Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection

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Abstract

CT-P59, a monoclonal antibody with potent neutralizing activity against severe acute respiratory syndrome coronavirus 2, may ameliorate symptoms and prevent hospitalization in outpatients with mild-to-moderate disease. We report findings from part one of a two-part randomized, placebo-controlled, double-blind study (NCT04602000; EudraCT: 2020-003369-20). Outpatients with mild-to-moderate COVID-19 received a single dose of CT-P59 40 mg/kg (*n*=101), CT-P59 80 mg/kg (*n*=103), or placebo (*n*=103). Median (95% confidence interval [CI]) time to conversion to negative RT-qPCR result (coprimary endpoint) was 12.8 days (9.00–12.84) with CT-P59 40 mg/kg, 11.9 days (8.94–12.91) with CT-P59 80 mg/kg, and 12.9 days (12.75–13.99) with placebo. Median (95% CI) time to clinical recovery (coprimary endpoint) was 5.4 days (3.97–6.78) with CT-P59 40 mg/kg, 6.2 days (5.53–7.85) with CT-P59 80 mg/kg, and 8.8 days (6.72–11.73) with placebo. The proportion (95% CI) of patients requiring hospitalization or oxygen therapy was lower with CT-P59 40 mg/kg (4.0% [1.6–9.7%]) and CT-P59 80 mg/kg (4.9% [2.1–10.9%]) versus placebo (8.7% [4.7–15.8%). CT-P59 was well tolerated and no serious treatment-emergent adverse events or deaths occurred. In summary, CT-P59 accelerated viral and clinical recovery from COVID-19 and was well tolerated in patients with mild-to-moderate infection.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic represents an ongoing global health crisis of unprecedented scale[1-3]. While most patients experience asymptomatic or mild-to-moderate disease, some progress to experience more severe symptoms and may require hospitalization[4,5].

Effective treatments are urgently needed to reduce SARS-CoV-2 infection–related morbidity and mortality, and to reduce the associated burden on public health services[6]. Therapies that can be applied early in the course of clinical disease can speed clinical recovery, shorten the duration of viral shedding, and reduce the need for hospitalization, with a resultant reduction of the burden on the overall healthcare system. Anti–SARS-CoV-2 spike (S) antibodies, which target cellular entry of SARS-CoV-2 through interaction with the angiotensin-converting enzyme 2 (ACE2) receptor[7-11], have been demonstrated to reduce hospitalizations, viral titers, and clinical symptoms in patients with SARS-CoV-2 infection[12-14]; the therapy has also been shown to reduce the risk of infection with SARS-CoV-2 in nursing home residents[15,16].

CT-P59 is a potent neutralizing antibody against various SARS-CoV-2 isolates, including the D614G S protein variant[17]. Complex crystal structure studies of the CT-P59 Fab/SARS-CoV-2 receptor binding domain (RBD) suggest that CT-P59 blocks the interaction regions of the SARS-CoV-2 S protein RBD for ACE2[17]. Administration of CT-P59 was shown to reduce viral load and alleviate clinical symptoms in animal models of SARS-CoV-2 infection[17]. CT-P59 has also exhibited a promising safety profile in healthy volunteers and patients with mild SARS-CoV-2 infection, and potential antiviral and clinical efficacy has been observed in patients with mild SARS-CoV-2 symptoms[18]. Based on these findings, along with the

results reported in this manuscript, CT-P59 was granted conditional marketing authorization by the South Korean Ministry of Food and Drug Safety (MFDS) and an application has been submitted to the European Medicines Agency (EMA) for marketing authorization.

We report 28-day results from part 1 of a two-part phase 2/3 study of CT-P59 in outpatients with mild-to-moderate SARS-CoV-2 infection.

Results

Patient disposition and baseline characteristics. Patient enrolment began on 07 October 2020 and the last patient's Day 28 visit was on 18 December 2020. Screening was conducted at 23 centers across South Korea, Romania, Spain and USA. A total of 371 patients were screened and 327 were randomized and included in the intent-to-treat (ITT) population (CT-P59 40 mg/kg: *n*=105; CT-P59 80 mg/kg: *n*=111; placebo: *n*=111; Fig. 1). Eight patients (2.4%) discontinued the study during the treatment period (CT-P59 40 mg/kg: *n*=3; CT-P59 80 mg/kg: *n*=3; placebo: *n*=2). There was one major protocol deviation: one patient randomized to the placebo group had instead partially received CT-P59; this patient was considered as having received CT-P59 40 mg/kg and was included in the CT-P59 40 mg/kg treatment group for the efficacy and safety analyses, but was excluded from the PK analyses.

In the ITT population, participants were white (87.5%) or Asian (12.5%) and 49.2% were female; median age was 51.0 years (interquartile range: 41–60) and mean body mass index was 27.0 kg/m^2 (standard deviation: 4.4). Moderate disease was reported in 189 patients (57.8%). Baseline demographic and disease characteristics were generally well balanced between groups (Table 1). Concomitant medications are listed in Supplementary Table 1.

Twenty patients in the ITT population did not have confirmed SARS-CoV-2 infection by RT-qPCR at day 1 or both day 1 and day 2, and were excluded from the ITTI population (*N*=307 patients [CT-P59 40 mg/kg: *n*=101; CT-P59 80 mg/kg: *n*=103; placebo: *n*=103], see Supplementary Table 2).

Efficacy (ITTI population). The median time (95% CI) to conversion to negative RT-qPCR (threshold <2.33 $\log_{10}$ copies/ml) up to day 28 was numerically shorter in the CT-P59 40 mg/kg and 80 mg/kg groups than in the placebo group (median: 12.8 and 11.9 days vs 12.9 days, respectively) and in the combined CT-P59 versus placebo groups (median: 12.7 vs 12.9 days) (Table 2; Fig. 2a). The corresponding improvement rate ratios (with 95% CIs) were 1.346 (1.001–1.810; *P*=0.048), 1.215 (0.90–1.63; *P*=0.198), and 1.275 (0.99–1.65; *P*=0.063) for the CT-P59 40 mg/kg, 80 mg/kg, and combined groups, relative to placebo (Table 2). When a threshold of <3.0 $\log_{10}$ copies/ml was applied in a post-hoc analysis CT-P59 further reduced median time to conversion to negative RT-qPCR (6.0 days [combined CT-P59] vs 8.9 days [placebo]; Table 2 and Supplementary Fig. 1).

The proportion of patients achieving conversion to negative RT-qPCR was higher in the CT-P59 groups than in the placebo group up to days 14 and 28 (Table 2). Greater reductions from baseline in viral load were observed in the CT-P59 groups than in the placebo group. A 3-$\log_{10}$ copies/ml reduction in viral load

was achieved with CT-P59 between baseline and day 7; a similar reduction was not reached in the placebo group until day 10 (Supplementary Fig. 2).

The median (95% CI) time to clinical recovery up to day 14 was shorter in the CT-P59 combined group versus the placebo group (5.7 [5.15–7.00] vs 8.8 [6.72–11.73] days, respectively; Table 2 and Fig. 2b). Clinical recovery ratios (with 95% Cis) were 1.562 (1.11–2.20; *P*=0.010), 1.429 (1.02–2.01; *P*=0.039), and 1.489 (1.11–2.01; *P*=0.008) in the CT-P59 40 mg/kg, 80 mg/kg, and combined groups, respectively (Table 2). Clinical recovery ratios also favored CT-P59 over placebo in prespecified subgroups by disease status (Table 2). Clinical recovery rate ratios (with 95% Cis) for the CT-P59 combined group versus placebo group were 1.615 (1.05–2.49) in patients with mild SARS-CoV-2 infection (median 4.8 vs 6.9 days), 1.511 (0.99–2.30) in patients with moderate infection (median 6.5 vs 10.8 days), and 1.545 (0.90–2.65) in patients aged ≥50 years with moderate infection (median 6.8 vs 13.0 days).

The proportion of patients with clinical symptoms requiring hospitalization or oxygen therapy due to SARS-CoV-2 infection was significantly lower in the CT-P59 groups than in the placebo group (CT-P59 40 mg/kg: 4 [4.0%]; CT-P59 80 mg/kg: 5 [4.9%]; placebo: 9 [8.7%]; Fig. 2c and Table 2). Notably, only patients with moderate SARS-CoV-2 infection contributed events to this composite endpoint; the proportions of patients meeting this endpoint in the CT-P59 combined group was >50% lower than in the placebo group among patients with moderate infection (7.2% vs 15.8%, respectively) and in patients aged ≥50 years with moderate infection (8.8% vs 23.7%, respectively). CT-P59 also effectively reduced the proportion of patients reporting the requirement for supplemental oxygen, hospital admission, and rescue therapy, individually, and no all-cause mortality was reported up to day 28 (Table 2).

Safety. Overall, 182 TEAEs were reported in 92 patients (28.3%). A similar proportion of patients experienced ≥1 TEAE across treatment groups (Table 3) and the majority of TEAEs were CTCAE grade 1 or 2 in intensity. The most frequently reported TEAE considered related to study drug was hypertriglyceridemia in patients receiving CT-P59 40 mg/kg (3 patients [2.9%]) and infusion-related reaction or hypertriglyceridemia in patients receiving placebo (2 [1.8%] patients each), noting that except for those in the PK substudy, participants were not required to fast before administration of study drug. No TEAE considered to be related to study drug was reported in >1 patient in the CT-P59 80 mg/kg group. There were no TESAEs or TEAEs leading to permanent study discontinuation, and infusion-related reactions were reported in a low number of patients (CT-P59 40 mg/kg: 1 [1.0%]; CT-P59 80 mg/kg: 0; placebo: 2 [1.8%]).

Generally, there were no notable differences between groups in terms of changes from baseline in laboratory parameters (hematology and clinical chemistry), vital signs, or ECG results. The proportion of patients positive for ADAs was low in the CT-P59 groups (day 28 values were: CT-P59 40 mg/kg: 0; CT-P59 80 mg/kg: 3 [2.7%]; placebo: 5 [4.5%]). No antibody-dependent enhancement events were reported up to day 28.

Pharmacokinetics. The mean CT-P59 serum concentration was higher in the CT-P59 80 mg/kg group than in the 40 mg/kg group at all time points following intravenous infusion (Supplementary Fig. 3).

Serology. The proportions of patients with immunoglobulin (Ig) M or IgG positivity increased over time and was similar across groups at all time points (Supplementary Table 3).

Discussion

These data demonstrate that CT-P59 results in acceleration of clinical and viral improvement in outpatients with mild-to-moderate COVID-19. Additionally, CT-P59 reduced the need for hospitalization or oxygen therapy while being generally well tolerated.

CT-P59 was associated with a shorter time to conversion to a negative RT-qPCR result. While this analysis did not measure infectious virus, viral loads of <4 $\log_{10}$ copies/ml are not expected to be detected by cell culture method[19,20]. As such, the reductions seen in patients treated with CT-P59 could also reduce the risk of transmission. Further studies would need to be performed to confirm this finding but would add greater support for the early use of monoclonal antibodies (mAbs) among ambulatory patients with SARS-CoV-2 infection. These data are also in line with other studies of mAbs that shorten the duration of viral shedding with SARS-CoV-2[12-14].

CT-P59 was well tolerated, no clinically significant safety issues were identified, and there were no deaths up to day 28. Only one patient receiving CT-P59 (40 mg/kg) experienced an infusion-related reaction (Grade 2 pyrexia and Grade 1 dyspnea were experienced after the study drug was completely administered, but recovered on the same day after receiving paracetamol and oxygen therapy). CT-P59 did not appear to interfere with the formation of antibodies (no antibody-dependent enhancement events were reported), no ADAs were measured in the CT-P59 40 mg/kg group, and the proportion of patients with ADAs in the CT-P59 80 mg/kg group was <3.0%. Interestingly, ADAs were identified in 4.5% of patients in the placebo group; this is likely due to the presence of pre-existing antibodies, which are either part of the natural population of antibodies or part of the adaptive immune response to environmental antigens[21,22].

Despite having dose-dependent PK, no dose-response relationship was observed (data not shown). Based on these data, the second part of this study will only compare the 40 mg/kg dose with placebo in a larger population of patients with mild-to-moderate SARS-CoV-2 infection. Part 2 aims to confirm clinically meaningful therapeutic efficacy for CT-P59, as determined by the proportion of patients with clinical symptoms requiring hospitalization or oxygen therapy, or experiencing mortality, due to SARS-CoV-2 infection up to day 28.

To our knowledge, this study represents the fourth study to assess mAbs for the treatment of ambulatory adults. The published studies of bamlanivimab with or without etesevimab[13,14], and of casirivimab and imdevimab[12], much like the present study, have demonstrated improvement in clinical and virologic recovery, as well as reduction in the risk of hospitalization or medically attended visits. These clinically significant findings are confirmed in this study and suggest that early use of mAbs in patients with

COVID-19 may reduce the burden on the healthcare system, onward transmission, and symptoms more quickly.

The current study enrolled few black or Hispanic patients, populations that are disproportionately affected by SARS-CoV-2 infection[23,24]. Likewise, there was a relatively small proportion (20–30%) of elderly patients enrolled, another group that is at high risk of complications and death from COVID-19[25]. The impact of CT-P59 on infectious virus has not been studied but it would be important to assess this in order to inform treatment decisions to reduce the risk of transmission.

Based on these findings, we conclude that CT-P59 is well tolerated and has the potential to alleviate the substantial burden placed on healthcare systems by SARS-CoV-2 during the ongoing pandemic. On February 5, 2021, the South Korean MFDS granted conditional marketing authorization for the use of CT-P59 (regdanvimab) in patients with mild SARS-CoV-2 infection who are aged ≥60 years or who have at least one of the following underlying medical conditions (cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus), as well as in patients with moderate SARS-CoV-2 infection. The second part of the study is ongoing and will assess the impact of CT-P59 on clinical recovery and the complications of COVID-19.

Methods

Study design and oversight. This phase 2/3, randomized, parallel-group, placebo-controlled, double-blind study (NCT04602000; EudraCT: 2020-003369-20) enrolled outpatients with mild-to-moderate SARS-CoV-2 infection. The disease was classified as mild or moderate at baseline based on guidance from the World Health Organization[26]: a patient was considered to have moderate disease based on the presence of radiography-confirmed pneumonia, and to have mild disease based on the absence of radiography-confirmed pneumonia at baseline. Part 1 of the study (reported to 28 days in the present manuscript) comprised three periods: screening (days –7 to day 1), treatment (day 1 to day 90 end-of-treatment [EOT] visit), and follow-up (EOT visit to day 180). Patients received a single infusion of study drug on day 1. Part 2 of the study (ongoing) aims to confirm the effect of CT-P59 on clinical symptoms requiring hospitalization, oxygen therapy, or mortality due to SARS-CoV-2 infection, and will be reported separately.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the International Council for Harmonisation Good Clinical Practice and applicable regulatory requirements. The protocol and all applicable amendments were reviewed and approved by local or national independent ethics committees prior to study initiation and the study was monitored by an independent data safety monitoring board. All participants provided written informed consent.

Participants. Eligible participants were aged ≥18 years, diagnosed with SARS-CoV-2 infection at the study centers at screening using the sponsor-supplied rapid SARS-CoV-2 diagnostic test (DiaTrust™, Celltrion, Inc., Incheon, Republic of Korea) or locally conducted reverse transcription polymerase chain reaction (RT-PCR), had an oxygen saturation of >94% on room air, and did not require supplemental

oxygen. Participants were required to have symptom onset (feverishness, cough, shortness of breath, sore throat, body/muscle pain, fatigue, headache, chills, nasal congestion, loss of taste or smell, or diarrhea) within 7 days before study drug administration. Patients with a current serious health condition or with ongoing or history of active or severe infections were excluded. Comprehensive eligibility criteria are provided in the protocol (see Supplementary Information).

Randomization and masking. Randomization was performed using an interactive web response system and a randomization schedule prepared by unblinded biostatisticians. Randomization was stratified by age (≥60 vs <60 years), region (USA vs Asia vs EU vs other), baseline comorbidities (yes vs no for having at least one of cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, or pneumonia), and participation in the pharmacokinetic (PK) substudy (yes vs no). Participants, personnel, and outcome assessors were blinded to treatment allocation for the duration of the study. CT-P59 and placebo were supplied in identical vials identified by a study drug number. Designated unblinded personnel prepared the study drug for infusion.

Procedures. Participants were assigned randomly (1:1:1 ratio) to receive a single dose of CT-P59 40 mg/kg, CT-P59 80 mg/kg, or placebo. CT-P59 and placebo were reconstituted in 250 mL of 0.9% sodium chloride and administered via intravenous infusion over 90 ± 15 minutes. All patients received optimal standard-of-care treatment, including rehydration therapy, antipyretics, or antitussives at the investigator's discretion, but excluding antiviral drugs and/or possible SARS-CoV-2 active drugs (only to be administered as rescue therapies).

Nasopharyngeal swabs for assessment of viral shedding (based on quantitative RT-PCR [RT-qPCR]) were taken predose on day 1, and at 24, 48, 72, 96, 120, 144, 216, 312 (day 10), 384 (day 17), 480 (day 21), and 648 (day 28) hours after study drug administration.

Participants were required to complete a patient diary on days 1–28, which included a SARS-CoV-2 symptom checklist. The checklist, which was to be completed by all patients at screening and twice daily from days 1–28, included seven symptoms of SARS-CoV-2 infection (fever, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, and headache).

Disease status monitoring was performed throughout the study (e.g., requirement for supplemental oxygen, intensive care unit [ICU] transfer, mechanical ventilation use, hospitalization, and rescue therapy use).

Safety was assessed throughout the study based on the incidence, type, severity, and causality of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs of special interest. TEAEs were coded according to the Medical Dictionary for Regulatory Activities, Version 23.1, and graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Hypersensitivity monitoring was performed before and after administration of study drug on day 1. Vital signs measurements, physical examination findings (before study drug

administration and EOT only), electrocardiogram (ECG) findings, and clinical laboratory analyses were assessed periodically throughout the study.

Details of the study drug formulation; SARS-CoV-2 symptom checklist; and PK, serology (including anti-drug antibodies [ADAs]), and virology assessments are described in the Supplementary Information.

Study endpoints. The primary study endpoints were time to conversion to negative nasopharyngeal swab specimen based on RT-qPCR (negative titer threshold: 2.33 $\log_{10}$ copies/ml) up to day 28 and time to clinical recovery up to day 14.

Patients who had negative RT-qPCR results at two or more consecutive time points were considered as satisfying the criteria for conversion to negative nasopharyngeal swab specimen based on RT-qPCR result (the first of the two consecutive time points was taken as the time to conversion to negative RT-qPCR result). Clinical recovery was defined as all symptom scores of “absent” or “mild” for ≥24 hours based on checklist results; symptoms scored as moderate or severe at baseline were required to be scored as mild or absent at recovery, whereas symptoms rated as mild or absent at baseline were required to be rated as absent at recovery.

Secondary efficacy endpoints included the following: the proportion of patients with clinical symptoms requiring hospitalization (≥24 hours of acute care), oxygen therapy (≥24 hours of supplemental oxygen care, with oxygen saturation of ≤94% on room air prior to administration), or death due to due to SARS-CoV-2 up to day 28; the proportion of patients with conversion to negative RT-qPCR result; and the proportions of patients with hospital admission requiring supplemental oxygen, with mechanical ventilation use, requiring rescue therapy, with ICU admission (individual endpoints; each due to SARS-CoV-2 infection), or with all-cause mortality.

Primary endpoint definitions and a comprehensive list of efficacy, PK, and virology endpoints are described in the Supplementary Information.

Statistical analysis. It was estimated that a sample size of 100 individuals per group would provide at least 80% power at a two-sided significance level of 0.05 to detect an increase in the improvement rate ratio between CT-P59 groups and placebo for the primary endpoints.

Efficacy was assessed in the intent-to-treat infected (ITTI) population, which comprised all randomly assigned patients with confirmed SARS-CoV-2 infection assessed by pre-infusion RT-qPCR on day 1 and receiving a partial or complete dose of study drug. If the pre-infusion result on day 1 was confirmed negative or missing and the day 2 result was confirmed positive, the patient was also considered as having confirmed SARS-CoV-2 infection. The safety population included all randomized participants who received a partial or full dose of the study drug.

Primary efficacy analyses were performed using stratified log-rank test for time-to-event endpoints. Improvement/clinical recovery rate ratios (with 95% confidence intervals [CIs]) were estimated using a

stratified Cox proportional hazards model. Adjustments for multiple testing were not performed. Secondary efficacy endpoints were summarized using descriptive statistics, frequency tables, or Kaplan-Meier (time-to-event) methods.

Subgroup analyses of the primary endpoints and one of the secondary efficacy endpoints were conducted according to SARS-CoV-2 severity (mild vs moderate; prespecified) and age (≥50 years; exploratory). Post-hoc analyses of the primary efficacy outcome – time to conversion to negative RT-qPCR – were conducted based on negative titer thresholds of 3.0 and 4.0 $\log_{10}$ copies/ml.

All statistical analyses were conducted using Statistical Analysis System (SAS) software, Version 9.4 (SAS Institute Inc., Cary, NC, USA). Sample size calculation assumptions, definitions of additional analysis populations, and statistical methodologies (including missing data handling) are included in the statistical analysis plan (see Supplementary Information).

Data availability

The study protocol and statistical analysis plan are available online as supplementary information. Individual participant data cannot be made available.

Declarations

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Author contributions

S.J.L., S.H.K., I.C., J.H.S., S.G.L., M.R.K., D.R.C., H.N.K. designed the study and contributed to in data analysis / interpretation. J.Y.K**.** and Y.R.J. collected data and contributed to data analysis / interpretation. An.S.-C., O.S., L.-L.P., Y.-S.K., S.H.C, Ad.S-C. and J.S.E. collected data. All authors contributed to the preparation of the report, including critical review and revision of manuscript drafts, and approval of the final version.

Competing interests

M.G.I. received research support (paid to Northwestern University) from AiCuris, Janssen, and Shire; is a paid consultant for Adagio, AlloVir, Celltrion, Cidara, Genentech, Roche, Janssen, Shionogi, and Viracor Eurofins; and is also a paid member of Data and Safety Monitoring Boards for Janssen, Merck, SAB Biotherapeutics, Sequiris, Takeda, and Vitaeris.

An.S.-C., O.S., and Ad.S.-C. have been investigators in COVID-19 clinical trials by Algernon Pharmaceuticals, Atea Pharmaceuticals, Diffusion Pharmaceuticals, and Regeneron Pharmaceuticals, outside the scope of the submitted work, and by Celltrion, Inc., within the scope of the submitted work.

L.-L.P., Y.-S.K., and S.H.C. declare no conflicts.

J.S.E. has been an investigator in COVID-19 clinical trials by Enzychem Lifesciences, Bukwang Pharm.Co., Ltd, and SK chemicals outside the scope of the submitted work, and by Celltrion, Inc., within the scope of the submitted work.

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S.J.L. and S.H.K. are employees of, and hold shares in, Celltrion, Inc. I.C., J.H.S., S.G.L., M.R.K., D.R.C., and H.N.K. are employees of Celltrion, Inc.

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Tables

Table 1. Baseline demographics and characteristics (ITT population)

	CT-P59 40 mg/kg *n*=105	CT-P59 80 mg/kg *n*=111	CT-P59 combined *n*=216	Placebo *n*=111
Age, years				
Median (IQR)	51.0 (42, 60)	51.0 (40, 60)	51.0 (40, 60)	52.0 (41, 61)
≥60, *n* (%)	27 (25.7)	28 (25.2)	161 (74.5)	30 (27.0)
<60, *n* (%)	78 (74.3)	83 (74.8)	55 (25.5)	81 (73.0)
Male, *n* (%)	59 (56.2)	59 (53.2)	98 (45.4)	48 (43.2)
Race, *n* (%)				
White	94 (89.5)	96 (86.5)	190 (88.0)	96 (86.5)
Asian	11 (10.5)	15 (13.5)	26 (12.0)	15 (13.5)
Ethnicity, *n* (%)				
Hispanic or Latino	6 (5.7)	11 (9.9)	17 (7.9)	10 (9.0)
Non-Hispanic or non-Latino	99 (94.3)	100 (90.1)	199 (92.1)	101 (91.0)
Region, *n* (%)				
USA	1 (1.0)	4 (3.6)	5 (2.3)	3 (2.7)
Asia	11 (10.5)	15 (13.5)	26 (12.0)	14 (12.6)
Europe	93 (88.6)	92 (82.9)	185 (85.6)	94 (84.7)
BMI, mean (SD), kg/m^2	27.1 (4.8)	27.1 (4.1)	27.1 (4.5)	26.8 (4.2)
Baseline comorbidities, *n* (%)				
Yes	78 (74.3)	80 (72.1)	158 (73.1)	82 (73.9)
Confirmed SARS-CoV-2 infection[a], *n* (%)	101 (96.2)	103 (92.8)	204 (94.4)	103 (92.8)
Time since symptom onset, median (IQR), days	3.0 (2, 4)	3.0 (2, 4)	3.0 (2, 4)	3.0 (2, 4)
Moderate disease[b], *n* (%)	64 (61.0),	65 (58.6)	129 (59.7)	60 (54.1)
Received ≥1 prior medication, *n* (%)	19 (18.1)	23 (20.7)	42 (19.4)	26 (23.4)

[a]All patients were enrolled based on a local rapid SARS-CoV-2 diagnostic test or RT-PCR–positive result; following enrollment, SARS-CoV-2 infection was confirmed centrally by RT-qPCR.
[b]Based on presence of x-ray or computed tomography–confirmed pneumonia at screening.
BMI, body mass index; IQR, interquartile range; ITT, intent to treat; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Table 2. Efficacy endpoints (ITTI population)

Endpoint	CT-P59 40 mg/kg *n*=101	CT-P59 80 mg/kg *n*=103	CT-P59 combined *n*=204	Placebo *n*=103
Primary endpoints				
Conversion to negative RT-qPCR to day 28				
Negative titer threshold of 2.33 log_{10} copies/ml				
Median (95% CI) time to negative RT-qPCR, days	12.75 (9.00–12.84)	11.89 (8.94–12.91)	12.65 (9.03–12.83)	12.94 (12.75–13.99)
Improvement rate ratio (95% CI)	1.346 (1.001–1.810)	1.215 (0.903–1.634)	1.275 (0.986–1.649)	–
Log-rank test *P*-value[a]	0.048	0.198	0.063	–
Negative titer threshold 3 log_{10} copies/ml[b], *n*	99	99	198	101
Median (95% CI) time to negative RT-qPCR, days	5.94 (5.72–8.83)	6.08 (5.82–8.89)	5.96 (5.85–8.83)	8.92 (8.84–12.79)
Improvement rate ratio (95% CI)	1.599 (1.185–2.158)	1.317 (0.976–1.777)	1.451 (1.120–1.882)	–
Log-rank test *P*-value[a]	0.001	0.071	0.005	–
Negative titer threshold 4 log_{10} copies/ml[b], *n*	95	94	189	92
Median (95% CI) time to negative RT-qPCR, days	4.03 (3.73–4.86)	4.81 (3.97–5.85)	4.69 (3.97–4.90)	5.80 (4.85–8.80)
Improvement rate ratio (95% CI)	1.642 (1.205–2.236)	1.188 (0.871–1.621)	1.389 (1.063–1.815)	–
Log-rank test *P*-value[a]	0.001	0.139	0.009	–
Clinical recovery to day 14				
All patients				
Median (95% CI) time to event, days	5.35 (3.97–6.78)	6.23 (5.53–7.85)	5.72 (5.15–7.00)	8.77 (6.72–11.73)
Clinical recovery ratio (95% CI)	1.562 (1.11–2.20)	1.429 (1.02–2.01)	1.489 (1.11–2.01)	–
Log-rank test *P*-value[a]	0.010	0.039	0.008	–
Mild SARS-CoV2 infection[c], *n*	38	40	78	46
Median (95% CI) time to event, days	4.37 (2.15–	5.49 (3.15–	4.83 (3.03–	6.88 (4.80–8.78)
Clinical recovery ratio (95% CI)				
Moderate SARS-CoV2 infection[c], *n*				

Median (95% CI) time to event, days	7.67)	7.60)	5.92)	–
Clinical recovery ratio (95% CI)	1.512 (0.90–2.54)	1.741 (1.06–2.86)	1.615 (1.05–2.49)	57
Moderate SARS-CoV2 infection and aged ≥50 years[b,c], *n*	62	63	125	10.81 (6.81–n.c.)
Median (95% CI) time to event, days	5.73 (4.13–7.33)	7.30 (5.58–10.72)	6.52 (5.53–7.69)	–
Clinical recovery ratio (95% CI)	1.689 (1.06–2.70)	1.347 (0.83–2.18)	1.511 (0.99–2.30)	38
	40	40	80	12.97 (6.81–n.c.)
	6.64 (4.13–11.94)	7.29 (5.54–12.33)	6.79 (5.50–10.72)	–
	1.584 (0.86–2.91)	1.504 (0.81–2.78)	1.545 (0.90–2.65)	
Secondary endpoints				
Patients with clinical symptoms requiring hospitalization or oxygen therapy due to SARS-CoV-2 infection to day 28, *n/N* (%)	4/101 (4.0)	5/103 (4.9)	9/204 (4.4)	9/103 (8.7)
Mild SARS-CoV-2 infection[c]	0/38	0/40	0/78	0/46
Moderate SARS-CoV2 infection[c]	4/62 (6.5)	5/63 (7.9)	9/125 (7.2)	9/57 (15.8)
Moderate SARS-CoV2 infection aged ≥50 years[b,c]	3/40 (7.5)	4/40 (10.0)	7/80 (8.8)	9/38 (23.7)
Patients achieving conversion to negative RT-qPCR (negative titer threshold: 2.33 log_{10} copies/ml), *n/N* (%)				
Up to day 14	68/101 (67.3)	68/103 (66.0)	136/204 (66.7)	62/103 (60.2)
Up to day 28	93/101 (92.1)	90/103 (87.4)	183/204 (89.7)	86/103 (83.5)
Patients with ≥1 disease status to day 28[d]	7 (6.9)	11 (10.7)	18 (8.8)	15 (14.6)
Patients requiring hospital admission, *n* (%)	4 (4.0)	5 (4.9)	9 (4.4)	9 (8.7)
Patients requiring supplemental oxygen, *n* (%)	4 (4.0)	4 (3.9)	8 (3.9)	9 (8.7)

Patients requiring mechanical ventilation, *n* (%)	0	1 (<1.0)	1 (<1.0)	0
Patients requiring rescue therapy, *n* (%)	7 (6.9)	11 (10.7)	18 (8.8)	15 (14.6)
Patients requiring ICU transfer, *n* (%)	0	0	0	0
All-cause mortality, *n* (%)	0	0	0	0
Patients achieving clinical recovery, *n/N* (%)				
Up to day 7	53/95 (55.8)	46/92 (50.0)	99/187 (52.9)	37/98 (37.8)
Up to day 14	73/95 (76.8)	72/92 (78.3)	145/187 (77.5)	62/98 (63.3)
Up to day 28	83/95 (87.4)	79/92 (85.9)	162/187 (86.6)	70/98 (71.4)

Table 3. Safety and tolerability (safety population)

	CT-P59 40 mg/kg *n*=105	**CT-P59 80 mg/kg *n*=110**	**Placebo *n*=110**
Any TEAE	31 (29.5)	27 (24.5)	34 (30.9)
Related to study drug	7 (6.7)	5 (4.5)	5 (4.5)
≥1 grade 3 TEAE[a]	5 (4.8)	4 (3.6)	2 (1.8)
Related to study drug	1 (1.0)	0	0
Any TESAE	0	0	0
Any TEAE leading to discontinuation	0	0	0
Any TEAE of special interest			
Infusion-related reactions	1 (1.0)	0	2 (1.8)
Deaths	0	0	0

Data shown as *n* (%).

[a]No patients experienced grade 4 or 5 TEAEs up to day 28.
TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Figures

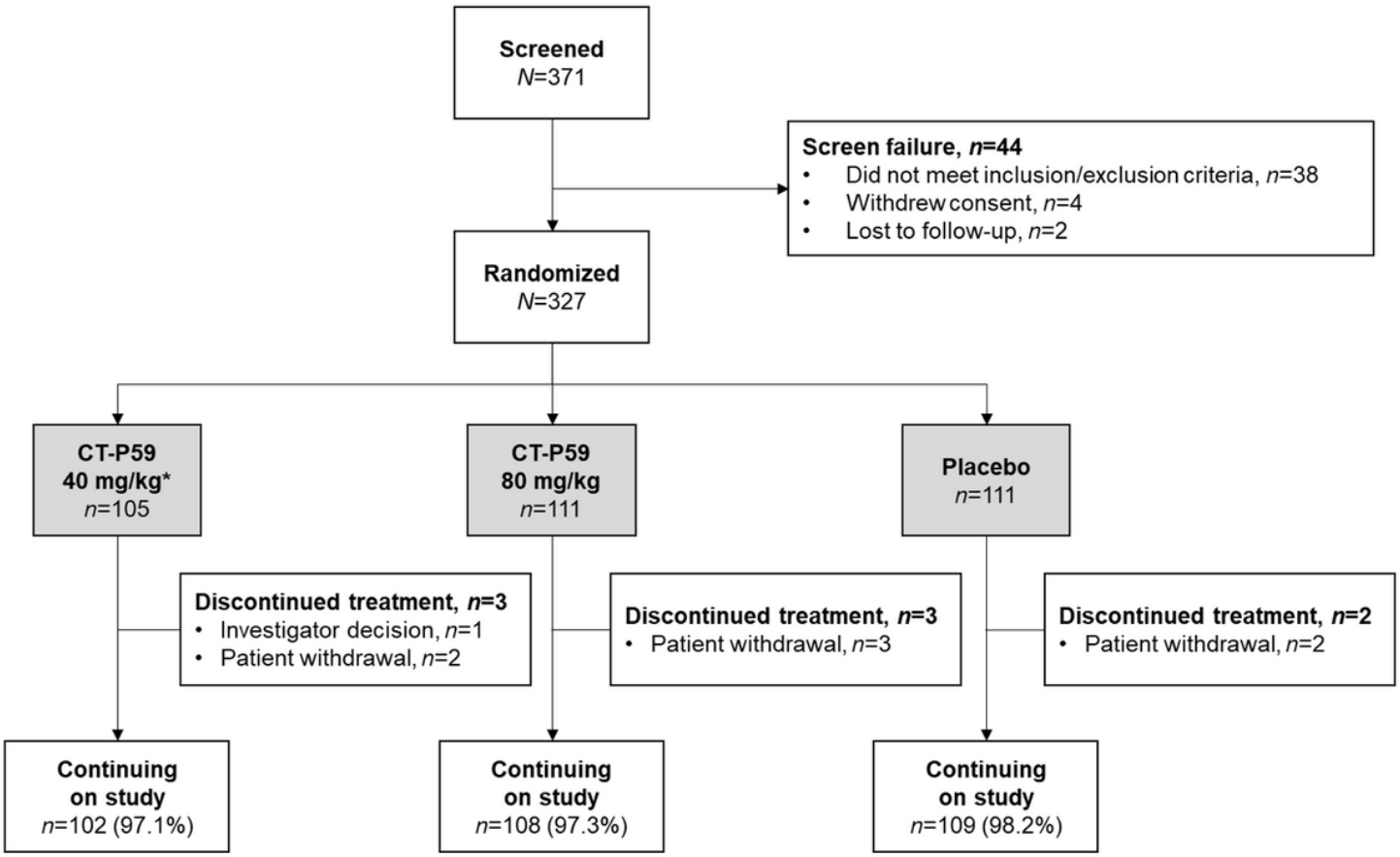

Figure 1

Patient disposition. *One patient was randomized to the placebo group but was administered study drug partially containing CT-P59; the individual was considered as having received CT-P59 40 mg/kg and was excluded from the pharmacokinetic population.

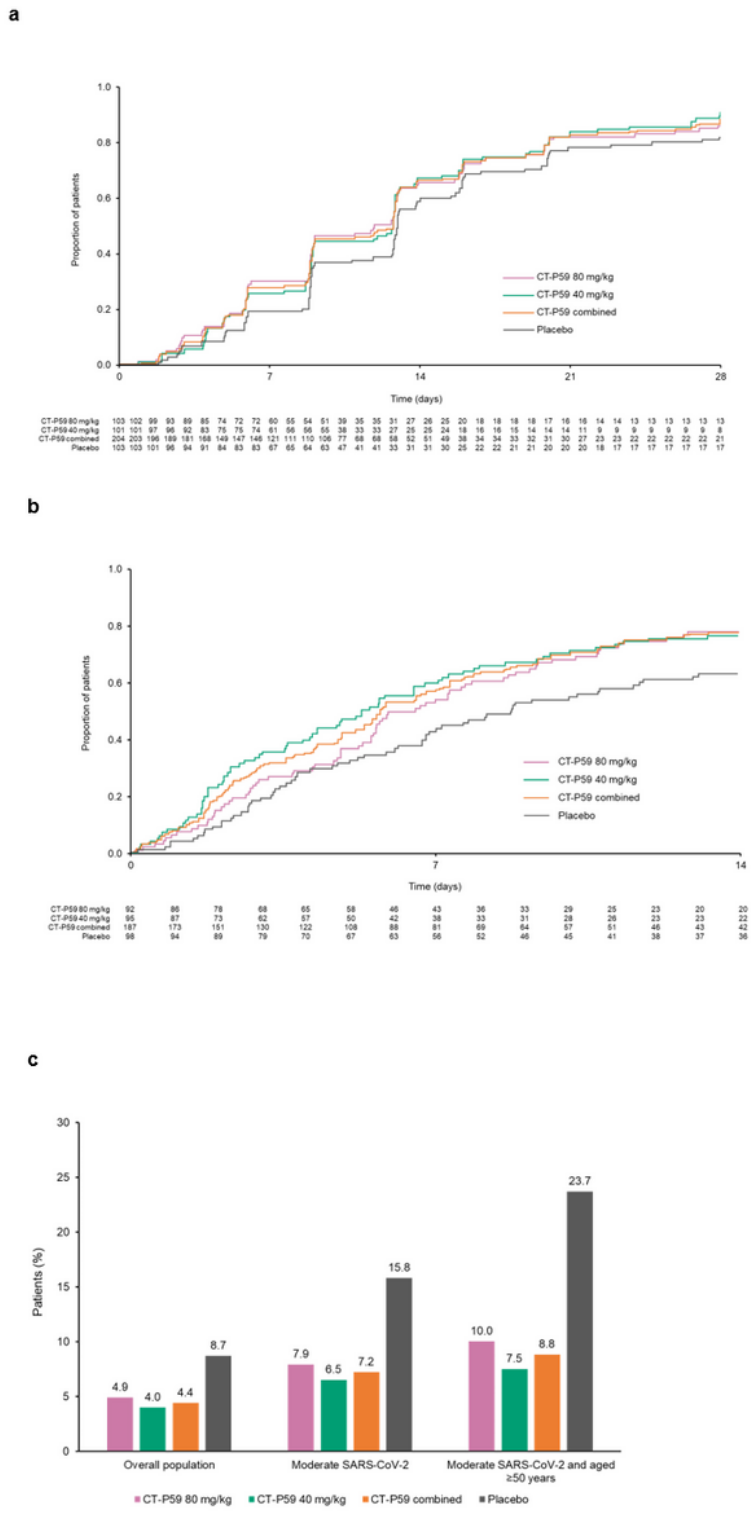

Figure 2

Efficacy endpoints (ITTI population). a, Kaplan-Meier plot of primary endpoint 'time to negative conversion' to day 28 (SARS-CoV-2–negative threshold: 2.33 log10 copies/ml). b, Kaplan-Meier plot of primary endpoint, time to clinical recovery to 14 days. c, Proportion of patients with clinical symptoms requiring hospitalization or oxygen therapy due to SARS-CoV-2 infection to day 28 in the overall

population and subgroups by disease severity and age. ITTT, intent-to-treat infected; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CTP59Study3.2supplementaryinfo03Mar2021.docx
- CTP59AppendixCLEAN18Dec2020.pdf
- CTP59protocolXSAP.zip