Date: 15 August 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

REGKIRONA

International non-proprietary name: regdanvimab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): 60 mg / mL

Route(s) of administration: intravenous

Marketing Authorisation Holder: IQONE HEALTHCARE SWITZERLAND

Marketing Authorisation No.: 68356

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 12 January 2022

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
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
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
CE-SDS	Capillary electrophoresis sodium dodecyl sulfate
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
COVID-19	Coronavirus disease 2019
CPK	Creatine kinase
CYP	Cytochrome P450
DDI	Drug-drug interaction
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IEC	Ion exchange chromatography
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
ITTI	Intention-to-treat infected
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
mRNA	Messenger ribonucleic acid
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PRNT	Plaque reduction neutralisation test
PSP	Pediatric Study Plan (US-FDA)
RBD	Receptor-binding domain
RMP	Risk Management Plan
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SEC	Size exclusion
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event

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TESAE	Treatment-emergent serious adverse event
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)
VOC	variant of concern
VOI	variant of interest

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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 substance regdanvimab of the medicinal product mentioned above.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

Authorisation for a COVID-19 medicinal product
In connection with the COVID-19 pandemic, the applicant requested a rolling questions procedure.

OPEN project EMA
Swissmedic participates in the EMA's OPEN project. Further information is available 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

Regkirona is indicated for the treatment of confirmed coronavirus disease 2019 (COVID-19) in adult patients who do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19. Regkirona should be administered as soon as possible after a positive viral test for SARS-CoV-2 and within 7 days of symptom onset.

Risk factors may include but are not limited to:

- advanced age
- obesity
- cardiovascular disease, including hypertension
- chronic lung disease, including asthma
- type 1 or type 2 diabetes mellitus
- chronic kidney disease, including those on dialysis
- chronic liver disease
- immunosuppression, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia and prolonged use of immune-weakening medications.

2.2.2 Approved Indication

Regkirona is indicated for the treatment of adults with proven coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen or hospitalisation for COVID-19 and who are at high risk of progressing to severe COVID-19.
The use of regdanvimab should take into account national recommendations and the local epidemiology of circulating SARS-CoV-2 variants.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

Regkirona is to be administered as an IV infusion via pump. Regkirona may only be administered in settings in which healthcare providers have immediate access to medicinal products to treat a severe

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infusion reaction, such as anaphylaxis. Patients should be clinically monitored during administration and be observed for at least 1 hour after infusion is complete.

Usual dosage

The recommended dosage of Regkirona in adults is a single intravenous (IV) infusion of 40 mg/kg.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	27 July 2021
Formal control completed	8 August 2021
List of Questions (LoQ)	4 October 2021, 12 October 2021
Answers to LoQ	27 October 2021
Predecision	1 December 2021
Answers to Predecision	26 December 2021
Final Decision	12 January 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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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 (significant lung involvement leading to impairment of gas exchange function) or critical disease (including respiratory failure, thrombosis, multiorgan failure), whichmight ultimately lead to death. Patients with risk factors (e.g. obesity, old age, chronic lung, kidney or heart disease, active cancer or immunosuppression, diabetes) in particular are at higher risk of severe course and death.

Vaccines based on various technologies (mRNA, viral vectors, protein-based) have been developed and are the major component in the prevention of severe COVID-19.

Apart from the usual standard of care techniques, several drugs have been approved for the treatment of COVID-19 throughout the course of the pandemic for the management of hospitalised patients and are used depending on the state of the disease and patients 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

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4 Quality Aspects

4.1 Drug Substance

Regdanvimab is a recombinant human monoclonal antibody (IgG1) that binds to the SARS-CoV-2 receptor-binding domain (RBD) of the spike protein (S protein), inhibiting the interaction between SARS-CoV-2 RBD and the cellular receptor, ACE2, thus blocking SARS-CoV-2 infection. Regdanvimab consists of two heavy and two light chains connected by inter-chain disulfide bonds. Both heavy chains contain one oligosaccharide chain in the conserved Fc site (Asn308).

Regdanvimab is expressed in a Chinese hamster ovary (CHO) cell line, and is manufactured using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps. The drug substance manufacturing process is performed by Celltrion Inc., Incheon, Republic of Korea. The fermentation and purification process was validated on ten batches, demonstrating a consistent manufacturing process that effectively reduces process-related impurities. The impurity clearance validation studies are supported by the impurity levels measured in the drug substance and/or spiking studies. The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity/impurity tests (e.g. SEC-HPLC, non-reduced CE-SDS, reduced CE-SDS, IEC-HPLC), protein concentration and a potency assay (RBD-binding ELISA). Specifications are based on clinical data and batch analysis, and are in conformance with current compendial or regulatory guidelines.

Batch analysis data from development, clinical and process validation batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release. All specific analytical methods are described and are fully validated.

The drug substance is stored frozen. No changes were observed under the proposed storage conditions. A shelf life of 12 months has been accepted.

4.2 Drug Product

The finished product Regkirona is available as 960 mg product, which is supplied as a sterile liquid in a single-use vial. It is intended for intravenous infusion together with normal saline. All excipients used comply with the European Pharmacopoeia. The finished product manufacturing process consists of pooling and mixing of the drug substance, sterile filtration, aseptic filling, capping and inspection steps, and is conducted at Celltrion, Incheon, Republic of Korea, or Samsung Biologics, Incheon, Republic of Korea. Process validation studies were executed at commercial scale using three validation batches at both manufacturers.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, osmolality, purity and impurities tests (SEC-HPLC, non-reduced CE-SDS, reduced CE-SDS, IEC-HPLC), a potency assay (RBD-binding ELISA), protein concentration, particles, sterility and bacterial endotoxins. All specific methods are validated in accordance with ICH guidelines.

Batch analysis data from development, clinical and process validation batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release.

The drug product is stored in 20 mL type I glass vials at 2-8°C, protected from light. Each vial is closed with a chlorobutyl rubber stopper. The stoppered vial is sealed with an aluminium closure with a flip-off cap. All primary components are Ph.Eur. and USP compliant. A shelf life of 12 months has been accepted.

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4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

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5 Nonclinical Aspects

5.1 Pharmacology

Regdanvimab bound with high affinity to the receptor-binding domain (RBD) of the spike (S) protein of SARS-CoV-2 (EC_{50} of 4.4 ng/mL and K_D of 0.06 nM) and completely inhibited virus binding to human angiotensin converting enzyme 2 (hACE2) and entry into the host cells. As shown by X-ray crystallography, regdanvimab competed with ACE2 for binding to the SARS-CoV-2 RBD as their epitope residues substantially overlap.

Regkirona does not induce any Fc-mediated activity as part of its mode of action. In virus neutralisation assays, regdanvimab mediated concentration-dependent inhibition of wild-type SARS-CoV-2 virus (BetaCoV/Korea/KCDC03/2020) entry into Vero E6 cells with IC_{50} and IC_{90} of 9.70 ng/mL and 25.09 ng/mL, respectively.

Regdanvimab was unable to neutralise the escape virus mutation S494P, which is located in the RBD site, in the plaque reduction neutralisation test (PRNT) in Vero E6 cells.

In PRNT using authentic virus variants, regdanvimab showed comparable neutralising activity against Alpha (UK, B.1.1.7), Zeta (Brazil, P.2), Iota (New York, B.1.526) and Eta (Nigeria, B.1.525) variants. Reduced (24- to 310-fold reduction) neutralising activity was found against Gamma (Brazil, P.1), Beta (South Africa, B.1.351), Epsilon (California; B.1.427 and B.1.429) and Kappa/Delta (India B.1.617.1/B.1.617.2) variants compared to the wild-type virus. Similar results with authentic Alpha, Beta and Gamma variants were achieved in micro-neutralisation assays. This is consistent with results of binding studies, where regdanvimab showed decreased affinity towards Epsilon, Beta, Kappa/Delta and Gamma variants compared to wild type. In pseudovirus assays, regdanvimab showed reduced neutralising activity against all tested mutants (Gamma, Zeta, Beta, Epsilon, Iota, Eta, Kappa, Delta, Delta Plus, Lambda and Mu).

Further analysis of mutants in a pseudovirus assay showed that spike mutations involved in the virus variants Beta, Gamma and Kappa led to an increase in IC_{50} values compared to wild type. Regdanvimab showed significantly reduced activity against S494P, S494L, Q493R and Q493K mutations (IC_{50} values >500 ng/mL). Potential mutants associated with the regdanvimab binding epitope are L455F, Y449N and Y486I. The relevance of these data for the clinical outcome is not known.

Further monitoring of variants and regular submission of the respective studies as a post-approval commitment is requested.

There were no indications that Regkirona induces antibody-dependent enhancement (ADE) of disease either *in vivo* or *in vitro*.

The efficacy of Regkirona in the treatment and prevention of COVID-19 disease was studied in various animal models. Prophylactic treatment one day before challenge with wild-type SARS-CoV-2 virus had a beneficial effect on survival, reduction of body weight and reduction of the viral load in lungs in human ACE transgenic mice.

Therapeutic efficacy (at the clinically relevant concentration) was shown in various animal models (ACE transgenic mice, ferrets, golden Syrian hamsters and Rhesus macaques) and included studies with virus variants (Beta, Gamma and Delta). In most animals, treatment with regdanvimab (8-24 h after infection) reduced virus titers in the nose and lungs, which correlated with the histopathology results of reduced inflammation.

Taken together, numerous animal pharmacology studies showed activity for prophylactic and therapeutic treatment. However, the clinical efficacy outcome cannot be predicted from the nonclinical data.

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

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5.2 Pharmacokinetics

The pharmacokinetics (PK) of Regkirona were studied in male golden Syrian hamsters following a single intraperitoneal injection. The results point to linear PK as expected for monoclonal antibodies directed against an exogenous target. The exposure increased in a generally dose-proportional manner. The mean half-life ranged between 64 h (15 mg/kg) and 153 h (60 mg/kg), which is shorter than the terminal half-life in human (16.6-22.0 days).

In the repeated dose study in Cynomolgus monkeys, the exposure increased in a dose-proportional manner and there was no accumulation. ADAs were not detected.

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

5.3 Toxicology

The toxicology profile of Regkirona was characterised in 2- and 3-week repeated dose toxicity studies (10-week recovery period) in Cynomolgus monkeys, with once weekly intravenous administration at 0, 100, 200 or 400 mg/kg. Findings related to treatment with regdanvimab included reversible changes in haematology, coagulation and clinical chemistry parameters. They were not considered adverse except for the decrease in neutrophil count in high-dose animals (exposure 4.5-fold the human exposure after single dosing with 40 mg/kg). In tissue cross-reactivity studies using human adult and foetal/neonatal tissues and Cynomolgus monkey tissues, regdanvimab showed specific positive staining in meningeal arachnoid cap cells in the brain and spinal cord. However, these findings were not associated with any histopathological findings or neurological symptoms in the repeated dose toxicity study. Since only single administration is foreseen for clinical use and no neurological findings were noted in the clinical trials, the applicant's conclusion that these findings have no relevance for human use was accepted.

In line with ICH S6 (R1), carcinogenicity, genotoxicity and reproductive toxicology studies were not conducted given that regdanvimab is directed against an exogenous target.

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

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

5.4 Nonclinical Conclusions

The submitted nonclinical documentation is considered appropriate to support the approval of Regkirona in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Risk of infections due to neutropenia is the only issue identified in the nonclinical studies that would be of concern for human use. 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

ADME

Biopharmaceutical Development
Two drug materials (derived from Process 2 and Process 3) were used in the clinical studies, while Process 1 material was used in the nonclinical studies. Bridging for these two materials was conducted via analytical methods. In addition, following the proposed 40 mg/kg single dose, comparable exposures, based on C_{max} and AUC, were observed in studies CT-P59 1.1, 1.2 and 3.2 Part 1. The formulation intended for commercialisation was used in study CT-P59 3.2 Part 2. Currently, there are no PK data following the administration of Process 3 material; however, clinical efficacy and safety data following the administration of Process 3 material are available.

Dose Proportionality
Dose-proportional increases in C_{max} and AUC were observed in healthy subjects at doses of 10 mg/kg to 80 mg/kg) and in COVID-19 patients (single doses of 20 mg/kg to 80 mg/kg).

Pharmacokinetics after multiple dosing
Only a single dose was administered to humans. Since regdanvimab is intended for single dose intravenous use, no information is required on time to reach steady-state and the exposures observed at steady-state.

Distribution
The geometric mean (CV%) apparent volume of distribution at steady-state (V_{ss}) after intravenous administration of regdanvimab at 40 mg/kg was 99.7 mL/kg (21.9%) in COVID-19 patients.

Metabolism
No studies regarding the metabolism of regdanvimab have been conducted considering the biological nature of the molecule.

Elimination
The regdanvimab clearance of a typical patient was estimated to be 0.2 ± 0.02 mL/hr/kg; the terminal half-life was 15.8 days.

Special Populations

Dedicated studies in patients with renal or hepatic impairment are typically not required for monoclonal antibodies. No major age or weight-related differences in clearance or volume of distribution were observed in COVID-19 patients.

Interactions

An effect of regdanvimab on CYPs, UGTs or transporters by its metabolism, chemical properties or mechanism of action appears unlikely. No *in vitro* or clinical interaction studies were conducted.

6.2 Dose Finding and Dose Recommendation

No specific dose-finding study was performed. The selected dose of regdanvimab 40 mg/kg used in Part 2 of study CT-P59 3.2 is based on the clinical results from studies CT-P59 1.1, CT-P59 1.2 and CT-P59 3.2 Part 1.

Selection of the dosing regimen is based on results of *in vivo* efficacy studies conducted in SARS-CoV-2 infected ferrets, hamsters and rhesus macaques and results of several Phase I studies in healthy subjects, and PK bridging to enable extrapolation from animal data to human data.

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On the basis of partial AUC values in rhesus macaques, the effective exposures (at the pharmacologically active dose of 45 mg/kg) were associated with human exposures that in turn correspond to clinical doses of approx. 40 mg/kg.

In consideration of the safety profile as observed during study CT-P59 1.1 and PK/PD analysis, the selected doses of 40 mg/kg and 80 mg/kg were considered appropriate for study CT-P59 3.2. The proposed maximum dose of 80 mg/kg was selected to minimise any chances of suboptimal efficacy in patients at higher risk.

In study CT-P59 3.2 Part 1, the efficacy of the proposed clinical regimen (40 mg/kg) and a higher regimen (80 mg/kg) were evaluated, and overall the study provided evidence that regdanvimab was effective for the treatment of patients with mild to moderate COVID-19. Clinical efficacy data did not show a dose-response relationship for regdanvimab treatment for this dosing regimen. Viral shedding results from studies CT-P59 1.2 and CT-P59 3.2 Part 1 were also suggestive of a relatively flat dose-response relationship. In addition, clinical safety showed that treatment-emergent adverse events (TEAEs) were comparable across the regdanvimab and placebo treatment groups. The majority of TEAEs were mild to moderate in severity and most events were singular and without associated dose-dependence.

The serum concentration of regdanvimab in human lung tissues was estimated using antibody distribution coefficients. Based on the literature, the concentration of monoclonal antibody in lung tissues was estimated to be 15%. Based on this, the regdanvimab 40 mg/kg dose is expected to achieve approximately 14.9 µg/mL (99.5 µg/mL x 0.15) of serum concentration in lung tissues at 28 days after study drug administration in mild to moderate COVID-19 patients. The estimated serum concentration is above the *in vitro* EC_{90} value (25.09 ng/mL) of viral neutralisation against SARS-CoV-2 (BetaCoV/Korea/KCDC03/2020) strains. In conclusion, a single dose of 40 mg/kg is considered to be the appropriate dosing regimen to treat patients with mild to moderate COVID-19 and was selected for study CT-P59 3.2 Part 2.

6.3 Efficacy

The applicant submitted a single pivotal study (CT-P59 3.2). It was a Phase 2/3, randomised, placebo-controlled, parallel group, double-blind study to evaluate the efficacy and safety of regdanvimab in combination with standard of care in outpatients with SARS-CoV-2 infection not requiring supplemental oxygen therapy or hospitalisation.

The study was performed in two parts that were conducted successively. **Part 1** investigated two Regkirona dosing regimens (40 mg/kg, 80 mg/kg) vs placebo in adult outpatients presenting with mild or moderate COVID-19 without uncontrolled high-risk criteria. **Part 2** investigated one dosing regimen (40 mg/kg) vs placebo in adult outpatients presenting with mild or moderate COVID-19, including patients with high-risk criteria. For both studies, inclusion criteria required COVID-19 patients to present within 7 days of symptom onset, to have an oxygen saturation >94% on room air and to be clinically stable.

High-risk patients were defined as patients at high risk of progressing to severe COVID-19 and/or hospitalisation because of at least one of the following criteria: advanced age (>50 years), obesity (body mass index >30 kg/m^2), cardiovascular disease (including hypertension), chronic lung disease (including asthma), type 1 or type 2 diabetes mellitus, chronic kidney disease (including dialysis), chronic liver disease and immunosuppression (based on prescriber's assessment).

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In Part 1, which excluded patients with uncontrolled high-risk criteria, 371 patients were screened, 327 were randomised (105 in the 40 mg/kg treatment arm, 111 in the 80 mg/kg treatment arm and 111 in the placebo group). Overall, included patients were young (median age 51 years old, approx. 74% less than 60 years old). Baseline characteristics were balanced between the regdanvimab and placebo groups, except for there being more male patients in the regdanvimab (55%) than in the placebo (43%) group. The median time from the initial symptom to the date of study drug administration was 3 days. Baseline serology indicated that the proportion of patients with positive SARS-CoV-2 IgG was low (less than 5%). The primary efficacy endpoint was the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28. Analysis of the primary endpoint was performed in the intention-to-treat infected (ITTI) analysis population, meaning that patients without confirmed SARS-CoV-2 infection by RT-PCR at Day 1 (pre-infusion) or Day 2 were excluded. Overall, the ITTI set included 307 patients (101, 103 and 103 patients in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg and placebo groups, respectively). The results of the primary endpoint showed that there was a trend towards a lower rate of hospitalisations in the pooled regdanvimab treatment groups in comparison to the placebo group of 4.4% vs 8.7%, respectively. This difference was, however, not statistically significant.

In Part 2, which specifically aimed at including high-risk patients, 1,467 patients were screened and 1,315 were randomly assigned to the study treatment at Day 1 (656 patients in the regdanvimab 40 mg/kg group, 659 patients in the placebo group). The included patients had a median age of 49 years old and 47 years old in the treatment and placebo groups, respectively. 77% were less than 60 years old. The median time from the initial symptoms to the date of study drug administration was 4 days (balanced between groups). Baseline serology indicated that the proportion of patients with positive SARS-CoV-2 IgG was 11% (balanced between groups). The ITT – high-risk population set (n=880) was used for efficacy analysis of the primary efficacy endpoint. This consisted of 446 patients in the treatment group and 434 patients in the placebo group. The primary efficacy endpoint was the proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28. The results of the primary efficacy endpoint showed a statistically significantly? lower rate of hospitalisations in the regdanvimab group in comparison to the placebo group: 3.1% (n=14/446, 95% CI 1.9%-5.2%) vs 11.1% (n=48/434, 95% CI 8.4%-14.4%), respectively. The absolute difference was -8.0% (95% CI -11.7% – -4.5%). In the whole ITT set, the proportion of patients meeting the endpoint was still significantly lower in the regdanvimab group 2.4% (16/656) compared to the placebo group 8.0% (53/659). In the ITT – high-risk set, the proportion of patients meeting the primary efficacy endpoint was lower in the regdanvimab group compared to the placebo group, both when symptom duration before drug administration was 0-5 days (3.5% [13/376] vs 10.9% [39/357]) and 6-7 days (1.5% [1/65] vs 13.2% [9/68]). There was no difference in all-cause mortality up to Day 28 between arms. One patient died in the regdanvimab 40 mg/kg group vs two patients in the placebo group. The investigator considered that the cause of death was worsening of COVID-19 for all cases.

6.4 Safety

A total of 906 patients were exposed to regdanvimab in two Phase 1 studies (CT-P59 1.1 n=24, CT-P59 1.2 n=15) and one Phase 2/3 study (CT-P59 3.2 Part 1 n=215, and CT-P59 3.2 Part 2 n=652). 889 patients received the approved dose of 40 mg/kg or a higher dose (80 mg/kg).
In all studies, the number of patients who experienced at least one TEAE was similar between the treatment and placebo groups. Relevant safety data largely come from the Phase 2/3 study CT-P59 3.2.

In study CT-P59 3.2 Part 1, the majority of TEAEs were grade 1 in intensity and occurred at a similar proportion in all groups (29.5%, 24.5% and 30.9% in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg and placebo groups, respectively). The most commonly reported TEAEs were hypertriglyceridaemia (5.7%, 0 and 2.7% in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg and

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placebo groups, respectively) and hyperglycaemia (1.9%, 1.8% and 2.7% in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg and placebo groups, respectively). The most frequently reported TEAEs considered to be related to study drug were hypertriglyceridaemia for patients in the regdanvimab 40 mg/kg group (3 [2.9%] patients) and infusion-related reactions and hypertriglyceridaemia for patients in the placebo group (2 [1.8%] patients). Grade 3 TEAEs were reported for 5 (4.8%), 4 (3.6%) and 2 (1.8%) patients in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg and placebo groups, respectively. All grade 3 TEAEs were considered unrelated to the study drug except one event of grade 3 hypertriglyceridaemia reported in the regdanvimab 40 mg/kg treatment group. There were no grade 4 or higher TEAEs.

In study CT-P59 3.2 Part 2, the number of patients who experienced at least one TEAE in the treatment groups was 30.4% and 31.1% in the regdanvimab 40 mg/kg and placebo groups, respectively. The most commonly reported TEAEs were hypertriglyceridaemia (4.6% and 4.9% patients in the regdanvimab 40 mg/kg and placebo groups, respectively) and increase in hepatic enzymes or ALT (39 [6%] and 46 [7.1%] in the regdanvimab 40 mg/kg and placebo groups, respectively. The proportion of patients who experienced at least one TEAE considered by the investigator to be related to study drug was similar between the groups (44 [6.7%] and 46 [7.1%] patients in the regdanvimab 40 mg/kg and placebo groups, respectively). The most frequently reported TEAEs considered to be related to study drug by the investigator were hepatic enzyme increase and hypertriglyceridaemia for patients in the regdanvimab 40 mg/kg group (7 [1.1%] patients) and increased alanine aminotransferase for patients in the placebo group (10 [1.5%] patients). Grade 3 or higher TEAEs were reported for 61 (9.4%) and 69 (10.6%) patients in the regdanvimab 40 mg/kg and placebo groups, respectively. The most frequently reported grade 3 or higher TEAE was hypertriglyceridaemia (2.0% and 1.5% patients in the regdanvimab 40 mg/kg and placebo groups, respectively). In the treatment group, the grade 4 events were hypertriglyceridemia (n=1) in a patient who already exhibited high triglyceride levels at screening and was on a fat-rich diet, elevated CPK (n=1) without symptoms at Day 28 and neutropenia (n=1) at Day 28 in one patient in CT-P59 in the regdanvimab 40 mg/kg group. Apart from neutropenia, these were considered by the investigator as not related to the study drug.

Regarding **serious adverse events**, other than one unrelated treatment-emergent serious adverse event (TESAE) of accidental limb injury, which occurred 36 days after the study drug administration in the regdanvimab 20 mg/kg group of study CT-P59 1.1, no TEAEs were considered as serious in studies CT-P59 1.1, CT-P59 1.2 and CT-P59 3.2 Part 1. In study CT-P59 3.2 Part 2, five TESAEs were reported, involving four patients in the regdanvimab 40 mg/kg treatment group and one patient in the placebo group. The TESAE considered by the investigator to be related to the study drug was a grade 2 infusion-related reaction in the regdanvimab 40 mg/kg treatment group that consisted of grade 2 generalised urticaria and grade 1 pruritus, without systemic symptoms, that appeared 1 day after drug infusion. The three other TESAEs were considered by the investigator to be unrelated to the study drug. These three other TESAEs were one acute myocardial infarction 11 days after drug administration, one case of nosocomial pneumonia and one pulmonary embolism in a patient with Factor V Leiden mutation.

Regarding **deaths**, three patients died in study CT-P59 3.2 Part 2 (two in the placebo group, one in regdanvimab 40 mg/kg group). The investigator considered these to be due to worsening of COVID-19.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

There is a need for therapeutics for the treatment of mild/moderate COVID-19 to prevent progression to severe disease, especially in high-risk patients. COVID-19 vaccination is the cornerstone of this strategy. The early administration of monoclonal antibodies in high-risk patients infected with SARS-CoV-2 is an attractive option, particularly in those unable to mount an adequate response to vaccines.

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In support of the current application, the applicant provided a single Phase 2/3 study, CT-P59 3.2. When used in high-risk patients, regdanvimab treatment was associated with a significant reduction in hospitalisation for the main COVID-19-related morbidities, that is progression of infection in the respiratory tract leading to severe pneumonia and the need for supplemental oxygen and hospitalisation. In the study CT-P59 3.2 Part 2, the primary endpoint "*proportions of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection"* was 3.1% in the regdanvimab treatment group in comparison with 11.1% in the placebo group.

The efficacy of regdanvimab has not been established in patients without high-risk criteria or when administered after 7 days of SARS-CoV-2 infection symptom onset. As vaccinated patients were not included in the study, the efficacy of regdanvimab in this population cannot be determined.
Based on *in vitro* assays, the activity of regdanvimab against the most prevalent SARS-CoV-2 variant of concern (VOC) at the time of this evaluation (VOC Delta) is clearly reduced. When study CT-P59 3.2 was performed, there was no or low Delta variant circulation. Since the Delta variant represented the vast majority of SARS-CoV-2 circulating in Switzerland at the time of this application evaluation, the clinical efficacy of regdanvimab might be significantly lower. The *in vitro* activity of regdanvimab against VOCs Beta, Gamma and Epsilon is also reduced.
The applicant is currently performing *in vitro* and *in vivo* testing to assess the activity of regdanvimab against the VOC Omicron. The applicant has a strategy to monitor the efficacy of regdanvimab based on active monitoring of genomic data for new variants of interest (VOIs) and VOCs, and performs *in vitro* and *in vivo* studies to characterise regdanvimab activity in relation to the identified strain.

The treatment-emergent adverse events that occurred most frequently in the clinical studies of regdanvimab were also related to the pathogenesis of COVID-19 (e.g. hypertriglyceridemia, increase in liver function tests) and no drug-related adverse event can be singled out. Among infusion-related reactions, there was one episode of probable anaphylaxis in the regdanvimab treatment group, which is not unexpected during monoclonal antibody infusions. Other immunologic adverse events related to monoclonal antibody infusions (e.g. serum sickness) were not seen in the presented studies.

Post-regdanvimab treatment, virological samples show an enrichment in Q493K/R and S494P/L mutations in the RBD of the SARS-CoV-2 spike protein. These mutations have been identified in non-clinical studies as being important for reduced susceptibility to regdanvimab. In the currently available genomic dataset, post-treatment RBD variants harbouring these mutations were identified at an allelic fraction ≥15% in 16.7% (25/150) of patients in the regdanvimab groups and none in the placebo group. The applicant mentions that none of the patients with these SARS-CoV-2 spike protein amino acid mutations required hospitalisation or died due to COVID-19. However, potential onward transmission in the community of treatment-emergent resistance mutations cannot be ruled out.

The overall benefit-risk of regdanvimab for the treatment of mild/moderate COVID-19 to prevent progression to severe COVID-19, the need for oxygen therapy, hospitalisation or death in SARS-CoV-2 infected high-risk patients is positive. The clinical efficacy of regdanvimab against emerging new VOCs remains to be determined and must be actively monitored.

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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 Regkirona 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.

Regkirona is temporarily authorised – see "Properties/Effects" section.

Regkirona

Composition

Active substances

Regdanvimab*

* produced through recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary).

Excipients

L-histidine, L-histidine hydrochloride monohydrate, Polysorbate 80, L-arginine hydrochloride, Water for injections q.s. to solution for 16 mL

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for i.v. infusion (sterile concentrate).
Each 1 mL of concentrate contains 60 mg of regdanvimab (960 mg / 16 mL per vial).

Indications/Uses

Regkirona is indicated for the treatment of adults with proven coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen or hospitalization for COVID-19 and who are at high risk for progressing to severe COVID-19.
The use of regdanvimab should take into account national recommendations and local epidemiology of circulating SARS-CoV-2 variants.

Dosage/Administration

Regkirona may only be initiated under the supervision of a qualified physician in settings in which health care providers have immediate access to medicinal products to treat a severe infusion reaction, including anaphylaxis.
Regkirona should be given as soon as possible after a positive virustest for SARS-CoV-2 (see Properties/Effects).
To confirm COVID-19, a Nucleic Acid Amplification Test (NAAT) is preferred.

Usual dosage

The recommended dosage of Regkirona in adults is a single intravenous (IV) infusion of 40 mg/kg.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Patients with hepatic disorders

No dose adjustments are recommended (see "Pharmacokinetics" section).

Patients with renal disorders

No dose adjustments are recommended (see "Pharmacokinetics" section).

Elderly patients

No dose adjustment of Regkirona is required in elderly patients (see “Pharmacokinetics” section).

Children and adolescents

The safety and efficacy of regdanvimab in paediatric patients have not yet been demonstrated. No data are available.

Mode of administration

For IV use only.
Regkirona should be diluted and administered intravenously over 60 minutes.
The rate of infusion may be slowed or interrupted if the patient develops any signs of infusion-related reactions or other adverse events and appropriate resuscitation equipment should be available (see “Warnings and Precautions” section).
For instructions on dilution of the medicinal product before administration, see “Instructions for Handling” section.

Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in “Composition” section.

Warnings and precautions

Patients should be clinically monitored during administration and be observed for at least 1 hour after infusion is complete.

Hypersensitivity including Infusion-Related Reactions
Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of regdanvimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, administration of regdanvimab should be discontinued and appropriate therapy should be administered.

Infusion-related reactions have been observed with administration of regdanvimab (see “Undesirable Effects” section).
Signs and symptoms of infusion-related reactions may include fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia, palpitation), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., presyncope, syncope), dizziness and diaphoresis.
If an infusion-related reaction occurs, slowing or stopping the infusion should be considered and appropriate therapy should be administered.

Antiviral resistance

The clinical trials with regdanvimab were conducted in subjects who were predominantly infected with the wild-type virus and the Alpha (B.1.1.7 lineage) variant. Clinical efficacy data for regdanvimab against some circulating SARS-CoV-2 variants with decreased *in vitro* susceptibility is currently limited (see Properties/Effects section, Table 2).

Interactions

Pharmacokinetic interactions

No interaction studies have been performed with regdanvimab.
Regdanvimab is a monoclonal antibody, which is not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are considered unlikely.

Pharmacodynamic interactions

No interaction studies have been performed. Concomitant administration of regdanvimab with COVID-19 vaccines has not been studied. A potential interference with a COVID-19 vaccine following the treatment with Regkirona was not assessed and cannot be excluded. Vaccination should be deferred for at least 90 days from regdanvimab administration to avoid potential interaction between the antibody therapy and vaccine-induced immune responses. National vaccination guidelines must be taken into account.

Pregnancy, lactation

Pregnancy

Reproductive and developmental studies have not been performed with regdanvimab.
Nonclinical reproductive toxicity studies have not been conducted with regdanvimab (see “Preclinical Data” section). Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, regdanvimab has the potential to be transferred from the mother to the developing foetus. It is unknown whether the potential transfer of regdanvimab provides any treatment benefit or risk to the developing foetus.

Regkirona should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Lactation

It is not known whether regdanvimab is excreted in human milk or absorbed systemically after ingestion. For humans, there are insufficient data available on the transfer of regdanvimab into breast milk. A risk to the infant cannot be excluded. A decision should be made whether to discontinue breastfeeding or to forego regdanvimab therapy. The benefits of breastfeeding for the infant and the benefits of therapy for the mother must be weighed.

Fertility

No fertility studies have been performed.

Effects on ability to drive and use machines

Regkirona is predicted to have no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

Overall, 906 subjects have been exposed to regdanvimab in clinical trials in both healthy subjects and non-hospitalised patients. The safety of regdanvimab is based on exposure of ambulatory (non-hospitalised) patients with COVID-19.
In Study CT-P59 3.2, a total of 867 patients were treated with a single IV infusion of regdanvimab (40 mg/kg [N=757] or 80 mg/kg [N=110]) while 760 patients received placebo. Treatment-emergent adverse events (TEAEs) were reported for 29.9% of regdanvimab-treated patients and 31.2% of placebo-treated patients who were followed for at least 28 days. The most frequently reported adverse reaction (≥3% of patients) in the regdanvimab treatment group was hypertriglyceridaemia (4.2% of regdanvimab-treated patients and 4.6% of placebo-treated patients).
Treatment-emergent serious adverse events (TESAEs) were reported in 4 regdanvimab-treated patients (0.5%) and 1 placebo-treated patient (0.1%). There were no TESAEs reported for >1 patient in the regdanvimab treatment group. Infusion-related reactions were the only TESAEs considered to be related to study treatment (1 [0.1%] patient, Grade 2 generalized urticaria) in the regdanvimab treatment group, and all other TESAEs were considered to be unrelated to study treatment.

List of adverse reactions

Adverse reactions reported with regdanvimab based on experience from clinical trials in healthy subjects and mild to moderate COVID-19 patients as well as adverse reactions reported from post-marketing experience are listed in Table 1 by system organ class and frequency. Frequencies are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100);

rare (≥1/10,000 to <1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Tabulated list of adverse reactions

System organ class Frequency	Adverse reaction
Injury, poisoning and procedural complications	
Uncommon	Infusion-related reactions[1]

[1] Infusion-related reaction (IRR) includes hypersensitivity and anaphylaxis, and symptoms reported as IRRs are described below in 'Infusion-related reactions'. Anaphylaxis was identified from post-marketing experience.

Description of specific adverse reactions and additional information

Infusion-related reactions

Immediate infusion-related reactions were noted for 0.6% of regdanvimab-treated patients and 1.2% of placebo-treated patients. Reported events of fever, pruritus, hypertension and dyspnoea were mild in the regdanvimab-treated patients. Two cases of fever, 1 case of palpitation, 1 case of presyncope and 1 case of urticaria were moderate and 1 case of hypertension was severe in severity. All patients in the regdanvimab treatment group recovered from the events.

In post-marketing experience, one case of anaphylaxis was reported during infusion of regdanvimab with symptoms of dyspnoea, chest discomfort and cough.

Immunogenicity

As with all therapeutic proteins, the possibility of immunogenicity remains. Detection of antibody development is highly dependent on the sensitivity and specificity of the test. In addition, the observed incidence of antibodies (including neutralizing antibodies) in a test may be influenced by several factors, including test methodology, samples handling, timing of samples collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to regdanvimab in the studies described below with the incidence of antibodies in other studies or to other drugs may be misleading.

In Study CT-P59 3.2 Part 2, the proportions of patients with positive conversion in anti-drug antibodies at post-treatment visits up to Day 28 visit were 10/635 (1.6%) patients in the regdanvimab 40 mg/kg treatment group and 15/619 (2.4%) patients in the placebo group.

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

Signs and symptoms

No cases of overdose have been reported. Single doses up to 8,000 mg have been administered in clinical trials without dose-limiting toxicity.

Treatment

Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with regdanvimab.

Properties/Effects

ATC code

not yet assigned
Pharmacotherapeutic group: Antivirals for systemic use

Mechanism of action

Regdanvimab is a recombinant human IgG1 monoclonal antibody that binds to the receptor binding domain (RBD) of the spike (S) protein of SARS-CoV-2 (K_D=0.065 nM) consequently blocking cellular entry and SARS-CoV-2 infection.

Antiviral Activity

The *in vitro* neutralisation activity of regdanvimab against SARS-CoV-2 (BetaCoV/Korea/KCDC03/2020) was assessed by plaque reduction neutralisation test (PRNT) using VeroE6 cells. Regdanvimab neutralised this SARS-CoV-2 strain with an IC_{50} value of 9.70 ng/mL and an IC_{90} value of 25.09 ng/mL.

Antibody Dependent Enhancement

There was no evidence of antibody dependent enhancement (ADE) triggered by regdanvimab with sub-therapeutic doses in the *in vivo* study, which was in line with *in vitro* experiments with sub-neutralizing concentrations of regdanvimab.

Antiviral Resistance

In vitro virus passaging with authentic SARS-CoV-2 viruses in VeroE6 cells in the presence/absence of regdanvimab identified a S494P amino acid substitution located in the RBD of the spike protein. Pseudovirus assay results with Q493K, Q493R, S494L and S494P showed IC_{50} above 500 ng/mL. The plaque reduction neutralisation test (PRNT) using authentic SARS-CoV-2 variant virus indicate that regdanvimab retained activity against the Alpha (UK origin/B.1.1.7 lineage), Zeta (Brazilian origin/P.2), Iota (New York origin/B.1.526) and Eta (Nigerian origin/B.1.525) variants. Reduced neutralising activity against Gamma (Brazilian origin/P.1), Beta (South African origin/B.1.351), Epsilon (Californian origin/B.1.427 and B.1.429), Kappa (Indian origin/B.1.617.1) and Delta (Indian origin/B.1.617.2) variants were observed (Table 2). Microneutralisation data using authentic SARS-

CoV-2 variant virus indicate that regdanivimab retains activity against the Alpha variant and has reduced activity against the Beta and Gamma variants (Table 2).

Table 2: Authentic SARS-CoV-2 and Pseudovirus Neutralisation Data for Regdanvimab

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility (Authentic Virus)	Fold Reduction in Susceptibility (Pseudovirus)[f]
B.1.1.7 (Alpha)	N501Y/P681H	No change[b, d, e]	No change[b, g, h]
P.1 (Gamma)	K417T/E484K/N501Y	137.88[e]/167.90[d]	61.42[g]/127.49[h]
P.2 (Zeta)	E484K	No change[b, d]	8.66[g]
B.1.351 (Beta)	K417N/E484K/N501Y	19.75[e]/310.06[d]	184.29[g]/253.16[h]
B.1.427 (Epsilon)	L452R	73.89[d]	34.97[g]
B.1.429 (Epsilon)	L452R	54.08[d]	34.97[g]
B.1.526 (Iota)[c]	E484K/A701V	No change[b, d]	6.84[g]
B.1.525 (Eta)	E484K/Q677H	No change[b, d]	7.22[g]
B.1.617.1 (Kappa)	L452R/E484Q/P681R	23.89[d]	44.14[h]
B.1.617.2 (Delta)	L452R/T478K/P681R	182.99[d]	27.70[h]
AY.1 (Delta plus)	K417N/L452R/T478K	Not determined	63.65[h]
C.37 (Lambda)	L452Q/F490S	Not determined	15.50[h]
B.1.621 (Mu)	R346K/E484K/N501Y/P681H	Not determined	38.65[h]

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed
[b] No change: <5-fold reduction in susceptibility
[c] Not all isolates of the New York lineage harbours E484K substitution (as of February 2021)
[d] The study was conducted using plaque reduction neutralisation test
[e] The study was conducted using microneutralisation assay
[f] Key substitutions for global variants have been tested using a pseudovirus assay
[g] The study was conducted at Kbio Health
[h] The study was conducted at National Institute of Health

Although the potential escape mutant (S494P) have been observed after regdanvimab treatment in regdanvimab monotherapy treatment arms, none of these patients required oxygen therapy or hospitalisation or experienced mortality due to SARS-CoV-2 infection.
It is possible that regdanvimab resistance-associated variants could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. The clinical relevance is not known.

Clinical efficacy

Study CT-P59 3.2 Part 2 was a randomised, double-blind, placebo-controlled clinical trial studying regdanvimab for the treatment of unvaccinated adult patients with mild to moderate COVID-19 and was conducted in multiple countries including the European Union (79.5%), the United States (7.6%) and Asia (0.9%). This study enrolled adult patients who were not hospitalised, had at least one or more symptoms of COVID-19 for ≤7 days, oxygen saturation >94% on room air and not requiring supplemental oxygen therapy and they were enrolled from January 18, 2021 and clinical efficacy endpoints were analysed based on data up to the cut-off date of May 21, 2021. Treatment was

initiated after obtaining a positive SARS-CoV-2 test.

A total of 1315 patients were randomised in a 1:1 manner to receive a single infusion of regdanvimab at doses of 40 mg/kg (N=656) or placebo (N=659) over 60 minutes.

The primary efficacy endpoint was the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28. This was analysed in all patients randomly assigned to the study drug, who are at high risk of progressing to severe COVID-19 and/or hospitalisation and who meet at least one of the high risk criteria (defined as having at least one of the following risk factors for severe COVID-19: age >50 years; BMI >30 kg/m^2; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; and immunosuppressed, based on investigator's assessment).

Among all randomised patients, 66.9% of patients were at high risk of progressing to severe COVID-19 and/or hospitalisation. Among patients at high risk of progressing to severe COVID-19 and/or hospitalisation, the baseline median age was 54 years (range: 18 to 87); 19.4% of patients aged 65 or older and 4.0% of patients aged 75 or older; 53.6% of patients were male; 88.6% were White, 19.9% were Hispanic or Latino, 0.8% were Asian and 0.8% were Black or African American. The median time from the initial symptom onset was 4 days; mean viral load at baseline was 5.8 log10 copies/mL in the regdanvimab treatment group and 5.9 log10 copies/mL in placebo group. Forty-seven percent and 52.4% of patients had mild and moderate COVID-19, respectively. The most common risk factors were advanced age (age >50 years) (66.1%), cardiovascular disease, including hypertension, (50.3%) and obesity (BMI >30 kg/m^2) (47.2%).

Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Table 3: Result of Primary Endpoint in Study CT-P59 3.2 Part 2

		Regdanvimab (40 mg/kg IV infusion)	**Placebo**
Proportion of Patients with Clinical Symptoms Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28	**Proportion (n, %)**	14/446 (3.1%)	48/434 (11.1%)
	Difference (95% CI)[a]	-8.0 (-11.7, -4.5)	
	P-value[b]	<0.0001	

Note: Clinical symptom which requires hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 is included. Criterion of hospitalisation is ≥24 hours of acute care. Criteria of oxygen therapy are at least 24 hours of supplemental oxygen care and SpO_2 measure in room air before applying supplemental oxygen showing ≤94%.

[a] The difference of proportions between two treatment groups estimated using CMH (Cochran-Mantel-Haenszel) weights, and the 95% stratified Newcombe confidence interval (CI) with CMH weights are presented. Analysis was stratified by Age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).

[b] The p-value from stratified CMH test is presented. The CMH test is stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).

A total of 3 patients died (1 regdanvimab-treated patient and 2 placebo-treated patients) due to

worsening of COVID-19.

Temporary authorisation

The medicinal product, Regkirona, has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

Absorption

Following the administration of the recommended dose regimen (a single dose of 40 mg/kg) in COVID-19 patients, the mean (CV%) C_{max} level was 1016.6 µg/mL (26.5%).

Distribution

The mean (CV%) apparent volume of distribution at steady-state (V_{ss}) after IV administration of regdanvimab 40 mg/kg was 83.4 mL/kg (26.2%) in COVID-19 patients.

Metabolism

Regdanvimab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

No major age- or weight-related differences in clearance or volume of distribution were observed in COVID-19 patients.

In studies with COVID-19 patients, the mean (± SD) clearance of regdanvimab 40 mg/kg was 0.2 ± 0.05 mL/hr/kg.

The mean terminal half-life ranged from 16.6 days to 22.0 days for 10, 20, 40 and 80 mg/kg of regdanvimab administered to healthy subjects. In patients with COVID-19, the geometric mean terminal half-life for 40 mg/kg of regdanvimab was 15.6 days.

Linearity

Based on the PK analysis in healthy subjects, regdanvimab was approximately dose proportional in terms of maximal and systemic exposure (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$) over the dose range of 10 mg/kg to 80 mg/kg.

Kinetics in specific patient groups

Hepatic impairment

The pharmacokinetics of regdanvimab has not been evaluated in patients with hepatic impairment. Elimination of regdanvimab is likely to occur through normal degradation pathways for immunoglobulins and the clearance is not expected to be affected by hepatic impairment.

Renal impairment

The pharmacokinetics of regdanvimab has not been evaluated in patients with renal impairment. Regdanvimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of regdanvimab.

Elderly patients

Based on pharmacokinetic subgroup analyses in study CT-P59 3.2 Part 1 and Part 2 (in which 13.7% of patients were 65 years or older, and 2.7% of patients were 75 years of age or older), there is no difference in pharmacokinetics of regdanvimab in elderly patients compared to younger patients.

Children and adolescents

The pharmacokinetics of regdanvimab in paediatric patients has not been evaluated.

Preclinical data

Repeated dose toxicity

In a 3-week repeat-dose toxicity study, administration of regdanvimab in cynomolgus monkeys at 400 mg/kg (at 9.7 times the human clinical exposure based on AUC in COVID-19 patients at 40 mg/kg single intravenous administration) transient, moderate to marked decreases in neutrophils and haematology parameter changes were observed in 2 of 10 animals.
In tissue cross-reactivity (TCR) studies with regdanvimab using human adult, neonatal, and cynomolgus tissues, specific positive stainings in meningeal arachnoid cap cells in the brain and/or spinal cord tissues were observed. These findings were not associated with neurological symptoms and histopathological findings in the toxicity study, indicating that this TCR finding is less likely to have clinical relevance.

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

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in “Instructions for Handling” section.

Shelf life

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

Shelf life after opening

Diluted solution for infusion

Chemically and physical in-use stability has been demonstrated for 72 hours at 2°C - 8°C or 4 hours at ≤30°C after dilution in sodium chloride 9 mg/mL (0.9%) solution for infusion.
From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store in a refrigerator (2-8°C).
Do not freeze. Keep the medicinal product in its outer carton in order to protect from light.
Keep out of the reach of children.
For storage conditions after dilution of the medicinal product, see “Shelf life” section.

Instructions for handling

Preparation

Regkirona solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Remove Regkirona vial(s) from refrigerated storage and allow to equilibrate to room temperature (not exceeding 30°C) for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vial(s).**
- Regkirona is a clear to opalescent, colourless to pale yellow solution for infusion. Inspect Regkirona vial(s) visually for particulate matter and discolouration prior to dilution. Should either be observed, the vial(s) must be discarded, and new vial(s) should be used for preparation.
- Calculate total volume of Regkirona to be administered. The volume of Regkirona is calculated as follows.

Calculation to determine the total volume of Regkirona to be administered:

$$\frac{\text{Patient's body weight (kg) x Regkirona dose (40 mg/kg)}}{\text{Vial concentration (60 mg/mL)}} = \text{Volume of Regkirona (mL)}$$

Calculation to determine the total number of Regkirona vials needed:

$$\frac{\text{Total Regkirona volume (mL) to be administered}}{\text{Total volume per vial (16 mL/vial)}} = \text{Number of Regkirona vials needed}$$

Table 4: Sample calculations for patients receiving the recommended dose of 40 mg/kg of Regkirona for weights ranging from 40 kg to 120 kg

Body weight (kg)	Total dose (mg)	Volume (mL)	Vials (n)
40	1,600	27	2
60	2,400	40	3
80	3,200	53	4
100	4,000	67	5
120	4,800	80	5

Note: If a patient's weight is more than 200 kg, the dose calculation should use 200 kg. The maximal recommended dose is 8,000 mg.

- Dilute Regkirona in a bag containing sodium chloride 9 mg/mL (0.9%) solution for infusion. The total volume of the medicinal product and sodium chloride should be 250 mL.
    - In a 250 mL bag of sodium chloride, withdraw and discard the required volume (which is identical to the calculated volume of Regkirona) of sodium chloride 9 mg/mL (0.9%) from the infusion bag.
    - Withdraw the calculated volume of Regkirona from the vial(s) using a sterile syringe.
    - Transfer Regkirona to the infusion bag.
- Gently invert IV bag by hand approximately 10 times to mix. **Do not shake.**

Administration

Regkirona solution for infusion should be administered by a qualified healthcare professional.

- Gather the recommended materials for infusion: Infusion set with in-line filter (PES (Polyethersulfone) filter with a pore size of 1.2 µm or less would be recommended).
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer as an IV infusion via pump over 60 minutes.
- The prepared solution for infusion should not be administered simultaneously with any other medicinal product.

Disposal

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

Authorisation number

68356 (Swissmedic)

Packs

1 vial of Regkirona contains 960 mg of regdanvimab in 16 mL (60 mg/mL) (A)

Marketing authorisation holder

iQone Healthcare Switzerland SA,
1290 Versoix

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