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Repurposing bromocriptine for Aβ metabolism in Alzheimer’s disease (REBRAnD) study: randomised placebo-controlled double-blind comparative trial and open-label extension trial to investigate the safety and efficacy of bromocriptine in Alzheimer’s disease with presenilin 1 (PSEN1) mutations

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ABSTRACT

Introduction Alzheimer’s disease (AD) is one of the most common causes of dementia. Pathogenic variants in the presenilin 1 (PSEN1) gene are the most frequent cause of early-onset AD. Medications for patients with AD bearing PSEN1 mutation (PSEN1-AD) are limited to symptomatic therapies and no established radical treatments are available. Induced pluripotent stem cell (iPSC)-based drug repurposing identified bromocriptine as a therapeutic candidate for PSEN1-AD. In this study, we used an enrichment strategy with iPSCs to select the study population, and we will investigate the safety and efficacy of an orally administered dose of bromocriptine in patients with PSEN1-AD.

Methods and analysis This is a multicentre, randomised, placebo-controlled trial. AD patients with PSEN1 mutations and a Mini Mental State Examination-Japanese score of ≤25 will be randomly assigned, at a 2:1 ratio, to the trial drug or placebo group (≥4 patients in TW-012R and ≥2 patients in placebo). This clinical trial consists of a screening period, double-blind phase (9 months) and extension phase (3 months). The double-blind phase for evaluating the efficacy and safety is composed of the low-dose maintenance period (10 mg/day), high-dose maintenance period (22.5 mg/day) and tapering period of the trial drug. Additionally, there is an open-labelled active drug extension period for evaluating long-term safety. Primary outcomes are safety and efficacy in cognitive and psychological function. Also, exploratory investigations for the efficacy of bromocriptine by neurological scores and biomarkers will be conducted.

Strengths and limitations of this study

► This trial will provide the safety and efficacy data of bromocriptine for Alzheimer’s disease patients with mutations in the presenilin 1 (PSEN1) gene (PSEN1-AD).
► Bromocriptine is an approved drug with safety information accumulated over decades.
► The trial design includes enrichment of the patient population by induced pluripotent stem cell technology.
► Minimally invasive biomarkers, using plasma samples, positron emission tomography and digital tools, will be investigated in addition to amyloid β-protein and tau in cerebrospinal fluid samples.
► A possible limitation may be a difficulty in recruiting a large-enough number of patients due to the rarity of PSEN1-AD.

Ethics and dissemination The proposed trial is conducted according to the Declaration of Helsinki, and was approved by the Institutional Review Board (K070). The study results are expected to be disseminated at international or national conferences and published in international journals following the peer-review process.

Trial registration number jRCT2041200008, NCT04413344.
INTRODUCTION
Alzheimer’s disease (AD) was first reported by Dr Aloys Alzheimer in 1906, and it is now regarded as the most prevalent neurodegenerative disease, accounting for 60%–80% of dementia cases. Over 50 million people are estimated to live with dementia globally, a figure set to increase to 152 million by 2050. The number of AD patients is also expected to increase explosively in Japan in line with our super-ageing society. Although this disease should be treated promptly, available treatments are limited to several symptomatic therapies.

AD is a neurodegenerative disease that presents clinical symptoms, primarily including progressive decline in memory. Elucidation of the central pathology of AD began in the 1980s with the identification of amyloid β-protein (Aβ) by biochemical methods. Aβ is a major component of senile plaques, which represent a pathological characteristic of AD. Subsequently, in the 1990s, genetic approaches identified the Aβ precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 as causative genes for familial AD, thereby rapidly advancing the understanding of such condition. Notably, AD patients with mutations in the PSEN1 gene (PSEN1-AD) experience onset in their 20s–50s, and their cognitive function deteriorates rapidly, leading to death within several years, as curative therapies are unavailable.

To develop therapeutic compounds for PSEN1-AD, we previously established induced pluripotent stem cells (iPSCs) from patients with PSEN1-AD. iPSCs were established by introducing a small number of genes into patients’ cells. Established iPSCs can differentiate into any type of cell in the body and proliferate indefinitely. iPSC technology provided in vitro models of inaccessible human cell types and impacted investigations of disease mechanisms especially in brain disorders. We established an iPSC-based screening system by modelling Aβ phenotypes of PSEN1-AD. We utilised an existing drug library the safety and pharmacokinetic profile of which had already been confirmed clinically and approved for use in humans. After the screening, we found bromocriptine to be the most potent modifier of Aβ production for PSEN1-AD neurons among existing drugs. Dose-dependency assay showed that bromocriptine reduced the Aβ42 dose and Aβ42/40 ratio by up to ~50% and ~40%, respectively. Furthermore, we prepared cortical neurons of several patients with PSEN1-AD and sporadic AD to evaluate the specificity of bromocriptine for PSEN1-AD. Bromocriptine reduced the Aβ42 dose and Aβ42/40 ratio of PSEN1-AD neurons more strongly than those of sporadic AD neurons. From these results, we selected patients with PSEN1-AD as a bromocriptine-responsive subgroup in AD.

Bromocriptine is an already approved drug with few safety concerns and a long history of usage in clinical settings. Bromocriptine was approved for the treatment of Parkinson’s disease (approved dosage 22.5 mg/day), pituitary tumour and hyperprolactinaemia, and was proven to penetrate the blood–brain barrier. Based on iPSC studies, as we hypothesised that bromocriptine might attenuate the clinical symptoms of PSEN1-AD patients, we decided to conduct a clinical trial to evaluate the safety and efficacy of the first-time administration to PSEN1-AD patients as an investigator-initiated clinical trial (exploratory study), which will confirm its safety and provide evidence of its efficacy.

Objectives
The aim of this study is to investigate the safety and efficacy of an orally administered dose of bromocriptine in patients with PSEN1-AD using a placebo group as control. In addition, long-term safety will be examined in an open-label extension trial.

METHODS AND ANALYSIS
Trial population and rationale for selecting participants
The following patients will be included in this study. Detailed eligibility criteria are presented in ‘box 1’. This ongoing clinical trial started to enrol participants in June 2020. The study is planned to end in March 2022.

- Alzheimer’s disease patients with PSEN1 mutations (PSEN1-AD).
- Patients diagnosed with ‘probable AD’ according to the diagnostic guideline of National Institute on Aging-Alzheimer’s Association (NIA-AA) or ‘probable Alzheimer-type dementia’ according to the diagnostic criteria for AD specified in Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
- Mini Mental State Examination-Japanese (MMSE-J) score of ≤25.

PSEN1-AD is the target disease. The MMSE-J score will be specified at 25 points or lower to enrol patients with dementia and mild cognitive impairment (MCI) and to exclude those with normal cognitive function. We will exclude MCI participants with MMSE-J scores of 26 or 27, who are reported to have lower risk and longer duration of MCI conversion to AD. The concomitant use of existing drugs for the treatment of AD (donepezil, galantamine, rivastigmine and memantine) will be allowed to evaluate the safety and efficacy of future practical bromocriptine use on approval, but patients who have changed their regimen within 2 months before providing informed consent will be excluded because the efficacy of bromocriptine alone will be difficult to evaluate. Patients taking oral donepezil hydrochloride will be carefully monitored because the blood concentration may be increased by the additional oral administration of the trial drug. Recruiting will be done by neurologists who
Exclusion criteria

1. Difficulty with the oral intake of tablets.
2. Patients receiving anti-dementia drugs who have changed the dosing regimen during the 2 months prior to providing informed consent.
3. Patients with dementia due to a pathology other than AD (eg, vascular dementia, frontotemporal dementia, Lewy body dementia, progressive supranuclear palsy, corticobasal degeneration, Huntington’s disease, prion diseases).
4. Presence of clinically relevant or unstable medical disorders. Patients with major depression in remission can be enrolled.
5. Body mass index of ≤17 or ≥35.
6. History of alcohol dependence, drug dependence or drug abuse within 5 years before providing informed consent.
7. HBs antigen positive.
8. Anti-HIV antibody positive.
9. Anti-human T-lymphotropic virus type 1 (HTLV-1) antibody positive.
10. Patients with a history of alcohol dependence, drug dependence or drug abuse within 5 years before providing informed consent.
11. Presence of clinically relevant or unstable medical disorders. Patients with major depression in remission can be enrolled.

Box 1 Eligibility criteria of REBRAnD study

Eligibility criteria

Patients who meet all the following inclusion criteria and do not meet any of the exclusion criteria will be enrolled as eligible participants.

Inclusion criteria

1. Alzheimer’s disease (AD) patients with presenilin 1 (PSEN1) mutations.
2. Patients diagnosed with ‘probable AD’ according to the diagnostic guideline of National Institute on Aging-Alzheimer’s Association (NIA-AA) or ‘probable Alzheimer-type dementia’ according to the diagnostic criteria for AD specified in Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
3. An Mini Mental State Examination-Japanese score of ≤25.
4. Patients whose cognitive function and every-day function are obviously impaired based on their medical record or information provided by a person well acquainted with the patient.
5. Patients for whom intellectual disability and mental disorders other than dementia can be ruled out based on their academic background, work history and life history.
6. Patients with a reliable and close relationship with a partner/carer.
7. Age ≥20 years at the time of providing informed consent.
8. Written informed consent has been obtained from the patient or his/her legally acceptable representative to participate in this trial.

Exclude criteria

1. Patients with current or a history of thickened heart valve cusps, restricted heart valve motion and associated heart valve lesions, such as stenosis, confirmed by echocardiography.
2. Pregnant females, lactating females and females who may be pregnant (pregnancy test will be performed to confirm this status), and females who wish to become pregnant.
3. Other patients who are considered inappropriate for participating in this trial at the discretion of the investigator or subinvestigator.

*CYP3A4 inhibitors/inducers and dopamine antagonists are contraindicated for patients receiving anti-depressants or anti-psychotics.

Sample size

The number of PSEN1-AD patients confirmed by genetic diagnosis in Japan is approximately 100 according to the Japanese Familial Alzheimer’s Disease (JFAD) database and a report of a research project on the support system for individuals with famial AD and their families in Japan. This number corresponds to the global data of reported cases from Asia, the UK and the USA. In addition, compared with patients with sporadic AD without PSEN1 mutations, PSEN1-AD patients have a more rapid progression of cognitive decline and a more substantial decrease in the ability to perform daily living activities (ADLs) owing to the overlap of various neurologic symptoms, including spastic paralysis and extrapyramidal symptoms. Hence, the number of patients is more limited to those who meet the inclusion criteria in the limited trial duration. Given such rarity, the patient accumulation is extremely low and the targeted sample treat PSEN1-AD patients and are blinded to their allocation. All participants in the study need to be confirmed for the presence of PSEN-1 mutation by genetic analyses. Given that PSEN1-AD patients are very few, the planned feasible recruitment duration will be 10 months.

Subinvestigator considers that there is a significant medical risk in the patient’s participation in the trial.
14. Patients with long QT syndrome or tendency towards prolonged corrected QT (QTc) interval (male: ≥470 ms, female: ≥480 ms), or patients with a history of arrhythmia (eg, ventricular tachycardia or torsades de pointes).
15. Patients with a history of malignancies within 5 years prior to providing informed consent. However, patients with the following diseases can be enrolled if they are treated appropriately:
   a. Skin cancer (basal cell, squamous cell).
   b. Cervical carcinoma in situ.
   c. Localised prostate cancer.
   d. Malignancies that have not recurred for at least 3 years since surgery and the patient’s physician has determined that the risk of recurrence is low.
16. Patients with clinically significant vitamin B1/B12 deficiency or folic acid deficiency within 6 months prior to providing informed consent.
17. Patients who participated in other clinical research/trials involving interventions within 3 months prior to providing informed consent.
18. Patients who previously received bromocriptine or TW-012R.
19. Patients with a history of hypersensitivity to bromocriptine or ergot alkaloids.
20. Patients with a history of malignancies within 5 years prior to providing informed consent.
size for this randomised trial is ≥4 patients in TW-012R and ≥2 patients in placebo based on feasibility and the aforementioned validity. Unequal randomisation will be employed because of ethical considerations. There is no formal hypothesis or power sample size calculation due to the exploratory nature of this study. Thus, we did not perform sample size calculation. To ensure that sufficient participants complete the trial, clinical research coordinators will communicate well and frequently both with the central coordinating centre and the participants/care givers.

Intervention and control

This clinical trial consists of the screening period (8 weeks), double-blind phase (37 weeks) and extension phase (13 weeks). The double-blind phase for evaluating the efficacy and safety is composed of the low-dose maintenance period (up to 10 mg/day), high-dose maintenance period (up to 22.5 mg/day) and tapering period of the trial drug. Additionally, there is an open-labelled active drug extension period (up to 10 or 22.5 mg/day) for evaluating long-term safety.

Figure 1 Design of REBRAnD study. The study consists of the screening period (8 weeks), double-blind phase (37 weeks) and extension phase (13 weeks). The double-blind phase for evaluating the efficacy and safety is composed of the low-dose maintenance period (up to 10 mg/day), high-dose maintenance period (up to 22.5 mg/day) and tapering period of the trial drug. Additionally, there is an open-labelled active drug extension period (up to 10 or 22.5 mg/day) for evaluating long-term safety.
COVID-19 pandemic in 2020, we amended our protocol to make it possible to deliver study drugs if a participant cannot visit a medical facility. For participant retention and safety reasons, a participant will have 10 phone-visits in addition to monthly onsite-visits.

As for drug interactions, CYP3A4 inhibitors/inducers and dopamine antagonists are prohibited because bromocriptine is primarily metabolised by CYP3A4 and drug interaction is anticipated. Benzodiazepines are also prohibited because they might result in reduced efficacy in the clinical phenotype, especially cognitive function.

This study will be conducted at six academic hospitals and one community hospital in Japan.

Standard Protocol Items: Recommendations for Intervventional Trials (SPIRIT checklist) was followed in designing the study protocol.

**Randomisation, allocation, and blinding**

Patients meeting all the inclusion criteria and not meeting any of the exclusion criteria (box 1) at the time of enrolment in the trial will be randomly assigned, at a 2:1 ratio, to receive either TW-012R or placebo. Owing to the ethical issue for patients assigned to the placebo group, unequal randomisation will be employed. Randomisation will be performed using permuted blocks and stratified based on the important confounding variable of the baseline MMSE-J score (<13 or ≥13). The allocation sequence will be prepared by an external contract research organisation, and trial participants, care givers, outcome assessors and investigators will be blinded. Registration will be done by investigators, etc., using the web enrolment system. When a patient is determined to be eligible by the web enrolment system, the allocated drug number will be displayed as the enrolment result. Under emergency circumstances such as severe adverse events (AEs), unblinding is permissible by the discretion of the coordinating investigators.

**Outcomes**

**Primary endpoint (1) safety**

As the primary analysis, safety will be evaluated by collecting incidence information and severity of AEs or adverse reactions from the starting time of the administration of the trial drug to the end of the follow-up period (table 1). Known frequent adverse effects of bromocriptine include nausea and vomiting (8.3%), anorexia (2.5%) and gastric discomfort, based on 5212 cases with Parkinson’s syndrome.21

**Primary endpoint (2) Severe Impairment Battery-Japanese (SIB-J)**

Severe Impairment Battery-Japanese (SIB-J) is validated in the Japanese version and will be used to evaluate cognitive function.22–24 Higher scores indicate better cognitive function (range 0–100). Participants will be questioned and assessed by the investigator, subinvestigator, clinical psychologist or speech therapist. Individual time courses of observed values and changes from baseline in SIB-J score up to week 20 and week 36 after trial drug administration will be shown (table 1).

**Primary endpoint (3) Neuropsychiatric Inventory (NPI)**

Neuropsychiatric Inventory (NPI) (Japanese version) is a validated clinical instrument for evaluating psychopathology in dementia.23–27 Higher scores indicate more severe neuropsychiatric derangements (range 10–120). Caregivers will be interviewed and assessed by the investigator, subinvestigator, clinical psychologist or speech therapist. Individual time courses of observed values and changes from baseline in NPI score up to weeks 20 and 36 after trial drug administration will be shown (table 1).

**Secondary endpoints**

Changes in the following (1)–(11) will be shown individually. For the blood bromocriptine concentration on day 1, key pharmacokinetic parameters (Cmax, Tmax) will be calculated (table 1).

1. Mental Function Impairment Scale (MENFIS).28
2. MMSE-J.29–31
3. Disability Assessment for Dementia (DAD).32
4. Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale Part III.33
5. Apathy Evaluation Scale Informant Version.34 35
6. Plasma Aβ protein.36
7. Plasma neurofilament light chain protein (NfL).37
8. Plasma total tau and plasma phosphorylated tau protein.36 38–40
9. Cerebrospinal fluid Aβ (CSF Aβ).41 42
10. Cerebrospinal fluid total tau and phosphorylated tau protein (CSF total/ p-tau).41 42
11. Blood bromocriptine concentration.

**Reference endpoints**

For exploratory purposes, additional measurement with wearable physical activity metre (SilmeeW20, TDK Corporation, Tokyo, Japan),43 measurement with magnetic sensing finger tap device (UB-2, Maxell, Ltd., Tokyo, Japan),44 45 brain amyloid positron emission tomography (PET),46 brain tau PET,47 Upper Motor Neuron Burden Score (UMNB)48 and plasma Aβ-related peptides49 will be assessed as reference endpoints (table 1). The wearable physical activity metre continuously monitors activity, sleep habits, amount of speech, time of physical movement and heart rate variability. Finger tapping is correlated with cognitive function and Parkinsonian signs, and it allows obtaining parameters directly related to ADLs not limited to cognitive function evaluated by questionnaires.

All neuropsychological testing will be conducted by certified physicians or psychologists who completed the assessment training of this trial. Learning effect cannot be negligible, but this trial has a placebo arm, and previous trials using SIB-J, NPI, MENFIS and DAD adopted similar measuring time frames and no obvious learning effects were reported.50 51

Kondo T, et al. BMJ Open 2021;11:e051343. doi:10.1136/bmjopen-2021-051343
## Table 1 Trial schedule

| Timing                     | Screening period | Double-blind phase                     | Escalation to four tablets/day | Escalation to nine tablets/day | Taper |
|----------------------------|------------------|----------------------------------------|-------------------------------|--------------------------------|-------|
|                            | Before enrolment | Before start of trial treatment        | At start of administration    | Week 1                         |       |
| Visit/medical examination  | ○                | ○                                      | ○                             | ○                              | ○     |
| Neuropsychological/motor assessment | ○              | ADAS-J cog                             | SB-J                          | ○                              | ○     |
|                             |                  | SIB-J                                  | NPI                           | ○                              | ○     |
|                             |                  | MENFIS                                 | MMSE-J                        | ○                              | ○     |
|                             |                  | DAD                                    | UPDRS part III                | ○                              | ○     |
|                             |                  | Apathy                                 | Scale                         | ○                              | ○     |
|                             |                  | UMN B                                  |                               |                                | ○     |
| Laboratory biomarkers       | Plasma biomarkers| CSF biomarkers                         |                               |                                |       |
| Digital biomarkers          | Wearable physical activity             | Finger tapping                       |                               |                                |       |
| PET                        | Brain amyloid   | PET                                     | Brain tau PET                 | ○                              | ○     |
| Safety assessment           | Cardiac ultrasound |                                      |                                |                                |       |
|                            | Chest X-ray     |                                        |                                |                                |       |
|                            | ECG             |                                        |                                |                                |       |
|                            | Head MRI        |                                        |                                |                                |       |
|                            | Blood bromocriptine concentration |                                    |                                |                                |       |
|                            | Laboratory tests|                                      |                                |                                |       |
|                            | AEs             |                                        |                                |                                |       |

Continued
| Table 1 Continued |
|-------------------|
| **Extension phase** |
| **Escalation to 4–9 tablets/day†** |
| **Timing** | **Week 37** | **Week 38** | **Week 39** | **Week 40** | **Week 41** | **Week 42** | **Week 43** | **Week 44** | **Week 45** | **Week 46** | **End of trial** |
| Visit/medical examination |  |  |  | Phone | Phone |  |  | Phone | Phone |  |  |  |
| Informed consent | ADAS-J cog |  |  |  |  | SIB-J |  |  |  |  |  |  |
| Neuropsychological/motor assessment |  |  |  |  |  | NPI |  |  |  |  |  |  |
|  | MENFIS |  |  |  |  | MMSE-J |  |  |  |  |  |  |
|  | DAD |  |  |  |  | UPDRS part III |  |  |  |  |  |  |
|  | Apathy scale |  |  |  |  |  |  |  |  |  |  |  |
|  | UMNB |  |  |  |  |  |  |  |  |  |  |  |
| Laboratory biomarkers | Plasma biomarkers |  |  |  |  | CSF biomarkers |  |  |  |  |  |  |
| Digital biomarkers | Wearable physical activity |  |  |  |  | Finger tapping |  |  |  |  |  |  |
| PET | Brain amyloid PET |  |  |  |  |  |  |  |  |  |  |  |
| Safety assessment |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Cardiac ultrasound |  |  |  |  |  |  |  |  |  |  |  |
|  | Chest X-ray | ▲ | ▲ | ▲ | ▲ |  |  |  |  |  |  |  |
|  | ECG | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ | ▲ |
|  | Head MRI |  |  |  |  |  |  |  |  |  |  |  |
|  | Blood bromocriptine concentration |  |  |  |  |  |  |  |  |  |  |  |
|  | Laboratory tests |  |  |  |  |  |  |  |  |  |  |  |
|  | AEs |  |  |  |  |  |  |  |  |  |  |  |

Continued
The Data Centre will manage the data using the participant identification code or enrolment number. In direct access to source data related to the conduct of this trial, the participants’ informed consent forms, and publication of the trial results, full consideration should be given to the protection of privacy and personal information, such as the participants’ names and diseases. The full data set without personal identifiable information will be accessed by data managers, statisticians and investigators. An independent data monitoring committee has been established to assess the safety data.

Trial auditing will be conducted multiple times by an outside contract research organisation. Biological specimens will be preserved for future use in ancillary studies with the participants’ consent.

### Statistical analysis

Safety analyses will be performed for patients who undergo at least part of the trial treatment. Efficacy analyses will be performed among patients who undergo at least part of the trial treatment, provide efficacy information and satisfy study inclusion criteria. Descriptive statistics will be used to analyse safety data; results will be summarised as counts and percentages. For efficacy endpoints, changes from baseline will be summarised and compared at weeks 20 and 36 using descriptive statistics including mean differences with 95% CIs and p values derived from Student’s t test with the assumption of normality. If the assumption is violated, non-parametric tests will be considered. No imputation will be performed for missing data. Owing to the exploratory nature of this study, no adjustments will be made for multiple testing.

To support the robustness of the results, a sensitivity analysis with and without non-compliant patients will be conducted. A subgroup analysis in accordance with the baseline MMSE-J score (<13 or ≥13) will be performed to investigate the patient response to bromocriptine. All statistical analyses will be performed using SAS software, V.9.4 or higher (SAS Institute, Cary, NC). The statistical analysis plan will be developed prior to database lock.

### Patient and public involvement

No patient or public were involved in this study design. However, in the design of this study, patients and their family burdens were assessed with the help of neurologists and clinical trial coordinators of Kyoto University Hospital.

### Ethics and dissemination

This trial will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki (1964) and its revisions, namely, ‘Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices’, ‘Ministerial Ordinance on Good Clinical Practice for Drugs,’ and its related notifications, written procedures and this protocol. This trial was approved by the Institutional Review Board of Kyoto University Hospital.

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**Table 1 Continued**

| Time after first administration of trial drug (hour) | Plasma bromocriptine |
|---------------------------------------------------|-----------------------|
| -2 hours before administration | ◯ | To be performed |
| 1 hour before administration | ◯ | To be performed |
| 2 hours before administration | ◯ | To be performed |
| 3 hours before administration | ◯ | To be performed |
| 4 hours before administration | ◯ | To be performed |
| 6 hours before administration | ◯ | To be performed |
| 15 minutes after administration | ◯ | To be performed |
| 30 minutes after administration | ◯ | To be performed |
| 60 minutes after administration | ◯ | To be performed |

To be performed if donepezil hydrochloride is coadministered.
Review Board (K070, Kyoto University Hospital; F-2020-016, Mie University Hospital; 209001-A, Osaka University Hospital; 2105 (02-5), Tokushima University Hospital; T19-04 Tokyo Metropolitan Geriatric Hospital; 20200421, Kawasaki Medical School Hospital; 20200624, Asakayama Hospital).

The investigator will prepare the written information for participants and the informed consent form and will obtain approval from the Institutional Review Board in advance. Items to be described in the written information shall be prepared based on Article 51 of the ‘Ministerial Ordinance on Good Clinical Practice for Drugs’. If the investigator, etc., obtains any information that may affect the intention of the participant or the participant’s legally acceptable representative to continue to participate in the trial, he/she will promptly provide the information to the participant or the participant’s legally acceptable representative to confirm the intention of whether to continue to participate in the trial. The investigator will also promptly revise the written information, submit it to the head of the trial site and obtain approval from the Institutional Review Board. The investigator will provide another explanation to the participant who has already been participating in the trial or his/her legally acceptable representative using the revised written information, confirm the participant’s will as to whether or not to continue participation in the trial and obtain written consent from the participant. If an adverse event occurs due to the conduct of the trial, leading to health injury in participants, the investigator will immediately provide the participant with appropriate diagnosis, treatment and necessary measures including compensation insurance.

Persons involved in this trial shall comply with applicable laws and ordinances, shall exert their utmost efforts to protect personal information and privacy of the participants and shall not leak personal information obtained in the conduct of the trial without justifiable reasons. The same shall apply after their retirement. When submitting the patient enrolment forms and case report forms, the investigator, subinvestigator and clinical trial collaborator will use the participant identification code and will not enter information that allows persons outside the trial site to identify the participant (eg, name, address and telephone number). The central trial office, data centre and statisticians will use only the participant identification codes and cannot access the participants’ personal information.

The proposed study will evaluate both the safety and efficacy of bromocriptine in PSEN1-AD, and the study results are expected to be disseminated at international and/or national conferences and published in international journals following the peer-review process.

**DISCUSSION**

This study evaluates the safety and explores the efficacy of bromocriptine for patients with PSEN1-AD. The potential efficacy of bromocriptine for PSEN1-AD patients has already been identified by an approach applying iPSC-based drug repurposing. We previously developed a phenotypic screening system to evaluate compounds with a readout of Aβ42 reduction using familial and sporadic AD patient-iPSCs. Our high-throughput screening system revealed that bromocriptine, among 1258 pharmaceutical compounds, reduced the Aβ42 level most effectively. This drug reduced Aβ42 by 50% in PSEN1-AD iPSCs, and by 20%–30% in sporadic patient-iPSC models. A recent report implies that inhibition of less than 50% of Aβ might preserve neuronal signalling because the APP family plays an important role in synaptic plasticity underlying learning and memory. Thus, we designed the clinical trial for PSEN1-AD with the expectation that bromocriptine will become a candidate as a molecularly targeted drug for AD, and especially for PSEN1-AD.

Bromocriptine is a therapeutic agent used for the treatment of patients with Parkinson’s disease, and the accumulated data of long usage verifies its safety for patients with Parkinson’s disease. However, evaluation of the safety of bromocriptine in AD patients is required in order to support its development for the treatment of AD. This clinical trial consists of a 20-week low-dose maintenance period followed by a 16-week high-dose maintenance period to assess its safety. For recruitment and ethical considerations, we also added a 13-week open extension period to continue to follow the safety of the trial drug.

Safety information has been accumulated from long usage of bromocriptine since the 1970s. While nausea and vomiting are the most commonly reported AEs, it is generally manageable by slow titration of the medication and use of antiemetics. While the occurrence and management of AEs in AD patients seem to be comparable to those with Parkinson’s disease, this study was designed to evaluate any unacceptable AEs that specifically occur in PSEN1-AD patients. During the recruiting period of this study, the COVID-19 pandemic is influencing study recruitment, onsite monitoring and participants’ visit schedules all over the world. Our study protocol enabled the delivery of the study drugs. Furthermore, remote informed consent and cognitive/neuropsychiatric evaluation by tablet or digital devices can be used in future trials for AD to reduce the study burden for participants and their caregivers.

In this study, we will limit the included patients to those with PSEN1-AD, because bromocriptine is most effective in PSEN1-AD patient-derived iPSCs compared with other types of familial AD and sporadic AD patients’ iPSCs. This enrichment will make it difficult to recruit many patients for this study, considering the rarity of such patients in Japan. Although the variety of clinical severities among patients is one of the reasons that cause difficulty for clinical trial evaluation, our inclusion criteria admit a broad disease-stage as we consider that PSEN1-AD patients would be the best candidates
for bromocriptine administration. To explore the efficacy of the trial drug, various promising biomarkers in AD, plasma Aβ, plasma Aβ-related peptide, plasma NfL, plasma total/p-τ, CSF Aβ, CSF total/p-τ, amyloid/tau PET and digital biomarkers will be evaluated in this study. These biomarkers might indicate the target engagement, and its alteration might reflect the effect of bromocriptine treatment. Of note, digital biomarkers will potentially reduce participants’ and caregivers’ burden in future trials. Strengths of our study include participant enrichment using iPSC technology and exploratory biomarker investigation. A possible limitation of this study may be the difficulty in recruiting large numbers of patients due to the rarity of PSEN1-AD.

This study is the first to use bromocriptine for PSEN1-AD patients, and it presents both a low-dose and a high-dose safety verification as well as cognitive, neuropsychiatric, and biomarker safety verification as well as cognitive, neuropsychiatric modification of AD therapy.

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Competing interests TK has a patent, agent for preventing and/or treating Alzheimer’s disease, licensed to HIn and TK; HB reports funding for this clinical trial from Time Therapeutics, trial drugs from Towa Pharmaceutical Co., during the conduct of the study; personal fees from Sumitomo Dainippon Pharma Co., outside the submitted work; RU reports personal fees from Eisai, Sawai Pharmaceutical Co. and CAC Crot, outside the submitted work; SM reports personal fees from AstraZeneca KK, Bristol-Myers Squibb Company, Chugai Pharmaceutical Co. 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