Date: 20 July 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ronapreve

International non-proprietary name: casirivimab, imdevimab
Pharmaceutical form: solution for injection/infusion
Dosage strength(s): casirivimab 120 mg/mL; imdevimab 120 mg/mL
Route(s) of administration: intravenous, subcutaneous
Marketing Authorisation Holder: Roche Pharma (Schweiz) AG
Marketing Authorisation No.: 68329
Decision and Decision date: approved on 23 December 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell cytotoxicity
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	Coronavirus Disease 2019
CYP	Cytochrome P450
Da	Dalton
DDI	Drug-drug interaction
ELF	Epithelial lining fluid
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL	Interleukin
INN	International nonproprietary name
IRR	Infusion-related reaction
ISR	Injection site reaction
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MAV	Medically attended visit
Max	Maximum
MCP-1	Monocyte chemoattractant protein-1
mFAS	Modified full analysis set
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NP	Nasopharyngeal
PBPK	Physiology-based pharmacokinetic
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)

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Q4W	Every 4 weeks
RBD	Receptor binding domain
RMP	Risk Management Plan
RT-PCR	Reverse transcription polymerase chain reaction
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAF	Safety
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SOC	System organ class
S protein	Spike protein
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VSV	Vesicular stomatitis virus

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substances casirivimab and imdevimab of the medicinal product mentioned above.

Authorisation for a COVID-19 medicinal product
Connected with the COVID-19 pandemic, the applicant requested a rolling submission procedure.

OPEN project EMA
Swissmedic has been participating in the EMA's OPEN project. Further information at: *EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu).*

2.2 Indication and Dosage

2.2.1 Requested Indication

Treatment
Ronapreve is indicated for the treatment of confirmed COVID-19 infection 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 high risk of progressing to severe COVID-19.

Prevention
Ronapreve is indicated for the prevention of COVID-19 in individuals aged 12 years and older and weighing at least 40 kg who meet one or more of the following criteria:

- have been exposed or are at high risk of exposure to SARS-CoV-2
- have a medical condition making them unlikely to respond to or be protected by vaccination

Ronapreve is not intended to be used as a substitute for vaccination against COVID-19.

2.2.2 Approved Indication

Ronapreve is indicated for:

- Treatment of confirmed coronavirus disease 2019 (COVID-19) in adults and adolescents (12 years of age and older and weighing at least 40 kg) who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at high risk of developing severe COVID-19 (see "Properties/Effects")
- Prevention of COVID-19 in adults and adolescents (12 years of age and older and weighing at least 40 kg) who cannot produce an adequate immune response to the SARS-CoV-2 vaccination.
  Ronapreve is not intended to be used as a substitute for vaccination against COVID-19.

Ronapreve should be used according to official recommendations, and local epidemiology of circulating SARS-CoV-2 variants needs to be taken into account.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

Intravenous administration
Casirivimab and imdevimab must be administered together, after dilution, as a single intravenous (IV) infusion.

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Subcutaneous administration
Casirivimab and imdevimab must be administered consecutively by subcutaneous injection.

Treatment
The dosage in patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered either together as a single IV infusion via pump or gravity or by subcutaneous injection.
For intravenous administration the solutions of casirivimab und imdevimab must be diluted before infusion.
Casirivimab with imdevimab should be given together as soon as possible after a positive viral test for SARS-CoV-2.

Prevention – single dose
The dosage in individuals 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered together either as a single IV infusion via pump or gravity or by subcutaneous injection.
Casirivimab and imdevimab should be given concurrently as soon as possible following exposure to SARS-CoV-2.

Prevention – repeat dose
For individuals who require repeat dosing for ongoing prevention, i.e. those who have a medical condition making them unlikely to respond to, or be protected by, vaccination:

- the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by IV infusion or subcutaneous injection.
- subsequent doses are 300 mg of casirivimab and 300 mg of imdevimab by IV infusion or subcutaneous injection once every 4 weeks.
- repeat dosing regimens for prevention of COVID-19 allow for switching from intravenous infusion to subcutaneous injection or vice versa over the course of treatment.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	5 March 2021
Formal control completed	10 March 2021
List of Questions (LoQ)	12 July 2021 – 20 October 2021
Answers to LoQ	26 July 2021 – 3 November 2021
Predecision	22 November 2021
Answers to Predecision	7 December 2021
Final Decision	23 December 2021
Decision	approval

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3 Medical Context

Coronavirus Disease 2019 (COVID-19) is a pandemic disease that started in Wuhan, China, in December 2019. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 clinical spectrum ranges from asymptomatic infection to severe disease. The majority of patients present non-severe (flu-like syndrome) or mild symptoms. However, up to 20% of patients develop severe (important lung involvement leading to impairment of gas exchange function) or critical disease (including respiratory failure, thrombosis, multiorgan failure) that might ultimately lead to death. Patients with risk factors (e.g. obesity, old age, chronic lung, kidney or heart disease, active cancer or immunosuppression, diabetes, pregnant women) are especially at higher risk of a severe course and death.

Vaccines based on various technologies (mRNA, viral vectors, protein-based) have been developed and are the major component of the prevention of severe COVID-19.
For the treatment of COVID-19, apart from the usual standard of care techniques, several drugs have been approved throughout the course of the pandemic for the management of hospitalised patients and are used depending on the state of the disease and patient characteristics.

Monoclonal antibody-based therapies exhibit virus neutralising properties principally by targeting epitopes such as the receptor binding domain of the SARS-CoV-2 spike protein, inhibiting virus binding to the angiotensin-converting enzyme 2 (ACE2) receptor and therefore preventing viral entry into the target cells.
Casirivimab and imdevimab are two monoclonal non-competing antibodies targeting the receptor binding domain (RBD) of the SARS-COV-2 spike protein at non-overlapping sites, thus blocking the interaction with the host receptor ACE2.
The combination of monoclonal antibodies might have the advantage that even if one antibody loses the activity against a variant the other might not. Furthermore, the theoretical concern of promoting the emergence of treatment-resistant variants with a combinational product is less likely than for a single antibody.

On 15 April 2021 casirivimab/imdevimab (REGN-COV-2) combination has been listed in Annexes 4 and 5 of the COVID-19 Ordinance 3.

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4 Quality Aspects

4.1 Drug Substance

Casirivimab (REGN10933) and imdevimab (REGN10987) are two high-affinity human IgG1 antibodies directed against the spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Casirivimab and imdevimab bind to non-overlapping epitopes of the receptor binding domain of the S protein, thereby blocking the interaction of the S protein with angiotensin converting enzyme 2 (ACE2) on the host cells and blocking viral entry into the host cells. In addition to their neutralising activity, the two antibodies mediate antibody-dependent cell cytotoxicity (ADCC), but not complement-dependent cytotoxicity (CDC).
Casirivimab is a glycoprotein (molecular weight approx. 148,000 Da) composed of two heavy chains (γ1) consisting of 450 amino acid residues each and two light chains (κ) consisting of 214 amino acid residues each.
Imdevimab is a glycoprotein (molecular weight approx. 147,000 Da) composed of two heavy chains (γ1) consisting of 450 amino acid residues each and two light chains (λ) consisting of 216 amino acid residues each.
The intra-chain and inter-chain disulphide bonding pattern, as well as the single N-linked glycosylation site on each heavy chain of casirivimab and imdevimab, are typical for human IgG1.

Casirivimab and imdevimab are each produced separately in Chinese hamster ovary (CHO) cells. A two-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) is in place. After thawing of the respective WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The culture is harvested, and purification is performed with a series of chromatography steps, ultra-/diafiltration steps and viral inactivation and viral filtration steps. The two antibodies are formulated separately with the excipients.

The fermentation and purification processes for casirivimab and imdevimab are validated at each manufacturing site with several consecutive batches, and the data demonstrated a consistent production and an efficient removal of impurities.

Several changes were implemented during the development of the casirivimab and imdevimab drug substance manufacturing processes, including changes to manufacturing site and production scale. However, the analytical comparability studies, which included batch release data, extended characterisation data and forced degradation studies, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the casirivimab and imdevimab drug substances and their impurities was performed using state-of-the-art methods.

The specifications for casirivimab and imdevimab drug substance release and stability include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity and potency. Specifications are based on clinical experience, batch analysis data and stability data, and are in conformance with current compendial or regulatory guidelines.

Batch analysis data for non-clinical batches, clinical batches, batches for emergency use and process performance qualification batches of casirivimab and imdevimab drug substance were provided. All specific analytical methods are described and are fully validated.

The casirivimab and imdevimab drug substances are stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

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4.2 Drug Product

Ronapreve, solution for injection/infusion, is supplied as a combination pack consisting of two borosilicate glass vials, i.e. one vial containing formulated casirivimab (120 mg/mL) and one vial containing formulated imdevimab (120 mg/mL). The two presentations for each monoclonal antibody consist of either a 1332 mg multidose vial or a 300 mg single-dose vial.

A platform formulation approach was used to identify the drug product formulations, which did not change during clinical development. The excipients, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injection, are of compendial grade and commonly used for the formulation of biopharmaceuticals. The two formulations (casirivimab, imdevimab) do not contain antimicrobial preservatives.
During process development of the two drug products, an additional manufacturing site was implemented after completion of the clinical studies. However, comprehensive characterisation studies, release data and forced degradation studies demonstrated comparability between the different processes.
The 20 mL and 6 mL glass vials and 20 mm rubber stoppers for Ronapreve are commonly used for other medicinal products, and the materials meet compendial requirements.
Several compatibility studies were conducted to establish the in-use stability of: (a) the 1332 mg drug products after first puncture of the vial; (b) the casirivimab/imdevimab mixture intended for intravenous infusion; and (c) the casirivimab and imdevimab drug products stored in syringes intended for subcutaneous injection. However, owing to the absence of antimicrobial preservatives in the formulations, every in-use shelf life is limited to 24 hours.

The casirivimab and imdevimab drug products are manufactured separately. The drug product manufacturing processes consist of thawing of the respective formulated drug substance, pooling and mixing, sterile filtration and aseptic filling at the respective target fill volume, capping, visual inspection, labelling and secondary packaging.

The drug product manufacturing processes for casirivimab and imdevimab are validated with both fill volumes (nominal volume 11.1 mL or 2.5 mL) and at each manufacturing site with several consecutive batches. The data demonstrated a consistent production.

The specifications for release and stability of the drug products include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug products, including non-clinical batches, clinical batches, batches for emergency use and process performance qualification batches, were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are validated.

The vials are stored at 2 – 8°C protected from light. A shelf life of 24 months was granted.

4.3 Quality Conclusions

Satisfactory and consistent quality of the casirivimab and imdevimab drug substances and drug products has been demonstrated.
Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

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5 Nonclinical Aspects

5.1 Pharmacology

Casirivimab and imdevimab bind to non-overlapping epitopes of SARS-CoV-2 receptor binding domain (RBD) (K_D 45.8 and 46.7 pM), thereby preventing binding of the virus to angiotensin converting enzyme 2 (ACE2). Binding of antibodies alone or in combination to SARS-CoV-2 RBD, was concentration-dependent with EC_{50} values in the nanomolar range. Both antibodies have Fc mediated functions and induced antibody-dependent phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC), but not complement-dependent cytotoxicity (CDC). In virus neutralisation assays, Ronapreve mediated a concentration-dependent inhibition of non-replicating vesicular stomatitis virus (VSV) pseudotyped with SARS-CoV-2 S protein (pVSV-SARS-CoV-2-S pseudoparticles), replicating VSV encoding the SARS-CoV-2 S protein (VSV-SARS-CoV2-S virus) and wild-type virus SARS-CoV-2 (USA-WA1/2020 isolate) entry into Vero or Vero E6 cells, with IC_{50} and IC_{90} values in the picomolar range.

In viral escape studies using VSV-SARS-CoV-2-S virus and Vero E6 cells, casirivimab and imdevimab alone lost antiviral activity even at high antibody concentration, whereas antiviral activity remained with the combination. Further *in vitro* neutralisation studies demonstrated that Ronapreve retains its potency against numerous S protein variants of concern/interest. Ronapreve mediated neutralisation of the following authentic SARS-CoV-2 variants: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), AY.1 (Delta plus) and B.1.617.1 (Kappa) variants. In the pseudovirus assay, Ronapreve additionally retained neutralising activity against B.1.427/9 (Epsilon), B.1.526 (Iota), C.37 (Lambda) and B.1.619 (Mu) variants. The relevance of these data for the clinical outcome is not known. The E406W variant is the only one that reduced the potency of Ronapreve by >50-fold. Among naturally occurring variants tested, at least two co-occurring amino acid substitutions in the RBD (e.g., K417R/K444Q) were required to reduce Ronapreve neutralisation potency by >6-fold. Further monitoring of variants and regular submission of the respective studies as a post-approval commitment is requested. There were no indications that Ronapreve induced antibody-dependent enhancement (ADE) either *in vitro* or *in vivo*.

The efficacy of Ronapreve in the prevention and treatment of COVID-19 disease was studied in Rhesus monkeys and Golden Syrian hamsters. In prophylactic treatment two to three days prior to challenge with SARS-CoV-2 virus, Ronapreve induced a reduction in genomic (g) and sub-genomic (sg) viral RNA in nasopharyngeal swabs and oral swabs, and reduced lung inflammation in treated animals compared with animals receiving placebo. In hamsters, Ronapreve showed protective effects on body weight loss.

Therapeutic administration of Ronapreve to hamsters one day post infection resulted in reduced weight loss relative to placebo-treated animals, but had no clear effects on viral load in lung tissue. Monkeys that received Ronapreve one day after infection demonstrated accelerated clearance of gRNA and sgRNA via both nasopharyngeal swabs and oral swabs compared to animals receiving placebo. Thus, Ronapreve provided protection against viral replication in the upper and lower respiratory tract, but did not reduce the inflammation in the lung of treated animals.

In conclusion, the benefit of prophylactic treatment was shown; however, treatment with Ronapreve 24 hours after challenge (therapeutic treatment) showed only very limited efficacy.

Safety pharmacology endpoints integrated in the repeated dose study in Cynomolgus monkeys revealed no concerns regarding cardiovascular, respiratory or central nervous system function.

5.2 Pharmacokinetics

Pharmacokinetics (PK) of casirivimab and imdevimab alone or in combination was studied in male Cynomolgus monkeys following single IV and SC administration. Results point to classical linear PK, as expected for monoclonal antibodies directed against an exogenous target. Clearance and volume of distribution at steady state were concentration-independent. Mean half-life values for casirivimab and imdevimab were between 10-18 days, which is shorter compared to humans (>25 days).

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Bioavailability for the SC dose of casirivimab and imdevimab was estimated to be >81%. Steady state was achieved after 4 days. There were no meaningful differences in PK parameters between casirivimab and imdevimab when dosed individually or in combination.

In repeated dose studies (weekly administration IV or SC), C_{max} and AUC_{tau} increased dose-proportionally. Continued exposure was maintained throughout the treatment period. Following SC dosing, peak concentration was observed after 1.8 days, which is faster than in humans (mean around 6.6 days). There were no sex-related differences in exposure. ADAs were not measured but there was no evidence of ADAs impacting the exposure. Ronapreve accumulated 1.8- to 2.4-fold; steady-state was achieved after the 4th dose.

No studies on distribution, metabolism and excretion were conducted, which is in line with ICH S6 (R1).

5.3 Toxicology

The toxicology profile of Ronapreve was characterised in a 4-week repeated dose toxicity study in Cynomolgus monkeys that received one weekly IV (bolus) or SC injection of casirivimab and imdevimab, either alone or in combination. Except for minor liver enzyme elevations (AST and ALT), which were not considered adverse due to the lack of histopathological correlates, there were no findings. The highest dose was considered the NOAEL, corresponding to 37.5-fold (casirivimab) and 52-fold (imdevimab) the human exposure after single dosing at 1200 mg IV for treatment or acute prevention. Sporadic increases in IL-6, IL-10, TNFα and IL-8 were observed in the *in vitro* cytokine release assay, but were not considered treatment-related. An increase in MCP-1 was of uncertain relation to treatment. The infusion reaction in clinics cannot be excluded. No binding was detected in tissue cross-reactivity studies using human adult and fetal tissues.

Genotoxicity, carcinogenicity and reproductive toxicology studies were not conducted with casirivimab and imdevimab. This is accepted given that both antibodies are directed against an exogenous target and consistent with ICH S6 (R1).

The evaluation of the reproductive tract (organ weights and histopathological evaluation) in the repeated dose toxicity study did not show changes in the testes, epididymides, ovaries, uterus or vagina in young Cynomolgus monkeys that were not sexually mature. Therefore, a risk to fertility is unknown due to the lack of adequate data.

The summary of the key findings from the nonclinical studies in the RMP is considered adequate.

There is no risk for the environment due to the protein nature of Ronapreve.

5.4 Nonclinical Conclusions

The submitted nonclinical documentation is considered appropriate to support the approval of Ronapreve. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered to be sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Biopharmaceutical Development

Overall, three manufacturing processes have been used to produce the monoclonal antibodies casirivimab and imdevimab for clinical and emergency use. The initial manufacturing process at the 2000 L scale was scaled up to 10,000 L. Drug substance from these two manufacturing processes has been used in the clinical studies. Available PK data indicate comparable exposures for drug substances manufactured at the 2000 L scale and 10,000 L scale. Subsequently, the manufacturing process was transferred to a new site and scaled up to 25,000 L. The formulation of the drug product remained the same, and analytical comparability was demonstrated for the drug substances produced with the three manufacturing processes (see section 4).

ADME

Pharmacokinetic data were collected in four studies with healthy subjects and patients and contributed primarily to the population pharmacokinetic, PK/PD and exposure-response analyses. Single IV doses between 300 mg (150 mg per antibody) and 8000 mg (4000 mg per antibody) were administered, whereas only 600 mg and 1200 mg were evaluated as single SC doses. Furthermore, multiple SC doses of 1200 mg casirivimab and imdevimab administered Q4W were investigated.

Absorption

The exposures following the administration of the proposed single dose of 1200 mg IV or SC casirivimab and imdevimab were predicted using the population PK models (see Appendix, information for healthcare professionals).

Following SC administration, the times of maximal plasma concentrations (t_{max}) were estimated at 6.7 days for casirivimab and 6.6 days for imdevimab. The bioavailability was estimated to be 71.8% for casirivimab and 71.7% for imdevimab based on the population PK analysis. Consequently, lower exposures were reached following SC administration as compared to IV administration. Although not investigated, a significant impact of injection site on the bioavailability of casirivimab and imdevimab is unlikely.

The exposures after the proposed multiple dose regimen, including a loading dose of 1200 mg IV or SC casirivimab and imdevimab followed by Q4W IV or SC doses of 600 mg, were predicted using the population PK models (see Appendix, information for healthcare professionals).

The steady state was reached after three doses in a 1200 mg SC Q4W dosing regimen and both the casirivimab and imdevimab concentrations accumulated approximately two-fold based on the trough levels. Following the proposed multiple dose regimen, the population PK analysis estimated accumulation ratios around 1, suggesting that the steady state is reached after the loading dose.

Dose-normalised AUCs after single IV doses between 300 mg and 8000 mg and after single SC doses between 600 mg and 1200 mg indicated an approximately dose-proportional increase. Considering comparable half-lives across the dose cohorts and that all investigated dosing regimens exhibited near-maximal antiviral activity, linear PK appears likely for casirivimab and imdevimab within the investigated dose range.

Distribution

Based on the population PK analysis, the total volumes of distribution for casirivimab and imdevimab were estimated at 7.2 L/h and 7.4 L/h, respectively, underlining their restriction to the vascular compartment.

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Metabolism and Elimination

No studies investigating the metabolism of casirivimab and imdevimab have been conducted considering the biological nature of the molecules.

The concentration-time profiles suggest a monophasic, linear elimination following the distribution phase resulting in half-lives that were comparable across the dose cohorts. Based on the population PK analysis, the clearances and the elimination half-lives of casirivimab/imdevimab were estimated at 0.19/0.23 L/day and 29.8/26.2 days, respectively.

Special Populations / Intrinsic Factors

Since renal and hepatic impairment are not expected to have a major impact on the pharmacokinetic behaviour of monoclonal antibodies, no dedicated studies were conducted in these populations. Based on the population PK analysis, no dose adjustments are necessary for patients with mild, moderate or severe renal impairment, end-stage renal disease (ESRD) or for those with mild or moderate hepatic impairment.

The PK of both casirivimab and imdevimab was well described by a two-compartment distribution model with first-order absorption following SC administration, direct IV administration into the central compartment and linear elimination. Body weight is known to have an impact on the PK of monoclonal antibodies and was therefore already included in the base models. Overall, no dose adjustments are required for any of the evaluated covariates, including baseline age, baseline albumin, body weight, mild or moderate hepatic impairment, race, renal impairment, serostatus, sex and viral load.

Following the administration of the proposed dose of 1200 mg IV and SC, the exposures in adolescent subjects ≥40 kg overall appeared to be similar as compared to adult exposures, although the C28 was increased by up to 1.6-fold. To date, only very limited data on paediatric subjects <12 years are available.

Interactions

Considering the biological nature of the molecules and the mechanism of action, the interaction potential with other drugs or CYP enzymes is expected to be low, and no dedicated DDI studies were conducted.

Pharmacodynamics

Mechanism of Action and primary Pharmacology

The two high affinity monoclonal antibodies casirivimab and imdevimab bind to non-overlapping epitopes on the receptor-binding domain (RBD) of the SARS-CoV-2 S protein, thereby blocking the interaction with ACE2. SARS-CoV-2 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 allows binding to the host receptor ACE2, which leads to membrane fusion and entry of the virus into susceptible cells. The S protein is divided into two functional subunits: the S1 subunit, which contains the RBD responsible for binding to ACE2 on host cells, and the S2 subunit, which catalyses fusion of the viral and cellular membranes.

The PD effects of casirivimab and imdevimab measured by viral load reduction are described in section 6.3.

Overall, current data suggest that the proposed doses result in exposures that are sufficient for achieving maximal antiviral activity against the circulating variants, as outlined in the information for healthcare professionals, for at least 28 days, as measured by 90% neutralisation concentrations (IC_{90}) in respiratory tract fluids NF and lung ELF (Cs, target). No data are available for the Omicron variant (these data are requested as post-marketing requirement).

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Relationship between Plasma Concentration and Effect

In an exposure-response analysis, the drug effect expressed as reduction of viral load was well described with an exposure-independent model, indicating that all investigated dosing regimens exhibited near-maximal antiviral activity. Covariate analysis revealed that the presence of a high-risk factor for severe COVID-19 illness resulted in a reduction of the elimination rate of the productively infected cells by 4.81%, whereas sero-antibody-positive/other status at baseline led to an increase in the elimination rate of the productively infected cells by 110%. These findings confirm the graphical analyses, suggesting the absence of an exposure-response relationship.

6.2 Dose Finding and Dose Recommendation

No formal dose-finding study was conducted.
For details on the proposed dose please refer to the Clinical Pharmacology section above.

Study R10933-10987-COV2067 (COV-2067) phase 1/2 used a single IV dose of 8000 mg, 2400 mg and placebo. Based on the similarity in virological efficacy, clinical efficacy and safety profiles of the 2400 mg and 8000 mg doses, the 2400 mg IV dose and a lower IV dose of 1200 mg were selected for (final) evaluation in phase 3.
For treatment, a subcutaneous administration is also proposed, although only the IV administration was used in the pivotal clinical efficacy study.
Pharmacokinetic data showed that a C_{max} is significantly lower in case of SC administration (median values for casirivimab: 51.6 SC and 166.9 IV; for imdevimab: 48.7 SC and 166.9 IV). Furthermore, the T_{max} is longer than 6 days for both monoclonal antibodies in the case of SC users. It is acknowledged that systemic concentrations of casirivimab/imdevimab exceed the IC_{90} shortly, 24-48 hours, after a single 1200 mg SC dose. However, the SC administration might cause a delay in the treatment effect. In the case of the appearance of a variant with a higher IC_{90} value, the IV administration resulting in higher C_{max} would also be preferred. Thus, for treatment with casirivimab/imdevimab, the intravenous administration should be prioritised over the subcutaneous administration, as it is presented in the information for healthcare professionals.

Dose-ranging Study R10933-10987-COV-20145 (COV-20145) in patients not at high risk of severe disease (symptomatic with no risk factors / asymptomatic) assessed several IV and SC doses and showed a comparable virological reduction.

For prevention, a single SC dose of 1200 mg casirivimab/imdevimab was evaluated in Study COV-2069, and 1200 mg SC Q4W x 6 doses of casirivimab+imdevimab were evaluated in Study R10933-10987-HV-2093 (HV-2093). However, the proposed 600 mg for the repeat dose pre-exposure prophylaxis was not supported by clinical efficacy data and a clinical preventive benefit could not be easily concluded. In their response to respective concerns raised in the list of questions the applicant's argumentation to support the reduced dose included the results of Study COV-2069 using a 1200 mg SC dose, the results of Study HV-2093 demonstrating similar efficacy in prevention in the first month and beyond up to 6 months. Furthermore, PopPK simulation showed that the $C_{trough,ss}$ of casirivimab and imdevimab in serum for different combinations of IV and/or SC repeat-dose regimens, including the proposed 600 mg maintenance dosing after a 1200 mg loading dose, is similar to the observed median day 28 concentrations in serum for the single 1200 mg SC dose in Study R10933-10987-COV-2069 (COV-2069), which also applies to patients with high body weight. The provided arguments were accepted, although supporting the dose by specific clinical efficacy data would have been preferred. Thus, the reduced dose of 600 mg Ronapreve for repeat dose (for pre–exposure prophylaxis) following an initial dose of 1200 mg was accepted.

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6.3 Efficacy

Study COV-2067 is an adaptive, seamless, phase 1/2/3, randomised, double-blind, placebo-controlled master protocol to evaluate the efficacy, safety and tolerability of casirivimab/imdevimab combination therapy in outpatients with COVID-19, including (in phase 2) asymptomatic patients with SARS-CoV-2 infection. Phase 1 and phase 2 had been completed, while phase 3 was ongoing.

The phase 1/2 part of the study showed that treatment with 2400 or 8000 mg casirivimab/imdevimab resulted in a statistically significant, greater least squares (LS) mean reduction in time-weighted average (TWA) daily change from baseline in viral load from day 1 to day 7 compared to placebo. However, the correlation between viral load reduction and clinical efficacy has not been established.

The phase 3 part of Study COV-2067 was the pivotal study submitted in support of the treatment indication.

The assessment was based on phase 3 cohort 1, which included outpatient adults with a positive diagnostic test for SARS-CoV-2 infection ≤ 72 hours of randomisation, who maintained O_2 saturation ≥ 93% on room air (not receiving supplemental oxygen), had an onset of COVID-19 symptoms ≤ 7 days of randomisation and had at least one risk factor for developing severe COVID-19.
Several changes were implemented by protocol amendments, prior to unblinding or database lock. The last protocol amendment (8) was issued at a very late stage, already following data cut-off. It revised the statistical analysis for cohort 1, including the primary endpoint, key secondary endpoints, hierarchical testing and the plan for interim/final analyses. The amendments were partially driven by health authority requests and the continuously accumulating information on COVID-19, which were considered acceptable during a pandemic, especially as a significant impact on the results was considered unlikely.
The phase 3 efficacy analysis used a statistical hierarchy to test the primary and key secondary endpoints to control for the type 1 error.
The primary endpoint of the phase 3 was the proportion of patients with ≥ 1 COVID-19-related hospitalisation or all-cause death through day 29, which is considered clinically meaningful and accepted. It was assessed on the mFAS, defined as all randomised patients with qualitatively positive RT-qPCR (via central laboratory) in NP swab samples at randomisation or collected within 2 hours after study drug infusion was initiated, based on the treatment allocated (as randomised). The mFAS consisted of n=1341 subjects receiving placebo IV, with n=736 subjects in the 1200 mg, n=1355 subjects in the 2400 mg and n=625 subjects in the 8000 mg casirivimab+imdevimab IV treatment arms.
A total of 548, i.e. 13.5%, patients in the mFAS were above 65 years of age, and the most common risk factors were obesity (body mass index over 30 kg/m^2) in 58 %, age ≥ 50 years (51.8%) and cardiovascular disease with hypertension (36.3%), and other risk factors such as chronic lung disease and type 1/2 diabetes mellitus in 16.4% and 14.9% of patients respectively. Only 3% of the subjects were immunocompromised. Chronic kidney disease and chronic liver disease were uncommon (≤3% frequency).
Baseline viral load (as measured quantitatively in NP swabs) and serostatus were balanced. 68.6% of patients in the mFAS were seronegative at baseline, 23.6% were seropositive and 7.8% had a status of 'other'. Participants in the seronegative mFAS had a baseline viral load (mean [SD]: 7.20 [1.478] log10 copies/mL) that was higher compared to the mFAS, and markedly higher than those who were seropositive at baseline (5.25 [1.681]log10 copies/mL).

A 71.3% reduction in the proportion of patients with a COVID-19-related hospitalisation or all-cause death was observed for the 2400 mg group compared to placebo (p<0.0001).
The proportion of participants who had at least one COVID-19-related hospitalisation or all-cause death through day 29 was significantly lower with casirivimab/imdevimab 1200 mg compared to placebo (1.0% vs. 3.2%), corresponding to a relative risk reduction of 70.4% (p<0.0024).
For a tabulated presentation of the primary efficacy endpoint results please refer to Table 5 of the information for healthcare professionals.

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The outcome of the composite primary endpoint was mainly driven by COVID-19-related hospitalisations; there were three deaths in the placebo group and one death in the 1200 mg treatment group by day 29. Thus, based on these data the beneficial effect of casirivimab/imdevimab on reducing mortality is not demonstrated.

As the clinical efficacy between the 1200 mg and 2400 mg doses was consistent, a dose-response effect - similarly to the phase 1/2 results - could not be observed.
Kaplan-Meier curves for time to COVID-19-related hospitalisation or all-cause death showed that the difference in the proportion of participants with events between placebo and either of the casirivimab/imdevimab treatment groups became apparent approximately 2 days after treatment initiation (study day 3), suggesting that the occurrence of early events may be less modifiable by treatment.
Overall, most medically attended visits (MAVs) were COVID-19-related hospitalisations: 82 of 172 [47.7%] participants with a medically attended visit across the casirivimab/imdevimab 2400 mg, 1200 mg and placebo groups.
A sensitivity analysis gave consistent results with the main analysis when performed using the primary efficacy parameters in the FAS population with ≥1 risk factor for severe COVID-19.
Most of the secondary endpoints demonstrated a statistically significant benefit of casirivimab/imdevimab treatment. However, the proportion of participants who were admitted to an intensive care unit due to COVID-19 by day 29 in the casirivimab+imdevimab 1200 mg group was not significantly different compared to the placebo group, although the number of events was low.

The available efficacy and virology data suggested a more modest benefit in baseline seropositive subjects and in subjects with lower baseline viral load ($\leq 10^6$).
No conclusion could be made as to whether a similar clinical benefit could be expected in previously vaccinated subjects, as no data were submitted in this regard.
Since the casirivimab/imdevimab treatment was administered intravenously, no clinical data were available for the subcutaneous administration regarding the treatment effect. Based on pharmacokinetic data (for details please refer to the dosing section of the SwissPAR above) IV administration should be prioritised over SC administration, as presented in the information for healthcare professionals.

The proposed indication included adolescents 12-18 years of age weighing at least 40 kg, although no clinical efficacy data were available in this group for the treatment of COVID-19.
Initially, the inclusion of adolescents aged 12 and over and weighing at least 40 kg was supported by data from an allometric scaling approach, which was later confirmed by specific PK data from this age group. See also the Clinical Pharmacology section above.

Data in support of the prevention indication came from the pivotal prevention study COV-2069. This study evaluated the efficacy of casirivimab/imdevimab in reducing the risk of COVID-19 or any SARS-CoV-2 infection in those living in the same household with a known SARS-CoV-2-infected index person. The study enrolled adults and adolescents (age ≥ 12 years) who were household contacts of the first household member known to be infected with SARS-CoV-2 infection (index case), but who were themselves either not infected or asymptomatic at the time of screening. In this study, the participants had been sharing the same residence as the index case and had a close exposure to the index case. Subjects were randomised within 96 hours of collection of the index cases' positive SARS-COV-2 diagnostic test samples.
Final analyses were provided for the primary and key secondary endpoints at day 29 of the efficacy assessment period (EAP).
Several protocol amendments were issued during the study. Amendments 5 and 6 contained relevant changes in the study conduct: the sample size was increased and the endpoint revised for Cohort A; a primary objective was added for Cohort B; the analysis set definition was also updated. The last protocol amendment 6 was issued on 25 March 2021, i.e. after the *Primary Completion Date:* 11 Mar

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2021 (last participant last visit in the efficacy assessment period) and only a couple days before the database lock.
554 participants randomised to cohort A between the study start date through 16 Oct 2020 were included in the “administrative assessment”, which was an initial descriptive analysis performed to assess study assumptions. These participants were excluded from the primary efficacy analysis for cohort A, but were included in the safety analysis.
The administrative assessment was only introduced in protocol amendment 5, at a late stage of the study, shortly before the data cut-off. The uncertainties regarding the transmission rates as well as the continuously developing insights into COVID-19 were acknowledged and partially explained the modifications. Since the data for the administrative assessment (554 Cohort A) subjects were not included in the primary analysis, this late introduction of the administrative assessment did not raise further concerns.
Two study-populations were analysed separately: cohort A (COV-2069A) consisted of *asymptomatic* participants *uninfected at baseline* (i.e. with a negative central-laboratory confirmed molecular SARS-CoV-2 test from a nasopharyngeal [NP] swab sample); cohort B (COV-2069B) consisted of asymptomatic participants who were *infected at baseline* (i.e. with a positive central-laboratory confirmed molecular SARS-CoV-2 test from an NP swab sample).
Eligible participants were randomised 1:1 to receive a single dose of 1200 mg (600 mg casirivimab and 600 mg imdevimab) or placebo administered as four SC injections on day 1. Randomisation was stratified for assignment of treatment group by test result of a local diagnostic assay for SARS-CoV-2.
For the 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.
The use of local tests for stratification of randomisation was explained by the applicant to the effect that treatment would be delayed if central tests were used, as their results were usually not available for several days to a week after sample collection. Furthermore, the sensitivity and specificity of these local tests were considered to be inferior to the central laboratory test and their availability was limited generally. Thus, cohort allocation for data analysis was pre-specified to be based on only central laboratory baseline SARS-CoV-2 RT-qPCR. The above reasoning is acknowledged and the approach can be accepted. However, 44.3% of the subjects in Cohort B were not randomised to the infected stratum (Cohort B) by local laboratory results. For Cohort A, a discrepancy was observed in 14.5% of the subjects. With this amount of discordance, Cohort A and B cannot be considered as fully independent in a statistical sense and therefore, the type 1 error might be inflated. As a consequence, statistical inference for Cohort A and B should have been embedded in a multiplicity strategy.

Based on the results of cohort A with asymptomatic PCR negative subjects, casirivimab/imdevimab at the proposed dose of 1200 mg administered SC as a post-exposure prophylaxis significantly reduced the risk of developing COVID-19 infection. For a detailed and tabulated presentation of the primary endpoint results for Cohort A and Cohort B please refer to the efficacy section in the information for healthcare professionals (Tables 6 and 7).
Efficacy was based on the seronegative mFAS for both cohorts, which is not in line with the proposed indication, as the indication is not limited to seronegative subjects.
Additional data were presented for both initially seronegative and seropositive subjects for both cohorts (Cohort A and B). The relative risk reduction in symptomatic infections for the small number of seropositive subjects was similar to the seronegative subjects and similar to subjects regardless of serostatus in each of the cohorts. Consequently, a serology assessment before the initiation of the prevention is not considered necessary.

The population studied was not fully in line with the proposed target population for prevention, as only a few individuals at risk of an insufficient immune response to vaccination due to medical conditions were included in the study. However, prophylaxis would be most beneficial for those that are unable to mount an adequate immune response to vaccination, and this target population is therefore specified in the indication.

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In both pivotal studies, mostly young/middle-aged adults were enrolled, leaving some uncertainty as to the exact effect of the treatment/prophylaxis in elderly subjects with multiple risk factors. Furthermore, very few subjects were immunocompromised or had chronic kidney disease or chronic liver disease (≤ 3% frequency) in the treatment study.

Clinical efficacy data were not available for the circulating Delta variant for treatment or for prevention. Based on in vitro neutralisation assays, the activity of casirivimab and imdevimab is retained against the Alpha, Beta, Gamma and the currently (i.e. at the time of the approval) dominant Delta variants. The WHO Technical Advisory Group on SARS-CoV-2 designated Omicron a variant of concern on 26 November 2021. Omicron was primarily of concern due to the large number of mutations it has in the spike gene. At the time of the decision (middle of December 2021) Omicron was reported in 2.1% of the confirmed COVID-19 cases in Switzerland, but could become the predominant variant within a short period of time.

On 17 December 2021, the applicant shared a statement from Regeneron. According to the statement, the Ronapreve antibodies “have diminished potency versus Omicron, but are active against predominant Delta variant”. A non-peer reviewed publication also reported reduced activity against the Omicron variant. The in-vitro activity of Ronapreve against Omicron and other new variants will be monitored and submitted (Non-clinical post-marketing requirement).

6.4 Safety

The safety evaluation was based on 7671 participants who received casirivimab/imdevimab either IV or SC in the randomised clinical studies.
Of these participants:
• 5248 received a single dose of casirivimab/imdevimab IV (with doses ranging from 300 mg to 8000 mg)
• 1694 received a single dose of casirivimab/imdevimab SC (1200 mg SC and 600 mg SC)
• 729 received repeated administrations of casirivimab/imdevimab SC Q4W x 6 doses (1200 mg SC).
When administered as an IV infusion, the study drug was infused over approximately 60 min. ± 15 min. When administered as a SC injection, the study drug was given via four injections, each containing 2.5 mL.

Participants have been followed for safety for various durations depending on the data cut-off dates and the duration of follow-up in the respective studies, but at least all participants had the opportunity to complete 28 days of follow-up, and approximately 4470 and 2270 participants had at least 4 weeks of exposure after single-dose IV and SC administration, respectively, at the dose to be marketed of 1200 mg and above.
The safety (SAF) population includes all randomised patients who received at least one dose or part of a dose of the study drug.

Pooled safety data were available for the combined symptomatic cohorts of Study COV-2067 phases 1/2/3. Of the 6311 participants included in the SAF, 2777 (44.0%) had completed the study as of the data cut-off date of 18 February 2021, and 53.4% were ongoing. Overall, 2.6% of participants discontinued the study early, where 1.3% were lost to follow-up and 1.0% discontinued due to participant decision.
A total of 4206 subjects received a single dose of 8000 mg or 2400 mg and, following protocol amendment 6, 1200 mg of casirivimab/imdevimab IV.
Targeted treatment-emergent adverse events (TEAEs), as treatment-emergent SAEs, grade ≥ 2 hypersensitivity reactions, grade ≥ 2 infusion-related reactions, TEAEs that led to a medically attended visit (MAV) regardless of COVID-19 relatedness, were collected for all cohorts and all phases, while only all grade ≥ 3 TEAEs were collected in Cohort 1, phase 1.

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Safety follow up continued until Day 29, and phase 3 included a 29-day treatment and a 169-day follow-up (for some of the patients, and only for SAEs deemed related to study drug as per investigator's assessment).
The most frequently reported adverse drug reactions are hypersensitivity reactions, including infusion-related reactions (IRRs) and injection site reactions (ISRs).

The incidence of deaths was low. More participants in the placebo group experienced a fatal event from day 1 to the last available data cut-off compared to any casirivimab/imdevimab groups (5 in the placebo group and one each in the 1200 mg and 2400 mg groups). Most deaths (5 of 7) occurred prior to day 29. All were considered unrelated 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.

The incidence of serious TEAEs from day 1 to the last available data cut-off was also higher in the placebo group compared to the casirivimab+imdevimab groups.
This was driven by a higher incidence of TEAEs in the infections and infestations SOC, with a higher incidence of COVID-19, COVID-19 pneumonia and Pneumonia in the placebo group compared to any casirivimab+imdevimab group, and by a higher incidence of TEAEs in the Respiratory, thoracic and mediastinal disorders SOC, driven by a higher incidence of Dyspnoea and Hypoxia in the placebo group compared to any casirivimab+imdevimab group. More participants in the placebo group compared to any active group experienced a grade 3 or grade 4 TEAE, which was mostly driven by COVID-19 pneumonia, COVID-19 and Pneumonia (PTs).
COVID-19-associated TEAEs or associated clinical complications were the most frequently reported SAEs in all treatment groups. Most other treatment-emergent SAEs were reported by a single participant, and no dose-dependent patterns were identified.

Seven participants discontinued the study due to TEAEs (4 participants in the placebo group, 2 in the casirivimab+imdevimab 2400 mg and 1 in the 8000 mg group). Most events were due to COVID-19 or associated complications (PT: COVID-19 in 2 participants and COVID-19 pneumonia, Dyspnoea and Deep vein thrombosis each in a single participant); all events were SAEs.
Five participants experienced TEAEs leading to study infusion discontinuation; 1 participant in the placebo group and 4 in the combined casirivimab+imdevimab groups, 1 in the 2400 mg and 3 in the 8000 mg group. These participants did not receive the full dose of the study drug.
Four participants (1 in the placebo group, 1 in the casirivimab+imdevimab 1200 mg group and 2 in the casirivimab+imdevimab 8000 mg group) experienced TEAEs leading to infusion interruption. Events in 3 participants were considered AESIs (1 in the placebo group had grade 2 hypersensitivity and 2 in the 8000 mg group had grade ≥ 2 IRR).
A total of 3 participants in the placebo group (0.1%) experienced a grade ≥ 2 hypersensitivity reaction, compared to only 1 participant (< 0.1%) in the combined casirivimab+imdevimab treatment group (casirivimab/imdevimab 2400 mg group), and 1 event in the placebo group led to infusion interruption.
Clinically relevant changes in laboratory parameters were not observed; mostly changes due to COVID-19 disease and disease progression were documented.

As only selected (targeted) AEs were collected, this leaves uncertainties regarding the safety profile of casirivimab/imdevimab based on these data. The safety profile cannot be fully characterised.

Safety data from Study COV-2069 were based on all randomised participants (N=3029) included as of the data cut-off. All participants who received any study drug were included in the safety analysis, SAF-A consisted of 2617 participants, including those who were analysed in the administrative assessment, and SAF-B consisted of 311 participants. In addition, 74 participants whose baseline RT-qPCR status was inconclusive or missing were reported separately (SAF-Undetermined).

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SAF-A: Cohort A
Fewer participants in the casirivimab/imdevimab group reported TEAEs during the overall study period, which was consistent with a higher incidence of COVID-19-related TEAEs in placebo-treated participants. The proportion of participants reporting non-COVID-19 TEAEs were comparable between the placebo and casirivimab/imdevimab groups. Overall, the majority of TEAEs were mild or moderate in severity (grade 1 or grade 2).
Fewer than 2% of participants in either treatment group experienced SAEs or severe (grade 3 or grade 4) TEAEs, and incidences were comparable between treatment groups.
Four participants (2 [0.2%] in each treatment group) died during the study, in all cases during the follow-up period.
No participant in either treatment group reported an AESI (i.e. grade ≥ 3 injection site reaction or hypersensitivity reaction) or a TEAE that led to the withdrawal of study drug.

Compared to the placebo group (2.5%), more cohort A participants in the casirivimab/imdevimab group (4.3%) reported treatment-related TEAEs during the overall study period, consistent with a higher incidence of injection site reactions (ISRs) in this treatment arm.
Injection site reaction was also the most frequently reported treatment-related TEAE in both treatment groups (4% vs 1.3 %), and none were grade ≥ 3.
No other treatment-related TEAE was experienced by more than two participants in either treatment group.

A few, <5%, participants in cohort A reported ISRs, and none met the criteria for an AESI. The majority of ISRs were mild in severity, and the rest were moderate.
More participants in the casirivimab/imdevimab group reported ISRs, but a greater proportion of participants in the placebo group reported a duration > 4 days. The two most frequently reported signs or symptoms of ISR were Erythema and Pruritus.
The median time to ISR was 62 minutes for the placebo group and 30 minutes for the casirivimab/imdevimab group. Of all 75 participants with an ISR, eight in the casirivimab/imdevimab group and three in the placebo group had ISRs that resolved after treatment with an oral antihistamine and/or topical hydrocortisone. None of the remaining ISRs required treatment or other forms of medical intervention.
One participant who received casirivimab/imdevimab experienced an ISR that led to drug interruption.
As of the data cut-off date, there were no PTs of Hypersensitivity reactions. Four (0.3%) participants in the placebo group and 1 participant in the casirivimab/imdevimab group had treatment-related TEAEs related to skin disorders
There were no clinically meaningful findings in laboratory parameters or vital sign measurements.

Few adolescents were enrolled in Cohort A: 88 in total, with 45 subjects in the active treatment group. No adolescent participant (age ≥ 12 to ≤ 18 years) in cohort A reported grade 3 or grade 4 TEAEs during the overall study period. Overall, the types and severities of TEAEs experienced by adolescent participants were generally similar to those experienced by adults in the study, although the proportion of adolescent participants with a TEAE of Injection site reaction was higher in the casirivimab/imdevimab group compared to placebo and also compared to adults.

A total of 175 participants in cohort A received vaccinations against COVID-19, and the number of participants receiving vaccines was comparable between the treatment groups. The majority of these participants received their COVID-19 vaccine after day 29, with a mean time to first vaccination of 85.3 days. Three participants in the placebo group and 6 in the casirivimab/imdevimab group received COVID-19 vaccination before day 29, and none of these participants experienced TEAEs after vaccination.

SAF-B: 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

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casirivimab/imdevimab group compared to the placebo group. Injection site reaction was reported with a higher rate in the active treatment group vs placebo (3.9% vs 0.6%).
COVID-19 was the most frequently reported TEAE in both treatment groups, with a higher incidence in the placebo group compared to the casirivimab/imdevimab group. The incidences of other COVID-19-related AEs (i.e. Asymptomatic COVID-19 and COVID-19 pneumonia) were also higher in the placebo group compared to the casirivimab/imdevimab group.
The majority of TEAEs were mild or moderate in severity.
Treatment-emergent SAEs occurred in 4 (2.6%) participants in the placebo group and none in the casirivimab/imdevimab group.

No unexpected safety trends were observed between adolescent (N=38) and adult (N=273) participants.
The most often reported treatment-related TEAE was ISR in the casirivimab/imdevimab group and COVID-19 in the placebo group. No other treatment-related TEAE was experienced by more than 1 participant in either treatment group.
As of the data cut-off date, there were no deaths in cohort B.
In cohort B 2.6% participants (3 COVID-19-related and 1 Pancreatitis acute) in the placebo group and none in the casirivimab/imdevimab group experienced an SAE.
No participant experienced a TEAE that led to study treatment discontinuation.
As of the data cut-off date, no AESIs (defined as ISRs or hypersensitivity reactions with a severity of grade 3 or higher) met the pre-specified criteria in cohort B.

Fewer than 5% of participants in either treatment group reported treatment-related TEAEs during the overall study period, and the incidences were comparable between treatment groups. All were mild in severity, and none met the criteria for an AESI (grade 3 or higher). The two most frequently reported signs or symptoms of ISR were Erythema and Ecchymosis.
Event start time was available for 5 of 7 participants with ISRs, and the majority had ISRs that started within an hour of dosing.
In the casirivimab+imdevimab group, 6 participants experienced ISRs (4 of which occurred within an hour after dosing, 1 occurred approximately 5 hours after dosing, and 1 occurred on day 3). None required treatment, and the median time to resolution was 8.5 days.
One participant who received casirivimab/imdevimab experienced an ISR that led to drug interruption. During study drug injection at the third and fourth injection sites, the participant experienced an ISR with symptoms of pain at each site, which led to study drug interruption at both sites.
There were no PTs of hypersensitivity reactions in cohort B. However, two (1.3%) placebo-treated participants experienced treatment-related TEAEs of note in the SOC of Skin and subcutaneous tissue disorders.
No treatment-related TEAEs related to skin disorders were reported in the casirivimab/imdevimab group.
Relevant changes in the laboratory parameters or vital signs were not observed.

12 participants in cohort B received vaccinations against COVID-19 during the study, with nine vs. three participants receiving vaccine in the placebo and casirivimab/imdevimab groups, respectively. All of these participants received their COVID-19 vaccine after day 29, with a mean time to first vaccination of 106.0 days. After vaccination, 1 placebo-treated participant reported 2 TEAEs (Asymptomatic COVID-19 (i.e. a second positive infection and Rash), compared to none in the casirivimab/imdevimab group. No participant had a grade ≥ 3 TEAE. No participant experienced SAEs or AESIs after receiving a COVID-19 vaccine. No unexpected safety signal was observed in either treatment group.

In the SAF 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. There were no deaths, SAEs, AESIs or TEAEs resulting in study drug withdrawal. All TEAEs were mild or moderate in severity (i.e. grade 1 or grade 2). No participant had ISR.

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The double-blind, placebo-controlled, parallel group Study COV-20145 evaluated the safety and tolerability of casirivimab/imdevimab IV single doses of 2400 mg, 1200 mg, 600 mg, 300 mg and Placebo IV single dose and SC single doses of 1200 mg, 600 mg compared to a corresponding IV or SC placebo dose in asymptomatic or low-risk symptomatic subjects.
A small number of participants experienced SAEs or AESIs. For both the IV and SC administrations of casirivimab/imdevimab compared to placebo, there were no dose-dependent trends in AEs, as supported by the results for total TEAEs, grade 3 or 4 TEAEs, SAEs and AESIs. There were no deaths among the study participants.

The phase 1, randomised, double-blind, placebo-controlled Study HV-2093 assessed the safety and tolerability of repeated subcutaneous doses of casirivimab/imdevimab in adult volunteers. The safety results were based on an interim clinical study report. There were 969 participants in the SAF: 240 participants treated with placebo and 729 participants treated with casirivimab/imdevimab 1200 mg.
Approximately 60% of participants in each treatment group had received all 6 doses and more than 80% of all participants had received at least 5 doses and 0 participants had completed the entire study through the follow-up period.
A greater percentage of participants experienced at least one 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 (15.8%).
Between the first and fourth monthly dose administrations ISRs varied only slightly: from 12.1% to 13.6% in the casirivimab/imdevimab 1200 mg SC group, and from 2.3% to 4.2% in the placebo group. For monthly dose administrations 5 and 6, the frequency of ISRs in participants who received casirivimab/imdevimab 1200 mg SC increased to 18.2% and 23.4%, respectively, and to 4.5% and 5.6%, respectively, for participants in the placebo group.
For the entire study period (defined as up until COVID-19 vaccination or end of study) 5 of 729 (0.7%) participants in the casirivimab/imdevimab group and 1 of 240 (0.4%) participants in the placebo group experienced an SAE. None were assessed as related to the study drug.
AESIs, defined as grade 3 or greater ISRs or hypersensitivity reactions, were not observed during the entire study period.
No death occurred during the treatment period (one death in the follow-up period was considered not related to study drug).
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 due to an AE.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Coronavirus Disease 2019 (COVID-19) is a pandemic disease that started in Wuhan, China, in December 2019. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Monoclonal antibody-based therapies exhibit virus-neutralising properties principally by targeting epitopes such as the receptor binding domain of the SARS-CoV-2 spike protein, inhibiting virus binding to the angiotensin-converting enzyme 2 (ACE2) receptor and therefore preventing viral entry into the target cells.
Casirivimab and imdevimab are two monoclonal non-competing antibodies targeting the receptor binding domain (RBD) of the of the SARS-COV-2 spike protein at non-overlapping sites, thus blocking the interaction with the host receptor ACE2.

The pharmacokinetic profiles of casirivimab and imdevimab evaluated in the clinical pharmacology program are generally consistent with that of a monoclonal antibody. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for any of the evaluated covariates including, amongst others, age, body weight, sex and race.
The immunogenicity assessment is not yet completed.

The manufacturing process of the product has been scaled up twice since the initial manufacture (2000 L bioreactor scale to 10,000 L and 25,000 L), and the manufacturing site has changed. Analytical comparability between the manufacturing processes has been demonstrated, which is also in line with the quality assessment. Furthermore, the applicant provided PK data for the 2000 L (C1P1) and 10,000 L (C1P2) materials that were used in clinical studies. However, no data were provided for the comparability of the 25,000 L (C1P3) material. As no clinical comparability has been shown, some level of uncertainty remains regarding the safety and efficacy of the product to be marketed.

The treatment with a single 1200 mg IV dose of casirivimab/imdevimab in adults with symptomatic COVID-19 who are not hospitalised or who do not require supplemental oxygen for COVID-19 and with at least one risk factor for progression to severe disease demonstrated a clinical benefit.
The treatment effect in adolescents was not tested in clinical efficacy studies. However, the inclusion of adolescents aged 12 years and older and weighing at least 40 kg can be supported as the exposure of casirivimab/imdevimab is expected to be similar to the exposures observed in adults.
The proposed treatment indication was modified to be more representative of the studied population, thus it was indicated that the subjects should not be hospitalised (for COVID-19).

Results in asymptomatic, uninfected individuals living in a household with an infected index case showed that a single 1200 mg SC dose of casirivimab/imdevimab significantly prevented overall infections, including symptomatic and asymptomatic infections, reduced the duration of symptomatic infection in those who developed symptomatic infection and reduced the duration of viral shedding in those who became infected.
A single IV dose for acute prevention was not tested in clinical studies. However, as the systemic concentrations for casirivimab and imdevimab are higher following an IV dose, a similar clinical benefit is expected as with the SC administration.
The proposed repeat use of a 600 mg SC or IV dose of casirivimab/imdevimab following an initial 1200 mg dose for pre-exposure prophylaxis is accepted even in the lack of direct clinical efficacy data supporting this reduced dose as, based on pharmacokinetic bridging, a similar exposure is expected as for the clinically supported 1200 mg.

During the conduct of both pivotal studies several late amendments were issued influencing the primary endpoints and the study population.
To conclude on the benefits demonstrated in the prevention study, the statistical concerns regarding the study integrity and the control for type-I error could not be fully eliminated, although the results are partially accepted.

Currently, the vaccination is considered the primary prevention against COVID-19, and monoclonal antibodies are not a substitute for vaccination. The use for prevention needs to be limited to those who are unable to mount an adequate immune response to vaccination against COVID-19. Due to the above reasoning and the special circumstances of the pandemic, even though it is acknowledged that the studied population is not fully representative of the intended population, a clinical benefit is anticipated.

Based on in vitro data, the activity of casirivimab/imdevimab against the currently (i.e. at the time of the approval) dominant Delta variant is retained, although clinical efficacy has not been evaluated. For the Omicron variant, data were not available at the time of approval.

The safety profile of casirivimab/imdevimab was acceptable and in line with adverse events related to monoclonal antibodies. Hypersensitivity reactions, including anaphylaxis, infusion-related reactions and injection site reactions were observed and require monitoring (and treatment) of the treated subjects.

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No dose-dependent safety concerns were observed. Safety data were also available for (6 times) higher than the proposed doses.
Monthly repeat (6 times) SC administration of the proposed dose of 1200 mg casirivimab/imdevimab was associated with a higher incidence of injection site reactions compared to placebo.

In the pivotal treatment study, since only targeted AEs were collected, the safety profile of a 1200 mg IV dose is not fully characterised in subjects with risk factors. Uncertainties remain regarding the exact rate of hypersensitivity and IRR, as only grade ≥ 2 hypersensitivity reactions and grade ≥ 2 infusion-related reactions were collected.
Safety data are limited for adolescents, as adolescents were enrolled only in Study COV-2069.

Based on the submitted data, the benefit/risk profile of Ronapreve in the proposed dose for treatment and for prevention is considered positive.

Final (or interim) study reports for those studies that were part of the submission dossier, but were not yet available and/or were still ongoing, and the impact of these results on the benefit/risk profile of Ronapreve were requested as clinical stipulations.
Further monitoring of variants (variants of concern/variants of interest and escape mutants) and regular submission of in vitro neutralisation studies using pseudoparticles and authentic virus was a non-clinical stipulation, thus no further requirements regarding variants were imposed from the clinical side.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Ronapreve was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

RONAPREVE®

Composition

Active substances

Casirivimabum, Imdevimabum (genetically produced in CHO [Chinese Hamster Ovary] cells).

Excipients
Casirivimab vial: L-histidinum, L-histidini hydrochloridum monohydricum, polysorbatum 80*, saccharum**, aqua ad iniectabile q.s. ad solutionem per 1 ml
Imdevimab vial: L-histidinum, L-histidini hydrochloridum monohydricum, polysorbatum 80*, saccharum**, aqua ad iniectabile q.s. ad solutionem per 1 ml

(*produced from genetically modified maize, ** produced from genetically modified sugar beet).

Pharmaceutical form and active substance quantity per unit

Solution for injection/infusion

For IV/SC use

Ronapreve is available as:

Co-packaged 6 mL single-use vials
Each casirivimab vial contains 300 mg of casirivimab per 2.5 mL (120 mg/mL).
Each imdevimab vial contains 300 mg imdevimab per 2.5 mL (120 mg/mL)
Co-packaged 20 mL multidose vials
Each casirivimab vial contains 1 332 mg of casirivimab per 11.1 mL (120 mg/mL).
Each imdevimab vial contains 1 332 mg imdevimab per 11.1 mL (120 mg/mL).

Indications/Uses

Ronapreve is indicated for:
- Treatment of confirmed coronavirus disease 2019 (COVID-19) in adults and adolescents (12 years of age and older and weighing at least 40kg) who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at high risk of developing severe COVID-19 (see “Properties/Effects”)

- Prevention of COVID-19 in adults and adolescents (12 years of age and older and weighing at least 40kg) who cannot produce an adequate immune response to the SARS-CoV-2 vaccination.
Ronapreve is not intended to be used as a substitute for vaccination against COVID-19.

Ronapreve should be used according to official recommendations and local epidemiology of circulating SARS-CoV-2 variants need to be taken into account.

Dosage/Administration

Preparation and administration of Ronapreve should be initiated and monitored by a qualified healthcare provider. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible.
In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and/or administered is Ronapreve.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage

Treatment

The dosage in adults and adolescents 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion.
Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment.
Ronapreve should be given as soon as possible after a positive viral test for SARS-CoV-2 (see “Properties/Effects”).
For confirmation of COVID-19, a nucleic acid amplification test (NAAT) is preferred.

Prevention

Post-exposure prophylaxis

The dosage in adults and adolescents 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered either together as a single intravenous (IV) infusion or by subcutaneous injection.

Ronapreve should be given as soon as possible following exposure to SARS-CoV-2 (see “Properties/Effects”)

Pre-exposure prophylaxis

The initial dose is 600 mg of casirivimab and 600 mg of imdevimab administered by intravenous infusion or subcutaneous injection. Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab can be administered every 4 weeks as a single intravenous infusion or subcutaneous injection (see “Properties/Effects”, “Pharmacokinetics”). There are no data on repeat administration extending beyond 24 weeks.

Delayed administration

If a repeat dose of Ronapreve is missed it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the appropriate interval between doses.

Dose adjustment/titration

Patients with hepatic disorders

No dose adjustment is required in individuals with mild hepatic impairment. Limited data are available in patients with moderate hepatic impairment. Casirivimab and imdevimab have not been studied in individuals with severe hepatic impairment (see paragraph “Kinetics in specific patient groups”).

Patients with renal disorders

No dosage adjustment is required in individuals with mild or moderate renal impairment, or in patients with CrCl <15 mL/min including those on dialysis. Limited data are available in patients with severe renal impairment (see paragraph “Kinetics in specific patient groups”).

Elderly patients

No dose adjustment of casirivimab and imdevimab is required in elderly patients (see paragraph “Kinetics in specific patient groups”).

Children and adolescents

No dosage adjustment is required in paediatric individuals 12 years of age and older and weighing 40kg (see section “Undesirable effects”, “Properties/Effects” and “Kinetics in specific patient groups”). The safety and efficacy of casirivimab and imdevimab in children <12 years of age have not yet been established. No data are available.

Mode of administration

Ronapreve is intended for intravenous infusion or subcutaneous injection.

Intravenous Infusion
For detailed instructions on the preparation and administration of Ronapreve, see subsection “Dose Preparation and Administration” in “Other information / Instructions for handling”.

Table 1: Recommended dilution instructions for Ronapreve (casirivimab and imdevimab) for intravenous infusion

Indication	**Ronapreve dose (total)**	**Total volume for 1 Dose**	**Withdrawable volume from each vial to inject into a prefilled 0,9 % sodium chloride or 5 % dextrose infusion bag***
Treatment, post-exposure prophylaxis – single dose and pre-exposure prophylaxis - initial dose	600 mg casirivimab and 600 mg imdevimab (1200 mg dose)	10 mL	2.5 mL from **two** 6 mL vials of casirivimab 2.5 mL from-**two** 6 mL vials of imdevimab
			5.0 mL from one 20 mL multi-dose vial of casirivimab 5.0 mL from one 20 mL multi-dose vial of imdevimab
Pre-exposure prophylaxis - subsequent dose	300 mg casirivimab and 300 mg imdevimab (600 mg dose)	5 mL	2.5 mL from one 6 mL vial of casirivimab 2.5 mL from one 6 mL vial of imdevimab
			2.5 mL from one 20 mL multi-dose vial of casirivimab 2.5 mL from one 20 mL multi-dose vial of imdevimab

***Bag sizes of 50mL, 100mL, 150mL or 250mL can be used**

The minimum infusion time for Ronapreve in 250 mL infusion bags is 30 minutes. For infusion bags 150 mL, 100 mL or 50 mL, the minimum infusion time is 20 minutes.

The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of infusion-associated events or other adverse events.

Subcutaneous injection
For detailed instructions on the preparation and administration of Ronapreve, see subsection “Dose Preparation and Administration” in “Other information / Instructions for handling”.
Administer the subcutaneous injections at a different injection site each time: the thighs, the upper outer arms, or the abdomen, except for 5 cm around the nave (periumbilical). The waistline should be avoided.

When administering the subcutaneous injections, it is recommended that healthcare professionals use different quadrants of the abdomen or upper thighs or outside of the upper arms to space apart each 2,5 mL subcutaneous injection of casirivimab and imdevimab to reduce injection site reactions (see section «Undesirable effects»).

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Table 2: Preparation of Ronapreve (casirivimab and imdevimab) for subcutaneous injection

Indication	Ronapreve dose (total)	Total volume for 1 dose	Volume to be withdrawn to prepare 4 syringes
• Treatment • Post-exposure prophylaxis – single dose and • Pre-exposure prophylaxis - initial dose	600 mg casirivimab and 600 mg imdevimab (1200 mg dose)	10 mL	2,5 mL from two 6 mL vials of casirivimab 2,5 mL from two 6 mL vials of imdevimab
			2,5 mL (2x) from one-20 mL multidose vial of casirivimab 2,5 mL (2x) from one 20 mL multidose vial of imdevimab
• Pre-exposure prophylaxis	300 mg casirivimab and 300 mg imdevimab (600 mg dose)	5 mL	2,5 mL from one 6 mL vial of casirivimab 2,5 mL from one 6 mL vial of imdevimab
			2,5 mL from one 20 mL multidose vial of casirivimab 2,5 mL from one 20 mL multidose vial of imdevimab

Contraindications

Ronapreve is contraindicated in patients who have hypersensitivity to the active substances or any of its excipients.

Warnings and precautions

Individuals should be monitored after administration according to local medical practice. Clinically monitor patients during intravenous dose administration and observe patients for at least 1 hour after administration is complete.

Serious hypersensitivity reactions including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of Ronapreve. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion related reactions

Infusion-related reactions (IRRs) have been observed with intravenous administration of Ronapreve. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion. The commonly reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, infusion related reactions may present as severe or life threatening events and may include other signs and symptoms.

If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Interactions

No interaction studies have been performed. Casirivimab and imdevimab are monoclonal antibodies, which are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

COVID-19 Vaccines

Casirivimab and imdevimab bind to epitopes on spike protein used as immunogen in all COVID-19 vaccines, therefore it is possible that casirivimab and imdevimab may impact responses to COVID-19 vaccines. Refer to current vaccination guidelines with respect to timing of vaccination post treatment with anti-SARS-CoV-2 monoclonal antibodies.

Pregnancy, lactation

Pregnancy

There are no or limited data on the use of casirivimab and imdevimab in pregnant women. No animal studies were conducted on reproductive toxicity (see “Preclinical data”). Human immunoglobulin G1 (IgG1) antibodies are known to cross the placenta. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to developing foetus. Ronapreve should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors. If a woman becomes pregnant while taking this medicine, the individual should be informed that any potential risk to the foetus is unknown.

Breast-feeding

It is unknown whether casirivimab and imdevimab are excreted in human milk.

A risk to new borns/infants cannot be excluded.

Because maternal IgG is known to be present in human milk and any potential risk of adverse reactions from the drug in breast-feeding infants is unknown, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ronapreve therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No fertility studies have been performed.

Effects on ability to drive and use machines

Ronapreve has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Overall, approximately 7`116 subjects (approximately 4`666 via intravenous administration and 2`450 via subcutaneous administration) have been exposed to Ronapreve in clinical trials.
The most frequently reported adverse drug reactions are hypersensitivity reactions, which include infusion related reactions (IRRs) and injection site reactions (ISRs).

Summary of the safety profile

List of adverse reactions

Adverse drug reactions (Table 3) are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1`000 to <1/100), rare (≥1/10`000 to <1/1000), very rare (<1/10`000).

Table 3 Tabulated list of adverse reactions identified from Clinical Trials:

System organ class	Adverse Reaction	Frequency Category
Intravenous administration		
Immune system disorders	Anaphylaxis[3]	Rare
Nervous system disorders	Dizziness[2]*	Uncommon
Vascular disorders	Flushing[2]*	Rare
Gastrointestinal disorders	Nausea[2]*	Uncommon
Skin and subcutaneous tissue disorders	Rash[2]*	Uncommon
	Urticaria[2]*	Rare

General disorders and administration site conditions	Chills[2]*	Uncommon
Injury, poisoning and procedural complications	Infusion related reactions[2]	Uncommon
Subcutaneous administration		
Blood and lymphatic system disorders	Lymphadenopathy[1, 4*]	Uncommon
Nervous system disorders	Dizziness[5]	Uncommon
Skin and subcutaneous tissue disorders	Pruritus[5]*	Rare
General disorders and administration site conditions	Injection site reactions[5]	Common

[1] Observed with repeat dose subcutaneous administration in Study HV-2093
[2] Frequency determined from study COV-2067
[3] Frequency determined from studies using IV administration (COV-2066, COV-2067 and COV-20145)
[4] Frequency determined from study HV-2093 (repeat dose subcutaneous study)
[5] Frequency determined from study COV-2069. ISRs include erythema, pruritus, ecchymosis, oedema, pain, tenderness and urticaria
* In some cases, symptoms of IRRs and ISRs have been reported as individual ADRs

Description of specific adverse reactions and additional information

Hypersensitivity Including anaphylaxis

The following hypersensitivity reactions of varying severity were observed across the clinical development program.
Anaphylaxis/anaphylactic reaction: has been observed in the clinical development program but was a rare event and occurred within 1 hour of completion of the infusion and resolved after supportive treatment which included epinephrine (see section “Warnings and Precautions”).

Infusion-related reactions (IRR)
Infusion-related reactions have been observed with IV administration of casirivimab and imdevimab across all dose groups in clinical studies. These reactions were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion and resolved either without intervention or with usual standard of care. Commonly reported signs and symptoms for infusion related reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. Other known clinical presentations of IRR may also be expected (see section “Warnings and Precautions”).

Injection Site Reactions (ISR):
Injection site reactions were reported in all studies with subcutaneous administration including single dose and repeat dose studies. All ISR were mainly local, mild to moderate in severity and were resolved either without intervention or with usual standard of care. Commonly reported signs and

symptoms for these reactions were erythema, pruritus, ecchymosis, oedema, pain/tenderness and urticaria. In the repeat dose study, (HV-2093) localized lymphadenopathy was also observed.

Paediatric Population

Intravenous administration: No data are available for paediatric patients <18 years old.
Subcutaneous administration: Adolescents ≥12 and <18 years old received treatment with Ronapreve in study COV-2069 and the observed safety profile was similar to that in adult patients.

Elderly

Intravenous administration: In study COV-2067, patients aged ≥ 65 years received treatment with Ronapreve. The safety profile was similar to that in adult patients < 65 years old.
Subcutaneous administration: In study COV-2069 individuals ≥ 65 years old were treated with Ronapreve and the safety profile was similar to that in adults < 65 years old.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to casirivimab and imdevimab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Interim analysis of immunogenicity in all subjects who received Ronapreve by intravenous infusion (n = 2'484 and 2`417 for casirivimab and imdevimab, respectively, for a single dose of 1200, 2400 or 8000 mg) or subcutaneous injection (n = 1`667 and 1`664 for casirivimab and imdevimab, respectively, for a 1200 mg single dose or in six monthly doses), found the incidence of anti-casirivimab and anti-imdevimab antibodies were 0,8 % and 1,7 %, respectively. For subjects who received placebo, the incidence of anti-casirivimab and anti-imdevimab antibodies were 1,9 % and 4,5 %, respectively.

In 707 subjects treated with Ronapreve 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) subcutaneously every 4 weeks, the incidence of treatment-emergent anti-casirivimab and anti-imdevimab antibodies was 0,1 % and 2,0 %, respectively. Among 232 repeat dose placebo subjects, the incidence of treatment emergent anti-casirivimab and anti-imdevimab antibodies were 0 % and 2,6 %, respectively. The antibody titres in both Ronapreve and placebo repeat dose subjects were low.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Doses up to 8000 mg (4000 mg each of casirivimab and imdevimab, approximately 7 times the recommended dose) have been administered in clinical trials with a safety profile similar to the approved dose. There is no specific antidote for casirivimab and imdevimab overdose. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Properties/Effects

ATC code

tbd

Mechanism of action

Casirivimab (IgG1κ) and imdevimab (IgG1λ) are two recombinant human monoclonal antibodies which are unmodified in their respective Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants K_D = 45,8 pM and 46,7 pM, respectively. Casirivimab, imdevimab and casirivimab and imdevimab together blocked RBD binding to the human ACE2 receptor with IC_{50} values of 56,4 pM, 165 pM and 81,8 pM, respectively.

In cell-based assays, imdevimab and casirivimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) but no complement-dependent cytotoxicity. No antibody-dependent enhancement (ADE) activity was found as shown in vitro in cellular assays.

Antiviral Activity

In a SARS-CoV-2 virus neutralisation assay in Vero E6 cells, casirivimab, imdevimab, and casirivimab and imdevimab together neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 37,4 pM (0,006 µg/mL), 42,1 pM (0,006 µg/mL), and 31,0 pM (0,005 µg/mL) respectively.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together.

The neutralisation potency of casirivimab and imdevimab together was assessed against S protein variants, including known Variants of Concern/Interest (VOC/VOI), variants identified in in vitro escape studies, and variants from publicly available SARS-CoV-2 genome data obtained from the Global Initiative on Sharing All Influenza Data (GISAID) (table 4).

Table 4: Pseudotyped Virus-Like Particle Neutralisation Data for Full Sequence or Key SARS-CoV-2 S-Protein Variant Substitutions and Authentic Viruses from Variants of Concern/Interest with casirivimab and imdevimab

Lineage with Spike Protein Substitutions	Key Substitutions Tested	Reduced Susceptibility (Pseudovirus)	Reduced Susceptibility(Authentic virus)	
B.1.1.7 (UK origin/Alpha)	Full S protein[a]	no change[d]	no change[d]	
B.1.351 (South Africa origin/Beta)	Full S protein[b]	no change[d]	no change[d]	
P.1 (Brazil origin/Gamma)	Full S protein[c]	no change[d]	no change[d]	
B.1.427/B.1.429 (California origin/Epsilon)	L452R	no change[d]	n.d.	
B.1.526 (New York origin/Iota)[e]	E484K	no change[d]	n.d.	
B.1.617.1/B.1.617.3 (India origin/Kappa)	L452R+E484Q	no change[d]	no change[d]	
B.1.617.2 (India origin/Delta)	L452R+T478K	no change[d]	no change[d]	

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F

[d] No change: ≤ 5-fold reduction in susceptibility.

[e] Not all isolates of the New York lineage harbour the E484K substitution (as of February 2021).

n.d., not determined.

*Variants of interest/concern as defined by the Centers for Disease Control and Prevention (CDC, 2021) {https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html}

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

Pharmacodynamics

Clinical efficacy

Treatment of COVID-19

Study COV-2067

The Phase 3 trial, COV-2067, is a randomized, double-blinded, placebo-controlled clinical trial evaluating Ronapreve (casirivimab and imdevimab) for the treatment of symptomatic adult subjects with RT-qPCR confirmed COVID-19 who are not hospitalized or requiring supplemental oxygen. Subjects were randomised within 7 days of symptom onset.

In the Phase 3 cohort 1, 4`567 subjects with at least one risk factor for severe COVID-19 were randomized within 7 days of symptom onset to the following groups: single intravenous infusion of Ronapreve 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) (n=838), Ronapreve 2400 mg (1200 mg of casirivimab and 1200 mg of imdevimab) (n=1`529), Ronapreve 8000 mg (4000 mg of casirivimab and 4000 mg of imdevimab) (n=700), or placebo (n=1`500) . The two Ronapreve doses at the start of Phase 3 were 8000 mg and 2400 mg; however, based on Phase 1/2 efficacy analyses showing that the 8000 mg and 2400 mg doses were similar, the Phase 3 portion of the protocol was amended to compare the 2400 mg dose vs. placebo and the 1200 mg dose vs. placebo. Comparisons were between subjects randomized to the specific Ronapreve dose and subjects who were concurrently randomized to placebo.

At baseline, in all randomized subjects with at least one risk factor, the median age was 50 years (with 13 % of subjects ages 65 years or older), 52 % of the subjects were female, 84 % were White, 5 % were Black or African American; 36 % identified as Hispanic or Latino. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups. The median time from symptom onset to randomisation was 3 days for all groups.

Primary endpoint

The primary endpoint was the proportion of subjects with ≥1 COVID-19-related hospitalisation or all-cause death through Day 29, in 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, i.e., the modified full analysis set (mFAS). Protocol risk factors for developing severe COVID-19 included age > 50 years; obesity defined as BMI ≥ 30 kg/m^2, cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 and type 2 diabetes mellitus; chronic

kidney disease, including dialysis patients; chronic liver disease, pregnancy and immunosuppressed patients.

Table 5: Primary endpoint for Study COV-2067

	1200 mg IV	**Placebo**	**2400 mg IV**	**Placebo**
	n = 736	n=748	n = 1`355	n = 1`341
Patients with ≥1 COVID-19-related hospitalization or death through day 29				
Risk reduction	70 % (p=0,0024)		71 % (p<0,0001)	
# of patients with events	7 (1,0 %)	24 (3,2 %)	18 (1,3 %)	62 (4,6 %)

Prevention of COVID-19

COV-2069 was a randomised, double-blind, placebo-controlled clinical trial that compared 600 mg casirivimab and 600 mg imdevimab given subcutaneously to placebo for prevention of COVID-19 in asymptomatic household contacts of symptomatic individuals infected with SARS-CoV-2 (index cases). Subjects had not been previously vaccinated against SARS-CoV-2.
Subjects were randomised 1:1 to casirivimab and imdevimab or placebo within 96 hours of collection of the first index case sample that gave a positive result (RT-qPCR) for SARS-CoV-2.
Randomised subjects with a negative SARS-CoV-2 RT-qPCR test result at baseline were assigned to Cohort A and those with a positive SARS-CoV-2 RT-qPCR test result were assigned to Cohort B.

Cohort A
The primary analysis population included subjects who were SARS-CoV-2 RT-qPCR negative and seronegative at baseline. Subjects who were seropositive or who had undetermined/missing baseline serology were excluded from the primary efficacy analysis.

For the primary analysis population at baseline, the median age was 44 years (with 9 % of subjects ages 65 years or older) and 54 % of the subjects were female. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.
The primary endpoint was the proportion of subjects who developed symptomatic RT-qPCR-confirmed COVID-19 through Day 29. There was a statistically significant 81 % risk reduction in the development of COVID-19 with casirivimab and imdevimab treatment versus placebo. In a sensitivity analysis that included all RT-qPCR negative subjects at baseline, regardless of baseline serological

status, there was a statistically significant 82 % risk reduction in development of COVID-19 with casirivimab and imdevimab treatment compared to placebo.

Table 6: Primary Analysis of study COV-2069, Cohort A

	Ronapreve (single 1 200 mg dose)	**Placebo**
Primary Analysis Population: Seronegative at Baseline	n = 753	n = 752
Risk of COVID-19		
Through Day 29 (primary endpoint)		
Unadjusted Risk reduction (Adjusted Odds ratio, p-value)	81 % (0.17; p < 0.0001)	
Number of individuals with events	11 (1,5 %)	59 (7,8 %)

The confidence interval (CI) with p-value is based on the odds ratio (casirivimab and imdevimab group vs placebo group) using 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).

Cohort B

The primary analysis population included asymptomatic subjects who were SARS-CoV-2 RT-qPCR positive and seronegative at baseline.

For the primary analysis population at baseline, the median age was 40 years (with 11 % of subjects ages 65 years or older) and 55 % of the subjects were female. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary efficacy endpoint was the proportion of subjects who developed RT-qPCR-confirmed COVID-19 through Day 29. There was a 31 % risk reduction in the development of COVID-19 with casirivimab and imdevimab treatment vs. placebo. In a sensitivity analysis that included all RT-qPCR positive subjects at baseline, regardless of baseline serological status, there was a 35 % risk reduction in RT-qPCR-confirmed COVID-19 with casirivimab and imdevimab treatment compared to placebo.

Table 7: Primary analysis of study COV-2069, Cohort B

	Ronapreve (single 1 200 mg dose)	**Placebo**
Primary Analysis Population: Seronegative at Baseline	n = 100	n = 104
Risk of COVID-19		
Overall risk reduction through Day 29 (primary endpoint)		
Unadjusted Risk reduction (Adjusted Odds ratio, p-value)	31 % (0,54; p = 0,0380)	
Number of individuals with events	29 (29 %)	44 (42,3 %)

The confidence interval (CI) with p-value is based on the odds ratio (casirivimab and imdevimab group vs placebo group) using 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).

Pharmacokinetics

Absorption

Both casirivimab and imdevimab exhibited linear and dose-proportional pharmacokinetics (PK) between 300 mg Ronapreve (150 mg casirivimab and 150 mg imdevimab) to 8000 mg Ronapreve (4000 mg casirivimab and 4000 mg imdevimab) following intravenous administration of single dose. A summary of PK parameters after a single (600 mg casirivimab and 600 mg imdevimab) intravenous dose, calculated using a population PK model for each antibody based on data from 3`687 subjects (casirivimab) or 3`716 subjects (imdevimab), is provided in Table 8.

Table 8: Summary of PK parameters for casirivimab and imdevimab after a single 1200 mg IV dose of Ronapreve

PK Parameter[1]	**casirivimab**	**imdevimab**
$AUC_{0\text{-}28}$ (mg·day/L)[2]	1754,9 (380,50)	1600,8 (320,88)
AUC_{inf} (mg·day/L)[3]	3563,6 (1239,61)	2890,5 (876,31)
C_{max} (mg/L)[4]	182,7 (81,45)	181,7 (77,78)
C_{28} (mg/L)[5]	37,9 (10,33)	31,0 (8,24)
Half-life (day)	31,2 (10,59)	27,3 (7,73)

[1] Mean (SD), where SD is standard deviation of the arithmetic mean; [2] $AUC_{0\text{-}28}$ = Area under the concentration time curve from time 0 to 28 days after dosing; [3] AUC_{inf} = Area under the concentration time curve from time 0 to infinite time; [4] C_{max} = Maximum concentration in serum and represents concentration at the end of infusion; [5] C_{28} = Concentration 28 days after dosing, i.e., on day 29

A summary of PK parameters after a single (600 mg casirivimab and 600 mg imdevimab) subcutaneous dose based on the population PK model for each antibody is shown in Table 9.

Table 9: Summary of PK parameters for casirivimab and imdevimab after a single 1200 mg SC Dose of [Ronapreve]

PK Parameter[1]	casirivimab	imdevimab
AUC_{0-28} (mg·day/L)[2]	1121,7 (243,12)	1016,9 (203,92)
AUC_{inf} (mg·day/L)[3]	2559,5 (890,35)	2073,3 (628,60)
C_{max} (mg/L)[4]	52,2 (12,15)	49,2 (11,01)
t_{max} (day)[5, 6]	6,7 [3,4, 13,6]	6,6 [3,4, 13,6]
C_{28} (mg/L)[7]	30,5 (7,55)	25,9 (6,07)

[1] Mean (SD), where SD is standard deviation of the arithmetic mean; [2] AUC_{0-28} = Area under the concentration time curve from time 0 to 28 days after dosing; [3] AUC_{inf} = Area under the concentration time curve from time 0 to infinite time; [4] C_{max} = Maximum concentration in serum; [5] t_{max} = Time to reach C_{max}; [6] Median [minimum, maximum]; [7] C_{28} = Concentration 28 days after dosing, i.e., on day 29

A summary of PK parameters after a single 1200 mg intravenous loading dose of Ronapreve (600 mg casirivimab and 600 mg imdevimab) followed by multiple 600 mg Ronapreve intravenous Q4W doses (300 mg casirivimab and 300 mg imdevimab) based on the population PK model for each antibody is shown in Table 10.

Table 10: Summary of PK parameters for casirivimab and imdevimab after a single 1200 mg IV loading dose and 600 mg IV Q4W maintenance doses of Ronapreve

PK Parameter[1]	casirivimab	imdevimab
$AUC_{tau,ss}$ (mg·day/L)[2]	1767,5 (605,79)	1436,8 (432,87)
$C_{max,ss}$ (mg/L)[3]	133,8 (46,51)	122,4 (41,67)
$C_{trough,ss}$ (mg/L)[4]	42,6 (19,72)	31,7 (13,56)
C_{28} (mg/L)[5]	37,9 (10,32)	31,0 (8,24)
AR[6]	1,0 (0,241)	0,893 (0,174)

[1] Mean (SD), where SD is standard deviation of the arithmetic mean; [2] $AUC_{tau,ss}$ = Area under the concentration time curve during a dosing interval at steady-state; [3] $C_{max,ss}$ = Maximum concentration at steady-state; [4] $C_{trough,ss}$ = Trough concentration at steady-state; [5] C_{28} = Concentration 28 days after the first dose; [6] The accumulation ratio (AR) is calculated as $\frac{AUC_{\tau,ss}}{AUC_{\tau,FD}}$ (FD = first dose); Q4W = every 4 weeks.

A summary of PK parameters after a single subcutaneous 1200 mg loading dose of Ronapreve (600 mg casirivimab and 600 mg imdevimab) followed by multiple subcutaneous Q4W doses of 600 mg Ronapreve (300 mg casirivimab and 300 mg imdevimab) based on the population PK model for each antibody is shown in Table 11.

Table 11: Summary of PK parameters for casirivimab and imdevimab after a single 1200 mg subcutaneous loading dose and 600 mg subcutaneous Q4W maintenance doses of Ronapreve

PK Parameter[1]	casirivimab	imdevimab
$AUC_{tau,ss}$ (mg·day/L)[2]	1268,9 (434,68)	1030,1 (310,30)
$C_{max,ss}$ (mg/L)[3]	56,0 (16,81)	47,0 (12,43)
$C_{trough,ss}$ (mg/L)[4]	34,0 (14,56)	26,1 (10,17)
C_{28} (mg/L)[5]	30,5 (7,55)	25,9 (6,07)
AR[6]	1,13 (0,288)	1,01 (0,213)

[1] Mean (SD), where SD is standard deviation of the arithmetic mean; [2] $AUC_{tau,ss}$ = Area under the concentration time curve during a dosing interval at steady-state; [3] $C_{max,ss}$ = Maximum concentration at steady-state; [4] $C_{trough,ss}$ = Trough concentration at steady-state; [5] C_{28} = Concentration 28 days after the first dose; [6] The accumulation ratio (AR) is calculated as $\frac{AUC_{\tau,ss}}{AUC_{\tau,FD}}$ (FD = first dose); Q4W = every 4 weeks.

With regard to the repeat dose of intravenous and subcutaneous regimens for prevention, population pharmacokinetic simulations predict that median predicted casirivimab and imdevimab $C_{trough,ss}$ in serum are similar to observed mean day 29 concentrations in serum after a single 1200 mg subcutaneous dose of Ronapreve 1200 mg (600 mg of casirivimab and 600 mg of imdevimab).

Based on population pharmacokinetic modeling, mean (standard deviation) C_{max} and C_{28} estimates for casirivimab and imdevimab following single IV or single subcutaneous dose 1200 mg (600 mg each monoclonal antibody) are listed in Table 8 and Table 9, respectively. Median (range) time to reach maximum serum concentration of casirivimab and imdevimab (T_{max}) estimates following a single subcutaneous dose of Ronapreve 1200 mg (600 mg each monoclonal antibody) are 6,7 (3,4 – 13,6) days and 6,6 (3,4 – 13,6) days for casirivimab and imdevimab, respectively (Table 9).
Following casirivimab and imdevimab administered as a single dose of Ronapreve 1200 mg subcutaneously (600 mg each monoclonal antibody), casirivimab and imdevimab had a population PK estimated bioavailability of 71,8 % and 71,7 %, respectively.

Distribution

The total volume of distribution estimated via population pharmacokinetic analysis is 7,161 L and 7,425 L for casirivimab and imdevimab, respectively.

Metabolism

Specific metabolism studies were not conducted because casirivimab and imdevimab are proteins. 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.

Elimination

The mean (5th, 95th percentile) elimination half-lives and clearance after a single 600 mg dose of each monoclonal antibody were 29,8 (16,4, 43,1) days and 0,188 (0,11, 0,3) L/day for casirivimab, respectively, and 26,2 (16,9, 35,6) days and 0,227 (0,15, 0,35) L/day for imdevimab, respectively, based on a population PK analysis.

Excretion

Casirivimab and imdevimab are monoclonal antibodies and are therefore not likely to undergo renal excretion.

Kinetics in specific patient groups

The effect of all tested covariates, and observed statistically significant covariates (gender, body weight and baseline albumin on clearance [CL] and on volume of central compartment [Vc]; and race, mild hepatic impairment and baseline viral load on CL), on the pharmacokinetics of Ronapreve was evaluated by population PK analysis. Such analysis suggested no clinically meaningful effect on the exposure of casirivimab and imdevimab:age (median: 42 y, range: 18-96 y), gender (male, female), body weight (median: 81,5 kg, range: 35,5-201 kg), race (Black, Others [White, Asian, Native American), baseline albumin level (median: 43 g/L, range: 26-56 g/L), renal impairment (normal, mild, moderate, severe, kidney failure), and mild hepatic impairment (normal, mild, moderate).

Among all evaluated covariates, body weight was the main covariate that affected the exposure of both casirivimab and imdevimab. Compared to a reference 81 kg subject, exposures (AUC_{day28}, C_{max} and C_{day28}) are predicted to be 20- 30 % higher in subjects at the 5th percentile of body weight (55,4 kg) and 20-25 % lower in subjects at the 95th percentile of body weight (123 kg) for both casirivimab and imdevimab.

Compared to a reference 81 kg subject, the subject with the combination of covariates leading to the highest population casirivimab-imdevimab CL (White, male, albumin 29 g/L, 151,8 kg) is predicted to have AUC_{day28}, C_{max}, and C_{day28} ratios of 0,48, 0,56, and 0,31 respectively for casirivimab, and 0,47, 0,56, and 0,28 respectively for imdevimab.

Hepatic impairment

Casirivimab and imdevimab are not expected to undergo significant hepatic elimination. The effect of hepatic impairment on the exposure of casirivimab and imdevimab was evaluated by population PK analysis in patients with mild hepatic impairment (n = 586 for casirivimab and n = 599 for imdevimab) (total bilirubin [TB] greater than 1,0 to 1,5 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST]); no clinically important differences in the exposure of casirivimab and imdevimab were found between patients with mild hepatic impairment and patients with normal

hepatic function. Limited data (n = 11) are available in patients with moderate hepatic impairment. The pharmacokinetics in patients with severe hepatic impairment has not been studied.

Renal impairment

Casirivimab and imdevimab are monoclonal antibodies that are not expected to undergo significant renal elimination due to their molecular weight (>69 kDa). Based on population PK analysis, trough concentrations of casirivimab and imdevimab in serum at steady state were comparable between patients with mild or moderate renal impairment, and patients with CrCl <15 mL/min including those on dialysis, and patients with normal renal function. Limited data are available in patients with severe renal impairment (n = 3).

Elderly patients

In the population PK analysis, age (18 years to 96 years) was not identified as a significant covariate on PK of either casirivimab or imdevimab.

Compared to patients < 65 years of age, exposures of casirivimab and imdevimab were similar in patients who were aged > 65 years or ≥ 75 years after either intravenous or subcutaneous administration.

Children and adolescents

For adolescent patients with COVID-19 (12 years of age and older and weighing at least 40 kg in COV-2067) receiving a single 1200 mg intravenous dose, the mean ± SD concentration at the end of infusion and at 28 days after dosing was 172 ± 96,9 mg/L and 54,3 ± 17,7 mg/L for casirivimab and 183 ± 101 mg/L and 45,3 ± 13,1 mg/L for imdevimab.

For adolescents not infected with SARS-CoV-2 (12 years of age and older and weighing at least 40 kg in COV-2069) receiving a single 1200 mg subcutaneous dose, the mean ± SD concentration 28 days after dosing was 44,9 ± 14,7 mg/L for casirivimab and 36,5 ± 13,2 mg/L for imdevimab. The pharmacokinetics of casirivimab and imdevimab in children < 12 years of age has not yet been established.

Preclinical data

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with casirivimab and imdevimab.

In a toxicology study in cynomolgus monkeys, minor transient increases in AST and ALT not associated with side effects, likely of skeletal muscle origin and thus likely procedure-related were observed at exposures in excess of 30-fold of the human therapeutic exposures.

In tissue cross-reactivity studies with casirivimab and imdevimab using human and monkey adult tissues and human foetal tissues, no binding was detected.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. For intravenous administration, compatibility with the diluents 0.9 % sodium chloride injection or 5 % dextrose injection solution has been demonstrated.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Co-packaged 20 mL multidose vials

The casirivimab and/or imdevimab solution contains no preservatives. After initial puncture: If not used immediately, the product in the vial can be stored for 4 hours at room temperature up to 25 °C or for no more than 24 hours refrigerated between 2 °C to 8 °C. Beyond these times and conditions, in-use storage is the responsibility of the user.

Co-packaged 6 mL single-dose vials

The casirivimab and/or imdevimab solution contains no preservatives. After initial puncture: the medicinal product should be used immediately, any remaining product should be discarded.

Diluted solution for intravenous administration

Solution in vial requires dilution prior to administration. The diluted solution of casirivimab and/or imdevimab contains no preservatives. 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 should normally not exceed 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, allow the IV infusion bag to equilibrate to room temperature for approximately 30 minutes prior to administration.

Storage of syringes for subcutaneous administration

The casirivimab and/or imdevimab solution contains no preservatives. Therefore, 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 should normally not exceed 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

Special precautions for storage

Store in the refrigerator (2-8 °C).
Do not freeze. Do not shake.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.
For storage conditions after dilution of the medicinal product, as well as for the syringes for subcutaneous administration, see section “Shelf life after opening”.

Instructions for handling

Dose Preparation and Administration

General precautions

Casirivimab and imdevimab vials should be inspected visually to ensure there is no particulate matter or discolouration prior to the administration. If particulate matter or discolouration is observed the vial should be discarded per local disposal guidelines.

Intravenous infusion

Preparation of Ronapreve for intravenous infusion

Ronapreve should be prepared by a healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation.
   - Do not expose to direct heat.
   - **Do not shake the vials.**
2. Inspect casirivimab and imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colourless to pale yellow.

3. Obtain a prefilled IV infusion bag [made from polyvinyl chloride (PVC) or polyolefin (PO)] containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0,9 % sodium chloride injection or 5 % dextrose injection.
4. Using a sterile syringe and needle, withdraw the appropriate volume of casirivimab and imdevimab from each respective vial and inject into a prefilled infusion bag containing 0,9 % sodium chloride injection or 5 % dextrose injection (see section "Dosage/Administration", Table 1).
5. Gently mix infusion bag by inversion. Do not shake.
6. Ronapreve is preservative-free and therefore, the diluted infusion solution should be administered immediately from a microbiological point of view.
    - If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not exceed 24 hours at 2 °C to 8 °C, unless the dilution has taken place in controlled and validated aseptic conditions. 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. If refrigerated, allow the intravenous infusion bag to equilibrate to room temperature for approximately 30 minutes prior to administration.

Administration of Ronapreve by Intravenous Infusion

- Gather the recommended materials for infusion:
    - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
    - In-line or add-on 0,2 µm to 5 µm polyethersulfone, polysulfone, or polyamide end filter for intravenous administration.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2 µm to 5 µm pore size polyethersulfone, polysulfone, or polyamide end filter for intravenous administration (see section "Dosage/Administration").
- The prepared infusion solution should not be administered simultaneously with any other medicinal products. The compatibility of casirivimab and imdevimab injection with IV solutions and medicinal products other than 0,9 % sodium chloride injection or 5 % dextrose injection is not known.
- After infusion is complete, flush the tubing with 0,9 % sodium chloride injection or 5 % dextrose injection to ensure delivery of the required dose.
- Patients should be monitored post intravenous infusion according to local medical practice.

Subcutaneous injection

Preparation of Ronapreve for subcutaneous injection

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation.
Do not expose to direct heat.
Do not shake the vials.

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discoloration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colourless to pale yellow.

1. Ronapreve should be prepared using the appropriate number of syringes (see section "Dosage/Administration", Table 2). Obtain 3 mL or 5 mL polypropylene syringes with luer connection and 21-gauge transfer needles.
2. Using a sterile syringe and needle, withdraw the appropriate volume of casirivimab and imdevimab from each respective vial into each syringe (see section "Dosage/Administration", Table 2) for a total of 4 syringes for the 1 200 mg combined total dose and a total of 2 syringes for the 600 mg combined total dose. Store any remaining product in the multidose vial as directed (see section "Shelf life after opening").
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not exceed 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions. 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 refrigerated, allow the syringes to equilibrate to room temperature for approximately 10 - 15 minutes prior to administration.

Administration of Ronapreve by subcutaneous injection

- For the subcutaneous injection of Ronapreve 1200 mg dose (600 mg of casirivimab and 600 mg of imdevimab), gather 4 syringes (see section "Dosage/Administration", Table 2) and prepare for subcutaneous injections.

- For the subcutaneous injection of Ronapreve 600 mg dose (300 mg of casirivimab and 300 mg of imdevimab), gather 2 syringes (see section “Dosage/Administration”, Table 2) and prepare for subcutaneous injections.
- Administer the subcutaneous injections consecutively, each at a different injection site, into the upper thigh, the upper outer arms, or abdomen, except for 5 cm around the navel (periumbilical). The waistline should be avoided.
- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or upper outer arms to space apart each 2,5 mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred.

Disposal of unused/expired medicines

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68329 (Swissmedic)

Packs

20 mL multidose vials packaged together:
2 multidose vials, each containing 11,1 mL solution for injection/infusion/ [A]

6mL single dose vials packaged together:
2 single dose vials, each containing 2,5 mL solution for injection/infusion/ [A]

Marketing authorisation holder

Roche Pharma (Schweiz) AG, Basel.

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