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Efficacy and safety of camostat mesylate in early COVID-19 disease in an ambulatory setting: a randomized placebo-controlled phase II trial

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ABSTRACT

Objectives: This study aimed to assess the efficacy and safety of 300 mg camostat mesylate three times daily in a fasted state to treat early phase COVID-19 in an ambulatory setting.

Methods: We conducted a phase II randomized controlled trial in symptomatic (maximum 5 days) and asymptomatic patients with confirmed COVID-19 infection. Patients were randomly assigned in a 2:1 ratio to receive either camostat mesylate or a placebo. Outcomes included change in nasopharyngeal viral load, time to clinical improvement, the presence of neutralizing antibodies, and safety.

Results: Of 96 participants randomized between November 2020 and June 2021, analyses were performed on the data of 90 participants who completed treatment (N = 61 camostat mesylate, N = 29 placebo). The estimated mean change in cycle threshold between day 1 and day 5 between the camostat and placebo group was 1.183 ($P = 0.511$). The unadjusted hazard ratio for clinical improvement in the camostat group was 0.965 (95% confidence interval, 0.480–1.942, $P = 0.921$ by Cox regression). The percentage distribution of the 50% neutralizing antibody titer at day 28 visit and frequency of adverse events were similar between the two groups.

Conclusion: Under this protocol, camostat mesylate was not found to be effective as an antiviral drug against SARS-CoV-2.

Trial registration: ClinicalTrials.gov [NCT04625114](https://clinicaltrials.gov/ct2/show/study/NCT04625114); November 12, 2020.

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Introduction

The SARS-CoV-2 discovered at the end of 2019 quickly turned into a global pandemic. About one year later, highly effective vaccines have been introduced, and large-scale immunization cam-

paigns are aimed at attenuating disease severity and preventing hospital admission. However, variants emerge with immune escape by changing domain in the spike (S) protein to which neutralizing antibodies bind (Willett et al., 2022). As such, vaccine effectiveness remains challenging. Therefore, the development and deployment of effective SARS-CoV-2 antiviral treatment are critical in combating the pandemic.

Infection of SARS-CoV-2 is initially mediated by its S glycoprotein consisting of the S1 and S2 domains. The S1 subunit binds with its receptor-binding domain to the host angiotensin-converting enzyme 2 (ACE-2), followed by subsequent membrane fusion. Two proteolytic activation events are associated with this S-mediated fusion process: a priming furin cleavage occurs at the interface of the S1 and S2 domain (S1/S2) and a cleavage within

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the S2 region (S2'). Cleavage of the S2' site occurs in the presence of transmembrane protease serine 2 (TMPRSS2). Cleavage may also be performed by cathepsins followed by clathrin-mediated endocytosis when TMPRSS2 is insufficiently present in the vicinity of the SARS-CoV-2-ACE-2 complex. In both distinct and redundant cleavage and entry pathways, fusion pore formation is initiated and allows the viral genome to enter the host cell cytoplasm (Hoffmann et al., 2020; Jackson et al., 2022).

Camostat mesylate is a serine protease inhibitor licensed for treating chronic pancreatitis and postoperative reflux esophagitis in Japan since 1985 and 1994, respectively. Previously, camostat mesylate was found to block the spread and pathogenesis of SARS-CoV in a pathogenic mouse model (Zhou et al., 2015) and has been shown by Hoffmann et al. (2020) to inhibit TMPRSS2-mediated entry of SARS-CoV-2 into Calu-3 cell line, derived from human airway epithelial cells. In addition, it has the advantage as a safe and inexpensive drug that is administered orally (Uno, 2020). As such, camostat mesylate was predicted to be a good candidate for the treatment of COVID-19.

To date, only a small number of human trials have reported the results of giving camostat for COVID-19. Sakr et al. (2021) performed a retrospective analysis of 371 adult patients admitted to the intensive care unit (ICU), of which 141 (38%) received camostat mesylate 200 mg three times daily for 7 days. The need for invasive mechanical ventilation (9.2% vs 17.8%, $P < 0.001$) and ICU/hospital mortality rate (9.9% vs 26.5%, $P < 0.001$) were significantly lower in patients treated with camostat, whereas their hospital length of stay was longer compared with those who did not receive camostat (19 days vs 17 days, $P = 0.011$). In a phase II randomized (2:1) controlled multicentre trial, Gunst et al. (2021) evaluated the efficacy and safety of camostat mesylate treatment in 205 adults hospitalized with COVID-19. For 5 days, participants received 200 mg camostat mesylate or placebo three times daily. Camostat mesylate treatment did not significantly improve median time to clinical improvement (5 days with interquartile range [IQR] 3–7 vs 5 days with IQR 2–10, $P = 0.37$), progression to ICU admission (10% vs 12%, $P = 0.66$) nor 30-day mortality (6% vs 6%, $P = 0.75$), as compared with the placebo group. There was no difference in viral load between the camostat and placebo arms. The frequency of adverse events was low and similar in both groups (28% vs 32%).

These studies did not show consistent effects of camostat mesylate on clinical outcomes in severely ill patients with COVID-19. However, given the nature of the viral disease, it remains possible that patients may benefit from the treatment in the early stage of illness before inflammation drives the pathophysiology. Furthermore, there is no consensus about the optimal dosing for treating COVID-19 with camostat mesylate. Although the approved oral doses are 200 mg and 100 mg three times daily for chronic pancreatitis and postoperative reflux esophagitis, respectively, Kitagawa et al. (2021) reported the safe use of high-dose (600 mg four times daily) camostat mesylate under fasted state conditions in a phase I clinical trial. In addition, according to their pharmacokinetic/pharmacodynamics simulations, the time above half-maximal effective concentration (EC_{50}) was equal to 5.3 hours per day at an intake of 300 mg three times daily in fasting conditions (Kitagawa et al., 2021). Moreover, animal studies measured a 1-fold to 3.8-fold higher concentration of camostat in the lung than plasma (Midgley et al., 1994). This will result in an even longer time above EC_{50} using the previously mentioned dosing regimen if the same accumulation occurs in humans.

Given these results, a phase II clinical trial was initiated to assess the efficacy and safety of 300 mg camostat mesylate three times daily in a fasted state to treat early phase COVID-19 in an ambulatory setting.

Methods

Participants

Participants included symptomatic (maximum 5 days) and asymptomatic patients with confirmed COVID-19 infection by a reverse transcription-polymerase chain reaction (RT-PCR) showing a cycle threshold (Ct) value below 30. Other inclusion criteria were that participants should be 18 years or older, willing to follow the study interventions, and capable of understanding and signing the informed consent form. Women of childbearing potential or men of reproductive potential had to be willing to use contraception during and until the end of the study. Exclusion criteria included the need for or being at high risk of hospitalization, pregnancy as checked by a urine pregnancy test at baseline or breastfeeding, severe chronic pancreatitis, and postoperative reflux esophagitis.

Participants were actively recruited at the emergency department, the COVID-19 consultation center, and the test center at the Ghent University Hospital, Belgium. Patients were passively recruited through an advertisement on the employee intranet and Facebook.

Randomization and blinding

Participants were enrolled at the emergency department. Subjects who met the inclusion and exclusion criteria were randomly assigned to two parallel groups in a 2:1 ratio to receive either camostat mesylate or placebo. Active drug and placebo tablets were provided by the pharmacy at the Ghent University Hospital in identical sealed, blinded, and consecutively numbered packages following EudraLex Volume 4, Good Manufacturing Practice Annex 13, and Belgian circular 596 requirements. The unblinded study personnel managed the allocation of the study medication of each participant chronologically, according to the computer-generated randomization list (www.randomization.com, random block size of 18) created by the pharmacy.

Study interventions

A standardized history was taken, including socio-demographic parameters such as age, gender, body mass index (BMI), smoking behavior, co-morbidities, and medication use. Clinical parameters were measured (heart rate [HR], oxygen saturation, and body temperature) followed by a clinical examination by a study physician. A rescreening COVID-19 RT-PCR test (primers targeting the E-gene) with a nasopharyngeal swab and blood analyses were performed. All study data were collected by blinded study personnel using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Ghent University Hospital (Harris et al., 2009; Harris et al., 2019). The study medication was initiated on day 1, as soon as possible after inclusion and randomization, which could be the morning, midday, or evening dose. Three 100 mg camostat mesylate or three placebo tablets were administered three times daily for 5 consecutive days under fasting conditions (minimum 60 minutes before the next meal and 2 hours after the previous meal) and respecting at least 4 hours between two intakes. Patients were asked to monitor HR, blood oxygen saturation, and body temperature three times daily, preferentially at the time of medication intake, with a home telemonitoring kit (Byteflies COVIDCare@Home). This allowed the study physician to assess the patient's condition remotely.

A day 5 visit (V5) was scheduled to re-evaluate participants as of day 1: clinical parameters and examination, COVID-19 RT-PCR test, and blood analyses. When clinical symptoms had not improved or had worsened compared with day 1, the treatment was extended up to day 10 at the same dosage in both treatment arms

for 5 consecutive days. In this case, the patient was asked to continue home monitoring until day 10.

At a day 10 visit (V10), participants whose treatment was prolonged up to day 10 were seen again for a clinical examination, including monitoring HR, oxygen saturation, and body temperature.

From day 1 to day 14 (or until day 28 if participants still had symptoms at day 14), participants were asked daily to fill out a questionnaire mapping the presence of 38 symptoms and signs on a 5-point Likert scale.

A day 28 visit (V28) was scheduled for all participants to draw an additional blood sample for neutralizing antibodies (NAbs) titer assessment.

Study visits were only scheduled on weekdays, resulting in minimal deviations in the visit days for V5 and V10. The V28 schedule was more flexible, according to the subject's availability, because quarantine was over and daily life activities had generally been resumed. Returned study medication packages were checked for remaining tablets by unblinded study personnel.

SARS-CoV-2 RT-PCR

At V1 and V5, a COVID-19 RT-PCR test with a nasopharyngeal swab was performed with primers targeting the E-gene, according to the protocol of [Corman et al. \(2020\)](#).

SARS-CoV-2 microneutralization assay

After clotting, V28 blood samples were centrifuged for 10 minutes at 1500 g at room temperature. Serum was transferred to a new tube and stored at -80°C before shipment on dry ice to a collaborative lab which performed the microneutralization assays as previously described ([Devos et al., 2022](#)). Results are expressed as the reciprocal of the serum dilution that inhibits 50% of the virus (NT₅₀). The NT₅₀ value of 40 is the detection limit, and values determined to be less than 40 are treated as 40.

End points

The primary end point to assess drug efficacy was a change in the shedding of the SARS-CoV-2 virus as measured by Ct obtained from nasopharyngeal swabs on days 1 and 5. Secondary end points were: (1) time to clinical improvement, defined as an improvement of the five most self-reported symptoms in at least one point from baseline on the 5-point Likert scale, whichever came first; (2) the presence of NAbs at V28, and (3) safety.

Statistical analysis

Data were analyzed with SPSS 28 IBM Corporation, Armonk, New York, United States. The distribution of numerical data was checked for normality. Means and SDs were calculated in the case of normal distribution, median and IQR for data that were not normally distributed. Proportions are presented for categorical data. Differences between both treatment groups were tested using the unpaired Student's *t*-test or Mann-Whitney U test for numerical data and chi-square test for categorical variables. Differences in Ct between V1 and V5 within each treatment arm were tested using the Wilcoxon or paired Student's *t*-test.

Change in Ct between day 1 and day 5 was compared using a linear mixed-effects model with random intercepts for the participant. Estimates for change in Ct for camostat compared with placebo and corresponding 95% confidence intervals (CI) for the linear models were reported.

A Kaplan-Meier curve was constructed for time to clinical improvement. Hazard ratios with 95% CI were estimated by Cox proportional hazards model with and without adjustment for potential

confounders. Patients were censored at the time of the last assessment or the end of the trial. A 2-sided α value of less than 0.05 was considered significant.

We intended to include 132 patients to complete the entire trial based on a sample size calculation ($\alpha = 0.05$, $\beta = 0.10$, moderate standardized effect size = 0.3). In May 2021, however, recruitment decreased significantly after the third wave of the COVID-19 epidemic in Belgium (no inclusions for more than two weeks). According to the study protocol, we decided to interrupt the inclusion to perform an interim analysis of the data of 90 participants, 68.2% of the total intended inclusion number. All included participants received a full follow-up until V28.

Results

Participants

Between November 2020 and June 2021, a total of 108 participants were enrolled in the study ([Figure 1](#)). Of these, 12 subjects did not meet the inclusion and exclusion criteria and were excluded from randomization. A total of 96 participants received either camostat mesylate (N = 66) or placebo (N = 30). Treatment was immediately interrupted in four subjects that had to be hospitalized because of clinical deterioration. Two other subjects chose to withdraw from the study. Analyses were performed on the data of 90 participants who completed treatment (N = 61 camostat mesylate, N = 29 placebo). Baseline characteristics are listed in [Table 1](#).

Most participants (N = 78, 86.7%) were recruited actively by the study team. In total, 49 participants (54.4%) were female. The median age was 40 (range 19–70 years). A total of 77 (85.6%) subjects showed symptoms at V1, including coughing (N = 68, 79.1%), asthenia (N = 64, 74.4%), sneezing (N = 62, 72.1%), stuffy nose (N = 56, 65.1%), and abnormal sense of smell or taste (N = 17, 19.8%). Significant differences in baseline characteristics were not observed between the camostat mesylate and placebo group ($P > 0.05$). A first COVID-19 vaccination dose was received by three patients before enrollment and by three subjects during the study period. One subject received two doses before enrollment.

Because of persistent symptoms at V5, investigational medicinal product (IMP) treatment was extended to day 10 for 10 patients (16.4%) who received camostat mesylate and four (13.8%) who received a placebo.

Primary end point

The presence of SARS-CoV-2 E-gene was measured at baseline and V5. The median Ct was 17.8 at baseline and 22.7 at V5, comparable between the camostat and placebo groups ([Figure 2](#)). Whereas the Ct value increased for most patients between both visits, this value decreased within this time frame for 11 participants (seven out of the camostat and four out of the placebo group). This subgroup of 11 subjects showed no or only recent symptomatology (0–2 days) at enrolment, whereas the median time from symptom onset to enrolment was 3 days (IQR 1–4) for the whole study population. The estimated mean change in Ct between day 1 and day 5 between the camostat and placebo group was 1.183 ($P = 0.511$). Potential risk factors for worse COVID-19 disease did not impact on change in Ct (aged 60+ years, $P = 0.684$; obesity, $P = 0.087$; smoking in the past, $P = 0.426$; smoking currently, $P = 0.795$; hypertension, $P = 0.266$; diabetes mellitus, $P = 0.266$). In addition, the COVID-19 vaccination had no effect on Ct change ($P = 0.942$).

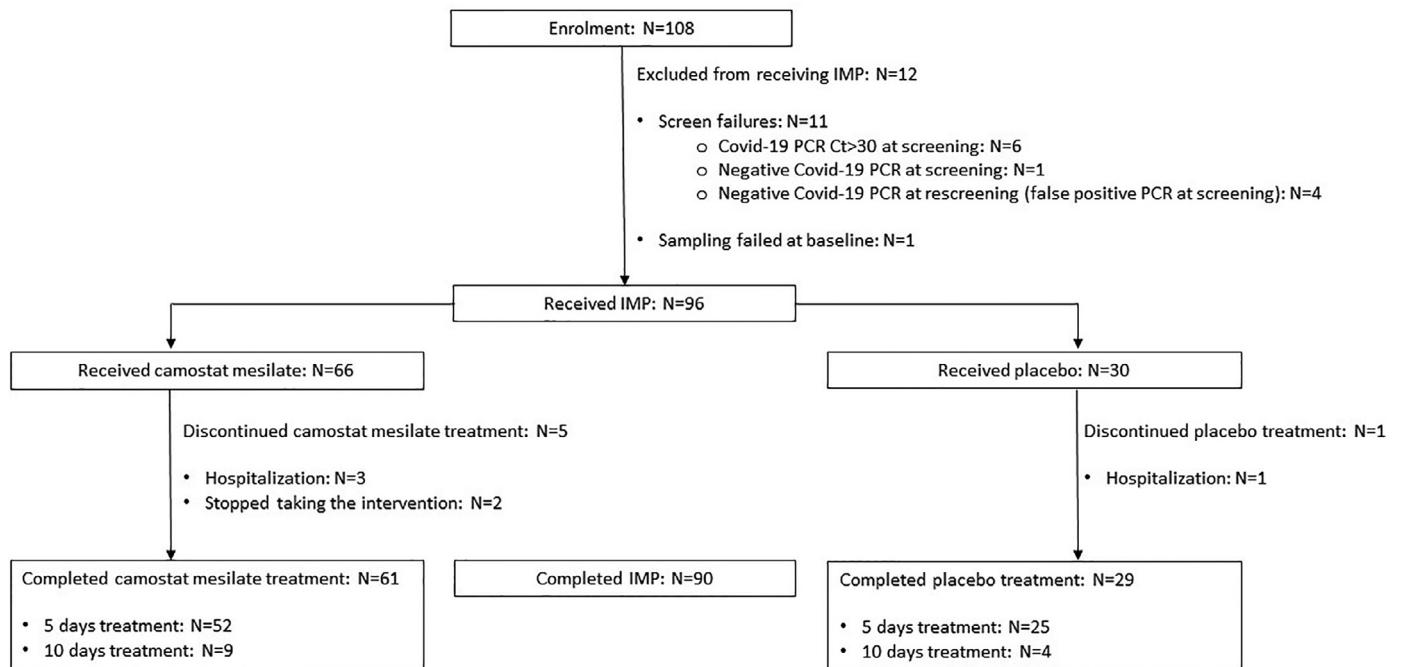


Figure 1. Flow diagram

Table 1
Baseline characteristics of participants who completed study treatment.

Characteristics	Total sample N=90	Camostat mesilate N=61	Placebo N=29	p
Median age (IQR), years	40 (24-53)	38 (25-53)	37 (22-51)	0.434
Female gender, N (%)	49 (54.4)	33 (54.1)	16 (55.2)	1,000
Type of recruitment, N (%)		50 (82.0)	28 (96.6)	0.057
Active	78 (86.7)	11 (18.0)	1 (3.4)	
Passive	12 (13.3)			
Symptomatic at baseline, N (%)	77 (85.6)	51 (83.6)	26 (89.7)	0.446
Cough	68 (79.1)	44 (77.2)	24 (82.8)	0.549
Sneeze	62 (72.1)	40 (70.2)	22 (75.9)	0.578
Abnormal sense of smell or taste	17 (19.8)	12 (21.1)	5 (17.2)	0.675
Asthenia	64 (74.4)	44 (77.2)	20 (69.0)	0.408
Stuffy nose	56 (65.1)	35 (61.4)	21 (72.4)	0.311
Mean body mass index ± SD, kg/m ²	24.2 ± 3.0	23.8 ± 2.8	25.0 ± 3.9	0.021
Obesity, N (%)	6 (6.7)	2 (3.3)	4 (13.8)	
Smoking behaviour, N (%)	28 (31.1)	19 (31.1)	9 (31.0)	0.991
Smoked in the past	15 (16.7)	10 (16.4)	5 (17.2)	0.920
Smokes currently				
Comorbidities, N (%)	2 (2.2)	1 (1.6)	1 (3.4)	0.586
Diabetes	1 (1.1)	1 (1.6)	0 (0)	0.488
Cancer	6 (6.7)	4 (6.6)	2 (6.9)	0.952
Hypertensia				
Use of medication, N(%)	6 (6.7)	6 (9.8)	0 (0)	0.080
Antihistamins	59 (65.6)	40 (65.6)	19 (65.5)	0.996
Analgesics/antipyretics	7 (7.8)	5 (8.2)	2 (6.9)	0.830
Covid-19 vaccination				
Clinical parameters	77.6 ± 14.1	77.5 ± 15.0	77.9 ± 12.3	0.706
Mean heart rate ± SD, beats per minute	98.1 ± 1.2	98.2 ± 1.1	98.0 ± 1.2	0.901
Mean arterial oxygen saturation ± SD, %	36.5 ± 0.8	36.4 ± 0.9	36.7 ± 0.8	0.538
Mean body temperature ± SD, °C				
Viral load in nasopharyngeal swab (rescreening PCR)	17.8 (15.6-21.2)	17.4 (15.6-21.2)	18.4 (15.3-21.2)	0.988
Median cycle threshold (IQR)				
Blood parameters	1200 (938-1635)	1190 (930-1548)	1200 (962-1750)	0.367
Median lymphocyte count (IQR), /L	2280 (1753-2940)	2240 (1735-2920)	2320 (1768-3010)	0.756
Median neutrophil count (IQR), /μL	29 (13-48)	26 (12-47)	39 (18-69)	0.069
Median C-reactive protein (IQR), mg/L	270 (270-350)	270 (270-385)	270 (270-310)	0.131
Median D-dimers (IQR), ng/mL	1800 (1540-2073)	1780 (1540-1950)	1980 (1565-2150)	0.115
Median lactic acid dehydrogenase (IQR), U/L				

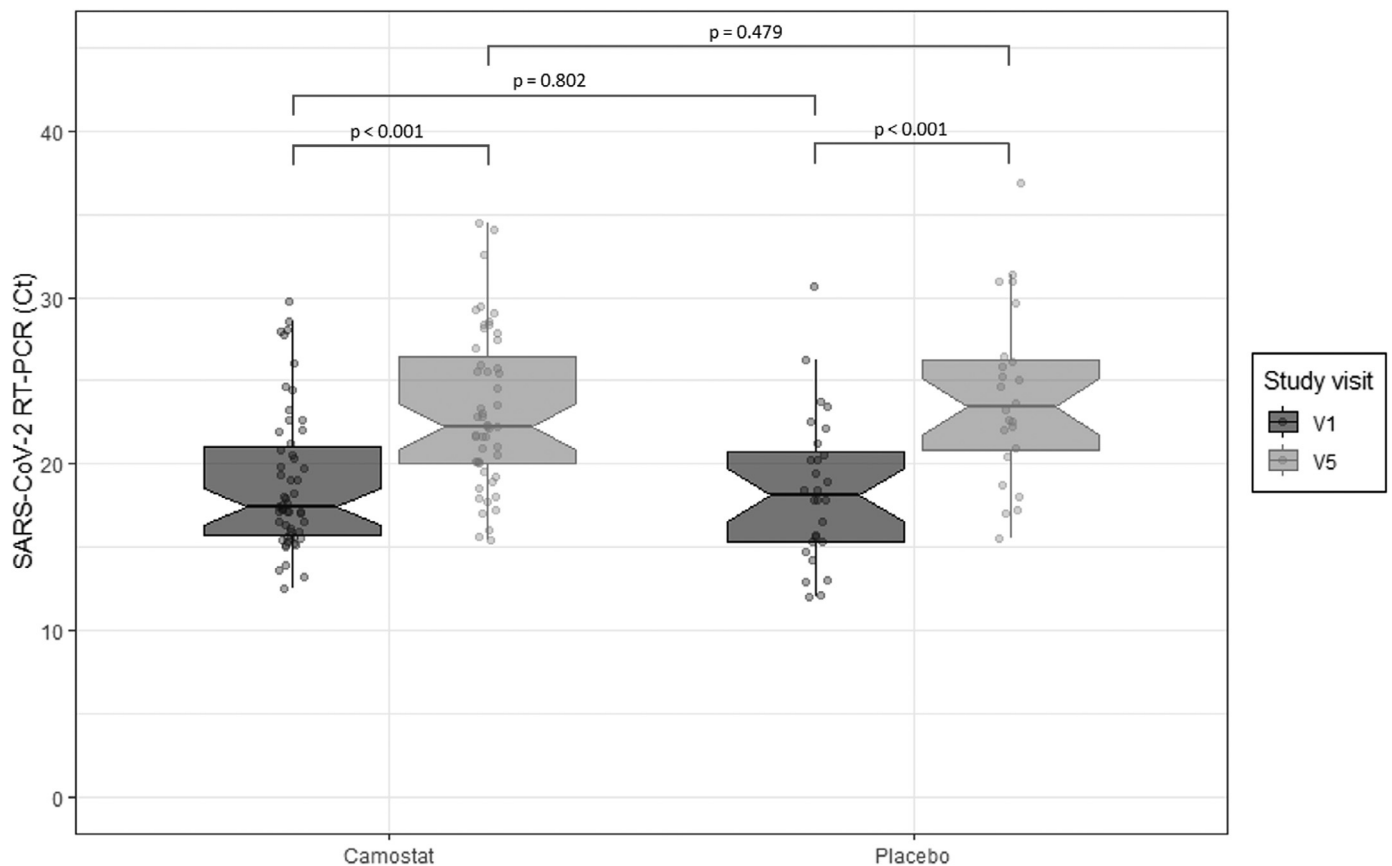


Figure 2. Polymerase chain reaction (PCR) cycle threshold (Ct) values at baseline (V1) and day five visit (V5). Each data point represents the Ct value from one patient in the camostat mesylate versus the placebo group. A lower Ct value corresponds to a higher viral load.

Secondary end points

Of 90 subjects, four did not fill out the questionnaire at baseline, and consequently, the data of 86 participants were included in the survival analysis. The top five self-reported symptoms during the whole study period were coughing, asthenia, sneezing, stuffy nose, and abnormal sense of smell or taste. A total of 35 participants (40.7%) experienced a clinical improvement in at least one point on the 5-point Likert scale: 22 (38.6%) in the camostat group and 13 (44.8%) in the placebo group. The Kaplan-Meier curve for time to clinical improvement is shown in [Figure 3](#). The unadjusted hazard ratio for clinical improvement in the camostat group was 0.965 (95% CI, 0.480–1.942, $P = 0.921$ by Cox regression). The hazard ratio adjusted for age was 1.083 (95% CI, 0.534–2.195, $P = 0.826$). Other variables did not influence clinical improvement (gender, $P = 0.641$; aged 60+ years, $P = 0.483$; BMI, $P = 0.618$; obesity, $P = 0.209$; smoking in the past, $P = 0.227$; smoking currently, $P = 0.354$; hypertension, $P = 0.391$; diabetes mellitus, $P = 0.286$; COVID-19 vaccine, $P = 0.405$, time from symptom onset to the first visit, $P = 0.579$).

Sampling for NAbs assessment was performed at V28 (median day 28, IQR 28–30). Of 90 participants, 30 (33.3%) showed an NT₅₀ value below 40, comprising 23 of 61 (37.7%) in the camostat mesylate and seven of 29 (24.1%) in the placebo group. A total of 60 participants (66.6%) showed an NT₅₀ higher than the detection limit (≥ 40). The percentage distribution was not significantly different between the camostat mesylate and the placebo group ([Figure 4](#), $P = 0.091$). Six of seven subjects that received at least one vaccination dose against COVID-19 showed an NT₅₀ higher than the detection limit (≥ 40).

A total of 82 (91.1%) patients experienced adverse events during the trial, 59 (96.7%) in the camostat mesylate group and 23 (79.3%) in the placebo group ([Table 2](#)). Four participants were hospitalized after progressive disease and unrelated to the study medication ([Figure 1](#)).

Discussion

In this randomized, placebo-controlled phase II clinical trial, we assessed the efficacy of orally administered camostat mesylate (300 mg three times daily for 5 or 10 consecutive days) in treating early phase COVID-19 in an ambulatory setting. The change in RT-PCR measured Ct value targeting the E-gene of SARS-CoV-2 was not significantly different in the camostat group compared with the placebo group from baseline to follow-up at day five. Time to clinical improvement of the five most self-reported symptoms did not differ between both treatment arms.

These findings are consistent with the randomized controlled trial performed by [Gunst et al. \(2021\)](#), who described the lack of positive effects of camostat mesylate treatment on efficacy outcomes, including viral load and time to clinical improvement. Nevertheless, [Gunst et al. \(2021\)](#) targeted hospitalized patients, possibly beyond the most active stage of viral replication. In contrast, we focused on patients with COVID-19 with a mild to moderate illness in the early stage of illness, as camostat mesylate inhibits viral entry into the cells *in vitro* ([Hoffmann et al., 2020](#)). In addition, we used a higher treatment dose (300 mg three times daily) than administered in previous efficacy trials (200 mg three times daily) ([Gunst et al., 2021](#); [Sakr et al., 2021](#)) to ensure sufficient plasma concentrations of camostat mesylate ([Kitagawa et al., 2021](#)). De-

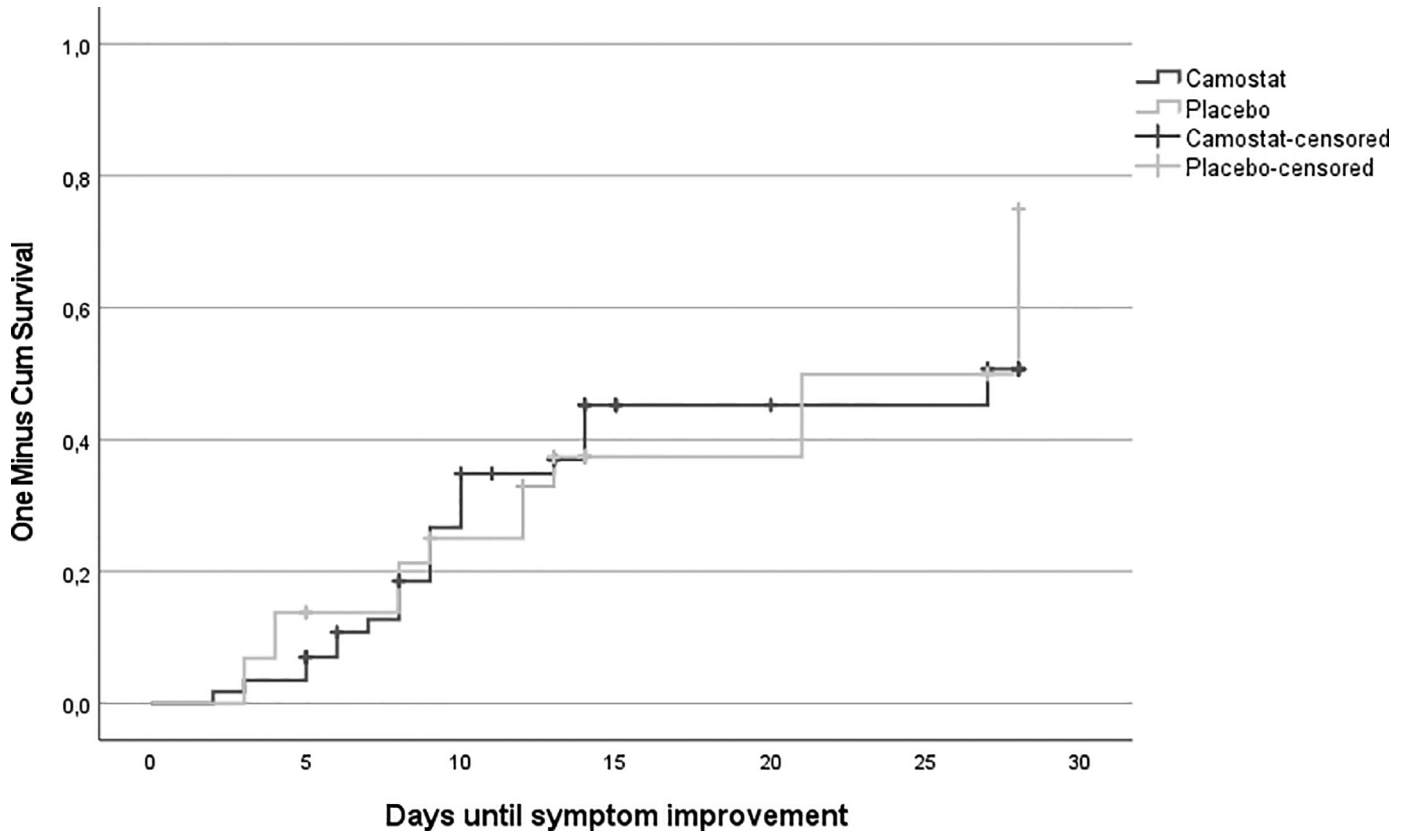


Figure 3. Kaplan-Meier curve for time to clinical improvement

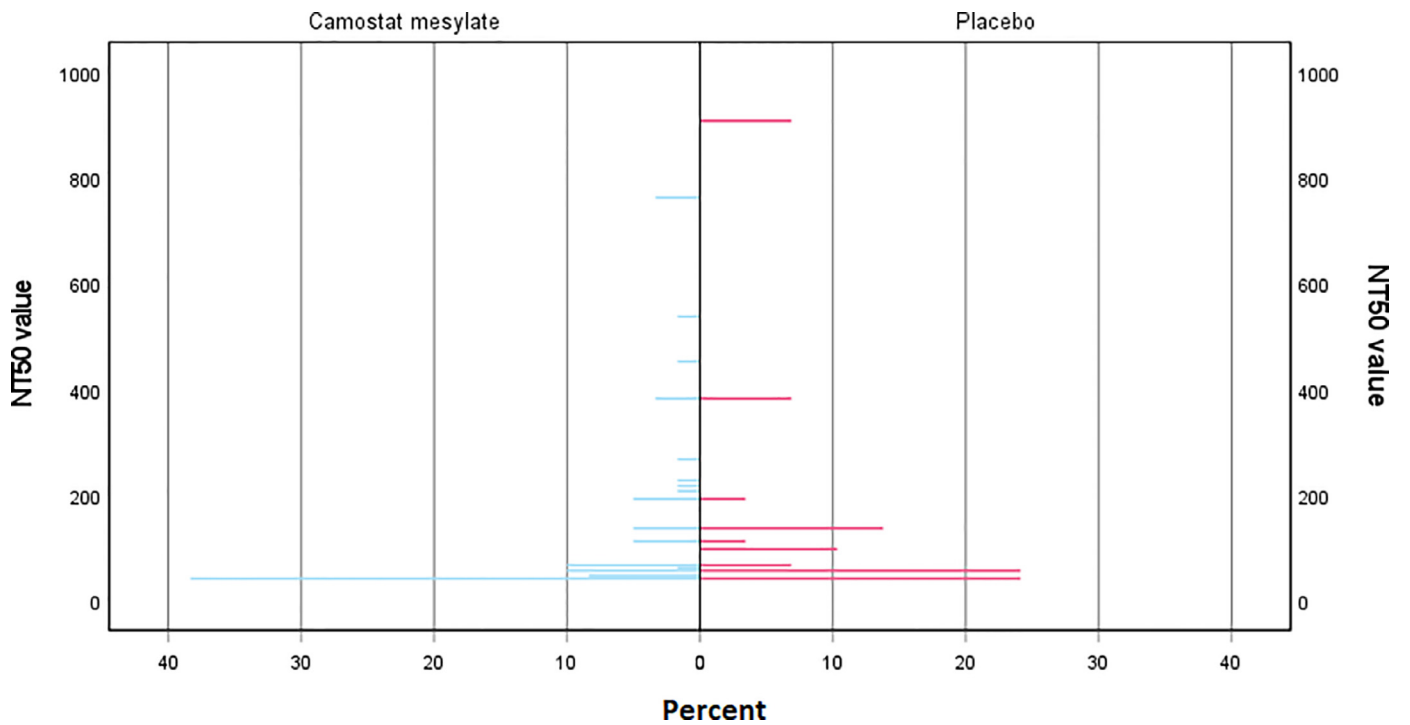


Figure 4. Distribution of 50% neutralizing antibody titer (NT₅₀, reciprocal serum dilution) of participants treated with camostat mesylate (blue) and placebo (red). The NT₅₀ value of 40 is the detection limit, and values determined to be less than 40 are treated as 40.

Table 2
Adverse events of participants who completed study treatment.

Adverse event, N (%)	Total sample N=90	Camostat mesilate N=61	Placebo N=29
fatigue	23 (25.6)	19 (31.1)	4 (13.8)
change in appetite	11 (12.2)	9 (14.8)	2 (6.9)
diarrhea	11 (12.2)	7 (11.5)	4 (13.8)
nausea	11 (12.2)	9 (14.8)	2 (6.9)
headache	7 (7.8)	5 (8.2)	2 (6.9)
flatulence	4 (4.4)	4 (6.6)	0 (0.0)
dizziness	3 (3.3)	3 (4.9)	0 (0.0)
constipation	2 (2.2)	1 (1.6)	1 (3.4)
dry mouth	2 (2.2)	2 (3.3)	0 (0.0)
palpitations	2 (2.2)	0 (0.0)	2 (6.9)
abdominal pain	1 (1.1)	1 (1.6)	1 (3.4)
amnesia	1 (1.1)	0 (0.0)	1 (3.4)
anaemia	1 (1.1)	1 (1.6)	0 (0.0)
burping	1 (1.1)	1 (1.6)	0 (0.0)
migraine	1 (1.1)	1 (1.6)	0 (0.0)
mouth ulcer	1 (1.1)	0 (0.0)	1 (3.4)
pruritus	1 (1.1)	1 (1.6)	0 (0.0)
reflux	1 (1.1)	1 (1.6)	0 (0.0)
stomach cramps	1 (1.1)	1 (1.6)	0 (0.0)
thirst increase	1 (1.1)	1 (1.6)	0 (0.0)
weight loss	1 (1.1)	1 (1.6)	0 (0.0)
neutropenia	11 (12.2)	9 (14.8)	2 (6.9)
leucopenia	9 (10.0)	7 (11.5)	2 (6.9)
CRP increase	6 (6.7)	4 (6.6)	2 (6.9)
lymphopenia	6 (6.7)	4 (6.6)	2 (6.9)
ALT increase	5 (5.6)	3 (4.9)	2 (6.9)
ferritin increase	5 (5.6)	3 (4.9)	2 (6.9)
fibrin D dimer increase	5 (5.6)	3 (4.9)	2 (6.9)
eosinopenia	3 (3.3)	2 (3.3)	1 (3.4)
APTT increase	2 (2.2)	2 (3.3)	0 (0.0)
AST increase	2 (2.2)	2 (3.3)	0 (0.0)
ferritin decrease	2 (2.2)	2 (3.3)	0 (0.0)
gamma-glutamyltransferase increase	2 (2.2)	1 (1.6)	1 (3.4)
granulocytopenia	2 (2.2)	2 (3.3)	0 (0.0)
hyperkalaemia	2 (2.2)	0 (0.0)	2 (6.9)
INR increase	2 (2.2)	2 (3.3)	0 (0.0)
thrombocytopenia	2 (2.2)	1 (1.6)	1 (3.4)
bicarbonate decrease	1 (1.1)	0 (0.0)	1 (3.4)
calcium decrease	1 (1.1)	1 (1.6)	0 (0.0)
glucose increase	1 (1.1)	1 (1.6)	0 (0.0)
haematocrit increase	1 (1.1)	1 (1.6)	0 (0.0)
haemoglobin increase	1 (1.1)	1 (1.6)	0 (0.0)
hypereosinophilia	1 (1.1)	1 (1.6)	0 (0.0)
liver enzymes increase	1 (1.1)	1 (1.6)	0 (0.0)
lymphocytosis	1 (1.1)	1 (1.6)	0 (0.0)
platelets increase	1 (1.1)	0 (0.0)	1 (3.4)

sprite these protocol adaptations, camostat mesylate did not improve clinical outcomes.

It may be hypothesized that SARS-CoV-2 enters the host cells through clathrin-mediated endocytosis when TMPRSS2-mediated entrance is blocked by camostat mesylate (Jackson et al., 2022). If this is the case, additional inhibition of the cathepsin-mediated entry pathway might lead to a decreased infection rate and improved efficacy. Kreutzberger et al. (2021) indeed found a synergistic block of SARS-CoV-2 infection in different single-cell types by the combined use of a TMPRSS2 protease inhibitor (camostat mesylate or nafamostat mesylate) and the lipid kinase inhibitor apilimod (PIKfyve kinase), which interferes with late endosomal viral traffic, or the cathepsin protease inhibitor E-64. The described 5-fold to 10-fold increase in efficacy of the combined use of these inhibitors *in vitro* highlights the potential advantage of using this simultaneous inhibition to reduce the viral load and potentially ameliorate clinical improvement of patients with COVID-19 (Kreutzberger et al., 2021).

The inhibitory effect of camostat alone or in combination may also differ between SARS-CoV-2 viral strains. The original Wuhan-

Hu-1 and Alpha variants, dominant in Belgium at the time the present study was performed, together with the Delta variant, seem to prefer fusion at the cell surface as shown to be primarily inhibited by a TMPRSS2 inhibitor *in vitro* (Willett et al., 2022). In contrast, the later emerged Omicron variant exhibits E-64 sensitivity in cell lines, indicating a preferred switch from the cell surface to endosomal fusion because of genotypic change (Willett et al., 2022) and rendering the use of camostat futile.

The strengths of the present study are the follow-up of participants using subjective and objective efficacy measures and the similarity of the study population characteristics in both treatment arms (Table 1). A limitation of our study is that the study visits were scheduled within a range of different days. Nevertheless, we did control for this variance in the linear mixed-effects model analysis.

The present trial does not show evidence that camostat mesylate under the present conditions (300 mg three times daily for five or 10 consecutive days, fasted state) is effective as an antiviral drug against early phase SARS-CoV-2 disease. However, analysis was performed on the data of 68% of the total calculated sample size because the trial was discontinued when recruitment decreased significantly. In addition, we cannot exclude the possibility that a combined treatment, blocking both the TMPRSS2- and clathrin-mediated viral entrance, might lower disease progression.

Conflict of interest

The authors have no conflicts of interest to declare.

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Ono Pharmaceuticals Co. Ltd. (Osaka, Japan) provided the study drug, camostat mesylate. Byteflies (Antwerp, Belgium) provided telemonitoring devices and technological support. No further funding was received regarding this manuscript.

Ethical approval statement

This phase II double-blind, placebo-controlled prospective study was approved by the Belgian Federal Agency for Medicines and Health Products (FAMHP, 2020-003475-18) and the institutional Ethical Review Board of the Ghent University Hospital (BC-07707). An independent safety monitoring committee regularly monitored unblinded data to ensure trial participants' safety.

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Author contributions

MADS conceived and designed the analysis, contributed to data collection and analysis and review, ET wrote the paper and contributed to data collection and analysis; LD, SB, SVH and LVD contributed to data collection; SDG, VH, MR, IT, EP contributed to data analysis; SC contributed to the protocol and review.

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