EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2021
EMA/192245/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 5(3) of Regulation (EC) No 726/2004

Celltrion use of regdanvimab for the treatment of COVID-19

INN/active substance: regdanvimab

Procedure number: EMEA/H/A-5(3)/1505

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. Information on the procedure

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, is the causative agent of coronavirus disease 2019 (COVID-19). Early treatment of patients with confirmed COVID-19 presenting only mild symptoms can reduce the number of patients that progress to more severe disease and require hospitalisation or admittance to ICU.

The European Medicines Agency (EMA) is aware of several therapeutic candidates with putative antiviral action which are currently in development for the treatment of these patients. Amongst those treatments the recombinant monoclonal antibody CT-P59 or regdanvimab has demonstrated an antiviral effect *in vitro*, *in vivo*, and in clinical data, where it has been associated with a numerical trend towards lower rates of progression to disease requiring hospitalisation and/or oxygen therapy.

These results were considered of great relevance and their application in the clinical setting before a formal marketing authorisation is considered important in view of the current pandemic situation. In that respect, there is public health interest to seek a harmonised scientific opinion at EU level on currently available information on regdanvimab and on potential conditions of use with a view to supporting national decisions.

On 26 February 2021 the Executive Director therefore triggered a procedure under Article 5(3) of Regulation (EC) No 726/2004, and requested the CHMP to give a scientific opinion on the currently available quality, preclinical and clinical data on the potential use of regdanvimab for the treatment of confirmed COVID-19 in patients that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

2. Scientific discussion

2.1. Introduction

CT-P59 or regdanvimab is a recombinant human monoclonal antibody targeted against the receptor binding domain (RBD) of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is being developed as a potential treatment for SARS-CoV-2 infection.

It is a recombinant monoclonal antibody expressed in CHO-K1 cells, engineered after screening a library of antibodies in the sera of a Korean convalescent patient identified sequences of an antibody with high avidity to the receptor binding domain of the spike protein of SARS-CoV-2.

CT-P59 drug product is formulated for administration by intravenous (IV) infusion as a sterile liquid solution 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. The formulation of CT-P59 drug product includes L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, L-arginine monohydrochloride and water for injection. The pH of the drug product solution is 6.0.

The anticipated dosing and administration for CT-P59 is a single intravenous (IV) infusion of 40 mg/kg administered over 90 ± 15 minutes in settings which health care providers have immediate access to medications to treat severe infusion reactions, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary.

In view of clinical data, part 1 of study CT-P59 3.2, data is available from a phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study to evaluate the efficacy and safety of two

different doses of CT-P59 in combination with standard of care in outpatients with SARS-CoV-2 infection.

The result of the main primary endpoint was the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in patients receiving any dose of CT-P59 compared to placebo (see detailed results in section 2.2 below).

The company initially proposed a use in the following indication: *"for the treatment of mild to moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalisation.*

High risk is defined as patients who meet at least one of the following criteria:

· *Are ≥60 years old*

· *Are ≥50 years of age AND have pneumonia but no signs of severe pneumonia and does not require supplemental oxygen therapy"*

In parallel to this procedure, a rolling review is on-going aiming at an EU Marketing Authorisation.

The CHMP considered all available data, including data on quality, non-clinical and clinical aspects. A summary of the most relevant information is included below.

2.2. Clinical aspects

The CT-P59 clinical development program includes two Phase 1 studies (healthy volunteers and mild COVID-19 patients) and a Phase 2/3 study (mild to moderate COVID-19 patients).

- *Phase 1 study CT-P59 1.1 in healthy volunteers*
  Dose levels: 10, 20, 40 and 80 mg/kg (N=6 per dose group). PK sampling up to Day 90 after dose.
- *Phase 1 study CT-P59 1.2 in patients with mild COVID-19*
  Dose levels: 20, 40 and 80 mg/kg (N=5 per dose group). Limited sampling (up to Day 14). No PK analysis.
- *Phase 2/3 study CT-P59 3.2 (Part 1) in patients with mild to moderate COVID-19*
  Dose levels: 40 mg/kg (N=29) and 80 mg/kg (N=32). PK sampling up to Day 28 after dose.

The data pivotal for the purpose of this procedure are derived from part 1 of study CT-P59 3.2. This is 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 (see table 1).

Patients are ≥18 years old at time of receipt of the study medication, with a diagnosis of Sars-CoV-2 infection, who are symptomatic for no more than 7 days prior to study drug administration, and whose SpO_2 is over 94% and who are not requiring supplemental oxygen. Patients with clinical signs of pneumonia but no signs of severe pneumonia was eligible to participate in this study at investigator's discretion. These patients' disease was deemed of "moderate" severity by the company.

Figure 1. Schematic overview of study CT-P59 3.2 Part 1 and 2

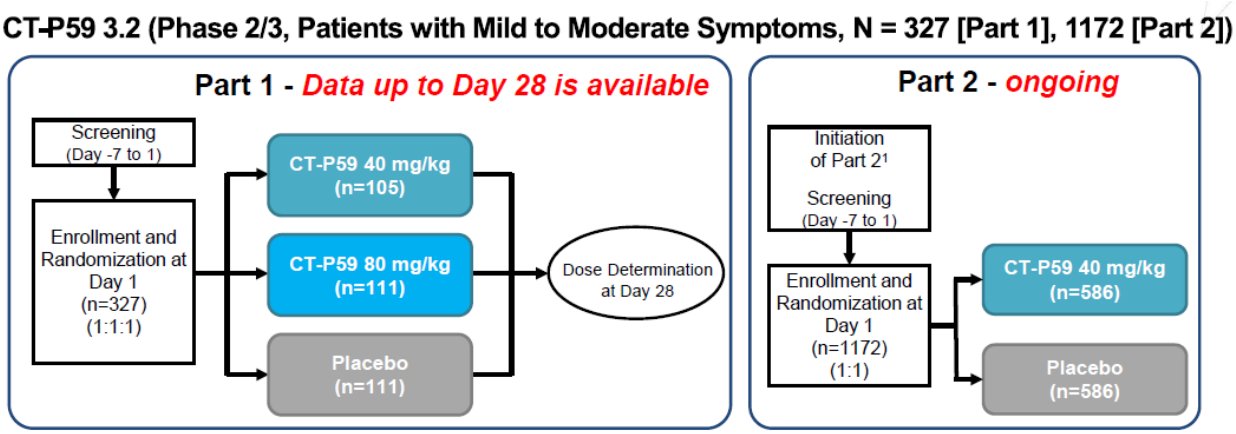


Table 1 – Overview of key efficacy data submitted

Study id and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main efficacy results
CT-P59 3.2 (Part 1), 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	*Key primary objective:* Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28	Adult Outpatients with SARS-CoV-2 Infection	*Inclusion Criteria:* Adult patients aged 18 or above with SARS-COV-2 infection not more than 7 days prior to study drug administration, O_2 saturation >94% on room air and not requiring supplemental oxygen , body weight 50 - 100 kg, body mass index (BMI) of ≥18.0 kg/m2. *Exclusion criteria:* Current serious COVID-19 condition, actual or possible antiviral treatments and/or other possible anti-SARS-CoV-2 medications, prior SARS-CoV-2 vaccine, allergies/hypersensitivities against product components, serious other medical conditions, pregnancy, breastfeeding, alcohol/ drug abuse.	• 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	Compared to placebo treatment, a lower proportion of patients treated with CT-P59 was hospitalised or received oxygen therapy up to Day 28 due to SARS-CoV-2 infection. These Proportions were 4/101 (4.0%), 5/103 (4.9%) and 9/204 (4.4%) patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg and pooled CT-P59 groups, respectively, compared with 9/103 (8.7%) patients in the Placebo group. There were no

					deaths in this study.

2.2.1. Clinical pharmacology

The serum exposure of CT-P59 (regdanvimab) was assessed in all three submitted clinical studies. In line with the proposed posology, CT-P59 was administered as a single intravenous infusion over 90 minutes.

Serum concentrations of regdanvimab were quantitatively measured using a validated ligand-binding assay with a lower limit of quantification of 800 ng/ml. Immunogenicity, i.e. ADA against regdanvimab was assessed using a multitiered strategy (screening, confirmation, titre, neutralisation).

The results showed that the pharmacokinetics of regdanvimab was characterized by a low clearance, a small volume of distribution and a terminal half-life of 12 days. The serum exposure (AUC and C_{max}) increased in proportion to dose in the investigated dose interval. The pharmacokinetics in patients was similar to that in healthy volunteers. The incidence of anti-drug antibodies was low.

The table below summarizes the PK results from the Phase 2/3 study CT-P59 3.2 (Part 1) in patients. Data are presented as mean (CV%). The interindividual variability is considered moderate.

Table 2: PK results from study CT-P59 3.2 (Part 1)

Parameter		**40 mg/kg (N=29)**	**80 mg/kg (N=32)**
$AUC_{0\text{-}inf}$ (μg·h/ml)	Mean (%CV)	182095 (18.7%)	355087 (21.7%)
C_{max} (μg/ml) [1]	Mean (%CV)	1017 (26.5%)	2008 (23.8%)
$C_{Day\ 28}$ (μg/ml)	Mean (%CV)	99.5 (22.7%)	181.5 (29.1%)
CL (ml/h/kg)	Mean (%CV)	0.227 (19.2%)	0.237 (25.3%)
V_z (ml/kg)	Mean (%CV)	87.2 (22.3%)	94.6 (16.0%)
$t_{1/2}$ (hours)	Mean (%CV)	276 (31.1%)	287 (22.3%)

[1] Peak levels were typically observed at the end of infusion

No interaction studies, metabolism and excretion studies or dedicated studies in special populations and no population PK analysis were performed which is acceptable within the framework of this procedure. Elimination of regdanvimab is likely to occur through normal degradation pathways for immunoglobulins and the clearance is not expected to be affected by renal or hepatic impairment. For the same reason, regdanvimab is not expected to cause or be susceptible to drug interactions with concomitantly administered medicinal products.

No PK data in adolescents or children have been provided.

Dose selection was based on previous non-clinical and PK studies with a structurally similar anti-influenza antibody. The starting dose in the first in human studies were 10 mg/kg and the maximal dose deemed to be 80 mg/kg based on preserving the preclinical safety margin. No PK/PD arguments relating to antiviral activity are presented. The clinical efficacy of 40 mg/kg and 80 mg/kg was tested in the study that is pivotal for this procedure (see below).

2.2.2. Data on efficacy

Available information on efficacy are derived from part 1 of study CT-P59 3.2.

This is a, randomised, parallel-group, placebo-controlled, double-blind study with 2 parts to evaluate the efficacy, safety, PK and virology of CT-P59 in outpatients with SARS-CoV-2 infection considered mild to moderate by the company, not requiring supplemental oxygen therapy.

Study population

Male or female outpatients aged 18 or above, diagnosed with SARS-CoV-2 infection at Screening by using a sponsor-supplied rapid SARS-CoV-2 diagnostic test, or reverse transcription polymerase chain reaction (RT-PCR) were to be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

'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.

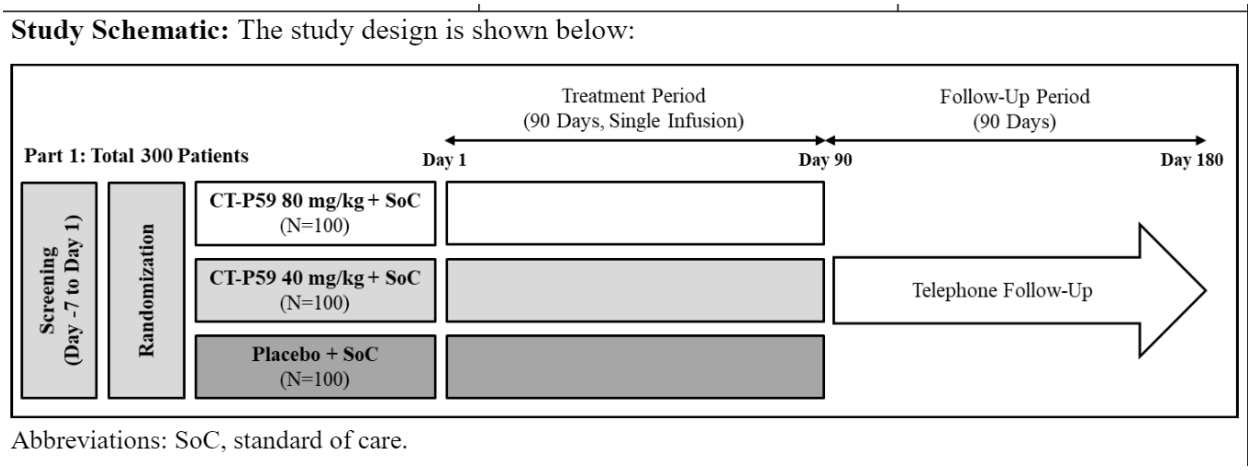
The patients had to have 1 or more of the following (but not limited to) SARS-CoV-2 infection-associated symptoms within but not more than 7 days prior to study drug administration: feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, headache, 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.

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.

Study design

The study consisted of 3 study periods (Screening, Treatment Period, and Follow-Up Period). 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 2: Study design of CT-P59 3.2(Part 1)



In the Treatment Period, patients were randomly assigned in a 1:1:1 ratio to receive a single dose of CT-P59 40 mg/kg, CT-P59 80 mg/kg, or Placebo matching in volume of CT-P59 80mg/kg

This 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 100kg and were allocated to the CT-P59 80mg/kg group or Placebo group received 8,000mg of CT-P59 or a matching volume of Placebo.

Figure 3: Interventions in study CT-P59 3.2(Part 1)

Day	1	2	3	4	5	6	7	10	14	17	21	28	56	90	180
Administration of Study Drug	●														
Viral Shedding (RT-qPCR and Cell culture)	●	●	●	●	●	●	●	●	●	●	●	●			
Patient Diary							●								
SARS-CoV-2 infection related signs and symptoms assessment								●							
Pharmacokinetics	●	●	●		●		●	●	●			●	●	●	
Safety								●							

Statistical aspects

The study was powered based on a virological endpoint: With 100 patients per group, in the range of 30% to 90% of patients with negative conversion in nasopharyngeal swab specimen based on RT-qPCR or cell culture in the group, the half of the width of 95% confidence interval (CI) of the point estimate of the percentage would have been no more than ±9.8%.

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).

There is no assignation of alpha to a given primary endpoint, according to the SAP. In the absence of a plan for type 1 error control, all endpoints are understood as exploratory. The following endpoints were designated as "primary"

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

The primary analysis population was the ITT-infected (ITTI) set. The ITTI Set was defined as all randomly assigned patients with confirmed SARS-CoV-2 infection by pre-infusion (Day 1) result based on RT-qPCR or cell culture and who received a complete or partial dose of the study drug.

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 lower limit of detection (LLOD95) of the RT-qPCR was determined as 2.33 (95% CI: 1.74 – 3.72) log_{10} cp/ml. There was also a cell culture assay with a LOD of 0.8 log10 cp/ml, however no results from this assay were provided as part of this procedure.

Viral titers were treated in the descriptive summary and AUC calculation as "Positive" when they were above or equal these detection limits or "Negative" when results were below detection limits or negative.

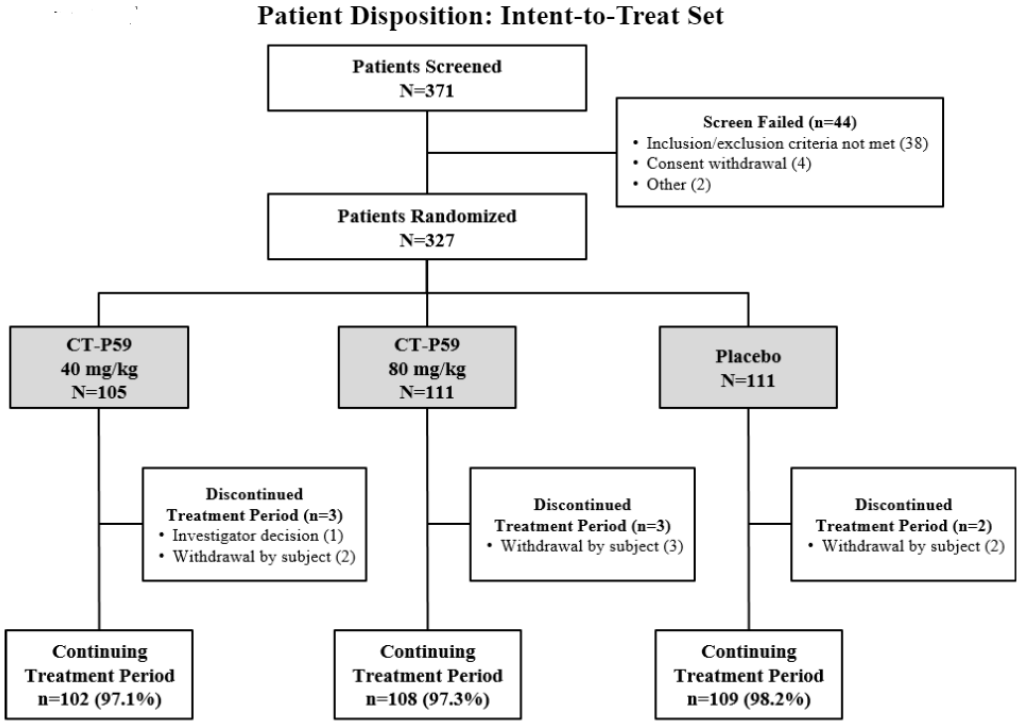
Serological methods

IgG or IgM antibodies as determined by a sponsor-supplied rapid diagnostic test.

Study subject disposition

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.

Figure 4. Patient disposition for study CT-P59 3.2



All randomized 327 patients were included in the ITT Set (105, 111, and 111 patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively).

The ITTI Set included 307 patients (101, 103, and 103 patients in the CT-P59 40 mg/kg, CT-P59 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.

Table 3 Analysis Set

	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

Baseline demographic and disease characteristics

Table 4 Demographics and Stratification Details: Intent-to-Treat Set

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)

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

Notably, baseline comorbidities in the table above curiously conflates 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 CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively).

Results

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)

A total of 15 patients were identified to meet the criteria for the hospitalisation (≥24 hours of acute care, in a hospital or similar acute care facility) and all of them received at least 3 days of supplemental oxygen care. In all cases the SpO_2 measured in room air before applying supplemental oxygen was ≤94%.

In addition, there were 2 patients who didn't have a record of the hospital admission in the eCRF Form but had at least 3 days of supplemental oxygen care in response to a prior SpO_2 measure in room air ≤94%. There was also one patient who received remdesivir for 5 days and this patient was considered to meet the definition of hospitalisation as remdesivir is required to be administered in healthcare facilities in which patients can be monitored closely. Since all patients who received at least 3 days of supplemental oxygen care in response to prior SpO_2 measures in room air ≤94%, or received remdesivir were counted, they all are considered to meet a conservative condition of hospitalisation due to COVID-19.

Thus, the hospitalisation outcome reported below includes 18 cases.

Compared to placebo treatment, a lower proportion of patients treated with CT-P59 was hospitalised or received oxygen therapy up to Day 28 due to SARS-CoV-2 infection. These portions were 4/101 (4.0%), 5/103 (4.9%) and 9/204 (4.4%) patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg and pooled CT-P59 groups, respectively, compared with 9/103 (8.7%) patients in the Placebo group (Table 5). There were no deaths in this study.

Table 5 - 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%)**
[95% CI]	[1.6-9.7]	[2.1-10.9]	[2.3-8.2]	[4.7-15.8]
P-value	0.2513	0.4073	0.1962	
Subgroup analyses				
Patients who were ≥50 years of age	**3/59 (5.1%)**	**4/55 (7.3%)**	**7/114 (6.1%)**	**9/57 (15.8%)**
[95% CI]	[1.7-13.9]	[2.9-17.3]	[3.0-12.1]	[8.5-27.4]
P-value	0.0720	0.2384	0.0524	
Patients who were ≥50 years of age AND had pneumonia symptoms	**3/40 (7.5%)**	**4/40 (10%)**	**7/80 (8.8%)**	**9/38 (23.7%)**
[95% CI]	[2.6-19.9]	[4.0-23.1]	[4.3-17.0]	[13.0-39.2]
P-value	0.0626	0.1343	0.0418	
Patients who were ≥60 years of age OR Patients who were ≥50 years of age AND had pneumonia symptoms	**3/47 (6.4%)**	**4/46 (8.7%)**	**7/93 (7.5%)**	**9/46 (19.6%)**
[95% CI]	[2.2-17.2]	[3.4-20.3]	[3.7-14.7]	[10.7-33.2]
P-value	0.0700	0.2305	0.0485	

Note: Clinical symptom which requires hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28. Criteria of Hospitalisation is ≥24 hours of acute care. Criteria of oxygen therapy is at least 24 hours of supplemental oxygen care and SpO_2 measure in room air before applying supplemental oxygen shows ≤94%. Wilson (score) confidence interval and P-value from fisher's exact test are presented.

Post-hoc analyses were performed for patients who were ≥50 years old and had pneumonia, the proportion of patients with clinical symptoms requiring hospitalisation or oxygen therapy due to SARS-CoV-2 infection up to Day 28 was significantly lower in the pooled CT-P59 group compared to the Placebo group (7/80 [8.8%] and 9/38 [23.7%] patients in the pooled CT-P59 and Placebo groups, respectively, p=0.0418). This indicates that, as expected, the risk of hospitalisation was higher in those with known risk factors for severe COVID-19.

Altogether there is a trend to lower rates of hospitalisation in the regdanvimab-treated groups. However, this was neither an alpha-protected endpoint, nor does it reach nominal statistical significance at the two-sided 0.05 level.

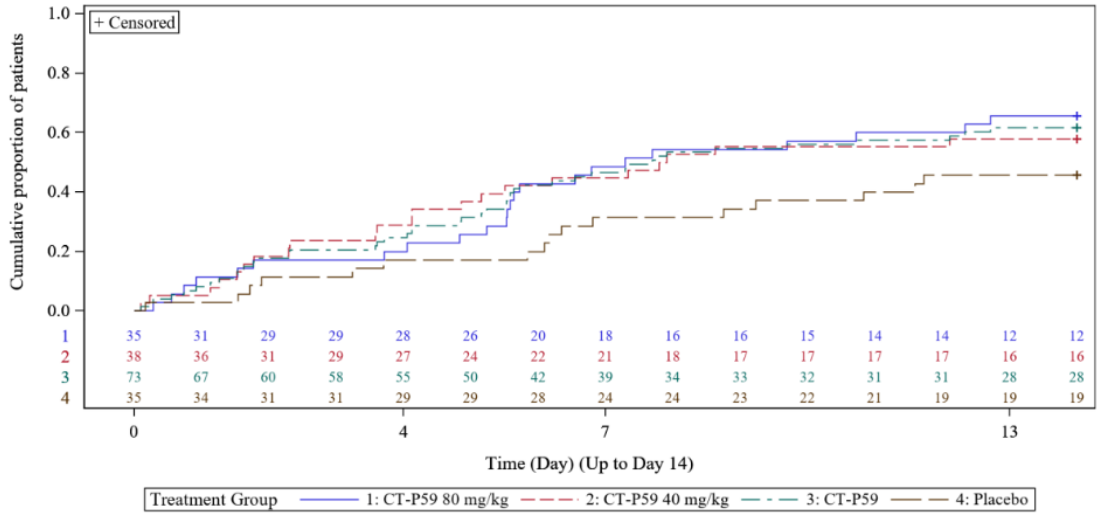
Time to clinical recovery

Clinical recovery included improvement or absence of symptoms on the SARS-CoV-2 Infection Symptom Checklist 1 (feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, and headache) for at least 48 hours.

The median [95% CI) time to clinical recovery up to Day 14 was numerically shorter in the CT-P59 groups than the Placebo group (7.18 [5.50, 9.37), 7.30 [5.72, 9.33), and 8.80 [6.88, 13.09) days in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively). The p-values for the difference between the sum CT-P59 treated groups and the placebo group is 0.06 or 0.04 depending on the use of the log-rank or Wilcoxon test.

The company also presented a subgroup analysis of patients ≥60 Years of Age OR Patients Who Were ≥50 Years of Age AND had Pneumonia Symptoms provide some indication of an effect of CT-P59.

Figure 5 Summary of Time to Clinical Recovery Up to Day 14 (Moderate SARS-CoV-2 Infection Aged ≥50 Years; Kaplan-Meier Plot): Intent-to-Treat Infected Set



While suggestive of the possibility of an effect, none of these data establish an effect on duration of symptoms.

Time to Negative Conversion up to Day 14 (Virologic Endpoint)

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.

The median [95% CI) time to negative conversion by RT-qPCR was similar in the CT-P59 groups compared to the Placebo group (12.75 [9.00, 12.84), 11.89 [8.94, 12.91), 12.65 [9.03, 12.83) and 12.94 [12.75, 13.99) days in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, pooled CT-P59 and Placebo groups, respectively).

Table 6. Time to Negative Conversion based on RT-qPCR up to Day 14 in Study CT-P59 3.2 Part 1 (<2.33 log_{10}cp/ml as negative): Intent-to-Treat Infected Set

	CT-P59 40 mg/kg (N=101)	CT-P59 80 mg/kg (N=103)	Pooled CT-P59 (N=204)	Placebo (N=103)
Number of Patients with Negative Conversion based on RT-qPCR up to Day 14	68/101 (67.3%)	68/103 (66.0%)	136/204 (66.7%)	62/103 (60.2%)
Number of Patients with Censoring	33/101 (32.7%)	35/103 (34.0%)	68/204 (33.3%)	41/103 (39.8%)
Early Withdrawal for any reason	1/101 (1.0%)	1/103 (1.0%)	2/204 (1.0%)	2/103 (1.9%)
Ongoing study without event	26/101 (25.7%)	29/103 (28.2%)	55/204 (27.0%)	30/103 (29.1%)
Rescue Therapy before the Event	6/101 (5.9%)	5/103 (4.9%)	11/204 (5.4%)	9/103 (8.7%)
Time to Negative Conversion[1]				
Median [95% CI)	12.75 [9.00, 12.84)	11.89 [8.94, 12.91)	12.65 [9.03, 12.83)	12.94 [12.75, 13.99)
Proportion with Negative Conversion[1]				
4 Days	8.9%	13.6%	11.3%	8.7%
7 days	25.7%	30.1%	27.9%	19.4%
10 days	44.6%	46.6%	45.6%	36.9%
13 days	62.4%	63.1%	62.7%	54.4%
P-value (log-rank test)	0.1846	0.2076	0.2076	
P-value (Wilcoxon test)	0.1504	0.1305	0.1305	
Negative Conversion Ratio (95% CI)	1.262 (0.89, 1.78)	1.247 (0.88, 1.76)	1.253 (0.93, 1.69)	

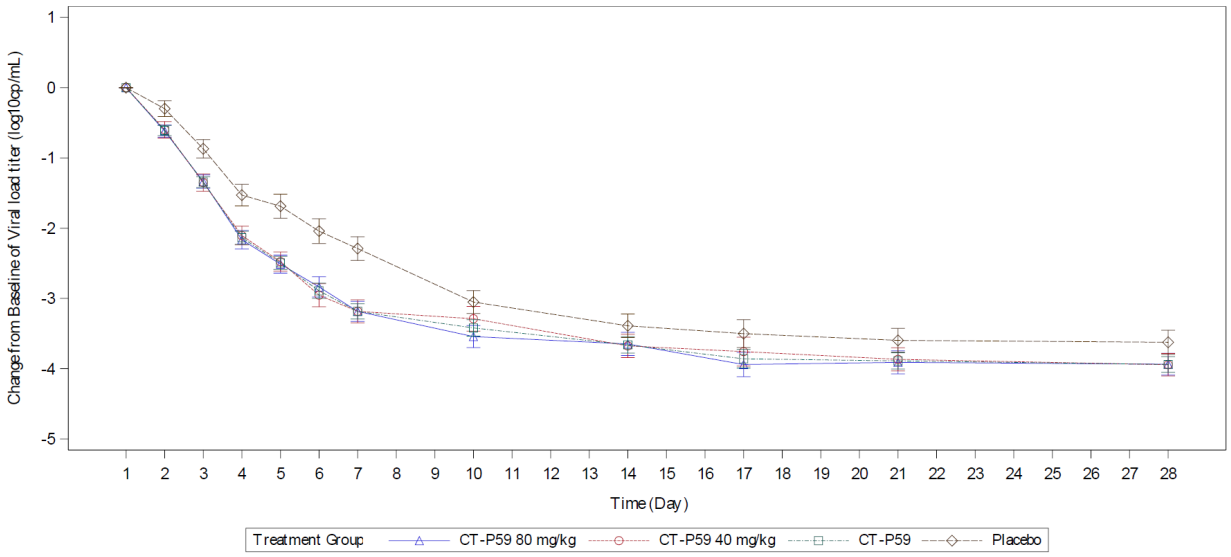
Note: P-value from log-rank and Wilcoxon test are presented. Patients who have negative or missing result at baseline and do not have positive at Day 2 are excluded in this analysis.
[1] Time to negative conversion (days) is calculated as (Date/time of Event/Censoring - Date/time of study drug administration) and Kaplan-Meier estimates are presented.

There was no significant difference between CT-P59 treatment groups and placebo on time to negative conversion with the limit of detection <2.33 log_{10} cp/ml set as negative. However, with a post hoc change of the negative limit <3.31 log_{10} cp/ml based on the mean virus titre at the time point of achieving clinical recovery in the current study, the time to negative conversion was approximately 3 days shorter in the CT-P59 combined group compared to placebo (5.81 days vs. 8.86 days in the ITTI set).

Viral Shedding

The mean virus titre detected by RT-qPCR at baseline was slightly lower in the placebo group (5.958 log_{10} cp/ml) than in the CT-P59 40 mg/kg group (6.280 log_{10} cp/ml) and CT-P59 80 mg/kg group (6.288 log_{10} cp/ml). After study drug administration on Day 1, greater reductions from baseline viral load were shown in CT-P59 groups compared to the Placebo group, mostly notable up to Day 10. At Day 7 patients treated with CT-P59 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 CT-P59 treatment groups and -2.290 (1.709) log_{10} copies/ml in the Placebo group.

Figure 6 - Mean (±SE) Change from Baseline of Viral Load Titres (log_{10}cp/ml) – Intent-to-Treat Infected Set



Serology for SARS-CoV-2 IgG and IgM Antibodies

At baseline (Day 1), the proportion of patients positive with IgG was 0, 6 (5.8%), and 3 (2.9%) in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively. The proportions of each group gradually increased and were similar in all 3 groups at all time points.

At baseline (Day 1), the proportion of patients positive with IgM was 2 (2.0%), 6 (5.8%), and 4 (3.9%) in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively. The proportions of each group gradually increased up to Day 14, and slightly decreased at Day 28 in all 3 groups. The results were generally similar in all 3 groups at all time points.

With the rapid antibody test used in this study, a very low number of patients were seropositive at baseline. The potential benefit of CT-P59 is mainly expected when the drug is administered to patients who have not yet mounted a specific humoral immune response. However, 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, making a comparison difficult.

Conclusions on Efficacy

Evidence of clinical efficacy is limited to the exploratory study CT-P59 3.2 Part 1. This small study in outpatients with mild/moderate COVID-19 did not have a type-1 error controlled primary endpoint.

There was a trend towards an impact on hospitalisations due to COVID-19, with a total of 4.4 vs 8.7% of patients required hospitalisation in the pooled treatment and placebo groups, respectively. However, this difference is not nominally statistically significant at the 0.05 level.

While an impact on time to negative qRT-PCR in NPH secretions was only statistically significant after a post hoc re-definition of negativity, data on viral shedding over time are indicative that regdanvimab does display antiviral activity *in vivo*, as would be anticipated. The magnitude of this effect, however, is difficult to compare with what has been seen in other programs of mAbs against the spike protein in view of potential differences between studies in terms of patient populations and assays used. It is

known that serostatus and viral load at baseline are strong and correlated effect modifiers. Data on serostatus was determined with rapid diagnostic tests, presumably lacking the sensitivity of the quantitative methods.

There was no dose-response relationship seen between 40 mg/kg and 80 mg/kg. The lower dose was selected for further study, in comparison with placebo, in the confirmatory CT-P59 3.2 part 2 study.

No effects have been established with the statistical certainty that is required to provide substantial evidence of efficacy.

2.2.3. Data on safety

Safety database

Across the 3 studies with CT-P59, 254 subjects received at least 1 dose of CT-P59.

Table 7. 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

Demographics and Baseline Characteristics

Study CT-P59 1.1

In Study CT-P59 1.1, 24 subjects were administered CT-P59. Of these, 6 subjects received 10 mg/kg, 6 subjects 20 mg/kg, 6 subjects 40 mg/kg and 6 subjects 80 mg/kg. A total of 8 subjects were administered placebo. All 32 subjects were included in the safety set.

The median age of subjects was 24.0 (range 19-43) years and all subjects were male and Asian. The mean (SD) body mass index (BMI) of subjects was 23.843 (2.5997) kg/m^2 at Screening. Overall, the demographic profiles of subjects across the treatment groups were comparable.

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

In Study CT-P59 1.2, 15 patients were administered CT-P59. Of these, 5 patients received 20 mg/kg, 5 patients 40 mg/kg and 5 patients 80 mg/kg. A total of 3 patients were administered with placebo. All 18 patients were included in the ITT set.

The median age of patients was 52.0 (range 25-61) years. There was a higher percentage of male patients than female patients (11 [61.1%] male patients compared with 7 [38.9%] female patients)

and a high percentage of White patients than Asian patients (12 [66.7%] White patients compared with 6 [33.3%] Asian patients). The mean (SD) BMI of patients was 26.832 (3.1074) kg/m^2 at Screening. Overall, the demographic profiles of patients across the cohorts were comparable.

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

In Study CT-P59 3.2 Part 1, 215 patients were administered CT-P59. Of these, 105 patients received 40 mg/kg and 110 patients 80 mg/kg. A total of 110 patients were administered with placebo. All 325 patients were included in the safety set.

Overall, demographic characteristics were generally well balanced between the 3 groups. The mean (SD) age of patients was 50.4 (12.48), 51.1 (14.79), and 51.4 (13.05) in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively. The majority of patients were White (286 [87.5%] patients). The mean (SD) screening BMI of patients was 27.101 (4.8086), 27.095 (4.1364), and 26.819 (4.2071) kg/m^2 in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, and Placebo groups, respectively.

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 CT-P59 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 CT-P59 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 CT-P59 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 CT-P59 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).

Study CT-P59 3.2 (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 CT-P59 40 mg/kg, CT-P59 80 mg/kg, pooled CT-P59 and Placebo groups, respectively) and hyperglycaemia (7 [2.2%] patients overall; 2 [1.9%], 2 [1.8%], 4 [1.9%] and 3 [2.7%] patients, respectively).

Table 8. 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	57	58	115	67
N (%) of patients with at ≥ 1 TEAE	31 (29.5%)	27 (24.5%)	58 (27.0%)	34 (30.9%)
Blood and lymphatic system disorders	**8 (7.6%)**	**4 (3.6%)**	**12 (5.6%)**	**4 (3.6%)**
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	**4 (3.8%)**	**8 (7.3%)**	**12 (5.6%)**	**5 (4.5%)**
Bacteriuria	2 (1.9%)	2 (1.8%)	4 (1.9%)	2 (1.8%)
Cystitis	2 (1.9%)	2 (1.8%)	4 (1.9%)	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	**7 (6.7%)**	**9 (8.2%)**	**16 (7.4%)**	**8 (7.3%)**
Blood creatine phosphokinase increased	3 (2.9%)	0	3 (1.4%)	0
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	**10 (9.5%)**	**8 (7.3%)**	**18 (8.4%)**	**11 (10%)**
Dyslipidaemia	3 (2.9%)	1 (0.9%)	4 (1.9%)	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%)**
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%)**	**4 (3.6%)**	**5 (2.3%)**	**3 (2.7%)**
Insomnia	0	2 (1.8%)	2 (0.9%)	1 (0.9%)
Respiratory, thoracic and	**2 (1.9%)**	**2 (1.8%)**	**4 (1.9%)**	**1 (0.9%)**

	CT-P59 40 mg/kg (N=105)	CT-P59 80 mg/kg (N=110)	Pooled CT-P59 (N=215)	Placebo (N=110)
mediastinal disorders				
Epistaxis	2 (1.9%)	1 (0.9%)	3 (1.4%)	0
Skin and subcutaneous tissue disorders	**4 (3.8%)**	**2 (1.8%)**	**6 (2.8%)**	**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, most of the TEAEs were CTCAE grade 1 in intensity. Grade 3 TEAEs were reported for 5 (4.8%), 4 (3.6%), 9 (4.2%) and 2 (1.8%) patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, pooled CT-P59 and Placebo groups, respectively. No Grade 4 or higher TEAEs were reported up to Day 28. Grade 3 TEAEs reported for > 1 patient in either group was hypertriglyceridaemia (2 [1.9%], 0, 2 [0.9%] and 1 [0.9%] patients in the CT-P59 40 mg/kg, CT-P59 80 mg/kg, pooled CT-P59 and Placebo groups, respectively).

Table 9. 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	**5 (4.8%)**	**4 (3.6%)**	**9 (4.2%)**	**2 (1.8%)**
Related	1 (1.0%)	0	1 (0.5%)	0
Unrelated	4 (3.8%)	4 (3.6%)	8 (3.7%)	2 (1.8%)
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**
Cystitis	0	1 (0.9%)	1 (0.5%)	0
Investigations	**1 (1.0%)**	**1 (0.9%)**	**2 (0.9%)**	**1 (0.9%)**
Alanine aminotransferase increased	0	1 (0.9%)	1 (0.5%)	0
Blood creatine phosphokinase increased	1 (1.0%)	0	1 (0.5%)	0
Gamma-glutamyl transferase 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

Deaths, Other Serious Adverse Events and Discontinuations

One unrelated treatment-emergent serious adverse event (TESAE) of limb injury occurred 36 days after the study drug administration in the CT-P59 20 mg/kg treatment group of Study CT-P59 1.1. No other TEAEs were considered as serious and no TEAEs leading to study drug discontinuation and deaths were reported in Studies CT-P59 1.1, CT-P59 1.2 and CT-P59 3.2 Part 1.

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 CT-P59 treatment groups during the study period.

In Study CT-P59 3.2 Part 1, IRRs were reported for 1 (1.0%) patient in the CT-P59 40 mg/kg treatment group and 2 (1.8%) patients in the Placebo group. All TEAEs of IRR were Grade 1 or Grade 2.

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 14 for Studies CT-P59 1.1 and CT-P59 1.2. In Study CT-P59 3.2 Part 1, there were 4 (3.7%) patients with positive ADA conversion in the CT-P59 80 mg/kg treatment group, while there was no positive ADA conversion in the CT-P59 40 mg/kg treatment 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 ADE.

Conclusions on Safety

No excess of infusion related reactions has been shown, but this remains a potential risk which requires monitoring as specified in the Conditions for Use document. Further, given that the safety database consists of only 254 subjects, it cannot be excluded that more uncommon adverse drug reactions have not been detected.

It is noted that treatment-emergent grade 3 hepatocellular injury and/or ALT increase has been reported in a total of 3 patients receiving CT-P59 while no such cases were reported in the placebo groups. Notably, transaminitis may be a manifestation of COVID-19. While hepatotoxicity is not anticipated for a mAb specific for an exogenous target, a risk of drug-induced liver injury cannot presently be ruled out.

Overall, the safety profile of CT-P59 appears favourable, in line with what is expected from a monoclonal antibody targeting a viral protein, and with no intrinsic effector function.

2.3. Non-clinical aspects

The company provided an overview of the non-clinical studies conducted (pharmacological, pharmacokinetic and toxicological) and their status (finished, ongoing).

In the primary pharmacology studies, the specificity and efficacy of the antibody was assessed (see below). In the *in vivo* studies, treatment effects on viral titre levels and clinical symptoms in four different animal models were assessed. One pharmacology study is presently ongoing ("Neutralization of variants and potential escape mutants by CT-P59 by *in vitro* pseudovirus assay").

In the secondary pharmacology, the possibility of regdanvimab promoting viral uptake in FcγR I and II expressing cells was investigated. The results did not indicate such a scenario. An in-vivo mouse study was conducted to assess the possibility of antibody-dependent enhancement (ADE), but no strong conclusions could be drawn from the results. Tissue cross-reactivity studies were conducted in human and cynomolgus. Safety pharmacology studies were integrated into cynomolgus repeat-dose toxicity studies.

In view of pharmacokinetics (PK) the company has presented one dedicated PK study (i.p. uptake in Syrian Golden hamster) where CT-P59 presence was measured with ELISA. The systemic exposure in hamster was slight greater than dose-proportional and the termination half-life decreased at higher doses. Two cynomolgus studies also included toxicokinetics measurements (study reports in the toxicology section).

A more in-depth overview of the pharmacodynamics and toxicity studies is provided below:

2.3.1. Primary pharmacodynamics

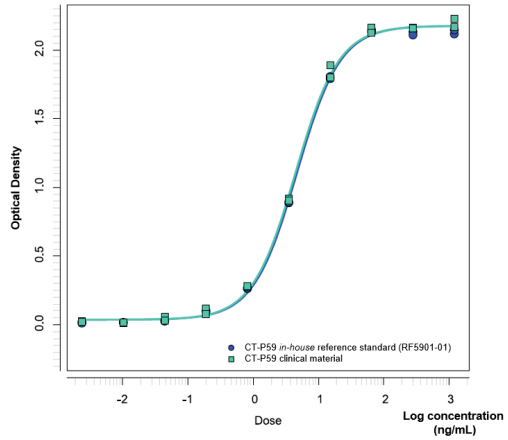
The primary pharmacodynamics data presented contained 8 study report whereof 2 were in-vitro study reports and 4 were in-vivo study reports (treatment effects in infected hACE2 expressing transgenic mice, infected Syrian Golden hamster, infected ferret, infected rhesus macaque) and two were tissue-cross reactivity reports (should have been in secondary pharmacodynamics section).

2.3.1.1. Biochemical and in-vitro studies

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

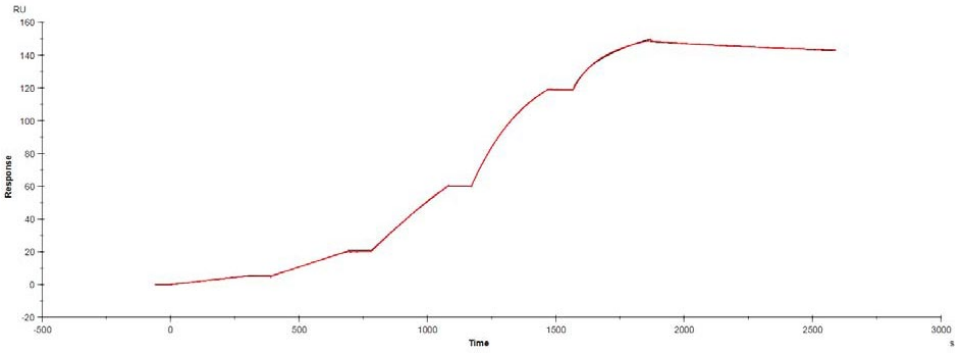
The dose-dependent binding of a CT-P59 clinical batch to RBD was found as shown in the half-maximal effective concentration (EC50) of CT-P59 to SARS-CoV-2 RBD protein was 4.4 ng/ml and relative binding affinity against in-house reference standard was 105%.

Figure 7. SARS-CoV-2 RBD Binding Affinity of CT-P59 by ELISA



Five concentrations of a CT-P59 process validation batch were serially injected and dissociated then the dissociation constant was evaluated by sensorgram fitting using the kinetic model (bivalent analyte) as shown in the Figure below. The binding affinity (KD) of CT-P59 for the RBD by surface plasmon resonance (SPR) was calculated as 6.5E-11 M.

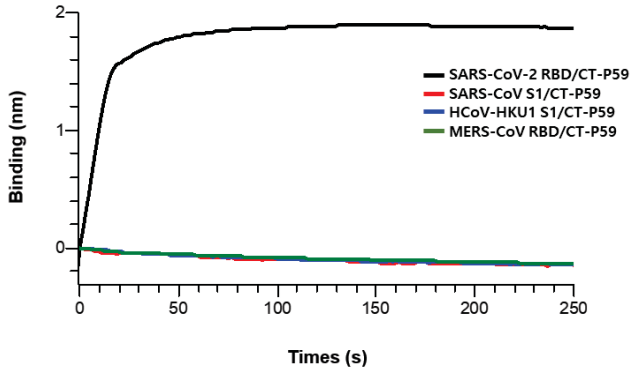
Figure 8. SARS-CoV-2 RBD Binding Affinity of CT-P59 by SPR (Sensorgram of 1st run)



Binding specificity of CT-P59 by biolayer interferometry (BLI)

Binding specificity of CT-P59 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. CTP59 could bind specifically to SARS-CoV-2 RBD but could not bind to other coronaviruses.

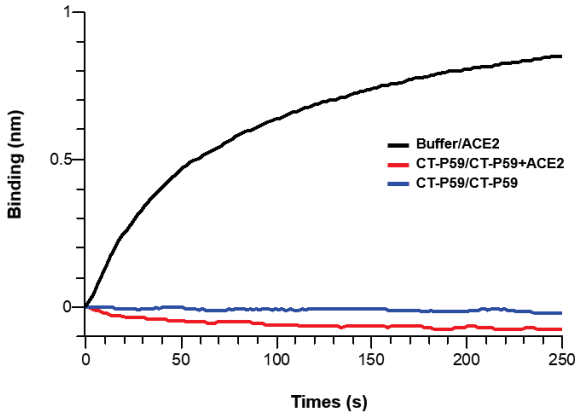
Figure 9. Binding Specificity of CT-P59 to various coronaviruses by biolayer interferometry



Inhibitory effect of CT-P59 on the interaction between SARS-CoV-2 RBD and ACE2 by biolayer interferometry (BLI)

Once SARS-CoV-2 RBD is saturated by CT-P59, there were no responses even in the presence of hACE2 (Figure 10). This suggests that CT-P59 completely inhibits binding of hACE2 to SARS-CoV-2 RBD.

Figure 10. Inhibition of Binding between SARS-CoV-2 RBD and ACE2 by CT-P59



Neutralizing effect of CT-P59 against wild type, mutant clinical isolates (S/V/L/G/GH/GR) and variants of SARS-CoV-2

The ability of CT-P59 to neutralize SARS-CoV-2 viruses even bearing D614G mutation in a plaque reduction neutralization test (PRNT) was observed in the neutralization activity curve of CT-P59 against wild type and mutant SARS-CoV-2 viruses.

The neutralizing ability of CT-P59 against newly emerging variants of SARS-CoV-2 viruses was also evaluated. IC50 values of the variants isolated as UK variant (B.1.1.7 or 20I/501Y.V1) and South Africa variant (B.1.351 or 20H/501Y.V2) were 3.77 ng/ml and not calculated, respectively. Due to lack of activity, efficacy is not anticipated against the South Africa variant.

Epitope mapping by X-ray crystallography

The CTP59/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 CT-P59 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 CT-P59, when a distance cut-off of 4.5 Å is applied.

CT-P59 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 CT-P59 to RBD directly occludes the binding surface of ACE2.

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 CT-P59 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.

Binding affinity to wild type and mutant RBD protein of SARS-CoV-2 by biolayer interferometry (BLI)

Binding affinity of CT-P59 was evaluated with a total of 68 mutant RBDs by BLI. There were no substantial differences between binding affinity of CT-P59 to wild type RBD and that of mutant RBDs except L452R and S494P.

Generation and characterization (genotyping, neutralization, and SPR) of potential escape mutants by CT-P59 by *in vitro* virus passaging

Generation of escape viruses

In vitro virus passaging was performed with SARS-CoV-2 viruses in the presence/absence of CT-P59 (Jianhua Sui et al., 2014[1]). Four plaques (the 4th passage) were observed at the 1 μg concentrations of CT-P59.

Genotyping

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.

[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

Neutralization activity of CT-P59 against escape mutant by PRNT

To determine the ability of CT-P59 to neutralize the escape mutants, the plaque reduction neutralization test (PRNT) was conducted using mutant viruses and control virus. The control virus was in parallel passaged without CT-P59. VeroE6 cells were infected with viruses in the presence of CT-P59 concentrations from 1 to 0.98 x 10^{-3} µg/ml. Neutralization was assessed by calculating IC50 and the results are described in Table 10. The results suggest that even at high concentration (1 µg/ml), CT-P59 was unable to neutralize the escape virus.

Table 10. IC50 Values of CT-P59 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)

***In vitro* Antibody-dependent cellular cytotoxicity (ADCC)**

More than 10 lots of peripheral blood mononuclear cell (PBMC) donors have been screened for the CT-P59 PBMC ADCC assay using CT-P59 in-house reference standard against S-glycoprotein expressing target cells (CHO-K1 cell line). None of them initiated PBMC ADCC activity with CT-glycoprotein expressing CHO cells even though the PBMC donor cells were capable of ADCC activity when used as effector cells in an ADCC assay using trastuzumab as positive control.

Complement-dependent cytotoxicity (CDC)

When measuring CDC activity by CT-P59 normalized against the negative control (CT-P59 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 CT-P59.

Other Fc-mediated functions

The test results of these additional Fc-mediated functions of CT-P59 are summarized in the Table below. CT-P59 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 11. Fc-mediated functions of CT-P59

	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

2.3.1.2. In-vivo studies

In-vivo primary pharmacological studies (treatment 24h after SARS-CoV-2 infection followed by observation for 5d-7d) all showed a reduction in viral titres in samples from nasopharyngeal and lungs from Syrian Golden hamster, Ferret and rhesus macaque. A prophylactic study with treatment 24h before infection in hACE2 transgenic mice did also reduce viral titre levels but provided poor protection against the clinical symptoms of the infection.

Genotyping of potential escape mutants by CT-P59 in *in vivo* Hamster study by Next Generation Sequencing (NGS)

No mutations in the receptor binding domain (RBD) of the spike protein, were identified in the *in vivo* efficacy study samples.

All mutations which were presented in the CT-P59 treated group were also presented in the vehicle control group and there were no mutations which was particularly presented in only CT-P59 treatment groups.

Genotyping of potential escape mutants by CT-P59 in *in vivo* Monkey study by Next Generation Sequencing (NGS)

One mutation, P463S, found in the receptor binding domain (RBD) of the spike protein, was identified but the percentage amount was very low (less than 2.97%) and the mutation is not part of the epitope which CT-P59 binds to.

2.3.2. Secondary pharmacodynamics

The secondary pharmacodynamics (sPD) section contained 2 study reports (one in-vitro and one in-vivo sPD study) but should have included the tissue cross-reactivity studies (n=2) as well.

2.3.2.1. 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 CT-P59, 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 CT-P59. 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 CT-P59 did not induced ADE effect in all concentrations tested in both cells.

The company argues that CT-P59 is unlikely to enhance SARS-CoV-2 virus infection and subsequent disease via a virus-antibody complex, and the study supports this argument.

2.3.2.2. In-vivo studies

The potential of CT-P59 to exacerbate viral infection or clinical signs through antibody-dependent enhancement (ADE) was also investigated in hACE2 transgenic mice(study #GR2-RD-20-314).

Table 12. Overview of study on antibody-dependent enhancement (ADE) of CT-P59 in hACE2 transgenic mice.

Study	*Design*	*Results*
GR2-RD-20-314 *Non-GLP* ***In vivo* assessment of ADE of CT-P59 against SARS-CoV-2 virus in human ACE2 transgenic mice**	# Animal model: Transgenic female mouse (B.6Cg-Tg(K18-ACE2)2Prlmn/J) # Disease model: Pre-SARS-CoV-2 infection CT-P59 treatment (1d before intranasal infection with 1 x 10^5 PFU/50µL). Observations until 6-days post infection (dpi). # Administration route: IP (single dose). # Doses (CT-P59,: 0.001mg/kg (n=8), 0.01mg/kg (n=8), 0.1mg/kg (n=8) or 1mg/kg (n=8). Dose volume: 10ml/kg.	*Mortality*: No unscheduled deaths reported. *Body weight*: Similar extent of body weight reduction (-20 to -25%) in controls and at doses <1mg/kg. *Viral replication (*in nasal washes and lungs at 3 and 6 dpi, measured by plaque assay in Vero cells): Only 1mg/kg had a statistically significant decrease in viral titers.

Dose	Lungs
0.0	5.7 log10 PFU/ml (3dpi) and 3.7 log10 PFU/ml (6dpi)
0.001	3dpi: 1.01x ↓ 6dpi: 3.7x ↓
0.010	3dpi: 1.3x ↑ 6dpi: 1.9x ↓
0.100	3dpi: 1.5x ↓ 6dpi: 1.73x ↓
1.000*	3dpi: 22.3x ↓ 6dpi: 1347.5x ↓

The company argues that the absence of an increase in viral titres at lower doses is support that there was no ADE phenomenon in the hACE2 mice. It is unclear how well this animal model and the used exposure settings represents a putative SARS-CoV-2 ADE phenomenon. The study cannot be considered conclusive.

2.3.2.3. Tissue-cross reactivity

The company submitted two tissue cross-reactivity (TCR) studies as primary pharmacology studies. These were assessed under secondary pharmacology. One TCR study was performed on a full panel of human and non-human primate (cynomolgus monkey) adult tissues (study #20251203). An additional study with human foetal and neonatal tissues (study #20265175) was also conducted. Binding was detected to plasma and cytoplasmic parts of meningeal arachnoid cap cells in the human cerebellum and spinal cord and also in human neonatal spinal cord. Similar binding was also found in adult cynomolgus.

2.3.3. Toxicology

In accordance with the ICH Safety Guideline S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH, 2011), a 2-week repeat-dose toxicity study and a 3-week repeat-dose toxicity study with a 10-week recovery period via IV infusion with CT-P59 in NHP (cynomolgus monkey) to support the safety of the investigational use of CT-P59 in humans.

The two repeat-dose toxicity studies were conducted in cynomolgus monkeys using intravenous administration of regdanvimab at dose levels of 0, 100, 200 or 400 mg/kg once weekly.

The 2-week repeat-dose toxicity study with IV infusion of regdanvimab once weekly was performed in male and female cynomolgus monkeys. Following repeated weekly (intravenous) administration of 100, 200, or 400 mg/kg for 2 weeks, 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, no overserved adverse effect level (NOAEL) was concluded to be 400 mg/kg.

The 3-week repeat-dose toxicity study was conducted in male and female cynomolgus monkeys with a 10-week recovery period. Intravenous administration of regdanvimab to cynomolgus monkeys by once weekly intravenous infusion for 3 total doses was clinically well tolerated at different doses. All animals survived for the study duration, and test article-related effects included changes in haematology, coagulation, and clinical chemistry parameters. With the exception of the moderately to markedly decreased neutrophils from a few 400 mg/kg dosed animals no other findings were considered adverse. During a 10-week recovery period, there were no regdanvimab-related changes in clinical pathology parameters, indicating complete recovery. The markedly decreased neutrophils were deemed adverse based on increased risk for infection; therefore, the NOAEL was considered to be 200 mg/kg. The company should consider discussing the clinical relevance of the observations on neutropenia in the cynomolgus monkey, calculate the exposure margin based on systemic exposure at the NOAEL and the LOAEL and discuss the need for additional monitoring in patients as part of the on-going rolling review.

Toxicokinetics (TK) was also assessed in the above study and the maximum serum concentrations (Cmax) of CT-P59 generally occurred at the first time point. TK assessment through 168 hours post-dose on Days 1 and 15 indicated that the terminal elimination phase was not well characterized for most profiles. Individual half-life (T1/2), when estimable, ranged from 54.0 to 60.7 hours (2.3 to 2.5 days). Clearance (CL) ranged from 0.624 to 0.953 ml/hr/kg and the volume of distribution (Vz) ranged from 54.6 to 83.4 ml/kg. Inclusion of the recovery animals from the 400 mg/kg dose group allowed better characterization of the terminal elimination phase. Consequently, individual CL was estimated between 0.748 and 1.42 ml/hr/kg and T1/2 was longer, ranging from 180 to 258 hours (7.5 to 10.8

days). Individual Vz increased, ranging from 232 to 369 ml/kg, exceeding the total blood volume (73 ml/kg) in monkeys and indicating distribution beyond the vasculature. Systemic exposure to CT-P59, as defined by the mean Cmax and AUC0-168.667 increased with increasing dose. Taking into consideration the variability observed, the increase in exposure was dose proportional on both days for the dose levels evaluated. No apparent gender differences in systemic exposure were observed. 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.

A tissue cross-reactivity study with a full panel of human and cynomolgus monkey tissues and a selected panel of human foetal and neonatal tissues showed specific positive staining in meningeal arachnoid cap cells in the brain and/or spinal cord in human, non-human primate, and human neonatal spinal cord tissues. However, these findings were not associated with any in life and histopathological findings during toxicity studies, which presents that these TCR findings are less likely to have an *in vivo* relevance. The company is also conducting a further immunohistochemistry study using brain and spinal cord tissue sections from the 3-week toxicity study and an off-target study to identify the off-target protein(s) and characterize the protein(s) and evaluate the *in vivo* relevance.

No Developmental and Reproductive Toxicity (DART)-, genotoxicity- or carcinogenicity studies have been conducted or planned This is in line with ICH S6 guidance for mAbs specifically targeting an exogenous protein.

2.3.4. Conclusions on non-clinical aspects

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

The antigenic affinity and specificity were assessed by several biochemical and in-vitro studies. The binding affinity for RBD was assessed with enzyme-linked immunosorbent assay (ELISA; EC50 4.4ng/ml corresponding to 3.0 x 10-11M).

The CT-P59/SARS-CoV-2 RBD complex crystal structure indicates that CT-P59 competes with ACE2 for the binding to SARS-CoV-2 RBD. CT-P59 thus directly blocks the binding surface of ACE2.

Double mutations (S494P+R685H) were detected in all *in vitro* escape viruses. The amino acid 494 is located in the RBD and CT-P59 was unable to neutralize the escape virus.

Neutralizing activity was shown against wild type and mutant clinical isolates of SARS-CoV-2 viruses (V/L/G/GH/GR) including the UK variant (B.1.1.7), with IC50 values in the range of 5-10 ng/ml.

However, neutralizing activity against the South Africa variant (B.1.351) was not shown, and activity thus presumed to be absent. According to the company they will continue to monitor and study newly emerging variants and escape mutants and duly report the results as they become available.

In vitro assessment of Fc-mediated function for ADCC and CDC suggest that CT-P59 is not able to mediate Fc-related activities and this is unlikely to be a MoA of CT-P59.

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.

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. 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.

Overall, the mechanism of action of regdanvimab has been established, as well as its neutralising ability against tested strains, including representatives of the Wuhan strain as well as the UK strain. There seem to be no activity against the South Africa strain.

In vivo proof of concept was generated in three different animal models, showing the ability of regdanvimab to reduce viral shedding.

Toxicology

No findings in the repeat dose toxicity studies were considered adverse, with the exception of the moderately to markedly decreased neutrophils from some of the 400 mg/kg dosed animals. The company should therefore discuss the clinical relevance of the observations on neutropenia in the cynomolgus monkey, calculate the exposure margin based on systemic exposure at the NOAEL and the LOAEL and discuss the need for additional monitoring in patients as part of the on-going rolling review.

Toxicokinetics (TK) of CT-P59 was also assessed in 2-week and 3-week repeat dose toxicity studies and did not raise any concerns.

In the tissue cross-reactivity studies, binding was detected to meningeal arachnoid cap cells in the human cerebellum and spinal cord and also in human neonatal spinal cord. Binding was also found in adult cynomolgus arachnoid cells. These locations were not associated with any histopathological findings in 2- and 3-week cynomolgus monkey repeat-dose toxicity studies.

2.4. Quality aspects

2.4.1. Introduction

The company has provided an IMP dossier that contains quality data on IMP manufacture, characterisation, pharmaceutical development, stability and control.

In general, the IMP dossier largely fulfils requirements of guidance EMA/CHMP/BWP/534898/2008 rev.1 Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials.

The company provided a list of references to EudraGMDP/certificates for the finished product manufacturers both located within and outside EEA. For the active substance manufacturing sites outside of EEA a declaration from the QP of the site performing batch release in the EEA has been provided.

This medicinal product contains regdanvimab as active substance.

Regdanvimab finished product is presented as concentrate for solution for infusion. Each vial contains 960 mg in 16 ml (corresponding to a concentration of 60 mg/ml). Regdanvimab is formulated with a

L-histidine buffer, polysorbate 80, L-arginine and water for injection. The formulation does not contain preservatives.

2.4.2. Active Substance

General Information

The active substance regdanvimab (CT-P59) is a recombinant human monoclonal IgG1 antibody targeting the Receptor Binding Domain (RBD) of the SARS-CoV-2 spike protein. It exhibits neutralisation activity. The blockage of the S protein interaction with angiotensin-converting enzyme 2 (ACE2) prevents subsequent viral entry into human cells and viral replication.

Regdanvimab contains a single N-linked glycosylation site on 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.

Although IgG1 antibodies typically triggers effector mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC), the available characterisation data indicates that regdanvimab is unable to mediate Fc-related activities.

The biological and physico-chemical properties of the antibody have been acceptably described.

Manufacture, process controls and characterisation

Manufacture

The active substance is produced in a CHO cell line and the final cell culture is harvested via centrifugation, followed by 2 stage 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.

The manufacturing process is considered standard for the production of monoclonal antibodies and the level of detail in the method description is found acceptable in the context of this procedure.

Information regarding the manufacturing and testing sites and their EU GMP status was provided.

Control of materials

Sufficiently detailed information has been provided for source, history and generation of the cell substrate. Available information and or characterisation data for the MCB and WCB was provided. The data presented is acceptable in the context of this procedure.

The list of raw materials used in the manufacture of regdanvimab was provided.

Control of critical steps and intermediates

The control of process parameters in the manufacturing processes are presented together with acceptance ranges and in-process tests with their corresponding limits are listed in the flow charts. The controls in place are found acceptable. The control strategy and criticality assignment are being assessed as part of the parallel rolling review for a future MAA.

Process validation

No formal validation of the drug substance manufacturing processes has been presented yet. This is acceptable in the context of this procedure. Formal process validation studies will be assessed at the time of MAA.

Manufacturing process development

Information to support various changes introduced during development was provided. Comparability studies were performed, and the company concludes that the comparability data demonstrate that the processes are comparable and that there are no clinically meaningful differences. The argumentation presented by the company is found reasonable and the information provided is considered adequate in the context of this procedure.

Characterisation

Analytical characterisation was performed using a panel of orthogonal state-of-the-art tests including studies of primary and higher order structure, post-translational modifications, charge variants, glycosylation and biological activity. Regarding biological characterisation, different methods including binding ELISA, SPR, FcγRIIIa and FcRn as well as *In vitro* Plaque Reduction Neutralisation Test, ADCC and CDC activity are used. It is noted that *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 part of the mechanism of action of regdanvimab. Characterisation data for product-related and process related impurities have been presented. Certain impurities are controlled at release. The characterisation is considered adequate in the context of this procedure.

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 non-compendial analytical procedures are described, and validation summaries are provided.
The information is acceptable in the context of this procedure.

Analytical procedures

The active substance is tested by a combination of compendial and non-compendial methods. For compendial test methods, the relevant pharmacopoeia reference has been provided and the status of method validation/verification. The non-compendial analytical procedures were validated in accordance with the principle of ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology. A summary of the results of validation studies demonstrating the suitability of the non-compendial analytical procedures used to test regdanvimab active substance are provided.

For HCP a platform assay is used for which acceptable coverage has been presented but is noted that a process specific HCP assay will be developed at a later stage. The proposed limit should be reconsidered at MAA.

Batch analyses

Representative batch analyses data was provided for the manufacturing process of regdanvimab. All pre-defined acceptance criteria were met.

Reference standard

The proposed in-house reference standard was adequately characterised.

Container closure

The container closure systems for regdanvimab active substance were described. Results from extractables/leachables studies will be expected at the time of MAA.

Stability

Stability studies have been initiated using regdanvimab active substance to evaluate its stability profile, and to assign shelf life. All stability studies have been designed in compliance with the principles outlined in ICH Guideline Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological / Biological Products. The active substance is stored frozen and the currently proposed shelf life is found acceptable in the context of this procedure. Additional stability data will be expected at the time of MAA.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Regdanvimab finished product is presented as a concentrate for solution for infusion in a 20-ml Type I 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 qualitative and quantitative composition for the finished product is provided and found adequate. Each vial contains a justified overfill to ensure complete withdrawal of the volume stated on the label.

The finished product contains no novel excipient or 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 compendial and commonly used for the formulation of biopharmaceuticals.

Pharmaceutical development

The formulation development has been acceptably described and justified. The manufacturing process history is clearly described and comparability data to support the changes introduced during manufacturing process development is provided.

Manufacture of the product and process controls

Manufacture

The manufacturing and testing sites and their EU GMP status were provided.

The finished product manufacturing processes at the two different commercial manufacturing sites are in general acceptably described. Standard aseptic processing techniques are used for the manufacturing of the finished product.

Process validation

Process validation data are not provided except for media fill validation. The final conclusion in relation the proposed control strategy and criticality assignment will be assessed in a future MAA. The media fill routines and acceptance criteria are acceptably described. Media fill results from studies to support the aseptic filling process at both sites are provided.

Product specification

The finished product specification includes test parameters for general characteristics, identity, purity, content, potency, endotoxins and sterility. This is found to be in line with the requirements in the Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials EMA/CHMP/BWP/534898/2008 rev. 1 corrigendum. The justification provided for the specifications is acceptable in the context of this procedure.

The company is reminded that at the time of the MAA, a risk evaluation concerning the presence of nitrosamine impurities in the finished product should be provided, applying the principles outlined in Questions and answers on "Information on nitrosamines for marketing authorisation holders" (EMA/409815/2020 or current version) and Nitrosamine Impurities - Final Outcome of Article 5(3) (EMA/369136/2020 or current version). In case there is an identified risk of the presence of nitrosamines, the company will have to immediately start confirmatory testing and evaluating possible sources of contamination, together with a proposal of an appropriate method and acceptable levels of control of nitrosamines in the specification.

Analytical procedures

The finished product is tested by a combination of compendial and non-compendial methods. Methods are validated or verified according to ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology.

Batch analyses

Representative batch analyses data was provided for the two manufacturing process sites. All pre-defined acceptance criteria were met.

Reference standard

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

Stability of the product

A shelf life of 12 months when stored at 2°C to 8°C is proposed. The data presented to support this shelf life is limited and relies on extrapolation of real time data available at the time of this procedure. This is considered acceptable in the context of this procedure. At the time of MAA, shelf life determination should be based on ICH Q5C principles and additional stability data will be expected.

There is no information on photo stability studies in the IMPD although it is noted that the "condition of use" document states that the medicinal product should be kept in its outer carton in order to protect from light. This approach is supported and information on photo stability studies should be provided at the time of MAA.

Furthermore, the proposed in-use conditions for diluted product (5 ± 3 ºC for 72 hours or at 30±2°C / 75±5% RH for 4 hours prior to the start of infusion) is acceptably justified from a physical-chemical point of view.

Adventitious agents

Sufficiently detailed information has been provided from the TSE risk assessment. Results from viral testing of the MCBs have been provided. The test panel is in line with requirements in ICH Q5A. No adventitious virus was detected, only retrovirus-like particles as expected for CHO cells.

Viral testing results from unprocessed bulk are provided. No adventitious virus was detected. Testing of unprocessed bulk will be ongoing using an *in vitro* test.

A summary of data from virus clearance studies is provided. It is stated that worst case settings are used for parameters known or expected to affect virus reduction. Relevant model viruses have been used. The results indicate 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 only been performed with new resins. This is acceptable at this stage. The information provided is acceptable.

2.4.4. Discussion

In general, the extent of information on quality provided by the company corresponds to the level of a dossier for an investigational medicinal product.

The design of the manufacturing processes for the active substances and finished products is standard. However, critical steps have not been defined, process validation data are not yet available and only preliminary criteria for process controls and active substance and finished product specifications are set.

Additional data for the characterisation of the active substances will also be expected at the time of MAA.

Stability data to support the currently proposed active substance and finished product shelf lives is limited and relies on extrapolation, which is acceptable in the context of this procedure.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Regdanvimab is considered acceptable in the context of this procedure, when used in accordance with the conditions of use.

3. Conclusions

Quality aspects

Considering the data provided by the company on the manufacture, characterisation, pharmaceutical development, control and stability of the active substances and finished products, the overall quality of regdanvimab is acceptable in the context of this procedure, when used in accordance with the conditions of use.

Non-clinical aspects

The mechanism of action of regdanvimab has been established, as well as its neutralising ability against tested Sars-Cov-2 strains, including representatives of the Wuhan and UK (B.1.1.7) strains. There seems to be no activity against the South Africa strain.

In vivo proof of concept of antiviral activity was generated in three different animal models, showing the ability of regdanvimab to reduce viral shedding.

Clinical aspects

Results from an exploratory study (CT-P59 3.2 Part 1) in outpatients presenting with non-severe COVID-19 have been presented.

Data on viral shedding over time are indicative that regdanvimab does display antiviral activity *in vivo*, as would be anticipated. It is known that serostatus and viral load at baseline are strong and correlated

effect modifiers. Data on serostatus were determined with rapid diagnostic tests, presumably lacking the sensitivity of quantitative methods.

Numerical trends towards lower rates of hospitalisation in the overall population could be observed, which is considered an endpoint of clinical relevance, with a more pronounced effect in older patients and those with signs of pneumonia, compared to placebo. Also, a shorter duration of symptoms was seen in regdanvimab-treated subjects compared to placebo.

Regdanvimab is a mAb against a non-human target, without any effector function. The emerging safety profile is benign, and the likelihood of harm seems low.

CT-P59 3.2 part 2 is an RCT that is a prospective hypothesis test of CT-P59's effect on the risk of hospitalisation, in outpatients presenting with mild/moderate COVID-19. Pending the final results, this study seems capable in its design, of delivering substantial evidence of efficacy.

Altogether, there is presently no substantial evidence of efficacy for regdanvimab. However, based on what is generally known about the effects of mAbs against the Sars-Cov-2 spike protein on the risk of clinical progression, in patients that have not yet seroconverted and who have not yet developed severe disease, there is a reasonable possibility that regdanvimab may provide clinical benefit. However, treatment should not be initiated in patients with severe COVID-19, as several mAb programs have failed to show benefit in that setting. Based on the nature of the intervention, and available clinical data, the risk of harm is considered low.

It is also noted that in general the evidence base for use of mAbs in combination is larger to that for monotherapy. CHMP noted that for monotherapy a greater risk for the selection of escape mutants may exist, compared to the use of mAbs with non-overlapping target epitopes in combination. However, there is no data available for combination therapy where regdanvimab is one of the components.

The study population was not fully representative of the proposed target population - e.g., 'immunosuppressed' patients were excluded. Further, due to the way the company presents data, it is not known exactly how many patients had co-morbid conditions that predispose to severe COVID-19. However, the conclusion of a reasonable likelihood of benefit may be extrapolated to such patients.

The company proposed that regdanvimab be indicated for:

"the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalisation.

High risk is defined as patients who meet at least one of the following criteria:

- *Are ≥60 years of age*
- *Are ≥50 years of age AND have pneumonia but no signs of severe pneumonia and do not require supplemental oxygen therapy."*

The relevance of the distinction between mild and moderate disease, as well as the criteria for high risk, are presently not accepted. Furthermore, the reference to hospitalisation in the indication is not supported, as the focus is on disease status rather than its management. Of note, the same approach has also been undertaken in the assessments of other mAbs against spike protein assessed by CHMP in the framework of Article 5(3) procedures. Therefore, the data are considered to support the below indication:

For the treatment of confirmed COVID-19 in adult patients that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.
Risk factors may include but are not limited to:

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

In view of the safety profile of CT-P59 the CHMP also considered that it appears favourable, in line with what is expected from a monoclonal antibody targeting a viral protein, and with no intrinsic effector function. The Committee further considered that this medicine, once it is authorised for use, should be subject to additional monitoring. This enables to stimulate the ADR reporting in order for new safety information to be identified quickly. Healthcare professionals will be asked to report any suspected adverse reactions.

Overall conclusion

Considering the data provided by the company on quality aspects, preclinical aspects and the provided clinical dataset, regdanvimab monotherapy might provide clinical benefit for the treatment of confirmed COVID-19 in adult patients that do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19, when used in accordance with the conditions of use.