, independently conducted, study in hospitalized patients by Oxford University group (RECOVERY study).

Serious adverse event/deaths/other significant events

Outpatients (Study COV-2067 and Study COV-20145)

- **Study COV-2067**

Treatment-emergent SAE, treatment-emergent AESI or event leading to a medically attended event regardless of COVID-19 relatedness, or AESI of grade 2 or greater hypersensitivity reaction reported up to 19 August 2021 are summarised in Table 59.

Table 59. Study COV-2067: Overview of treatment emergent from day 1 up to day 169-Pooled phase 1, 2 and 3 Cohort I (Symptomatic patients) (SAF)

		R10933+R10987			
	Placebo (N=2609)	1200 mg IV (N=1329)	2400 mg IV (N=2614)	8000 mg IV (N=1272)	Combined (N=5215)
Total number of TEAE [1]	517	208	399	149	756
Total number of grade 3 or 4 TEAE	131	33	44	29	106
Total number of TE SAE	147	30	57	29	116
Total number of TE AESI	113	38	56	27	121
Total number of TE serious AESI	19	2	4	4	10
Patients with any TEAE	297 (11.4%)	129 (9.7%)	248 (9.5%)	100 (7.9%)	477 (9.1%)
Patients with any grade 3 or 4 TEAE	90 (3.4%)	23 (1.7%)	34 (1.3%)	20 (1.6%)	77 (1.5%)
Patients with any TE SAE	109 (4.2%)	22 (1.7%)	42 (1.6%)	21 (1.7%)	85 (1.6%)
Patients with any TE AESI	85 (3.3%)	33 (2.5%)	49 (1.9%)	18 (1.4%)	100 (1.9%)
Patients with at least one TE AESI of infusion related reaction (grade ≥2), through day 4 [2]	2 (<0.1%)	1 (<0.1%)	4 (0.2%)	7 (0.6%)	12 (0.2%)
Patients with at least one TE AESI of hypersensitivity reaction (grade ≥2), through day 4	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Patients with at least one TE AESI of hypersensitivity reaction (grade ≥2), through day 29	3 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Patients with TE AESI of event that led to a MAV, through day 29	81 (3.1%)	31 (2.3%)	44 (1.7%)	13 (1.0%)	88 (1.7%)
Patients with any TE serious AESI	15 (0.6%)	2 (0.2%)	4 (0.2%)	1 (<0.1%)	7 (0.1%)
Patients with SAE TE AESI of infusion related reactions (grade ≥2), through day 4 [2]	0	0	0	1 (<0.1%)	1 (<0.1%)
Patients with SAE TE AESI of hypersensitivity reactions (grade ≥2), through day 29	0	0	0	0	0
Patients with SAE TE AESI that led to a MAV, through day 29	15 (0.6%)	2 (0.2%)	4 (0.2%)	0	6 (0.1%)
Patients with any TEAE leading to death	11 (0.4%)	1 (<0.1%)	3 (0.1%)	0	4 (<0.1%)
Patients with any TEAE leading to withdrawal from the study	3 (0.1%)	1 (<0.1%)	2 (<0.1%)	1 (<0.1%)	4 (<0.1%)
Patients with any TEAE leading to study infusion interruption [3]	2 (<0.1%)	1 (<0.1%)	0	3 (0.2%)	4 (<0.1%)
Patients with any TEAE leading to study infusion discontinuation [4]	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	4 (0.3%)	6 (0.1%)
Day 30 to last available data*					
Patients with any TEAE	51 (2.0%)	26 (2.0%)	55 (2.1%)	11 (0.9%)	92 (1.8%)
Patients with any grade 3 or 4 TEAE	15 (0.6%)	9 (0.7%)	11 (0.4%)	2 (0.2%)	22 (0.4%)
Patients with any TE SAE	18 (0.7%)	9 (0.7%)	11 (0.4%)	2 (0.2%)	22 (0.4%)
Patients with any TEAE leading to death	5 (0.2%)	0	0	0	0
Patients with any TEAE leading to withdrawal from the study	0	0	1 (<0.1%)	0	1 (<0.1%)

Randomized patients through 24Feb2021. Data cutoff date is 19Aug2021.

TEAE = Treatment- Emergent Adverse Event. AESI = Adverse Event of Special Interest. SAE = Serious Adverse Event, MAV=Medically attended visit includes physician's office visit, telemedicine, urgent care visit, hospitalizations, or emergency room (ER) visit for COVID-19. MedDRA (Version 24.0) coding dictionary applied.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period which is from the time of study drug administration to the last study visit.

*Last available data = through data cutoff date of 19 Aug 2021 (ie, up to day 169)

[1] TEAEs collected include TE SAEs, AESIs and grade 3/4TEAEs, as well as ad-hoc/voluntarily reported TEAEs by some sites.

[2] TEAEs deemed treatment-related as per investigator assessment.

[3] Infusion interruption: the administration of the infusion was interrupted before being completed, but subsequently was re-started and the full planned dose was administered.

[4] Infusion discontinuation: the administration of the infusion was stopped before being completed, and the full planned dose was not administered

The imbalance in grade 3 or grade 4 TEAEs was due to the incidence of COVID-19 pneumonia in the placebo group. Most grade 3 and grade 4 events occurred in the first 29 days (109 events in 79 [3.0%] participants in the placebo group and 76 events in 56 [1.1%] participants in the combined casirivimab+imdevimab group. Six of these events (in 3 participants) were considered related to study treatment by the investigator, including urticaria and COVID-19 each in a unique 2400 mg participant and hyperhidrosis, nausea, vomiting and hyporesponsive to stimuli in one 8000 mg participant.

An evaluation of SAEs reported by onset up to day 29 and from day 30 up to day 169 did not show any specific safety trends. The majority of SAEs (123/147 SAEs in the placebo group and 84/116 SAEs in the combined casirivimab+imdevimab group) were reported within first 29 days after treatment and 40 participants (18 placebo and 22 casirivimab+imdevimab) experienced SAEs during the follow-up period after day 29.

Two participants reported SAEs from day 1 to day 29 that were considered related to study treatment - COVID-19 in 1 participant in the casirivimab+imdevimab 2400 mg group and Nausea, Vomiting, Hyporesponsive to stimuli and Hyperhidrosis in another participant in the 8000 mg group. No treatment-related SAEs were reported after day 29.

There were 15 deaths reported as of the data cut; 11 in the placebo group, 1 in the casirivimab+imdevimab 1200 mg group and 3 in the casirivimab+imdevimab 2400 mg group). Most deaths (10 of 15) occurred prior to day 29. All TEAEs leading to death were considered not related to study treatment by the investigator and most were considered related to advanced and progressive COVID-19 disease or due to complications of participant-specific concurrent medical conditions.

Study COV-20145

Two participants (1 participant, each, in the casirivimab+imdevimab 1200 mg IV and 2400 mg IV groups) experienced an SAE. Both participants had a spontaneous abortion (miscarriage). Both events were not considered to be related to study treatment.

There were no SAEs with SC administration of casirivimab+imdevimab.

No SAEs with fatal outcome reported in participants in any dose groups or placebo.

Study COV-2069 Cohort A

As of the data cut-off date, 15/1306 (1.1%) participants in the placebo group and 10/1311 (0.8%) participants in the casirivimab+imdevimab group experienced an SAE during the overall study period in cohort A (Table 69). With the exception of COVID-19 and COVID-19 pneumonia, no other SAE was experienced by more than 1 participant in each treatment group. No participant in the casirivimab+imdevimab group experienced a COVID-19-related SAE.

Seven participants (4 [0.3%] in the placebo group and 3 [0.2%] in the casirivimab+imdevimab group) experienced SAEs during the EAP and 19 participants (12 [0.9%] in the placebo group and 7 [0.5%] in the casirivimab+imdevimab group) experienced SAEs during the follow-up period, of which 4 had a fatal outcome (see below). None of the SAEs were considered related to study treatment.

***Table* 60**. Study COV-2069: Summary of serious treatment emergent adverse events by SOC and PT: Overall study period (SAF-A)

Primary System Organ Class Preferred Term	Placebo (N=1306)	R10933+R10987 (N=1311)
Subjects with at least one serious TEAE	15 (1.1%)	10 (0.8%)
Infections and infestations	9 (0.7%)	4 (0.3%)
Gastroenteritis	0	1 (<0.1%)
Pneumonia	1 (<0.1%)	1 (<0.1%)
Sepsis	0	1 (<0.1%)
Soft tissue infection	0	1 (<0.1%)
Appendicitis	1 (<0.1%)	0
COVID-19	4 (0.3%)	0
COVID-19 pneumonia	2 (0.2%)	0
Scrotal abscess	1 (<0.1%)	0
Urinary tract infection	1 (<0.1%)	0
Cardiac disorders	1 (<0.1%)	1 (<0.1%)
Acute myocardial infarction	0	1 (<0.1%)
Cardiac failure congestive	0	1 (<0.1%)
Cardiac arrest	1 (<0.1%)	0
Gastrointestinal disorders	1 (<0.1%)	1 (<0.1%)
Abdominal pain upper	0	1 (<0.1%)
Abdominal pain	1 (<0.1%)	0
General disorders and administration site conditions	0	1 (<0.1%)
Sudden death	0	1 (<0.1%)
Hepatobiliary disorders	0	1 (<0.1%)
Cholecystitis acute	0	1 (<0.1%)
Injury, poisoning and procedural complications	1 (<0.1%)	1 (<0.1%)
Ankle fracture	0	1 (<0.1%)
Foot fracture	0	1 (<0.1%)
Tibia fracture	0	1 (<0.1%)
Gun shot wound	1 (<0.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<0.1%)	1 (<0.1%)
Cervix carcinoma recurrent	0	1 (<0.1%)
Breast cancer	1 (<0.1%)	0
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1%)
Respiratory failure	0	1 (<0.1%)
Psychiatric disorders	2 (0.2%)	0
Mania	1 (<0.1%)	0
Suicidal ideation	1 (<0.1%)	0
Vascular disorders	1 (<0.1%)	0
Essential hypertension	1 (<0.1%)	0

MedDRA (Version 23.1) coding dictionary applied.
A subject who reported 2 or more TEAEs with the same PT is counted only once for that term.
A subject who reported 2 or more TEAEs with different PTs within the same SOC is counted only once in that SOC.

As of the data cut-off date, 2 (0.2%) participants in each treatment group in cohort A had an SAE with fatal outcome during the study (Table 61).

Table 61. Study COV-2069: Summary of treatment emergent adverse events leading to death by primary SOC and PT: Overall study period (SAF-A)

Primary System Organ Class Preferred Term	Placebo (N=1306)	R10933+R10987 (N=1311)
Subjects with at least one TEAEs leading to death	2 (0.2%)	2 (0.2%)
Cardiac disorders	1 (<0.1%)	1 (<0.1%)
Cardiac failure congestive	0	1 (<0.1%)
Cardiac arrest	1 (<0.1%)	0
General disorders and administration site conditions	0	1 (<0.1%)
Sudden death	0	1 (<0.1%)
Injury, poisoning and procedural complications	1 (<0.1%)	0
Gun shot wound	1 (<0.1%)	0

COVID-19, Coronavirus Disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; REGN10933, casirivimab; REGN10987, imdevimab; SAF-A, safety analysis set for cohort A; SOC, system organ class; TEAE, treatment-emergent adverse event; TEEAP, treatment-emergent efficacy assessment period

MedDRA (Version 23.1) coding dictionary applied.

A subject who reported 2 or more TEAEs with the same preferred term is counted only once for that term.

A subject who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.

All 4 deaths occurred during the follow-up period after Day 29 and were not considered to be related to study treatment by the investigator.

- **Study COV-2069 Cohort B**

As of the data cut-off date, 4/156 (2.6%) participants in the placebo group and none in the casirivimab+imdevimab group experienced an SAE.

Three participants experienced a COVID-19-related SAE, and 1 participant experienced an SAE of pancreatitis acute. No SAE was considered related to study treatment by the investigator, and all but 1 SAE (COVID-19) were resolved as of the data cut-off date

As of the data cut-off date, there were no deaths this cohort.

- **Study COV-2069 Cohort Undetermined**

As of the data cut-off date, no participant with undetermined baseline SARS-CoV-2 status experienced an SAE.

As of the data cut-off date, there were no deaths this cohort

- **Study HV-2093**

During the treatment period, 3 of 729 participants (0.4%) in the casirivimab+imdevimab 1200 mg group and 1 of 240 (0.4%) participants in the placebo group experienced at least 1 treatment-emergent serious adverse event (SAE). Treatment-emergent SAEs experienced in the casirivimab+imdevimab 1200 mg group during the treatment period included 1 event of angina pectoris, 1 event of post laminectomy syndrome and 1 event of procedural pain in the same participant, and 1 event of Major depression. Treatment emergent SAEs experienced in the placebo group during the treatment period included 1 event of enteritis.

During the follow-up period, 2 additional participants experienced treatment-emergent SAEs in the casirivimab+imdevimab 1200 mg group; these included 1 fatal event of diabetic complication and 1 event of spinal osteoarthritis. All SAEs were assessed as not related to study drug.

No deaths occurred during the treatment period. There was a single death during the follow-up period.

A participant aged between 70-79 in the casirivimab+imdevimab 1200 mg group experienced a grade 5 fatal TEAE of Diabetic complication on study day 171; the event was assessed to be not related to study drug.

Adverse events of special interest

Outpatients (Study COV-2067 and Study COV-20145)

The incidence of AESIs was low in both studies; ≤2.5% of patients in any treatment group in COV-2067, and ≤1.8% of patients in any treatment group COV-20145 had AESIs.

- **Study COV-2067**

Throughout the study, treatment-emergent AESI (serious and non-serious), were defined as:

- Grade ≥2 infusion-related reactions (IRRs), up to study day 4
- Grade ≥2 hypersensitivity reactions, up to study day 29

Note: After protocol amendment 7, TEAEs that led to a MAV were also collected as AESIs to further inform MAV narratives, but such events are not described in this section as they are primarily captured in the Efficacy section.

Three participants (0.1%) experienced a grade ≥2 hypersensitivity reaction in the placebo group compared to 2 participants (<0.1%) in the combined casirivimab+imdevimab treatment group.

The incidence of grade ≥2 IRRs was numerically lower in the casirivimab+imdevimab 1200 mg group (1 participant [<0.1%]) than in the 2400 mg group (4 participants [0.2%]) and 8000 mg group (7 participants, 0.6%). No participant in the 1200 mg group discontinued study treatment or had study drug interruption due to grade ≥2 IRRs.

- **Study COV-20145**

Per protocol, treatment-emergent AESIs (serious and non-serious) were defined as:

- Grade ≥2 infusion-related reactions up to study day 4
- Grade ≥3 injection-site reactions up to study day 4
- Grade ≥2 hypersensitivity reactions up to study day 29
- Any TEAE that led to a hospitalization or emergency room visit, regardless of whether the visit is related to COVID-19

No patients experienced a grade ≥2 IRR, hypersensitivity reaction or grade ≥3 ISR.

One participant in the placebo IV group (grade 1 mental confusion and grade 2 hallucinations), 1 participant in the casirivimab+imdevimab 600 mg IV group (grade 3 diverticulitis), and 2 participants in the casirivimab+imdevimab 1200 mg IV group (grade 3 COVID-19 [worsening diarrhoea] and grade 1 COVID-19 [shortness of breath]) had TEAEs that led to hospitalization or emergency room visits, of which 2 were considered to be related to underlying COVID-19 symptoms and the other 2 were related to the participant's medical history. None of the events were considered related to study treatment

One participant in the casirivimab+imdevimab 1200 mg SC arm had an AESI of grade 2 Deep vein thrombosis, which was not considered to be related to study treatment by the investigator but related to COVID-19.

Prevention (Study COV-2069 and Study HV-2093)

- **Study COV-2069**

Adverse events of special interest (AESIs) in this study included ISRs or hypersensitivity reactions with a severity of grade 3 or higher. As of the data cut-off date, there were no AESIs meeting the pre-specified criteria in either cohort.

- **Study HV-2093**

For this study, AESIs were defined as grade 3 or greater ISRs or hypersensitivity reactions including but not limited to anaphylaxis, laryngeal/pharyngeal oedema, severe bronchospasm, chest pain, seizure, or severe hypotension. As of the data cut-off for this report, AESIs were neither reported in the placebo group nor in the active treatment group.

Laboratory findings

Outpatients (Study COV-2067 and Study COV-20145)

In general, no clinically meaningful trends in mean or median change from baseline to day 29 were observed in laboratory parameters or the incidence was low.

Prevention (Study COV-2069 and Study HV-2093)

There were no observable trends over time or notable differences between the treatment groups in mean or median change from baseline at day 8 or at any other planned collection timepoint through the end of the treatment period or over the entire period for any haematology parameter or chemistry parameter in either of the studies

Safety in special populations

Elderly Participants (Age ≥65 Years)

- **Study COV-2067**

A greater percentage of participants in the ≥65 years of age subgroup compared to the 18 to <65 years of age subgroup experienced at least 1 treatment emergent SAE from day 1 to the last available data. More participants in the ≥65 years of age subgroup experienced treatment-emergent SAEs in the infections and infestations and respiratory, thoracic and mediastinal disorders SOCs compared to the 18 to <65 years of age subgroup.

The number of participants in each age subgroup who experienced grade ≥2 hypersensitivity reactions was very low (<0.5%).

- **Study HV-2093 (all TEAEs)**

Compared to the overall population, a smaller proportion of participants who were ≥65 years old (n=126) experienced a TEAE during the treatment period, with a greater frequency of at least 1 TEAE reported in the casirivimab+imdevimab 1200 mg treatment group (38.9%) than in the placebo group (30.6%). The most frequently reported TEAEs (≥5%) were ISRs (16.7% in the casirivimab+imdevimab 1200 mg group versus 11.1% in the placebo group) and headache (6.7% in the casirivimab+imdevimab 1200 mg group versus 2.8% in the placebo group).

In the small subset of participants who were ≥75 years old (n=16), TEAEs occurred in 9.1% of participants in the casirivimab+imdevimab group and 20.0% in the placebo group.

Paediatric patients

Study COV-2069 cohort A and B enrolled adolescents (≥12 to<18 years). No adolescent participant (age ≥12 to ≤18 years) reported grade 3 or grade 4 TEAEs during the overall study period

No data are available in paediatric patients aged <12 years.

Pregnancy and Lactation

There are limited data on pregnancies occurring in patients administered casirivimab+imdevimab. Across the studies that allowed enrolment of pregnant women (Study COV-2067, Study COV-2069 and StudyCOV-20145), a total of 10 patients were either pregnant at study entry or became pregnant during the study at the time of the data cut-off dates (of which 6 received casirivimab+imdevimab and 4 received placebo). A further 3 patients reported pregnancies under the EUA or compassionate use program. Of these 13 patients, 5 had early termination of the pregnancy (1 voluntary termination, 3 SAEs of spontaneous abortion and 1 SAE of ruptured ectopic pregnancy). The 4 SAEs were reported in patients receiving casirivimab+imdevimab; none of the SAEs were considered related to study drug. Of the remaining patients with available follow-up information, 4 had either delivered babies without complication or had ongoing pregnancies with no concerns or irregularities reported at the time of last contact.

Two events of exposure to casirivimab+imdevimab during pregnancy were reported under the EUA and 1 event of similar exposure during pregnancy was reported in the CU program. No outcome data was available for the patients in the EUA program while the patient in the CU program gave birth without complications.

Immunological events

Injection Site Reactions

- **Study COV-2069 Cohort A**

Few (<5%) participants in cohort A reported ISRs during the efficacy assessment period, all were grade 2 or below, and the majority were mild in severity. The 2 most frequently reported signs or symptoms of ISR were erythema (0.5% and 2.1% of participants in the placebo and casirivimab+imdevimab group, respectively) and pruritis (0.4% and 1.2% of participants in the placebo and casirivimab+imdevimab group, respectively.

- **Study COV-2069 Cohort B**

A few (<5%) participants in cohort B reported ISRs during the efficacy assessment period. All ISRs experienced by participants in cohort B were grade 2 or below and all were mild in severity. The 2 most frequently reported signs or symptoms of ISR were erythema (0.6% and 1.3% of participants in the placebo and casirivimab+imdevimab group, respectively) and ecchymosis (0% and 1.3% of participants in the placebo and casirivimab+imdevimab group, respectively.

- **Study HV-2093**

There were no grade 3 or greater ISRs reported in this repeat dose study. More participants in the casirivimab+imdevimab group (253/729 participants; 34.7%) reported symptoms of ISRs compared to the placebo group (38/240 participants; 15.8%) during the treatment period. The 2 most common symptoms of the ISRs were erythema and pruritus in the casirivimab+imdevimab group (26.6% and

12.5% of participants, respectively), and erythema and ecchymosis in the placebo group (both experienced by 5.8% of participants).

Safety related to drug-drug interactions and other interactions

As a monoclonal antibody, casirivimab+imdevimab is not anticipated to interact with cytochrome P450 (CYP) or drug transporters, and drug-drug interactions between casirivimab+imdevimab and other drugs is not anticipated.

Casirivimab+imdevimab binds to epitopes on spike protein used as immunogen in all COVID-19 vaccines; therefore, it may be possible that casirivimab+imdevimab could interfere with the development of effective immune responses to COVID 19 vaccines.

- Study HV-2093

At the time of the data cut for this study, 97 (10%) of participants had received a COVID-19 vaccination, of which 67 were in the 1200 mg casirivimab+imdevimab SC group. Vaccine administration was frequently in close temporal proximity to casirivimab+imdevimab 1200 mg SC administration, with a median of 18 days from last dose of casirivimab+imdevimab to vaccination (i.e., approximately the middle of the dosing interval). Thus, participants received vaccines at a time when casirivimab+imdevimab serum levels are expected to be in the therapeutic range.

Only 1 of 67 (1.5%) participants in the casirivimab+imdevimab group and 3 of 30 (10.0%) participants in the placebo group experienced TEAEs after vaccination. The participant who received casirivimab+imdevimab and was later vaccinated experienced a TEAE after vaccination of urinary tract infection (PT), which was considered not related to study drug by the investigator.

Overall, there were low numbers of TEAEs reported and no patterns could be identified. Of note, at the time of the finalization of this document, results from the analyses of immune response to COVID-19 vaccination were not available.

Discontinuation due to adverse events

Outpatients (Study COV-2067 and Study COV-20145)

In Study COV-2067 seven participants discontinued from the study due to TEAEs (3 placebo, 1 in the 1200 mg group, 2 in the 2400 mg group and 1 in the 8000 mg group). Six of the 7 discontinuations occurred through day 29 and most were due to COVID-19 or associated complications. Seven participants experienced TEAEs leading to study infusion discontinuation - 1 in the placebo group and 6 in the combined casirivimab+imdevimab groups. The TEAEs (PTs) of Presyncope (in 1 placebo participant), Nausea (in 1 1200 mg participant), Infusion-related reactions, Rash (in one 8000 mg participant) and Chills (in one 8000 mg participant) were considered related to study treatment and the TEAE of Abdominal pain (in one 8000 mg participant) was considered not related.

In Study COV-20145 one participant in the casirivimab+imdevimab 2400 mg IV group discontinued study treatment (i.e., did not receive full infusion) due to a TEAE (Infusion related reaction). Study drug was withdrawn as a result of this event. The TEAE was considered to be related to study treatment by the investigator and resolved the same day.

Prevention (Study COV-2069 and Study HV-2093)

As of the data cut-off date, no participant experienced a TEAE that led to study treatment discontinuation in any of these studies.

- **Study HV-2093**

As a result of AEs, a total of 19 participants (5.7%) withdrew from study treatment: 8 (1.1%) in the active treatment group and 11 (4.6%) in the placebo group.

Infection with COVID-19 accounted for 10 of the 11 discontinuations in the placebo group, and 1 participant discontinued due to the non-COVID-19 TEAEs of blood sodium decreased, anaemia, and fluid retention.

Infection with COVID-19 accounted for 2 of the 8 discontinuations in the casirivimab+imdevimab 1200 mg group. The other 6 participants discontinued from the active treatment group due to the non-COVID-19 TEAEs of alopecia, urticaria, angina pectoris, blood creatine phosphokinase increased, major depression, and post-traumatic stress disorder.

All TEAEs leading to treatment discontinuation were assessed as not related to study drug, with the exception of a single case of grade 1 pruritis (itching) occurring in a 50-59 year old participant in the active treatment group, for which this event occurred on study day 35, 6 days after the last dose of study drug.

Post marketing experience

Since 21 Nov 2020, 363 cases have reported 1,153 AEs, including 68 cases (with 168 events) reporting a medication error and 238 cases (714 events) reporting an SAE. The remaining cases were non-serious events that were reported outside the required SAEs and medication errors.

The most frequently reported SAEs at the PT level, defined as occurring in ≥10 patients, were COVID-19 pneumonia, dizziness, cough, dyspnoea, hypotension, hypoxia, nausea, chills, chest pain, pyrexia, vomiting, fatigue, and oxygen saturation decreased.

A total of 5 cases (5 events) of anaphylaxis have been reported.

A total of 8 fatal cases were reported with10 events (pulmonary embolism, oxygen saturation decreased, dyspnoea, acute respiratory failure, COVID-19, COVID-19 pneumonia, dyspnoea on exertion, death [3 events]); all cases were considered unrelated to study drug

These events are consistent with IRRs or symptoms of COVID-19 and are similar to AEs observed in the clinical trials

2.6.1. Discussion on clinical safety

No integrated analysis of safety data across the studies was performed due to differences in the study populations, dose regimens, and routes of administration and sample sizes.

In studies COV-20145, COV-2069 and HV-2093 all treatment-emergent AEs (TEAEs) were collected. However only select TEAE categories were required to be collected in COV-2067 and COV-2066. In both studies more fragile patients are enrolled either patients with risk factors for developing COVID-19 disease (Study COV-2067) or diseased patients in different stages of the disease. The reasons to restrict the collection to selected TEAEs is understandable. However, the safety profile in the fragile population cannot be fully established.

The safety evaluation is based on 7671 participants who received casirivimab+imdevimab either IV or SC in the randomized clinical studies contributing safety data to this application (Table 10). Of these participants:

- 5248 received a single dose casirivimab+imdevimab IV
- 1694 received a single dose casirivimab+imdevimab SC
- 729 received repeated administration of casirivimab+imdevimab SC Q4W x 6 doses.

With exception of the study in hospitalised patients (Study COV-2066 Cohort 2 (Phase 2)), the incidence of SAEs and AESIs was low, no dose-dependent pattern of AEs was observed, and no specific safety signal was identified in either study. Number of deaths was low. There were 7 death reported during the study period, none of the deaths were considered related to study drug but were all considered related to advanced and progressive COVID-19 disease. Five additional fatalities occurred in the follow up period, the event was assessed to be not related to study drug.

In COV-2066 Cohort 2 (Phase 2), which consisted of hospitalized patients on high-intensity oxygen therapy but not on mechanical ventilation, a greater percentage of patients receiving casirivimab+imdevimab than placebo experienced grade 3 or 4 TEAEs The IDMC recommended to pause further enrolment based on a potential safety signal and an unfavourable risk-benefit profile in cohorts 2 and 3 at the time. A review of complete follow-up data by the sponsor for Cohort 2 show that these imbalances were related to advanced and progressive COVID-19 with associated concurrent medical conditions resulting in the events. However, no imbalance was observed in the recently published, Recovery study conducted independently in a similar population.

In general, no clinically meaningful trends in mean or median change from baseline to day 29 were observed in laboratory parameters or the incidence was low.

There were no notable differences in the safety profile of casirivimab+imdevimab, including the occurrence of IRRs, in patients aged ≥65 years compared to aged ≥18 to 65 years. The findings observed in the elderly population are consistent with increased age being a known risk factor for developing more serious complications of COVID-19 disease.

Overall, the number of adolescents enrolled was relatively small, which limits the comparison with adults; however, no AEs reported in the adolescent population suggested a safety concern for casirivimab+imdevimab.

Among these participants who were vaccinated during the study period, there were no grade ≥3 TEAE, SAE or AESIs in the casirivimab+imdevimab groups following the vaccinations.

Assessment of paediatric data on clinical safety

Study COV-2069 cohort A and B enrolled adolescents ≥12 to<18 years). No adolescent participant (age ≥12 to ≤18 years) reported grade 3 or grade 4 TEAEs during the overall study period

No data are available in paediatric patients aged <12 years.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of Ronapreve appears manageable and in line with what is expected from a monoclonal antibody targeting a viral protein and with no intrinsic effector function.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

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

Pharmacovigilance plan

On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
COVID-PR (COVid-19 International Drug Pregnancy Registry) Planned	To estimate the effect which 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	Start date Annual report Final report	Q3 2021 Progress reports on enrolment and intermediate analysis results will be provided yearly Q4 2027

Risk minimisation measures

Safety concern	**Routine risk minimisation 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 minimisation activities recommending specific clinical measures to address the risk: None **Other routine risk minimisation measures beyond the Product Information:** Medicine's legal status: The combination of casirivimab and imdevimab is a prescription only medicine

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 107.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that casirivimab and imdevimab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers casirivimab and imdevimab to be new active substances as they are not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

Due to time constraints from the accelerated development of the clinical programme and the submission of the Marketing Authorisation Application and the applicant submitted the results of pilot user consultation with target patient groups on the package leaflet submitted by the applicant which showed that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

This was accepted but the CHMP requested that the results of a full user consultation with target patient groups on the package leaflet should be submitted once available.

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The Group agreed to the use of minimum particulars for the 20ml vial due to the limited space available on the label and the need to reflect the critical, for the safe and effective use of the product, information in a readable way. Moreover, the product is to be used by HCPs only.

As regards to the legal status, the CHMP endorsed a medical prescription status in the context of the pandemic situation to allow appropriate flexibility for the access and administration of the medicinal product under the appropriate monitoring recommendations provided in the product information.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ronapreve (casirivimab / imdevimab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The novel SARS-CoV-2 was initially identified during an outbreak of atypical viral pneumonia cases of unknown aetiology in China in December 2019. Subsequently this has emerged as the cause of the global Covid-19 pandemic

The majority of patients with SARS-CoV-2 infection exhibit relatively mild symptoms or are asymptomatic (Hu, 2020) (Oran, 2020), suggesting that most cases can be managed in an outpatient setting. However, a subset of infections leads to hypoxemia and other serious respiratory conditions that require hospitalization or can be fatal (Guan, 2020) (Richardson, 2020) (Wu, 2020). Infection is more likely to lead to hospitalization among patients with pre-existing risk factors or comorbidities, such as older age, obesity, diabetes mellitus, cardiovascular disease, or chronic lung disease (CDC, 2021) (Lighter, 2020). Such risk factors also include the likelihood of death following hospitalization (Wu, 2020). There is also a subset of patients, approximately 10% to 35%, who recover from the acute SARS-CoV-2 infection but experience persistent symptoms, which occur beyond 4 weeks from the initial SARS-CoV-2 infection and are not explained by an alternative diagnosis (Greenhalgh, 2020) (Tenforde, 2020).

Casirivimab and imdevimab are neutralizing antibodies that block the interaction between the transmembrane S protein and its canonical host receptor angiotensin-converting enzyme 2 (ACE2).

The proposed indications are:

- for the treatment of COVID-19 in adults and adolescents aged 12 years and older and weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- for the prevention of COVID-19 in adults and adolescents aged 12 years and older and weighing at least 40 kg.

3.1.2. Available therapies and unmet medical need

Remdesivir is approved in the EU to treat COVID-19 in adults and adolescents (≥12 years old and weighing ≥40 kg) with pneumonia requiring supplemental oxygen. No other treatments, including for the treatment of COVID-19 in outpatients, are currently approved in the EU.

Vaccination is the mainstay of prevention of COVID-19, but considering the time frame required to develop immunity, there remains an unmet need for acute prevention in persons who have been exposed to SARS-CoV-2. Additionally, there are patient populations for whom vaccination will not be effective or is highly unlikely to be effective in preventing COVID-19, i.e., those with altered immunocompetence such as due to primary or secondary immunodeficiencies. For these patients that require chronic prevention, there are currently no endorsed or approved non-vaccine options.

3.1.3. Main clinical studies

3.1.3.1. Treatment Studies

Study R10933-10987-COV-2067 (referred to as COV-2067) was the pivotal treatment study aimed to demonstrate clinical and virologic efficacy in high risk outpatients with COVID-19 not on supplemental oxygen. COV-2067 is an adaptive phase 1/2/3 study in outpatients with COVID-19. Clinical and virologic efficacy data from the phase 3 portion of this study provide the primary demonstration of efficacy for casirivimab+imdevimab in the treatment of these patients to markedly decrease viral load and reduce the risk of COVID-19-related hospitalization or death; the clinical and virologic efficacy data from the phase 1 and 2 portion of this study provide supportive data for the demonstration of efficacy.

3.1.3.2. Prevention

R10933-10987-COV-2069 (referred to as COV-2069) was the pivotal phase 3 prevention study to evaluate efficacy of casirivimab+imdevimab in reducing the risk of SARS-CoV-2 infection or COVID-19 in those living with a known SARS-CoV-2-infected person. Two study populations were analysed separately: cohort A (referred to as COV-2069A) consisted of asymptomatic participants uninfected at baseline and cohort B (referred to as COV-2069B) consisted of asymptomatic participants who were infected at baseline.

3.2. Favourable effects

3.2.1. Treatment

In study COV-2067 there was a reduction in the proportion of the mFAS population (RT-PCR positive with at least one protocol-listed risk factor) progressing to hospitalisation for COVID-19 or dying from any cause in patients treated with Ronapreve compared to the placebo group. There was a statistically significant treatment effect for each of 1200 mg and 2400 mg vs. placebo in the seronegative mFAS. The risk reduction was similar between the two doses, 72.5% for the 1200mg dose (11 cases Vs 40 for the placebo group) and 70.9% for the 2400 mg dose (23 case Vs 78 for the placebo group).

There was a statistically significant treatment effect for both the 1200 and the 2400 mg vs. their respective placebo groups in the seropositive subset. Ronapreve 1200 mg and 2400 mg both shortened the median time to symptom resolution by 3 day (median 10 days vs. 13 days for placebo).

3.2.2. Prevention

In Study 2069**,** in Cohort A (RT-PCR negative at baseline for SARS-CoV-2 infection), there was a statistically significant 81% relative risk reduction (from 7.8% to 1.5%) for development of symptomatic SARS-CoV-2 infection. A 31% reduction of symptomatic SARS-CoV-2 infection was seen in Cohort-B (RT-PCR positive at baseline) for SARS-CoV-2 infection in the same study for patients treated with Ronapreve (29%) compared to placebo (42.3%).

There was a nominally significant effect in the overall population, comprising all randomised subjects. Results indicate that treatment with casirivimab+imdevimab reduced the risk of progression to symptomatic RT-qPCR confirmed SARS-CoV-2 infection by 65.0% compared to placebo, from 9.1% (150/1657) to 3.2% (52/1641), nominal $p<0.0001$, suggesting that PCR testing may not be required to guide the decision to initiate prophylaxis.

Treatment reduced the viral load, the duration of symptomatic infection and the duration of viral shedding and no subject who developed COVID-19 despite having Ronapreve required hospitalisation or ER visits vs. 4 cases in the placebo group in Cohort and 6 cases in Cohort B.

3.3. Uncertainties and limitations about favourable effects

The primary endpoint in study 2067 of hospitalization for COVID-19 or all-case death is a composite endpoint, however results are driven by the incidence of hospitalization with only 5 deaths (3 in placebo treated patients) recorded up to day 29.Therefore the data currently do not allow any conclusion on an effect of treatment (neither positive nor negative) on the occurrence of death.

Study 2067 was also subject to numerous and late amendments, including changes to the primary endpoint and analysis. Some of these changes, including the definition of the interim analysis are post-hoc (data cut-off date: 18 Feb 2021, date of Amendment 8: 12 March 2021).

The effect of treatment seems to be substantially smaller in patients without documented risk factors, but currently it cannot be concluded whether specific risk factors are predictive of the effect of treatment.

Treatment using the SC route of administration was not studied in the pivotal trial and in the absence of convincing dose-response and exposure-response data, the extrapolation of efficacy from the 1200 mg IV dose to the proposed alternative 1200 mg SC dose in the treatment setting based on PK bridging is not accepted. It is therefore recommended that the subcutaneous route of administration is used only if intravenous administration is not feasible and would lead to a delay in treatment.

In study 2069, local testing for SARS-CoV-2 was utilized for screening based on assays available at the sites according to their local procedures. Patients were enrolled and stratified based on the positive result from a local sample because it was considered inappropriate to delay treatment for 2-3 days awaiting central lab RT-qPCR results that were obtained in all patients from nasopharyngeal samples acquired according to standardized instructions at baseline. However, as randomisation was stratified by local laboratory test and the distinction between cohort A or B was done based on a central laboratory test there is a portion of subjects who were assigned to cohort B although they were randomized in a different stratum (similar for cohort A).

Efficacy in the prevention study is not demonstrated under strong control of type-I-error, as this was controlled for each cohort (A and B) separately. The concept of two independent studies in cohorts A and B is not fully agreed and consequently there is uncertainty on the interpretation of statistical significance. While results in cohort A (subjects tested negative for SARS-CoV-2) are persuasive despite this uncertainty, cohort B results were considered somewhat uncertain. Results in strata of randomisation suggest that cohort B results may not have been statistically significant if investigated in an independent study ($p=0.23$). However, post-hoc analyses indicate that prophylaxis is beneficial in the overall population (relative risk reduction of 65.0%, nominal $p<0.0001$ in pooled cohorts A, B and subjects with undetermined PCR test). Observed results in positive and undetermined subjects therefore provide support that a negative PCR test should not be required before treatment.

3.4. Unfavourable effects

With exception of the study in hospitalised patients (Study COV-2066 Cohort 2 (Phase 2)), the incidence of SAEs and AESIS was low, no dose-dependent pattern of AEs was observed, and no specific safety signal was identified in either of the pivotal studies. A small number of infusion related reactions following IV administration were observed and adequate wording is included in the SmPC to manage these.

The number of deaths was low. None of the deaths were considered related to study drug but related to advanced and progressive COVID-19 disease.

There were no notable differences in the safety profile of casirivimab+imdevimab, including the occurrence of IRRs, in patients aged ≥65 years compared to aged ≥18 to 65 years. The findings observed in the elderly population are consistent with increased age being a known risk factor for developing more serious complications of COVID-19 disease.

Among these participants who were vaccinated during the study period, there were no grade ≥3 TEAE, SAE or AESIs in the casirivimab+imdevimab groups following the vaccinations.

3.5. Uncertainties and limitations about unfavourable effects

Select TEAE categories were required to be collected in COV-2067 and COV-2066. In both studies more fragile patients are enrolled either patients with risk factors for developing COVID-19 disease (Study COV-2067) or diseased patients in different stages of the disease. Whilst the reasons to restrict the collection to selected TEAEs is understandable it is possible that the safety characterisation in those studies may be incomplete

The number of adolescents enrolled was relatively small, which limits the comparison with adults; however, no AEs reported in the adolescent population suggested a safety concern for casirivimab+imdevimab.

3.6. Effects Table

Table 62. Effects Table for casirivimab/imdevimab for the treatment of COVID-19 who do not require supplemental oxygen and who are at high risk of progressing to severe COVID and for the prevention of COVID-19(data cut-off: 19 August 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects-Treatment of Covid-19						
COVID-19 hospitalisation or death	Proportion of patients with ≥ 1 COVID-19 related hospitalization or death through day 29	N(%)	23/1812 (1.3%) (2400 mg) 11/1192 (1.0%) (1200 mg)	78/1790 (4.4%) 40/1193 (3.4%))	- Small to no effect in patients without risk factors for progression - composite endpoint, no robust information on component of death	Study 2067 phase 3 mFAS
Time to COVID-19 symptom resolution	Median Time to COVID-19 symptom resolution	days	10 days	13 days	-Identical results reported for the 1200 and 2400 mg dose	Study 2067 phase 3 mFAS

Favourable Effects-Prevention of COVID-19						
Prevention of Symptomatic SARS-CoV-2 infection	patients with symptomatic RT-qPCR confirmed SARS-CoV-2 infection	N(%)	11(1.5%)	59(7.8%)	- inconsistent laboratory assays to define cohorts A and B	Study 2069 Cohort A SARS-CoV-2 RT-qPCR negative and seronegative at baseline.
Prevention of Symptomatic SARS-CoV-2 infection	patients with symptoms within 14 days of RT-qPCR confirmed SARS-CoV-2 infection	%	29(29.0%)	44(42.3%)		Study 2069 Cohort B Study 2069 seronegative mFAS-B
Unfavourable Effects*						
IRR	Infusion related reaction		10 (0,2%)	1 (< 0,1%)	Highest incidence / 7 cases) in the 8000 mg group; 2 Case in the in the 1200 mg group	Study 2067

Abbreviations: COVID-19: coronavirus disease 2019 RT-qPCR: Real-time Quantitative polymerase chain reaction; SARS COV2: Severe acute respiratory syndrome coronavirus 2

Notes: Cut-off date refers to Study 2067

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A reduction of COVID-19-related hospitalisation or all-cause death in symptomatic patients who do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19 was demonstrated under treatment with Ronapreve. The duration of symptomatic disease was reduced in patients receiving Ronapreve.

In the prophylactic setting progression to symptomatic disease was reduced in either uninfected or infected household contacts.

In uninfected subjects, the overall risk of infection as reduced. In infected subjects, the duration of symptoms was shortened.

Uninfected subjects had a reduction of the risk of developing a high viral load infection; while in infected subjects the duration of high viral load infection was reduced.

The effects are considered clinically meaningful and were consistent across all doses and routes of administration used.

The safety profile of Ronapreve and potential risks associated with its use can be adequately managed by labelling in the product information.

3.7.2. Balance of benefits and risks

The benefits of treatment with Ronapreve as demonstrated in two pivotal trials conducted for the treatment and prophylaxis of COVID-19 outweigh the risks which were observed in those clinical trials.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Ronapreve is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ronapreve is favourable in the following indications:

- 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.
- Prevention of COVID-19 in adult patients and in adolescent patients aged 12 years and older weighing at least 40 kg.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that casirivimab and imdevimab are new active substances as they are not constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plans P/0347/2021 and P/0348/2021 and the results of these studies are reflected in the

Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.