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STUDY PROTOCOL

Efficacy of Donepezil for Fatigue and Psychological Symptoms in Post-COVID-19 Condition: Study Protocol for a Multicenter Randomized, Placebo-controlled, Double-blind Trial

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ABSTRACT

BACKGROUND

Approximately 30% of coronavirus disease 2019 COVID-19 patients develop fatigue and psychological symptoms. We previously demonstrated the efficacy of donepezil, an acetylcholinesterase inhibitor that is widely used to treat dementia, in basic research.

METHODS

This is a multicenter, double-blind, randomized, controlled, phase II clinical trial in which 120 patients with COVID-19 will be randomized in a 1:1 ratio to a donepezil or placebo group. Inclusion criteria are as follows: (1) Adult. (2) With COVID-19 infection who had an upper respiratory tract infection, fever, or cough in the acute phase. (3) With a global binary fatigue score ≥4 on the Chalder Fatigue Scale assessment (4) Within 52 weeks of the onset of COVID-19. (5) Patients who provide consent themselves. In the donepezil group, a low dose (3 mg/day) is administered for the first week and is increased to 5 mg/day for 2 weeks. The control group receives placebo for 3 weeks. The primary endpoint is a change in and the absolute value of the Chalder Fatigue Scale score after 3 weeks of treatment. Secondary endpoints are a change in and the absolute value of the Chalder Fatigue Scale score after 8 weeks of treatment, the other mental scores after 3 and 8 weeks of treatment, a symptom survey, adverse events, and medication compliance rate.

RESULTS

This study protocol is ongoing and the results will be analyzed in April 2024.

CONCLUSIONS

The off-label use of donepezil at the default dose for dementia has potential for the treatment of post-COVID-19 condition.

KEY WORDS

Donepezil, depression, fatigue, COVID-19, acetylcholine

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INTRODUCTION

The coronavirus disease 2019 COVID-19 pandemic is a major social problem that continues to pose a threat worldwide. Some patient groups present with multiple systemic symptoms, both physical and psychological, a long period of time after acute phase symptoms, such as acute respiratory failure and fever[1]. Symptoms that persist 12 weeks after the onset of COVID-19 are defined as Post-COVID-19 condition (PCC)[2], and the WHO identifies this condition as long COVID[3]. PCC has enormous negative social and economic effects by depriving patients of their vitality and increasing the difficulty of reintegrating into society. Previous studies on PCC indicated that approximately 30% of COVID-19 patients developed fatigue and psychological symptoms, such as anxiety and depression, in the first 6 months after its onset[4,5]. Fatigue and the psychological symptoms of PCC occur regardless of the severity of acute phase symptoms or vaccination[6]. Therefore, even after the development of a vaccine and treatment during the acute phase, the number of patients with psychiatric symptoms is expected to increase concomitantly with the number of infected patients[5,7]. However, there are several promising options for PCC[8,9], but since an effective treatment has not yet been established, the development of effective pharmacological treatments is a pressing issue worldwide[10].

In our previous basic research[11], S1 protein, one component of COVID-19 virus, decreased intracerebral acetylcholine production via intranasal administration in a mouse model of COVID-19 infection, which linked to brain inflammation and clinical symptoms of malaise/depression. In this model, donepezil, the cholinesterase inhibitor, decrease brain inflammation and improve clinical symptoms, even with converted dose which were usually used for dementia[11]. Herein, we hypothesized that donepezil would be effective for PCC, especially for fatigue and the psychological symptoms, and conducted this randomized control trial in the patients after COVID-19 infection.

Furthermore, as a novel approach, we designed this trial to include eConsent, online medical care, and home visits. To allow patients to participate in the clinical trial even during the COVID-19 isolation period, we obtain consent with eConsent. In addition, patients will be followed up on the specified items after the administration of the study drug either by telemedicine using online medical services or by home-visit medical services.

AIMS/OBJECTIVES

The purpose is to investigate the efficacy of donepezil versus a placebo for fatigue and psychological symptoms, which are frequently observed in PCC. Based on our previous basic research[11], we developed the present trial with the off-label use of donepezil.

METHODS

FUNDING/SUPPORT

The present study was supported by the Research Program on Emerging and Re-emerging Infectious Diseases of the Japan Agency for Medical Research and Development under Grant Numbers JP21fk0108486 and JP22fk0108512.

COORDINATION AND CONDUCT OF THE TRIAL

The principal investigator and study coordinator is Kensuke Nakamura, Yokohama City University. The biomarker researcher is Kazuhiro Kondo, The Jikei University School of Medicine. The statistical analysis manager is Tadahiro Goto, TXP Medical Corporation. Shigeki Fujitani, St. Marianna University School of Medicine, plays a role in coordination and study management. The investigators constitute the trial steering committee. The monitoring committee is established by Dee-Lites Corporation. Central monitoring is performed by monitors belonging to Dee-Lites.

DESIGN AND SETTING

This trial registration data is shown in **Table 1**. This is a multicenter, placebo-controlled, double-blind, superiority, 1;1 allocated, randomized, phase II clinical trial to demonstrate the efficacy of donepezil for mild to moderate COVID-19 with fatigue symptoms. This study was supported by the Research Program on Emerging and Re-emerging Infectious Diseases of the Japan Agency for Medical Research and Development under Grant Numbers JP21fk0108486 and JP22fk0108512.

PARTICIPATING FACILITIES

This trial is conducted at the following 6 medical institutions in Japan: St. Marianna Medical University Hospital; a university hospital, Kawasaki City Tama Hospital; a city-run hospital, Hitachi General Hospital; a private hospital, Hirahata Clinic; a private clinic, Ohisama Home Clinic and Yushokai Home Clinic Shinagawa; home-visit medical clinics.

Table 1 Trial registration data

Data category	Information
Trial identifying number	The Japan Registry of Clinical Trials jRCT 2031220510
Date of registration in primary registry	14 December, 2022
Source(s) of monetary or material support	the Japan Agency for Medical Research and Development (AMED): JP21fk0108486, JP22fk0108512
Contact for public queries	Kensuke Nakamura, M.D., Ph.D. e-mail:knakamura-tky@umin.ac.jp
Contact for scientific queries	Trial office (Yokohama City University Hospital, Japan) e-mail:info@dnpac.jp
Public title	Efficacy of donepezil for fatigue and psychological symptoms in post-COVID-19 syndrome: Study protocol for a multicenter randomized, placebo-controlled, double-blind trial
Scientific title	Drug repositioning of donepezil for the treatment of post-COVID-19 syndrome.—Repositioning of donepezil for the treatment of psychological symptoms—.
Countries of recruitment	Japan
Health condition(s) or problem(s) studied	Post-COVID-19 syndrome, fatigue and psychological symptoms

Table 2 Trial summary

Data category	Information
Intervention(s)	Active comparator: *Donepezil* (3 mg/day for 1 week, followed by 5 mg/day for 2 weeks) Placebo comparator: Lactose (0.6 g/day for 1 week, followed by 1 g/day for 2 weeks, containing no active ingredients)
Key inclusion and exclusion criteria	Ages eligible for study: ≥20 years, <75 years Sexes eligible for study: both Accepts healthy volunteers: no Inclusion criteria: (1) Adult. (2) With COVID-19 infection who had an upper respiratory tract infection, fever, or cough in the acute phase. (3) With a global binary fatigue score ≥4 on the Chalder Fatigue Scale (CFS) assessment during the previous observation period. (4) Within 52 weeks of the onset of COVID-19. (5) Patients who provide consent themselves. Exclusion criteria: respiratory disease (Hugh-Jones class ≥2); heart failure (NYHA class ≥2); on dialysis or likely to start dialysis; cirrhosis (Child-Pugh class C); pregnant women; with influenza infection; already taking donepezil or anticholinesterase inhibitors; already participated in this study; judged to be ineligible by the investigator; considered to be at risk of suicide.
Study type	A Interventional, multicenter, placebo-controlled, double-blind (subject, investigator), randomized, phase II clinical trial. Primary purpose: treatment
Recruitment status	Recruiting since October 2022, target sample size 120.
Primary outcome(s) Key secondary outcomes	Primary outcome: a change in and the absolute value of the Chalder Fatigue Scale score after 3 weeks of treatment.
Secondary outcomes:(1) a change in and the absolute value of the Chalder Fatigue Scale after 8 weeks of treatment, (2) the HADS score, (3) IES-R score, (4) EQ-5D-5L score, and (5) PHQ-9 score after 3 and 8 weeks of treatment, (6) a symptom survey, (7) adverse events, and (8) medication compliance rate.	

STUDY POPULATION

This trial summary is shown in **Table 2**. Eligible patients are adults with COVID-19 with fatigue symptoms, who have not been treated with mechanical ventilation or admitted into intensive care units in the acute period of COVID-19. Inclusion criteria are as follows: 1) patients aged between 20 and 75 years at the time of consent; 2) patients with COVID-19 infection who had an upper respiratory tract infection, fever, or cough in the acute phase; 3) With a global binary fatigue score ≥4 on the Chalder Fatigue Scale CFS assessment during the previous observation period before intervention; 4) patients with a positive COVID-19 antigen or polymerase chain reaction test and within 21 days from the onset of COVID-19 to randomization; 5) patients providing consent themselves.

We investigated herpes virus-6 reactivation, a candidate cause of prolonged sequelae in our group's study. A total of 61% of patients with prolonged PCC became positive for the Small protein encoded by the Intermediate stage Transcript of human herpesvirus-6-1 SITH-1 antibody within one year (7.3% positive rate in healthy individuals), and SITH-1 also exerted inflammatory effects in the brain. Therefore, Item 4), the period from the onset of COVID-19 to randomization, was revised to expand the period from "within 21 days" to "within 52 weeks" in order to increase the number of eligible patients on February 13, 2023. Similarly, Item 2), "those who did not had a fever >38.0°C for 24 hours.", was deleted to remove the condition of post-fever resolution and revised to not require the presence of fever resolution.

Complications to be excluded were set as follows: Patients with a previous diagnosis or suspected diagnosis of psychiatric disorders or chronic fatigue syndrome relevant to F0–F3 in International Statistical Classification of Diseases and Related Health Problems-10; respiratory disease (Hugh-Jones class ≥2); heart failure (New York Heart Association class ≥2); on dialysis or likely to start dialysis; cirrhosis (Child-Pugh class C); pregnant women; with influenza infection; already taking donepezil or anticholinesterase inhibitors; patients who are unable to answer the questionnaire in person (including those with cognitive decline); allergy to any component of the investigational drug; history of hypersensitivity to piperidine derivatives and already participated in this study. Patients judged to be ineligible by the investigator will also be excluded. Treatment introduced in the acute phase of COVID-19 is not relevant into inclusion. Patients who answered "yes" to The Columbia Suicide Severity Rating Scale question on suicidal ideation during the pre-evaluation period undergo a consultation with a psychiatrist and are excluded if considered to be at risk of suicide.

RANDOMIZATION

Patients diagnosed with mild to moderate COVID-19 are screened for eligibility by the investigator or sub-investigator. After confirming eligibility, patients are randomized using a computer-generated, online response system to donepezil or placebo in a 1:1 ratio.

STUDY INTERVENTIONS

The outline of this study protocol is shown in **Fig. 1** and the schedule is shown in **Table 3**. Participants with a positive COVID-19 antigen test or polymerase chain reaction assay receive the standard treatment if necessary. Patients are evaluated for eligibility within 52 weeks from the onset of COVID-19, consent will be obtained, and they will be enrolled and randomized in a 1:1 ratio to the donepezil or placebo group. This trial will be performed in a double-blind manner until its completion. Consent may be obtained even during COVID-19 treatment, and

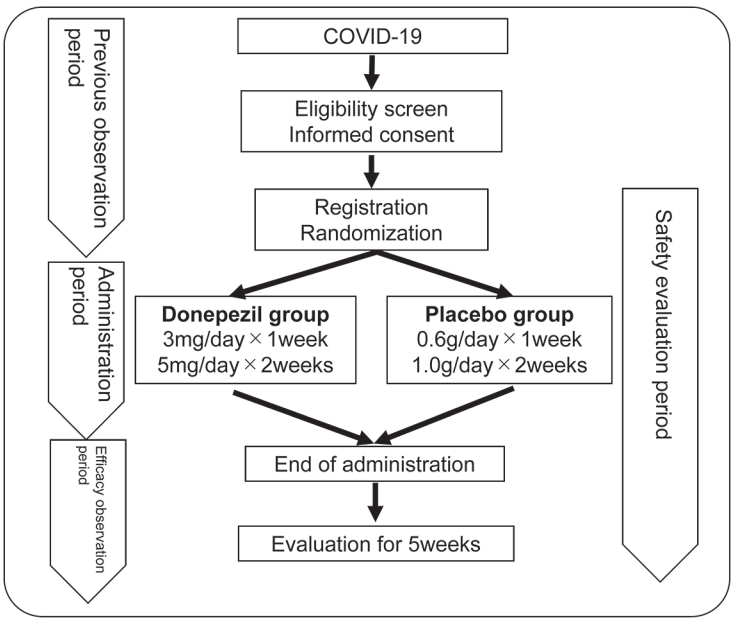

Fig. 1 **Study outline**

participants in isolation may provide their consent via eConsent. After registration, the investigator performs blood tests and collects the participant's condition and vital signs. For participants in isolation, these surveys will be conducted via telemedicine or home visits. By utilizing telemedicine, patients at home receive the investigational drug or placebo medication by mail for 3 weeks from the date of assignment. Outcome symptom surveys are evaluated based on the CFS, Hospital Anxiety and Depression Scale HADS, Impact of Event Scale-Revised IES-R, EuroQol-5Dimention-5Level EQ-5D-5L, and Patient Health Questionnaire PHQ-9. Since our previous report showed sufficient efficacy at 3 weeks after the start of study drug administration, the primary outcome survey is conducted at 3 weeks. Secondary outcome surveys are also conducted at 8 weeks for evaluation of sequelae over time as a follow-up assessment. Adverse event assessments are conducted on the start date and 1, 3, and 8 weeks after the start of treatment. The evaluation is conducted at the hospital if the patient is able to come to the hospital. Follow-ups may also be conducted via telemedicine or home visits. Remote assessments are limited to when the items specified in **Table 3** are feasible, and if they are not, the investigator instructs the participant to come to the hospital if necessary.

Donepezil group

A low dose of 3 mg is administered once daily for one week. If no adverse events are observed or the dose is tolerated at that time, it is increased to 5 mg once daily for 2 weeks. This is the default dosage for dementia in Japan. Based on the results of our basic studies[11], we consider that sufficient efficacy may be assessed.

Table 3 Event schedule

Period	Previous observation	Administration		Efficacy evaluation		
TIMEPOINT	Previous observation	Drug prescription	1 week	3 weeks	8 weeks	At discharge
±Tolerable range (days)		1	7 (−3)	21 (−2~+1)	56 (±7)	
ENROLLMENT:						
Eligibility screen	○	○				
Informed consent	○					
Background survey	○					
Vaccination history	○					
Symptoms of COVID-19	○			●	●	
Height•Weight	○					
Vital signs	○					
Saturation	○					
Blood test	○			●	●	
Biomarker	○					
INTERVENTIONS:						
Drug prescription		○				
ASSESSMENTS:						
Outcome survey	○			●	●	
C-SSRS	○			●	●	
Adverse events survey		●	●	●	●	●
Drug recovery				●		●

Items marked with ○ are to be performed before the start of the investigational drug administration. Items marked with ● are to be performed after the start of the investigational drug administration. Outcome symptom surveys are evaluated based on the Chalder Fatigue Scale, Hospital Anxiety and Depression Scale, Impact of Event Scale-Revised, EuroQol-5Dimention-5Level, and Patient Health Questionnaire.

Placebo group

The control group takes 0.6 g lactose once daily for 1 week, followed by 1 g lactose once daily for 2 weeks as the placebo.

Strategies to improve adherence to interventions

Unused investigational drugs, empty boxes, and empty bags are collected at the 3-week visit after the start of administration to check the medication status. If the patient cannot visit the clinic, the medication is collected by mail. If the study is discontinued, the medication is collected at that time. If the medication compliance rate is <80%, it is treated as a deviation.

Relevant concomitant care permitted or treatments prohibited during the trial

The concomitant use of the following drugs, which may have an impact on the effects of donepezil through drug-drug interactions, is prohibited: antiepileptic drugs, antipsychotics, antidepressants, anxiolytics, central stimulants, antiparkinsonian drugs and antipyretics, within 24 hours prior to the investigation of outcome symptoms in the previous observation period. Prohibited therapies are repetitive transcranial magnetic stimulation therapy and epipharyngeal abrasive therapy.

STUDY OUTCOMES

The investigation on outcome symptoms (CFS, HADS, IES-R, EQ-5D-5L, and PHQ-9) is conducted online in Weeks 3 and 8 using questionnaires. The investigator confirms the answers.

Primary outcome

The primary endpoint is a change in and the absolute value of the CFS score, an 11-item scale designed to measure the severity of fatigue. Each item is rated on a 4-point scale, and participants are asked to select the most appropriate response. Note that since a binary score is used in this trial, scores of 0 and 1 are counted as score 0 and scores of 2 and 3 as score 1. The primary endpoint is assessed at 3 weeks after the start of treatment.

Secondary outcome

Secondary endpoints were set as follows. (1) A change in and the absolute value of the CFS score (set as the primary endpoint, an 11-item scale to measure the severity of fatigue) 8 weeks after the administration. The other endpoints are a change in and the absolute value of each of the following four scores 3 and 8 weeks after administration: (2) HADS score (a simple 14-item questionnaire to assess mental anxiety and depression), (3) IES-R score (a 22-item questionnaire to measure posttraumatic stress symptoms), (4) EQ-5D-5L score (a questionnaire and visual analog scale to quantify the health status of a participant), (5) PHQ-9 score (a 9-item questionnaire to screen for the presence and severity of depression). The remaining three are (6) a symptom survey including fatigue (to assess the presence and severity of symptoms associated with COVID-19 infection, such as cough, sputum, and fever during the pre-treatment period, 3 and 8 weeks after starting the treatment, (7) adverse events due to study drug use (including the worsening of depression, arrhythmia, and peptic ulceration, collected at Weeks 1, 3, and 8), and (8) The medication adherence rate (unused medication and empty bags are collected and evaluated by the investigator or sub-investigator 3 weeks after the start of treatment to check medication adherence, and <80% is counted as a deviation. If the patient was unable to come to the hospital, the medication was collected by mail.)

In addition, since the investigational drug acts on the central nervous system, it is recommended to check for the presence of suicidal ideation or suicide attempts. The Columbia Suicide Severity Rating Scale question is used to evaluate the presence of them during the previous observation period before intervention, 3 and 8 weeks after the start of treatment.

SAMPLE SIZE

In a double-blind randomized controlled trial (n = 200)[12] using CFS of COVID-19 as the outcome, the mean CFS values of patients in the placebo group at 8, 11, and 14 days after COVID-19 onset were 21.75, 20.55, and 19.91, respectively. The CFS value at the time of patient participation, i.e., the baseline CFS value, was set to 20. In this study, CFS values decreased from baseline from day 0 in both groups. The mean CFS value of 128 COVID-19 patients averaged 15.8 ± 5.9 a few months after its onset[13], which was consistent with that reported in another study on 458 outpatients[14]. Based on these findings, the mean CFS value of the non-treated group after one month was set to 15 ± 5 and the extent of the decrease to 5, and the expected treatment effect was set to a decrease of 3 points of minimal important difference[15]. Assuming a discontinuation rate of approximately 25%, α error = 0.5 and β error = 0.20. Based on these values, the number of patients in each group was set to 120 (60 patients in each group).

Revised on 2023/2/12:Inclusion criteria were revised from “within 21 days from COVID-19 onset” to “within 52 weeks from COVID-19 onset to randomization” due to the difficulties associated with collecting a sample due to a decrease in the number of patients infected with COVID-19. Due to the extended time period of the

study, we referred to CFS scores obtained from previous studies approximately one year after the onset of COVID-19. In an Irish study that followed patients hospitalized with COVID-19 for one year, CFS score was 16.7 ± 5.6 after an average follow-up of 430 days[16]. In a Spanish population-based study, CFS score was 8 ± 3 after an average of 36 weeks[17]. In a German study, 42 patients followed up with severe fatigue had CFS score of 21 ± 517 after approximately one year[18], with values varying among patients. Based on the patient population used for sample size calculations, CFS score of 15 ± 5 several months after COVID-19 onset and CFS score of 16.7 ± 5.6 after an average follow-up of 430 days in Ireland are considered to be consistent. Therefore, we estimated CFS score one year after COVID-19 onset to be 15 ± 5 and set the minimal important difference to a 3-point decrease in the CFS score. Given an α error of 0.5 and β error of 0.20, each group requires 45 patients, resulting in a total of 90 patients. In addition, even when accounting for an anticipated discontinuation rate of 25%, a sample size of 120 participants (60 in each group) has been determined to be sufficient. There is no change in sample size from the original analysis.

BLINDING

The donepezil and placebo groups are double-blind, and allocation is blinded until the end of the trial for all participants and all investigators. Prescriptions and evaluations are performed by the same investigator, who remains blinded from allocation to the end of the study for all participants. Participants also remain blinded for the same period of time, the investigational drug is packaged in aluminum, and the appearance of the investigational drug and placebo is indistinguishable. S.D.Logi Corporation stores and manages the study drugs, which are then delivered to each medical institution. The investigator unblinds the participant through the web registration system in an emergency. It is used only in an emergency to allow the investigator or sub-investigator to provide appropriate medical treatment to the participant or to ensure safety. The reason for unblinding is noted in the report and communicated to the coordinating investigator and coordinating office.

DATA MANAGEMENT

Patient data are stored in raw medical records at each hospital and anonymized Electronic Data Capture (EDC) for at least 5 years. Changes in EDC are preserved with a log showing information on who and when to initiate changes. These data belong to the investigator.

CONFIDENTIALITY

All patient data are anonymized in the EDC system. Only study physicians, who were given the original ID and password, access EDC, and solely input data on patients at their facility. The statistician and central monitor have exclusive access to all participants' data.

STATISTICAL ANALYSIS

The primary endpoint

Outcomes are compared by *t*-tests and regression models adjusted for baseline scores (an analysis of covariance). In addition, we also analyzed data using regression model adjusting for known confounders including age, sex, medical history, and disease severity[19]. Sensitivity analyses include both intention-to-treat and per-protocol analyses. Subgroup analyses are performed based on age, sex, medical history, and disease severity.

Secondary endpoints

Outcomes are compared by *t*-tests, and regression models adjusted for baseline scores (an analysis of covariance). In addition, we also analyzed data using regression model adjusting for known predictors including age, sex, medical history, and disease severity. Other outcomes and observations are compared by *t*-tests, an analysis of covariance, the Wilcoxon test, χ^2 test, and regression models. Mixed effects models and generalized estimating equations are used for time series data.

ADDITIONAL ANALYSES

An outcome is defined as the response of donepezil, and characteristic biomarkers are examined using multivariable regression models and machine learning approaches, including Lasso regression. In the additional analyses, we will perform explorative analysis to find target population by subgroup analyses using biomarkers of SITH-1 antibody level, Zinc Finger Protein 36 Homolog and inflammatory markers; C reactive protein, white blood cell count, interleukin-6, interleukin-1beta and tumor necrosis factor-α. In the secondary analysis, we will compare the percentage of individuals in each group who improved beyond the minimal clinically important difference[20].

NON-ADHERENCE AND MISSING DATA

If the compliance rate is <80% at the end of the trial or at the time of discontinuation, it is treated as an exclusion. Participants with missing data on primary or secondary outcomes are not analyzed in Full Analysis Set to evaluate the outcomes. Other observation items are analyzed with missing data. When the analysis requires covariate

adjustment and there is an imbalance in groups after randomization, we impute missing data on covariates for the item.

MONITORING

The monitoring manager is the manager of the Clinical Development Division in Dee-Lites Corporation. It confirms that the human rights and safety of participants are protected and that the study is being conducted in accordance with the latest study protocol and good clinical practice by checking against source documents and records. It ensures that trial data are accurate and complete. Auditing is conducted by Multiplex Limited Liability Company in the present study. Protocol adherence and input data are checked by monitoring, which is led by the monitoring committee.

INTERIM ANALYSES

Safety monitoring is conducted in a timely manner, as described in monitoring section. Severe adverse events are immediately reported to the principal investigator, who needs to report them to each investigator within a specific number of days according to their severity. The principal investigator stops the study when a marked difference is noted in safety based on a report of severe adverse events or safety monitoring. Interim analyses are not performed.

ADVERSE EVENT REPORTING AND HARM

Adverse events are collected 1, 3, and 8 weeks after administration. If an adverse event is observed in a participant during the clinical trial, the investigator or sub-investigator immediately takes appropriate medical measures to ensure the participant's safety and inform the participant if treatment for the adverse event is necessary. If blood sampling is not performed because the patient is unable to come to the hospital, clinical symptoms and abnormal laboratory values need to be described in the case report form. If an exacerbation of depressive symptoms is observed, a consultation with the medical institution for clinical trial implementation or a consultation with a psychiatrist or sub-investigator needs to be conducted. If an adverse event occurs up to 8 weeks after the start of the administration of the investigational drug and the investigator decides that the event is serious, the investigator reports it to the head of the site within 24 hours. The coordinating physician reports to the investigator and notifies each investigational site. If deemed necessary, a report is made to the Minister of Health, Labour, and Welfare, an "organizing sheet" is prepared and reported to the Pharmaceuticals and Medical Devices Agency, and this information is provided to Eisai Corporation.

CRITERIA FOR DISCONTINUING OR MODIFYING ALLOCATED INTERVENTIONS

A participant will be withdrawn when the participant declines to participate in the clinical trial or withdraws their consent or when it becomes difficult to continue the clinical trial due to adverse events or other reasons. The clinical trial will also be discontinued when the investigator or sub-investigator decides that it is appropriate to discontinue the clinical trial. No intervention modifications will be made after allocation. Adverse events are collected 1, 3, and 8 weeks after administration. If an event occurs, the investigator carefully monitors the patient and decides whether to continue the clinical trial. Patients undergo a consultation with a psychiatrist if they answer "yes" to the Columbia Suicide Severity Rating Scale question suicidal ideation question in the 3- and 8-week assessments after drug administration. If the psychiatrist decides that the patient is at risk of suicide, the patient is excluded.

ETHICAL ASPECTS

The study protocol and patient information documents were approved by the Ethics Committee of St. Marianna Medical University Hospital. This study protocol is registered with the registration number jRCT 2031220510 on the Japan Registry of Clinical Trials. The investigator may use eConsent to obtain consent for both telemedicine and hospitals. The investigator explains the procedure and obtains consent from the participants. If the participants are unable to come to the hospital during the COVID-19 isolation period, the investigator may obtain consent from the participants using eConsent after explaining the procedure online.

POST-TRIAL CARE

If the exacerbation of depressive symptoms is observed, the participant needs to visit the medical institution for clinical trial implementation or be examined by a psychiatrist or sub-investigator. Follow-ups are conducted at the medical institution for clinical trial implementation until the participant recovers and is then referred to an appropriate medical institution.

BIOMARKER SURVEY

Blood samples are collected from participants and analyzed during the pre-observation period. We

comprehensively search for genes, such as cholinergic anti-inflammatory response-related genes, which are relevant to this study in national and international reports. They are analyzed for these genes as well as for residual viruses, human herpesvirus-6 reactivation, and autoantibodies that may be involved in the pathogenesis of the disease.

DISCUSSION

The mental symptoms of PCC develop in approximately 33% of patients; they do not spontaneously improve and are known to persist[5,21]. The incidence of mental symptoms does not correlate with the severity of COVID-19 and is slightly higher in non-inpatients, many of whom are young; therefore, it is a social and economic problem[22–26]. We aim to establish an effective treatment for the mental symptoms of post-COVID in this clinical trial. Basic research is beginning to elucidate the various mechanisms underlying mental symptoms, such as inflammation and oxidative stress[27–29]. In previous studies, we demonstrated that mental symptoms were caused by decreases in acetylcholine-producing cells and acetylcholine levels and that the acetylcholinesterase inhibitor donepezil was effective for the treatment of mental symptoms[11]. Therefore, research using existing drugs is safer than the development of new drugs, enables an immediate response, and is expected to make a significant contribution to society.

In addition, a new initiative in this study regarding COVID-19, which requires isolation in the acute phase, is the use of eConsent to remotely obtain consent. Since the mental symptoms of post-COVID persist, outpatient interventions and follow-ups are required over a long period of time. Therefore, this study incorporates follow-ups with online medical care and house calls to improve medication adherence, ensure follow-ups, and reduce the burden on patients.

In recent years, Decentralized Clinical Trial has been attracting attention as a new clinical trial method that utilizes online medical services. This is a system that decentralizes the clinical trial process, which is concentrated at the medical institution for clinical trial implementation so that patients may participate in a clinical trial without having to visit the site[30]. This study was devised based on the concept of decentralized clinical trial.

From the participant's perspective, this method reduces the time burden of hospital visits and also has the advantage of eliminating geographical restrictions, such as remote locations. In the case of an adverse event, the safety of participants is ensured through a rapid response, and the participant's satisfaction is high. From the viewpoint of the medical institution for clinical trial implementation, it is expected to increase recruitment, improve adherence to medication, and increase follow-up rates, thereby enabling the smooth implementation of clinical trials. The decentralized clinical trial method, which combines online and home care, is novel in that it requires the long-term follow-up of patients with emerging infectious diseases that require isolation.

This method will be useful in the investigation of emerging infectious diseases that may occur in the future. decentralized clinical trial is a method that is beginning to be used in clinical studies on non-COVID-19 patients, but is not common in studies on COVID-19 infection. If this trial is successful, this technique may become a gold standard and is expected to be introduced into various clinical trials in the future.

TRIAL STATUS

This study protocol is version 3 made on 13 February 2023. The recruitment period is between 1 October 2022 and 31 January 2024.

DECLARATIONS

ACKNOWLEDGMENTS

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

FUNDING

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AUTHOR CONTRIBUTIONS

KK, MI: drafting the manuscript, KN: design, interpretation, and revision of the manuscript. KK: conception of the study, KN, KY, Ki, SF: conduction of the study. TG: design and statistical analyses, SF: supervision of the study. All authors have read and approved the manuscript.

COMPETING INTERESTS

We declare that we have no competing interests related to this manuscript or the study.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol and patient information documents were approved by the Ethics Committee of St. Marianna Medical University Hospital.

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