EU Risk Management Plan for CT-P59

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

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LIST OF ABBREVIATIONS

Term	Explanation
ACE2	Angiotensin Converting Enzyme 2
ADE	Antibody-dependent enhancement
AE	Adverse event
ADR	Adverse drug reaction
A/G	Albumin to globulin
ALB	Albumin
AUC	Area under curve
CDC	Centers for Disease Control and Prevention
cf.	compared with
CHF	Congestive heart failure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CSR	Clinical study report
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
FPFV	First patient first visit
GVP	good pharmacovigilance practices
HIV	Human immunodeficiency virus
ICSR	Individual case safety report
IgG	Immunoglobulin G
IRR	Infusion-related reaction
i.v.	intravenous
L	litre
LLN	Lower limit of normal
LMP	Last menstrual period
LPLV	Last patient last visit

Term	Explanation
m^2	Square metres
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle east respiratory syndrome
mg	milligrams
mL	millilitre
PD	pharmacodynamic
PHE	Public Health England
PhV	pharmacovigilance
PK	pharmacokinetic
PL	Package leaflet
PMS	Post-marketing surveillance
PSUR	Periodic safety update report
PT	Prothrombin time
PY	Patient-year
RBC	Red blood cell
RBD	Receptor Binding Domain
RMP	Risk management plan
RSV	Respiratory syncytial virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse events
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 1 Part I.1: Product Overview

Active substance(s) (INN or common name)	Regdanvimab
Pharmacotherapeutic group(s) (ATC Code)	Antivirals for systemic use
Marketing Authorisation Holder or Applicant	CELLTRION Healthcare Hungary KFT.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Regkirona
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Regdanvimab is a recombinant human monoclonal IgG1 antibody.
	Summary of mode of action The main mechanism of action for regdanvimab is the binding to SARS-CoV-2 RBD, inhibiting the interaction between SARS-CoV-2 RBD and the cellular receptor, ACE2, thus preventing membrane fusion between SARS-CoV-2 and alveolar cells/intestinal epithelia.
	Important information about its composition The antibody is manufactured by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell line.
Hyperlink to the Product Information	CTD Module 1.3.1
Indication(s) in the EEA	**Proposed** Regdanvimab is indicated for the treatment of adults with coronavirus disease 2019 (COVID-19) that do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
Dosage in the EEA	**Proposed** The recommended dosage of regdanvimab in adults is a single intravenous (IV) infusion of 40 mg/kg. Regdanvimab should be administered within 7 days of onset of symptoms of COVID-19.

Pharmaceutical form(s) and strengths	**Proposed** Concentrate for solution for infusion (sterile concentrate) Each 16 mL vial contains 960 mg of regdanvimab Each mL of concentrate contains 60 mg of regdanvimab
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

Coronavirus Disease 2019 (COVID-19)

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly emergent coronavirus. Genetic sequencing of the virus suggests that it is a betacoronavirus closely linked to the SARS virus (WHO Interim Guidance 2020). On December 29, 2019, the first 4 cases reported and since then, an increasing number of cases of novel coronavirus-infected pneumonia have been identified in Wuhan, China. The virus became widespread throughout other Chinese cities more than a dozen countries around the world via suspected human-to-human transmission (Li 2020a). On 11 March 2020, the World Health Organization (WHO) declared that the COVID-19 can be characterized as a pandemic due to alarming spread and severity of COVID-19 worldwide (WHO Speech, 2020). As of 23 May 2021, nearly 166.4 million-cases and over 3.4 million deaths have been reported globally (WHO COVID-19 Weekly Epidemiological Update, 25 May 2021).

Although a complete understanding of transmission has not been identified yet, there is evidence that transmission can occur through aerosol or fomite transmission of SARS-CoV-2 since the virus was found to remain viable and infectious in aerosols for hours and on surfaces up to days, depending on the inoculum shed (van Doremalen 2020). Asymptomatic or pre-symptomatic persons infected with SARS-CoV-2 are also potential sources of COVID-19 infection, though the mechanism by which asymptomatic carriers could acquire and transmit SARS-CoV-2 requires further study (Bai 2020, Kimball 2020, Rothe 2020). Several studies provide evidence of both direct and indirect transmission of SARS-CoV-2. Santarpia et al, collected air and surface samples from individuals who were infected with COVID-19. Viral contamination was detected among all samples, indicating that SARS-CoV-2 may spread through both direct (droplet and person-to person) as well as indirect mechanisms (contaminated objects and airborne transmission) (Santarpia 2020). A similar study in China also implies aerosol transmission of SARS-CoV-2. Liu et al collected air samples from rooms, hallways and toilets of hospitals located in Wuhan, China during COVID-19 outbreak and the samples were mostly positive for SARS-CoV-2 (Liu 2020). In another study, SARS-CoV-2 remained viable in experimentally-induced aerosols for up to 3 hours (van Doremalen 2020). In order to protect public health from COVID-19, toilets should be properly used and cleaned (e.g. ventilation and sterilization) as a toilet can be a potential source of COVID-19 with relatively high risk caused by aerosolization of the virus and contamination of surfaces after use. The general public should use personal protection measures such as performing hand hygiene, wearing masks and avoiding busy crowds. Effective sanitization of high risk areas and the use of high level protection masks for medical staff is also important (Liu 2020, WHO Interim Guidance 2020).

Genetic variations of SARS-CoV-2 occur over time and those variations affect the characteristics of the virus. They have been emerging and circulating around the world. Some of genetic variations are classified as Variant of Concern (VOC) for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures (Variants and Genomic Surveillance for SARS-CoV-2, CDC). Due to their characteristics, it is closely monitored by each regulatory authority, as well as WHO. As of 25 May 2021, a total of 4 types of SARS-CoV-2 VOC

was identified. It is updated on vaccine performance against VOCs (WHO COVID-19 Weekly Epidemiological Update, 25 May 2021).

Incidence and Prevalence

As of 23 May 2021, there were 166,352,007 cumulative cases reported worldwide, according to data as received by WHO from national authorities. Americas currently has the largest number of cases reported (65,980,739; 40%), followed by Europe (54,110,276; 33%), South-East Asia (30,088,649; 18%), Eastern Mediterranean (9,863,946; 6%), Africa (3,446,089; 2%) and Western Pacific (2,861,544; 2%) (WHO COVID-19 Weekly Epidemiological Update, 25 May 2021).

Demographics of the Population in the Proposed Indication and Risk Factors for the Disease

Although all age groups are vulnerable to SARS-CoV-2 infection, in most cases patients were 30 to 79 years old, with the median age ranging from 49 to 59 years. There were few cases in children below 15 years of age (He 2020, Yang 2020). Clinical findings in China showed that children (age below 15) with COVID-19 usually presented mild respiratory infections, as compared with adult cases (Cai 2020). On another study in China, all paediatric patients (aged 0-16 years) had mild to moderate type of COVID-19 (Qiu 2020). In the United States, most reported COVID-19 infection in children aged below 18 are asymptomatic or mild. Less is known about severe COVID-19 in children requiring hospitalization (U. S. Centers for Disease Control and Prevention (CDC) 2020).

More than half of patients are male. In China, the proportion of male patients ranged from 51% to 58% of total reported cases (Guan 2020, WHO Report of WHO-China Joint Mission on COVID-19 2020), and was as high as 70% in some hospitals (Yang 2020, Zhou 2020). A higher proportion of fatal outcomes among male patients compared to females has been reported in China and the EU/EAA (Chen 2020, European Centre for Disease Prevention and Control (ECDC) 2020, Onder 2020). However, males with COVID-19 may also be more likely to have acute respiratory distress syndrome (ARDS) and patients with ARDS have a higher proportion of comorbid conditions such as hypertension and diabetes that resulted in less rigorous immune response (Wu 2020a).

The Main Existing Treatment Options

Currently, the nucleoside reverse transcriptase inhibitor remdesivir was granted conditional marketing authorisation by the EMA for the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (Remdesivir EU RMP version 1.0). Remdesivir was also approved by the FDA for the treatment of adults and paediatric (12 years of age and older and weighing at least 40 kg) COVID-19 patients requiring hospitalization (Veklury US Prescribing Information, 2020).

Meanwhile, in addition to corticosteroid dexamethasone, there was advice to Member states on treatments that are not yet authorized specifically for patients with COVID-19: bamlanivimab / etesevimab, casirivimab / imdevimab, sotrovimab, and regdanvimab. All 4 treatments including regdanvimab, are designed to target RBD of the spike protein of SARS-CoV-2, and the data provided by each company might provide clinical benefit for the treatment of confirmed COVID-19 in adult patients (bamlanivimab and etesevimab assessment report, casirivimab and imdevimab assessment report, sotrovimab assessment report, regdanvimab assessment report). They are currently under rolling review for authorization.

For patients with severe illness, a number of potential treatments, such as the nucleoside analogues ribavirin and favipiravir, the antimalarial agents chloroquine and hydroxychloroquine, the protease inhibitor lopinavir and ritonavir, pegylated interferon alfa-2a and -2b, have been used clinically against COVID-19 during the pandemic (Li 2020b, Lu 2020). The IL-6 receptor antagonist tocilizumab was considered a possible candidate drug for managing the cytokine storm associated with COVID-19, with encouraging results observed in patients with severe and critical COVID-19 patients in China (Ragab 2020). Clinical trials are being performed globally to assess efficacy and safety of the treatments and to develop novel vaccines and treatments.

Two mRNA vaccines were approved by EMA to be used for preventing COVID-19 caused by SARS-CoV-2 virus. The nucleoside-modified messenger RNA is formulated in lipid nanoparticles, which enable delivery of the non-replicating RNA into host cells to direct transient expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19 (Comirnaty EPAR 2021, COVID-19 Vaccine Moderna CHMP Opinion 2021). In addition, two vaccines made up of adenovirus family were proved by EMA for preventing COVID-19 in people aged 18 years and older. They work by producing the spike protein and develop person's immune system to recognise the spike protein as foreign and produce antibodies and activate T cells to target it (COVID-19 Vaccine AstraZeneca CHMP Opinion 2021, COVID-19 Vaccine Janssen CHMP Opinion 2021).

Natural History of the Indicated Condition including Mortality and Morbidity

Available information on the history and course of COVID-19 is described in an interim guidance document published by the World Health Organization. The onset of symptoms due to SARS-CoV-2 infection appears following the incubation period, which is the time between exposure to the virus (becoming infected) and symptom onset, is, on average, 5–6 days, but can be up to 14 days. Most people with SARS-CoV-2 infection develop only mild (40%) or moderate (40%) disease (WHO Interim Guidance 2020).

Most people experience fever (83-99%), cough (59-82%), fatigue (44-70%), anorexia (40-84%), shortness of breath (31-40%), or myalgia (11-35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported. Anosmia or ageusia preceding the onset of respiratory symptoms has also been reported. Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, and absence of fever.

COVID-19 is also associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningo-encephalitis, impaired sense of smell or taste, anxiety, depression, and sleep problems. In many cases, neurological manifestations have been reported even without respiratory symptoms. Case reports of Guillain-Barré syndrome and meningo-encephalitis among people with COVID-19 have also been reported. Clinical manifestations of COVID-19 are generally milder in children compared with adults. Relatively few cases of infants confirmed with COVID-19 have been reported. However, most recently, a multisystem inflammatory syndrome temporally associated with COVID-19 in children and adolescents has been described.

Approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury, and cardiac injury. Older age, smoking and underlying noncommunicable diseases, such as diabetes,

hypertension, cardiac disease, chronic lung disease, and cancer have been reported as risk factors for severe disease and death.

Although observed on small patient groups, among patients transferred to the intensive care unit (ICU), acute respiratory distress syndrome (ARDS) is the most frequent complication. Results from study of 138 hospitalized patients with COVID-19 infected pneumonia in Wuhan, China on January and February 2020, 36 patients (26.1%) were transferred to the intensive care unit (ICU) because of complications including acute respiratory distress syndrome (22 [61.1%]). (Wang 2020). According to systemic literature review for which the search date was March 2020, ARDS was the most common complication, with a pooled event rate of 18.4% (95% CI, 7.4 – 32.4%) (Zhang 2020). Excessive production of proinflammatory cytokines leads to ARDS aggravation and widespread tissue damage resulting in multi-organ failure and death (Ragab 2020).

Mortality proportionately increases as patients are older. In an analysis of COVID-19 cases from early 2020 adjusting for demography and under-ascertainment of cases, the age-specific case fatality ratios in China were estimated to be substantially higher in older age groups (0.32%, 6.4%, and 13.4% among those 60 years and younger, greater than 60 years old, and 80 years and older respectively). Estimates from the same study for international cases also showed the same trend. (Verity 2020) Under the result of a systemic review of literature conducted until April 2020, advanced age conferred an increased risk of in-hospital death (Figliozzi 2020).

Important Co-morbidities

Although severe symptoms due to COVID-19 can occur in individuals of any age without underlying conditions, a greater risk of hospitalization, severe disease and/or fatal outcome due to COVID-19 has been documented among patients with the following co-morbidities: (Guan 2020, Huang 2020, Wu 2020b, Zhou 2020, Pranata 2020, Petrakis 2020)

- Cancer
- Cardiovascular disease
- Chronic renal disease
- Chronic obstructive pulmonary disease
- Chronic respiratory disease
- Diabetes mellitus
- Hypertension
- Cerebrovascular disease
- Obesity

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- **key issues identified from repeat-dose toxicity study**

  *Monkey (*Cynomolgus *Monkey):*

  1. Three animals/sex/group, doses of CT-P59 at 0, 100, 200 and 400 mg/kg i.v. on Days 1 and 8 (Study No.G220016)

  In accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH 2011), a 2-week repeat-dose toxicity study in cynomolgus monkeys was conducted.

  Administration of CT-P59 up to 400 mg/kg were generally well-tolerated. However, test item-related changes of clinical pathology and macro and microscopic findings were observed in mostly one male at 400 mg/kg (Animal no. 4M0002). In clinical pathology, increased CRP level, decrease of A/G ratio and increased large unstained cell counts were observed. In microscopic examination, sinusoidal increased cell of the liver (including Animal no. 4M0001) and increased cellularity of the bone marrow were noted. These findings were considered test item-related but not adverse (Lewis, et al., 2002) since these were noted only in one male and they were not accompanied by degenerative changes. Moreover, there was thymic atrophy in the microscopic findings and this change was associated with the decreased size and weights of the thymus and considered to be secondary changes caused by body weight loss or stress (Everds, et al., 2013; Moriyama, et al., 2008). Decreased ALB was also considered to be secondary changes caused by decreased food consumption and body weight (Moriyama, et al., 2008). Besides, decrease in RBC parameters, prolonged PT, macroscopic increased size and increased weights of the kidneys and liver were observed. These changes were considered not adverse, but it was unclear whether the changes were related to the test item, because the changes were minimal and there were no microscopic correlates.

  In conclusion, there were no CT-P59 related toxicological changes in mortality, clinical signs, body weights, food consumption, ophthalmology, electrocardiography, haematology, coagulation, urinalysis, organ weights, macroscopic and microscopic observations.

  2. Dose of CT-P59 at 0, 100, 200 and 400 mg/kg with once weekly, i.v. infusion for 3-weeks (total three doses; on Days 1, 8, and 15) with 10-week recovery period. (Study No.20251637)

  The study was conducted in accordance with following guidelines: Committee for Medicinal Products for Human Use (CHMP), ICH Harmonised Tripartite Guideline M3 (R2), ICH Harmonised Tripartite Guideline S3a, ICH Harmonised Tripartite Guideline S6 (R1), ICH Harmonised Tripartite Guideline S7A, and the Japanese Guidelines for Nonclinical Studies of Drugs Manual (1995). Guidelines for Nonclinical Pharmacokinetic Studies, Guidelines for General Pharmacology Studies, and (Chapter 3, Repeated Dose Toxicity Studies).

  Administration of CT-P59 up to 400 mg/kg were clinically well-tolerated. All animals survived for the study duration and there were no CT-P59-related effects in the following parameters: clinical observations, food consumption, body weights, ophthalmology examinations, electrocardiograms, urinalysis parameters, organ weights, macroscopic or microscopic findings.

Acute phase response

CT-P59-related changes in hematology parameters were observed in some individual animals at all dose levels. Animals received CT-P59 (11 out of 22 Animals) had transient moderately to markedly decreased neutrophils associated with decreased white blood cell counts in some animals on Days 8, 15, and/or 22. Among them, three animals at 200 or 400 mg/kg/dose had mildly to markedly increased monocytes and/or lymphocytes on Days 8 and/or 15. Monocyte and lymphocyte values generally recovered by Day 22. CT-P59-related changes in coagulation and clinical chemistry parameters also consisted of an acute phase response for several males and females at 100 or 200 mg/kg/dose that included minimally to markedly increased fibrinogen, C-reactive protein, and/or globulins, and mildly decreased albumin and albumin/globulin ratio on Days 8 and/or 15 with recovery on Day 22 except for globulins in two animals at 100 and 200 mg/kg/dose.

Two animals administered the highest dose of CT-P59 (400 mg/kg/dose), had dose dependent changes in clinical pathology parameters that were either not present in other animals or were more pronounced compared to other animals dosed at 100, 200, or 400 mg/kg/dose and are discussed separately in the paragraphs below.

Hematology changes in one or both animals included transient moderate to marked decreases in neutrophils associated with decreased white blood cell counts. There was recovery of the white blood cell count by Day 22 for one animal. There were minimal to marked neutrophil Döhle bodies observed during blood smear evaluation on Day 15 or 22 suggestive of accelerated maturation in the bone marrow. Monocytes were mildly decreased for one animal on Day 8 followed by a moderate increase on Day 22. Red blood cell mass (hemoglobin, red blood cell count, and hematocrit) was mildly to moderately decreased on Days 8, 15, and/or 22. Reticulocytes were moderately decreased on Day 8 followed by mild to moderate increases on Days 15 and 22 for one animal or were not adequately increased on Day 22 for remaining animal. Red cell distribution width was moderately increased, and along with increased reticulocytes for one animal, correlated with minimal to mild anisocytosis and polychromasia observed during blood smear evaluation on Days 15 and/or 22. Platelets were transiently, mildly decreased with decreased plateletcrit and increased platelet distribution width on Day 8 or 15 with recovery on Day 15 or 22 except for platelet distribution width for one animal. Changes in coagulation and clinical chemistry included minimally prolonged activated partial thromboplastin time for one animal on Day 8 only and an acute phase response consisting of minimally to markedly increased fibrinogen, C-reactive protein, globulins, triglycerides, and/or total bilirubin, and moderately decreased albumin and albumin/globulin ratio. Other changes in clinical chemistry parameters included minimally to mildly increased cholesterol and mildly decreased calcium (associated with decreased albumin). During a 10-week recovery period, there were no CT-P59-related changes in clinical pathology parameters, indicating complete recovery.

In conclusion, test article-related effects included changes in hematology, coagulation, and clinical chemistry parameters, however, with the exception of the transient moderately to markedly decreased neutrophils from two (Animal Nos. 4004 and 4105) out of ten 400 mg/kg dosed animals, all other CT-P59-related findings were not considered adverse. The markedly decreased neutrophil count, though fully reversible, were considered adverse based on the inherent related increased risk for infections (Ramaiah *et al*., 2017) rather than a direct high toxic effect; and the no-observed-adverse-effect (NOAEL) was defined 200 mg/kg IV

accordingly. Additionally, no remarkable findings were reported from the macroscopic and microscopic examination of injection sites from all animals.

There were no serious hypersensitivity reactions, including anaphylaxis, with administration of CT-P59 have reported during the clinical trials; the changes from baseline in all available hematology and clinical chemistry laboratory parameters showed no notable differences among the CT-P59 40 mg/kg, CT-P59 80 mg/kg and Placebo groups. Therefore, there is no clinical relevance of the acute phase reaction found several animals including two of the high dose animals in the 3-week repeat-dose study.

- **Reproductive/developmental toxicity**

  No reproductive and developmental toxicity studies were conducted. This is in accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH 2011), which does not recommend reproductive and developmental studies for monoclonal antibodies that target exogenous proteins, since these types of antibodies are unlikely to cause reproductive or developmental toxicity. In the 2-week repeat dose non-human primate toxicity study, no adverse effects were noted in the reproductive organs of males or females.

- **Genotoxicity**

  No genotoxicity studies were conducted. This is in accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH 2011), which does not recommend genotoxicity for monoclonal antibodies that target exogenous proteins, since these types of antibodies are unlikely to be genotoxic.

- **Carcinogenicity**

  No carcinogenicity studies were conducted. This is in accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH 2011), which does not recommend carcinogenicity studies for monoclonal antibodies that target exogenous proteins since these types of antibodies are unlikely to be carcinogenic.

Safety pharmacology

- **General Safety Pharmacology**

  No stand-alone safety pharmacology study was performed according to the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH 2011). Safety end-points were incorporated into the 2-week and 3-week repeat-dose toxicity study in cynomolgus monkeys. There was no evidence of cardiotoxicity in the repeat-dose study performed as part of non-clinical investigations. Consequently, no stand-alone non-clinical cardiotoxicity study has been conducted with CT-P59.

Other toxicity-related information or data

- **Mechanisms for Drug Interactions**

  On the basis of the specificity of regdanvimab, no non-clinical studies pertinent to drug interaction have been conducted.

- **Juvenile Toxicity Studies**

  Juvenile toxicity studies were not performed in line with the ICH guideline S11 on nonclinical safety testing in support of development of paediatric pharmaceuticals.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Regdanvimab is a human monoclonal antibody targeted against the receptor binding domain (RBD) of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is being developed as a treatment for SARS-CoV-2 infection. The dosage form of regdanvimab is solution concentrate for dilution for administration in a single intravenous (IV) infusion.

Clinical studies with regdanvimab in patients with SARS-CoV-2 infection comprised one completed and one ongoing studies,

- a pilot phase 1, randomized, double-blind, placebo-controlled, parallel group, single ascending dose study to evaluate the safety, tolerability and virology of CT-P59 in patient with mild symptoms of severe acute respiratory syndrome coronavirus (SARS-CoV-2) Infection (Study CT-P59 1.2) (Completed);
- a randomized, parallel-group, placebo-controlled, double-blind, Phase 2/3 study in patients with mild to moderate symptoms of SARS-CoV-2 infection to evaluate the efficacy and safety of CT-P59 in combination with standard of care (Study CT-P59 3.2) (Ongoing).

As of June 11th, 2021, a total of 882 subjects with SARS-CoV-2 infection were exposed to regdanvimab.

Duration of exposure is unavailable since all clinical trials were designed as single treatment with regdanvimab.

Table 2 Part II.SIII.1: Age group and Gender

	CT-P59 (N = 882)			
	Person (n)		Person time (days)	
Age Group (years)	**Male**	**Female**	**Male**	**Female**
18 – 40	125	122	3612	3401
41 – 50	123	94	3519	2670
51 – 60	115	110	3473	3343
61 – 70	77	61	2102	1660
> 70	30	25	821	670
Total	470	412	13527	11744

Source Data: Study 1.2, 3.2 (Part 1, Day 28) and 3.2 (Part 2, Day 28)

Person time (days) = End of Treatment Period Date (for ongoing patients, Cut-off Date for each report) - Date of Study Drug Administration + 1

Table 3 Part II.SIII.2: Dose

	CT-P59 (N = 882)	
Dose of treatment	**Person (n)**	**Person time (days)**
20 mg/kg	5	420
40 mg/kg	762	21407
80 mg/kg	115	3444
Total	882	25271
Actual Administered Dose per Weight (mg/kg)		
Mean	45.1	
Median	40.0	
Minimum	20	
Maximum	80	
Actual Administered Dose (mg)		
Mean	3673.1	
Median	3400.0	
Minimum	1156	
Maximum	8000	
Source Data: Study 1.2, 3.2 (Part 1, Day 28) and 3.2 (Part 2, Day 28) Person time (days) = End of Treatment Period Date (for ongoing patients, Cut-off Date for each report) - Date of Study Drug Administration + 1		

Table 4 Part II.SIII.3: Ethnic Origin

	CT-P59 (N = 882)	
Dose of treatment	**Person (n)**	**Person time (days)**
White	757	21628
Black or African American	6	170
American Indian or Alaska Native	5	131
Asian	39	1286
Native Hawaiian or Other Pacific Islander	1	28
Not Allowed by Investigator Country Regulations	0	0
Others	74	2028
Total	882	25271

Source Data: Study 1.2, 3.2 (Part 1, Day 28) and 3.2 (Part 2, Day 28)

Person time (days) = End of Treatment Period Date (for ongoing patients, Cut-off Date for each report) - Date of Study Drug Administration + 1

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

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Patient who has known allergy or hypersensitivity reaction to any monoclonal antibody or to any components of study drug.

Reason for exclusion: These patients were excluded from the clinical development programme for safety reasons. Patients with a known allergy would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information?: No

Rationale: As per the EU SmPC, regdanvimab is contraindicated in patients who have hypersensitivity to the active substance(s) or to any of the excipients of the drug, therefore, it is unlikely that regdanvimab will be used in these patients.

Female patient who is currently pregnant or breastfeeding or planning to be pregnant or to breastfeed, or male patient who is planning to father a child or donate sperms throughout the study (up to 6 months after the study drug administration).

Reason for exclusion: The use of regdanvimab is not contraindicated during pregnancy or breast-feeding, however, whether regdanvimab is secreted in human milk and how regdanvimab affects developing foetus are still unknown with a limited evidence.

Is it considered to be included as missing information?: Yes

Paediatric patient aged under 18.

Reason for exclusion: The safety and efficacy of regdanvimab have not been established in paediatric patients. No data are available.

Is it considered to be included as missing information?: No

Rationale: As per the EU SmPC, regdanvimab is not recommended in paediatric patients, therefore it is unlikely that regdanvimab will be used in this population.

Patient who has received drugs with actual or possible antiviral drugs and/or possible anti-SARS-CoV-2 activity including but not limited to remdesivir, chloroquine, hydroxychloroquine, dexamethasone (alternative corticosteroids to dexamethasone), interferon beta-1b, ribavirin, and other immunomodulatory agents and human immunodeficiency virus (HIV) protease inhibitors (lopinavir-ritonavir, etc.) for therapeutic purpose of SARS-CoV-2 infection prior to regdanvimab.

Reason for exclusion: Patients who have taken other antiviral drugs were excluded from the pivotal clinical studies to prevent confounding interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: Regdanvimab is not renally excreted or metabolized 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.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure or cumulative exposure.

A total of 882 subjects with SARS-CoV-2 infection were exposed to regdanvimab during the clinical trials. Adverse drug reactions (ADRs) with a frequency greater than approximately 1 in 294 subjects with SARS-CoV-2 infection may be detected with a data set of this size.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 5 Part II.SIV3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Female patients who are pregnant or breastfeeding were excluded from clinical trials for regdanvimab. It is generally known that human IgG immunoglobulins cross the placental barrier. However, there are no adequate and well-controlled data with
Breastfeeding women	

	regdanvimab from studies in pregnant women. Therefore, the decision to treat nursing mothers with regdanvimab should be based on an individualized assessment of risk and benefit. Whether regdanvimab is excreted in human milk and what impact regdanvimab will have on infant who is exposed to regdanvimab during lactation are not known. As experience is limited, regdanvimab should be considered only when benefit to mother outweighs possible risk to child upon assessment of a duly qualified health care professional.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	17 subjects with chronic liver disease were treated with regdanvimab in clinical trials.
• Patients with renal impairment	12 subjects with chronic kidney disease including those on dialysis were treated with regdanvimab in clinical trials.
• Patients with cardiovascular impairment	241 subjects with cardiovascular disease including hypertension were treated with regdanvimab in clinical trials.
• Immunocompromised patients	Immunosuppressed patients were included in clinical trials, but there was no subject who was treated with regdanvimab.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	The majority of subjects with SARS-CoV-2 infection who were exposed to regdanvimab in Study CT-P59 1.2 and Study CT-P59 3.2 were White (n=757). Asian (n=39), Black or African American (n=6), American Indian or Alaska Native (n=5), Native Hawaiian or Other Pacific Islander (n=1) and Others (n=74) were also enrolled in clinical trials for regdanvimab. (Table 4)
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms that affect metabolism, degradation or pharmacological effects of regdanvimab. Hence, genetic polymorphisms are not evaluated during clinical development program.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

As of September 15th, 2021, a total of 1,677 patients were exposed to regdanvimab in Study CT-P59 4.1. A total of 63,732 vials were released worldwide until September 15th, 2021, which includes 63,301 vials released to health care institutions in Korea including quantities released for Study CT-P59 4.1, 180 vials released in Brazil, and 251 vials released to health care institutions in Spain, Cyprus and Austria, in which countries regdanvimab was supplied for individual basis treatment prior to marketing authorisation. Approximately 21,244 patients were exposed to regdanvimab in total on the presumption that a patient is given 3 vials of regdanvimab on average.

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

Potential for misuse for illegal purposes

Abuse is unlikely. Regdanvimab will only be administered by intravenous infusion by healthcare professionals. Regdanvimab has no psychoactive effects, and no other properties that might appeal to people intent upon misusing it for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

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

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Antibody-dependent enhancement (ADE)

There were no patients with suspected antibody-dependent enhancement (ADE) during the clinical trials and no ADE was reported from *in vitro* or *in vivo* non-clinical studies. Although ADE has been observed in SARS, MERS and other human respiratory virus infections including RSV and measles, presently there is no proof that ADE occurs in SARS-CoV-2 infection and there are merely various hypotheses as per the earlier reports of SARS and MERS-CoV and also with few *in vitro* studies with SARS-CoV-2. The ability of the antibody to neutralize the virus has a role in the production of ADE, however, clinical data has not established a role for ADE in human COVID-19 pathology. As evidence for a potential causal relationship between regdanvimab and ADE is lacking and only a theoretical risk exists, ADE is not considered important for inclusion in the list of safety concerns.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk

No identified risks considered important for inclusion in the list of safety concerns in the RMP.

Important Potential Risk

No potential risks considered important for inclusion in the list of safety concerns in the RMP.

Missing Information 1: Use during pregnancy

Risk-benefit impact: The safety of regdanvimab in pregnant women is not known as no studies of regdanvimab have been conducted in pregnant women. The use of regdanvimab in pregnant female patients is possible in clinical practice.

Missing Information 2: Long-term safety data

Risk-benefit impact: Long-term safety data of regdanvimab are limited from clinical trials. There may be long-term consequences that have not yet been seen in patients that have been studied so far. The impact on risk-benefit in terms of long-term safety is unknown.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

The data available for the assessment of the risk of regdanvimab are derived from one completed and one ongoing trials (Study CT-P59 1.2 and Study CT-P59 3.2).

SVII.3.1. Presentation of important identified risks and important potential risks

There are no important identified and potential risks for regdanvimab.

SVII.3.2. Presentation of the missing information

Missing information - Use during pregnancy

Evidence source:

The safety of regdanvimab in pregnant women is not known as no studies of regdanvimab have been conducted in pregnant women.

Population in need of further characterisation:

The use of regdanvimab in pregnant female patients is possible in clinical practice. As experience is limited, the use of regdanvimab in pregnancy should only be considered if the possible benefit to the patient is thought to outweigh any possible risk to the foetus.

Anticipated risk/consequence of the missing information:

IgG immunoglobulins are known to cross the placental barrier, therefore regdanvimab has the potential to be transferred from the mother to the developing foetus. There are no adequate and well-controlled data with regdanvimab from studies in pregnant women.

Missing information - Long-term safety data

Evidence source:

Long-term safety data of regdanvimab are limited from clinical trials.

Population in need of further characterisation:

There may be long-term consequences that have not yet been seen in patients that have been studied so far. More information on long-term safety of regdanvimab is required.

Anticipated risk/consequence of the missing information:

Considering regdanvimab is intended to be given as a single dose and a half-life of regdanvimab at a recommended dose of 40 mg/kg is estimated as 15.6 days, long-term consequences that may be unexpectedly observed after treatment with regdanvimab are anticipated to be uncommon. Nonetheless, a potential long-term consequences that regdanvimab may have will be monitored.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 6 Part II.SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Not applicable
Important potential risks	Not applicable
Missing information	Use during pregnancy Long-term safety data

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for lack of efficacy (LOE):

Lack of efficacy report form will be provided to reporters once lack of efficacy is received via individual case safety reports (ICSRs) from post-marketing data sources, in order to obtain structured information of lack of efficacy including reaction information, patient demographics, treatment information such as dose, route, therapy date and batch number, concomitant medications, medical history, product-related complaints, immunogenicity information and investigational result regarding genetic variations of virus. This form is intended to see if the reported lack of efficacy is associated with emerging variants. The information regarding lack of efficacy due to emerging variants will be retrospectively collected and will be properly reflected into each ICSR as follow-up information.

Monitoring of data on treatment failure due to emerging variants:

As part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, data on treatment failure due to emerging variants are to be monitored from all available data sources, including but not limited to

- Spontaneous cases (via targeted follow-up questionnaire for LOE including fields to request information on the variant)
- Clinical trial data
- Literature
- Reports received from regulatory authorities

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

Other forms of routine pharmacovigilance activities:

A new variant of concern or variant of interest newly classified by the Agencies (i.e. WHO; World Health Organization, PHE; Public Health England, CDC; Centers for Disease Control and Prevention and etc.) or any newly emerging variants will be continuously monitored, and their risk will be assessed. If the risk is identified, non-clinical studies to characterise regdanvimab in relation to the variant in question will be initiated.

III.2 Additional pharmacovigilance activities

Summary of Study CT-P59 3.2

Study short name and title:

CT-P59 3.2: A Phase 2/3, Randomized, Parallel-group, Placebo-controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Outpatients with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection

Rationale and study objectives:

There are currently no approved monoclonal antibody therapy available to treat coronaviruses such as SARS-CoV-2 and there is an urgent public health need for rapid development of such interventions.

The study is initiated to evaluate efficacy and safety of CT-P59 in outpatients with mild to moderate symptoms of SARS-CoV-2 infection, not requiring supplemental oxygen therapy.

The safety concern addressed in this study is long-term safety data which is missing information. The data generated from this ongoing clinical study will allow more confident assessment of the safety profile of regdanvimab.

Study design:

Randomized, parallel-group, placebo-controlled, double-blind

Study population:

Male or female outpatients, aged 18 or above with SARS-CoV-2 infection, confirmed SARS-CoV-2 diagnostic test or RT-PCR at Screening, or having a previous RT-PCR result within 72 hours prior to the study drug administration.

Milestones:

Final report: 30/06/2022

Summary of Study CT-P59 4.1

Study short name and title:

CT-P59 4.1: Post-Marketing Surveillance of REGKIRONA® 960 mg (Regdanvimab) (monoclonal antibody, gene recombination) to Evaluate Its Safety and Efficacy

Rationale and study objectives:

The objectives of this post-marketing surveillance (PMS) are to evaluate the safety and efficacy of REGKIRONA® 960 mg (Regdanvimab) in Korea under routine care.

The safety concern addressed in this study is use during pregnancy which is missing information. The data generated from this post-marketing surveillance will allow more confident assessment of the safety profile of regdanvimab.

Study design:

Post-marketing surveillance

Study population:

All patients who receive REGKIRONA® 960 mg for the first time according to the approved indication in Korea, adult patients with confirmed COVID-19 through reverse transcription polymerase chain reaction (RT-PCR) etc. and among them, high-risk mild patients* to moderate patients meeting all of the following conditions:

1) Oxygen saturation >94% on room air.

2) Not requiring supplemental oxygen supply.

3) Developed COVID-19 symptoms within 7 days prior to drug administration.

*High-risk mild patients are defined as patients with 1 or more of the following risk factors: Age > 50 years; BMI > 30Kg/m^2; Cardiovascular diseases, 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 status due to disease or treatment (such as cancer treatment, bone-marrow or organ transplantation, immune deficiencies, human immunodeficiency virus, sickle-cell anemia, thalassemia, and prolonged use of immune-weakening medications) base on investigator's assessment.

Milestones:

Final report: 31/12/2027

Summary of COVID-PR

Study short name and title:

COVID-19 International Drug Pregnancy Registry (COVID-PR)

Rationale and study objectives:

Medicine developers, academic labs, and other organizations globally are developing medical products to treat COVID-19. Potential treatments include medications currently used or studied to treat other diseases ("repurposed" treatments), as well as medications newly identified or designed to treat COVID-19. Pregnant women will be treated with these medications which, for the most part, lack scientific evidence regarding safety for the mother and the developing offspring.

The objective of the COVID-19 International Drug Pregnancy Registry (COVID-PR) is to estimate the effect that medications indicated for mild to severe COVID-19 have on obstetric, neonatal, and infant outcomes.

The safety concern addressed in this study is use during pregnancy which is missing information. The data generated from this registry will allow more confident assessment of the safety profile of regdanvimab.

Study design:

The COVID-PR is an international, non-interventional, post-marketing cohort study designed to collect prospective safety data among pregnant women treated pharmacologically for mild to severe COVID-19 at any time during pregnancy or within 90 days prior to the first day of the last menstrual period (LMP). It includes maternal and offspring follow-up until the infant's one year of age.

Study population:

The study population includes women 18 years of age and older who required in-hospital or ambulatory pharmacological treatment for mild to severe COVID-19 at any time during pregnancy or within 90 days prior to the first day of the LMP. Registration and participation via website especially developed for the COVID-PR are voluntary. Eligible women can enroll at any time during pregnancy and up to 30 days after the end of pregnancy. Postpartum mothers and their live offspring are followed-up to the infant's one year of age.

Milestones:

Estimated primary completion date: 30/09/2026

Final report: 30/09/2027

III.3 Summary Table of additional Pharmacovigilance activities

Table 7 Part III.1 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Study concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
CT-P59 3.2 Ongoing	To evaluate efficacy and safety of CT-P59 in outpatients with mild to moderate symptoms of SARS-CoV-2 infection, not requiring supplemental oxygen therapy	- long-term safety data	Final report	30/06/2022
CT-P59 4.1 Ongoing	To evaluate the safety and efficacy of REGKIRONA® 960 mg (monoclonal antibody, gene recombination) in Korea under routine care	- use during pregnancy	Final report	31/12/2027
COVID-PR Planned	To estimate the effect that medications indicated for mild to severe COVID-19	- use during pregnancy	Estimated primary completion date	30/09/2026

Study Status	Summary of objectives	Study concerns addressed	Milestones	Due dates
	have on obstetric, neonatal, and infant outcomes		Final report	30/09/2027

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

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

V.1. Routine Risk Minimisation Measures

Table 8 Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing information- Use during pregnancy	Routine risk communication: SmPC section 4.6: Fertility, pregnancy and lactation PL section 2: What you need to know before you are given Regkirona Routine risk minimisation activities recommending specific clinical measures to address the risk: Precautions to be taken prior to administration for the prevention of use during pregnancy is included in the SmPC section 4.6: Fertility, pregnancy and lactation and PL section 2: What you need to know before you are given Regkirona Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription
Missing information- Long-term safety data	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Table 9 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information- Use during pregnancy	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Legal status: Medicinal product subject to medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: CT-P59 4.1 COVID-PR
Missing information- Long-term safety data	Routine risk minimisation measures: None Legal status: Medicinal product subject to medical prescription Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: CT-P59 3.2

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Regkirona

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

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

This summary of the RMP for Regkirona should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Regkirona's RMP.

I. The medicine and what it is used for

Regkirona is authorised for treatment of confirmed coronavirus disease 2019 (COVID-19) in adults (see SmPC for the full indication). It contains regdanvimab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Regkirona’s benefits can be found in Regkirona’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Regkirona, together with measures to minimise such risks and the proposed studies for learning more about Regkirona's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Regkirona is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Regkirona are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Regkirona. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Not applicable
Important potential risks	Not applicable
Missing information	Use during pregnancy Long-term safety data

II.B Summary of important risks

Missing information - Use during pregnancy	
Risk minimisation measures	Routine risk minimisation measures - SmPC section 4.6 - PL section 2 Legal status: Medicinal product subject to medical prescription Additional risk minimisation measures - None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - CT-P59 4.1 - COVID-PR See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information - Long-term safety data	
Risk minimisation measures	Routine risk minimisation measures - None Legal status: Medicinal product subject to medical prescription Additional risk minimisation measures - None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - CT-P59 3.2 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation of Regkirona.

II.C.2 Other studies in post-authorisation development plan

CT-P59 3.2: A Phase 2/3, Randomized, Parallel-group, Placebo-controlled, Double-Blind Study to Evaluate the Efficacy and Safety of CT-P59 in Combination with Standard of Care in Outpatients with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection

Purpose of the study: There are currently no approved monoclonal antibody therapy available to treat coronaviruses such as SARS-CoV-2 and there is an urgent public health need for rapid development of such interventions.

The study is initiated to evaluate efficacy and safety of CT-P59 in outpatients with mild to moderate symptoms of SARS-CoV-2 infection, not requiring supplemental oxygen therapy.

The safety concern addressed in this study is long-term safety data which is missing information. The data generated from this ongoing clinical study will allow more confident assessment of the safety profile of regdanvimab.

CT-P59 4.1: Post-Marketing Surveillance of REGKIRONA® 960 mg (Regdanvimab) (monoclonal antibody, gene recombination) to Evaluate Its Safety and Efficacy

Purpose of the study: The objectives of this post-marketing surveillance (PMS) are to evaluate the safety and efficacy of REGKIRONA® 960 mg (monoclonal antibody, gene recombination) in Korea under routine care.

The safety concern addressed in this study is use during pregnancy which is missing information. The data generated from this post-marketing surveillance will allow more confident assessment of the safety profile of regdanvimab.

COVID-19 International Drug Pregnancy Registry (COVID-PR)

Purpose of the study: Medicine developers, academic labs, and other organizations globally are developing medical products to treat COVID-19. Potential treatments include medications currently used or studied to treat other diseases ("repurposed" treatments), as well as medications newly identified or designed to treat COVID-19. Pregnant women will be treated with these medications which, for the most part, lack scientific evidence regarding safety for the mother and the developing offspring.

The objective of the COVID-19 International Drug Pregnancy Registry (COVID-PR) is to estimate the effect that medications indicated for mild to severe COVID-19 have on obstetric, neonatal, and infant outcomes.

The safety concern addressed in this study is use during pregnancy which is missing information. The data generated from this registry will allow more confident assessment of the safety profile of regdanvimab.

PART VII: ANNEXES

ANNEX 1 EudraVigilance Interface

Available in electronic format only.

ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

ANNEX 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

ANNEX 4 Specific adverse drug reaction follow-up forms

- Lack of efficacy report form

ANNEX 5 Protocols for proposed and on-going studies in RMP part IV

Not applicable.

ANNEX 6 Details of proposed additional risk minimisation activities

None

ANNEX 7 Other supporting data (including referenced material)

- List of publications and other bibliographic material referenced in this RMP.

ANNEX 8 Summary of changes to the risk management plan over time

Regdanvimab: Questionnaire for Lack of Efficacy

This request for follow up information is being sent to obtain additional information about the reported event of lack of efficacy. This request does not constitute a company assessment that the adverse event was associated with the use of Regdanvimab. Confidentiality of this report will be maintained.

General instruction:

Please provide requested information below by filling in the blanks or placing a check mark in the appropriate box(es)

Reporter Information	
Name/Initial of reporter completing this form:	Phone Number / Fax Number:
Health Care Provider? ☐Yes ☐No If yes, please specify: _____	Email Address:
Date of Report:	Country of Report:

Reaction information
Event term (PT term):
Onset date:
Outcome of the event:

Patient Demographics	
Case ID:	Other Patient Identifiers (if provided):
Name/Initials:	Gender: ☐Male ☐Female
Age: _____	Height: _____ cm Weight: _____ kg
Current condition (Indication for therapy):	Date of Diagnosis:

Regdanvimab Treatment Information	
Dose and unit:	Route of administration:
Treatment date From: To:	Batch number:
Action taken with regdanvimab ☐Discontinued ☐Continued ☐Unknown ☐Dose changed ( ) ☐ Others (Please specify):	

Were there any product-related complaints, such as breakage or impurity present in the drug?
☐ No ☐ Yes (If yes, please describe in as much details as possible)

Medical History/Risk Factors (Provide information on risk factors or conditions that may affect the outcome of treatment)		
Medical History/Risk Factors		Comment
☐	None ☐ Unknown	
☐	Hypertension	
☐	Diabetes; if yes, specify type	
☐	Allergies; if yes, please specify	
☐	Infection	
☐	Smoking/use of alcohol; specify	
☐	Obesity	
☐	Other condition that may pose a risk factor; specify	

Concomitant Medications taken prior to or during regdanvimab treatment:				
Product Name	Indication	Total daily dose and unit	Start date	Stop date/Ongoing

Please describe investigation result regarding genetic variations of virus	
Virus investigation result available? ☐ Yes ☐ No	Genetic variations of virus identified? ☐ Yes ☐ No ☐ Not applicable
Please provide detailed information on the variant virus, if applicable	

Please specify immunogenicity assessment information, including Anti-Drug Antibodies (ADA)	
Immunogenicity test result available? ☐ Yes ☐ No If yes, please provide a type of immunogenicity analysis:	Type of immunogenicity analysis Results of immunogenicity assessment ☐ Positive ☐ Negative
Please provide detailed information on the result of immunogenicity test, if applicable	

Please describe medical assessment for lack of efficacy

For additional information, please enter text in dynamic box below:

Completed by:

Name:		Position:	
Signature:		Date:	
E-mail:			

Contact name for further information

Function		Tel no.	
Contact address		Fax no.	
		Email	

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