EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 November 2021
EMA/679271/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Regkirona

International non-proprietary name: regdanvimab

Procedure No. EMEA/H/C/005854/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Background information on the procedure 6
1.1. Submission of the dossier 6
1.2. Steps taken for the assessment of the product 7

2. Scientific discussion 10
2.1. Problem statement 10
2.1.1. Disease or condition 10
2.1.2. Epidemiology and risk factors 10
2.1.3. Aetiology and pathogenesis 10
2.1.4. Clinical presentation and diagnosis 11
2.1.5. Management 11
2.2. About the product 12
2.3. Quality aspects 12
2.3.1. Introduction 12
2.3.2. Active Substance 12
2.3.3. Finished Medicinal Product 17
2.3.4. Discussion on chemical, pharmaceutical and biological aspects 21
2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects 22
2.3.6. Recommendation for future quality development 22
2.4. Non-clinical aspects 22
2.4.1. Pharmacology 22
2.4.2. Pharmacokinetics 24
2.4.3. Toxicology 25
2.4.4. Ecotoxicity/environmental risk assessment 27
2.4.5. Discussion on non-clinical aspects 27
2.4.6. Conclusion on the non-clinical aspects 28
2.5. Clinical aspects 28
2.5.1. Introduction 28
2.5.2. Clinical pharmacology 31
2.5.3. Discussion on clinical pharmacology 53
2.5.4. Conclusions on clinical pharmacology 55
2.5.5. Clinical efficacy 56
2.5.6. Discussion on clinical efficacy 87
2.5.6. Conclusions on the clinical efficacy 89
2.5.7. Clinical safety 90
2.5.8. Discussion on clinical safety 112
2.5.9. Conclusions on the clinical safety 112
2.6. Risk Management Plan 112
2.6.1. Safety concerns 112
2.6.2. Pharmacovigilance plan 113
2.6.3. Risk minimisation measures 114
2.6.4. Conclusion 115
2.7. Pharmacovigilance 115

2.7.1. Pharmacovigilance system 115
2.7.2. Periodic Safety Update Reports submission requirements 115
2.8. Product information 116
2.8.1. User consultation 116
2.8.2. Labelling exemptions 116
2.8.3. Quick Response (QR) code 116
2.8.4. Additional monitoring 117
3. Benefit-Risk Balance 117
3.1. Therapeutic Context 117
3.1.1. Disease or condition 117
3.1.2. Available therapies and unmet medical need 117
3.1.3. Main clinical studies 118
3.2. Favourable effects 119
3.3. Uncertainties and limitations about favourable effects 119
3.4. Unfavourable effects 120
3.5. Uncertainties and limitations about unfavourable effects 120
3.6. Effects Table 120
3.7. Benefit-risk assessment and discussion 121
3.7.1. Importance of favourable and unfavourable effects 121
3.7.2. Balance of benefits and risks 122
3.7.3. Additional considerations on the benefit-risk balance 122
3.8. Conclusions 122
4. Recommendations 123

List of abbreviations

ACE2	Angiotensin converting enzyme 2
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADE	Antibody-dependent enhancement
AUC0-168h dose	Area under the serum concentration curve from the start of dosing to 168 hours after
AUC0-504h dose	Area under the serum concentration curve from the start of dosing to 504 hours after
BLI	Biolayer interferometry
CDC	Complement-dependent cytotoxicity
CFR	The Code of Federal Regulations
Cmax	Maximum observed peak serum concentration
COVID-19	Coronavirus disease 2019
ECG	Electrocardiography
dpi	Days post infection
EC50	The half-maximal effective concentration
EMA	European Medicines Agency
ELISA	Enzyme-linked immunosorbent assay
Fc	Fragment crystallizable region
FcR	Fc receptor
FDA	US Food and Drug Administration
GLP	Good Laboratory Practice
hr	Hour(s)
IC50	The half maximal inhibitory concentrations
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IP	Intraperitoneal
IV	Intravenous
KD	Equilibrium dissociation constant
MFDS	Minister of Food and Drug Safety
N/A	Not applicable
NGS	Next generation sequencing
NHP	Non-human primate
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Cooperation and Development
PD	Pharmacodynamic
PK	Pharmacokinetic
PRNT	Plaque reduction neutralization test

RBD	Receptor binding domain
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPR	Surface plasmon resonance
t1/2	Half-life
TCR	Tissue cross-reactivity
TG	Transgenic
TK	Toxicokinetic
US	United States
WHO	The World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Celltrion Healthcare Hungary Kft. submitted on 1 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Regkirona, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication "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 (see section 5.1)".

Legal basis and dossier content

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0234/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0234/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

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

Applicant's request for consideration

New active Substance status

The applicant requested the active substance regdanvimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication

subject to the present application:

Date	Reference	SAWP co-ordinators
1 July 2020	EMA/CHMP/SAWP/336054/2020	Brigitte Schwarzer-Daum, Jens Reinhardt and Ingrid Schellens
14 September 2020	EMA/CHMP/SAWP/470378/2020	Ingrid Schellens and Elena Wolff-Holz

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

- The strategy for using preliminary clones to produce CT-P59 used in Part 1 (Phase 1) and early stage of Part 2 of the Phase 1/2 clinical study and then switching to a single clone to produce CT-P59 during the Part 2 (Phase 2) of the Phase 1/2 clinical study.
- In-vitro pharmacodynamics. Preclinical toxicology studies to support clinical development and MAA.
- Design of a proposed study with a part 1 in healthy subjects evaluating safety and PK of escalating doses, and a part 2 in patients with mild symptoms of SARS-CoV-2 infection evaluating efficacy, in particular selection of endpoints and study duration, and plan for a possible early MAA submission.
- Design of (i) Study CT P59 3.1 to evaluate the efficacy of CT-P59 in hospitalized patients with SARS-CoV-2 infection, and (ii) study CT P59 3.2 study to evaluate the efficacy of CTP59 in patients with mild symptoms of SARS-CoV-2 infection, specifically: selection of endpoints and efficacy analysis of the primary endpoint for Part 1 and 2; study duration; dose selection; target population; sample size; pooling of patients from Part 1 to Part 2 for the efficacy analysis. Whether evidence from Part 1 with supporting data could allow MAA.

This program was overall in line with CHMP advice.

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

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

A request for rapid SA was discussed by the ETF on 23 June 2020. The ETF endorsed the Scientific Advice letter and confirmed eligibility to the rolling review procedure based on the information provided by the applicant. Subsequently the ETF agreed the start of the rolling review on 23 February 2021.

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

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Jan Mueller-Berghaus

The CHMP confirmed eligibility to the centralised procedure on	12 January 2021
The ETF recommended to start the rolling review procedure on	23 February 2021
Submission of the first package via eCTD	24 February 2021
The procedure (Rolling Review 1) started on	24 February 2021
Rapporteurs' CHMP ARs and draft overviews to ETF, CHMP and EMA for 48 h consultation and comments	27 May 2021
Deadline for comments	31 May 2021
BWP discussion	01 June 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	02 June 2021
ETF discussions on the consolidated List of Questions	08 June 2021
Start of CHMP written procedure	10 June 2021
Adoption of the 1st interim opinion for this rolling review	11 June 2021
Submission of the second package via eCTD	19 July 2021
The procedure (Rolling Review 2) started on	20 July 2021
Rapporteurs' CHMP ARs and draft overviews to peer reviewer, ETF, CHMP and EMA for 48 h consultation and comments	19 August 2021
Deadline for comments	23 August 2021
BWP discussion	24 August 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	25 August 2021
ETF discussions on the consolidated List of Questions	27 August 2021
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF	10 September 2021
Adoption of the 2nd interim opinion for this rolling review	16 September 2021
The application was received by the EMA on	1 October 2021
The procedure started on	4 October 2021
The PRAC Rapporteur's first Assessment Report was circulated to all CHMP, PRAC and ETF on	18 October 2021
The PRAC Rapporteur's updated Assessment Report was circulated to all CHMP, PRAC and ETF on	22 October 2021
The CHMP rapporteur's assessment reports were circulated to all CHMP, PRAC, BWP and ETF on	27 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to	28 October 2021

CHMP during an PRAC meeting on	
The CHMP rapporteur's updated assessment reports were circulated to all CHMP, PRAC, BWP and ETF on	03 November 2021
ETF discussions took place on	05 November 2021
BWP meeting was held on	05 November 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Regkirona on	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

At the end of December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally, on 30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

According to European Centre for Disease Prevention and Control (ECDC), histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.2. Epidemiology and risk factors

As of 8 November 2021, there have been over 244 million confirmed cases of SARS-CoV-2 infection globally with approximately 5.04 million deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation and diagnosis

The severity of COVID-19 disease varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical disease may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy (e.g. Veklury (EMEA/H/C/005622)), antibodies administered from convalescent plasma and hyperimmune immunoglobulins. These therapies have shown variable effect on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

On the other hand, in the EU there are 4 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease, these are Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675) and COVID-19 vaccine Janssen(EMEA/H/C/005737).

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent need for vaccines and therapeutics able to prevent, mitigate and treat COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. In addition, some studies have shown that patients might experience potential sequelae, including chronic fatigue, thrombotic events post infection, non-reversible lung disease, etc; although these aspects have not been fully determined yet.

2.2. About the product

Regdanvimab is a recombinant human IgG1 monoclonal antibody produced through recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary) that binds to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 consequently blocking cellular entry and SARS-CoV-2 infection.

The recommended dosage of regdanvimab in adults is a single IV infusion of 40 mg/kg. Regdanvimab should be administered within 7 days of onset of symptoms of COVID-19.

The applicant applied for the following indication "Regkirona is indicated for the treatment of adults with coronavirus disease 2019 (COVID-19) that do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19 (see section 5.1)."

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 60 mg/ml of regdanvimab (CT-P59) as active substance.

Other ingredients are: L-histidine and L-histidine hydrochloride monohydrate, L-arginine, polysorbate 80 and water for injection.

The product is available in type I glass vial with a chlorobutyl rubber stopper. Pack size of 1 vial (16 ml).

2.3.2. Active Substance

General Information

The active substance Regdanvimab (CT-P59) is a recombinant human monoclonal IgG1 antibody produced in Chinese hamster ovary (CHO) cells. Regdanvimab is a glycoprotein with one N-linked glycosylation site (Asn308) in the CH2 domain of each heavy chain. Each heavy chain consists of 457 amino acids with 11 cysteine residues, and each light chain consists of 216 amino acids with 5 cysteine residues. The amino acid sequences of the heavy and light chains are presented in the dossier. The theoretical molecular mass of the intact molecule is 145,931 g/mol.

The proposed mechanisms of action include binding to SARS-CoV-2 RBD, inhibiting the interaction between SARS-CoV-2 RBD (Receptor Binding Domain) and the cellular receptor, ACE2, thus blocking SARS-CoV-2 infection. Data presented in the characterisation section of the dossier shows that Regdanvimab only mediate low levels of Fc-related activities not contributing significantly to the overall activity.

Manufacture, process controls and characterisation

Regdanvimab active substance is manufactured by Celltrion Inc, Plant I (CLT1), 23, Academy-ro, Yeonsu-gu, Incheon, 22014, Republic of Korea. The facility is GMP compliant.

Description of manufacturing process and process controls

The Regdanvimab active substance manufacturing process has been adequately described. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance is produced in a CHO cell line in a bioreactor operated in fed-batch mode. The final cell culture is harvested via centrifugation, followed by depth filtration and membrane filtration. The clarified harvests are subsequently purified by affinity chromatography and mixed mode chromatography. Viral inactivation and clearance are achieved by low pH and nanofiltration. Finally, the concentrated and diafiltered active substance is filtered into sterile bottles.

Each active substance batch is derived from a single vial of the MCB (Master Cell Bank) and purified from the harvest of a single production bioreactor. The batch numbering system is described in the dossier. Separate flow diagrams are included for vial thaw & inoculum, seed bioreactor, production bioreactor, harvest & recovery, affinity chromatography, virus inactivation, mixed mode chromatography, viral filtration, concentration & diafiltration and final fill.

Information on column dimensions (diameter, bed height and approximate column volumes) are given in the narrative process description, bed heights are also listed in the flow charts. Criteria for collection of the eluates and representative chromatograms for the affinity chromatography and mixed mode chromatography steps are presented.

Virus filters are used at the virus filtration step. Reprocessing of the viral filtration pool, the filtration pool in the ultrafiltration/diafiltration (UF/DF) and the final fill steps are described in separate flow charts. The conditions under which reprocessing can occur are listed in the dossier. It is clear that reprocessing is not expected to be a routine occurrence and that it only is allowed on one occasion per batch.

The active substance manufacturing process is considered acceptable.

Control of materials

Sufficiently detailed information has been provided for source, history and generation of the cell substrate. Acceptable information has been provided for the characterisation of the MCB and cells at the limit of in vitro cell age.

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the Regdanvimab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

The approach taken in development of the active substance control strategy, including establishment of QTPP (Quality Target Product Profile), CQAs (Critical Quality Attributes) and CPPs (Critical Process Parameters) is described in the dossier.

The established CPPs for the active substance manufacturing process are supported by risk assessment, development studies and/or historical production data. The justification for the CPPs and their acceptance criteria are acceptable described.

In-process tests (CIPTs and IPTs) are listed with defined ranges in the dossier. It is noted that there are additional process variables defined for monitoring (MPs and IPMs) but for these no defined ranges are included in the dossier. This is found acceptable.

Process hold times and storage conditions are defined for process hold points in the commercial active substance manufacturing process.

Process validation

The Regdanvimab active substance manufacturing process has been validated adequately. Consistency in production has been shown on 10 full scale commercial batches. The process validation of the manufacturing steps (at manufacturing scale) for active substance is adequately described and reported.

The process validation was performed at commercial scale, and the validation strategy was designed to incorporate active substance generated from all bioreactor trains. Several harvest cell culture fluid batches were produced purified and filled as a single active substance batch. There were some deviations in the validation runs, these are described and acceptably justified by the Applicant. Batch analysis results met the release specification.

An historical data assessment was made after process validation, based on an in-house risk assessment tool. The re-assessment resulted in re-classification of process variables and adjusted operating range and acceptance criteria for the CPPs and CIPTs. It is also stated that this kind of re-assessment activity may be incorporated in future exercises to improve process control upon accumulation of further knowledge.

Removal of impurities

A scale-down downstream process has been used to investigate clearance of process-related impurities The data demonstrate that the impurities were removed predominantly by the chromatography step. Acceptable removal capacity has been demonstrated.

Furthermore, product-related impurities, process-related impurities (HCP, DNA, rProtein A) and safety tests (endotoxin and bioburden) are routinely controlled by the active substance specification. The capacity to clear antifoam has been acceptably demonstrated.

Resin and membrane lifetime and sanitization studies

Scale-down resin lifetime study and the scale-down carry-over study for chromatography resins have been completed and the results are provided in the dossier. The target maximum number of cycles for the TFF membrane was determined.

Hold times

Process hold time studies were performed with in-process samples held in the representative small-scale vessels, both microbial and biochemical stability was demonstrated. The validated hold times are considered supportive of the hold times proposed.

Reprocessing

Reprocessing validations have been performed at laboratory scale and protocols for reprocessing at commercial scale has been provided. The conditions under which reprocessing can occur are listed in the dossier.

Freeze-Thaw Studies

Freeze and thaw studies was conducted with a bracketing approach for bottle size. Acceptable test results are presented after freeze-thaw cycles and the thawing times was determined.

Shipping validation

Results from shipping validation studies performed in the same bottles as used for active substance storage are presented in the dossier. Bottles filled with water are claimed to be representative of bottles filled with the same amount of active substance. This found acceptable for a frozen solution.

Manufacturing process development

Three different processes have been used throughout development. Process A was used for non-clinical studies, process B for non-clinical studies and initial clinical trials and finally process C, the commercial process was used for production of DP for later stage of clinical trials. Comparability assessments were conducted between Process A and Process B batches and between Process B and Process C batches, and the results are provided in the dossier.

Comparability studies were performed with Process A active substance and Process B active substance and with Process B active substance an Process C active substance.

Characterisation

Elucidation of structure and other characteristics

A comprehensive physicochemical and biological characterisation of the active substance Regdanvimab is presented. Several batches of active substance manufactured at scale in a production bioreactor and several lots of finished product were included in the studies.

An extensive panel of orthogonal state-of-the-art tests were applied. Studies of primary and higher order structure, post-translational modifications, charge variants, glycosylation and biological activity were included.

Several different binding ELISA methods as well SPR (Surface plasmon resonance) methods have been used in the characterisation studies. Results are presented including dose-response curves and sensorgrams.

The results show that the maximum cytotoxicity of Regdanvimab was less than 15%, that is a very low level in comparison to other therapeutic monoclonal antibodies where the major mechanism of action is *via* ADCC activity. Moreover, no significant differences were observed between process 2 and process 3 material, supporting comparability between material from the two processes, despite slight differences in the afucosylation level. It should be noted that it is expected that this new ADCC format, with more reliable results, will be included in future comparability studies that may be needed in connection with future changes to the active substance manufacturing process.

In conclusion, it is agreed that ADCC is not contributing significantly to the overall activity of Regdanvimab.

Results are presented showing that the *in vitro* Plaque Reduction Neutralisation Test (PRNT) and SARS-CoV-2 RBD binding (ELISA) correlate with each other. This supports the suitability of the binding ELISA as the potency assay for release testing.

Impurities

The product-related impurities include charge variants, high molecular weight (HMW) species, antibody fragments, oxidised variants and some glycan variants. Results presented from batch analysis confirm efficient removal of these product-related impurities.

The major process-related impurities are controlled at active substance release and batch analysis data are presented.

Reports covering risk assessments of the presence of nitrosamine for the active substance and active product have been provided as annexes to Module 1. The Applicant concludes that there is no risk of nitrosamine impurities in neither active substance nor finished product.

Specification

Specifications with acceptance criteria are set in accordance with ICH Q6B and include control of identity, glycosylation, purity and impurities, concentration, potency, and general safety tests.

The acceptance criteria are set based on clinical and commercial active substance batch data. Overall, the active substance specification are found adequate to control the quality of Regkirona.

The proposed acceptance criteria for the general tests are found approvable. The limits for the specific tests for glycosylation, purity and impurity and potency are acceptably justified and also supported by results from comparability and characterisation studies.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Potency testing measures SARS-CoV-2 RBD binding has been implemented. The test panel chosen is a combination of compendial and non-compendial methods. For compendial test methods reference is given to the relevant pharmacopeial. For the non-compendial methods the reference is given to the SOPs.

Several of the non-compendial analytical procedures described are used for testing of both active substance and finished product. The non-compendial analytical procedures are at large acceptable described, including information on acceptance criteria for system suitability testing.
Validation summaries are provided for all non-compendial methods confirming their suitability.

Batch analysis

Batch analysis data for several batches at commercial scale of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Batch analysis data are presented for all batches used for non-clinical and clinical studies, as well as batches produced during validation of the active substance manufacturing process.

Reference materials

Adequate information on the in-house reference standards used during development as well as current proposed primary reference standard is provided. The results from qualification of primary reference standard are provided and found acceptable. The working reference standard will be established using CT-P59 active substance which meets the release specification. Appropriate specification for requalification of the primary reference standard and working reference standard is in place.

Stability

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life in the proposed container. The proposed shelf life of Regkirona actives substance when stored

at the recommended conditions is based on long-term stability data. Stability studies have been conducted in line with ICH Q5C and ICH Q1B guideline and the results demonstrate that active substance is stable under the recommended conditions. Supporting information on intermediate, accelerated and stress stability and from photo-stability data have been provided

2.3.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Regkirona finished product is presented as a concentrate for solution for infusion in a 20-ml Type I borosilicate glass vial intended to deliver 960 mg of antibody per 16 ml at a concentration of 60 mg/ml. Prior to administration the finished product should be diluted using 0.9% (w/v) sodium chloride. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Besides the active substance, regdanvimab, the finished product solution of Regkirona contains L-histidine, L-histidine hydrochloride monohydrate, L-arginine, polysorbate 80 and water for injection.

The finished product contains no excipients of human or animal origin. The excipients L-histidine and L-histidine hydrochloride monohydrate, L-arginine, polysorbate 80 (stabilising agent) and water for injection are compliant with Ph. Eur standards and commonly used for the formulation of biopharmaceuticals.

Formulation development

The formulation development has been acceptably addressed and the chosen formulation sufficiently justified. There is no overage of active substance or excipient, only overfill which has been acceptably justified.

Manufacturing process development

The manufacturing process history is clearly described including information on the differences in manufacture between different Active product Processes.

Extensive comparability study between the commercial process and the process used in clinical studies was shown using additional physicochemical and biological characterisation studies and results were comparable.

In conclusion, the manufacturing process development is found acceptably addressed.

Container closure system

The evaluation of the suitability of the primary package materials is acceptably described. The primary packaging materials (a 20-ml glass type I vials and Fluro-Tec coated chlorobutyl rubber closures) comply with the compendial requirements of the Ph. Eur. The results from the extractables assessment support the compatibility of CT-P59 finished product with primary container closure system. Furthermore, available results from the on-going leachable study are provided which until now has not identified leachables present at levels of toxicological concern. For the unknown compound detected during the on-going leachable study the outcome of the identification as well as the toxicology evaluation should be provided when data is available. Although no safety concern is expected considering that the primary packaging is not new or unique for this kind of products, any potential risk to patient safety should be carefully addressed and proposed actions to be taken presented.

(Recommendation)

The photostability of CT-P59 finished product in its secondary packaging has been acceptably demonstrated. Furthermore, the container closure integrity has been verified based on vacuum decay test.

Compatibility

Prior to administration the finished product should diluted using 0.9% (w/v) sodium chloride in an infusion bag. Satisfactory compatibility for the finished product when diluted in saline has been demonstrated for the proposed in-use period. Furthermore, the compatibility of the finished product with the infusion bag in relation to leachables has been studied as well. The presence of leachables was evaluated at pre-defined time points. The results demonstrate that there are no leachable present at levels of toxicological concern.

Manufacture of the product and process controls

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Manufacture

The manufacturing process and process controls are acceptably described and summarized in separate flow-charts for the manufacturing sites. The manufacturing process for the finished product consists of formulation, filtration, aseptic filling, capping and visual inspection. Standard aseptic processing techniques are used for the manufacturing of the finished product.

Information on applied transport conditions for the transport of filled vials to the site responsible for the secondary packaging is presented and acceptably justified by transport validation data. Information on the conditions for sterilization of the vials and stoppers is found acceptable and performed in accordance with standard conditions using validated procedures.

No reprocessing of finished product has been described in the dossier.

Operating parameter or performance parameter are given for the different steps if applicable and process parameters (CPP)/critical operating parameters (COP) and critical in process tests (CIPT)/performance parameters (CPP) are clearly identified. Although confusing using different definitions of the control parameters/tests for the two sites the controls as such are found adequate and acceptably described.

Process controls

The chosen approach and development of the control strategy is in general acceptably described. The CQAs of relevance for the finished product manufacture are defined and discussed in this section. The CQA s are controlled during the manufacturing process at the finished product manufacturing site A through critical process parameters (CPPs) and the results are monitored by critical in-process test (CIPT). Similar approach is used at the finished product manufacturing site B but using different terms due to facility policies; critical operating parameters (COPs) and the results are monitored by critical performance parameters (CPPs).

The acceptance criteria for the CIPTs and IPTs at manufacturing site A were established through process development, historical production data and/or process validation data. Information to define Critical Process Parameters (CPPs) and justify the acceptance criteria is limited. However, results from

the study to confirm the stability with various ranges of stabiliser and surfactant, is found to acceptably justify the proposed range of the stabiliser and surfactant.

For the manufacturing process at manufacturing site B, the pre-existing risk assessment tool for ranking of parameter criticality and definition of process variables in place are followed. Also, the existing system for deviation/investigation is used and it is claimed that the control strategy for CT-P59 finished product manufacture at manufacturing site B differs from that of manufacturing site A. Despite the different nomenclature used at the two sites, it has been acceptably addressed that the same basic principles apply for the two control strategies which will result in the same actions and evaluations in case of deviations of concern for the quality and safety for the final product.

Process variables (input and output variables) have been classified as critical or non-critical based on an in-house risk assessment tool described in the dossier.

Process and hold times have been acceptably defined and justified.

Process validation/verification

The process validation followed a traditional approach and covered several consecutive production scale batches for each site. The ability to meet acceptance criteria for IPCs, finished product specification as well as additional acceptance criteria for non-routine tests was conducted.

In conclusion, the results from the several production scale batches at each site verify compliance with the acceptance criteria. All results comply with the acceptance criteria and the proposed final products specification. It can be concluded that the finished product can be consistently manufactured at each proposed commercial production site within the defined processing time and holding times.

Product specification

Specifications

The specification has been generated taking into account ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products with the relevant monographs of the European Pharmacopoeia and United States Pharmacopeia.

Justification of specification

The applicant includes a suitable set of specifications for the finished product including appropriate physicochemical tests and tests for identity, purity and potency. Each chosen test parameter as well as proposed acceptance criteria has been discussed. The acceptance criteria and specification ranges are deemed acceptably justified.

Impurities

The Applicant concludes that no additional impurities are detected in the finished product compared to the active substance. For elemental impurities a summary of the risk assessment in accordance with ICH Q3D and results from the elemental impurity study are provided for both manufacturing sites. The results from the study demonstrates a low risk from elemental impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

However, updated data from the on-going leachable study on the glass vial and rubber stopper remains to be provided when data is available as given by the Recommendation.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

The test panel chosen is a combination of compendial and non-compendial methods. For compendial test methods reference is given to the relevant pharmacopeial. For the non-compendial methods the same methods are used as for the active substance and reference is given to the SOPs. The validation and demonstrating of the suitability of the test methods was performed using active substance samples. This approach is acceptable considering the identical composition for active substance and finished product.

Batch analysis

Batch analysis data of the finished product for each manufacturing process including non-clinical, clinical, commercial process were provided. The results comply well with the acceptance criteria and demonstrate in general an acceptable batch to batch consistency although differences between the different processes can be observed for some of the purity test attributes

Reference materials

The same reference standards as for Regdanvimab active substances is used.

Stability of the product

Data have been provided on finished product stability studies performed at the real time/real condition, at the accelerated storage condition, and at the stress storage condition. The studies are performed in accordance with ICH Q5C Stability Testing of Biotechnological/Biological Products.

The stability specifications are identical to the release specification except for certain tests. The accelerated and stress studies are partially completed. To study the stability profile over time, trend analyses have been performed for the parameters that have been identified to be stability-indicating. No noticeable differences in trends could be observed in finished product. The proposed shelf-life of 12 months when stored at 5 ± 3ºC is therefore found acceptably justified.

In addition, drug product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability study verifies the need for the protection from light and that the finished product marketing pack is effective in protecting the Regkirona from light exposure.

In conclusion, the proposed finished product shelf life is supported by the data presented.

Adventitious agents

Sufficiently detailed information has been provided from the TSE risk assessment. Results from viral testing of the MCBs and cells at the limit of in vitro cell age have been provided. The test panels are in line with requirements in ICH Q5A. No adventitious virus was detected, only retrovirus like particles as expected for CHO cells.

Viral testing results including MVM and in vitro testing data from unprocessed bulk are provided. No adventitious virus was detected.

A summary of data from virus clearance studies is provided. In addition, full study reports for the virus studies have also been provided. Worst case settings are used for parameters known or expected to affect virus reduction. Relevant model viruses have been used. The results demonstrate that several steps in the process is able to effectively reduce potential virus contamination of a broad spectrum of virus as requested in ICH Q5A. Virus clearance studies for chromatography steps have been performed with both new and aged resins.

Satisfactory information has been provided demonstrating that sufficient measures are in place to ensure safety with regards to a broad spectrum of virus.

GMO

Not applicable.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance Regdanvimab is produced in Chinese hamster ovary (CHO) cells. Characterisation of Regdanvimab was performed using an extensive panel of appropriate methods. Data presented shows that Regdanvimab only mediate low levels of Fc-related activities not contributing significantly to the overall activity.

Differences between the three versions of the manufacturing process used during development are clearly described and comparability has been demonstrated. The information on manufacture of the active substance is found acceptable.

The information on development and manufacture of the finished product has been presented in a satisfactory way. The comparability studies verify acceptable comparability between the different processes used in development and between the two commercial manufacturing sites. The results of tests carried out verify that the Finished Product is manufactured in a validated and well-controlled process.

The control of the active substance and finished product has been presented in a satisfactory way.

The stability results support the proposed shelf life of 12 months at 5 ± 3ºC for the finished product.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the leachable studies. This point is put forward and

agreed as recommendations for future quality development (See 2.3.6. **Recommendation for future quality development**).

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation for future quality development

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

- For the unknown compound detected during the on-going leachable study the outcome of the identification as well as the toxicology evaluation should be provided before end of Q1 2022. Any identified risk to patient safety should be carefully addressed and proposed actions to be taken presented.

2.4. Non-clinical aspects

2.4.1. Pharmacology

The non-clinical pharmacology section only covers the assessment of pharmacological in-vivo studies. For pharmacological in-vitro study assessment, see the clinical section (section "clinical pharmacology"). The active substance in Regkirona is the monoclonal IgG1 antibody regdanvimab (experimental name: CT-P59) which targets the non-endogenous epitope of the RBD domain of the spike protein in SARS-CoV-2 (a protein that is not produced by mammalian cells). The stipulated pharmacological mechanism of action of regdanvimab is the blocking of the binding between SARS-CoV-2 RBD and the cellular receptor, ACE2, thereby reducing SARS-CoV-2 infection. CT-P59 does not seem to promote removal of infected cells via antibody-dependent cellular cytotoxicity (ADCC).

2.4.1.1. Primary pharmacodynamic studies

In-vivo studies

The pharmacological in-vivo studies were conducted in transgenic mice (human angiotensin-converting enzyme 2 [hACE2] expressing) and a set of un-modified animal models (hamster, ferret and rhesus macaque). SARS-CoV-2 is known to enter mammalian (inclusive human) cells via the cell membrane attached ACE2 protein. Ferret and rhesus macaque have been shown to be very similar to human ACE2 with regard to SARS-CoV-2 interactions. The properties of hamster ACE2 are less clear but Syrian hamsters have been reported to be susceptible to SARS-CoV-2 infection developing moderate interstitial pneumonia leading to transient mild to moderate disease.

The primary pharmacodynamic studies covered the following studies:

- Prophylactic efficacy study in hACE2 expressing TG mice against SARS-CoV-2 infection (GR2-RD-20-251).

- Therapeutic efficacy of CT-P59 against wild type of SARS-CoV-2 virus in human ACE2 transgenic mice (GR2-RD-21-110)
- Therapeutic efficacy study in in Golden Syrian Hamster against SARS-CoV-2 infection (GR2-RD-20-253).
- Therapeutic Efficacy Study in Ferrets against SARS-CoV-2 Infection (ID-2020-Celltrion-03)
- Therapeutic efficacy study in ferret against South African variant and wild type of SARS-CoV-2 (GR2-RD-21-108). See also clinical pharmacology.
- Therapeutic Efficacy Study in Rhesus Monkeys against SARS-CoV-2 Infection (GR2-RD-20-249)

The prophylactic activity of regdanvimab against wt SARS-CoV-2 infection was also studied in the hACE2 mouse model. Female mice treated with between 0.1 and 10mg/kg regdanvimab (i.p., single administration) one day before infection (1×10^5 PFU/50µL, intranasal) died at all doses before 6-days post infection (dpi; 2/6 animals survived at 0.1 and 1.0mg/kg and 3/6 animals survived at 10mg/kg; compared to 1/5 non-treated animals). There was body weight reduction from ~2-3dpi with non-treated and 0.1mg/kg animals showing a ~25-30% reduction at 6dpi and 1 and 10mg/kg animals showing 3-11% reduction. The viral replication in non-treated animal lungs and nasal swabs topped at 3dpi and decreased at 6dpi. Regdanvimab decreased viral titres relative to those in control animals (statistically significant decrease for 1 and 10mg/kg at 3dpi in lungs and for 10mg/kg in 6dpi nasal swabs) and, only a trend of reduction at best for 1 and 10mg/kg at 6dpi). The data indicates that there were some ameliorating effects from prophylactic treatment but that these effects were primarily on reducing the viral load in lungs (on 3dpi and not on 6dpi) and modest at best on therapeutic outcomes (i.e., 50% survival at the highest dose of 10mg/kg).

Post-infection treatment (starting 8h after infection) of wildtype (wt) SARS-CoV-2 and variants of concern (VOC) has been conducted in hACE2 mice (B.6Cg-Tg(K18-ACE2)2Prlmn/J). Observation duration were between 3- and 6-days post infection (dpi). Wt-virus infected mice ($1x10^4$ PFU in 50µL, n=8 per group) were treated with CT-P59 8h after infection (5 and 20mg/kg i.p.) and observed until 6 dpi (necropsy on 4 animals on 3dpi and 6dpi respectively). Control group was a viral infection+formulation group that had their mean body weights decreased up to 18.7% while treated animals had a weight reduction less than 10%. Viral titres were non-measurable in lungs at 20mg/kg on 6dpi but near control levels form some animals at 5mg/kg. Viral levels were generally reduced but measurable at all doses on 3dpi. This profile was also seen for nasal wash viral levels. See Clinical Pharmacology for further details on the VOC studies.

Besides hACE2 mice, the post-infection treatment effectivity of regdanvimab was also characterized in naïve golden Syrian Golden hamster, ferret, and Rhesus macaque animals.

In Hamster, treatment (15, 30, 60 and 90mg/kg, i.p.) was on 1dpi and the animals were observed until 5dpi. No animal - treated or non-treated - died from infection. All animals lost body weight (-4% to -10%) with no statistically significant difference between treatment and control groups. Based on qRT-PCR and TCID50 (lung only) assay measurements, the viral replication in lungs and nasal turbines was reduced (statistically significant effects) on 2-3dpi (≥60mg/kg based on qRT-PCR, ≥15mg/kg base on TCID50 assay) and 5dpi (≥30mg/kg based on qRT-PCR, ≥15mg/kg base on TCID50 assay). Overall, the animals did not demonstrate any significant therapeutic effects (on body weight reduction) but did reduce the viral loads in lungs and nasal turbines.

In ferrets, treatment (3 and 30mg/kg, i.v., bolus) was on 1dpi and the animal were observed until 7dpi. Infection symptoms (coughing, nasal discharge, reduced activity) peaked in controls at 2-4dpi and then became weaker but still visible at 7dpi. Treatment reduced the viral titres in nasal and lung samples at 3 and 30mg/kg and also reduced clinical symptoms moderately with no observable symptoms seen at 7dpi (most clearly at 30mg/kg). There were indications that regdanvimab reduced

inflammation in ferret lung tissue, but the study is too small and lacking for any strong conclusion on this aspect.

For the rhesus macaque study (treatment at 1dpi with 45 or 90mg/kg i.v., observation until 6dpi), the infection was induced via multiple routes at once (intratracheal, intranasal, oral, ocular). There was no difference in clinical symptoms, body weight and haematology between non-treated and treaded animals. There was a strong effect on viral titres from nasopharyngeal and oropharyngeal swabs: the presence of viruses could only be detected between 1dpi and 2dpi (whereas control animals had a peak between 1-3 dpi and then showed gradual reduction until 6dpi).

The activity of regdanvimab in animal models infected with VOC's is discussed in the section on Clinical Pharmacology.

2.4.1.2. Secondary pharmacodynamic studies

In-vivo studies

To investigate the possibility of antibody-dependent enhancement (ADE), a study with 24h pre-infection treatment (between 0.001mg/kg and 1mg/kg regdanvimab) in hACE2 transgenic mice (B.6Cg-Tg(K18-ACE2)2Prlmn/J) was conducted (study code GR2-RD-20-314). There were no differences in lung viral titres at doses below 1mg/kg and down to 0.001mg/kg (as compared to controls), but it is impossible to conclude if this absence of titre difference at lower doses negates the possibility of ADE.

Next generation sequencing of the gene for the spike protein in hamster and Rhesus macaque samples (from primary pharmacodynamics studies, study code GR2-RD-20-356) did not detect any CT-P59 treatment-emergent specific mutations within or close to the epitope that CT-P59 binds to. In Rhesus macaque, there was a shift in frequency of amino-substitution variants due to treatment (compared to with before treatment) which may be due to genetic drift. This indicates that the likelihood of generating viral resistance via CT-P59 treatment in-vivo is low (at least in hamster and macaque).

Tissue cross-reactivity (TCR) studies were conducted on human (adult, foetal and neonatal) and cynomolgus (adult) tissues (study codes: 20251203 and 20265175). Regdanvimab showed specific positive staining in meningeal arachnoid cap cells in the brain and spinal cord in tissues derived from human (adult and neonatal) and the cynomolgus monkey (adult).

2.4.1.3. Safety pharmacology programme

The safety pharmacology was integrated into a 2-week repeat-dose toxicity test and a 3-week repeat-dose toxicity study with a 10-week recovery period. The endpoints included clinical observations for any unexpected events with central nervous system and respiratory behaviour, and electrocardiography (ECG) for the cardiovascular system (see Toxicology section).

2.4.2. Pharmacokinetics

Measurement of CT-P59 concentration have been conducted using ELISA and electrochemiluminescence (ECL; the latter only in toxicokinetic studies). Only one dedicated non-clinical pharmacokinetics study has been conducted and submitted (ELISA measurement of CT-P59 in Hamster serum, GR2-RD-20-250).

Male golden Syrian hamsters exposed to a single IP injection of CT-P59 at doses between 15 and 60mg/kg had blood samples collected between 0.5 and 504 hours after administration of each dose.

The concentrations of CT-P59 were measured in serum via ELISA (calibration range between 0.078ng/mL and 10ng/mL). CT-P59 was detectable in all exposed animals up to 504 hours post-dose. The mean Cmax and AUC0-504h values increased in a generally dose proportional manner for CT-P59. The mean Cmax was 86 (15mg/kg), 158 (30mg/kg), and 409µg/mL (60mg/kg) whereas the mean AUC0-504h was 14056 (15mg/kg), 35804 (30mg/kg) and 62128 (60mg/kg) µg x h/mL. The values are based on male animals (a preliminary study with males and females did not detect clear sex-differences). The mean half-life (t1/2) of CT-P59 was 64h (15mg/kg), 121h (30mg/kg), and 153h (60mg/kg). Additional PK (toxicokinetics) measurements were conducted in repeat-dose toxicity studies (see Toxicology). No specific non-clinical pharmacokinetic distribution, metabolism or excretion studies shave been conducted for CT-P59. The degradation of CT-P59 to individual amino acids will be added to the general amino acid pool, excess of which will be excreted through renal and hepatic mechanisms.

2.4.3. Toxicology

2.4.3.1. Single dose toxicity

No single-dose toxicity study was performed.

2.4.3.2. Repeat dose toxicity

Two repeat-dose toxicity studies, 2-and 3-week long, were conducted in the cynomolgus monkey using intravenous administration of regdanvimab at dose levels of 0, 100, 200 or 400 mg/kg once weekly.

In the 2-week repeat-dose toxicity study (G220016) in the cynomolgus test item-related findings were observed in one male only at the highest dose of 400 mg/kg. In clinical pathology, increased C-reactive protein (CRP) level, decrease of albumin to globulin (A/G) ratio and increased large unstained cell counts were observed. In microscopic examination, minimal sinusoidal increased cell of the liver and increased cellularity of the bone marrow were noted. These findings were considered CT-P59-related but not adverse since these were noted only in one male and they were not accompanied by degenerative changes. There was thymic atrophy in the microscopic findings which was associated with the decreased size and weight of the thymus and considered to be secondary changes caused by body weight loss or stress. Decreased albumin level was also considered to be a secondary change caused by decreased food consumption and body weight. In addition, decrease in red blood cell parameters, prolonged prothrombin time, 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 CT-P59 since the changes were minimal and there were no microscopic correlates. Based on the results, the NOAEL was considered to be 400 mg/kg/week in both sexes under this study condition.

In the 3-week repeat-dose toxicity (20251637) study in the cynomolgus 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.

CT-P59-related changes were observed in haematology parameters consisting of moderately to markedly decreased neutrophils associated with decreased white blood cell counts in some individual animals at all dose levels Days 8, 15, and/or 22. Among them, 3 animals had mildly to markedly increased monocytes and/or lymphocytes on Days 8 and/or 15. Monocyte and lymphocyte values

generally recovered by Day 22. During a 10-week recovery period, there were no CT-P59-related changes in haematology parameters at 400 mg/kg/dose, indicating complete recovery.

CT-P59-related changes in coagulation and clinical chemistry parameters 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 one animal each in the 100 mg/kg and 200 mg/kg dose groups.

Additionally, there were CT-P59-related changes for two animals at 400 mg/kg/dose on Days 8, 15, and/or 22 that were not observed for other animals including moderate to marked decrease in neutrophils with other changes in clinical pathology parameters; WBC counts, monocytes, red blood cell mass, reticultocytes, red cell distribution width, plateletcrit, platelet distribution width, prolonged activated partial thromboplastin time, fibrinogen, CRP, globulins, triglycerides, total bilirubin, A/G ratio, cholesterol, and/or calcium with no microscopic correlates. All changes were recovered following 10-week recovery period, indicating complete recovery. These observations were considered of no clinical relevance.

The markedly decreased neutrophil count, though fully reversible, were considered adverse based on the inherent related increased risk for infections rather than a direct high toxic effect and the NOAEL was considered to be 200 mg/kg/week.

No remarkable findings were reported from the macroscopic and microscopic examination of injection sites from all animals from both studies.

Systemic exposures of CT-P59 generally increased in a dose proportional manner. Mean Cmax values were 2800, 5570 and 9240 µg/mL in males, and 3090, 5370, and 10000 µg/mL in females at doses of 100, 200 and 400 mg/kg on Day 15, respectively. Mean AUC0-168h was 160000, 308000 and 454000 µg*hr/mL in males and 192000, 280000 and 535000 µg*hr/mL in females at doses of 100, 200 and 400 mg/kg on Day 15, respectively. Following repeated administration, no notable accumulation was observed on Day 15 compared to Day 1 (< 2 fold), with individual accumulation ratios ranging from 1.03 to 1.93 across the dose levels.

The applicant has presented exposure margins based on the exposure in patients (CT-P59 1.2) which has full data (up to Day 90) based on the recommended clinical single dosage for CT-P59 of 40 mg/kg and the lowest NOAEL from the non-clinical study with the highest number of 3 overall CT-P59 administrations and duration of 3 weeks. The exposure margins are approximately 4.5 and 5.6 based on AUC and Cmax, respectively.

2.4.3.3. Genotoxicity

Genotoxicity study was not conducted. This is in accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH, 2011), as it is not expected to have genotoxic potential.

2.4.3.4. Carcinogenicity

Carcinogenicity study was not conducted with CT-P59. This is in accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH, 2011), as it is not expected to have carcinogenic potential.

2.4.3.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity studies were not conducted with CT-P59. This is in accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH, 2011), since these types of antibodies are unlikely to cause reproductive or developmental toxicity.

2.4.3.6. Toxicokinetic data

Local tolerance at the injection site was assessed as part of the repeat-dose toxicity studies.

2.4.3.7. Local Tolerance

Local tolerance at the injection site was assessed as part of the repeat-dose toxicity studies. No remarkable findings were observed from the macro- and microscopic examination of injection sites from all animals.

2.4.4. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100 Corr 2), due to their nature monoclonal antibodies which are classified as proteins are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.4.5. Discussion on non-clinical aspects

Primary pharmacology

Overall, the pharmacological in-vivo studies demonstrated that regdanvimab is reasonably effective in reducing virus levels in various sampling locations - including lungs – if treatment is given 24h after infection. It should be noted that many of the studies were not designed (e.g., strength of infection, length of study) to let the animals develop strong infection symptoms (for instance in the hamster). As a result, the positive effects on the clinical symptoms in the different animal models remains unclear. The ferret study indicated that regdanvimab had positive effects both on general symptoms (e.g., coughs) and lung inflammation, but this study is not strong enough in its setup to support any strong conclusions - especially for the lung inflammation effects.

Secondary pharmacology

The in-vivo ADE study in hACE2 mouse was inconclusive. It can be noted that CT-P59 did not induced any ADE effect in in-vitro studies where SARS-CoV-2 were incubated with both permissive cells (VeroE6 cells) and Fc-bearing cells (Raji cells; FcγR II, U937 cells; FcγR I & II) in the presence of CT-P59. As a result, the ADE issue remains uncertain.

Tissue cross-reactivity (TCR) studies showed specific positive staining in meningeal arachnoid cap cells in the brain and spinal cord in tissues derived from human (adult and neonatal) and the cynomolgus monkey (adult). This location was not associated with any histopathology findings in the two adult cynomolgus 2 and 3-week long repeat-dose toxicity studies (see also Toxicology). There a number of other tissues stained but those findings were in endothelial cells (which are likely to have poor integrity in cryosection studies and therefore not relevant for antibody binding in-vivo) and in the cytoplasm of

cells in a number of other types of tissues and cells (also generally considered non-relevant due to poor in-vivo access). Sequencing data from Hamster and Rhesus macaque samples do no indicate that CT-P59 treatment generates novel SARS-CoV-2 variants with amino acid changes in the antibody-binding region.

Toxicology

Two repeat-dose toxicity studies, 2-and 3-week long, were conducted in the cynomolgus monkey using intravenous administration of regdanvimab at dose levels of 0, 100, 200 or 400 mg/kg once weekly.

In the 2-week study with IV infusion of regdanvimab once weekly there were no regdanvimab-related toxicological changes in mortality, clinical signs, body weight, food consumption, ophthalmology, ECG, haematology, coagulation, urinalysis, organ weights, macroscopic and microscopic observations at up to 400 mg/kg. Under the conditions of the study, the NOAEL was concluded to be 400 mg/kg.

In the 3-week study all animals survived for the study duration, and test article-related effects included changes in haematology, coagulation, and clinical chemistry parameters. In addition to moderately to markedly decreased neutrophils other changes in clinical pathology parameters were observed in two of the high dose animals (WBC counts, monocytes, red blood cell mass, reticultocytes, red cell distribution width, plateletcrit, platelet distribution width, prolonged activated partial thromboplastin time, fibrinogen, CRP, globulins, triglycerides, total bilirubin, A/G ratio, cholesterol, and/or calcium). These observations were considered of no clinical relevance. The markedly decreased neutrophils were deemed adverse based on increased risk for infection and the NOAEL was considered to be 200 mg/kg. The exposure margins are approximately 4.5 and 5.6 based on AUC and Cmax, respectively. Immunogenicity is discussed in the clinical section.

The lack of stand-alone local tolerance studies is endorsed. No specific injection site findings have been noted in the two repeat-dose toxicity studies performed with IV CT-P59.

No genotoxicity-, carcinogenicity- and DART studies have been conducted in line with ICH S6 guidance.

2.4.6. Conclusion on the non-clinical aspects

Overall, the non-clinical programme indicated that regdanvimab has a viral level reducing effect in animal models and is well tolerated. Toxicological findings were limited to changes in haematology, coagulation, and clinical chemistry parameters in high dose animals.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

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

No routine GCP inspection was conducted for this application and no issues and/or concerns that would warrant the need for a GCP inspection were identified in the course of the assessment of the clinical data submitted in support of the application. This is in addition to the listing of any GCP inspections conducted, with the respective reports, the standard statement that the Applicant claimed GCP compliance of all trials included in the application and the statement of compliance with Directive

2001/20/EC for trials conducted outside the EU.

- **Tabular overview of clinical studies**

Table 1: Overview of Clinical Study Program for CT-P59

Protocol No.	Population	Design	Objective(s)	Study Treatment	Status
CT-P59 1.1	HV Total: 32 • Cohort 1: 8 (CT-P59 10 mg/kg: 6, Placebo: 2) • Cohort 2: 8 (CT-P59 20 mg/kg: 6, Placebo: 2) • Cohort 3: 8 (CT-P59 40 mg/kg: 6, Placebo: 2) • Cohort 4: 8 (CT-P59 80 mg/kg: 6, Placebo: 2)	A Phase 1, Randomised, Double-blind, Placebo-controlled, Parallel Group, Single Ascending Dose Study to Evaluate the Safety, Tolerability and PK of CT-P59 in Healthy Subjects	**Primary Objective:** • To evaluate the preliminary safety and tolerability of CT-P59 up to Day 14 of the last enrolled subject **Secondary Objective:** • To evaluate the PK of CT-P59 • To evaluate additional safety of CT-P59 including immunogenicity	• Cohort 1: CT-P59 10 mg/kg or placebo on Day 1 • Cohort 2: CT-P59 20 mg/kg or placebo on Day 1 • Cohort 3: CT-P59 40 mg/kg or placebo on Day 1 • Cohort 4: CT-P59 80 mg/kg or placebo on Day 1	Completed Day 14 CSR completion: Sep 2020 Day 90 Final CSR completion: Jan 2021
CT-P59 1.2	Patients with mild symptoms of SARS-CoV-2 infection Total: 18 • Cohort 1: 6 (CT-P59 20 mg/kg: 5, Placebo: 1) • Cohort 2: 6 (CT-P59 40 mg/kg: 5, Placebo: 1) • Cohort 3: 6 (CT-P59 80 mg/kg: 5, Placebo: 1)	A Pilot Phase 1, Randomised, 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 SARS-CoV-2 Infection	**Primary Objective:** • To evaluate the preliminary safety and tolerability of CT-P59 up to Day 14 of the last enrolled patient **Secondary Objective:** • To evaluate the viral efficacy and characterisation of SARS-CoV-2 viral isolates • To evaluate the efficacy of CT-P59 • To evaluate the PK of CT-P59 • To evaluate additional safety of CT-P59 including immunogenicity	• Cohort 1: CT-P59 20 mg/kg or placebo with SoC on Day 1 • Cohort 2: CT-P59 40 mg/kg or placebo with SoC on Day 1 • Cohort 3: CT-P59 80 mg/kg or placebo with SoC on Day 1	Completed Day 14 CSR completion: Nov 2020 Final CSR (Day 180) completion: May 2021

Protocol No.	Population	Design	Objective(s)	Study Treatment	Status
CT-P59 3.2	Outpatients with SARS-CoV-2 Infection Part 1: 327 • CT-P59 40 mg/kg: 105 • CT-P59 80 mg/kg: 111 • Placebo: 111 Part 2: 1315 • CT-P59 40 mg/kg:656 • Placebo: 659	A Phase 2/3, Randomised, 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 SARS-CoV-2 Infection	**Primary Objective:** Part 1 Key Primary Objective • To assess the clinically meaningful therapeutic efficacy of CT-P59 as determined by proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 Supportive Primary Objective • To assess the potential therapeutic efficacy of CT-P59 as determined by time to clinical recovery up to Day 14 • To assess the potential therapeutic efficacy of CT-P59 as determined by time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture up to Day 14 • To assess the potential therapeutic efficacy of CT-P59 as determined by proportion of patients with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture at each visit up to Day 14 Part 2 • To demonstrate the clinically meaningful therapeutic efficacy of CT-P59 as determined by proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high risk patients **Key Secondary Objective:** Part 2 • To demonstrate the clinically meaningful therapeutic efficacy of CT-P59 as determined by	Part 1 • Treatment Group 1: CT-P59 40 mg/kg with SoC on Day 1 • Treatment Group 2: CT-P59 80 mg/kg with SoC on Day 1 • Treatment Group 3: Placebo with SoC on Day 1 Part 2 • Treatment Group 1: CT-P59 40 mg/kg with SoC on Day 1 • Treatment Group 2: Placebo with SoC on Day 1	For Part 1: Completed Part 1 Day 28CSR completion: Jan 2021 Final CSR (Day 180) completion: Aug 2021 For Part 2: Ongoing Part 2 Day 28 CSR completion: Jul 2021

Protocol No.	Population	Design	Objective(s)	Study Treatment	Status
			proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomised patients • To assess the potential therapeutic efficacy of CT-P59 as determined by time to clinical recovery up to Day 14 in high-risk patients • To assess the potential therapeutic efficacy of CT-P59 as determined by time to clinical recovery up to Day 14 in all randomised patients **Secondary Objective:** <u>Part 1 and Part 2</u> • To evaluate the additional efficacy of CT-P59 • To evaluate overall safety of CT-P59, including immunogenicity and potential effects on the incidence of ADE **Exploratory Objective:** <u>Part 1 and Part 2</u> • To assess the PK of CT-P59 (only for Part 1) • To assess the viral efficacy and genotype and phenotype of SARS-CoV-2 viral isolates • To assess the serology of SARS-CoV-2 antibody		

ADE: Antibody-dependent enhancement, HV: Healthy volunteers, PK: Pharmacokinetics, RT-qPCR: Reverse transcription-quantitative polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus, SoC: Standard of Care

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Regdanvimab is a human monoclonal IgG1 antibody with a molecular weight 145.9 kDa.
The drug product CT-P59 (Regkirona) is intended for single dose treatment in adults. The proposed therapeutic dose is 40 mg/kg administered as a single intravenous infusion over 60 minutes.

The pharmacokinetics of regdanvimab was assessed in all three submitted clinical studies using rich sampling schedules. No interaction studies, metabolism and excretion studies or dedicated studies in special populations were performed.

Methods

Analytical methods

For PK assessments, regdanvimab serum concentrations were quantitatively measured using a ligand-binding assay utilising MSD ECL platform. Biotinylated RBD and sulfo-tag labelled RBD were used as capture and detection reagents respectively, to measure the serum concentration of regdanvimab.

Immunogenicity testing followed a multi-tiered assay approach: (1) screening, (2) confirmation and (3) characterisation in terms of titration and neutralisation activity.

Anti-drug antibodies (ADA) against regdanvimab were determined using MSD ECL platform with Affinity Capture Elution (ACE) step. Biotinylated regdanvimab and sulfo-tag labelled regdanvimab were used as capture and detection reagents, respectively. Polyclonal anti-idiotypic antibody derived from rat immunised with regdanvimab were used as a surrogate positive control.

Neutralising activity of any ADA positives were characterised by a competitive ligand binding assay using MSD ECL platform with ACE step. RBD and sulfo-tag labelled regdanvimab were used as capture and detection reagents, respectively. Rat polyclonal anti-regdanvimab antibody was used as a surrogate positive control.

Pharmacokinetic analysis

The pharmacokinetic analysis and statistical methods used are considered adequate. Rich sampling for evaluation of the serum pharmacokinetics of regdanvimab was used in all three clinical studies. The PK was evaluated by non-compartmental analysis using Phoenix WinNonlin and parameter estimates were summarized by dose groups using descriptive statistics. No population PK analysis was performed, which is acceptable. CT-P59 is administered intravenously and is intended for single dose treatment only. As the indication does not include children, extrapolations are not applicable.

Absorption

CT-P59 is administered intravenously. Hence, the bioavailability is by definition 100% and absorption characteristics, including food effects, are not applicable. Following a single dose of 40 mg/kg in COVID-19 patients, the arithmetic mean (CV%) C_{max} level was 1017 µg/mL (26.5%).

Distribution

No plasma protein binding study was performed, which is considered acceptable.

The estimated volume of distribution (V_{ss}) was 83 mL/kg, indicating, as expected for a mAb, a limited distribution outside the blood compartment.

Elimination

The metabolism and excretion pathways of regdanvimab have not been investigated. This is acceptable. The clearance of regdanvimab from the body is likely through normal intracellular catabolism, following fluid-phase or receptor-mediated endocytosis, as observed for mAbs in general.

The clearance of regdanvimab was low, 0.2 mL/h/kg. Serum concentrations appeared to decline in a multi-phasic manner with a terminal half-life of 17 days. The pharmacokinetics was very similar in patients and healthy volunteers.

Dose proportionality and time dependencies

CT-P59 is to be administered as a single dose only so time dependency is not applicable.

Dose proportionality was assessed in all clinical studies. The exposure of regdanvimab appeared to increase in an approximately dose-proportional manner over the investigated range 10 to 80 mg/kg.

Special populations

Hepatic and renal impairment

Specific clinical pharmacology studies to evaluate the effect of renal impairment and hepatic impairment on the PK of CT-P59 have not been conducted. This is acceptable. As a monoclonal antibody regdanvimab is likely to be eliminated via proteolytic degradation to amino acids and hence not anticipated to be metabolized by CYP450 enzymes or cleared by renal excretion.

Elderly

Of the 327 patients with SARS-CoV-2 infection randomised in Study CT-P59 3.2, 16.5% were 65 years or older, and 3.06% were 75 years of age or older. Based on pharmacokinetic subgroup analyses, there is no difference in PK of regdanvimab in elderly patients compared to younger patients.

Children

The PK of regdanvimab in paediatric patients have not been evaluated. This is acceptable since Regdanvimab is not recommended for paediatric patients at the moment. This is reflected in the SmPC: *"The pharmacokinetics of regdanvimab in paediatric patients has not been evaluated".*

Weight, gender and race

No dose adjustment is currently proposed based on weight, gender or race. This has been adequately justified.

Pharmacokinetic interaction studies

No interactions studies have been performed which is acceptable. Regdanvimab is not expected to be renally cleared or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Concomitant administration of regdanvimab with COVID-19 vaccines has not been studied.

Pharmacokinetics in healthy volunteers

Study CT-P59 1.1 is a completed first-in-human study in healthy volunteers in which the PK of regdanvimab was determined at four dose levels, i.e. 10, 20, 40 and 80 mg/kg with N=6 subjects per group. Samples for PK evaluation were drawn up to Day 90 after dose.

The results showed that regdanvimab have pharmacokinetic characteristics typical for an IgG monoclonal antibody, i.e. a low clearance, a small volume of distribution and a long terminal half-life. The serum exposure (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) increased in proportion to dose in the investigated dose interval with no indication of target-mediated drug disposition. The inter-individual variability (CV%) was low to moderate; for clearance 12-24% and for the volume of distribution 8-15%.

The mean PK estimates in healthy subjects at the proposed therapeutic dose 40 mg/kg were: CL 18.46 mL/h (*ca* 0.2 mL/h/kg), V_{ss} 99 mL/kg and $t_{1/2z}$ 398.6 hours (*ca* 17 days).

There were no samples that tested positive for ADA.

Pharmacokinetics in the target population

Study CT-P59 1.2 is a completed Phase 1 pilot study in patients with mild COVID-19 in which the PK of regdanvimab is evaluated at three dose levels, i.e. 20, 40 and 80 mg/kg with N=5 patients per group. Samples for PK evaluation were drawn up to Day 90 after dose.

The mean parameter estimates at the proposed therapeutic IV single dose of 40 mg/kg were very similar to those in healthy volunteers, i.e. CL 17.46 mL/h (*ca* 0.23 mL/h/kg), V_{ss} 102 mL/kg and $t_{1/2z}$ 380.8 hours (16 days).

Of the 18 immunogenicity samples, one pre-dose sample produced a confirmed positive ADA result but was negative for anti regdanvimab neutralising antibodies (NAb).

Study CT-P59 3.2 is a completed Phase 2/3 study in patients with mild to moderate COVID-19. The PK set included 29 and 32 patients in the 40 and 80 mg/kg dose group, respectively. Samples for PK evaluation were drawn up to Day 90 after dose.

The arithmetic mean peak exposure at respective dose level was 1017 μg/mL (40 mg/kg) and 2008 μg/mL (80 mg/kg) and occurred at 2 hours after start of infusion. The corresponding $AUC_{0-\infty}$ exposure was 212461 and 426695 μg·h/mL, respectively. The serum concentrations of regdanvimab appeared to decline in a multi-phasic manner with a mean $t_{1/2z}$ of 17 to 19 days.

In accordance with dose proportionality, the mean clearance was independent of dose, i.e. 0.20 mL/h/kg at both dose levels. There was no indication of target-mediated drug disposition.

The arithmetic mean (CV%) parameter estimates at the proposed therapeutic IV single dose of 40 mg/kg were: CL 0.20 mL/h/kg (24%), V_{ss} 83 mL/kg (26%) and $t_{1/2z}$ 17 days (37%), i.e. very similar to those in Study CT-P59 1.1 and 1.2.

In part 1, the proportion of patients with positive conversion in ADA at post-treatment visits were 3/101 (3.0%) in the CT-P59 40 mg/kg treatment group, 8/109 (7.3%) patients in the CT-P59 80 mg/kg treatment group and 6/108 (5.6%) patients in the Placebo group. The proportion of patients with positive conversion in Nab at post-treatment visits were none in the CT-P59 treatment groups and 3/110 (2.7%) patients in the Placebo group.

In part 2, the proportion of patients with positive conversion in ADA at post-treatment visits up to Day 28 visit were 10/635 (1.6%) patients in the CT-P59 40 mg/kg treatment group and 15/619 (2.4%) patients in the Placebo group.

2.5.2.2. Pharmacodynamics

Mechanism of action

Coronavirus entry into host cells via binding to the angiotensin converting enzyme 2 (ACE2) receptor in alveolar cells and intestinal epithelia is an important determinant of viral infectivity and pathogenesis. The main mechanism of action of regdanvimab is blocking the binding between SARS-CoV-2 spike protein RBD and the cellular receptor, ACE2, thus blocking the SARS-CoV-2 infection. In vitro assessment of Fc-mediated Function for antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) were evaluated, and there was no evidence suggesting that

regdanvimab is able to mediate Fc-related activities. Epitopes of regdanvimab were mapped by X-ray crystallography, indicating that the interaction of regdanvimab to RBD directly occludes the binding surface of ACE2. Also, key residues of regdanvimab binding to RBD were identified by alanine scanning assay.

Primary and Secondary pharmacology

Primary pharmacodynamics in-vitro studies

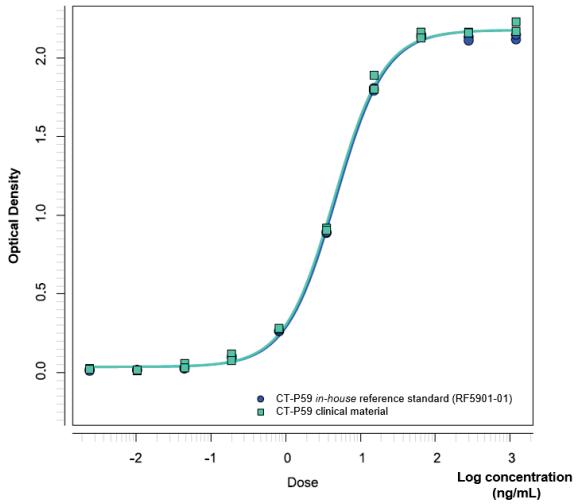
Binding affinity of CT-P59 to RBD of SARS-CoV-2 by ELISA and surface plasmon resonance

The dose-dependent binding of CT-P59 clinical batch (Lot No. 20100V001) to RBD was found as shown in the half-maximal effective concentration (EC50) of CT-P59 to SARS-CoV-2 RBD protein was 4.4 ng/mL and relative binding affinity against in-house reference standard (RF5901-01) was 105%.

Table 2: SARS-CoV-2 RBD Binding Affinity of CT-P59 by ELISA

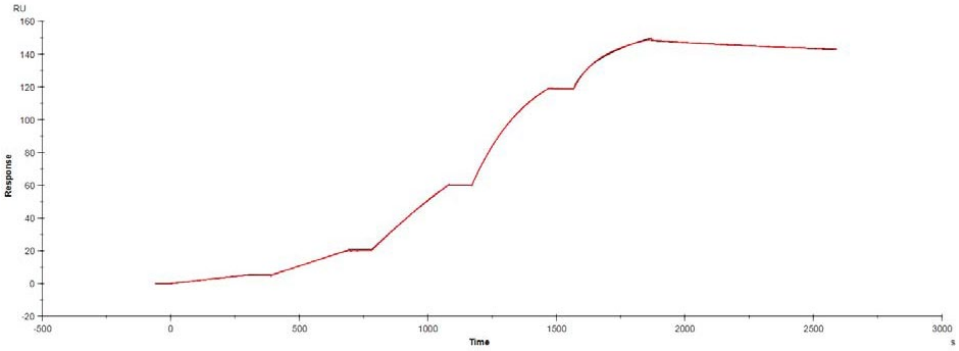
Lot No.	EC50 (ng/mL) / Log concentration (ng/mL)	Relative binding affinity (%)
RF5901-01	4.6810 / 0.67034	100
20100V001	4.4397/0.64735	105

Figure 1: SARS-CoV-2 RBD Binding Affinity of CT-P59 by ELISA



Five concentrations of CT-P59 process validation batch (Lot No. 20110V001) were serially injected and dissociated then the dissociation constant was evaluated by sensorgram fitting using the kinetic model (bivalent analyte). The binding affinity (KD) of CT-P59 for the RBD was calculated as 6.5E-11 M.

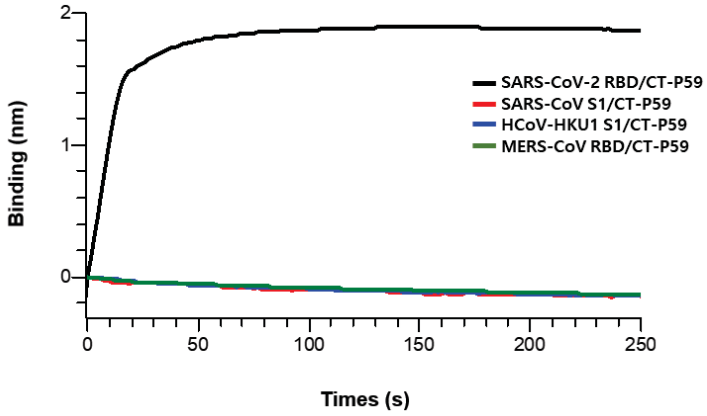
Figure 2: SARS-CoV-2 RBD Binding Affinity of regdanvimab by SPR (Sensorgram of 1st run)



Binding specificity of regdanvimab by biolayer interferometry (BLI)

Binding specificity of regdanvimab was measured with four different RBD and S1 proteins from closely related beta-coronaviruses (SARS-CoV-2 RBD, SARS-CoV S1, HCoV-HKU1 S1, MERS-CoV RBD) by BLI. Regdanvimab could bind specifically to SARS-CoV-2 RBD but could not bind to other coronaviruses.

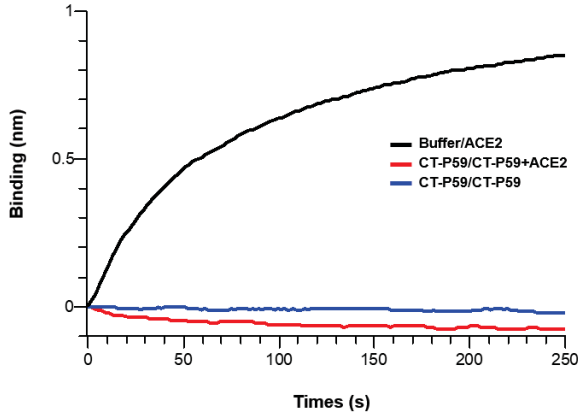
Figure 3: Binding Specificity of regdanvimab to various coronaviruses by biolayer interferometry



Inhibitory effect of regdanvimab on the interaction between SARS-CoV-2 RBD and ACE2 by biolayer interferometry (BLI)

Once SARS-CoV-2 RBD is saturated by regdanvimab, there were no responses even in the presence of hACE2 (Figure below). This suggests that regdanvimab completely inhibits binding of hACE2 to SARS-CoV-2 RBD.

Figure 4: Inhibition of Binding between SARS-CoV-2 RBD and ACE2 by regdanvimab

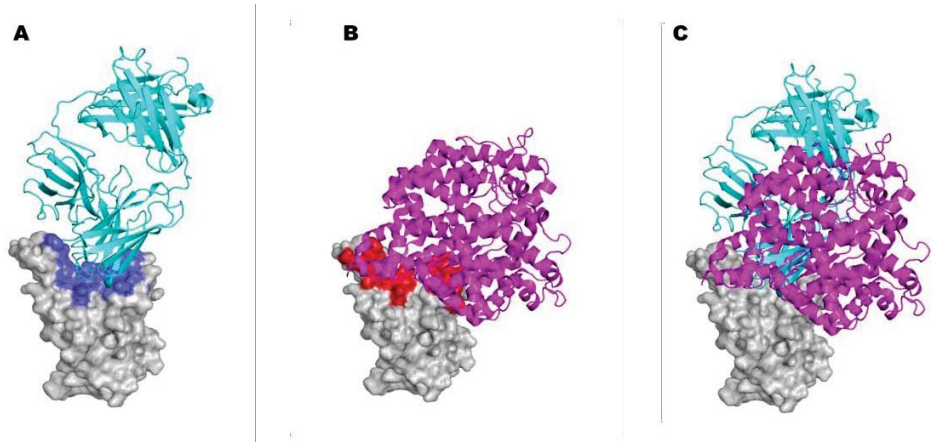


Epitope mapping by X-ray crystallography

The regdanvimab/SARS-CoV-2 RBD complex crystal structure showed that the epitope residues on SARS-CoV-2 RBD substantially overlap with the ACE2 binding region suggesting that regdanvimab competes with ACE2 for the binding to SARS-CoV-2 RBD. Among the 21 residues of RBD that interact with ACE2, 12 residues are also involved in the interaction with regdanvimab, when a distance cut-off of 4.5 Å is applied (see Figures below).

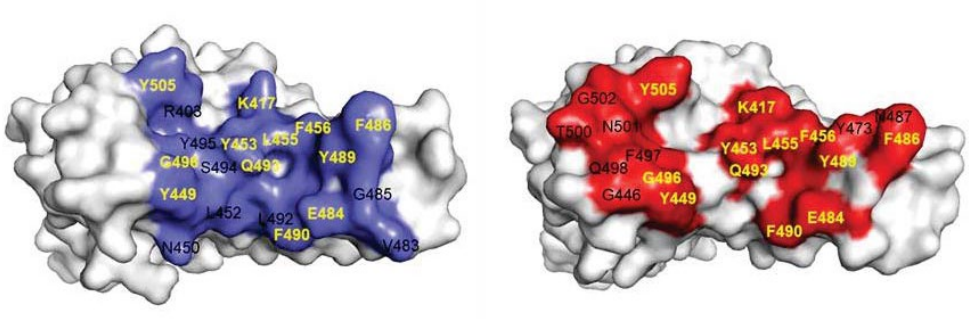
Regdanvimab mainly uses the CDR2 and CDR3 of the heavy chain for the interaction with SARS-CoV-2 RBD. The paratope consists of heavy chain (S32 of HCDR1; D54, W55, D56, D57, N58, Y60 of HCDR2; P101, G102, L104, R105, Y106, R107, R109, Y111, Y113 of HCDR3) and light chain (Y33 of LCDR1; Y50 and D51 of LCDR2). These observations indicate that the binding of regdanvimab to RBD directly occludes the binding surface of ACE2.

Figure 5: Structural comparison of SARS-CoV-2 RBD in complexed with CT-P59 versus ACE2.



(A) Crystal structure of the CT-P59 Fab (cyan) bound to the SARS-CoV-2 RBD (gray). Epitope residues on SARS-CoV-2 RBD are shown in light blue. (B) Crystal structure of the ACE2 (purple) bound to the SARS-CoV-2 RBD (gray) obtained from PDB code, 6LZG (Wang et al., (2020)). ACE2 interaction residues on SARS-CoV-2 RBD are shown in red. (C) Structural superposition of CT-P59/SARS-CoV-2 RBD and ACE2/SARS-CoV-2 RBD. Notable steric hindrance between CT-P59 and ACE2 are observed.

Figure 6: Comparison of RBD interfaces interacting with CT-P59 (left) and ACE2 (right).

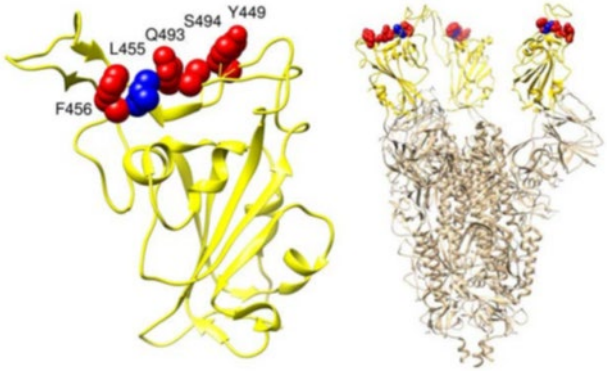


The residues interacting with CT-P59 and ACE2 are coloured in blue and red, respectively. The residues interacting both CT-P59 and ACE2 are labelled in yellow letters.

Determination of critical residues of SARS-CoV-2 RBD for binding to CTP59 by alanine scanning assay

Critical residues were identified by alanine scanning assay. This result indicates that 5 SARS-CoV-2 RBD residues were identified as critical for binding by regdanvimab of Y449, L455, F456, Q493, and S494. RBD residues Y449, F456, Q493, and S494 were the major contributors to mAb binding, with L455 having secondary importance.

Figure 7: Critical Residues of SARS-CoV-2 RBD for CT-P59 Binding



In vitro Antibody-dependent cellular cytotoxicity (ADCC)

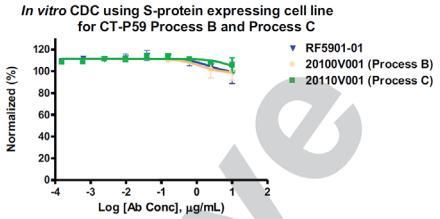
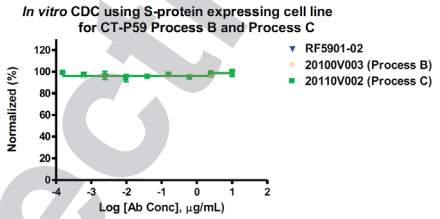
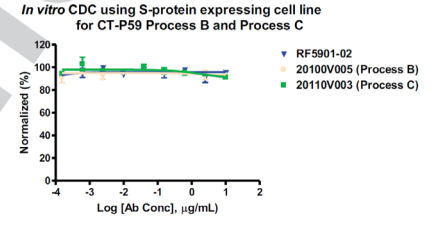
The results show that the maximum cytotoxicity of Regdanvimab was less than 15%, that is a very low level in comparison to other therapeutic monoclonal antibodies where the major mechanism of action is *via* ADCC activity.

In conclusion, it is agreed that ADCC is not contributing significantly to the overall activity of Regdanvimab.

Complement-dependent cytotoxicity (CDC)

When measuring CDC activity by regdanvimab normalized against the negative control (regdanvimab untreated) it was confirmed that none of the batches tested induced any significant *in vitro* CDC activity of target cells when incubated with complement, suggesting that CDC is unlikely to be a MoA of regdanvimab.

Figure 8: In vitro complement-dependent cytotoxicity for regdanvimab

20100V001 (Process B) vs. 20110V001 (Process C)	 *Normalization (%) was determined against the negative control (CT-P59 untreated).
20100V003 (Process B) vs. 20110V002 (Process C)	 *Normalization (%) was determined against the negative control (CT-P59 untreated).
20100V005 (Process B) vs. 20110V003 (Process C)	 *Normalization (%) was determined against the negative control (CT-P59 untreated).

Other Fc-mediated functions

The test results of these additional Fc-mediated functions of regdanvimab are summarized in the Table below. Regdanvimab had essentially undetectable levels of Fc-mediated activity in these assays in comparison with the positive control (CR3022 antibody, and convalescent plasma) and negative control (KZ52 antibody).

Table 3: Fc-mediated functions of regdanvimab

	ADCP [3] (Phagocytic Score)	ADNP [4] (Phagocytic Score)	ADCD [5] (MFI C3)	ADNKA % [6] CD107a+	ADNKA % [6] MIP-1β+
CT-P59	6,951	1,921	5,410	5	17
CR3022 [1]	21,240	3,870	6,544	3	11
KZ52 [2]	7,243	1,418	3,614	3	10
Convalescent plasma 1	25,642	56,544	71,106	19	32
Convalescent plasma 2	28,148	55,725	37,882	4	7

[1] Human monoclonal antibody to SARS-CoV-2 Spike Glycoprotein S1. This antibody binds the amino acids 318-510 in the S1 domain of the SARS-CoV Spike protein as well as SARS-CoV-2 (COVID-19) Spike protein. The antibody also binds to P462L-substituted S318–510 fragments of the SARS spike protein. The binding epitope is only accessible in the "open" conformation of the spike protein (Joyce et al. 2020)

[2] Human Anti-EBOV GP Antibody (KZ52) (CAT#: PABC-039). Recombinant Human Antibody (KZ52) is capable of binding to EBOV GP, expressed in HEK 293 cells. This antibody neutralizes Zaire ebolavirus in vitro and offers protection from lethal EBOV challenge in rodent models, but has minimal effects on viral pathogenicity in non-human primates.

[3] Antibody dependent cellular phagocytosis

[4] Antibody dependent neutrophil-mediated phagocytosis

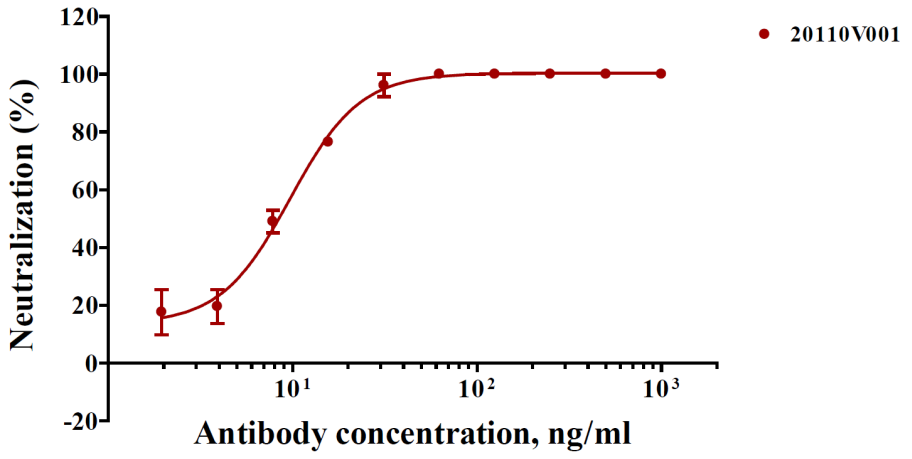
[5] Antibody dependent complement deposition

[6] Antibody dependent NK activation

Evaluation of the Neutralising Effect of Regdanvimab against Wild Type Virus

The neutralising ability of representative regdanvimab against wild type SARS-CoV-2 virus (BetaCoV/Korea/KCDC03/2020) was determined by an *in vitro* plaque reduction neutralisation test (PRNT). The half maximal inhibitory concentration (IC_{50}) and 90% of inhibitory concentration (IC_{90}) of regdanvimab toward SARS-CoV-2 is determined as 9.70 ng/mL and 25.09 ng/mL, respectively.

Figure 9: Neutralising Activity of Regdanvimab against Wild Type SARS-CoV-2 by In Vitro PRNT



Evaluation of the Neutralising Effect of Regdanvimab Against *In Vitro* Escape Mutants

Generation and genotyping of potential escape mutants by regdanvimab in vitro

In vitro virus passaging was performed with SARS-CoV-2 viruses in the presence/absence of

regdanvimab (Jianhua Sui et al., 2014[1]). Four plaques (the 4th passage) were observed at the 1 µg concentrations of regdanvimab. The spike gene of the four plaques at the 4th passage were sequenced and compared to wild type viruses. Comparative sequence analysis showed double mutations (S494P+R685H) in all escape viruses. Whilst amino acid 494 is located in the RBD, amino acid 685 is located in S1/S2 cleavage site.

Neutralisation activity of regdanvimab against escape mutant by PRNT

To determine the ability of regdanvimab to neutralize the escape mutants, the plaque reduction neutralisation test (PRNT) was conducted using mutant viruses and control virus. The control virus was in parallel passaged without regdanvimab. VeroE6 cells were infected with viruses in the presence of regdanvimab concentrations from 1 to 0.98 x 10^{-3} µg/ml. Neutralisation was assessed by calculating IC_{50} and the results are described in the Table below. The results suggest that even at high concentration (1 µg/ml), regdanvimab was unable to neutralise the escape virus.

Table 4: IC_{50} Values of regdanvimab against the escape virus

Virus	Spike sequence	IC_{50} (ng/mL)
Control virus	S494, R685	7.4
Escape virus	P494, H685	n/c

n/c: not calculated (> 1 µg/ml)

Evaluation of the Neutralising Effect against Newly Emerging Mutant SARS-CoV-2 viruses by PRNT

The neutralizing ability of regdanvimab against newly emerging variants of SARS-CoV-2 viruses was determined by an in vitro PRNT using authentic virus in Korea Centers for Control and Disease Control & Prevention (KCDC). Variants were tested with three different batches of regdanvimab.

Comparable neutralizing activity determined by PRNT was observed against UK (Alpha, B.1.1.7), Brazil (P.2), New York (Iota, B.1.526) and Nigeria (Eta, B.1.525) variants compared to the wild type. Regdanvimab had reduced neutralising activity against Brazil (Gamma, P.1), South Africa (Beta, B.1.351), California (B.1.427 and B.1.429) and India (Kappa B.1.617.1 and Delta, B.1.617.2) variants. The IC50 fold reductions relative wild type ranged between 24-310 with the largest change observed for the Beta and Delta variants with 310- and 183-fold reduction respectively.

[1] Jianhua Sui, et al. Effects of Human Anti-Spike Protein Receptor Binding Domain Antibodies on Severe Acute Respiratory Syndrome Coronavirus Neutralization Escape and Fitness, Journal of Virology Oct 2014, 88 (23) 13769-13780; DOI: 10.1128/JVI.02232-14

Table 5: IC50 and IC90 Values of Regdanvimab against Variants from Plaque Reduction Neutralization Test

No.	Virus	Clade	Lineage RBD mutation	IC_{50} (ng/mL)	Fold Reduction	IC_{90} (ng/mL)	Fold Reduction
Wild Type (Lot No.5911009)							
	BetaCoV/Korea/KCDC03/2020*	S	n/a	6.76	n/a	28.09	n/a
UK Variant (Lot No. 20100V001)							
A	hCoV-19/South Korea/KDCA0838/2020	GR	B.1.1.7	3.77	0.56	40.86	1.45
Brazil Variants (Lot No. 20100V001)							
B	hCoV-19/Korea/KDCA95637/2021	GR	P.1	1135	167.90	8272	294.48
C	hCoV-19/Korea/KDCA72731/2021	GR	P.2	14.62	2.16	62.29	2.22
South African Variant (Lot No. 20110V001)							
D	hCoV-19/South Korea/KDCA0463/2020	GH	B.1.351	2096	310.06	16550	589.18
California Variants (Lot No. 20110V001)							
E	hCoV-19/Korea/KDCA49671/2021	GH	B.1.427	499.5	73.89	3534	125.81
F	hCoV-19/Korea/KDCA59777/2021	GH	B.1.429	365.6	54.08	4324	153.93
New York Variant (Lot No. 20110V001)							
G	hCoV-19/Korea/KDCA82438/2021	G	B.1.526	22.55	3.34	76.01	2.71
Nigeria Variant (Lot No. 20110V001)							
H	hCoV-19/Korea/KDCA79765/2021/	G	B.1.525	16.02	2.37	41.22	1.47
Indian Variant (Lot No. 20110V001)							
I	hCoV-19/Korea/KDCA2950/2021	G	B.1.617.1	161.5	23.89	648	23.07
J	hCoV-19/Korea119861/KDCA/2021	G	B.1.617.2	1237	182.99	2093	309.62

*IC50 and IC90 of the wild type was used to calculate fold reduction of each variant.

Evaluation of the Neutralising Effect against Newly Emerging Mutant SARS-CoV-2 viruses by Micro-neutralisation Assay

In addition to the neutralisation studies conducted in KCDC, additional studies to assess the ability of regdanvimab to neutralise mutant SARS-CoV-2 viruses by an *in vitro* micro-neutralisation assay, using VeroE6 cells in Viroclinics. Three-fold serial dilutions from 1 to 10000 ng/mL of regdanvimab were incubated with approximately 100 infectious units of viruses/well and infected the VeroE6 cells.

Regdanvimab showed comparable neutralizing ability against UK variant compared to the wild type while reduced neutralising activity against SA and Brazil P.1 variants were observed. The IC_{50} was calculated according to the method described earlier (Zielinska et al., 2005).

Table 6: IC_{50} Values of CT-P59 against Variants from Micro-Neutralization Assay

Virus	Lineage	Geometric Mean IC_{50} (ng/mL)	Fold Reduction
BavPat1/2020	B.1	2.0	n/a
UK variant	B.1.1.7	2.8	1.4
SA variant	B.1.351	39.5	19.75
Brazil variant	P.1	275.75	137.88

n/a: not applicable, SA: South Africa, UK: United Kingdom

Evaluation of the Neutralising Effect against SARS-Cov-2 Variants and Potential Escape Mutants Using an In Vitro Pseudovirus Assay (virus-like particle (VLP) assay)

To analyse the effect of regdanvimab against variants and potential escape viruses, luciferase-based pseudovirus assay was carried out using wild-type and mutant spike-expressing lentiviruses. Mutations in spike gene were introduced by gene cloning method and its protein expression was confirmed by Western blot analysis. The pseudoviruses were produced by transfection with luciferase reporter plasmid along with Gag-Pol, Rev, and Spike expression plasmid and then the copy number of pseudoviruses was quantitated by qPCR. Pseudoviruses were mixed with diluted antibodies ranging from 100 to 0.005 ng/mL. The inocula infected ACE2-expressing HEK293T cells. After 72 h, luciferase activities were measured and IC_{50} values were calculated.

Table 7: IC_{50} Values of Regdanvimab from Pseudovirus Assay

	Spike Mutation	Wild-type IC_{50} (ng/mL)	Mutation IC_{50} (ng/mL)	Fold Reduction
Geographic Variants	69del+70del+144del+N501Y+A570D+ D614G+ P681H+T716I+S982A+D1118H [1]	0.219	0.625	2.85
	L18F+D80A+D215G+241del+242del+243del +K417N+E484K+N501Y+D614G+A701V [2]	0.219	40.360	184.29
	L18F+T20N+P26S+D138Y+R190S+K417T+E484K+ N501Y+D614G+H655Y+T1027I+V1176F [3]	0.219	13.450	61.42
	L452R+T478K+P681R [4]	0.219	21.520	98.26
	S13I+W152C+L452R+D614G [5]	0.219	6.819	31.14
	A67V+69del+70del+144del+E484K+D614G+ Q677H+F888L [6]	0.219	1.581	7.22
	L5F+T95I+D253G+E484K+D614G+A701V [7]	0.219	1.497	6.84
	L452R+E484Q+P681R [8]	0.219	11.080	50.59
	69-70 del [1, 6]	0.219	0.268	1.22
	69-70 del + N501Y [1]	0.219	0.533	2.43
	D80A [2]	0.219	0.372	1.70
	A222V [4]	0.352	0.410	1.16
	K417N [2]	0.219	0.186	0.85
	K417N+E484K+N501Y [2]	0.219	36.590	167.08
	K417T [3]	0.219	0.154	0.70
	N439K [6]	0.352	0.332	0.94
	L452R [4, 5, 7, 8]	0.378	13.220	34.97
	S477N [7]	0.352	0.362	1.03
	T478K [4]	0.219	0.213	0.97
	E484K [1, 2, 3, 6, 7, 9]	0.378	3.273	8.66
	N501Y [1, 2, 3]	0.219	1.202	5.49
	D614G [1, 2, 3, 4, 5, 6, 7, 8, 9]	0.378	0.352	0.93
	Q677H [6]	0.219	0.226	1.03
	P681H [1]	0.219	0.392	1.79
	A701V [2, 7]	0.219	0.381	1.74

	Spike Mutation	Wild-type IC_{50} (ng/mL)	Mutation IC_{50} (ng/mL)	Fold Reduction
	V1176F [3]	0.352	0.319	0.91
Potential Mutants associated with CT-P59 epitope	K417E	0.219	0.156	0.71
	Y449N	0.378	8.556	22.63
	Y453F	0.352	0.227	0.64
	L455F	0.378	10.490	27.75
	F456L	0.378	0.342	0.90
	F486I	0.219	4.485	20.48
	F486L	0.219	0.792	3.62
	F486S	0.219	0.608	2.78
	F486V	0.219	9.900	45.21
	Y489H	0.219	0.434	1.98
	F490S	0.378	0.873	2.31
	Q493A	0.219	1.352	6.17
	Q493K	0.378	n/c	n/c
	Q493M	0.219	0.830	3.79
	Q493R	0.219	n/c	n/c
	Q493Y	0.219	0.270	1.23
	S494L	0.219	n/c	n/c
	S494Q	0.219	153.400	700.46
***In vitro* CT-P59 driven escape mutants**	S494P+R685H	0.378	n/c	n/c
	S494P	0.378	n/c	n/c
	R685H	0.378	0.442	1.17
Therapeutic antibodies related mutants	N234Q	0.378	0.594	1.57
	E406Q	0.378	1.521	4.02
	E406W	0.219	3.006	13.73
	N440D	0.219	0.398	1.82
	K444Q	0.378	0.397	1.05
	V445A	0.378	0.676	1.79
	A475V	0.378	0.243	0.64
Other	A372V	0.219	0.305	1.39
	P384L	0.219	0.370	1.69
	D420N	0.219	0.592	2.70
	G446V	0.219	0.457	2.09
	G447R	0.219	4.901	22.38
	N460T	0.219	0.255	1.16
	Y473F	0.219	0.400	1.83
	G476S	0.219	0.374	1.71
	E484G	0.219	0.564	2.58
	Q498H	0.219	0.694	3.17

	Spike Mutation	Wild-type IC_{50} (ng/mL)	Mutation IC_{50} (ng/mL)	Fold Reduction
	N501T	0.219	0.085	0.39
	N501F	0.219	1.044	4.77

n/c: not calculated (IC_{50}: > 500 ng/mL)
[1] Involved in variants including UK variant (Alpha)
[2] Involved in variants including South African variant (Beta)
[3] Involved in variants including Brazilian variant (Gamma)
[4] Involved in variants including Indian variant (Delta)
[5] Involved in variants including Californian variant (Epsilon)
[6] Involved in variants including Nigerian variant (Eta)
[7] Involved in variants including New York variant (Iota)
[8] Involved in variants including Indian variant (Kappa)
[9] Involved in variants including Brazilian variant (Zeta)

Results showed that spike mutations involved in the virus variants Beta, Gamma and Kappa led to increased IC_{50} values compared to the original type. S494P, S494L, Q493R and Q493K mutations showed IC_{50} values above 500 ng/ml. Substitutions tested and associated with >20-fold but <100 fold-change include Y449N, L452R and L455F.

Evaluation of the Neutralising Effect against Globally Emerging Variants by Pseudovirus Assay (performed by the National Institute of Health)

To examine the effect of regdanvimab against globally emerging variants: Variants of Concern (VOC) including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2) in addition to variants of Interest (VOI) such as Kappa (B.1.617.1) and Lambda (C.37) variants, a pseudovirus assay was performed using wild-type and mutant spike-expressing luciferase reporter lentiviruses at National Institute of Health (NIH) (Neerukonda et al., 2021). Most variants showed a reduction in IC_{50} fold change compared to wildtype, see table below.

Table 8: IC_{50} Values of Regdanvimab against Globally Emerging Variants from Pseudovirus Assay (performed by NIH)

Antibody Lot#	Viruses (lineage)	Mutations	Wild-type IC_{50} (ng/mL)	Mutation IC_{50} (ng/mL)	Fold Reduction
59010029	Alpha (B.1.1.7)	69-70 del/144 del/N501Y/A570D/D614G/P681H/ T716I/S982A/D1118H	0.4530	0.9509	2.10
59010029	Beta (B.1.351)	D80A/D215G/241-243 del/K417N/E484K/N501Y/ D614G/A701V	0.4029	102.0000	253.16
59010029	Gamma (P.1)	L18F/T20N/P26S/D138Y/R190S/K417T/E484K/ N501Y/D614G/H655Y/T1027I/V1176F	0.5074	64.6900	127.49
20100V001	Delta (B.1.617.2)	T19R/G142D/E156G/157 del/158 del/L452R/T478K/ D614G/P681R/D950N	0.6177	17.1100	27.70
20100V001	Delta-plus (AY.1)	T19R/T95I/G142D/E156G/157 del/158 del/W258L/ K417N/L452R/T478K/D614G/P681R/D950N	0.5555	35.3600	63.65
20100V001	Kappa (B.1.617.1)	T95I/G142D/E154K/L452R/E484Q/D614G/P681R/ Q1071H	0.5324	23.5000	44.14

Antibody Lot#	Viruses (lineage)	Mutations	Wild-type IC_{50} (ng/mL)	Mutation IC_{50} (ng/mL)	Fold Reduction
20100V001	Lambda (C.37)	G75V/T76I/246-252 del/D253N/L452Q/F490S/ D614G/T859N	0.7270	11.2700	15.50
20100V001	Mu (B.1.621)	T95I/Y144S/Y145N/R346K/E484K/N501Y/ D614G/P681H/D950N	0.5032	19.4500	38.65

The IC_{50} values obtained from the two *in vitro* pseudovirus assay studies differed, potentially due to different experimental procedures. However, the neutralising effect of regdanvimab against key substitutions involved in South Africa (Beta), Brazil (Gamma) and Indian (Kappa) variants was reduced to varying degrees in both assays.

In the first pseudovirus assay mentioned above the combination of key substitutions involved in the Delta variant is not included, in the second assay performed by the NIH the fold reduction for the Delta variant is 27.7. In the SmPC it is indicated that the fold reduction in the pseudovirus assay is 27.70 for B.1.617.2 (India). The Applicant used the IC50 values determined in the Mlcochova et al.'s study, to calculate neutralizing effect against the Delta variant of FDA EUA approved mAb treatments taking into consideration its IC50 value and administration dosage. The Applicant concluded that because of the comparatively higher clinical dosage (40 mg/kg) of CT-P59 compared to other mAbs, but also with similar pharmacokinetics expected with IgG1 monoclonal antibodies, the partial reduction in neutralisation seen with CT-P59 against the current VoCs and VoIs is not expected to impact clinical efficacy at the proposed dose (40 mg/kg) of CT-P59 given to the patients.

The serum and estimated lung concentration at 96h post dose assuming 15% lung penetration are approximately 380000 ng/mL and 57000 ng/mL, respectively. At a more conservative estimate of 5% lung concentration, the 96h lung concentration would be approximately 19000 ng/mL. Thus, concentrations of regdanvimab in lungs would be estimated above the IC90 in vitro for all listed virus variants during the presumably crucial initial treatment phase. However, the (plasma or lung concentration/ in vitro susceptibility) quotient required for clinical efficacy has not been characterized. Furthermore, it is not clear that this is similar for all VOC's, given e.g., differences in viral replication rates.

In summary, PK/PD is compatible with clinical activity against the delta variant, and an ACE2 transgenic mouse animal model is supportive of such activity.

Evaluation of Binding Affinity to Wild Type and Mutant RBD Protein of SARS-CoV-2 by BLI

The binding affinity of regdanvimab to wild type and mutant SARS-CoV-2 RBDs was measured by BLI using the Octet OKe system (ForteBio). Each RBD (50 nM) was immobilized onto Anti-Penta-HIS Biosensor (ForteBio), and then regdanvimab was flowed with various concentrations (10 nM, 5 nM, 2.5 nM and 1.25 nM) for 10 min and 15 min to generate association curve and dissociation curve, respectively. The results of the binding affinity (KD) to a total of 71 mutant RBDs are presented in the Table below.

The binding affinity of regdanvimab to mutant SARS-CoV-2 RBDs involved in the California (B.1.427 and B.1.429), South Africa (Beta, B.1.351), Indian (Kappa B.1.617.1 and Delta, B.1.617.2) and Brazil (Gamma, P.1) variants was lower compared to wild type.

Table 9: Binding Affinity of Regdanvimab to Wild Type and Mutant RBD by BLI

No.	RBD mutant[1]	K_D (M)	No.	RBD mutant	K_D (M)
1	P337S	7.68 E-11 (WT: 5.99 E-11)	2	G446S	6.11 E-11 (WT: 7.25 E-11)
3	F338L	6.04 E-11 (WT: 5.99 E-11)	4	**L452R[2]**	4.71 E-10 (WT: 5.10 E-11)
5	V341I	5.75 E-11 (WT: 3.95 E-11)	6	Y453F	7.24 E-11 (WT: 9.33 E-11)
7	F342L	5.76 E-11 (WT: 4.72 E-11)	8	F456L	7.57 E-11 (WT: 7.25 E-11)
9	A344S	7.43 E-11 (WT: 5.99 E-11)	10	K458R	4.25 E-11 (WT: 4.72 E-11)
11	A348S	6.24 E-11 (WT: 5.99 E-11)	12	E471Q	5.84 E-11 (WT: 3.95 E-11)
13	A352S	9.94E-11 (WT: 1.02 E-10)	14	I472V	4.97 E-11 (WT: 3.95 E-11)
15	N354D	5.33 E-11 (WT: 4.72 E-11)	16	G476S	4.60 E-11 (WT: 4.72 E-11)
17	S359N	6.42 E-11 (WT: 5.99 E-11)	18	S477I	5.63 E-11 (WT: 1.02 E-10)
19	V367F	4.10 E-11 (WT: 4.72 E-11)	20	S477N	4.89 E-11 (WT: 3.95 E-11)
21	N370S	5.07 E-11 (WT: 1.02 E-10)	22	S477R	4.78 E-11 (WT: 3.95 E-11)
23	A372S	4.25 E-11 (WT: 5.99 E-11)	24	T478I	4.25 E-11 (WT: 3.95 E-11)
25	A372T	5.65 E-11 (WT: 1.02 E-10)	26	P479S	4.11 E-11 (WT: 3.95 E-11)
27	F377L	5.35 E-11 (WT: 5.99 E-11)	28	N481D	5.18 E-11 (WT: 7.25 E-11)
29	K378R	4.88 E-11 (WT: 5.99 E-11)	30	G482S	5.69 E-11 (WT: 5.10 E-11)
31	K378N	6.08 E-11 (WT: 5.99 E-11)	32	V483A	4.64 E-11 (WT: 4.72 E-11)
33	P384L	4.97 E-11 (WT: 5.99 E-11)	34	V483I	6.17 E-11 (WT: 6.75 E-11)
35	T385A	6.79 E-11 (WT: 5.99 E-11)	36	G485S	7.47 E-11 (WT: 6.75 E-11)
37	T393P	6.24 E-11 (WT: 5.99 E-11)	38	F486S	6.58 E-11 (WT: 7.25 E-11)

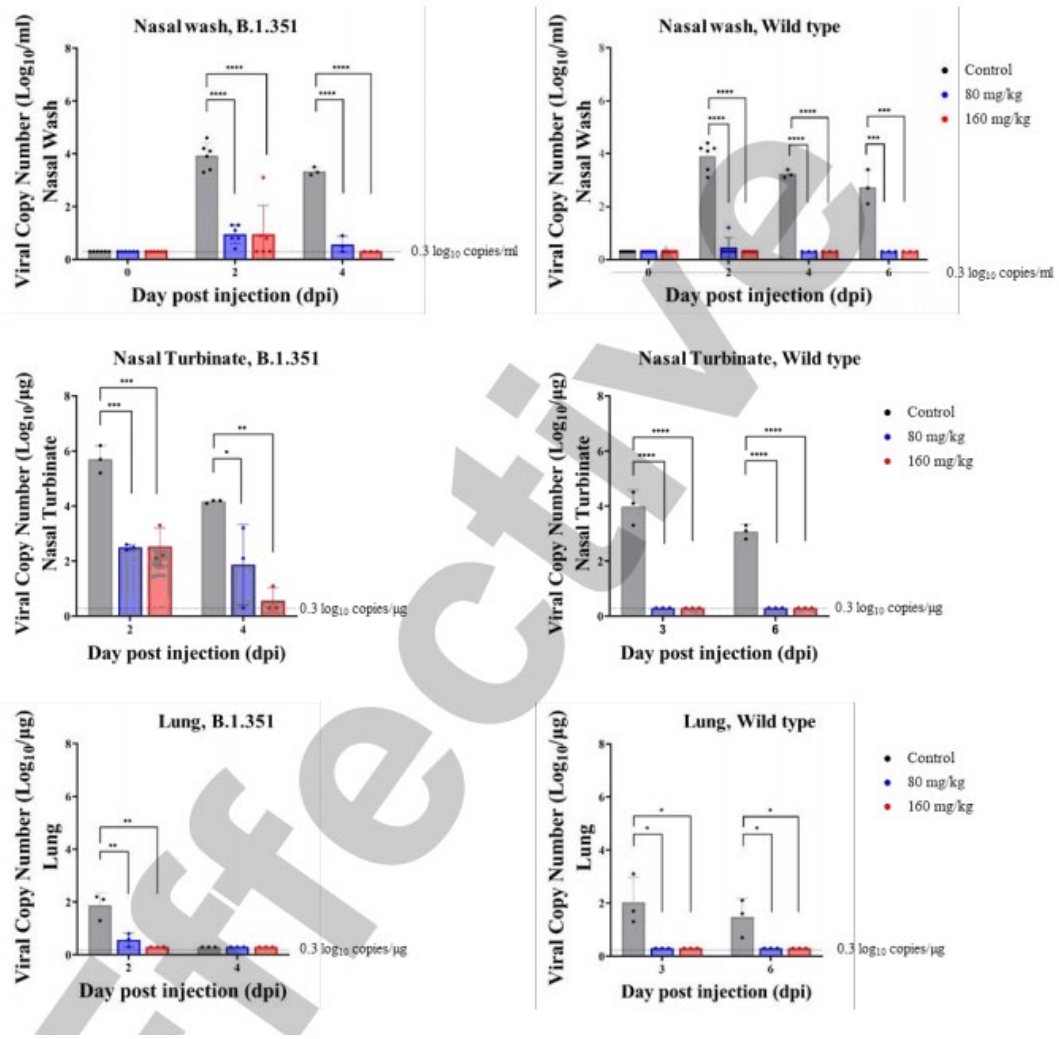
No.	RBD mutant[1]	K_D (M)	No.	RBD mutant	K_D (M)
39	V395I	7.01 E-11 (WT: 1.02 E-10)	40	F490S	6.89 E-11 (WT: 5.10 E-11)
41	E406Q	1.24 E-10 (WT: 3.95 E-11)	42	S494P	4.49 E-08 (WT: 6.75 E-11)
43	R408I	5.51 E-11 (WT: 3.95 E-11)	44	P499R	7.75 E-11 (WT: 7.25 E-11)
45	Q409E	6.83 E-11 (WT: 1.02 E-10)	46	V503F	4.91 E-11 (WT: 3.95 E-11)
47	D405V, Q414A	5.60 E-11 (WT: 5.99 E-11)	48	Y505C	7.16 E-11 (WT: 7.66 E-11)
49	Q414E	4.68 E-11 (WT: 5.99 E-11)	50	Y508H	4.28 E-11 (WT: 3.95 E-11)
51	Q414R	1.14 E-10 (WT: 1.02 E-10)	52	A520S	7.06 E-11 (WT: 5.99 E-11)
53	**K417N[2]**	5.14 E-11 (WT: 5.10 E-11)	54	A520V	5.42 E-11 (WT: 1.02 E-10)
55	A435S	5.52 E-11 (WT: 4.72 E-11)	56	P521S	5.59 E-11 (WT: 3.95 E-11)
57	W436R	3.98 E-11 (WT: 4.72 E-11)	58	P521R	5.85 E-11 (WT: 3.95 E-11)
59	N439K	6.93 E-11 (WT: 3.95 E-11)	60	A522V	5.31 E-11 (WT: 3.95 E-11)
61	N440K	5.88 E-11 (WT: 3.95 E-11)	62	A522S	5.97 E-11 (WT: 5.99 E-11)
63	K444R	9.29 E-11 (WT: 3.95 E-11)	64	K458Q	6.29 E-11 (WT: 6.41 E-11)
65	V445F	8.76 E-11 (WT: 7.25 E-11)	66	**E484K[2]**	1.10 E-10 (WT: 6.41 E-11)
67	G446V	7.48 E-11 (WT: 7.66 E-11)	68	**N501Y[2]**	9.30 E-11 (WT: 4.76 E-11)
69	F456E	4.47 E-10 (WT: 7.25 E-11)	70	**K417N/E484K /N501Y[2]**	9.41 E-10 (WT: 9.46 E-11)
71	**K417T/E484K /N501Y[2]**	7.69 E-10 (WT: 6.32 E-11)	72	**L452R/T478K[2]**	5.41 E-10 (WT: 5.56 E-11)
73	**L452R/E484Q[2]**	2.17 E-10 (WT: 5.56 E-11)			

[1] All of the mutant RBDs used were purchased from Sino Biological except E484K and K417N/E484K/N501Y triple mutant (both from Acro Biosystems).
[2] Mutant RBDs that are present in the UK (N501Y), South African (K417N, E484K and N501Y), Brazil (K417T, E484K and N501Y), Indian (L452R, E484Q and T478K) and California (L452R) variants

Animal models of efficacy against VOC's

A ferret study with the South-African (1.351, beta; 1.0 x $10^{5.5}$ $TCID_{50}$/mL) variant intranasal infection reported that CT-P59 (i.v., on 1dpi, observations until 4dpi) reduces nasal and lung viral levels at 80 and 160mg/kg (n=6 animals per group) with no measurable viral levels after 2-3dpi. A comparative wild type virus ferret study (also 1.0 x $10^{5.5}$ $TCID_{50}$/mL) was also conducted (CT-P59 i.v. treatment at 80mg/kg and 160mg/kg on 1dpi, observations until 6dpi; n=6 animals per group). Clear statistically significant reduction of viral levels in nose and lungs at 3dpi and 6dpi for wt-virus and at 2dpi and 4dpi respectively for the beta virus (see figure below). The viral levels in the lungs were more or less reduced below measurable levels for both viruses and at both doses. In the nose, the CT-P59 treatment was somewhat less efficient on beta compared to the wt-virus. The wt-virus levels were below measurable levels at 2-3dpi at both doses whereas the beta virus levels were effectively reduced at 160mg/kg (2dpi and 4dpi) but remained slightly over the base line at 80mg/kg (at 2dpi) in nasal wash samples. In the nasal turbinate samples, although the levels were reduced, they were clearly higher than base line at 80mg/kg at 2dpi and 4dpi and at 160mg/kg at 2dpi (see figure below). HED (80mg/kg) at 15.1mg/kg and HED (160mg/kg) at 30.2mg/kg.

Figure 10: Virus copy of B.1.351 and wild-type of SARS-CoV-2 in nasal wash, nasal turbinate and lung tissue (qRT-PCT)



A transgenic ACE2 mouse study was provided involving post-infection treatment 8h after a Brazilian (P.1; "gamma") variant challenge (intranasal exposure; 1 x 10^4 PFU/30µL; CT-P59 5, 20, 40 and 80mg/kg i.p.; n=8-11 animals per group; observation until 6dpi). There was no wild-type virus infection control/comparison. As such, a direct wild-type versus VOC treatment comparison is not possible. Compared to non-treated controls, the gamma virus titres in lungs were reduced or not detectable in treated animals (n=4 animals/group for viral measurements on 3dpi and 6dpi respectively). At 3dpi, 2-3 animals out of 4 in all CT-P59 dose groups had non-detectable levels of virus, with reduced expression in remaining animals. At 6dpi, all treated animals had non-detectable virus levels. Assessment of nasal wash sample levels is more uncertain as the controls unexpectedly showed very low viral levels at 3dpi or 6dpi (3 out of 4 animals had no detectable levels at 3dpi and 6dpi). All treatment groups had non-detectable levels). Viral titre reductions are shown in the figures below.

Figure 11: Mean infectious viral titres in nasal washes over time after SARS-CoV-2, Gamma variant (P.1) inoculation in hACE2 TG mice

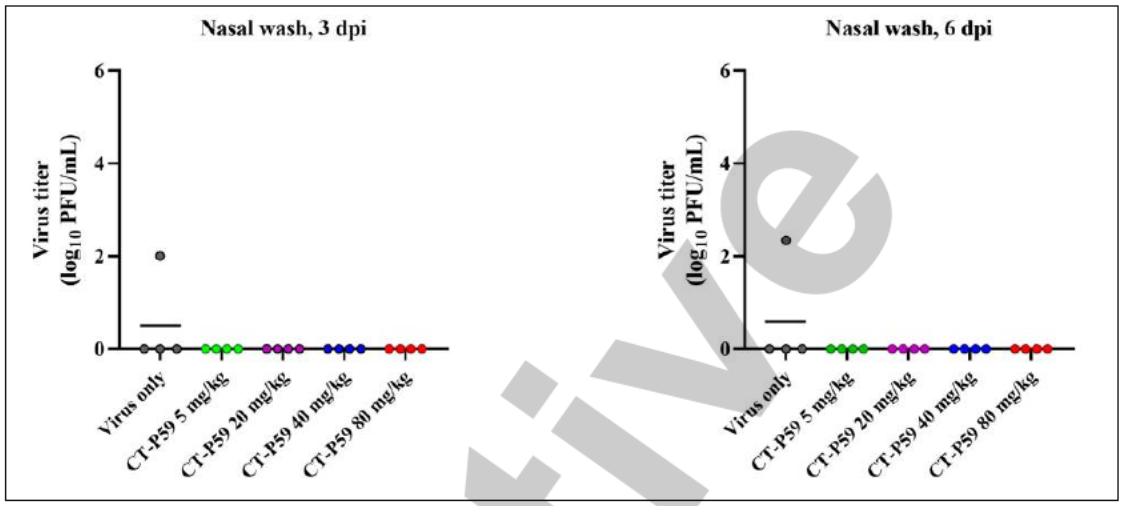
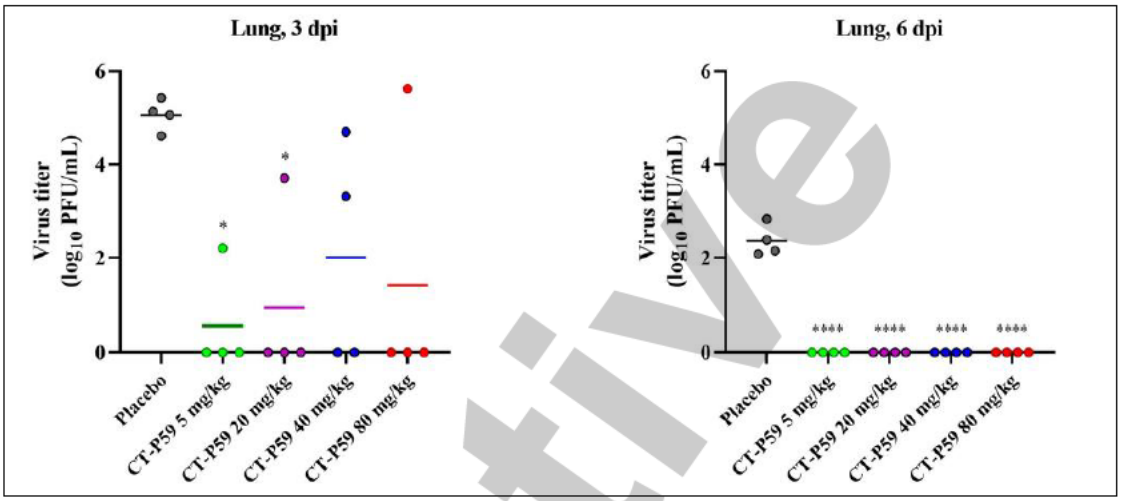


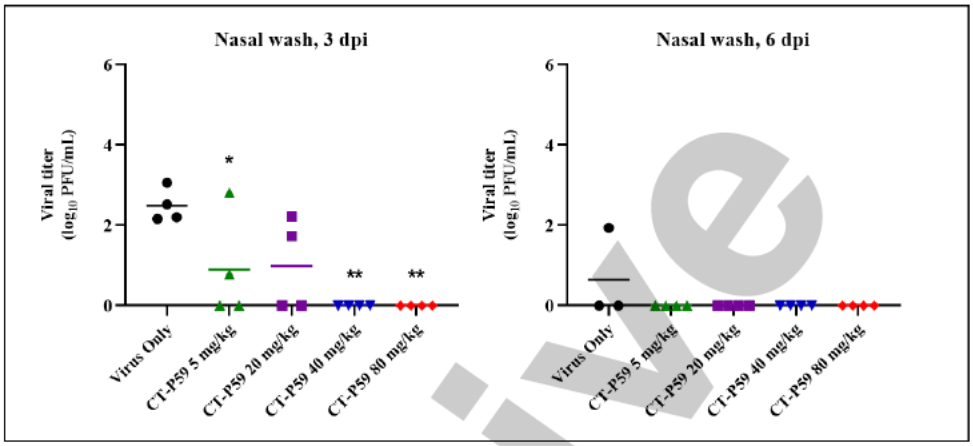
Figure 12: Mean infectious viral titres in lungs over time after SARS-CoV-2, Gamma variant (P.1) inoculation in hACE2 TG mice



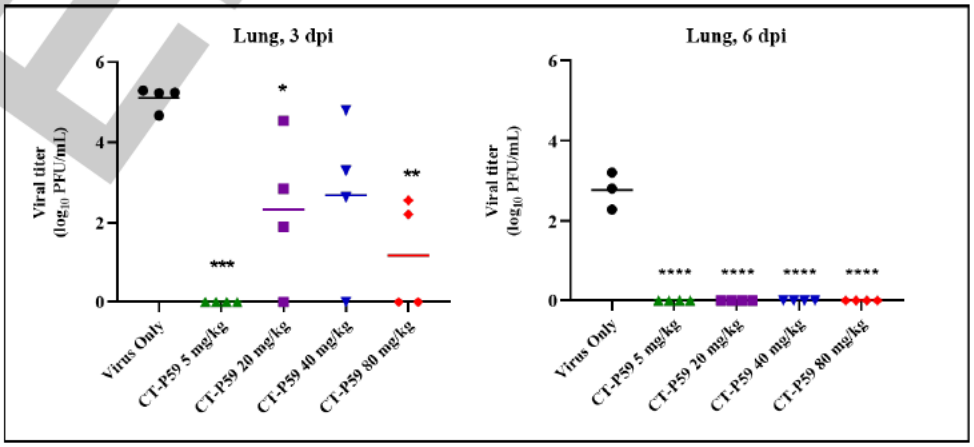
* and **** denotes $p<0.05$ and $p<0.0001$ between control and each treatment group.

Female hACE2 mice (n=8 animals/group) were exposed to the 'beta' variant (intranasally inoculation with $1x10^4$ PFU of Delta variant in a 50µL volume) followed 8h later with 5, 20, 40 or 80mg/kg i.p. CT-P59. There was also a virus+formulation control (n=8 animals). The animals were observed until 6dpi with necropsy on 3dpi (n=4 animals/group) and 6dpi (n=4 animals/group). Survival rate was assessed after 4dpi. In controls, 2/4 animals died before 6dpi. Surviving mice showed 35.27% body weight loss. No CT-P59 group animals died due to infection before 6dpi. Mean body weight was reduced in a roughly dose-dependent manner (between 15.99% and 3.61% reduction). Nasal viral titres were reduced on d3 (some individual variation) at 5 and 20mg/kg and non-measurable on 40mg/kg and 80mg/kg. No measurable levels were seen at 6dpi. Viral titres in lungs were reduced (some individual variation) at 3dpi and generally non-measurable at 6dpi at all doses. Viral titre reductions are shown in the figures below.

Figure 13: Mean infectious viral titres in nasal washes over time after SARS-CoV-2, Beta variant (B.1.351) inoculation in hACE2 TG mice



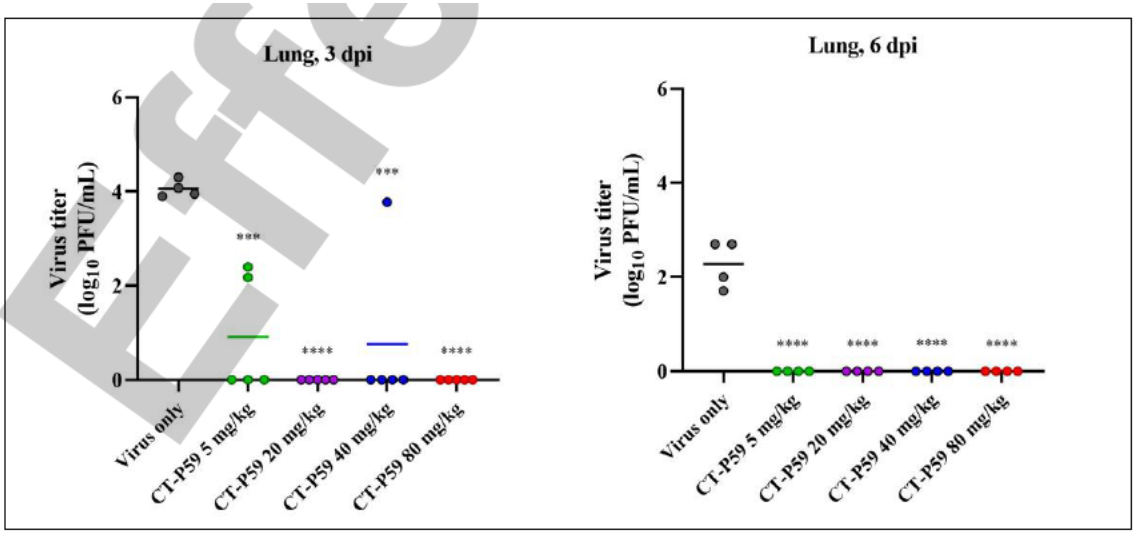
* and ** denote p<0.05 and p<0.01, respectively, between control and each treatment group.



*,**, *** and **** denote p<0.05, p<0.01, p<0.001, and p<0.0001 between control and each treatment group.

Transgenic female hACE2 mice (n=8-9 animals/group) were exposed to the delta variant (intranasally inoculation with $1x10^4$ PFU of Delta variant in a 30µL volume) followed 8h later with 5, 20, 40 or 80mg/kg i.p. CT-P59. There was also a negative (formulation) control and a virus-only group (n=8 animals). The animals were observed until 6 days post infection (6dpi) with necropsy on 3dpi and 6dpi. Virus only group animals showed an average body weight loss of 16.3% at 4dpi, and eventually showed an average of 22.7% decrease for three mice while a single euthanized mouse excluded from statistical analysis at 5dpi. No animal survived at 6dpi in the virus-only group. There was no death in the CT-P59 groups. All CT-P59 treatment group animals relatively maintained their body weight until 6dpi showing some dose-dependent body weight reduction (between 14.3% and 4.6% reduction) but no statistical significance compared to the negative control group. The mean virus titre in lung tissues reached 4.1 log_{10} PFU/mL at 3 dpi and declined to 2.43 log_{10} PFU/mL at 6 dpi in the virus only group. In treatment groups, viral levels were undetectable at 20 and 80mg/kg CT-P59 but detectable at 5 mg/kg (3.1 log_{10} PFU/mL) and 40mg/kg (3.3 log_{10} PFU/mL). Viral titre reductions are shown in the figure below.

Figure 14: Mean infectious viral titres in nasal washes over time after SARS-CoV-2, Delta variant inoculation in hACE2 TG mice



*** and **** denotes p<0.001 and p<0.0001 between control and each treatment group.

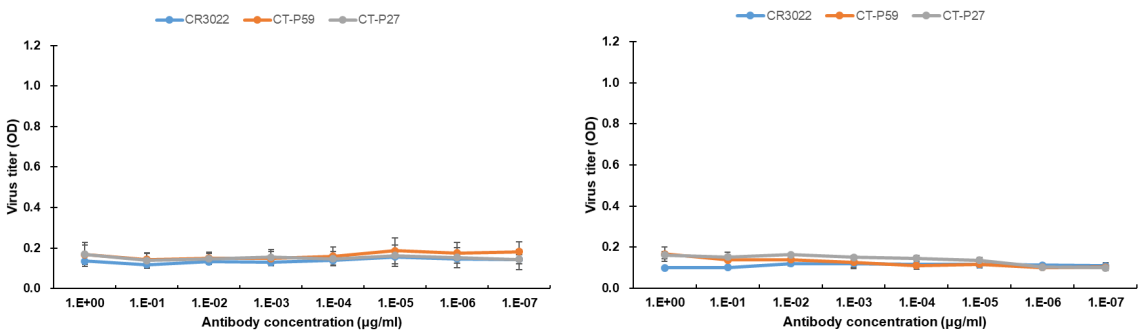
The HED for the hACE2 studies (using the same doses) were 0.41mg/kg, 0.81mg/kg, 1.63mg/kg, 3.25mg/kg and 6.50mg/kg respectively. See non-clinical section for studies using the wt-virus.

Secondary pharmacodynamics in-vitro studies

Antibody-dependent enhancement (ADE) in FcR-bearing cells (Raji & U937) and no FcR-bearing cells (VeroE6)

To address the potential ADE effect of regdanvimab, SARS-CoV-2 (BetaCoV/Korea/KCDC03/2020) viruses (0.05 MOI) were incubated with both permissive cells (VeroE6 cells) and Fc-bearing cells (Raji cells; FcγR II, U937 cells; FcγR I & II) in the presence of regdanvimab. Two antibodies, CR3022 (SARS neutralizing antibody) and CT-P27 (Influenza A neutralizing antibody) were used as non-neutralizing antibody and unrelated control, respectively. It is confirmed that regdanvimab did not induced ADE effect in all concentrations tested in both cells.

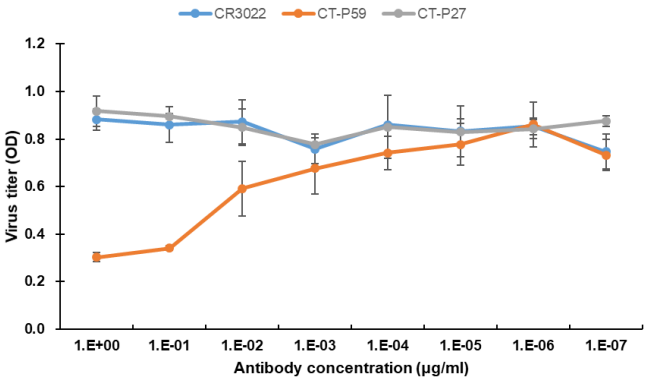
Figure 15: No effect of ADE by CT-P59 bound with SARS-CoV-2 in Fc receptor-bearing cells



(Left panel) FcγR II-dependent ADE. SARS-CoV-2 was mixed with a wide range of antibodies; CT-P59 (orange), CR3022 (blue) and CT-P27 (grey). Raji cells were infected with virus-antibody complex. The virus titres were determined by optical density (OD) using anti-nucleocapsid antibody (Right panel) FcγR I&II-dependent ADE. In vitro ADE assay was carried out as described in (left panel) except using U937 cells. The experiments were performed in triplicates (CR3022 and CT-P27) or in quadruplicates (CT-P59). Average and standard deviation of virus titres were depicted as dot and error bar,

respectively.

Figure 16: No effect of ADE by regdanvimab bound with SARS-CoV-2 in permissive cells FcR-independent ADE.



SARS-CoV-2 was mixed with a wide range of antibodies; CT-P59 (orange), CR3022 (blue) and CT-P27 (gray). VeroE6 were infected with virus-antibody complex. The virus titres were determined by optical density (OD) using antinucleocapsid antibody. The experiments were performed in triplicates (CR3022 and CT-P27) or in quadruplicates (CT-P59). Average and standard deviation of virus titres were depicted as dot and error bar, respectively.

The company argues that regdanvimab is unlikely to enhance SARS-CoV-2 virus infection and subsequent disease via a virus-antibody complex, and the study supports this argument.

2.5.3. Discussion on clinical pharmacology

Regdanvimab is a recombinant human monoclonal IgG1 antibody. CT-P59 (Regkirona) is intended for single dose treatment in adults with a proposed therapeutic dose of 40 mg/kg administered as an intravenous infusion over 60 minutes.

The pharmacokinetics of regdanvimab has been well characterized; in healthy volunteers over a dose range of 10 to 80 mg/kg, and in patients with COVID-19 at (primarily) 40 and 80 mg/kg. Rich PK sampling, up to Day 90 after dose, was used in all three studies. Serum concentrations of regdanvimab were quantitatively measured using a validated ligand-binding assay with a lower limit of quantification of 800 ng/mL. Pharmacokinetic parameters were estimated using non-compartmental analysis. No population PK analysis results were submitted which is acceptable.

The phase 1 study CT-P59 1.1 in healthy volunteers showed that regdanvimab have PK characteristics typical for an IgG monoclonal antibody, i.e. a low clearance, a small volume of distribution and a long terminal half-life (17-22 days). The exposure increased in proportion to dose with no indication of target-mediated drug disposition.

The phase 1 pilot study CT-P59 1.2 in patients with mild COVID-19 showed that the pharmacokinetics of regdanvimab was very similar to that observed in healthy volunteers.

The phase 2/3 study CT-P59 3.2 in patients with mild to moderate COVID-19 included a PK set of 29 and 32 patients in the 40 and 80 mg/kg dose group, respectively. The pharmacokinetic results were very similar to those in the other two studies. Clearance was independent of dose. At the 40 mg/kg dose, the PK of reganvimab was characterized by a (arithmetic mean (CV%)) CL of 0.20 mL/h/kg (24%), a V_{ss} of 83 mL/kg (26%) and a $t_{1/2z}$ of 17 days (37%).

The table below shows the observed mean serum concentrations and the predicted lung concentrations of regdanvimab following a single intravenous dose of 40 mg/kg.

Time	Serum conc. (ng/mL)*	Lung conc. (ng/mL)**
End of infusion	987607 (28.7%)	148141
Day 4 (96 hrs)	382080 (16.9%)	57312
Day 14	172480 (18.3%)	25872

* Observed arithmetic mean (CV%) serum concentration (CT-P59 3.2 Part 1 Day 28 Clinical Study Report; Table 14.4.1.1)

** Predicted lung concentration assuming a lung/serum distribution coefficient of 0.15, as reported for a mAb (Shah & Betts, 2013)

No interaction studies or studies in special populations were performed with CT-P59 which is acceptable. Regdanvimab is a monoclonal antibody and expected to be eliminated via proteolytic degradation to amino acids and is not anticipated to be eliminated intact in the urine or metabolized by CYP450 enzymes. No dose adjustments in renal or hepatic impairment are considered necessary. Also, it has been adequately justified that no dose adjustment is needed depending on age, weight, gender or race.

The conclusion that the immunogenicity potential of regdanvimab is low is agreed.

The monoclonal antibody regdanvimab (CT-P59) targets the non-endogenous epitope of the RBD domain of the spike protein in SARS-CoV-2. It is a protein that is not produced by mammalian cells.

Primary pharmacology

In ELISA and surface plasmon resonance assays, regdanvimab bound to RBD of SARS-CoV-2 EC50 of 4.4 ng/mL. Critical residues for regdanvimab binding to its target were identified by alanine scanning assay. These were Y449, L455, F456, Q493, and S494.

The neutralising ability of representative regdanvimab against wild type SARS-CoV-2 was determined by an *in vitro* plaque reduction neutralisation test (PRNT). The IC_{50} and IC_{90} of regdanvimab toward SARS-CoV-2 was 9.70 ng/mL and 25.09 ng/mL, respectively.

In vitro assessment of Fc-mediated function for ADCC and CDC suggest that regdanvimab is not able to mediate Fc-related activities and this is unlikely to be a MoA of regdanvimab.

Viral drug resistance

In vitro virus passaging was performed with SARS-CoV-2 viruses in the presence/absence of regdanvimab. Comparative sequence analysis showed double mutations (S494P+R685H) in all escape viruses. Whilst amino acid 494 is located in the RBD, amino acid 685 is located in S1/S2 cleavage site. Regdanvimab was unable to neutralise the escape virus at all concentrations tested.

Results from a VLP (pseudovirus) assay showed that S494P, S494L, Q493R and Q493K mutations exhibit IC_{50} values above 500 ng/ml and are likely to completely abrogate clinical efficacy. Substitutions tested and associated with >20-fold but <100 fold-change include Y449N, L452R and L455F.

Activity against VOC's

Viral geno- and phenotyping from the pivotal trial is presently not available. It is likely, however, that wuhan and/or the alpha variant dominated at the times and places where this was conducted.

Neutralizing activity determined by PRNT was observed against UK (Alpha, B.1.1.7), Brazil (P.2), New York (Iota, B.1.526) and Nigeria (Eta, B.1.525) variants was comparable to the wild type.

Regdanvimab had reduced neutralising activity against Brazil (Gamma, P.1), South Africa (Beta, B.1.351), Epsilon (B.1.427 and B.1.429) and India (Kappa B.1.617.1 and Delta, B.1.617.2) variants. The IC50 fold reductions relative wild type ranged between 24-310 with the largest change observed for the Beta and Delta variants with 310- and 183-fold reduction respectively.

The VLP assays showed that spike mutations involved in the virus variants Beta, Gamma and Kappa led to increased IC_{50} values compared to the original type.

The applicant has provided data from a Ferret model infected with the Beta (B.1.351) variant, and from a ACE2 transgenic mouse model infected with Beta (B.1.351), Gamma (P.1) as well as Delta (B.1.617.2)virus, treated with human equivalent doses as post exposure prophylaxis. Both of these studies are indicative of antiviral effects. However, the clinical implications of this are not completely known, since the predictiveness of the models have not been established, and it is not known whether PK/PD is similar in these models and in humans.

PK/PD

Notably, the reported the IC90 value in vitro for the wild type virus is 28 ng/mL. The highest reported IC90 value in vitro is for the Beta 1.351 (South African) virus variant: 16550 ng/mL.

The applicant has provided measured estimates of plasma concentrations and IC50 values for the delta variant, along with literature-based estimates of the lung concentration at 15% and 5% of the serum concentration.

The serum and estimated lung concentration at 96h post dose assuming 15% lung penetration are approximately 380000 ng/mL and 57000 ng/mL, respectively. At a more conservative estimate of 5% lung concentration, the 96h lung concentration would be approximately 19000 ng/mL Thus, concentrations of regdanvimab in lungs would be estimated above the IC90 in vitro for all listed virus variants during the presumably crucial initial treatment phase. However, the (plasma or lung concentration/ in vitro susceptibility) quotient required for clinical efficacy has not been characterized. Furthermore, it is not clear that this is similar for all VOC's, given e.g., differences in viral replication rates.

In summary, PK/PD is compatible with clinical activity against the delta variant, and an ACE2 transgenic mouse animal model is supportive of such activity.

According to the Applicant, it will continue to monitor and study newly emerging variants and escape mutants and duly report the results as they become available.

Secondary pharmacology

As there is evidence to suggest that SARS-CoV-2 specific antibodies may promote viral entry into FcR-expressing cells (thereby promoting inflammation), a neutralization study was conducted in cells expressing FcR (Raji cells with FcγR II; U937 cells with FcγR I & II). Based on anti-SARS-CoV-2 antibody cytochemistry following 24h virus + antibody incubation, regdanvimab did not promote viral uptake into FcγR I and II expressing cells.

2.5.4. Conclusions on clinical pharmacology

The pharmacokinetics of regdanvimab has been well characterized in healthy volunteers and in the target population. The PK was typical for an IgG mAb with a low clearance, a small volume of distribution and a terminal half-life of 17 days. The serum exposure increased approximately in

proportion to dose over the investigated dose interval 10 to 80 mg/kg.

Overall, the mechanism of action of regdanvimab has been established. There is reduced in vitro activity against the South Africa (Beta), Brazil (Gamma) and India (Kappa and Delta) variants. It is unknown whether clinical efficacy is retained.

2.5.5. Clinical efficacy

Table 10: Overview of Clinical Efficacy Study Program for Regdanvimab (CT-P59) in Mild to Moderate COVID-19

Study ID	No. of study centres / locations	Design	Study Posology	Subjects by arm entered	Duration	Gender/ Median Age	Study population	Primary Endpoint
CT-P59 3.2 Part 1	A total of 23 study centres in Korea, Romania, Spain and United States	Phase 2/3 Randomized, Parallel-Group, Placebo-Controlled, Double-Blind	CT-P59 40 mg/kg, CT-P59 80 mg/kg, or Placebo intravenous (IV) infusion	Intention to treat: 327 patients. 105, 111, and 111 patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively	Treatment for 90 days, follow-up for 90 days	161 females; 166 males. Median age: 51	Outpatients with symptomatic SARS-CoV-2 infection confirmed by positive viral test	**Key Primary Endpoint** • Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 **Supportive Primary Endpoint** • Time to clinical recovery up to Day 14 • Time to negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture up to Day 14 • Proportion of patients with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture at each visit up to Day 14

Study ID	No. of study centres / locations	Design	Study Posology	Subjects by arm entered	Duration	Gender/ Median Age	Study population	Primary Endpoint
CT-P59 3.2 Part 2	A total of 58 study centres in Hungary, Spain, United States, Romania, Moldova, Ukraine, Korea, Poland, Peru, Mexico, Serbia, Italy and North Macedonia.	Phase 2/3 Randomized, Parallel-Group, Placebo-Controlled, Double-Blind	CT-P59 40 mg/kg or Placebo IV infusion	Intention to treat: 1315 patients. 656 and 659 patients in the CT-P59 40 mg/kg, and Placebo groups, respectively	Treatment for 90 days, follow-up for 90 days	641 females; 674 males. Median age: 48.0	Outpatients with symptomatic SARS-CoV-2 infection confirmed by positive viral test	• Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high-risk[1] patients

[1] The high risk patients with 1 or more of the following risk factors: Age >50 years; BMI > 30 kg/m^2 collected via vital signs CRF; 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 prescriber's assessment.

RT-PCR: Reverse transcription polymerase chain reaction, RT-qPCR: Reverse transcription-quantitative polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus

2.5.5.1. Dose response study(ies)

See Part 1 of main study below.

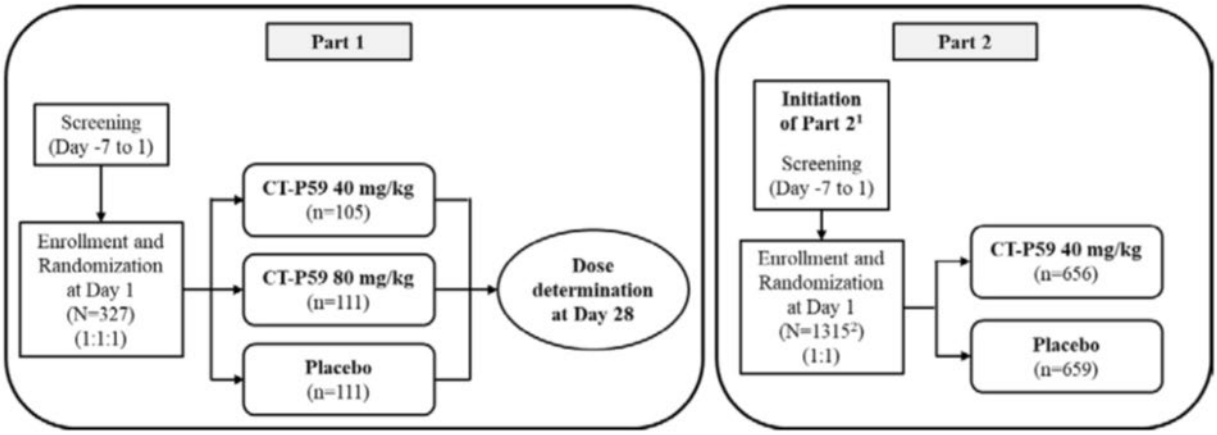
2.5.5.2. Main studies

Title of study: *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.*

This study was a randomized, parallel-group, placebo-controlled, double-blind, Phase 2/3 study with 2 parts designed to evaluate the efficacy, safety, PK, and virology of regdanvimab in combination with standard of care (SoC; except potential antiviral drugs and/or possible anti-SARS-CoV-2 activity drugs) in outpatients with mild to moderate SARS-CoV-2 infection, not requiring supplemental oxygen therapy.

The study consisted of 3 study periods; Screening, Treatment Period (90 days, single infusion), and Follow-Up Period (90 days). An End-of-Treatment (EOT) visit was scheduled on Day 90, and the total study duration was planned to be 180 days for each patient.

Figure 17: Schematic Diagram of Study Patients in Study CT-P59 3.2



Note: In Part 1, patients with body weight at or above 100 kg and who are allocated to CT-P59 80 mg/kg group or Placebo group received 8,000 mg of CT-P59 or matching volume of placebo. In Part 2, patients with body weight at or above 200 kg received 8,000 mg of CT-P59 or matching volume of placebo.
[1] Part 2 is initiated based upon the independent DSMB's review of all available data after all patients have reached Day 28 in Part 1.
[2] Of 1315 patients in Part 2, 880 high-risk patients were included.

Methods

Study Participants

In Part 1 patients were screened at 23 study centres across 4 countries, Republic of Korea, Romania, Spain and United States.

In Part 2 patients were screened at 60 study centres across 14 countries, Hungary, Ireland, Italy, Mexico, North Macedonia, Peru, Poland, Republic of Korea, Republic of Moldavia, Romania, Serbia, Spain, Ukraine and United States.

Main Inclusion Criteria

Male or female outpatients aged 18 or above, diagnosed with SARS-CoV-2 infection at Screening by using the sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR were to be considered for enrolment in the study. 'Outpatient' in this study included patients visiting the study centre, and

patients confined in the study centre or quarantine at home due to local regulation or at discretion of the investigator.

The patients had to have oxygen saturation >94% on room air, not requiring supplemental oxygen, and onset of SARS-CoV-2 infection associated symptom no more than 7 days prior to the study drug administration.

The patients had to have 1 or more of the following (but not limited to) SARS-CoV-2 infection associated symptoms within but not more than 7 days prior to study drug administration: feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, headache, chills, nasal obstruction or congestion, loss of taste or smell, nausea or vomiting, or diarrhoea as well as 1 of the following SARS-CoV-2 infection-associated symptoms within 48 hours prior to study drug administration: feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, or headache.

Main Exclusion Criteria

Part 1: Key exclusion criteria included severe COVID-19, immunocompromised, iatrogenic or due to disease, use of other drugs with activity or efficacy in COVID-19, as well as uncontrolled or unstable underlying medical conditions.

Part 2:

The main exclusion criteria were signs of severe SARS-Cov-2 infection, including respiratory distress with respiratory rate ≥30 breaths/min; required supplemental oxygen; experienced shock; complicated with other organ failures, and intensive care unit monitoring treatment was needed by investigator's discretion. Furthermore, patients could not have been vaccinated against SARS-CoV-2 and were not allowed concomitant medications with established or potential anti-SARS-CoV-2 activity.

Treatments

In Part 1, regdanvimab 40 mg/kg, regdanvimab 80 mg/kg, and Placebo matching in volume of regdanvimab 80 mg/kg was administered as an IV infusion over 90 minutes (±15 minutes). When calculating the total volume of study drug to be administered, the body weight of each patient measured on Day 1 was used. Patients who had a body weight at or above 100 kg and were allocated to the regdanvimab 80 mg/kg group or Placebo group received 8,000 mg of regdanvimab or a matching volume of Placebo.

In Part 2, based on the result from Part 1, regdanvimab 40 mg/kg and placebo matching in volume of regdanvimab 40 mg/kg were administered as an IV infusion over 60 minutes (±15 minutes). Patients with body weight at or above 200 kg were received 8,000 mg of regdanvimab or matching volume of placebo. When calculating total volume of study drug to be administered, the body weight of each patient measured on Day 1 was used.

All patients in both Part 1 and Part 2 were given optimal SoC. Optimal SoC can include rehydration therapy, antipyretics or antitussives prescribed by the investigator's discretion.

Objectives

Study CT-P59 3.2 Part 1

Primary and secondary objectives included exploration of the PK, antiviral effects, efficacy and safety of regdanvimab, including its impact on the risk of hospitalisation and time to clinical recovery.

Study CT-P59 3.2 Part 2

Primary Objective

- To demonstrate the clinically meaningful therapeutic efficacy of regdanvimab as determined by proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in patients at high risk for severe COVID-19.

Key Secondary Objectives

- To demonstrate the clinical meaningful therapeutic efficacy of regdanvimab as determined by proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients
- To assess the potential therapeutic efficacy of regdanvimab as determined by time to clinical recovery up to Day 14 in high-risk patients
- To assess the potential therapeutic efficacy of regdanvimab as determined by time to clinical recovery up to Day 14 in all randomized patients

Outcomes/endpoints

Part 1 is an exploratory study, and all endpoints are understood as exploratory. Concerning its objectives, see above. The confirmatory Part 2 study was planned to evaluate the efficacy and safety of regdanvimab in a larger number of patients.

Study CT-P59 3.2 Part 2

Primary Efficacy Endpoint

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

"High-risk patients" are defined as patients who are at high risk for progressing to severe COVID-19 and/or hospitalisation and who meet at least one of the following criteria:

- Advanced age (Age >50 years)
- Obesity (body mass index [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
- Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of acquired immune deficiency syndrome), sickle cell anaemia, thalassemia, and prolonged use of immune weakening medications.

Criteria of High-risk patients were suggested by EMA's Committee for Medicinal Products for Human Use (CHMP) in a scientific opinion (under Article 5(3) of Regulation 726/2004). In addition, these criteria are in line with CDC Recommendation (CDC, 2021).

Key Secondary Efficacy Endpoints

- Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomised patients
- Time to clinical recovery up to Day 14 in high-risk patients
- Time to clinical recovery up to Day 14 in all randomised patients

Clinical recovery is defined as all symptoms on the SARS-CoV-2 Infection Symptom Checklist 1 (feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pains or muscle pain, fatigue, and headache) being recorded as 'absent' or 'mild' in intensity for at least 48 hours. To meet the clinical recovery, symptoms 'severe' or 'moderate' in intensity at baseline should be changed to 'mild' or 'absent', or symptoms 'mild' in intensity at baseline should be changed to 'absent', after the study drug administration. Symptoms 'absent' in intensity at baseline should maintain as 'absent' for at least 48 hours. If a symptom 'absent' in intensity at baseline becomes 'severe', 'moderate', or 'mild' during the study, this should be changed back to 'absent' for at least 48 hours. In Part 2, missing symptoms at baseline should become 'absent' for at least 48 hours to meet the clinical recovery. Patients who report at least one symptom at baseline were included in the analysis.

Exploratory Virology Endpoints

- Viral shedding in nasopharyngeal swab specimen based on RT-qPCR
- Genotype and phenotype of SARS-CoV-2 viral isolates
- Viral serology for SARS-CoV-2 antibody

Quantification of SARS-Cov-2 in nasopharyngeal secretions

Based on the method performance results obtained from the method validation study of the RT-qPCR assay, the low limit of detection (LLOD95) of the RT-qPCR was determined as 2.33 (95% CI: 1.74 – 3.72) $\log_{10}$ cp/ml. To quantitate viral loads in clinical samples from Studies CT-P59 1.2 and CT-P59 3.2, one real-time qPCR method (Sarbeco E-gene assay) was employed which is specific to E gene of Sarbecoviruses including SARS-CoV and SARS-CoV-2.

The following rules present how viral titres were treated in the descriptive summary and AUC calculation and categorized as "Positive" or "Negative".

Table 11: Rules of Viral Titres

Reported Value	RT-qPCR	
	Treated as	Categorized as
≥ Negative threshold	Reported value	Positive
< Negative threshold	Negative threshold	Negative
Negative	Negative threshold	Negative

Abbreviations: RT-qPCR= reverse transcription-quantitative polymerase chain reaction.

Serological methods

IgG or IgM antibodies as determined by sponsor-supplied rapid diagnostic test, Celltrion DiaTrust COVID-19 IgG/IgM Rapid Test.

Assays was to be performed locally using the serum samples (if the assay was available).

Serostatus at Day 1 (Sero Positive, Sero Negative and Other):

- A patient was considered to have seropositive serostatus if there was at least 1 positive result of viral serology for SARS-CoV-2 Antibody IgG and IgM at Day 1.

- A patient was considered to have seronegative serostatus if there were both negative results of viral serology for SARS-CoV-2 Antibody IgG and IgM at Day 1.
- Otherwise, a patient was considered to have other serostatus

It is not known what the sensitivity of the sponsor-supplied rapid test is relative to tests used in the evaluations of other SARS-CoV-2-specific mAbs. Therefore, data are not readily comparable.

Randomisation and blinding (masking)

Study CT-P59 3.2 Part 1: 327 male or female patients with mild to moderate SARS-CoV-2 infection were randomly assigned at Day 1 in a 1:1:1 ratio to 1 of 3 groups (regdanvimab 40 mg/kg, 80 mg/kg, or Placebo).

Study CT-P59 3.2 Part 2: 1,315 male or female patients with mild to moderate SARS-CoV-2 infection were randomly assigned at Day 1 in a 1:1 ratio to 1 of 2 groups (regdanvimab 40 mg/kg or Placebo).

For both study parts the randomization was stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No, having at least one of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, and pneumonia), region (United States vs. Asia vs. European Union vs. other) and participation in PK sub-study (Yes vs. No, Part 1 only).

This study is double-blinded and will remain blinded to the investigator, all designated study staff (with the exception of the unblinded study pharmacists or unblinded staff designated to prepare the study drug for infusion and predefined unblinded teams in the sponsor and CRO), and patients until the final CSR is generated.

Statistical methods

Definition of analysis sets

Study CT-P59 3.2 Part 1

The intent-to-treat (ITT) Set: all randomly assigned patients to study drug.

The intent-to-treat infected (ITTI) Set: all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion result (Day 1) of RT-qPCR who receive a complete or partial dose of study drug. If the pre-infusion result at Day 1 is confirmed negative or missing and the Day 2 result is confirmed positive, this patient was considered as confirmed SARS-CoV-2 infection.

Study CT-P59 3.2 Part 2

The following patient analysis sets are defined: Intent-to-Treat (ITT) Set, ITT Set – High Risk, Intent-to-Treat Infected (ITTI) Set, ITTI Set – High Risk and Safety Set. The Safety Set was defined as all randomly assigned patients who received a complete or partial dose of study drug.

The intent-to-treat (ITT) Set: all randomly assigned patients to study drug.

The intent-to-treat infected (ITTI) Set: all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion result (Day 1) of RT-qPCR who receive a complete or partial dose of study drug. If the pre-infusion result at Day 1 is confirmed negative or missing and the Day 2 or Day 3 result is confirmed positive, this patient was considered as confirmed SARS-CoV-2 infection.

According the protocol only patients tested positive for SARS-CoV-2 infection at or prior to screening were eligible for the study. The applicant was asked to comment under which circumstances pre-infusion results were obtained. The Applicant laid down that amongst the randomised patients, those

with confirmed SARS-CoV-2 positive results at baseline based on RT-qPCR at the central laboratory and who received a complete or partial dose of the study drug were included in the Intent-to-treat Infected (ITTI) Set. In addition, if the pre-infusion result at Day 1 was confirmed negative or missing and the Day 3 result was confirmed positive, this patient was also considered as confirmed SARS-CoV-2 infection and included in the ITTI Set.

"High-risk patients": patients who are at high risk for progressing to severe COVID-19 and/or hospitalisation and who meet at least one of the following criteria: Age >50 years; BMI > 30 kg/m^2 collected via vital signs CRF; 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 prescriber's assessment.

ITT Set – High Risk: all randomly assigned patients to study drug, who are at high risk for progressing to severe COVID-19 and/or hospitalisation and who meet at least one of the high-risk criteria.

ITTI Set – High Risk: all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion result (Day 1) of RT-qPCR, who receive a complete or partial dose of study drug, who are at high risk for progressing to severe COVID-19 and/or hospitalisation and who meet at least one of the high-risk criteria. If the pre-infusion result at Day 1 is confirmed negative or missing and the Day 2 or Day 3 result is confirmed positive, this patient was be considered as confirmed SARS-CoV-2 infection.

For analysis of time to event endpoints, the following patients will be included in the analysis set:

- Time to clinical recovery: Patients who report at least one symptom at baseline
- Time to negative conversion: Patients who have positive result confirmed based on the negative threshold in the analysis at baseline (or Day 2/Day 3). The same analysis set will be used for the proportion of negative conversion

Study CT-P59 3.2 Part 1

Efficacy, virology and safety Analyses

There was no assignation of type 1 error control and all analyses are considered exploratory.

Study CT-P59 3.2 Part 2

Efficacy Analyses

The primary efficacy endpoint was analysed on the ITT set – High Risk using the p-value from stratified Cochran-Mantel-Haenszel (CMH) test at the 2-sided significance level of 5%. The difference of proportions between two treatment groups estimated using CMH weights was also provided along with the 95% stratified Newcombe CI with CMH weights. For sensitivity analysis, Fisher's exact test was conducted on ITT set – High Risk and the 95% exact CI (Chan and Zhang 1999) for the treatment difference was provided. Also, supportive analysis was performed on ITTI set – High Risk. Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high-risk patient were presented along with 95% Wilson (score) CI for the proportion in each treatment group.

The Cochran-Mantel-Haenszel (CMH)test was stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other). For the region, the patients in Asia are included in other category as the number of patients in Asia was confirmed to be around 1% during blinded DRM.

In addition, the analysis for the following subgroups will be conducted on ITT set – High Risk:

- Age (<60 years, ≥60 years, ≥50 years)

- Baseline comorbidities (Yes, No)
- Region (United States, Asia, European Union, Other)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Not Allowed by Investigator Country Regulations, Other)
- Sex (Male, Female)
- Non-high-risk (except for age category) and age (>60 years, >50 years) on ITT Set
- Disease severity (Mild, moderate)

Multiple testing - Key Secondary Efficacy Analysis

If the primary endpoint is statistically significant, the key secondary endpoints will be tested using the fixed sequence procedure in order to preserve the Type I error. The order of testing is as follows:

- Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients.
- Time to clinical recovery up to Day 14 in high-risk patients.
- Time to clinical recovery up to Day 14 in all randomized patients.

The first key secondary endpoint will be tested only if the primary endpoint is statistically significant, and the next key secondary endpoint will be tested only if the previous key secondary endpoint is statistically significant.

The key secondary endpoints were tested at the 2-sided significance level of 5% on the ITT set (for high-risk patients, ITT Set – High Risk) using the p-value from stratified CMH test for binary endpoints or stratified log-rank test for time to event endpoints. The supportive analysis was performed on ITTI set (for high-risk patients, ITTI set - High Risk).

Time to event is defined as the elapsed time (in days) from the study drug administration to the earliest day satisfying the condition and calculated as (Date/time of event or censoring – Date/time of study drug administration). The following patients will be considered censored at their scheduled visit of interest (Day 14).

- Patients who are ongoing in the study without event
- Patients with death or early withdrawal for any reason prior to their scheduled visit of interest (Day 14)
- Patients who administered the rescue therapy due to SARS Cov-2 infection prior to their scheduled visit of interest (Day 14)
- Patients who were hospitalized due to SARS-CoV-2 infection prior to their scheduled visit of interest (Day 14)

For time to clinical recovery endpoints, patients who report at least one symptom at baseline were included in the analysis.

The secondary efficacy endpoints will be analysed on both ITT and ITTI sets. Confidence interval and p-value will be presented for comparison between treatment groups in a descriptive manner with no adjustments for multiple testing.

Binary endpoints and time to event endpoints will be summarised and analysed using the same statistical method as the key secondary endpoints. Continuous endpoints will be summarised using

descriptive statistics and analysed using analysis of covariance presenting a point estimate, p-value and 95% CI for the treatment difference.

Virology Analyses:

Virology assessments were analysed on the ITTI Set and listed ITT Set. Actual values and change from baseline for viral shedding, percentage of patients with positive/negative viral shedding, duration (in days) of viral shedding, and area under the concentration-time curve of viral levels were summarized by treatment groups at each scheduled visit using descriptive statistics or frequency tables. Mean viral load titre (log values) for each scheduled time point was plotted. Serology results were summarized in tables by treatment groups. Genotype and phenotype results will be summarized in tables by treatment groups.

Results

Study CT-P59 3.2 Part 1

The study period was from 07 October 2020 (first patient's study drug administration date) to 27 May 2021 (last patient's last visit). After further data cleaning, the database was locked on 23 July 2021.

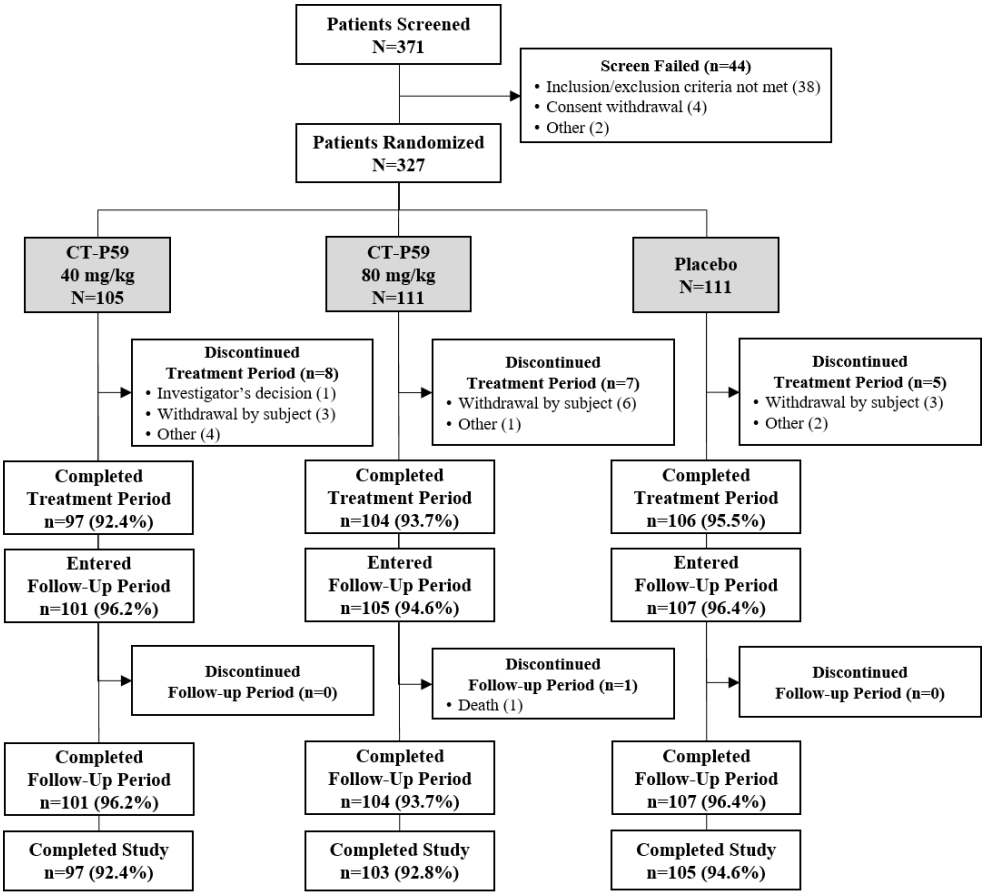
Study CT-P59 3.2 Part 2

The study period was from 18 January 2021 (first patient's study drug administration date) to 21 May 2021 (last patient's Day 28 visit).

Participant flow

Study CT-P59 3.2 Part 1

Figure 18: (E) – Patient Disposition "Study CT-P59 3.2 Part 1": Intent-to-Treat Set

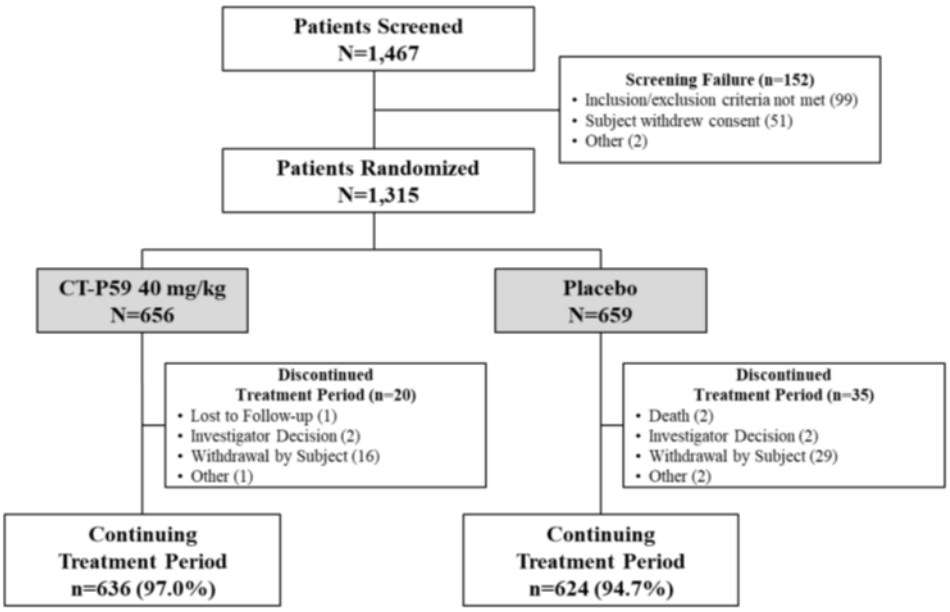


All randomized 327 patients were included in the ITT Set (105, 111, and 111 patients in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg, and Placebo groups, respectively).

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). Of 327 randomized patients in the ITT Set, 20 patients without confirmed SARS-CoV-2 infection by RT-qPCR at Day 1 or both Day 1 and Day 2 were excluded from the ITTI Set.

Study CT-P59 3.2 Part 2

Figure 19(E) - Patient Disposition in Study CT-P59 3.2 Part 2: Intent-to-Treat Set



In Study CT-P59 3.2 Part 2, 1467 patients were screened into the study and 1315 (including 880 high-risk patients) patients were randomly assigned to the study treatment at Day 1 (656, 659 patients in the regdanvimab 40 mg/kg, Placebo groups, respectively). Among the randomised patients, 1302 (652/656 [99.4 %], 650/659 [98.6 %] patients in the regdanvimab 40 mg/kg, Placebo groups, respectively) had received the study drug. There were 3 deaths in Study CT-P59 3.2 Part 2. Of the 3 death, 2 deaths were reported in placebo group during treatment period and 1 death was reported in 40 mg/kg group during follow up period.

Of these patients, 55/1315 (4.2%) patients discontinued the study during the Treatment Period. The most frequently reported primary reason for discontinuation during the Treatment Period was withdrawal by subject [45/1315 (3.4%)]. The mean (SD) time on study prior to discontinuation was 9.8 days (7.7 days) in the Treatment Period.

Baseline data

Study CT-P59 3.2 Part 1

Table 12: (E) - Demographics and Stratification Details: Intent-to-Treat Set, Part 1

Parameter Statistics	CT-P59 40 mg/kg (N=105)	CT-P59 80 mg/kg (N=111)	Placebo (N=111)	Total (N=327)
Age (years)				
n	105	111	111	327
Mean (SD)	50.4 (12.48)	51.1 (14.79)	51.4 (13.05)	51.0 (13.46)
Median	51.0	51.0	52.0	51.0
Min, Max	18, 75	23, 85	23, 88	18, 88
Sex, n (%)				
Male	59 (56.2)	59 (53.2)	48 (43.2)	166 (50.8)
Female	46 (43.8)	52 (46.8)	63 (56.8)	161 (49.2)
Female fertility status[1], n (%)				
Pre-menarche	0	0	0	0
Surgically sterilized	3 (6.5)	2 (3.8)	4 (6.3)	9 (5.6)
Post-menopausal	25 (54.3)	27 (51.9)	31 (49.2)	83 (51.6)
Potentially able to bear children	18 (39.1)	23 (44.2)	28 (44.4)	69 (42.9)
Race, n (%)				
White	94 (89.5)	96 (86.5)	96 (86.5)	286 (87.5)
African American/Black	0	0	0	0
American Indian/Alaska native	0	0	0	0
Asian	11 (10.5)	15 (13.5)	15 (13.5)	41 (12.5)
Native Hawaiian/Other Pacific Islander	0	0	0	0
Not allowed by investigator country regulations	0	0	0	0
Other	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	6 (5.7)	11 (9.9)	10 (9.0)	27 (8.3)
Non-Hispanic or Non-Latino	99 (94.3)	100 (90.1)	101 (91.0)	300 (91.7)
Unknown	0	0	0	0
Screening height (cm)				
n	105	111	111	327
Mean (SD)	172.91 (9.418)	171.38 (9.475)	170.81 (10.422)	171.68 (9.798)
Median	172.00	171.00	170.00	170.00
Min, Max	157, 198	150, 193	143.6, 195	143.6, 198
Screening weight (kg)				
n	105	111	111	327
Mean (SD)	81.32 (16.510)	79.87 (15.110)	78.46 (14.978)	79.86 (15.526)
Median	81.00	81.00	76.00	80.00
Min, Max	47, 128	52, 112	51, 120	47, 128
Screening body mass index (kg/m^2)				
n	105	111	111	327
Mean (SD)	27.101 (4.8086)	27.095 (4.1364)	26.819 (4.2071)	27.003 (4.3749)
Median	26.580	27.100	26.300	26.600
Min, Max	17.91, 45.9	17.99, 38.21	18.29, 38.28	17.91, 45.9

Parameter Statistics	CT-P59 40 mg/kg (N=105)	CT-P59 80 mg/kg (N=111)	Placebo (N=111)	Total (N=327)
Age, n (%)				
≥60 years	27 (25.7)	28 (25.2)	30 (27.0)	85 (26.0)
<60 years	78 (74.3)	83 (74.8)	81 (73.0)	242 (74.0)
Baseline comorbidities[2], n (%)				
Yes	78 (74.3)	80 (72.1)	82 (73.9)	240 (73.4)
No	27 (25.7)	31 (27.9)	29 (26.1)	87 (26.6)
Region, n (%)				
United States	1 (1.0)	4 (3.6)	3 (2.7)	8 (2.4)
Asia	11 (10.5)	15 (13.5)	14 (12.6)	40 (12.2)
European Union	93 (88.6)	92 (82.9)	94 (84.7)	279 (85.3)
Other	0	0	0	0
Participation in PK sub-study, n (%)				
Yes	29 (27.6)	34 (30.6)	31 (27.9)	94 (28.7)
No	76 (72.4)	77 (69.4)	80 (72.1)	233 (71.3)

Abbreviations: ITT, intent to treat; Max, maximum; Min, minimum; SD, standard deviation; PK, pharmacokinetic.

Note: Percentages were calculated by using the number of patients in the ITT Set as the denominator.

1. Percentages were based on the number of female patients.
2. Having at least one of cardiovascular disease, chronic respiratory disease, hypertension, diabetes

Table 13: (E) - Baseline Characteristics: Intent-to-Treat Infected Set, Part 1

Parameter Statistics	CT-P59 40 mg/kg (N=101)	CT-P59 80 mg/kg (N=103)	Pooled CT-P59 (N=204)	Placebo (N=103)	Total (N=307)
Disease severity, n (%)[1]					
Mild	38 (37.6%)	40 (38.8%)	78 (38.2%)	46 (44.7%)	124 (40.4%)
Moderate (Patients with Pneumonia)	62 (61.4%)	63 (61.2%)	125 (61.3%)	57 (55.3%)	182 (59.3%)
Age distribution in Moderate Patients, n (%)					
Age ≥ 60 years Moderate	19 (18.8%)	21 (20.4%)	40 (19.6%)	19 (18.4%)	59 (19.2%)
Age ≥ 50 years Moderate	40 (39.6%)	40 (38.8%)	80 (39.2%)	38 (36.9%)	118 (38.4%)
Day 1 Viral Load Titer, Median (log_{10} cp/ml)					
All Patients	6.73	6.57	6.66	5.96	6.42
Moderate (Patients with Pneumonia)	6.36	6.16	6.19	5.47	6.08
High Risk [2] Group, n (%)					
Yes	70 (69.3%)	76 (73.8%)	146 (71.6%)	71 (68.9%)	217 (70.7%)
No	31 (30.7%)	27 (26.2%)	58 (28.4%)	32 (31.1%)	90 (29.3%)

[1] One patient X had no radiography result at screening, disease severity of the patient was not categorised.
[2] The high-risk patients with one or more of the following risk factors: Age >50 years; BMI > 30 kg/m^2 collected via vital signs CRF; 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 prescriber's assessment.

Notably, baseline comorbidities conflate underlying conditions and the presence of clinical signs of COVID-19 pneumonia: "Having at least one of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, and pneumonia"

Overall, the median (minimum, maximum) time from the initial SARS-CoV-2 infection related symptom started to the date of study drug administration were similar among the 3 groups (3.0 [1, 6], 3.0 [0, 7], and 3.0 [0, 7] days in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg, and Placebo groups, respectively).

Study CT-P59 3.2 Part 2

Table 14: (E) - Demographics and Stratification Details: Intent-to-Treat Set, Part 2

Parameter Statistics	CT-P59 40 mg/kg (N=656)	Placebo (N=659)	Total (N=1,315)
Age (years)			
n	656	659	1315
Mean (SD)	48.4 (14.15)	47.5 (14.22)	48.0 (14.19)
Median	49.0	47.0	48.0
Min, Max	18, 87	18, 83	18, 87
Sex, n (%)			
Male	347 (52.9)	327 (49.6)	674 (51.3)
Female	309 (47.1)	332 (50.4)	641 (48.7)
Female fertility status[1], n (%)			
Pre-menarche	0	0	0
Surgically sterilized	27 (8.7)	22 (6.6)	49 (7.6)
Post-menopausal	133 (43.0)	155 (46.7)	288 (44.9)
Potentially able to bear children	149 (48.2)	155 (46.7)	304 (47.4)
Race, n (%)			
White	563 (85.8)	569 (86.3)	1132 (86.1)
African American/Black	6 (0.9)	1 (0.2)	7 (0.5)
American Indian/Alaska native	5 (0.8)	9 (1.4)	14 (1.1)
Asian	7 (1.1)	7 (1.1)	14 (1.1)
Native Hawaiian/Other Pacific Islander	1 (0.2)	0	1 (0.1)
Not allowed by investigator country regulations	0	0	0
Other	74 (11.3)	73 (11.1)	147 (11.2)
Ethnicity, n (%)			
Hispanic or Latino	137 (20.9)	139 (21.1)	276 (21.0)
Non-Hispanic or Non-Latino	515 (78.5)	513 (77.8)	1028 (78.2)
Unknown	4 (0.6)	7 (1.1)	11 (0.8)
Screening height (cm)			
n	656	659	1315
Mean (SD)	170.45 (10.146)	170.11 (9.872)	170.28 (10.007)
Median	170.00	170.00	170.00
Min, Max	138, 198	139, 195	138, 198
Screening weight (kg)			
n	656	659	1315
Mean (SD)	82.03 (18.246)	81.19 (18.405)	81.61 (18.324)
Median	81.00	80.10	80.50
Min, Max	45, 183	42, 159	42, 183

Parameter Statistics	CT-P59 40 mg/kg (N=656)	Placebo (N=659)	Total (N=1,315)
Screening BMI (kg/m²)			
n	656	659	1315
Mean (SD)	28.102 (5.1493)	27.981 (5.5833)	28.041 (5.3694)
Median	27.580	27.430	27.490
Min, Max	16.7, 56.29	16.8, 55.54	16.7, 56.29
Age, n (%)			
≥60 years	151 (23.0)	146 (22.2)	297 (22.6)
<60 years	505 (77.0)	513 (77.8)	1018 (77.4)
Baseline comorbidities[2], n (%)			
Yes	431 (65.7)	410 (62.2)	841 (64.0)
No	225 (34.3)	249 (37.8)	474 (36.0)
Region, n (%)			
United States	49 (7.5)	51 (7.7)	100 (7.6)
Asia	6 (0.9)	6 (0.9)	12 (0.9)
European Union	522 (79.6)	523 (79.4)	1045 (79.5)
Other	79 (12.0)	79 (12.0)	158 (12.0)
High-Risk Status[3], n (%)			
Yes	446 (68.0)	434 (65.9)	880 (66.9)
No	210 (32.0)	225 (34.1)	435 (33.1)
Screening Obesity, n (%)			
BMI >30 kg/m²	207 (31.6)	208 (31.6)	415 (31.6)
BMI ≤30 kg/m²	449 (68.4)	451 (68.4)	900 (68.4)
Screening Disease Severity[4], n (%)			
Mild SARS-CoV-2 infection patients	343 (52.3)	354 (53.7)	697 (53.0)
Moderate SARS-CoV-2 infection patients	308 (47.0)	302 (45.8)	610 (46.4)
Baseline Viral Load Titer (log_{10}cp/mL)			
n	648	644	1292
Mean (SD)	5.831 (1.7566)	5.920 (1.6588)	5.876 (1.7085)
Median	6.155	6.255	6.190
Min, Max	2.33, 9.03	2.33, 9.01	2.33, 9.03
Serostatus at Day 1[5], n (%)			
Serology Positive	76 (11.6)	72 (10.9)	148 (11.3)
Serology Negative	573 (87.3)	573 (86.9)	1146 (87.1)
Other	7 (1.1)	14 (2.1)	21 (1.6)

Abbreviations: BMI, body mass index; IgG, immunoglobulin G; IgM, immunoglobulin M; ITT, intent to treat; Max, maximum; Min, minimum; SD, standard deviation; SARS-CoV-2, severe actue respiratory syndrome coronavirus 2.

Note: Percentages were calculated by using the number of patients in the ITT Set as the denominator.
1. Percentages were based on the number of female patients.
2. Having at least 1 of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, and pneumonia.
3. High-risk patients were defined as patients with 1 or more of the following risk factors: age >50 years; BMI >30 kg/m²; 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.
4. Patients who did not have radiography result at screening were not categorized.

5. If there was at least 1 positive result of viral serology for SARS-CoV-2 antibody IgG and IgM at Day 1, then positive. If there were both negative results of viral serology for SARS-CoV-2 antibody IgG and IgM at Day 1, then negative.

Baseline characteristics for ITT Set – High Risk displayed a similar trend to the baseline characteristics for ITT Set.

Overall, the median (minimum, maximum) times (days) from the initial SARS-CoV-2 infection related symptom started to the date of study drug administration in ITT Set were similar between the 2 groups (4.0 [1, 12] and 4.0 [0, 11] days in the regdanvimab 40 mg/kg and Placebo groups, respectively). In ITT Set – High Risk, the results were same as ITT Set (4.0 [1, 12] and 4.0 [0, 11] days in the regdanvimab 40 mg/kg and Placebo groups, respectively).

Table 15: (E) - Proportion of Patient at High Risk Group by risk factor – Study CT-P59 3.2 Part 2

	CT-P59 40 mg/kg (N=656)	Placebo (N=659)	Total (N=1315)
Patients who meet the at least one of high risk criteria	446 (68.0%)	434 (65.9%)	880 (66.9%)
Advanced age (Age >50 years)	298 (45.4%)	284 (43.1%)	582 (44.3%)
Obesity (BMI>30 kg/m2)	207 (31.6%)	208 (31.6%)	415 (31.6%)
Cardiovascular disease, including hypertension	238 (36.3%)	205 (31.1%)	443 (33.7%)
Chronic lung disease, including asthma	19 (2.9%)	30 (4.6%)	49 (3.7%)
Type 1 or type 2 diabetes mellitus	73 (11.1%)	47 (7.1%)	120 (9.1%)
Chronic kidney disease, including those on dialysis	12 (1.8%)	12 (1.8%)	24 (1.8%)
Chronic liver disease	17 (2.6%)	15 (2.3%)	32 (2.4%)

As for Part 1 the baseline comorbidities in the table for Part 2 were conflated, however, in the table of *Proportion of Patient at High Risk Group by risk factor* the breakdown of high risk factors in the ITT set gives some insight. In the ITT set the patients with chronic lung disease including asthma were somewhat more common in the placebo group (2.9% for regdanvimab vs. 4.6% for placebo) and diabetes mellitus were more common in the regdanvimab treated group (11.1% for regdanvimab vs. 7.1% for placebo). Overall, the proportions of at least one high risk factor are similar between the treatment groups.

Numbers analysed

Study CT-P59 3.2 Part 1

Table 16: (E) – Analysis Sets

	CT-P59 40 mg/kg	CT-P59 80 mg/kg	Placebo	Total
	Number of patients			
Intent-to-Treat Set	105	111	111	327
Intent-to-Treat Infected Set	101	103	103	307
Safety Set	105	110	110	325
Pharmacokinetic Set	29	32	27	88

Abbreviations: ITT, intent to treat; ITTI, intent-to-treat infected; PK, pharmacokinetic.
Note: The randomized treatment at Day 1 prior to the study drug administration was used for ITT Set. The actual treatment was used for ITTI, Safety, and PK Sets.

Study CT-P59 3.2 Part 2

Table 17: (E) - Analysis Sets

	CT-P59 40 mg/kg	Placebo	Total
Intent-to-treat set	656	659	1315
Intent-to-treat set – High Risk[1]	446	434	880
Intent-to-treat infected set	612	618	1230
Intent-to-treat infected set– High Risk[1]	415	407	822
Safety set	652	650	1302

Note: The randomised treatment at Day 1 prior to the study drug administration are used for ITT Set, ITT Set –High Risk, ITTI and ITTI – High Risk. The actual treatment is used for Safety Set.
[1] The high-risk patients with one or more of the following risk factors: Age >50 years; BMI > 30 kg/m^2 collected via vital signs CRF; 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 prescriber's assessment.

Outcomes and estimation

Study CT-P59 3.2 Part 1

Proportion of Patients with Clinical Symptom Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28

There were no deaths in this study.

Table 18: (E) - Proportion of Patients with Clinical Symptom Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 in Study CT-P59 3.2 Part 1: Intent-to-Treat Infected Set

	CT-P59 40 mg/kg	CT-P59 80 mg/kg	Pooled CT-P59	Placebo
All patients	**4/101 (4.0%)**	**5/103 (4.9%)**	**9/204 (4.4%)**	**9/103 (8.7%)**
Risk Difference [95% CI]	-4.8 [-12.5, 2.4]	-3.9 [-11.7, 3.5]	-4.3 [-11.9, 1.5]	

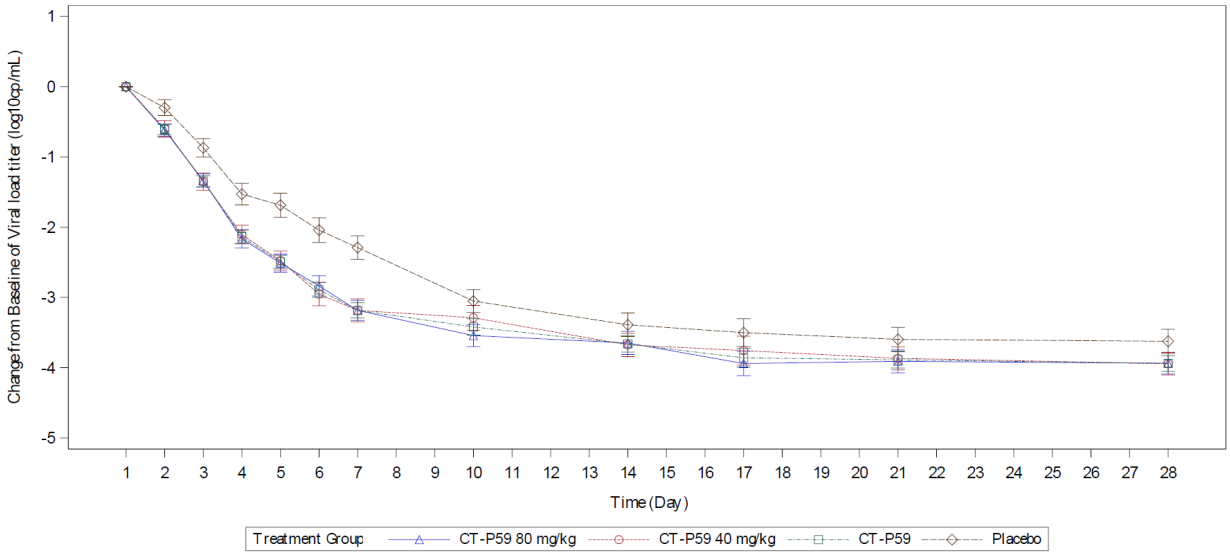
	CT-P59 40 mg/kg	CT-P59 80 mg/kg	Pooled CT-P59	Placebo
Patients at High Risk[1]	**3/70 (4.3%)**	**5/76 (6.6%)**	**8/146 (5.5%)**	**9/71 (12.7%)**
Risk Difference [95% CI]	-8.4 [-19.2, 1.1]	-6.1 [-16.9, 3.9]	-7.2 [-17.6, 1.0]	

Note: Clinical symptom which requires hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28. 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%. Exact unconditional confidence interval displayed for difference of each treatment group (CT-P59 - Placebo).
[1] The high risk patients with 1 or more of the following risk factors: Age >50 years; BMI > 30 kg/m^2 collected via vital signs CRF; 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 prescriber's assessment.

Viral Shedding

After study drug administration on Day 1, greater reductions from baseline viral load were shown in regdanvimab groups compared to the Placebo group, mostly notable up to Day 10. At Day 7 patients treated with regdanvimab had 39% more reduction in viral titre compared to Placebo. The mean (SD) change from baseline in viral titre at Day 7 was -3.184 (1.496) in the regdanvimab treatment groups and -2.290 (1.709) log_{10} copies/ml in the Placebo group.

Figure 20: (E) - Mean (±SE) Change from Baseline of Viral Load Titres (log_{10} cp/mL) – Intent-to-Treat Infected Set



Genotyping of clinical isolates

Nasopharyngeal samples with viral concentrations above the lower limit for sequencing and from patients who did not reach clinical recovery by Day 14 or did not show decrease in viral shedding are sequenced at baseline and post-treatment in order to monitor for potential regdanvimab-resistance associated spike variations. Samples from a total 158 patients (36, 40 and 82 patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg and Placebo groups, respectively) were analysed by next-generation sequencing (NGS).

Variant at spike protein amino acid positions Q493 or S494 at an allele fraction of ≥15% were detected for 16.7% (6/36) of patients in the CT-P59 40 mg/kg group and 7.5% (3/40) of patients in the CT-P59 80 mg/kg group post-treatment and included Q493K/R and S494P/L. In addition, E484G (23.256% allele frequency) was found at Day 3 in one patient.

At the present, there is no clear indication of any new emerging resistant SARS-Cov-2 variant in patients failing regdanvimab treatment. However, genotyping results from Part 2 are pending and a complete assessment will be made upon availability of those results.

Study CT-P59 3.2 Part 2

Primary Efficacy Endpoint

Proportion of Patients with Clinical Symptoms Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 in High-Risk Patients

A total of 69 patients were identified to meet the criteria for hospitalisation (e.g. supplemental oxygen therapy and/or ≥24 hours of acute care, in a hospital or similar acute care facility), or oxygen therapy (at least 24 hours of supplemental oxygen care and SpO_2 measure in room air before applying supplemental oxygen shows ≤94%), or experiencing mortality due to SARS-CoV-2 infection in all randomized patients. Among them, 62 patients were at high risk according to the criteria defined above.

In patients with high risk for progressing to severe COVID-19, the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was significantly lower in the regdanvimab 40 mg/kg group (14/446 [3.1 %]) compared to the Placebo group (48/434 [11.1 %]), which corresponds to a 72 % reduction. The difference between the proportions was statistically significant (p<0.0001 [stratified CMH test]; estimated difference [95% CI] = -8.0 [-11.7, -4.5]). The result for the ITTI Set - High Risk showed similar trend.

There were 1 and 2 deaths in the regdanvimab 40 mg/kg and Placebo groups, respectively. The cause of death was in all cases assessed as related to worsening of COVID-19.

Table 19: (E) - Proportion of Patients with Clinical Symptoms Requiring Hospitalization, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28: ITT set – High Risk, Part 2

n (%)	CT-P59 40 mg/kg (N=446)	Placebo (N=434)	Difference (95%CI)[1]	P-value[2]
SARS-CoV-2 infection patients at high-risk, (95% CI)[3]	14/446 (3.1) (1.9, 5.2)	48/434 (11.1) (8.4, 14.4)	-8.0 (-11.7, -4.5)	<0.0001

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

1. The difference of proportions between 2 groups estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights were 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).
2. The p-value from stratified CMH test was presented. The CMH test was stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).
3. 95% CI for each proportion was computed by Wilson (score) method.

The supportive analysis of the ITTI Set - High Risk and sensitivity analysis using fisher's exact test for the ITT Set – High risk showed essentially similar results.

The subgroup analysis for the primary endpoint was conducted in accordance with the predefined category in SAP. The subgroup analysis of age, sex, and baseline comorbidities in high-risk patients indicated a similar trend to the main analysis; the proportion of patients with clinical symptoms requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection was lower in the regdanvimab 40 mg/kg group compared to the Placebo group. The subgroup analysis of region and race showed no clear trend as majority of patients were enrolled from EU region and were White. See details in section Ancillary Analyses below.

As the primary endpoint was statistically significant, the first key secondary endpoint was tested following hierarchical principles. In the same manner, subsequent key secondary endpoints were tested based on a fixed sequence procedure in order to preserve the Type I error.

Key Secondary Efficacy Endpoints

Proportion of Patients with Clinical Symptoms Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 in All Randomised Patients

Table 20: (E) - Proportion of Patients with Clinical Symptoms Requiring Hospitalization, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28: Intent-to-Treat Set, Part 2

n (%)	CT-P59 40 mg/kg (N=656)	Placebo (N=659)	Difference (95%CI)[1]	P-value[2]
SARS-CoV-2 infection patients, (95% CI)[3]	16/656 (2.4) (1.5, 3.9)	53/659 (8.0) (6.2, 10.4)	-5.9 (-8.5, -3.3)	<0.0001

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.
1. The difference of proportions between 2 groups estimated using CMH weights, and the 95% stratified Newcombe CI with CMH weights were 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).
2. The p-value from stratified CMH test was presented. The CMH test was stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).
3. 95% CI for each proportion was computed by Wilson (score) method.

Time to Clinical Recovery up to Day 14 in High-Risk Patients

The median time to clinical recovery (at least 48 hours) in high-risk patients was 9.27 days in regdanvimab 40 mg/kg group, but the median time was not reached in Placebo group as less than 50% of patients in Placebo group achieved clinical recovery up to Day 14 (48.8%). Therefore, it can be inferred that the regdanvimab 40 mg/kg group shortened time to clinical recovery in high-risk patients by at least 4.73 days compared to the Placebo group. The difference in time to clinical recovery between treatment groups was statistically significant ($p<0.0001$ [stratified log-rank test]; clinical recovery ratio [95% CI] = 1.58 [1.31, 1.90]), see table below.

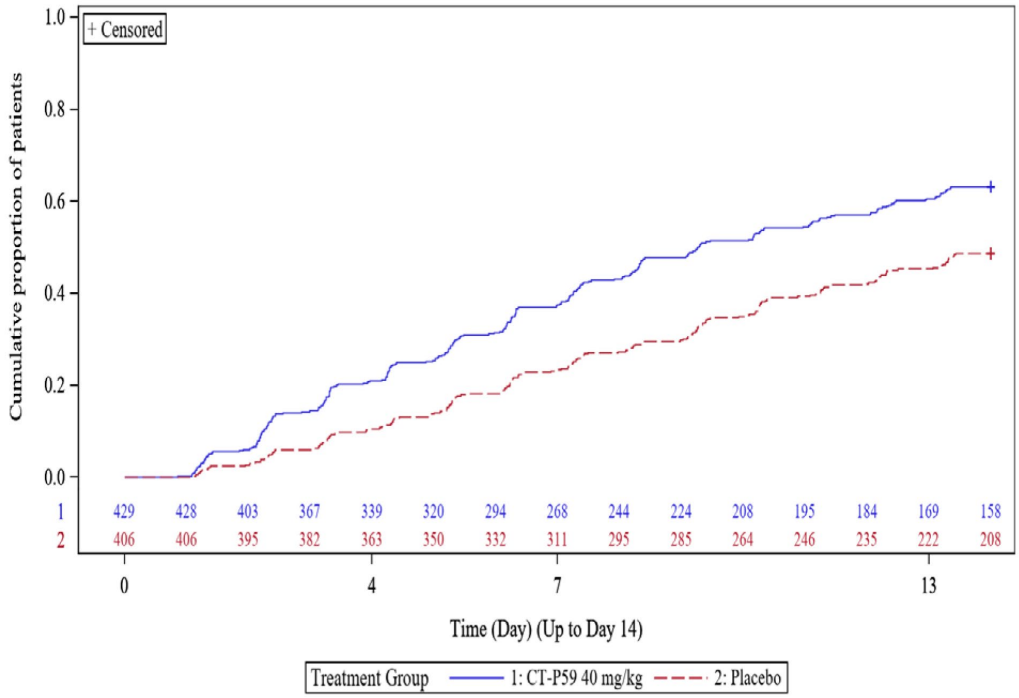
The Kaplan-Meier plot for the cumulative proportion of the patients with clinical recovery (at least 48 hours) up to Day 14 showed that the proportion gradually increased over time in all groups, and the proportions were consistently higher in the regdanvimab 40 mg/kg group compared to the Placebo group at all time points, see figure below. The results of time to clinical recovery in high-risk patients for the ITTI Set – High Risk showed similar trend.

Table 21 (E) - Time to Clinical Recovery (for at least 48 hours) up to Day 1: Intent-to-Treat Set – High Risk, Part 2

	CT-P59 40 mg/kg (N=446)	Placebo (N=434)
Number of Patients with Clinical Recovery up to Day 14	271/429 (63.2%)	198/406 (48.8%)
Number of Patients with Censoring	158/429 (36.8%)	208/406 (51.2%)
Ongoing study without event	119/429 (27.7%)	124/406 (30.5%)
Dearth or Early Withdrawal for any reason	5/429 (1.2%)	9/406 (2.2%)
Rescue Therapy	30/429 (7.0%)	63/406 (15.5%)
Hospitalisation	4/429 (0.9%)	12/406 (3.0%)
Time to Clinical Recovery[1]		
Median [95% CI)	9.27 [8.27, 11.05)	N.C. [12.35, N.C.)
Proportion with Clinical Recovery		
4 Days	21.0%	10.6%
7 days	37.5%	23.4%
10 days	51.5%	35.0%
13 days	60.6%	45.3%
Clinical Recovery Ratio (95% CI)[2]	1.58 (1.31, 1.90)	
P-value[3]	<0.0001	

Note: Patients who report at least one symptom at baseline are included in the analysis. A patient with two or more censoring reasons is included in the earliest occurred reason. If the dates are the same, the patient are included in a reason listed first in the table.
[1] Time to clinical recovery (days) is calculated as (Date/time of Event or Censoring – Date/time of study drug administration), and Kaplan-Meier estimates and 95% CI based on Brookmeyer-Crowley methodology (via loglog transformation) are presented.
[2] Clinical recovery ratio and its 95% CI estimated from the stratified Cox proportional hazard model are presented. The Cox proportional hazard model is stratified by Age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).
[3] The p-value from stratified log-rank test is presented. The log-rank test is stratified by Age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).
N.C: Not Calculated.

Figure 21(E) – Time to Clinical Recovery (for at least 48 hours) up to Day 14: Intent-to-Treat Set – High Risk, Part 2



Time to Clinical Recovery up to Day 14 in All Randomised Patients

The time to clinical recovery (at least 48 hours) was significantly shorter in patients who received regdanvimab than patients who received the placebo (median, 8.38 days vs. 13.25 days in the ITT set). The difference in time to clinical recovery between treatment groups was statistically significant (p<0.0001[stratified log-rank test]; clinical recovery ratio [95% CI]=1.50 [1.29, 1.73]).

A post-hoc analysis of the proportion of patients who met the criteria for clinical recovery (at least 48 hours) up to Day 14 and subsequently had a relapse up to Day 28 was conducted in ITT set, and showed that the relapse rate is slightly lower in the regdanvimab 40 mg/kg compared to the Placebo (169/412 [41.0%] and 144/323 [44.6%], respectively).

Ancillary analyses

Subgroup analyses of the primary endpoint

Some of the predefined subgroup analyses of the primary endpoint in ITT set – High Risk are presented below.

Age (<60 years, ≥60 years, ≥50 years)

Results show a difference in proportion of patients with clinical symptoms between the treatment groups for all age subgroups tested, see table below.

Table 22: (E) - Proportion of Patient with Clinical Symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection Up to Day 28 in ITT Set – High Risk, Part 2

Subgroup by Age: < 60 years

	CT-P59 40 mg/kg (N=295)	Placebo (N=288)	Difference (95% CI) [1]	P-value [2]
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI) [3]	5 (1.7%) (0.7, 3.9)	24 (8.3%) (5.7, 12.1)	-6.7 (-10.7, -2.7)	0.0002

Subgroup by Age: ≥ 50 years

	CT-P59 40 mg/kg (N=306)	Placebo (N=294)	Difference (95% CI) [1]	P-value [2]
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI) [3]	13 (4.2%) (2.5, 7.1)	42 (14.3%) (10.7, 18.7)	-10.0 (-15.0, -5.2)	<.0001

Subgroup by Age: ≥ 60 years

	CT-P59 40 mg/kg (N=151)	Placebo (N=146)	Difference (95% CI) [1]	P-value [2]
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI) [3]	9 (6.0%) (3.2, 10.9)	24 (16.4%) (11.3, 23.3)	-10.8 (-18.7, -3.1)	0.0032

Note: Clinical symptom which requires hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 is included.
[1] The difference of proportions between two treatment groups estimated using CMH weights, and the 95% stratified Newcombe 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).

[2] The nominal p-value from stratified CMH test is presented in descriptive purpose. 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).
[3] 95% CI for each proportion is computed by Wilson (score) method.

In Study CT-P59 3.2 Part 2, 14.2% of patients in the CT-P59 40 mg/kg group and 11.8% of patients in the Placebo group were aged 65 or older. In patients of ≥65 years, the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was lower in the CT-P59 40 mg/kg group (6/93 [6.5%]) compared to the Placebo group (14/78 [17.9%]).

Table 23: (E) - Proportion of Patients with Clinical Symptom Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 by Age: Intent-to-Treat Set - High Risk, Part 2

	CT-P59 40 mg/kg	Placebo	Difference (95% CI)[1]	P-value[2]
Age ≥ 65 years				
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI)[3]	6/93 (6.5%) (3.0, 13.4)	14/78 (17.9%) (11.0, 27.9)	-10.5 (-21.5, 0.1)	0.0391
Age < 65 years				
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI)[3]	8/353 (2.3%) (1.2, 4.4)	34/356 (9.6%) (6.9, 13.0)	-7.6 (-11.4, -3.8)	<.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 SpO2 measure in room air before applying supplemental oxygen showing ≤94%.
[1] The difference of proportions between two treatment groups estimated using CMH weights, and the 95% stratified Newcombe 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).
[2] The nominal p-value from stratified CMH test is presented in descriptive purpose. 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).
[3] 95% CI for each proportion is computed by Wilson (score) method.

Baseline comorbidities (Yes, No)

In Study CT-P59 3.2 Part 2, 65.7% of patients in the regdanvimab 40 mg/kg group and 62.2% of patients in the Placebo group had at least 1 of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, and pneumonia at baseline.

Table 24: (E) - Proportion of Patients with Clinical Symptom Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 by Baseline Comorbidities: Intent-to-Treat Set - High Risk, Part 2

	CT-P59 40 mg/kg	Placebo	Difference (95% CI)[1]	P-value[2]
Patients with Baseline Comorbidities				
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI)[3]	13/352 (3.7%) (2.2, 6.2)	45/339 (13.3%) (10.1, 17.3)	-9.6 (-14.0, -5.4)	<.0001
Patients without Baseline Comorbidities				
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI)[3]	1/94 (1.1%) (0.2, 5.8)	3/95 (3.2%) (1.1, 8.9)	-2.3 (-9.6, 5.7)	0.2787

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 SpO2 measure in room air before applying supplemental oxygen showing ≤94%.
[1] The difference of proportions between two treatment groups estimated using CMH weights, and the 95% stratified Newcombe 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).
[2] The nominal p-value from stratified CMH test is presented in descriptive purpose. 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).
[3] 95% CI for each proportion is computed by Wilson (score) method.

Results of the age and baseline comorbidities subgroup analyses adds support to the outcome of the primary analysis in high risk patients. The analysis in patients ≥65 years was not a prespecified subgroup analysis, however, a similar trend is shown for this age group.

Individual High Risk Factors

In Study CT-P59 3.2 Part 2, a subgroup analysis by individual risk factor for progressing to severe COVID-19 was conducted for proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28.

Table 25: (E) - Proportion of Patients with Clinical Symptom Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 by Individual Risk Factor: Intent-to-Treat Set, Part 2

	Treatment Group	N	Events	Proportion (95% CI)[1]	Difference (95% CI)[2]	P-value[3]	Relative Risk Reduction[4]
Advanced age (Age >50 years)	CT-P59 40 mg/kg	298	13	4.4% (2.6, 7.3)	-10.5 (-15.6, -5.5)	<.0001	70%
	Placebo	284	42	14.8% (11.1, 19.4)			
Obesity (BMI >30 kg/m^2)	CT-P59 40 mg/kg	207	7	3.4% (1.6, 6.8)	-8.2 (-14.0, -2.3)	0.0014	70%
	Placebo	208	24	11.5% (7.9, 16.6)			
Cardiovascular disease, including hypertension	CT-P59 40 mg/kg	238	12	5.0% (2.9, 8.6)	-8.8 (-14.8, -3.2)	0.0015	65%
	Placebo	205	29	14.1% (10.0, 19.6)			
Chronic lung disease, including asthma	CT-P59 40 mg/kg	19	1	5.3% (0.9, 24.6)	-7.2 (-25.3, 17.2)	0.4331	60%
	Placebo	30	4	13.3% (5.3, 29.7)			
Type 1 or type 2 diabetes mellitus	CT-P59 40 mg/kg	73	5	6.8% (3.0, 15.1)	-16.5 (-31.6, -1.9)	0.0148	73%
	Placebo	47	12	25.5% (15.3, 39.5)			
Chronic kidney disease, including those on dialysis	CT-P59 40 mg/kg	12	2	16.7% (4.7, 44.8)	-6.7 (-39.8, 25.4)	0.7144	33%
	Placebo	12	3	25% (8.9, 53.2)			
Chronic liver disease	CT-P59 40 mg/kg	17	2	11.8% (3.3, 34.3)	-10.3 (-39.1, 20.2)	0.4469	41%
	Placebo	15	3	20% (7.0, 45.2)			
Immuno-suppressed	CT-P59 40 mg/kg	0	N/A	N/A	N.C	N.C	N.C
	Placebo	2	0	0% (0.0, 65.8)			

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 SpO2measure in room air before applying supplemental oxygen showing ≤94%. Patient with two or more risk factor is included in each risk factor respectively.
[1] 95% CI for each proportion is computed by Wilson (score) method.
[2] The difference of proportions between two treatment groups estimated using CMH weights, and the 95% stratified Newcombe 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).
[3] The nominal p-value from stratified CMH test is presented in descriptive purpose. 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).
[4] Relative Risk Reduction = (Proportion in CT-P59 - Proportion in Placebo)/Proportion in Placebo*100
N/A: Not Applicable, N.C.: Not Calculated.

In non-high-risk patients, the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was lower in the

regdanvimab 40 mg/kg group (2/210 [1.0%]) compared to the Placebo group (5/225 [2.2 %]), which corresponds to a 55 % reduction (p=0.2511 [stratified CMH test]; estimated difference [95% CI] = -1.4 [-4.6, 2.6]).

Secondary Endpoints

The Applicant has performed a number of secondary analyses. These include the proportion of patients with all-cause mortality and time to negative conversion of Sars-Cov-2 NPH PCR.

Proportion of Patients with All-Cause Mortality – ITT set

The proportion of patients with all-cause mortality up to Day 28 in the regdanvimab 40 mg/kg group was lower than the Placebo group (1/656 [0.2%] and 2/659 [0.3%] patients in the regdanvimab 40 mg/kg and Placebo groups, respectively (p=0.5389 [stratified CMH test]).

Time to Negative Conversion up to Day 28 – ITT set

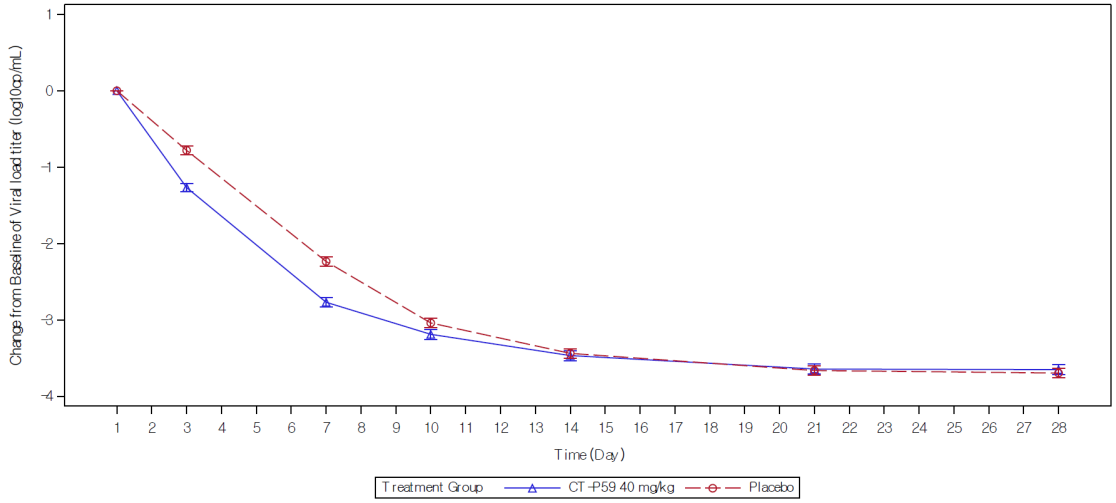
The time to negative conversion (<2.33 log10cp/mL as negative) up to Day 28 by RT-qPCR in the regdanvimab 40 mg/kg group was shorter than the Placebo group (median, 11.89 and 13.13 days in the regdanvimab 40 mg/kg and Placebo groups, respectively). The differences in time to negative conversion between the two treatment groups was significant (p<0.0001 [stratified log-rank test]; negative conversion ratio [95% CI]= 1.48 (1.30, 1.67)).

Virology and Serology Analyses

Viral Shedding

In the ITTI Set, the mean virus titre detected by RT-qPCR at baseline were similar between the 2 groups (6.055 log_{10} cp/mL and 6.089 log_{10} cp/mL in the regdanvimab 40 mg/kg and Placebo groups, respectively). By Day 7, patients in regdanvimab mg/kg group showed greater reduction of viral load compared to the patients in the Placebo group. The mean (SE) change from baseline for viral shedding at Day 7 were: -2.770 (0.0652) log_{10} cp/mL and -2.236 (0.0637) log_{10} cp/mL in regdanvimab 40 mg/kg and Placebo groups, respectively.

Figure 22(E) - Mean (±SE) Change from Baseline of Viral Load Titres (log_{10} cp/mL) – Intent-to-Treat Infected Set, Part 2.



These results confirm the viral shedding results in Part 1 of the study. The greater reduction in viral shedding at Day 7 in the regdanvimab treated patient group supports the clinical efficacy of regdanvimab.

However, as this is an exploratory endpoint in the protocol, and since this is neither of direct clinical

relevance nor a surrogate endpoint of efficacy, the Applicant was asked to remove the virology section, including the figure, from 5.1 in the SmPC.

Serology against Sars-Cov-2

In Study CT-P59 3.2 Part 2, 57/656 (8.7%) and 50/659 (7.6%) in the regdanvimab 40 mg/kg and Placebo groups, respectively, were positive at Day 1 for either IgG or IgM antibodies as determined by sponsor-supplied rapid diagnostic test, Celltrion DiaTrust COVID-19 IgG/IgM Rapid Test.

In the ITT-High Risk Set, a subgroup analysis for the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was conducted by serology status (table below).

Table 26: (E) - Proportion of Patients with Clinical Symptom Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28 by Serology Status: Intent-to-Treat Set – High Risk, Part 2

	CT-P59 40 mg/kg	Placebo	Difference (95% CI)[1]	P-value[2]
Patients with Day 1 IgG and IgM all negative				
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI)[3]	12/384 (3.1%) (1.8, 5.4)	45/374 (12.0%) (9.1, 15.7)	-9.1 (-13.1, -5.0)	<.0001
Patients with Day 1 IgG or IgM at least one positive				
Proportion of Patient with Clinical Symptom up to Day 28 (95% CI)[3]	2/57 (3.5%) (1.0, 11.9)	3/50 (6%) (2.1, 16.2)	-4.1 (-18.4, 9.0)	0.3306

Note: Clinical symptom which requires hospitalisation, oxygen therapy, or experiencing mortality due to SARSCoV-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 SpO2 measure in room air before applying supplemental oxygen showing ≤94%.
[1] The difference of proportions between two treatment groups estimated using CMH weights, and the 95% stratified Newcombe 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).
[2] The nominal p-value from stratified CMH test is presented in descriptive purpose. 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).
[3] 95% CI for each proportion is computed by Wilson (score) method.

It is not known if the sensitivity of the rapid test is comparable to tests used in the evaluations of other SARS-CoV-2-specific mAbs. The number of seropositive at baseline and the number of events is too scarce to give any insights on additional benefit of regdanvimab in patients that are seropositive at baseline.

Genotype and Phenotype of SARS-CoV-2 Viral Isolates

Results of genotype and phenotype will be presented in Part 2 Final CSR. Genotype and phenotype results will be summarized for the ITTI Set by treatment group at each scheduled visit using frequency tables. The applicant should provide timelines for the delivery of these data. Phenotyping assessment in Study CT-P59 3.2 Part 2 will be done with variants in RBD at allelic frequency of ≥15% and all variants in epitope found at post-treatment from patients who received CT-P59 in Study CT-P59 3.2 Part 2. Neutralization activity will be evaluated in the pseudovirus assay. Phenotyping results are expected to be available in December 2021.

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

Title: 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 - Part 2			
Study identifier	Protocol number CT-P59 3.2; EudraCT 2020-003369-20		
Design	Randomized, Parallel-group, Placebo-controlled, Double-Blind		
	Duration of main phase:		18 January 2021 to 21 May 2021 (last patient's Day 28 visit)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Exploratory		
Treatments groups	CT-P59 40 mg/kg + SoC		CT-P59 40 mg/kg as an IV infusion over 60 minutes (±15 minutes), n = 656
	Placebo + SoC		Placebo, n =659
Endpoints and definitions	Confirmatory endpoint	Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high-risk patients	Proportion of patients with clinical symptom requiring hospitalisation (>=24 hours of acute care), oxygen therapy (at least 24 hours of supplemental oxygen care and SpO2 measure in room air before applying supplemental oxygen shows =<94%) or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in high risk patients
	Confirmatory endpoint	Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients	Proportion of patients with clinical symptom requiring hospitalisation (>=24 hours of acute care), oxygen therapy (at least 24 hours of supplemental oxygen care and SpO2 measure in room air before applying supplemental oxygen shows =<94%) or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients

	Confirmatory endpoint	Time to clinical recovery up to Day 14 in high-risk patients	Day of clinical recovery is defined as the first day on which the patient records as 'absent' or 'mild' in intensity for all symptoms on the SARS-CoV-2 Infection Symptom Checklist 1 for at least 48 hours in high-risk patients
	Confirmatory endpoint	Time to clinical recovery up to Day 14 in all randomized patients	Day of clinical recovery is defined as the first day on which the patient records as 'absent' or 'mild' in intensity for all symptoms on the SARS-CoV-2 Infection Symptom Checklist 1 for at least 48 hours in all randomized patients
Database lock	11 June 2021		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT = Intent-to-treat Set		
Descriptive statistics and estimate variability	Treatment group	CT-P59 40 mg/kg	Placebo
	Number of subjects in ITT-HR	446	434
	Proportion of Clinical symptoms up to D28, %	3.1	11.1
	95%CI	1.9-5.2	8.4-14.4
	Number of subjects in ITT	656	659
	Proportion of Clinical symptoms up to D28, %	2.4	8.0
	95%CI	1.5-3.9	6.2-10.4
	Number of subjects in ITT-HR	446	434
	Time to recovery up to Day 14 (median days)	9.27	N.C
	95%CI	8.27-11.05	12.35-N.C.
	Number of subjects in ITT	656	659
	Time to recovery up to Day 14 (median days)	8.38	13.25

	95%CI	7.91-9.33	11.94-N.C.

2.5.5.3. Clinical studies in special populations

Study ID Analysis Set	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Study CT-P59 1.1			
ITT Set	0/32	0/32	0/32
PK set	0/24	0/24	0/24
Study CT-P59 1.2			
ITT Set	0/18	0/18	0/18
PK set	0/15	0/15	0/15
Study CT-P59 3.2 Part 1			
ITT Set	44/327	7/327	3/327
PK set	11/88	0/88	0/88
Study CT-P59 3.2 Part 2			
ITT Set	136/1315	33/1315	2/1315

No special studies in children or in patients with renal or hepatic impairment have been performed. Please refer to the subgroup analysis with regards to efficacy stratified by age ≥50, ≥ 60 and ≥65.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has conducted 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.

This study was designed in two parts. The first part tested two dose levels versus placebo (40 mg/kg and 80 mg/kg as a single dose). It indicated the anticipated antiviral effects. On the basis of results from part one, where no dose-response was seen, the 40 mg/kg dose was selected for the confirmatory part 2 of the study, which tested the hypothesis that regdanvimab given to outpatients with early disease might reduce the risk of hospitalisation or severe disease.

In the pivotal Part 2 of the study, patients were screened at 60 study centres across, Hungary, Ireland, Italy, Mexico, North Macedonia, Peru, Poland, Republic of Korea, Republic of Moldavia, Romania, Serbia, Spain, Ukraine and United States.

The study included outpatients aged 18 or above. Patients had to have oxygen saturation >94% on room air, not requiring supplemental oxygen, and onset of SARS-CoV-2 infection associated symptom no more than 7 days prior to the study drug administration. The key exclusion criterion was signs of severe COVID. Furthermore, patents were required to be unvaccinated for SARS-CoV-2.

Patients were randomised to receive a single dose of 40 mg/kg of regdanvimab, or placebo.

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 in high-risk patients

"High-risk patients" met at least one of the following criteria:

- Advanced age (Age >50 years)
- Obesity (body mass index [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
- Immunosuppressed.

If the primary endpoint is statistically significant, the key secondary endpoints was to tested using the fixed sequence procedure in order to preserve the Type I error. The order of testing was as follows:

1. Proportion of patients with clinical symptom requiring hospitalization, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomized patients.
2. Time to clinical recovery up to Day 14 in high-risk patients.
3. Time to clinical recovery up to Day 14 in all randomized patients.

Originally, a total of 1172 patients (586 patients per group) were planned for. This was changed to 1300 patients (650 patients per group) in a late protocol amendment. The primary objective was changed in the same amendment 6 of the protocol (dated 22 March 2021) to restrict the primary efficacy population to high-risk patients. Additionally, key secondary endpoints were defined together with a multiple testing procedure to control the type 1-error for the primary and key secondary analyses.

Efficacy data and additional analyses

The study period for the pivotal part 2, was from 18 January 2021 (first patient's study drug administration date) to 21 May 2021 (last patient's Day 28 visit). Approximately 80% of patients were treated in the EU; the majority of the rest in the US.

About 2/3 of recruited patients were over age 50 or had other recognised risk factors for severe COVID-19; however only two patients were classified as "immunosuppressed". 87% of patients had negative serology for SARS-CoV-2 at baseline.

In patients with high risk for progressing to severe COVID-19, the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was significantly lower in the regdanvimab group (14/446 [3.1 %]) compared to the placebo group (48/434 [11.1 %]) which corresponds to a 72 % reduction. The difference between the proportions was statistically significant (p<0.0001 [stratified CMH test]; estimated difference [95% CI] = -8.0 [-11.7, -4.5]).

In all randomised patients, the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was significantly lower in the regdanvimab group (16/656 [2.4 %]) compared to the Placebo group (53/659 [8.0 %]) which corresponds to a 70% reduction. The differences between the proportion was statistically significant (p<0.0001 [stratified CMH test]; estimated difference [95% CI]= -5.9 [-8.5, -3.3]).

In non-high-risk patients, the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was lower in the regdanvimab group (2/210 [1.0%]) compared to the Placebo group (5/225 [2.2 %]), which

corresponds to a 55% reduction (p=0.2511 [stratified CMH test]; estimated difference [95% CI] = -1.4 [-4.6, 2.6]).

Thus, in this substratum, efficacy was not independently demonstrated. Notably, the applicant is seeking an indication for patients at "high risk", which is appropriate. However, a Major Objection on the indication wording was issued, as "increased risk" was the preferred term of the Committee. The applicant acknowledged the CHMP comment and the wording of the indication was amended, and the risk factors listed in Section 4.1 deleted as recommended by the CHMP. The proposed indication wording is now in line with the CHMP request.

The median time to clinical recovery (at least 48 hours) in high-risk patients was 9.27 days in regdanvimab group, but the median time was not reached in Placebo group as less than 50% of patients in this group achieved clinical recovery up to Day 14 (48.8%). The difference in time to clinical recovery between treatment groups was statistically significant (p<0.0001 [stratified log-rank test]; clinical recovery ratio [95% CI] = 1.58 [1.31, 1.90])

The proportion of patients with all-cause mortality up to Day 28 in the regdanvimab 40 mg/kg group was lower than the Placebo group (1/656 [0.2%] and 2/659 [0.3%] patients in the regdanvimab 40 mg/kg and Placebo groups, respectively

The time to negative virological conversion (<2.33 log10cp/mL as negative) up to Day 28 by RT-qPCR of nasopharyngeal swabs was shorter in the regdanvimab group than the Placebo group (median, 11.89 and 13.13 days in the regdanvimab and Placebo groups, respectively). The differences in time to negative conversion between the two treatment groups was significant (p<0.0001 [stratified log-rank test]; negative conversion ratio [95% CI]= 1.48 (1.30, 1.67)).Viral strains circulating at the time, and the regions of the study, were predominantly Wuhan and/or the alpha (B.1.117) variant.

Regdanvimab has reduced neutralising activity against South Africa (Beta, B.1.351), Brazil (Gamma, P.1), California (B.1.427 and B.1.429) and India (Kappa B.1.617.1 and Delta, B.1.617.2) variants in the PRNT and pseudovirus assays. In particular, there was a 183-fold shift in susceptibility for the delta variant (B.1.617.2. in a PRNT assay with the authentic virus).

The applicant has submitted top line data from the 4.1. study, which is a post marketing cohort performed in South Korea. In this, patients are hospitalised with moderate disease at baseline. Among 330 patients known to have delta- or non-delta variants, disease progression rate was approximately 20% regardless of viral strain. It is evident from the substantially risk of progression to severe disease, that this cohort differs from the population in study 3.2. Thus, we lack an index of regdanvimab efficacy in this population. Altogether these data are compatible with clinical efficacy against the delta variant, but they do not demonstrate it.

2.5.6. Conclusions on the clinical efficacy

It has been demonstrated that regdanvimab provides a clinically relevant reduction of the risk for progression to severe disease requiring hospitalisation or oxygen therapy, in outpatients presenting with mild or moderate disease, that are at increased risk of severe disease. It has also been demonstrated that regdanvimab reduces the duration of symptoms in such patients. Thus, efficacy has been established.

PK/PD data, animal model data, as well as post marketing data from South Korea are compatible with activity also against the delta variant, for which in vitro susceptibility is decreased. Clinical efficacy against the delta variant, however, has not been demonstrated.

The CHMP considers the following measures necessary to address issues related to Clinical:

- A population-based approach should be conducted in order to have an overall description of PK data and to characterize in particular the influence of weight on PK. Estimated availability by February 2022.
- For Part 2 (Study CT-P59 3.2), final ADA and Nab analytical reports are planned to be available in February 2022 and should be submitted post-marketing.
- Results of genotype and phenotype will be presented in Part 2 Final CSR (June 2022). Genotype and phenotype results will be summarized for the ITTI Set by treatment group at each scheduled visit using frequency tables.

2.5.7. Clinical safety

2.5.7.1. Patient exposure

Across the 3 studies with CT-P59, 906 subjects received at least 1 dose of CT-P59. Of these, 889 received the proposed dose of 40 mg/kg or more.

Table 27: Number of Subjects who received at Least 1 Dose of CT-P59

Study	Total Number of Subjects Receiving CT-P59	Number of Subjects Receiving CT-P59 in Each Group
Study CT-P59 1.1	24 healthy volunteers	10 mg/kg (single dose): 6 20 mg/kg (single dose): 6 40 mg/kg (single dose): 6 80 mg/kg (single dose): 6
Study CT-P59 1.2	15 patients with mild COVID-19	20 mg/kg (single dose): 5 40 mg/kg (single dose): 5 80 mg/kg (single dose): 5
Study CT-P59 3.2 Part 1	215 patients with mild to moderate COVID-19	40 mg/kg (single dose): 105 80 mg/kg (single dose): 110
Study CT-P59 3.2 Part 2	652 patients with mild to moderate COVID-19	40 mg/kg (single dose): 652

2.5.7.2. Adverse events

Summary of Adverse Events

An overview of AEs reported from Study CT-P59 1.1 in healthy volunteers and from Studies CT-P59 1.2 and CT-P59 3.2 in patients with SARs-CoV-2 infection is presented below.

Table 28: Summary of TEAEs in Studies CT-P59 1.2 and CT-P59 3.2 (COVID-19 Patients): Safety Set

	Study CT-P59 1.2				**Study CT-P59 3.2 Part 1**			**Study CT-P59 3.2 Part 2**	
	CT-P59 20 mg/kg (N=5)	**CT-P59 40 mg/kg (N=5)**	**CT-P59 80 mg/kg (N=5)**	**Placebo (N=3)**	**CT-P59 40 mg/kg (N=105)**	**CT-P59 80 mg/kg (N=110)**	**Placebo (N=110)**	**CT-P59 40 mg/kg (N=652)**	**Placebo (N=650)**
Total number of TEAEs	6	8	3	3	62	66	70	430	442
N (%) of subjects with ≥ 1 TEAE	3 (60)	4 (80)	3 (60)	1 (33.3)	32 (30.5)	29 (26.4)	35 (31.8)	198 (30.4)	202 (31.1)
Related	0	0	0	0	7 (6.7)	5 (4.5)	5 (4.5)	44 (6.7)	46 (7.1)
Unrelated	3 (60)	4 (80)	3 (60)	1 (33.3)	28 (26.7)	28 (25.5)	32 (29.1)	167 (25.6)	165 (25.4)
N (%) of subjects with ≥ 1 TEAE (Grade 3 or higher)	0	3 (60)	0	1 (33.3)	6 (5.7)	5 (4.5)	3 (2.7)	61 (9.4)	69 (10.6)
Related	0	0	0	0	1 (1.0)	0	0	12 (1.8)	15 (2.3)
Unrelated	0	3 (60)	0	1 (33.3)	5 (4.8)	5 (4.5)	3 (2.7)	51 (7.8)	55 (8.5)
N (%) of subjects with ≥ 1 TESAE	0	0	0	0	0	0	0	4 (0.6)	1 (0.2)
Related	0	0	0	0	0	0	0	1 (0.2)	0
Unrelated	0	0	0	0	0	0	0	3 (0.5)	1 (0.2)
N (%) of subjects with ≥ 1 TEAE classified as IRR	0	0	0	0	1 (1.0)	0	2 (1.8)	4 (0.6)	7 (1.1)
Related	0	0	0	0	1 (1.0)	0	2 (1.8)	4 (0.6)	7 (1.1)
Unrelated	0	0	0	0	0	0	0	0	0

Note: No TEAEs leading to discontinuation or deaths were reported in Studies CT-P59 1.2 and CT-P59 3.2 Part 1 and Part 2. However, in Study CT-P59 3.2 Part 2, 3 patients died due to worsening of COVID-19 not due to TEAE.

IRR: Infusion related reactions, N: Number, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event

Common Adverse Events

Study CT-P59 1.1 (Healthy Subjects)

In Study CT-P59 1.1 in healthy subjects, the number of subjects who experienced at least 1 treatment-emergent adverse event (TEAE) in the treatment groups were 0, 4 (66.7%), 3 (50.0%) and 0 subjects in the regdanvimab 10 mg/kg, 20 mg/kg, 40 mg/kg and 80 mg/kg treatment groups, respectively, and 1 (12.5%) subject in the Placebo group. All TEAEs were CTCAE (Common Terminology Criteria for Adverse Events) grade 1 or 2 in intensity except for Grade 3 TEAEs of limb injury and urticaria in one subject in the regdanvimab 20 mg/kg treatment group.

Study CT-P59 1.2 (Patients with Mild COVID-19)

In Study CT-P59 1.2 in patients with mild symptoms to SARS-CoV-2 infection, the number of patients who experienced at least 1 TEAE in the treatment groups were 3 (60.0%), 4 (80.0%) and 3 (60.0%) patients in the regdanvimab 20 mg/kg, 40 mg/kg and 80 mg/kg treatment groups, respectively, and 1 (33.3%) patient in the Placebo group. Most of the TEAEs were CTCAE grade 1 or 2 in intensity. There were no TEAEs reported by the Investigator to be related to the study drug.

Grade 3 or higher TEAEs were reported for 3 (60.0%) patients in the regdanvimab 40 mg/kg treatment group (Grade 3 of hepatocellular injury, Grade 3 of alanine aminotransferase [ALT] increased and Grade 4 hypertriglyceridaemia) and 1 (33.3%) patient in the Placebo group (Grade 3 of COVID-19 pneumonia).

The frequency of grade 3 ALT abnormalities in the CT-P59 1.2 study are somewhat striking and unexpected given the treatment modality but have not been reproduced in the later studies.

Study CT-P59 3.2 Part 1 (Patients with Mild to Moderate COVID-19)

The most commonly reported TEAEs (> 2% patients overall) were hypertriglyceridaemia (9 [2.8%] patients overall; 6 [5.7%], 0, 6 [2.8%] and 3 [2.7%] patients in the regdanvimab 40 mg/kg, regdanvimab 80 mg/kg, pooled regdanvimab and Placebo groups, respectively), dyslipidaemia (9 [2.8%] patients overall; 4 [3.8%], 3 [2.7%], 7 [3.3%] and 2 [1.8%] patients, respectively), blood creatine phosphokinase increased (8 [2.5%] patients overall; 5 [4.8%], 2 [1.8%], 7 [3.3%] and 1 [0.9%] patients, respectively), and hyperglycaemia (7 [2.2%] patients overall; 2 [1.9%], 2 [1.8%], 4 [1.9%] and 3 [2.7%] patients, respectively).

Table 29: TEAEs of Patients by System Organ Class and Preferred Term Occurring in > 1% in at Least One Treatment Group in Study CT-P59 3.2 Part 1: Safety Set

	CT-P59 40 mg/kg (N=105)	**CT-P59 80 mg/kg (N=110)**	**Pooled CT-P59 (N=215)**	**Placebo (N=110)**
Total number of TEAEs	62	66	128	70
N (%) of patients with at ≥ 1 TEAE	32 (30.5)	29 (26.4)	61 (28.4)	35 (31.8)
Blood and lymphatic system disorders	**8 (7.6)**	**4 (3.6)**	**12 (5.6)**	**4 (3.6)**

	CT-P59 40 mg/kg (N=105)	CT-P59 80 mg/kg (N=110)	Pooled CT-P59 (N=215)	Placebo (N=110)
Leukopenia	3 (2.9)	3 (2.7)	6 (2.8)	0
Thrombocytosis	3 (2.9)	1 (0.9)	4 (1.9)	2 (1.8)
Gastrointestinal disorders	**3 (2.9)**	**3 (2.7)**	**6 (2.8)**	**4 (3.6)**
Abdominal pain upper	2 (1.9)	1 (0.9)	3 (1.4)	0
Constipation	0	2 (1.8)	2 (0.9)	1 (0.9)
Nausea	0	0	0	2 (1.8)
General disorders and administration site conditions	**0**	**1 (0.9)**	**1 (0.5)**	**3 (2.7)**
Hepatobiliary disorders	**1 (1.0)**	**2 (1.8)**	**3 (1.4)**	**1 (0.9)**
Infections and infestations	**5 (4.8)**	**8 (7.3)**	**13 (6.0)**	**5 (4.5)**
Bacteriuria	2 (1.9)	2 (1.8)	4 (1.9)	2 (1.8)
Cystitis	3 (2.9)	2 (1.8)	5 (2.3)	0
Infective myositis	2 (1.9)	1 (0.9)	3 (1.4)	1 (0.9)
Injury, poisoning and procedural complications	**3 (2.9)**	**0**	**3 (1.4)**	**2 (1.8)**
Infusion related reaction	1 (1.0)	0	1 (0.5)	2 (1.8)
Ligament sprain	2 (1.9)	0	2 (0.9)	0
Investigations	**9 (8.6)**	**11 (10)**	**20 (9.3)**	**9 (8.2)**
Blood creatine phosphokinase increased	5 (4.8)	2 (1.8)	7 (3.3)	1 (0.9)
Blood lactate dehydrogenase increased	1 (1.0)	2 (1.8)	3 (1.4)	2 (1.8)
Hepatic enzyme increased	0	2 (1.8)	2 (0.9)	0
Inflammatory marker increased	0	3 (2.7)	3 (1.4)	2 (1.8)
Metabolism and nutrition disorders	**11 (10.5)**	**11 (10)**	**22 (10.2)**	**11 (10)**
Dyslipidaemia	4 (3.8)	3 (2.7)	7 (3.3)	2 (1.8)
Hyperglycaemia	2 (1.9)	2 (1.8)	4 (1.9)	3 (2.7)
Hyperkalaemia	1 (1.0)	3 (2.7)	4 (1.9)	2 (1.8)
Hypertriglyceridaemia	6 (5.7)	0	6 (2.8)	3 (2.7)
Musculoskeletal and connective tissue disorders	**2 (1.9)**	**1 (0.9)**	**3 (1.4)**	**2 (1.8)**

	CT-P59 40 mg/kg (N=105)	CT-P59 80 mg/kg (N=110)	Pooled CT-P59 (N=215)	Placebo (N=110)
Back pain	2 (1.9)	1 (0.9)	3 (1.4)	2 (1.8)
Nervous system disorders	**0**	**2 (1.8)**	**2 (0.9)**	**4 (3.6)**
Dizziness	0	0	0	3 (2.7)
Psychiatric disorders	**1 (1.0)**	**5 (4.5)**	**6 (2.8)**	**3 (2.7)**
Insomnia	0	3 (2.7)	3 (1.4)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	**2 (1.9)**	**2 (1.8)**	**4 (1.9)**	**1 (0.9)**
Epistaxis	2 (1.9)	1 (0.9)	3 (1.4)	0
Skin and subcutaneous tissue disorders	**5 (4.8)**	**3 (2.7)**	**8 (3.7)**	**3 (2.7)**
Rash	2 (1.9%)	0	2 (0.9%)	1 (0.9%)
Urticaria	0	0	0	2 (1.8%)

N: Number, TEAE: Treatment-emergent adverse event

In Study CT-P59 3.2 Part 1, the majority of TEAEs were CTCAE grade 1 in intensity. Grade 3 or higher TEAEs were reported for 6 (5.7%), 5 (4.5%), 11 (5.1%) and 3 (2.7%) patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, pooled CT-P59 and Placebo groups, respectively.

The most frequently reported grade 3 or higher TEAE was blood creatine phosphokinase increased (4 [1.2%] patients overall; 2 [1.9%], 1 [0.9%], 3 [1.4%] and 1 [0.9%] patients, respectively). All grade 3 or higher TEAEs were unrelated to the study drug except for grade 3 hypertriglyceridaemia reported in 1 (1.0%) patient in the CT-P59 40 mg/kg treatment group.

Table 30: Grade 3 or Higher TEAEs of Patients by System Organ Class and Preferred Term, Relationship and Intensity in Study CT-P59 3.2 Part 1: Safety Set

System Organ Class Preferred Term	CT-P59 40 mg/kg (N=105)	CT-P59 80 mg/kg (N=110)	Pooled CT-P59 (N=215)	Placebo (N=110)
N (%) of patients with at ≥ 1 Grade 3 or Higher TEAE	**6 (5.7)**	**5 (4.5)**	**11 (5.1)**	**3 (2.7)**
Related	1 (1.0)	0	1 (0.5)	0
Unrelated	5 (4.8)	5 (4.5)	10 (4.7)	3 (2.7)
Blood and lymphatic system disorders	**1 (1.0)**	**0**	**1 (0.5)**	**0**
Anaemia	1 (1.0)	0	1 (0.5)	0
Infections and infestations	**0**	**1 (0.9)**	**1 (0.5)**	**0**

System Organ Class Preferred Term	CT-P59 40 mg/kg (N=105)	CT-P59 80 mg/kg (N=110)	Pooled CT-P59 (N=215)	Placebo (N=110)
Cystitis	0	1 (0.9)	1 (0.5)	0
Investigations	**2 (1.9)**	**2 (1.8)**	**4 (1.9)**	**2 (1.8)**
Alanine aminotransferase increased	0	1 (0.9)	1 (0.5)	0
Blood creatine phosphokinase increased	2 (1.9)	1 (0.9)	3 (1.4%)	1 (0.9)
Gamma-glutamyltransferase increased	0	0	0	1 (0.9)
Metabolism and nutrition disorders	**2 (1.9)**	**2 (1.8)**	**4 (1.9)**	**1 (0.9)**
Hyperkalaemia	0	1 (0.9)	1 (0.5)	0
Hypernatraemia	0	1 (0.9)	1 (0.5)	0
Hypertriglyceridaemia	2 (1.9)	0	2 (0.9)	1 (0.9)
Vascular disorders	**1 (1.0)**	**0**	**1 (0.5)**	**0**
Hypertension	1 (1.0)	0	1 (0.5)	0

N: Number, TEAE: Treatment-emergent adverse event

Study CT-P59 3.2 Part 2 (Patients with Mild to Moderate COVID-19)

In Study CT-P59 3.2 Part 2 in outpatients with mild to moderate SARS-CoV-2 infection, the number of patients who experienced at least 1 TEAE in the treatment groups were 198 (30.4%) and 202 (31.1%) patients in the CT-P59 40 mg/kg and placebo groups, respectively.

Table 31: TEAEs of Patients by System Organ Class and Preferred Term Occurring in > 1% in at Least One Treatment Group in Study CT-P59 3.2 Part 2: Safety Set

System Organ Class Preferred Term	CT-P59 40 mg/kg (N=652)	Placebo (N=650)
Total number of TEAEs	430	442
N (%) of patients with ≥ 1 TEAE	198 (30.4)	202 (31.1)
Blood and lymphatic system disorders	**29 (4.4)**	**30 (4.6)**
Leukopenia	6 (0.9)	11 (1.7)
Lymphopenia	5 (0.8)	12 (1.8)
Thrombocytopenia	4 (0.6)	8 (1.2)
Thrombocytosis	11 (1.7)	5 (0.8)
Cardiac disorders	**7 (1.1)**	**4 (0.6)**

System Organ Class Preferred Term	CT-P59 40 mg/kg (N=652)	Placebo (N=650)
Gastrointestinal disorders	**7 (1.1)**	**10 (1.5)**
Hepatobiliary disorders	**14 (2.1)**	**13 (2)**
Hepatitis cholestatic	7 (1.1)	7 (1.1)
Infections and infestations	**28 (4.3)**	**28 (4.3)**
Infective myositis	7 (1.1)	3 (0.5)
Urinary tract infection	12 (1.8)	9 (1.4)
Injury, poisoning and procedural complications	**4 (0.6)**	**7 (1.1)**
Infusion related reaction	4 (0.6)	7 (1.1)
Investigations	**104 (16.0)**	**105 (16.2)**
Alanine aminotransferase increased	18 (2.8)	31 (4.8)
Aspartate aminotransferase increased	8 (1.2)	8 (1.2)
Blood creatine phosphokinase increased	14 (2.1)	10 (1.5)
Blood triglycerides increased	8 (1.2)	6 (0.9)
C-reactive protein increased	19 (2.9)	10 (1.5)
Gamma-glutamyltransferase increased	8 (1.2)	20 (3.1)
Hepatic enzyme increased	21 (3.2)	15 (2.3)
Inflammatory marker increased	14 (2.1)	17 (2.6)
Platelet count increased	2 (0.3)	7 (1.1)
Troponin increased	5 (0.8)	8 (1.2)
Metabolism and nutrition disorders	**62 (9.5)**	**58 (8.9)**
Dyslipidaemia	7 (1.1)	9 (1.4)
Hyperglycaemia	13 (2.0)	9 (1.4)
Hyperkalaemia	9 (1.4)	6 (0.9)
Hypertriglyceridaemia	30 (4.6)	32 (4.9)
Musculoskeletal and connective tissue disorders	**11 (1.7)**	**11 (1.7)**
Nervous system disorders	**3 (0.5)**	**7 (1.1)**
Renal and urinary disorders	**12 (1.8)**	**15 (2.3)**
Proteinuria	9 (1.4)	6 (0.9)
Vascular disorders	**18 (2.8)**	**12 (1.8)**
Hypertension	15 (2.3)	11 (1.7)

N: Number, TEAE: Treatment-emergent adverse event

In Study CT-P59 3.2 Part 2, the majority of TEAEs were CTCAE grade 1 or 2 in intensity. Grade 3 or higher TEAEs were reported for 61 (9.4%) and 69 (10.6%) patients in the CT-P59 40 mg/kg and Placebo groups, respectively. The most frequently reported grade 3 or higher TEAE was hypertriglyceridaemia (23 [1.8%] patients overall; 13 [2.0%] and 10 [1.5%] patients in the CT-P59 40 mg/kg and Placebo groups, respectively). Individual descriptions of grade 4 TEAE are provided below.

Table 32: Grade 3 or Higher TEAEs of Patients by System Organ Class and Preferred Term in Study CT-P59 3.2 Part 2: Safety Set

System Organ Class **Preferred Term**	**CT-P59 40 mg/kg (N=652)**	**Placebo (N=650)**
N (%) of patients with at ≥ 1 Grade 3 or Higher TEAE	**61 (9.4)**	**69 (10.6)**
Related	12 (1.8)	15 (2.3)
Unrelated	51 (7.8)	55 (8.5)
Blood and lymphatic system disorders	**1 (0.2)**	**8 (1.2)**
Leukopenia - Grade 3	0	1 (0.2)
Lymphopenia – Grade 3	0	6 (0.9)
Neutropenia – Grade 3	0	3 (0.5)
Neutropenia – Grade 4	1 (0.2)	0
Cardiac disorders	**1 (0.2)**	**0**
Acute myocardial infarction – Grade 3	1 (0.2)	0
Hepatobiliary disorders	**2 (0.3)**	**3 (0.5)**
Hepatitis cholestatic – Grade 3	2 (0.3)	1 (0.2)
Hepatitis cholestatic – Grade 4	0	1 (0.2)
Hepatotoxicity – Grade 3	0	1 (0.2)
Infections and infestations	**0**	**1 (0.2)**
Pneumonia bacterial – Grade 4	0	1 (0.2)
Investigations	**38 (5.8)**	**45 (6.9)**
Alanine aminotransferase increased - Grade 3	7 (1.1)	10 (1.5)
Aspartate aminotransferase increased – Grade 3	2 (0.3)	1 (0.2)
Blood creatine phosphokinase MB increased – Grade 3	0	1 (0.2)
Blood creatine phosphokinase increased – Grade 3	5 (0.8)	0
Blood creatine phosphokinase increased – Grade 4	1 (0.2)	0

System Organ Class **Preferred Term**	**CT-P59 40 mg/kg (N=652)**	**Placebo (N=650)**
Blood creatinine increased – Grade 3	0	2 (0.3)
Blood potassium increased – Grade 3	1 (0.2)	0
Blood pressure increased – Grade 3	0	1 (0.2)
Blood triglycerides increased – Grade 3	4 (0.6)	2 (0.3)
C-reactive protein increased – Grade 3	8 (1.2)	3 (0.5)
Gamma-glutamyltransferase increased – Grade 3	3 (0.5)	8 (1.2)
Hepatic enzyme increased – Grade 3	1 (0.2)	2 (0.3)
Inflammatory marker increased – Grade 3	1 (0.2)	1 (0.2)
Lymphocyte count decreased – Grade 3	0	1 (0.2)
Neutrophil count decreased – Grade 3	0	1 (0.2)
Platelet count increased – Grade 3	0	1 (0.2)
Transaminases increased – Grade 3	0	2 (0.3)
Troponin I increased – Grade 3	5 (0.8)	5 (0.8)
Troponin increased – Grade 3	5 (0.8)	8 (1.2)
Metabolism and nutrition disorders	**17 (2.6)**	**12 (1.8)**
Diabetes mellitus – Grade 3	1 (0.2)	1 (0.2)
Diabetic metabolic decompensation – Grade 3	1 (0.2)	0
Dyslipidaemia – Grade 3	1 (0.2)	0
Hyperkalaemia – Grade 3	0	1 (0.2)
Hypertriglyceridaemia – Grade 3	12 (1.8)	9 (1.4)
Hypertriglyceridaemia – Grade 4	1 (0.2)	1 (0.2)
Hypokalaemia – Grade 3	1 (0.2)	0
Hyponatraemia – Grade 3	0	1 (0.2)
Nervous system disorders	**0**	**1 (0.2)**
Syncope – Grade 3	0	1 (0.2)
Psychiatric disorders	**0**	**1 (0.2)**
Insomnia – Grade 3	0	1 (0.2)
Renal and urinary disorders	**2 (0.3)**	**2 (0.3)**
Chronic kidney disease – Grade 3	0	2 (0.3)
Haematuria – Grade 3	1 (0.2)	0

System Organ Class Preferred Term	CT-P59 40 mg/kg (N=652)	Placebo (N=650)
Proteinuria – Grade 3	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	**1 (0.2)**	**0**
Pulmonary embolism – Grade 3	1 (0.2)	0
Vascular disorders	**1 (0.2)**	**2 (0.3)**
Hypertension – Grade 3	1 (0.2)	2 (0.3)

N: Number, TEAE: Treatment-emergent adverse event

Hypertriglyceridaemia (Grade 4) was reported for one patient in the CT-P59 40 mg/kg treatment group on Day 14. Triglyceride level was already over 300 mg/dL at Screening (333 mg/dL, reference range of 45 to 200 mg/dL) and the levels were reported between 275 to 318 mg/dL up to Day 10, but was 1427 mg/dL on Day 14 and reported as a grade 4 TEAE. However, the triglyceride level decreased to 296 mg/dL on Day 28 without treatment and the event was recovered. The patient was not obese with screening BMI of 25 kg/m^2. The Investigator confirmed that the patient was on fat-rich diet recently and considered the event to be unrelated to the study drug.

Blood creatinine phosphokinase increased (Grade 4) was reported for one patient in the CT-P59 40 mg/kg treatment group at Day 28 visit. The creatinine phosphokinase level was normal up to Day 14, but increased over 10xULN (4917 U/L, reference range of 24 to 207 U/L) at Day 28 visit and reported as a grade 4 TEAE. The levels decreased to 330 U/L 6 days after. No treatment was given. The patient did not present any cardiac signs or symptoms and the Investigator confirmed that the event is recovering and considered the event to be unrelated to the study drug.

Neutropenia (Grade 4) was reported for one patient in the CT-P59 40 mg/kg treatment group at Day 28 visit. The neutrophil count was normal up to Day 14 but decreased below $0.5x10^3/\mu L$ ($0.47x10^3/\mu L$, reference range of 1.70 to $7.90\times10^3/\mu L$) at Day 28 visit and reported as a grade 4 TEAE. The patient did not have any relevant symptoms, so no treatment was given. The Investigator confirmed that the event was recovering and considered the event to be related to the study drug.

There is an imbalance in the number of grade 3-4 CPK elevations between the treatment and placebo arms (6 vs 0). However, when reviewing the laboratory data, the number of grade 3-4 abnormalities are 13 in the treatment group and 9 in the placebo group.

Adverse Events of Special Interest

Infusion related reaction (hypersensitivity/anaphylactic reactions, IRR) is considered as an AESI because AEs related to infusion related reactions are seen with monoclonal antibody therapy.

In Studies CT-P59 1.1 and CT-P59 1.2, there was no TEAE of infusion-related reaction (IRR) including hypersensitivity/ anaphylactic reaction in patients in the regdanvimab treatment groups during the study period.

In Study CT-P59 3.2 Part 1, TEAEs classified as IRR were reported for 1 (1.0%) and 2 (1.8%) patients in the CT-P59 40 mg/kg and Placebo groups, respectively. No IRRs were reported in CT-P59 80 mg/kg treatment group. All IRR events were grade 1 or 2 in intensity and were considered related to the study drug. One patient in the CT-P59 40 mg/kg treatment group experienced pyrexia and dyspnoea but recovered from the events after taking paracetamol and oxygen therapy. In the Placebo group, one patient experienced hypotension and the other experienced itch and rash. They recovered from the event without any medication.

Table 33: TEAEs Classified as Infusion-Related Reaction, by System Organ Class and Preferred Term in Study CT-P59 3.2 Part 1: Safety Set

System Organ Class **Preferred Term**	**CT-P59 40 mg/kg (N=105)**	**CT-P59 80 mg/kg (N=110)**	**Pooled CT-P59 (N=215)**	**Placebo (N=110)**
Number (%) of patients with ≥ 1 TEAE classified as IRR	**1 (1.0)**	**0**	**1 (0.5)**	**2 (1.8)**
Related	1 (1.0)	0	1 (0.5)	2 (1.8)
Unrelated	0	0	0	0
Injury, poisoning and procedural complications	**1 (1.0)**	**0**	**1 (0.5)**	**2 (1.8)**
Infusion-related reaction	1 (1.0)	0	1 (0.5)	2 (1.8)
Related	1 (1.0)	0	1 (0.5)	2 (1.8)
Grade 1	0	0	0	1 (0.9)
Grade 2	1 (1.0)	0	1 (0.5)	1 (0.9)

IRR: infusion-related reaction; TEAE: treatment-emergent adverse event

In Study CT-P59 3.2 Part 2, TEAEs classified as IRR were reported for 4 (0.6%) and 7 (1.1%) patients in the CT-P59 40 mg/kg and Placebo groups, respectively. All IRR events were grade 1 or 2 in intensity and were considered related to the study drug. All patients from both groups were recovered during the treatment period.

Table 34: TEAEs Classified as Infusion-Related Reaction, by System Organ Class and Preferred Term in Study CT-P59 3.2 Part 2: Safety Set

System Organ Class **Preferred Term**	**CT-P59 40 mg/kg (N=652)**	**Placebo (N=650)**
Number (%) of patients with ≥ 1 TEAE classified as IRR	4 (0.6)	7 (1.1)
Related	4 (0.6)	7 (1.1)
Unrelated	0	0
Injury, poisoning and procedural complications	4 (0.6)	7 (1.1)
Infusion-related reaction	4 (0.6)	7 (1.1)
Related	4 (0.6)	7 (1.1)
Grade 1	1 (0.2)	1 (0.2)
Grade 2	3 (0.5)	6 (0.9)

IRR: infusion-related reaction; TEAE: treatment-emergent adverse event

Other Safety Parameters

In Studies CT-P59 1.1, CT-P59 1.2, and CT-P59 3.2 Part 1, there were no clinically notable abnormalities reported from other safety assessments, including vital signs, hypersensitivity reaction monitoring, ECG, and physical examination, following study drug administration.

There were no ADA-positive results reported at post-treatment visit up to Day 90 and up to Day 90 for Studies CT-P59 1.1 and CT-P59 1.2. In Study CT-P59 3.2 Part 1, there were 3 (3.0%) patients with positive ADA conversion in the 40 mg/kg regdanvimab group, 8 (7.3%) patients in the 80 mg/kg regdanvimab group and 6 (5.6%) patients in the placebo group. In study 3.2 part 2, there were 10 (1.6%) ADA positive patients in the 40 mg/kg regdanvimab group, and 15 (2.4%) patients in the placebo group.

For additional safety assessments in Studies CT-P59 1.2 and CT-P59 3.2, there were no significant safety issues with regards to SARS-CoV-2 infection related signs and symptoms assessments and there were no patients reported with suspicious antibody-dependent enhancement of disease.

2.5.7.3. Serious adverse event/deaths/other significant events

Other than 1 unrelated treatment-emergent serious adverse event (TESAE) of limb injury which occurred 36 days after the study drug administration in the regdanvimab 20 mg/kg treatment group of Study CT-P59 1.1, no TEAEs were considered as serious and no deaths were reported 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, 5 TESAEs were reported in 5 (0.4%) patients overall (4 [0.6%] patients in the CT-P59 40 mg/kg treatment group and 1 [0.2%] patient in the Placebo group). There were no TESAEs reported for >1 patient in either treatment group. TESAE considered by the Investigator to be related to study drug was IRR (1 [0.2%] patient, Grade 2) in the CT-P59 40 mg/kg treatment group, and all other TESAEs were considered by the Investigator to be unrelated to study drug.

Table 35: Summary of TESAEs by System Organ Class and Preferred Term in Study CT-P59 3.2 Part 2: Safety Set

System Organ Class **Preferred Term**	**CT-P59 40 mg/kg (N=652)**	**Placebo (N=650)**
Total Number of TESAEs	**4**	**1**
Number (%) of patients with ≥ 1 TESAE	4 (0.6)	1 (0.2)
Related	1 (0.2)	0
Unrelated	3 (0.5)	1 (0.2)
Cardiac disorders	1 (0.2)	0
Acute myocardial infarction - Grade 3, Unrelated	1 (0.2)	0
Infections and infestations	1 (0.2)	1 (0.2)
Pneumonia - Grade 2, Unrelated	1 (0.2)	0
Pneumonia bacterial - Grade 4, Unrelated	0	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)	0
Infusion related reaction - Grade 2, Related	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0
Pulmonary embolism - Grade 3, Unrelated	1 (0.2)	0

N: Number, TESAE: Treatment-emergent serious adverse event

There were 1 and 2 deaths in the CT-P59 40 mg/kg and placebo groups, respectively. The cause of death was in all cases assessed as related to worsening of COVID-19.

2.5.7.4. Laboratory findings

Study CT-P59 1.1 (Healthy Subjects)

The majority of patients had no CTCAE grade (the post baseline laboratory result did not satisfy any CTCAE grade), or CTCAE grade 1 (mild) or 2 (moderate) for each laboratory parameter and each subsequent time point. There were no laboratory test results of grade 3 or above per CTCAE grading. There was no notable trend in the laboratory abnormalities within or between CT-P59 and the Placebo groups. No dose-dependent relationship was observed for the laboratory abnormalities across the CT-P59 treatment groups.

Study CT-P59 1.2 (Mild COVID-19 Patients)

The majority of patients had no CTCAE grade, or CTCAE grade 1 (mild) for each laboratory parameter and each subsequent time point.

CTCAE grade 4 (hypocalcaemia and hypertriglyceridemia) clinically significant abnormal laboratory parameters were reported in 2 patients (1 [20%] patient in each of the CT-P59 20 mg/kg and CT-P59 40 mg/kg treatment groups).

One patient in the CT-P59 20 mg/kg treatment group had CTCAE grade 4 hypocalcaemia on Day 14 (calcium of 0.9 mmol/L; normal range of 2.15 to 2.525 mmol/L). The Investigator considered the laboratory result as not clinically significant and the patient's calcium level increased to normal range on Day 28 (calcium of 2.2 mmol/L) without any medication.

One patient in the CT-P59 40 mg/kg treatment group had CTCAE grade 4 hypertriglyceridemia on Day 10 (triglycerides of 13.097 mmol/L; normal range of 0.17 to 1.695 mmol/L) and it was reported as a TEAE and considered to be recovering at the end of the study (triglycerides of 6.272 mmol/L on Day 90) by the Investigator. The patient didn't take any medication related to the event during the treatment period. The event was considered to be worsening of patient's existing medical history of hypertriglyceridaemia.

Table 36: Summary of Most Severe CTCAE Grading (CTCAE Grade 3 or Higher) in Study CT-P59 1.2: Safety Set

Laboratory Category **CTCAE Term** CTCAE Grade	**CT-P59 20 mg/kg (N=5)**	**CT-P59 40 mg/kg (N=5)**	**CT-P59 80 mg/kg (N=5)**	**Placebo (N=3)**
	Number (%) of patients			
Clinical Chemistry				
Alanine aminotransferase increased				
Grade 3 (Severe)	0	2 (40)	0	0
GGT increased				
Grade 3 (Severe)	1 (20)	0	0	0
Hypertriglyceridemia				
Grade 3 (Severe)	0	0	2 (40)	0
Grade 4 (Life-Threatening)	0	1 (20)	0	0
Hypocalcaemia				
Grade 4 (Life-Threatening)	1 (20)	0	0	0
Haematology				
White blood cell decreased				

Laboratory Category CTCAE Term CTCAE Grade	CT-P59 20 mg/kg (N=5)	CT-P59 40 mg/kg (N=5)	CT-P59 80 mg/kg (N=5)	Placebo (N=3)
	Number (%) of patients			
Grade 3 (Severe)	1 (20)	0	0	0

Note: Percentages were calculated by using the number of patients in the Safety Set as the denominator. All values collected after first administration are considered as post-baseline values.

GGT: Gamma glutamyl transferase, CTCAE: Common Terminology Criteria for Adverse Events

Given the very limited study size the rates of laboratory abnormalities should be interpreted with caution. ALT elevations and hypocalcaemia are frequently seen in covid-19 patients.

Table 37: Study CT-P59 3.2 Part 1 (Mild to Moderate COVID-19 Patients)

Grade 1-4 laboratory abnormalities are presented in the table below.

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Alanine aminotransferase increased					
No Grade	60 (54.5%)	42 (40%)	102 (47.4%)	46 (41.8%)	148 (45.5%)
Grade 1 (Mild)	38 (34.5%)	47 (44.8%)	85 (39.5%)	51 (46.4%)	136 (41.8%)
Grade 2 (Moderate)	5 (4.5%)	8 (7.6%)	13 (6.0%)	6 (5.5%)	19 (5.8%)
Grade 3 (Severe)	7 (6.4%)	3 (2.9%)	10 (4.7%)	4 (3.6%)	14 (4.3%)
Grade 4 (Life-threatening)	0	0	0	0	0
Alkaline phosphatase increased					
No Grade	107 (97.3%)	99 (94.3%)	206 (95.8%)	106 (96.4%)	312 (96%)
Grade 1 (Mild)	2 (1.8%)	2 (1.9%)	4 (1.9%)	2 (1.8%)	6 (1.8%)
Grade 2 (Moderate)	1 (0.9%)	0	1 (0.5%)	0	1 (0.3%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
Aspartate aminotransferase increased					
No Grade	71 (64.5%)	68 (64.8%)	139 (64.7%)	73 (66.4%)	212 (65.2%)
Grade 1 (Mild)	37 (33.6%)	29 (27.6%)	66 (30.7%)	32 (29.1%)	98 (30.2%)
Grade 2 (Moderate)	0	3 (2.9%)	3 (1.4%)	2 (1.8%)	5 (1.5%)
Grade 3 (Severe)	2 (1.8%)	0	2 (0.9%)	1 (0.9%)	3 (0.9%)
Grade 4 (Life-threatening)	0	0	0	0	0

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Blood bilirubin increased					
No Grade	103 (93.6%)	92 (87.6%)	195 (90.7%)	104 (94.5%)	299 (92%)
Grade 1 (Mild)	6 (5.5%)	9 (8.6%)	15 (7.0%)	3 (2.7%)	18 (5.5%)
Grade 2 (Moderate)	1 (0.9%)	0	1 (0.5%)	1 (0.9%)	2 (0.6%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
CPK increased					
No Grade	72 (65.5%)	71 (67.6%)	143 (66.5%)	82 (74.5%)	225 (69.2%)
Grade 1 (Mild)	28 (25.5%)	24 (22.9%)	52 (24.2%)	21 (19.1%)	73 (22.5%)
Grade 2 (Moderate)	5 (4.5%)	7 (6.7%)	12 (5.6%)	2 (1.8%)	14 (4.3%)
Grade 3 (Severe)	2 (1.8%)	3 (2.9%)	5 (2.3%)	3 (2.7%)	8 (2.5%)
Grade 4 (Life-threatening)	3 (2.7%)	0	3 (1.4%)	1 (0.9%)	4 (1.2%)
Cholesterol high					
No Grade	30 (27.3%)	27 (25.7%)	57 (26.5%)	27 (24.5%)	84 (25.8%)
Grade 1 (Mild)	75 (68.2%)	72 (68.6%)	147 (68.4%)	72 (65.5%)	219 (67.4%)
Grade 2 (Moderate)	5 (4.5%)	6 (5.7%)	11 (5.1%)	10 (9.1%)	21 (6.5%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Creatinine increased					
No Grade	98 (89.1%)	96 (91.4%)	194 (90.2%)	88 (80%)	282 (86.8%)
Grade 1 (Mild)	0	1 (1.0%)	1 (0.5%)	0	1 (0.3%)
Grade 2 (Moderate)	12 (10.9%)	8 (7.6%)	20 (9.3%)	20 (18.2%)	40 (12.3%)
Grade 3 (Severe)	0	0	0	1 (0.9%)	1 (0.3%)
Grade 4 (Life-threatening)	0	0	0	0	0
GGT increased					
No Grade	91 (82.7%)	78 (74.3%)	169 (78.6%)	82 (74.5%)	251 (77.2%)
Grade 1 (Mild)	13 (11.8%)	19 (18.1%)	32 (14.9%)	25 (22.7%)	57 (17.5%)
Grade 2 (Moderate)	6 (5.5%)	3 (2.9%)	9 (4.2%)	1 (0.9%)	10 (3.1%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
Hypercalcemia					
No Grade	109 (99.1%)	105 (100%)	214 (99.5%)	106 (96.4%)	320 (98.5%)
Grade 1 (Mild)	0	0	0	3 (2.7%)	3 (0.9%)
Grade 2 (Moderate)	0	0	0	0	0
Grade 3 (Severe)	1 (0.9%)	0	1 (0.5%)	0	1 (0.3%)
Grade 4 (Life-threatening)	0	0	0	0	0

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Hyperkalemia					
No Grade	75 (68.2%)	67 (63.8%)	142 (66.0%)	76 (69.1%)	218 (67.1%)
Grade 1 (Mild)	26 (23.6%)	31 (29.5%)	57 (26.5%)	23 (20.9%)	80 (24.6%)
Grade 2 (Moderate)	8 (7.3%)	7 (6.7%)	15 (7.0%)	9 (8.2%)	24 (7.4%)
Grade 3 (Severe)	1 (0.9%)	0	1 (0.5%)	1 (0.9%)	2 (0.6%)
Grade 4 (Life-threatening)	0	0	0	0	0
Hypernatremia					
No Grade	96 (87.3%)	91 (86.7%)	187 (87.0%)	94 (85.5%)	281 (86.5%)
Grade 1 (Mild)	10 (9.1%)	11 (10.5%)	21 (9.8%)	13 (11.8%)	34 (10.5%)
Grade 2 (Moderate)	3 (2.7%)	3 (2.9%)	6 (2.8%)	2 (1.8%)	8 (2.5%)
Grade 3 (Severe)	1 (0.9%)	0	1 (0.5%)	0	1 (0.3%)
Grade 4 (Life-threatening)	0	0	0	0	0
Hypertriglyceridemia					
No Grade	23 (20.9%)	22 (21.0%)	45 (20.9%)	13 (11.8%)	58 (17.8%)
Grade 1 (Mild)	55 (50%)	56 (53.3%)	111 (51.6%)	62 (56.4%)	173 (53.2%)
Grade 2 (Moderate)	23 (20.9%)	22 (21.0%)	45 (20.9%)	27 (24.5%)	72 (22.2%)
Grade 3 (Severe)	9 (8.2%)	5 (4.8%)	14 (6.5%)	6 (5.5%)	20 (6.2%)
Grade 4 (Life-threatening)	0	0	0	1 (0.9%)	1 (0.3%)

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Hypoalbuminemia					
No Grade	103 (93.6%)	103 (98.1%)	206 (95.8%)	103 (93.6%)	309 (95.1%)
Grade 1 (Mild)	7 (6.4%)	2 (1.9%)	9 (4.2%)	5 (4.5%)	14 (4.3%)
Grade 2 (Moderate)	0	0	0	1 (0.9%)	1 (0.3%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
Hypocalcemia					
No Grade	81 (73.6%)	79 (75.2%)	160 (74.4%)	71 (64.5%)	231 (71.1%)
Grade 1 (Mild)	18 (16.4%)	22 (21.0%)	40 (18.6%)	35 (31.8%)	75 (23.1%)
Grade 2 (Moderate)	9 (8.2%)	2 (1.9%)	11 (5.1%)	1 (0.9%)	12 (3.7%)
Grade 3 (Severe)	1 (0.9%)	2 (1.9%)	3 (1.4%)	2 (1.8%)	5 (1.5%)
Grade 4 (Life-threatening)	1 (0.9%)	0	1 (0.5%)	0	1 (0.3%)
Hypoglycemia					
No Grade	99 (90%)	88 (83.8%)	187 (87.0%)	98 (89.1%)	285 (87.7%)
Grade 1 (Mild)	10 (9.1%)	17 (16.2%)	27 (12.6%)	9 (8.2%)	36 (11.1%)
Grade 2 (Moderate)	1 (0.9%)	0	1 (0.5%)	2 (1.8%)	3 (0.9%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Hypokalemia					
No Grade	103 (93.6%)	99 (94.3%)	202 (94.0%)	101 (91.8%)	303 (93.2%)
Grade 1 (Mild)	7 (6.4%)	6 (5.7%)	13 (6.0%)	8 (7.3%)	21 (6.5%)
Grade 2 (Moderate)	0	0	0	0	0
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
Hyponatremia					
No Grade	107 (97.3%)	101 (96.2%)	208 (96.7%)	101 (91.8%)	309 (95.1%)
Grade 1 (Mild)	2 (1.8%)	3 (2.9%)	5 (2.3%)	6 (5.5%)	11 (3.4%)
Grade 2 (Moderate)	1 (0.9%)	1 (1.0%)	2 (0.9%)	1 (0.9%)	3 (0.9%)
Grade 3 (Severe)	0	0	0	1 (0.9%)	1 (0.3%)
Grade 4 (Life-threatening)	0	0	0	0	0

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Anemia					
No Grade	100 (90.9%)	95 (90.5%)	195 (90.7%)	93 (84.5%)	288 (88.6%)
Grade 1 (Mild)	10 (9.1%)	7 (6.7%)	17 (7.9%)	12 (10.9%)	29 (8.9%)
Grade 2 (Moderate)	0	1 (1.0%)	1 (0.5%)	3 (2.7%)	4 (1.2%)
Grade 3 (Severe)	0	1 (1.0%)	1 (0.5%)	1 (0.9%)	2 (0.6%)
Grade 4 (Life-threatening)	0	0	0	0	0
Hemoglobin increased					
No Grade	101 (91.8%)	98 (93.3%)	199 (92.6%)	100 (90.9%)	299 (92%)
Grade 1 (Mild)	9 (8.2%)	6 (5.7%)	15 (7.0%)	8 (7.3%)	23 (7.1%)
Grade 2 (Moderate)	0	0	0	1 (0.9%)	1 (0.3%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
Leukocytosis					
No Grade	110 (100%)	104 (99.0%)	214 (99.5%)	109 (99.1%)	323 (99.4%)
Grade 1 (Mild)	0	0	0	0	0
Grade 2 (Moderate)	0	0	0	0	0
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Lymphocyte count decreased					
No Grade	82 (74.5%)	88 (83.8%)	170 (79.1%)	87 (79.1%)	257 (79.1%)
Grade 1 (Mild)	9 (8.2%)	6 (5.7%)	15 (7.0%)	7 (6.4%)	22 (6.8%)
Grade 2 (Moderate)	18 (16.4%)	9 (8.6%)	27 (12.6%)	11 (10%)	38 (11.7%)
Grade 3 (Severe)	1 (0.9%)	1 (1.0%)	2 (0.9%)	4 (3.6%)	6 (1.8%)
Grade 4 (Life-threatening)	0	0	0	0	0
Lymphocyte count increased					
No Grade	105 (95.5%)	99 (94.3%)	204 (94.9%)	102 (92.7%)	306 (94.2%)
Grade 1 (Mild)	0	0	0	0	0
Grade 2 (Moderate)	5 (4.5%)	5 (4.8%)	10 (4.7%)	7 (6.4%)	17 (5.2%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
Neutrophil count decreased					
No Grade	71 (64.5%)	66 (62.9%)	137 (63.7%)	78 (70.9%)	215 (66.2%)
Grade 1 (Mild)	9 (8.2%)	8 (7.6%)	17 (7.9%)	7 (6.4%)	24 (7.4%)
Grade 2 (Moderate)	18 (16.4%)	17 (16.2%)	35 (16.3%)	16 (14.5%)	51 (15.7%)
Grade 3 (Severe)	10 (9.1%)	13 (12.4%)	23 (10.7%)	7 (6.4%)	30 (9.2%)
Grade 4 (Life-threatening)	2 (1.8%)	0	2 (0.9%)	1 (0.9%)	3 (0.9%)

CTCAE Term Grade	CT-P59 80 mg/kg (N=110)	CT-P59 40 mg/kg (N=105)	CT-P59 (N=215)	Placebo (N=110)	Total (N=325)
Platelet count decreased					
No Grade	81 (73.6%)	85 (81.0%)	166 (77.2%)	92 (83.6%)	258 (79.4%)
Grade 1 (Mild)	28 (25.5%)	19 (18.1%)	47 (21.9%)	17 (15.5%)	64 (19.7%)
Grade 2 (Moderate)	1 (0.9%)	0	1 (0.5%)	0	1 (0.3%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0
White blood cell decreased					
No Grade	70 (63.6%)	72 (68.6%)	142 (66.0%)	76 (69.1%)	218 (67.1%)
Grade 1 (Mild)	19 (17.3%)	19 (18.1%)	38 (17.7%)	18 (16.4%)	56 (17.2%)
Grade 2 (Moderate)	21 (19.1%)	13 (12.4%)	34 (15.8%)	15 (13.6%)	49 (15.1%)
Grade 3 (Severe)	0	0	0	0	0
Grade 4 (Life-threatening)	0	0	0	0	0

Overall, laboratory parameters are very similar between treatment groups and the placebo group. However, a few imbalances are observed:

- CPK elevations appear more common in the treatment groups, with 4.6% vs 2.7% grade 3-4 elevations in the pooled treatment group vs placebo. Severe neutropenia appear more common in the treatment groups, with 11.6% vs 7.3% grade 3-4 decreases in the pooled treatment groups vs placebo.

Table 38: Study CT-P59 3.2 Part 2 (Mild to Moderate COVID-19 Patients)

Grade 1-4 laboratory abnormalities are presented in the table below.

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Alanine aminotransferase increased			
No Grade	359 (55.1%)	347 (53.4%)	706 (54.2%)
Grade 1 (Mild)	216 (33.1%)	212 (32.6%)	428 (32.9%)
Grade 2 (Moderate)	22 (3.4%)	45 (6.9%)	67 (5.1%)
Grade 3 (Severe)	20 (3.1%)	19 (2.9%)	39 (3.0%)
Grade 4 (Life-threatening)	0	0	0
Alkaline phosphatase increased			
No Grade	594 (91.1%)	591 (90.9%)	1185 (91.0%)
Grade 1 (Mild)	34 (5.2%)	35 (5.4%)	69 (5.3%)
Grade 2 (Moderate)	1 (0.2%)	1 (0.2%)	2 (0.2%)
Grade 3 (Severe)	0	0	0
Grade 4 (Life-threatening)	0	0	0
Aspartate aminotransferase increased			
No Grade	450 (69.0%)	441 (67.8%)	891 (68.4%)
Grade 1 (Mild)	144 (22.1%)	167 (25.7%)	311 (23.9%)
Grade 2 (Moderate)	16 (2.5%)	10 (1.5%)	26 (2.0%)
Grade 3 (Severe)	5 (0.8%)	5 (0.8%)	10 (0.8%)
Grade 4 (Life-threatening)	0	0	0

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Blood bilirubin increased			
No Grade	592 (90.8%)	600 (92.3%)	1192 (91.6%)
Grade 1 (Mild)	23 (3.5%)	20 (3.1%)	43 (3.3%)
Grade 2 (Moderate)	3 (0.5%)	3 (0.5%)	6 (0.5%)
Grade 3 (Severe)	0	0	0
Grade 4 (Life-threatening)	0	0	0
CPK increased			
No Grade	473 (72.5%)	480 (73.8%)	953 (73.2%)
Grade 1 (Mild)	147 (22.5%)	122 (18.8%)	269 (20.7%)
Grade 2 (Moderate)	16 (2.5%)	32 (4.9%)	48 (3.7%)
Grade 3 (Severe)	8 (1.2%)	5 (0.8%)	13 (1.0%)
Grade 4 (Life-threatening)	5 (0.8%)	4 (0.6%)	9 (0.7%)
Cholesterol high			
No Grade	283 (43.4%)	275 (42.3%)	558 (42.9%)
Grade 1 (Mild)	344 (52.8%)	351 (54%)	695 (53.4%)
Grade 2 (Moderate)	22 (3.4%)	17 (2.6%)	39 (3.0%)
Grade 3 (Severe)	0	0	0
Grade 4 (Life-threatening)	0	0	0

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Creatinine increased			
No Grade	580 (89.0%)	584 (89.8%)	1164 (89.4%)
Grade 1 (Mild)	7 (1.1%)	8 (1.2%)	15 (1.2%)
Grade 2 (Moderate)	39 (6.0%)	32 (4.9%)	71 (5.5%)
Grade 3 (Severe)	22 (3.4%)	19 (2.9%)	41 (3.1%)
Grade 4 (Life-threatening)	0	0	0
GGT increased			
No Grade	504 (77.3%)	462 (71.1%)	966 (74.2%)
Grade 1 (Mild)	96 (14.7%)	121 (18.6%)	217 (16.7%)
Grade 2 (Moderate)	25 (3.8%)	33 (5.1%)	58 (4.5%)
Grade 3 (Severe)	4 (0.6%)	11 (1.7%)	15 (1.2%)
Grade 4 (Life-threatening)	0	0	0
Hypercalcemia			
No Grade	644 (98.8%)	640 (98.5%)	1284 (98.6%)
Grade 1 (Mild)	5 (0.8%)	1 (0.2%)	6 (0.5%)
Grade 2 (Moderate)	0	1 (0.2%)	1 (0.1%)
Grade 3 (Severe)	0	1 (0.2%)	1 (0.1%)
Grade 4 (Life-threatening)	0	0	0

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Hyperkalemia			
No Grade	527 (80.8%)	524 (80.6%)	1051 (80.7%)
Grade 1 (Mild)	95 (14.6%)	92 (14.2%)	187 (14.4%)
Grade 2 (Moderate)	25 (3.8%)	25 (3.8%)	50 (3.8%)
Grade 3 (Severe)	3 (0.5%)	2 (0.3%)	5 (0.4%)
Grade 4 (Life-threatening)	0	0	0
Hypernatremia			
No Grade	633 (97.1%)	629 (96.8%)	1262 (96.9%)
Grade 1 (Mild)	17 (2.6%)	14 (2.2%)	31 (2.4%)
Grade 2 (Moderate)	0	0	0
Grade 3 (Severe)	0	0	0
Grade 4 (Life-threatening)	0	0	0
Hypertriglyceridemia			
No Grade	158 (24.2%)	174 (26.8%)	332 (25.5%)
Grade 1 (Mild)	325 (49.8%)	299 (46%)	624 (47.9%)
Grade 2 (Moderate)	119 (18.3%)	126 (19.4%)	245 (18.8%)
Grade 3 (Severe)	43 (6.6%)	39 (6%)	82 (6.3%)
Grade 4 (Life-threatening)	3 (0.5%)	5 (0.8%)	8 (0.6%)

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Hypoalbuminemia			
No Grade	629 (96.5%)	620 (95.4%)	1249 (95.9%)
Grade 1 (Mild)	18 (2.8%)	23 (3.5%)	41 (3.1%)
Grade 2 (Moderate)	3 (0.5%)	0	3 (0.2%)
Grade 3 (Severe)	0	0	0
Grade 4 (Life-threatening)	0	0	0
Hypocalcemia			
No Grade	421 (64.6%)	373 (57.4%)	794 (61.0%)
Grade 1 (Mild)	198 (30.4%)	235 (36.2%)	433 (33.3%)
Grade 2 (Moderate)	22 (3.4%)	28 (4.3%)	50 (3.8%)
Grade 3 (Severe)	4 (0.6%)	6 (0.9%)	10 (0.8%)
Grade 4 (Life-threatening)	4 (0.6%)	1 (0.2%)	5 (0.4%)
Hypoglycemia			
No Grade	589 (90.3%)	587 (90.3%)	1176 (90.3%)
Grade 1 (Mild)	56 (8.6%)	47 (7.2%)	103 (7.9%)
Grade 2 (Moderate)	3 (0.5%)	9 (1.4%)	12 (0.9%)
Grade 3 (Severe)	1 (0.2%)	0	1 (0.1%)
Grade 4 (Life-threatening)	0	0	0

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Hypokalemia			
No Grade	594 (91.1%)	595 (91.5%)	1189 (91.3%)
Grade 1 (Mild)	52 (8.0%)	48 (7.4%)	100 (7.7%)
Grade 2 (Moderate)	0	0	0
Grade 3 (Severe)	4 (0.6%)	0	4 (0.3%)
Grade 4 (Life-threatening)	0	0	0
Hyponatremia			
No Grade	585 (89.7%)	582 (89.5%)	1167 (89.6%)
Grade 1 (Mild)	51 (7.8%)	49 (7.5%)	100 (7.7%)
Grade 2 (Moderate)	12 (1.8%)	11 (1.7%)	23 (1.8%)
Grade 3 (Severe)	2 (0.3%)	1 (0.2%)	3 (0.2%)
Grade 4 (Life-threatening)	0	0	0

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Anemia			
No Grade	596 (91.4%)	590 (90.8%)	1186 (91.1%)
Grade 1 (Mild)	42 (6.4%)	41 (6.3%)	83 (6.4%)
Grade 2 (Moderate)	7 (1.1%)	8 (1.2%)	15 (1.2%)
Grade 3 (Severe)	1 (0.2%)	2 (0.3%)	3 (0.2%)
Grade 4 (Life-threatening)	0	0	0
Hemoglobin increased			
No Grade	594 (91.1%)	587 (90.3%)	1181 (90.7%)
Grade 1 (Mild)	48 (7.4%)	50 (7.7%)	98 (7.5%)
Grade 2 (Moderate)	3 (0.5%)	2 (0.3%)	5 (0.4%)
Grade 3 (Severe)	1 (0.2%)	2 (0.3%)	3 (0.2%)
Grade 4 (Life-threatening)	0	0	0
Leukocytosis			
No Grade	646 (99.1%)	641 (98.6%)	1287 (98.8%)
Grade 1 (Mild)	0	0	0
Grade 2 (Moderate)	0	0	0
Grade 3 (Severe)	0	0	0
Grade 4 (Life-threatening)	0	0	0

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Lymphocyte count decreased			
No Grade	547 (83.9%)	475 (73.1%)	1022 (78.5%)
Grade 1 (Mild)	32 (4.9%)	40 (6.2%)	72 (5.5%)
Grade 2 (Moderate)	53 (8.1%)	101 (15.5%)	154 (11.8%)
Grade 3 (Severe)	14 (2.1%)	24 (3.7%)	38 (2.9%)
Grade 4 (Life-threatening)	0	0	0
Lymphocyte count increased			
No Grade	632 (96.9%)	619 (95.2%)	1251 (96.1%)
Grade 1 (Mild)	0	0	0
Grade 2 (Moderate)	13 (2.0%)	21 (3.2%)	34 (2.6%)
Grade 3 (Severe)	1 (0.2%)	0	1 (0.1%)
Grade 4 (Life-threatening)	0	0	0
Neutrophil count decreased			
No Grade	523 (80.2%)	483 (74.3%)	1006 (77.3%)
Grade 1 (Mild)	47 (7.2%)	47 (7.2%)	94 (7.2%)
Grade 2 (Moderate)	54 (8.3%)	80 (12.3%)	134 (10.3%)
Grade 3 (Severe)	21 (3.2%)	29 (4.5%)	50 (3.8%)
Grade 4 (Life-threatening)	1 (0.2%)	1 (0.2%)	2 (0.2%)

CTCAE Term Grade	CT-P59 40 mg/kg (N=652)	Placebo (N=650)	Total (N=1302)
Platelet count decreased			
No Grade	513 (78.7%)	476 (73.2%)	989 (76.0%)
Grade 1 (Mild)	128 (19.6%)	164 (25.2%)	292 (22.4%)
Grade 2 (Moderate)	1 (0.2%)	0	1 (0.1%)
Grade 3 (Severe)	3 (0.5%)	1 (0.2%)	4 (0.3%)
Grade 4 (Life-threatening)	0	0	0
White blood cell decreased			
No Grade	492 (75.5%)	432 (66.5%)	924 (71.0%)
Grade 1 (Mild)	105 (16.1%)	129 (19.8%)	234 (18.0%)
Grade 2 (Moderate)	47 (7.2%)	75 (11.5%)	122 (9.4%)
Grade 3 (Severe)	2 (0.3%)	5 (0.8%)	7 (0.5%)
Grade 4 (Life-threatening)	0	0	0

Overall, laboratory abnormalities are similar between the treatment group and placebo group except for a few instances where abnormalities are seen more frequently in the placebo group. Grade 3-4 CPK elevations are seen slightly more frequent in the treatment group compared to placebo. There are no signs of a causal relation between regdanvimab treatment and transaminitis, neutropenia or hypocalcaemia where some imbalances were seen in the smaller studies.

2.5.7.5. Safety in special populations

Table 39: Safety in Special Populations in Study CT-P59 3.2 Part 2: Safety Set

Events	Age <65 number (percentage)		Age 65-74 number (percentage)		Age 75-84 number (percentage)		Age 85+ number (percentage)	
	CT-P59 40 mg/kg (N=560)	Placebo (N=573)	CT-P59 40 mg/kg (N=76)	Placebo (N=58)	CT-P59 40 mg/kg (N=14)	Placebo (N=19)	CT-P59 40 mg/kg (N=2)	Placebo (N=0)
Number of Patients with at Least One TEAE	164 (29.3%)	169 (29.5%)	29 (38.2%)	30 (51.7%)	5 (35.7%)	3 (15.8%)	0	N/A
Number of Patients with at Least One TESAE	3 (0.5%)	0	1 (1.3%)	1 (1.7%)	0	0	0	N/A
Fatal	0	0	0	0	0	0	0	N/A
Hospitalization/prolong existing hospitalization	3 (0.5%)	0	1 (1.3%)	1 (1.7%)	0	0	0	N/A
Life-threatening	1 (0.2%)	0	0	1 (1.7%)	0	0	0	N/A
Disability/incapacity	0	0	0	0	0	0	0	N/A
Other (medically significant)	0	0	0	0	0	0	0	N/A
Number (%) of patients with at least 1 TEAE leading to study drug discontinuation	0	0	0	0	0	0	0	N/A
Psychiatric disorders	3 (0.5%)	4 (0.7%)	0	0	0	1 (5.3%)	0	N/A
Nervous system disorders	3 (0.5%)	4 (0.7%)	0	3 (5.2%)	0	0	0	N/A
Accidents and injuries	0	0	0	0	0	0	0	N/A
Cardiac disorders	4 (0.7%)	2 (0.3%)	2 (2.6%)	1 (1.7%)	1 (7.1%)	1 (5.3%)	0	N/A
Vascular disorders	13 (2.3%)	11 (1.9%)	5 (6.6%)	0	0	1 (5.3%)	0	N/A
Cerebrovascular disorders	0	0	0	0	0	0	0	N/A
Infections and infestations	20 (3.6%)	25 (4.4%)	8 (10.5%)	3 (5.2%)	0	0	0	N/A
Anticholinergic syndrome	0	0	0	0	0	0	0	N/A
Quality of life decreased	0	0	0	0	0	0	0	N/A
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	0	2 (0.3%)	0	1 (1.7%)	0	0	0	N/A

N: Number, N/A: Not applicable, SOC: System organ class, TEAE: Treatment-emergent adverse event, TESAE: Treatment-emergent serious adverse event

2.5.7.6. Immunological events

See section above on adverse events of special interest for data in infusion-related reactions.

There were no ADA-positive results reported at post-treatment visit up to Day 90 and up to Day 90 for Studies CT-P59 1.1 and CT-P59 1.2, respectively.

In Study CT-P59 3.2 Part 1, the number of patients with the positive ADA conversion after study drug administration up to Day 90 was 3 (3.0%), 8 (7.3%), 11 (5.2%) and 6 (5.6%) in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, pooled CT-P59 and Placebo groups, respectively. In Study CT-P59 3.2 Part 2, the proportions of patients with the positive ADA conversion after study drug administration up to Day 28 were 1.6% and 2.4% in the CT-P59 40 mg/kg and Placebo groups, respectively. Among the patients with positive conversion in ADA, IRR was reported only for 1/10 (10%) in the CT-P59 40 mg/kg in Study CT-P59 3.2 Part 2.

Interestingly, the levels of anti-drug antibodies were higher in the placebo groups. This suggest that this is non-specific reactivity rather than a specific humoral response triggered by regdanvimab exposure. There were no patients with suspicious antibody-dependent enhancement of disease in any of the studies.

2.5.7.7. Discontinuation due to adverse events

There were no TEAEs leading to study drug discontinuation in any of the clinical studies.

2.5.7.8. Post marketing experience

As of 16 Jul 2021, post-marketing cumulative exposure to CT-P59 is estimated at approximately 8,457 patients in Republic of Korea. Among the 8,457 patients, 15 SAEs were reported in 8 (0.09%) patients overall, and most of the events were recovered with the exception of one patient. One case of suspected anaphylaxis was reported in a hospitalized patient who presented with dyspnoea, chest discomfort and cough during CT-P59 infusion; the infusion was immediately discontinued, and the patient received epinephrine. Thereafter, the patient was moved to intensive care unit and died the next day.

The post-marketing experience with almost 8500 doses administered provides some additional insight on the safety profile of regdanvimab. The SAEs reported are difficult to interpret, given that several of the events could have been caused by progression of covid-19 disease (from mild to moderate disease which is the intended target group for the emergency use approval in South Korea), but the timing in relation to administration could give further insight. The Applicant has provided narratives for the SAEs showing alternative causes of events for most cases. However, anaphylaxis should be listed in section 4.8 of the SmPC. The applicant argued that there was no numerical excess of urticaria cases, and that one of the two cases can be explained by a transfusion reaction. Therefore, they considered that urticaria should not be listed. This was accepted. However, the applicant agreed with addition of anaphylaxis and infusion-related reactions (IRRs) in Section 4.8 of the EU SmPC. Therefore, IRRs have been added to the tabulated list of adverse reactions in Section 4.8 and one anaphylactic case reported from post-marketing experience has been described in 'Infusion-related reactions' section.

2.5.8. Discussion on clinical safety

Regdanvimab is a mAb with a non-host target and no effector function. As such, the safety profile is anticipated to be characterised mainly by potential immune- or hypersensitivity reactions. Across the 3 studies with CT-P59, 906 subjects received at least 1 dose of CT-P59. Of these, 889 received the proposed single dose of 40 mg/kg or more, and 882 were infected with Sars-Cov-2.

Overall, the safety profile of regdanvimab appears favourable, in line with what is expected from a monoclonal antibody targeting a viral protein, and with no intrinsic effector function.

No excess of infusion related reactions has been shown, but this remains a potential risk which requires monitoring. Despite the size of the safety database, delineated above, it cannot be excluded that more uncommon adverse drug reactions have not been detected.

Cases of transaminitis, hypocalcaemia and neutropenia were reported in both regdanvimab and placebo-treated patients. Events are overall balanced between treatment and placebo groups and are more likely related to the underlying covid-19 disease than causally related to regdanvimab treatment. However, there remains an imbalance in cases of creative phosphokinase elevations in the grade 3-4 AE reporting from the CT-P59 3.2-part 2 study.

There were 1 and 2 deaths in the CT-P59 40 mg/kg and placebo groups, respectively. The cause of death was in all cases assessed as related to worsening of COVID-19.

The program has not provided any indication of antibody-dependent enhancement of disease. However, the sensitivity to detect such events, if rare, may be questioned.

2.5.9. Conclusions on the clinical safety

Overall, the safety profile of regdanvimab appears favourable, in line with what is expected from a monoclonal antibody targeting a viral protein, and with no intrinsic effector function.

2.6. Risk Management Plan

2.6.1. Safety concerns

The Applicant has submitted a RMP version 0.8 including the following 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

Risks considered important for the inclusion in the summary of safety concerns

The Applicant has not listed any "Important identified risks" nor "Important potential risks" which is acceptable

Missing information:

Use during pregnancy: The safety of regdanvimab in pregnant women is not known and no studies of regdanvimab have been conducted in pregnant women. Listing "Use during pregnancy" as missing information is supported.

Long-term safety data: Based on the limited number of patients exposed to CT-P59 in Study CT-P59 1.2 the Applicant has proposed "Long-term safety data" as missing information. This is acknowledged and acceptable. Study CT-P59 3.2 is still ongoing and long-term data will be presented at a later stage.

2.6.2. Pharmacovigilance plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: the applicant has proposed the implementation of 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.

Additional pharmacovigilance activities

The Applicant proposes the **following 3 studies** to further evaluate safety and to address missing information in the post marketing setting. There is one interventional study and two non-interventional studies.

The following table outlines proposed additional pharmacovigilance activities in RMP version 0.8.

Table 40: Summary of 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 have on obstetric, neonatal, and infant outcomes	- use during pregnancy	Estimated primary completion date	30/09/2026
			Final report	30/09/2027

2.6.3. Risk minimisation measures

Routine risk minimisation activities only are proposed to manage the safety concerns of the medicinal product. This is acceptable.

Table 41: Summary Table of Risk Minimization Activities and Pharmacovigilance 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

2.6.4. Conclusion

The CHMP and the PRAC considers that the risk management plan version 0.8 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 05.02.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

Furthermore, we can confirm that an addendum regarding layout discussion from the user consultation has been assessed and found acceptable. Hence, user consultation issue solved.

2.8.2. Labelling exemptions

The following exemptions from labelling requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC.

In addition, the derogations granted should be seen in the context of the flexibilities described in the Labelling flexibilities for COVID-19 therapeutics (EMA/35618/2021, from 12 March 2021) document which aims at facilitating the preparedness work of COVID-19 therapeutics developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 therapeutics for EU citizens within the existing legal framework.

1. Use of minimum particulars for the vial label. Based on the limited space of the vial label, the QRD group agreed to the use of minimum labelling requirements to ensure the legibility of the essential information for the safe and effective use of the medicine.

2. Outer and immediate labelling will be printed in English only.

3. Package leaflets will be printed in English only except for the leaflets for the following Member States: Belgium, Bulgaria, Croatia, Czech Republic and Greece. For the latter the package leaflet in the respective national languages will be separately distributed alongside the supply of Regkirona.

For the rest of the Members States which will receive the package leaflets printed in English, this will be included in the carton pack.

Alternative access to the package leaflet in the national languages of the Member States, where the medicinal product is marketed, will be provide via a QR code included in the printed package leaflet and the outer packaging.

4. Omission of country specific blue box requirements and use of one Global Trade Identification Number (GTIN) for serialization.

The duration of the exemptions will be limited to 6 months after the granting of the marketing authorisation.

2.8.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and patients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- package leaflet in all EU/EEA languages of the member states where the medicinal product is marketed. Healthcare professionals and patients will be able to access the information either by means of a smartphone/device or by typing the URL in an internet browser, if they do not have a smartphone/device.
- the blue box information where required.

The product information for circulation on the 3rd Nov has been updated with the URL for the QRD code (PL) in line with the Rapporteurs previously made comment as well as agreed according to the response from the Applicant.

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Regkirona (regdanvimab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

As regards to the legal status, the CHMP endorsed a medical prescription status in the context of the pandemic situation to allow appropriate flexibility for the access and administration of the medicinal product under the appropriate monitoring recommendations provided in the product information.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Regdanvimab is a recombinant monoclonal antibody targeting the receptor binding domain (RBD) of the spike (S) protein of SARS-CoV-2. The aim of therapy is to prevent the deterioration of patients to severe COVID, including a need for hospitalisation or oxygen therapy.

The presently sought indication is:

Regdanvimab is indicated for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (see section 5.1).

3.1.2. Available therapies and unmet medical need

The novel SARS-CoV-2 was initially identified during an outbreak of atypical viral pneumonia cases of unknown aetiology in China in December 2019. Subsequently this has emerged as the cause of the global Covid-19 pandemic.

Most people with SARS-CoV-2 infection develop only mild or moderate disease (WHO Interim Guidance on Clinical Management of COVID-19, 2020). However, some individuals develop severe disease that requires oxygen support, and some 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.

While mAbs with the present mechanism of action, and for the presently proposed use in outpatients with covid-19 to prevent deterioration, have been made available in EU countries based on various forms of temporary authorisation, there are no drugs for such use approved in the EU by regular procedure.

3.1.3. Main clinical studies

The applicant has conducted 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.

The confirmatory part 2 of the study tested the hypothesis that regdanvimab given to outpatients with early disease might reduce the risk of hospitalisation or severe disease.

In this, patients were screened at 60 study centres across, Hungary, Ireland, Italy, Mexico, North Macedonia, Peru, Poland, Republic of Korea, Republic of Moldavia, Romania, Serbia, Spain, Ukraine and United States. The study period for the pivotal part 2, was from 18 January 2021 (first patient's study drug administration date) to 21 May 2021 (last patient's Day 28 visit). Approximately 85% of patients were treated in the EU; the majority of the rest in the US.

The study included outpatients aged 18 or above. Patients had to have oxygen saturation >94% on room air, not requiring supplemental oxygen, and onset of SARS-CoV-2 infection associated symptom no more than 7 days prior to the study drug administration. The key exclusion criterion was signs of severe COVID. Furthermore, patents were required to be unvaccinated for Sars-Cov-2.

Patients were randomised to receive a single dose of 40 mg/kg of regdanvimab, or placebo.

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 in high-risk patients

"High-risk patients" met at least one of the following criteria:

- Advanced age (Age >50 years)
- Obesity (body mass index [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
- Immunosuppressed.

About 2/3 of recruited patients were over age 50 or had other recognised risk factors for severe COVID-19; however only two patients were classified as "immunosuppressed". 87% of patients had negative serology for SARS-CoV-2 at baseline.

3.2. Favourable effects

In patients with high risk for progressing to severe COVID-19, the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 was significantly lower in the regdanvimab group (14/446 [3.1 %]) compared to the Placebo group (48/434 [11.1 %]). The difference between the proportions was statistically significant (p<0.0001 [stratified CMH test]; estimated difference [95% CI] = -8.0 [-11.7, -4.5]).

The median time to clinical recovery (at least 48 hours) in high-risk patients was 9.27 days in regdanvimab group, but the median time was not reached in Placebo group as less than 50% of patients in this group achieved clinical recovery up to Day 14 (48.8%). The difference in time to clinical recovery between treatment groups was statistically significant (p<0.0001 [stratified log-rank test]; clinical recovery ratio [95% CI] = 1.58 [1.31, 1.90])

The time to negative virological conversion (<2.33 log10cp/mL as negative) up to Day 28 by RT-qPCR of nasopharyngeal swabs was shorter in the regdanvimab group than the Placebo group (median, 11.89 and 13.13 days in the regdanvimab and Placebo groups, respectively). The differences in time to negative conversion between the two treatment groups was significant (p<0.0001 [stratified log-rank test]; negative conversion ratio [95% CI] = 1.48 (1.30, 1.67)).

3.3. Uncertainties and limitations about favourable effects

Clinical efficacy against the presently circulating delta variant

At the time of the pivotal study, the circulating variants in the study region were predominantly wild-type and alpha. Therefore, clinical efficacy in patients infected with the delta variant was not shown.

In vitro neutralising activity was shown against the wild type virus as well as for the UK variant (Alpha, B.1.1.7). However, regdanvimab has reduced neutralising activity against South Africa (Beta, B.1.351), Brazil (Gamma, P.1), California (B.1.427 and B.1.429) and India (Kappa B.1.617.1 and Delta, B.1.617.2) variants in the PRNT and pseudovirus assays. Particularly, there was a 183-fold shift in susceptibility for the delta variant (B.1.617.2. in a PRNT assay with the authentic virus).

The reported the IC90 value in vitro for the wild type virus is 28 ng/mL. The highest reported IC90 value in vitro is for the Beta 1.351 (South African) virus variant: 16550 ng/mL.

The applicant has provided measured estimates of plasma concentrations and IC50 values for the delta variant, along with literature-based estimates of the lung concentration at 15% and 5% of the serum concentration.

The serum and estimated lung concentration at 96h post dose assuming 15% lung penetration are approximately 380000 ng/mL and 57000 ng/mL, respectively. At a more conservative estimate of 5% lung concentration, the 96h lung concentration would be approximately 19000 ng/mL. Thus, concentrations of regdanvimab in lungs would be estimated above the IC90 in vitro for all listed virus variants during the presumably crucial initial treatment phase. However, the (plasma or lung concentration/ in vitro susceptibility) quotient required for clinical efficacy has not been characterized. Furthermore, it is not clear that this is similar for all VOC's, given e.g. differences in viral replication rates.

The applicant has provided data from a Ferret model infected with the Gamma (B.1.351) variant, and from a ACE2 transgenic mouse model infected with Beta (P.1.), Gamma as well as Delta (B.1.617.2) virus, treated with human equivalent doses as post exposure prophylaxis. These studies are indicative of antiviral effects. However, the clinical implications are not completely known, since the

predictiveness of the models have not been established, and it is not known whether PK/PD is similar in these models and in humans.

Moreover, the applicant has submitted top line data from the 4.1. study, which is a post marketing cohort performed in South Korea. In this, patients are hospitalised with moderate covid at baseline. Among 330 patients known to have delta- or non-delta variants, disease progression rate was approximately 20% regardless of viral strain. It is evident from the substantially risk of progression to severe disease, that this cohort differs from the population in study 3.2. Thus, we lack an index of regdanvimab efficacy in this population. Altogether these data are compatible with clinical efficacy against the delta variant, but they do not demonstrate it.

In summary, PK/PD data, animal model data, as well as post marketing data from South Korea are compatible with activity also against the delta variant, for which in vitro susceptibility is decreased. Clinical efficacy against the delta variant, however, has not been demonstrated.

Efficacy in the immunocompromised

There is no index of efficacy in patients that are "immunosuppressed". It is assumed on a mechanistic basis that there will be relevant efficacy in such patients.

3.4. Unfavourable effects

Across the 3 studies with CT-P59, 906 subjects received at least 1 dose of CT-P59. Of these, 889 received the proposed single dose of 40 mg/kg or more, and 882 were infected with SARS-CoV-2.

Regdanvimab is a mAb with a non-host target and no effector function. As such, the safety profile is anticipated to be characterised mainly by potential immune- or hypersensitivity reactions. No excess of infusion related reactions has been shown, but this remains a potential risk which requires monitoring.

There were 1 and 2 deaths in the CT-P59 40 mg/kg and placebo groups, respectively. The cause of death was in all cases assessed as related to worsening of COVID-19. The program has not provided any indication of antibody-dependent enhancement of disease.

3.5. Uncertainties and limitations about unfavourable effects

Despite the size of the safety database, it cannot be excluded that more uncommon adverse drug reactions have not been detected.

The sensitivity of the study program to detect potential, rare events of antibody dependent enhancement of disease (ADE) may be questioned.

3.6. Effects Table

Table 42 Effects Table for Regkirona for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Proportion of Patients with Clinical Symptoms	i.e., Hospitalisation/Oxygen Therapy/ Mortality due to SARS-CoV-2 Infection up to Day 28 in High-Risk Patients		14/446 [3.1 %]	48/434 [11.1 %]	Statistically significant. Clinically relevant reduction. Changes of primary objectives and confirmatory strategy at late stage of the study may implicate interpretation of study results. Clinical efficacy against some variants of concern, including delta is uncertain.	
Time to Clinical Recovery	Up to Day 14 in High-Risk Patients	Median days	9.27 [8.27, 11.05]	N.C [12.35, N.C]	Statistically significant reduction in duration of symptoms.	
Time to Negative Conversion ITT set	Up to Day 28. (<2.33 log10cp/mL as negative)	Median days	11.89	13.13	Minor but statistically significant change.	
Unfavourable Effects						
IRR*	Infusion-related reactions		4 (0.6%)	7 (1.1%)	No excess in study CT-P59 3.2 part 2	

*Note: 1 case of suspected anaphylaxis that was fatal was registered in post-marketing reports.

Abbreviations: N.C: not calculated, ITT: intention to treat, IRR: infusion-related reactions, N/A: not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clinically relevant reduction in the risk of disease deterioration requiring hospitalisation and/or oxygen therapy, in outpatients with covid-19 infection that do not yet have severe disease, but are at risk for such, has been demonstrated for regdanvimab.

As outlined above, in the section on uncertainties on favourable effects (section 3.3.), the delta variant, which displays a 183-fold reduction in in vitro susceptibility (authentic virus, PRNT assay) was not circulating at the time and in the regions of the pivotal trial. Consequently, an inference of efficacy must be based on PK/PD, animal model data, and post marketing data from Korea. While these taken together are supportive of efficacy, this has not been shown, and the inference of efficacy is therefore fraught with uncertainty. Consequently, the following wording is implemented in the SmPC section 4.4:

"The clinical trials with regdanvimab were conducted in subjects who were predominantly infected with the wild-type virus and the Alpha (UK origin/B.1.1.7 lineage) variant. Clinical efficacy data for

regdanvimab against some circulating SARS-CoV-2 variants with decreased susceptibility in vitro is currently limited (see section 5.1)."

The Applicant has stated that it intends to monitor emerging variants continuously. In case a new variant of concern (VoC) or variant of interest (VoI) classified by the Agencies (i.e. WHO, PHE, CDC and etc.) or any variant is found in South Korea, the Applicant will determine their risk and initiate studies to characterize regdanvimab in relation to the variant in question. This should be included in part III of the RMP.

Overall, the safety profile of regdanvimab is favourable, in line with what is expected from a monoclonal antibody targeting a viral protein, and with no intrinsic effector function.

3.7.2. Balance of benefits and risks

The demonstrated benefits outweigh the risks. Data include a decently sized randomised controlled trial and are deemed comprehensive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of Regkirona is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Regkirona is favourable in the following indication:

"Regdanvimab is indicated for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (see section 5.1)".

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that regdanvimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.