Efficacy of clarithromycin in patients with mild COVID-19 pneumonia not receiving oxygen administration: protocol for an exploratory, multicentre, open-label, randomised controlled trial (CAME COVID-19 study)

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ABSTRACT

Introduction The COVID-19 pandemic has emerged worldwide. Although several medications have been approved for treating moderate-to-severe COVID-19, very few treatment strategy has been established for patients with mild COVID-19 who do not require oxygen administration. Clarithromycin is a macrolide antimicrobial agent that has been widely used for bacterial respiratory infectious diseases. Clarithromycin also acts an immunomodulating drug and suppresses cytokine storms in viral respiratory diseases, including influenza. In this study, we aim to evaluate the efficacy of clarithromycin in patients with mild COVID-19.

Methods and analysis This is an exploratory, multicentre, open-label, randomised controlled trial. This study was initiated in May 2021 and will end in July 2022. Patients with mild COVID-19 pneumonia who do not require oxygen administration will be enrolled and randomly assigned in a 1:1:1 ratio to group A (administration of clarithromycin 800 mg/day), group B (administration of clarithromycin 400 mg/day) or group C (standard treatment without clarithromycin). The planned number of enrolled patients is 60 (20 patients × three groups). The primary endpoint is the number of days required to improve the clinical symptoms as measured by the severity score. Secondary endpoints include days for recovery of the body temperature, proportion of patients with oxygen administration, inflammatory cytokines, viral load, serum immunoglobulins, peripheral blood lymphocytes, blood biomarkers and pneumonia infiltrations.

Ethics and dissemination The study protocol was approved by the Clinical Research Review Board of Nagasaki University in accordance with the Clinical Trials Act in Japan. The study will be conducted in accordance with the Declaration of Helsinki, the Clinical Trials Act and other current legal regulations in Japan. Written informed consent will be obtained from all the participants. The results of this study will be reported as journal publications.

Trial registration number jRCTs071210011.

INTRODUCTION

The COVID-19 pandemic is currently a major concern worldwide. In Japan, a cumulative of 932,361 PCR test-positive cases have been confirmed, and 15,190 deaths were reported by the Ministry of Health, Labour and Welfare in Japan as of 1 August 2021. Approximately 5% of the patients with COVID-19 were hospitalised, 1.6% had severe symptoms requiring intensive care and 1.0% died in Japan. Recently, dexamethasone and remdesivir have been used as standard treatments for patients with moderate-to-severe COVID-19 who require respiratory support, and the monoclonal antibody therapy, such as casirivimab/imdevimab antibody cocktail, have been demonstrated as effective for mild to moderate COVID-19. However, these treatments require intravenous drip infusion, and no oral medical treatment has been established for mild COVID-19, which accounts
for the majority (approximately 80%) of patients with COVID-19.

The mechanism of exacerbation in COVID-19 has been reported to correlate with dysregulation of the immune response, resulting in exaggerated inflammation to produce excessive cytokines (the so-called cytokine storm). Indeed, infection with the SARS-CoV-2 induces high expression of inflammatory cytokines, such as granulocyte macrophage colony-stimulating factor and interleukin-6 (IL-6), thereby accelerating the inflammation. Therefore, suppression of inflammatory cytokines is an important target for preventing the exacerbation of COVID-19. This is supported by the evidence that tocilizumab, an antihuman IL-6 receptor monoclonal antibody that inhibits IL-6 signalling, and dexamethasone, anti-inflammatory and immunosuppressing steroid, reduced risk of mortality and exacerbation that required ventilation.11–13

Clarithromycin is a macrolide antibiotic that has been widely used as a monotherapy for bacterial respiratory infectious diseases. Clarithromycin has also been used as a standard combination therapy with beta-lactam antibiotics for severe community-acquired pneumonia,14 owing to its ability to suppress inflammatory cytokines.15 16 Viral respiratory diseases, such as influenza, are not an exception in the mechanism of exacerbation, and combination therapy with clarithromycin and antiviral agents demonstrated clinical efficacy in influenza A infection.17 18 Considering the use of macrolides for COVID-19, evidence in the efficacy of azithromycin to COVID-19 is controversial; some reported the beneficial effect of azithromycin on COVID-19,19 20 while others reported no benefit in patients with COVID-19.21–23 Clarithromycin has several advantages over azithromycin. First, clarithromycin is well tolerated, with even lower frequency of adverse events (AEs)/side effects compared with azithromycin.24 25 Second, dose of clarithromycin can be adjusted based on patients’ age, weight and symptoms by using a tablet of 200 mg in Japan. Third, clarithromycin and azithromycin affect differently to suppress immune cells and inflammatory cytokine production,26 27 and to inhibit NF-κB activation.28 Together with these, clarithromycin is a good candidate for alleviating symptoms and preventing the exacerbation of COVID-19 by suppressing inflammatory cytokines and could be safely used in patients with COVID-19. This trial is planned to estimate the efficacy of clarithromycin in patients with mild COVID-19 pneumonia who do not require oxygen administration.

METHODS AND ANALYSIS
Study design and setting
‘The CAM (Clarithromycin) Effectivity for COVID-19 pneumonia that does not require oxygen administration; multicenter, randomized-controlled, open-label, 3-armed parallel group comparison, exploratory trial’ (CAME COVID study) was initiated in May 2021, following the approval by the Clinical Research Review Board in Nagasaki University in March 2021 and the registration/publication at the Japan Registry of Clinical Trials (jRCT) (registration number: jRCTs071210011) in April 2021. This study is scheduled to culminate in July 2022. Patients have been enrolled since May 2021, and enrolment will culminate in February 2022. This study will be conducted in 10 medical institutions in Japan (Nagasaki University Hospital, Nagasaki Harbor Medical Center, Sasebo City General Hospital, Japan Community Health Care Organization JCHO Isahaya General Hospital, Japanese Red Cross Nagasaki Genbaku Hospital, Hospital of the University of Occupational and Environmental Health, Japan, Wakamatsu Hospital of the University of Occupational and Environmental Health, Japan, Kitakyushu City Yahata Hospital, Fukuoka University Chikushi Hospital, and Saiseikai Nagasaki Hospital). As shown in figure 1, patients who are eligible for this study will be asked to participate in this study, and informed consent will be obtained prior to the registration/randomisation. After written consent is obtained from the eligible patients, they will be enrolled and randomised into group A (administration of clarithromycin 800 mg/day), group B (administration of clarithromycin 400 mg/day), and group C (standard treatment without clarithromycin).
of clarithromycin 400mg/day) or group C (standard treatment without clarithromycin). The rationale for the doses of clarithromycin is as follows: clarithromycin-naproxen-oseltamivir combination therapy for Influenza A using 1000mg/day of clarithromycin (500mg twice daily) was tolerated and reduced mortality and length of hospital stay, and 400mg/day and 800mg/day of clarithromycin have been approved for bacterial respiratory infectious diseases and non-tuberculous mycobacterial infection, respectively, in Japan, and the safety of these doses of clarithromycin has been confirmed.

Sample size calculation
Since no prior clinical trial has evaluated the effect of clarithromycin on COVID-19 pneumonia, no reference data are available for the statistical sample size calculation for this study. Therefore, this study is planned as an exploratory trial, and the target number of enrolled patients is defined as 60 (20 subjects×3 groups), based on the possible number of patients who could give their consent during the planned enrolment period in this study at the participating medical institutions.

Eligibility criteria
Patients with mild COVID-19 pneumonia who do not require oxygen administration will be included in this study. Eligibility criteria are as follows: (1) patients in whom SARS-CoV-2 is detected by PCR tests or loop-mediated isothermal amplification method within 3 days before the informed consent, (2) patients with pneumonia by routine chest radiography or chest CT, (3) Japanese patients who are aged 20 years or older and (4) patients who give their written consent for participating in the study. The exclusion criteria are as follows: (1) patients who had symptoms of 8 days or longer, (2) patients who were treated with macrolide antimicrobial agents, (3) patients who were treated with steroids (except inhalants) or immunosuppressive agents, (4) patients who are diagnosed with influenza viral infection, (5) patients whose SpO₂ is 93% or less under room air condition, (6) patients with hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase is more than five times the upper limit of normal in each medical institution), (7) patients with renal dysfunction (creatinine is more than twice the upper limit of normal in each medical institution), and estimated glomerular filtration rate is less than 30mL/min/1.73m², (8) patients whose peripheral blood neutrophils are less than 1000/µL, (9) patients who have a history of hypersensitivity to macrolide antimicrobial agents, (10) patients who are pregnant or breast feeding, (11) patients who have a history of vaccination against COVID-19 and (12) patients with other conditions that the investigator thinks may render them inappropriate to participate in the study.

Recruitment and consent
The informed consent document (see online supplemental file 1) would be provided to the candidates who meet all of the inclusion criteria and who do not forsake any of the exclusion criteria to provide a comprehensive explanation of this study. Written consent will be obtained. After obtaining consent, the participants will be enrolled in this study.

Random allocation
After obtaining informed consent, eligible patients are randomly assigned in a 1:1:1 ratio to group A (administration of clarithromycin 800mg/day), group B (administration of clarithromycin 400mg/day) or group C (standard treatment without clarithromycin). The randomisation sequence is generated using a computer-based dynamic allocation method with a minimisation procedure to balance the allocation factors (age ≥20 years and less than 40 years, ≥40 years and less than 60 years or ≥60 years) and sex.

Study intervention and observation
All enrolled patients in this study will be hospitalised, since the Infectious Diseases Control Law in Japan designated COVID-19 as category II infectious diseases, which warrants the isolation of the patients, and the COVID-19 infectious disease treatment guidelines by the Ministry of Health, Labour and Welfare in Japan warrant hospitalisation of the patients of COVID-19 with pneumonia. The enrolled patients will be subsequently observed for 7 days for a comprehensive follow-up during the intervention. Patients assigned to group A will commence with 400mg of clarithromycin orally twice daily (after breakfast and supper) following hospitalisation. Patients assigned to group B will commence with 200mg of clarithromycin orally twice daily (after breakfast and supper) following hospitalisation. Patients assigned to group C will commence with the standard care for COVID-19 pneumonia in each medical institution without the administration of clarithromycin following hospitalisation. Since this is an open-label trial, placebo is not used in the group C. In groups A and B, clarithromycin is administered 14 times (twice daily for 7 days). If the administration starts on the morning of day 1 (the day of hospitalisation), clarithromycin will be administered until the evening of day 7. If the administration starts on the evening of day 1, clarithromycin will be administered until the evening of day 8. The study patients are observed on days 1, 2, 3, 4, 5, 6, 7, 8 and 14. The day of hospitalisation is considered the day when observation starts (reference date). During the study intervention period (days 1 to 7 or 8), the patients are not allowed to use macrolide antimicrobial agents, immunosuppressive agents or anticancer agents. Following the completion of the study intervention (day 8), the study patients will be discharged.
day 8 (post-treatment observation period), all the study patients will receive standard care for COVID-19 pneumonia in each medical institution without the administration of clarithromycin.

Table 1 shows the schedule of assessments performed at each observation point, including the mandatory and optional assessments. Inspection of subjects’ characteristics (height, weight, body mass index, onset of COVID-19, detection date of SARS-CoV-2, date of hospitalisation, anamnesis and comorbidity), vital signs (body temperature, systolic blood pressure, diastolic blood pressure, pulse, percutaneous oxygen saturation and frequency of breath), haematology tests (red blood cell, haemoglobin, haematocrit, white cell count, neutrophil, lymphocyte, eosinophil, monocyte, basophil and platelet), general blood biochemical tests (total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-guanosine triphosphate, total cholesterol, total protein, albumin, blood urea nitrogen, creatinine-estimated glomerular filtration rate based on creatinine, lactate dehydrogenase, creatine phosphokinase, brain natriuretic peptide, troponin T, C reactive protein, procalcitonin, ferritin, Na, pH, haemoglobin A1c and glucose), blood coagulation tests (prothrombin time, activated partial thromboplastin time and d-dimer), chest radiography and CT, and inspection of medications of other pharmaceutical agents are conducted by general inspection and interview. The severity of COVID-19 pneumonia is measured by the severity classification according to the COVID-19 infectious disease treatment guidelines by the Ministry of Health, Labour and Welfare in Japan30 (mild: $\text{SpO}_2 \geq 96\%$, no respiratory symptoms or only with coughing without dyspnoea and without pneumonia findings; moderate I: $93\% < \text{SpO}_2 < 96\%$, with dyspnoea and with pneumonia findings; moderate II: $\text{SpO}_2 \leq 93\%$ and oxygen administration required; and severe: admission to intensive care unit or ventilator required), pneumonia severity index31 and A-DROP defined in the guidelines for the management of community-acquired pneumonia in adults released from the Japanese Respiratory Society.32

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Secondary endpoints are as follows: (1) days to recover the body temperature to below 37°C following registration, (2) change in inflammatory cytokines in serum and nasal discharge from baseline, (3) proportion of patients in whom all the clinical symptoms measured by the severity score completely disappeared, (4) proportion of patients in whom each clinical symptom measured by the severity score is improved by 50% or more from baseline, (5) reduction rate of the SARS-CoV-2 from baseline, (6) change in serum immunoglobulin G, immunoglobulin M and immunoglobulin A antibodies from baseline, (7) recovery rate of peripheral blood lymphocytes, (8) proportion of patients with oxygen administration, (9) change in other general blood biomarkers and vital signs from baseline and (10) change in pneumonia image by chest radiography or chest CT. The severity score33 is measured by enquiring the effect of seven pneumonia-related symptoms (cough, shortness of breath, fatigue, headaches, anosmia, dysgeusia and general unwellness) on the patients’ daily life on a 4-point Likert scale (0=not affected, 1=little affected, 2=affected and 3=severely affected), and the number of days required to decrease the total score of the five symptoms by 50% or more from baseline will be analysed for the primary endpoint. The questionnaire for the severity score is shown in the online supplemental table 1.

Data collection, data management and monitoring
A case report form is used for data collection. A central registration number is used to identify the participants for anonymisation. Data collection and management are carried out by third-party entities to avoid bias. Data management is performed by Soiken, Data Management Group (Data Center). To manage and ensure quality, the study is monitored by Soiken, Monitoring Group.

Safety evaluation
During this study, the investigators constantly monitor any AEs through regular medical checkups. All the related AEs, not only side effects to the study agents but also any abnormal clinical laboratory test values and any untoward medical occurrence, are reported and documented. If the AEs meet the following criteria, the events are referred to as serious adverse events (SAEs) based on the ICH E2A, ICH E2D and the ‘Ethical Guidelines for Medical and Health Research Involving Human Subjects’ in Japan34: (1) AEs that result in death, (2) AEs that are life-threatening, (3) AEs that require hospitalisation or prolongation of existing hospitalisation, (4) AEs that result in persistent or significant disability or incapability, (5) other AEs that are medically important or critical, (6) AEs that are equivalent to severe to criteria (1) to (5) and (7) AEs that are congenital abnormality or birth defects. AEs are followed up until normalisation or recovery to a level not considered to be an AE. The first hospitalisation following the registration to day 8 and prolongation of the first hospitalisation after day 8 without worsening of pneumonia-related symptoms are not considered
### Table 1  Schedule of assessments performed at each observation point

<table>
<thead>
<tr>
<th>Observation items</th>
<th>Registration</th>
<th>Study intervention period‡</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Eligibility</td>
<td>☒*</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
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<tr>
<td>2. Patients’ characteristics</td>
<td>☒*</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
</tr>
<tr>
<td>3. Severity of COVID-19 pneumonia</td>
<td>☒*, †</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
</tr>
<tr>
<td>4. Vital signs</td>
<td>☒*, †</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
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<tr>
<td>5. Quantity of oxygen administration</td>
<td>←</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
</tr>
<tr>
<td>6. PCR test for SARS-CoV-2</td>
<td>☒*, †</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
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<tr>
<td>7. Haematology tests</td>
<td>☒*, †</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
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<tr>
<td>8. General blood biochemical tests</td>
<td>☒*, †</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
</tr>
<tr>
<td>9. Blood coagulation tests</td>
<td>☒*, †</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
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<tr>
<td>10. Chest radiography and CT</td>
<td>☒*, †</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
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<tr>
<td>11. Nasal drip tests</td>
<td>☒*</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
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<tr>
<td>12. Special blood tests</td>
<td>☒*</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
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<tr>
<td>13. Medication adherence of study agent</td>
<td>☒*</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
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<tr>
<td>14. Medications of other pharmaceutical agents</td>
<td>←</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
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<tr>
<td>15. Meal intake</td>
<td>←</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
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<tr>
<td>16. Subjective symptoms</td>
<td>←</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
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<tr>
<td>17. Adverse events</td>
<td>←</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
</tr>
<tr>
<td>18. Preservation of blood serum</td>
<td>☒*</td>
<td>Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7 Day 8 Day 14</td>
<td></td>
</tr>
</tbody>
</table>

○=mandatory item; ◊=optional item.
*Data should be obtained before the administration of the study agent in the group A or B.
†Data obtained within 72 hours before consenting can be used in the all groups.
‡Length of hospital stay can be changed based on the subjects’ disease condition.
as AEs/SAEs in this study, since this study enrolled patients of COVID-19 with pneumonia who should be treated by hospitalisation until the complete disappearance of pneumonia-related symptoms, according to the COVID-19 infectious disease treatment guidelines by the Ministry of Health, Labour and Welfare in Japan.²⁹

Statistical analysis
All the tests will be two sided, and a p value of <0.05 will be considered statistically significant. A statistical analysis plan will be developed prior to the database lock. All the statistical analyses will be conducted by independent biostatisticians.

Three analysis sets are defined in this study; the full analysis set (FAS) included all the patients who are registered in this study and assigned to one of the intervention groups. However, patients with a severe protocol violation, such as registration without consent or registration out of the enrolment period, will be excluded from the FAS. The per-protocol set (PPS) excludes patients with a protocol violation from the FAS, such as violation of eligibility criteria, use of prohibited or restricted concomitant drugs, or poor adherence to the study agent (less than 75% or more than 120%). The safety analysis set includes all the patients who are registered in this study and receive at least one dose of the study agent or control treatment.

Patient characteristics at baseline will be presented as frequencies and proportions for categorical data, and summary statistics (number of patients, mean, SD, 95% CI for mean, minimum, the first quartile, median, the third quartile and maximum) for continuous data. Patient characteristics will then be compared using the \( \chi^2 \) test or Fisher’s exact test for categorical endpoints and analysis of variance or Kruskal-Wallis test for continuous variables.

The primary endpoint of this study is the number of days required to improve the clinical symptoms measured by the severity score³³ by 50% or more from the baseline. The primary endpoint will be analysed using the FAS and PPS. The cumulative incidence curves for the days required to improve the clinical symptoms measured by the severity score will be drawn, and a log-rank test with a closed testing procedure will be conducted for comparison among the three groups. In addition, HRs among the groups will be estimated using the Cox proportional hazard model, and a 95% CI will be calculated. The HR adjusted by allocation factors (age and sex) as covariates will also be estimated.

For the secondary endpoints, summary statistics (number of patients, mean, SD, 95% CI for mean, minimum, the first quartile, median, the third quartile and maximum) for measurements, changes from baseline and per cent changes from baseline will be calculated for continuous data. Frequencies and proportions will be calculated for the categorical data. Two-sample t-test or Wilcoxon rank sum test for intergroup comparisons of the continuous data, one-sample t-test or Wilcoxon signed-rank test for intragroup comparisons of the continuous data and the \( \chi^2 \) test or Fisher’s exact test for intergroup comparisons of the categorical data will be performed. Multiplicity will not be adjusted for the secondary endpoints.

For the safety endpoints, summary statistics for the frequency of AEs will be calculated, and Fisher’s exact tests will be performed for intergroup comparisons. Multiplicity will not be adjusted for the safety endpoints.

Patient and public involvement
The patients and the public are not involved in the study, including planning, execution, analysis and evaluation.

Ethics and dissemination
This study and its protocol were approved by the Clinical Research Review Board of Nagasaki University (approval no. CRB20-027) in accordance with the Clinical Trials Act of Japan. The study will be conducted in accordance with the Declaration of Helsinki, the Clinical Trials Act and other current legal regulations in Japan. Written informed consent will be obtained from all participants after a full explanation of the study. The results of this study will be disseminated at medical conferences and through journal publications.

DISCUSSION
This is the first randomised controlled trial to evaluate the efficacy of clarithromycin against COVID-19 pneumonia. Although several in vitro or bioinformatics analyses have reported the positive effect of macrolide antimicrobial agents on coronaviruses,³⁵ evidence in the efficacy of azithromycin to COVID-19 is still controversial,¹⁹ ²⁰ and no clear clinical evidence has confirmed the efficacy of clarithromycin on coronaviruses, especially SARS-CoV-2. Although recent studies demonstrated the usefulness of monoclonal antibody therapy for mild to moderate COVID-19,⁶ ⁷ no treatment strategy has yet been established to prevent exacerbation in patients with mild COVID-19 who do not require oxygen administration. In addition, since the monoclonal antibodies need to be administered to the patients by drip infusion, oral drug treatment could have an advantage, especially for persons receiving treatment or waiting for treatment at home or non-medical accommodation facilities. Development of a proper treatment strategy for patients with mild COVID-19 is important, considering the medical aspects and in social and economic aspects, such as, for example, to reduce the hospital bed occupancy by patients with COVID-19 exacerbation or to suppress the treatment costs for patients with severe COVID-19. Clarithromycin may also contribute to the prevention of secondary infections owing to its antimicrobial/antiviral effects. Therefore, this study aims to evaluate the efficacy of clarithromycin in patients with mild COVID-19 pneumonia who do not require oxygen administration. The results of this study could contribute to the development of new treatment strategies for COVID-19 pneumonia.
Our study has several limitations. First, it is exploratory in nature. Owing to the lack of previous clinical evidence that evaluated the effect of clarithromycin on COVID-19 pneumonia, the target number of enrolled patients is defined based on the feasible number of patients who can give their consent during the planned enrolment period in this study at the participating medical institutions. Second, the target sample size is relatively small. Third, this is an open-label trial. Thus, bias for the patients and investigators/physicians cannot be completely avoided. Fourth, this study is conducted only in medical institutions in Japan and enrolls only Japanese patients. These constraints could limit the generalisability of this study. Further international clinical trials on a larger scale are required in the future.

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Competing interests KYa has received grants from Bayer Yakuhin and has received honoraria for scientific lecture presentations, speaker bureaus, manuscript writing or educational events from AstraZeneca K.K., Kyorin Pharmaceutical, Boehringer Ingelheim Pharmaceuticals, GlaxoSmithKline K.K. and Novartis Pharma K.K. HM has received grants from Taisho Pharmaceutical, Boehringer Ingelheim Pharmaceuticals, Otsuka Pharmaceutical, Shionogi and Kyorin Pharmaceutical, has received honoraria for scientific lecture presentations, speaker bureaus, manuscript writing or educational events from Taisho Pharmaceutical, AstraZeneca K.K., Astellas Pharma, Shionogi, Daiichi Sankyo, Pfizer Japan, MSD K.K., Boehringer Ingelheim Pharmaceuticals and Kyorin Pharmaceutical and has received donation from FUJIFILM Toyama Chemical, Taiko Pharmaceutical, Chugai Pharmaceutical, Daiichi Sankyo, Meiji Seika Pharma, Kyorin Pharmaceutical and Shionogi. All funding agencies play no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The other authors declare no conflict of interest.

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REFERENCES


For patients

Informed Consent Document for

CAME COVID study

“**CAM (Clarithromycin)** Effectivity for **COVID-19** pneumonia which does not require oxygen administration. A multicenter, randomized-controlled, open-label, three-armed parallel group comparison, exploratory trial.”

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Ver.1.1 created: February 18, 2021
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Ver.2.1 created: May 11, 2021
Ver.2.2 created: May 13, 2021
Ver.2.3 created: May 20, 2021
Ver.2.4 created: June 3, 2021
Ver.2.5 created: July 26, 2021

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1. Introduction

This informed consent document aims to explain to you a clinical study “CAM (Clarithromycin) Effectivity for coronavirus disease 2019 (COVID-19) pneumonia which does not require oxygen administration. A multicenter, randomized-controlled, open-label, three-armed parallel group comparison, exploratory trial” (CAME COVID study), which is conducted in the name of the department (name of medical institution).

Clarithromycin is not approved for the treatment of mild COVID-19 that does not require oxygen administration. This clinical trial aims to explore whether clarithromycin is as efficacious for mild COVID-19 as expected.

After hearing a full explanation of this study and understanding the content of the study, you will be given the opportunity to decide whether or not you will participate in this study of your own free will.

If you choose to participate in this study, please sign the informed consent form and give it to one of your attending physicians. If you decide not to participate in this study, you will not suffer any disadvantages in subsequent treatments.

- Withdrawal from participation in this study.

You can withdraw your consent to participate in this study at any time, even after you agree to participate in this study. In case of withdrawal of consent, give the signed consent withdrawal form to one of your attending physicians, or inform them verbally that
you wish to withdraw your consent.

Even if you withdraw your consent to participate in this study, you will not suffer any disadvantages in subsequent treatments. If you withdraw your consent to participate in this study, the information and samples obtained will be discarded.
2. What is a clinical trial?

The current diagnosis and treatment for diseases are established through long-term progress and development. Further progression and development of medical science are important to develop safer and more efficacious treatments. Many experiments and studies are required to develop ways of diagnosing and treating diseases, including investigations using healthy volunteers or patients. Such medical investigations on human subjects are called “clinical trials.”

To conduct clinical trials, human rights and patient safety need to be considered. This study was conducted according to the Clinical Trials Act (rules for preserving human rights and the safety of participating patients). This study was approved by the certified review board below, which has obtained a certification from the Ministry of Health, Labour and Welfare in Japan after a strict examination. This study was approved by the administrator of the medical institution. A summary of the plan of this study was submitted to the Ministry of Health, Labour and Welfare in Japan and registered in the clinical study database (jRCT) established by the Ministry of Health, Labour and Welfare in Japan.

The standard operation procedures, list of committee members, and records of the examination (title of clinical studies, examination results) of the certified review board are publicly available on the website of the Clinical Research Center, Nagasaki University Hospital (http://www.mh.nagasaki-u.ac.jp/research/index.html).
Name of certified review board:

The Clinical Research Review Board in Nagasaki University

Certification number:

CRB7180001

Address:

1-7-1, Sakamoto, Nagasaki, Nagasaki

Tel:

095-819-7229

3. About your disease

COVID-19 causes symptoms such as fever, cough, shortness of breath, and dyspnea if pneumonia occurs. The severity of COVID-19 differs depending on one’s age and underlying health conditions. Elderly and people with chronic diseases (such as severe heart diseases or diabetes mellitus) are more likely to have severe symptoms that can lead to death. Patients with COVID-19 that do not require oxygen administration often spontaneously recover after some time. However, patients with severe COVID-19 may need mechanical ventilation to administer oxygen as part of their treatment plan. Unfortunately, no treatment strategy has been established for COVID-19 pneumonia.
4. Background, purpose, and significance of this study

<Background>

The COVID-19 pandemic is currently a major concern worldwide. In Japan, 932,361 positive cases have been confirmed using a polymerase chain reaction (PCR) test, and 15,190 deaths have been reported by the Ministry of Health, Labour, and Welfare in Japan as of August 1, 2021. The proportion of COVID-19 patients leading to death tends to be lower in Japan than in Western countries. Nevertheless, in Japan, approximately 5% of patients with COVID-19 have required hospitalization, 1.4% have had severe symptoms requiring intensive care, and 1.6% have died. Although dexamethasone was reported to be effective in patients with moderate-to-severe COVID-19, no treatment strategy to prevent exacerbation has been established for patients with mild COVID-19 that do not require oxygen administration.

In this study, we focused on clarithromycin, an antiviral agent that is expected to prevent exacerbations of COVID-19. Clarithromycin has been widely used for general infectious diseases and has been reported to improve symptoms such as coughing, sputum, inflammation, and exacerbation in patients with influenza.

<Purpose>
This study aims to investigate the safety and efficacy of clarithromycin in patients with mild COVID-19 who do not require oxygen administration.

5. Study agent in this study

If you are assigned to the groups in which the study agent is administered, you will be asked to take the following medical agent that has been commercially available and widely used for treating general infectious diseases. For the treatment of general infectious diseases, 400 mg daily is usually administered. For the treatment of pulmonary atypical mycobacteriosis, 800 mg daily is usually administered. The same doses will be administered in this study.

The cost of this study agent is funded by the study and will be provided to you by one of your attending physicians.

<Summary of the study agent in this study>

General name: Clarithromycin
Brand name: Clarith tablets 200
Active constituent: Clarithromycin 200 mg/tablet
Manufacture: Taisho Pharmaceutical Co., Ltd.
Dose and usage: See “Study intervention (treatments)” (page 6).
Administration period: every day for seven days.
6. Methods of this study

(1) Patients who can participate in this study

Patients who meet the following criteria can participate in this study:

1) Patients who were positive for SARS-CoV-2 using either a PCR test or LAMP method within three days before informed consent was obtained.

2) Patients with pneumonia seen on routine chest radiography or chest CT.

3) Japanese patients aged 20 years or older.

4) Patients who give their written consent form to participate in the study.

Patients who met any of the following criteria cannot participate in this study:

1) Patients who have had symptoms for eight days or longer.

2) Patients treated with macrolide antimicrobial agents.

3) Patients treated with steroids (except inhalants) or immunosuppressive agents.

4) Patients diagnosed with influenza.

5) Patients whose SpO₂ is less than or equal to 93% (at room).

6) Patients with hepatic dysfunction. (AST/ALT more than five times the facility standard value or Child-Pugh B/C).

7) Patients with renal dysfunction. (Cre more than twice the facility standard value and eGFR of <30 ml/min)

8) Patients whose peripheral blood neutrophils are less than 1,000/uL.
9) Patients with a history of hypersensitivity to macrolide antimicrobial agents.

10) Patients who are pregnant or breastfeeding.

11) Patients vaccinated against COVID-19.

12) Patients with other conditions that the investigator thinks are inappropriate for them to participate in the study.

The attending physicians will judge whether or not you can participate in this study based on your treatment history, current disease condition, current use of other medical agents, and/or screening test results.

Even if you want to participate in this study, the attending physician may deem that you cannot participate due to the screening test results.

(2) Study intervention (treatments)

The treatment or use of medicinal agents for study purposes is called an “intervention”

This study has three intervention groups. If you agree to participate, you will receive one of the three interventions. Neither you nor the attending physician can select the intervention. See “Randomization and blinding” below for more information on how the different interventions are allocated.
Group A: receive 800 mg clarithromycin daily

If you are assigned to this group, you will receive 400 mg of clarithromycin twice daily (after breakfast and dinner).

Group B: receive 400 mg clarithromycin daily

If you are assigned to this group, you will receive 200 mg of clarithromycin twice daily (after breakfast and dinner).

Group C: receive standard treatment group without clarithromycin

If you are assigned to this group, you will not receive clarithromycin. Instead, you will receive standard care for COVID-19.

The components of this standard care will be explained to you by an attending physician.

<Randomization and blinding>

Participants will be randomly divided into three groups in an approximate ratio of 1:1:1. This grouping method is called “random assignment.” Random assignment is performed using a specific web system on a computer. Neither you nor the attending physician can select the intervention. This means that you may not receive the intervention (treatment).
<Flow of this study>

The flow of this study is shown in the Figure below.
① Obtaining consent

You will be asked to participate in this study if you meet the criteria described on page 5. If you agree to participate in this study, please sign the informed consent form.

② Registration/Random assignment

If you consent to participate in this study, an attending physician will register you onto a specific website for random assignment. Following this, you will be informed which intervention (treatment) you will receive by an attending physician.

③ At the registration or observation point, day one (baseline)
The tests conducted at the registration or observation point on day one (baseline) are as follows:

- Vital signs, PCR tests, general blood tests, special blood tests, chest radiography, computerized tomography, special nasal drip tests, safety information (adverse events*).

*Adverse events are designated as untoward medical events, including worsening of a pre-existing underlying disease.

④ Start of intervention (treatment)/supply of diary

As described on page 6, you will be asked to start receiving the study intervention (treatment) based on your assigned group.

In addition, a diary is supplied to you. Please record the following information every day during the participation period of this study (until observation point day 14).

- Meal intake.
- On a four-point scale, subjective symptoms (cough, shortness of breath, fatigue, headaches, loss of smell, loss of taste, and general unwellness). Since this is important information in this study, please record all symptoms.
- Use of medical agents.
Observation point day four

The tests conducted on days three to five during hospitalization are as follows:

- Vital signs, PCR tests, general blood tests, special blood tests, chest radiography, computerized tomography, special nasal drip tests, and safety information (adverse events).

Observation point day eight

The tests conducted on days seven to nine during hospitalization are as follows:

- Vital signs, PCR tests, general blood tests, special blood tests, chest radiography, computerized tomography, special nasal drip tests, and safety information (adverse events).

Observation point day 14

The ambulatory tests conducted on days 14 to 17 are as follows.

- Vital signs, PCR tests, general blood tests, special blood tests, chest radiography, computerized tomography, special nasal drip tests, and safety information (adverse events).

Sample preservation (serum)
For future study, serum (7 mL × four times) will be obtained and preserved at Nagasaki University Hospital, Department of Respiratory Medicine, for ten years after the end of this study.

(3) Schedule

The tests and investigations in this study will be conducted based on the following schedule.

<table>
<thead>
<tr>
<th>Observation items</th>
<th>Registration</th>
<th>day 1</th>
<th>day 2</th>
<th>day 3</th>
<th>day 4 (≤ 1 day)</th>
<th>day 5</th>
<th>day 6</th>
<th>day 7</th>
<th>day 8 (≤ 1 day)</th>
<th>day 14 (≤ 3 days)</th>
<th>discontinuation</th>
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<td>4. Vital signs</td>
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<td>5. Quantity of oxygen administration</td>
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<td>6. PCR test for SARS-CoV-2</td>
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<td>7. Hematology tests</td>
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<td>10. Chest radiography and computerized tomography</td>
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<td>13. Medication adherence of study agent</td>
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<td>14. Medications of other pharmaceutical agents</td>
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<td>15. Meal intake</td>
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<td>16. Subjective symptoms</td>
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<td>17. Adverse events</td>
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<td>18. Preservation of blood serum</td>
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○ Mandatory item, △ Optional item

* Data should be obtained before administration of the study agent in groups A or B.
** Data obtained within 72 h before consent can be used in all groups.

*** Length of hospital stay can be changed based on the subjects’ disease condition.

(4) Observation items

All tests and investigations will be conducted according to the schedule described above.

1. Eligibility

   Sex, date of birth (age), inclusion and exclusion criteria, and date that consent is obtained.

2. Background characteristics

   Height, weight, BMI, date of COVID-19 onset, date of SARS-CoV-2 detection, date of hospitalization, anamnesis, and comorbidities.

3. Severity of COVID-19

   i) Severity classification according to the COVID-19 Infectious Disease Treatment Guidelines by the Ministry of Health, Labour and Welfare in Japan.
ii) Pneumonia severity index.

iii) A-DROP is defined in the guidelines for the management of community-acquired pneumonia in adults released from the Japanese Respiratory Society.

4. Vital signs

Body temperature, blood pressure, pulse SpO$_2^*$, frequency of breath

*SpO$_2$ is recorded daily during hospitalization.

5. Quantity of oxygen administration

Daily quantity of oxygen administration during hospitalization.

6. PCR test for SARS-CoV-2

The nasal mucosa is sampled by nasopharynx swabbing. The viral load of SARS-CoV-2 will be tested by PCR to amplify the viral gene.

7. Hematology testing

Red blood cells, hemoglobin, hematocrit, white blood cells, neutrophils, lymphocytes, eosinophils, monocytes, basophils, and platelets.
8. General blood biochemical tests

Total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-guanosine triphosphate, total cholesterol, total protein, albumin, blood urea nitrogen, creatinine, estimated glomerular filtration rate based on creatinine, lactate dehydrogenase, creatine phosphokinase, brain natriuretic peptide, troponin T, C-reactive protein, procalcitonin, ferritin, Na, pH, HbA1c, and glucose.

9. Blood coagulation tests

Prothrombin time, activated partial thromboplastin time, and d-dimer.

10. Chest radiography and computerized tomography

Condition of pneumonia.

11. Nasal drip tests

Interleukin (IL)-1beta, IL-6, IL-8, IL-10, IL-17, tumor necrosis factor-alpha, interferon-gamma, beta-defensin, granulocyte-macrophage colony-stimulating factor, and immunoglobulin A.
12. Special blood tests

Cytokines, chemokines, IL-33, immunoglobulin M, immunoglobulin G, and immunoglobulin A.

13. Medication adherence of study agent

You are asked to record whether you take clarithromycin every day in a diary.

14. Other pharmaceutical agents/medications

Use of pharmaceutical agents other than clarithromycin.

15. Meal intake

You are asked to record your meal intake every day in the diary provided.

16. Subjective symptoms

You are asked to record your subjective symptoms (cough, shortness of breath, fatigue, headaches, loss of smell, loss of taste, and general unwellness) on a four-point scale every day in a diary.

17. Adverse events

During the observation period of each participant, information on adverse events
(any untoward medical events, including the worsening of a pre-existing underlying disease) will be collected.

(5) Prohibited drugs

The following drugs are prohibited during participation in this study:

- Macrolide antimicrobial agents
- Immunosuppressive agents
- Anticancer agents

If severe risk is expected by prohibiting the drugs above, the attending physician will take appropriate measures, such as discontinuation of the study intervention.

(6) Restricted drugs and treatments

No drug or treatment is restricted in this study.

However, please tell your attending physician if you need to start taking a new drug or treatment.

(7) Participation period

If you agree to participate in this study, the participation period will be 14 days (+ three days).

If you withdraw your consent, your participation will end at the time of withdrawal.
(8) Discontinuation of study in each participant

If any of the following occurs, your participation in this study may be discontinued, even after you agree to participate in this study:

1) When you voluntarily want to discontinue the study or withdraw consent to participate in this study.

2) If the attending physician identifies a significant issue after the registration that may affect the study.

3) When the continuation of the study agent is judged not to be appropriate due to worsening of the primary disease or complications.

4) When continuation of the study is judged to be difficult due to the occurrence of any adverse events.

5) If pregnancy is found.

6) When investigators judge that discontinuation of the study is appropriate due to other reasons.

<Measurements after discontinuation>

If your participation in this study is discontinued, data obtained until discontinuation will be used. In addition, even if your participation in the study is discontinued, follow-up observations will be frequently conducted to ensure your safety.
(9) Treatment after the participation period

If further treatment for COVID-19 is required after discharge from the hospital or after the observation period of this study, standard treatment will be provided to you.

(10) Provision of test results

You can review your test results obtained in this study if you ask your attending physician.

7. Other treatments

Many types of drugs other than the study agent in this study are available for COVID-19, and various treatment methods have been tested for COVID-19. However, no treatment strategy has yet been established for COVID-19.

If you do not participate in this study, the standard treatment for COVID-19 will be provided to you. Ask the attending physician for details on this standard treatment.

8. Study execution period

(1) Study execution period.

From the date of publication of this study on JRCT to July 31, 2022.
(2) Patient enrollment period:

From the date of publication of this study on jRCT to February 28, 2022.

9. Number of participants

We plan to enroll 60 patients in this study.

10. Expected benefits, burden, and side effects

(1) Expected benefits

If you participate in this study, nasal drip tests and special blood tests will be performed. The fees for these tests will be funded by the study. Thus, participating in this study could reduce your financial burden.

In addition, since the attending physicians review your condition more carefully than usual, you may receive more thorough treatment than if you do not participate in this study.

Furthermore, since the results of this study may contribute to the future treatment of patients with COVID-19, your participation in this study may benefit society as a whole.

(2) Expected burden
If you participate in this study, you need to be hospitalized for about eight days as a general health insurance treatment. In addition, several tests are required to be conducted as part of this study (PCR, nasal drip, and special blood tests). PCR tests will be conducted at registration or observation point day one (baseline), observation point day four, and observation point day eight (three times). Nasal drip tests will be conducted at registration or observation point day one (baseline), observation point day four, observation point day eight, and observation point day 14 (four times). For the special blood tests, an additional 7 mL/time of blood will be collected in addition to general blood collection at registration or observation point day one (baseline), observation point day four, observation point day eight, and observation point day 14 (four times). If you feel unwell during the tests, the tests will be immediately discontinued, and appropriate measures will be taken. Furthermore, for the preservation of serum for future studies, an additional 7 mL/time of blood will be collected at registration or observation point day one (baseline), observation point day four, observation point day eight, and observation point day 14 (four times).

Since random assignment is conducted, you may not receive the treatment you would prefer.

In addition, clarithromycin administration may cause side effects, as described below. You also need to record your meal intake and subjective symptoms in a diary every day during your participation period.
(3) Expected side effects

<Known severe side effects of clarithromycin>

(from the package insert of Clarith tablets 200; version September 2, 2020)

Shock, anaphylaxis (frequency unknown), QT prolongation, ventricular tachycardia (including torsades de pointes), ventricular fibrillation (frequency unknown), fulminant hepatitis, hepatic dysfunction, jaundice, hepatic failure (frequency unknown), thrombocytopenia, pancytopenia, hemolytic anemia, leukopenia, agranulocytosis (frequency unknown), toxic epidermal necrolysis (TEN) (frequency unknown), TEN, Stevens-Johnson syndrome group, erythema multiforme (frequency unknown), PIE syndrome group, interstitial pneumonia (frequency unknown), pseudomembranous colitis, hemorrhagic colitis (frequency unknown), rhabdomyolysis (frequency unknown), seizure (frequency unknown), IgA vasculitis (frequency unknown), and drug-induced hypersensitivity syndrome group (frequency unknown).

Other side effects that are not described above may also occur. If you notice anything unusual, please inform your attending physician.

If any information that may affect your decision to continue participating in this study becomes apparent during the participation period, we will immediately inform you. In such
cases, you may be asked to sign a further informed consent form.

11. Compensation against health hazards

This study has been scientifically planned based on previous studies and will be carefully conducted. If any health hazards, such as side effects, occur during or after the study, an attending physician will provide appropriate treatment. If you notice anything unusual, please inform your attending physician.

This study is covered by “clinical research insurance” in case of emergency. Suppose you suffer health problems because of participating in this research, and it is determined that there is a causal relationship with this research (or that a causal relationship cannot be denied). In that case, the clinical research insurance will provide monetary compensation to you or your family for death, permanent disability, or medical expenses and benefits necessary to treat the health problems. In addition, the principal investigator and subcontracting physicians will be covered by the physician’s liability insurance in case of any negligence issues. However, health damage caused by intentional or gross negligence may not be covered, or compensation may be limited.
12. Your financial burden and remuneration

<Your financial burden>

You need to receive treatment while hospitalized for about eight days as general health insurance treatment. The days of hospitalization may change based on the disease condition. The fees for the tests required and the study agent (clarithromycin) are funded by this study.

<Remuneration>

For participating in the study (tests and diary recording), you will receive 5,000 yen after observation point day eight (at discharge) and observation point day 14 (ambulatory tests) (a total of 10,000 yen) on a QUO card.

13. Information about this study

If you want to know more information about this study (study plan or other relevant information), this can be provided to you except for the personal information of other participants or the information that may affect the study execution. Please ask your attending physician if you require further information.

A summary of the study plan is also publicly available at jRCT
(https://jict.nipph.go.jp/). Personal information will continue to be protected, even when the results of this study are published.

14. Protection of personal information

To protect personal information, a number (so called “central registration number”) will be assigned to each participant. This central registration number is used for all information or samples in this study (anonymization). A table will be used to identify you and your central registration number. This table will be stored only at this medical institution and will not be supplied to other medical institutions.

To ensure that this study is conducted properly, monitoring/auditing staff or staff from the Ministry of Health, Labour, and Welfare may survey your medical records directly. Such monitoring and auditing is conducted in accordance with the Personal Information Protection Act, and private information (name, address, and telephone number) is protected. By signing the informed consent form of this study, you consent to your records being audited in the future.

The results of this study may be published at scientific meetings, in articles, or in documents that need to be submitted to the Ministry of Health, Labour and Welfare. However, identifiable information will not be provided outside of this medical institution.
15. Provision and storage of information and samples

(1) Provision of information and samples

This is a multicenter study.

The information obtained in this study will be stored at a third-party data center (Soiken Inc.). Your information will be collected using a central registration number, as is described in ‘14. Protection of personal information’.

The samples obtained in this study (nasal drip, blood, PCR test samples) will be sent to the test department at Nagasaki University Hospital to measure the levels of inflammatory cytokines. Samples or images of chest radiography and computerized tomography will be collected using the central registration number, as is described in ‘14. Protection of personal information’.

Your personal information will not be disclosed to anyone outside of this medical institution.

(2) Storage of information and samples

Your samples obtained in this study (nasal drip, blood, PCR test samples) will be sent to the test department at Nagasaki University Hospital to measure the levels of inflammatory cytokines. Samples will then be stored at the Department of Respiratory Medicine, Nagasaki University Hospital, for ten years.
Appropriate measures will be taken to avoid personal information being disclosed to others outside our medical institution when discarding the samples.

All information is stored during the study and five years after the end of this study. After the end of the storage period, all information, including your data, will be anonymized and destroyed physically or electromagnetically.

16. Secondary use of samples obtained in this study

Since blood samples obtained from you in this study may be important for future medical studies, your blood sample (serum) will be stored for ten years after the end of this study. If the samples are secondarily used for future studies, protocols for the studies will be developed and then reviewed by an appropriate institutional review board.

After the end of the storage period, Nagasaki University Hospital will discard the samples according to the rules of our institution.

17. Discontinuation of the whole study

Even after participating in this study, the study itself could be discontinued in the following cases:

1) Critical information about the quality, safety, and efficacy of the study agent is
obtained.

2) The recruiting of study subjects is difficult, and the planned number of study subjects to be enrolled is challenging to achieve.

3) If the study results can be expected before the achievement of the planned number of study subjects, based on the purpose or contents of this study.

4) The purpose of this study was achieved before the achievement of the planned number of study subjects or before the end of the study execution period.

5) When a protocol modification is required but unable to be executed.

18. Things you need to comply with during the study

To ensure your safety and the collection of accurate information, please comply with
the following during the study:

- Take the study agent in accordance with the dose and usage instructions of the attending physician.
- Record your medication, meal intake, and your subjective symptoms in your diary every day.
- If you are taking any medical agents prescribed by another department or institution or over-the-counter drugs bought at a pharmacy, please inform your attending physician.
- When you want to discontinue the study or withdraw your consent to participate in this study, at any time, even before or after the start of the study intervention (treatment), inform the attending physician as soon as possible.
- Visit the medical institution and take the required tests and examinations on the date and time instructed by your attending physician.
- If you receive a consultation from another department or institution, please inform your attending physician. In addition, please inform your attending physician before any such consultations, if possible.
- **If you notice anything unusual (including bone fracture or accident), inform one of the attending physicians as soon as possible.**
19. Conflicts of interest and source of study funding

(1) Conflict of interest

Conflict of interest refers to a situation in which a third-party may be concerned that research is not being conducted fairly and appropriately, such as falsification of research data or preferential treatment of a specific company, due to financial interests with an outside party.

The principal investigator of this study, the responsible investigator and sub-investigators in each medical institution for conducting the study, and other persons related to this study have reported any such conflicts of interest. The management standards of the conflict of interest and management plan of the conflicts of interest identified have been submitted, inspected, and approved by the Clinical Research Review Board of Nagasaki University.

(2) Funder of this study

This study was financially supported by Taisho Pharmaceutical Co., Ltd. (3-24-1, Takada, Toshima-ku, Tokyo). Taisho Pharmaceutical Co., Ltd. was not involved in this study, including its planning, execution, data management, statistical analysis, evaluation, or write-up.
20. Intellectual property rights

The results of this study may result in intellectual property rights such as patent rights. However, the principal investigator will own any such intellectual property rights, not the participants.

21. Study organizations

« Principal investigator »

Prof. Hiroshi Muke

Department of Respiratory Medicine, Nagasaki University Hospital

Address: 1-7-1, Sakamoto, Nagasaki, Nagasaki

Tel: 095-819-7271

« Collaborating medical institutions and responsible investigators »

<table>
<thead>
<tr>
<th>Medical institution</th>
<th>Responsible investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagasaki University Hospital</td>
<td>Hiroshi Muke</td>
</tr>
<tr>
<td>1-7-1, Sakamoto, Nagasaki, Nagasaki</td>
<td></td>
</tr>
<tr>
<td>095-819-7271</td>
<td></td>
</tr>
<tr>
<td>Nagasaki Harbor Medical Center</td>
<td>Toyomitsu Sawai</td>
</tr>
<tr>
<td>Address</td>
<td>Person</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>6-39, Shinchi-machi, Nagasaki, Nagasaki</td>
<td>Yuichi Fukuda</td>
</tr>
<tr>
<td>095-822-3251</td>
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<tr>
<td>Sasebo City General Hospital</td>
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<td>9-3, Hirase-machi, Sasebo, Nagasaki</td>
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<tr>
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<tr>
<td>Japan Community Health care Organization</td>
<td>Makoto Sumiyoshi</td>
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<td>Isahaya General Hospital</td>
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<td>24-1, Eisyo-Higashi-machi, Isahaya, Nagasaki</td>
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<td>Japanese Red Cross Nagasaki Genbaku Hospital</td>
<td>Kohji Hashiguchi</td>
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<tr>
<td>3-15, Shigesato-cho, Nagasaki, Nagasaki</td>
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<tr>
<td>095-847-1511</td>
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<tr>
<td>Hospital of the University of Occupational and Environmental Health, Japan</td>
<td>Kei Yamasaki</td>
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<tr>
<td>1-1, Iseigaoka, Yahata-Nishi-ku, Kitakyushu, Fukuoka</td>
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<td>Kitakyusyu City Yahata Hospital</td>
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<td>2-6-2, Ogura, Yahata-Higashi-ku, Kitakyusyu, Fukuoka</td>
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<th>Fukuoka University Chikushi Hospital</th>
<th>Hiroshi Ishii</th>
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<th>Yoji Fusuki</th>
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<td>2-5-1, Katafuchi, Nagasaki</td>
<td></td>
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<tr>
<td>095-826-9236</td>
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</table>

22. Contact details

If you would like more information or have any concerns, do not hesitate to contact the following:

Person in charge: ____________________________

Department: _________________________________
23. Consultation regarding your opinions and complaints

____________________ established a consultation service for patients and their families (excluding medical treatments and contents of the clinical study).

Consultation service: __________________________

Address: __________________________

Tel: __________________________
Informed Consent Form

CAME COVID study

“CAM (Clarithromycin) Effectivity for COVID-19 pneumonia which does not require oxygen administration. A multicenter, randomized-controlled, open-label, three-armed parallel group comparison, exploratory trial.”

<Contents to be explained>

1. Introduction 13. Information about this study
2. What is a clinical trial? 14. Protection of personal information
3. About your disease 15. Provision and storage of information and samples
4. Background, purpose, and significance of this study 16. Secondary use of samples obtained in this study
5. Study agent in this study 17. Discontinuation of the whole study
6. Methods of this study 18. Things you need to comply with during the study
7. Other treatments 19. Conflicts of interest and source of study funding
8. Study execution period 20. Intellectual property rights
9. Number of participants 21. Study organizations
10. Expected benefits, burden, and side effects 22. Contact details
11. Compensation against health hazards 23. Consultation regarding your opinions and complaints
12. Your financial burden and remuneration

● I have explained the study to the patient.

Date of explanation: ____________________
Signature of explainer: ______________________

• I received a full explanation of the study, have understood its aim, what is expected, and agree to participate in this study of my own free will.

I received the informed consent documents and a copy of this informed consent form.

Date of consent: ______________________

Your signature: ______________________
Consent Withdrawal Form

________________________

________________________

CAME COVID study

“CAM (Clarithromycin) Effectivity for COVID-19 pneumonia which does not require oxygen administration. A multicenter, randomized-controlled, open-label, three-armed parallel group comparison, exploratory trial.”

● Although I received a full explanation of the study and initially agreed to participate, I would now like to withdraw my consent.

Date of withdrawal: _______________________

Your signature: _______________________

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I confirm that the patient signed the above form to withdraw their consent.

Date of confirmation: __________________________

Signature of physician: __________________________
Supplementary Table 1 Questionnaire for the Severity Score

<Subjective symptoms>

How are you affected by the following symptoms on your daily activities, compared with before the infection of new coronavirus?

Select only one option in each symptom.

<table>
<thead>
<tr>
<th>Subjective symptoms</th>
<th>Cough</th>
<th>Shortness of breath</th>
<th>Fatigue</th>
<th>Headaches</th>
<th>Loss of smell</th>
<th>Loss of taste</th>
<th>General unwellness</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>□ 0: not affected, □ 1: little affected, □ 2: affected, □ 3: severely affected</td>
<td>□ 0: not affected, □ 1: little affected, □ 2: affected, □ 3: severely affected</td>
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