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ORIGINAL ARTICLE

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Study of effects of ifenprodil in patients with methamphetamine dependence: Protocol for an exploratory, randomized, double-blind, placebo-controlled trial

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Abstract

Aims: Pharmacotherapy for methamphetamine dependence has not yet been developed in Japan or elsewhere in the world. Ifenprodil is a blocker of G protein-activated inwardly rectifying potassium channels that play a key role in the mechanism of action of addictive substances. Our aim is to examine the safety, efficacy, and outcomes of ifenprodil for the treatment of methamphetamine dependence in a randomized, double-blind, placebo-controlled trial.

Methods: The recruitment of outpatients with methamphetamine dependence began in January 2018. The patients will be randomized into three arms: placebo, 60 mg/d ifenprodil, or 120 mg/d ifenprodil. Placebo or ifenprodil will be taken for 84 days. We will use Cerocral fine granule 4%® (ifenprodil tartrate). Follow-up assessments will be conducted for 84 d after the drug administration period. All of the patients will be assessed by self-administered questionnaires and urine tests. The primary outcome will be the presence or absence of methamphetamine use during the 84-day administration period in the 120 mg/d ifenprodil and placebo groups. Secondary outcomes will include the number of days and percentage of

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days of abstinence from methamphetamine use, positive urine for methamphetamine, relapse risk, and drug craving.

Discussion: This study is the first clinical trial of ifenprodil treatment for methamphetamine dependence and is designed as an intervention test with off-label drug use. The present study is expected to provide evidence of the effects of ifenprodil treatment on methamphetamine dependence.

Trial registry: This trial was registered in the UMIN clinical trial registry (UMIN000030849; date of registration: January 17, 2018).

KEYWORDS

G protein-activated inwardly rectifying potassium channel, ifenprodil, methamphetamine dependence, randomized, double-blind, placebo-controlled trial

1 | INTRODUCTION

Methamphetamine is a derivative of amphetamine that increases intrasynaptic levels of norepinephrine, dopamine, and serotonin.[1] These synaptic neurotransmitters alter physiological and psychological status, causing tachycardia, elevations of blood pressure, euphoria, vigor, agitation, and a decrease in fatigue.[2] Repeated abuse of methamphetamine produces tolerance and sensitization to methamphetamine. Subsequent drug deprivation induces withdrawal symptoms. Methamphetamine dependence is classified as a stimulant-related disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5).[3] Methamphetamine dependence is a serious worldwide public health[4] and social concern that often results in suicide[5] and criminal acts.[6] The history of methamphetamine abuse in Japan began after World War II and is characterized by three epidemics of methamphetamine abuse.[7] Methamphetamine-related crime accounts for approximately 80% of drug-related crime in Japan.[8] The recidivism rate for methamphetamine use has increased over the past decade.[9] Methamphetamine continues to be a widely abused drug in Japan and worldwide. Currently, however, research on pharmacotherapies for methamphetamine dependence is still only in the exploratory phase.

Although various molecules are involved in the mechanisms of action of addictive substances, we have focused on the G protein-activated inwardly rectifying potassium (GIRK) channel. Functional GIRK channels are identified as heterotetramers of GIRK subunits (GIRK1-4).[10–12] Cardiac GIRK channels consist of GIRK 1 and 4 subunits.[11] The GIRK 1, 2, and 3 subunits are expressed in various rodent brain regions, such as the cerebral cortex, amygdala, hippocampus, ventral tegmental area, locus coeruleus, dorsal raphe nucleus, and cerebellum.[13,14] The activation of G protein-coupled receptors (GPCRs) that couple $G_{\alpha i/o}$ proteins of the $G_{i/o}$ family, including M_2 muscarinic, μ-opioid, α_2 adrenergic, somatostatin, γ-aminobutyric acid-B, dopamine D_2, and serotonin 5-hydroxytryptamine-1A receptors, activates GIRK channels through G protein βγ subunits.[15–23] Activated GIRK channels hyperpolarize the cell membrane and decrease neuronal excitability. Ethanol was found to directly open GIRK channels without interacting with the G protein signaling pathway in a *Xenopus* oocyte expression assay.[24] *Weaver* mutant mice that possessed a missense mutation in the channel pore of the GIRK2 subunit exhibited a reduction of the antinociceptive effects of ethanol and opioids.[24,25] GIRK2 or GIRK3 knockout mice exhibited a decrease in cocaine self-administration.[26] These studies suggest that the GIRK channel is a key molecule in the mechanism of action of addictive substances.

Previous studies reported that the selective serotonin reuptake inhibitors fluoxetine and paroxetine but not fluvoxamine inhibited GIRK channels and reduced methamphetamine-induced conditioned place preference.[27,28] Additionally, GIRK channel inhibitors (including ifenprodil) facilitated alcohol abstinence in outpatients with alcohol dependence.[29] Ifenprodil is a blocker of GluN2B subunit-containing *N*-methyl-D-aspartate receptors and α_1 adrenergic receptors.[30,31] Ifenprodil concentration-dependently inhibited GIRK channel currents.[32] Pretreatment with ifenprodil dose-dependently suppressed morphine-induced conditioned place preference.[33] Mice that were pretreated with ifenprodil and cyproheptadine did not exhibit locomotor sensitization to D-amphetamine, whereas mice that were pretreated with saline did.[34] Ifenprodil is not a specific blocker of GIRK channels and does not produce serious side effects.[35] Paroxetine has been reported to have several adverse effects, including serotonin syndrome, neuroleptic malignant syndrome, convulsions, toxic epidermal necrosis, antidiuretic hormone incompatible secretion syndrome, severe liver dysfunction, rhabdomyolysis, lower white blood cell counts, and anaphylaxis.[36] Fluoxetine is currently not approved for use in Japan. These previous studies suggest that ifenprodil may be a candidate medication for the treatment of substance dependence.

Ifenprodil, 60 mg/d, is currently used as a cerebral circulation/metabolism ameliorator that is covered by medical insurance in Japan. Although not covered by insurance, high-dose ifenprodil (60-300 mg/d) is also used as an analgesic. Ifenprodil has been used broadly in clinical practice in Japan. A recent study reported that ifenprodil treatment (60 mg/d) for 3 months decreased alcohol use scores in patients with alcohol dependence compared with patients who received the control medication (Cinal).[37] Hori et al[38] showed that 120 mg/d ifenprodil effectively reduced craving in a patient who

used Bron® (SSP Co., Ltd., Tokyo, Japan) cough medicine and in a patient with alcohol dependence. These reports suggest that high-dose ifenprodil may be safe and effective for the treatment of substance dependence.

The present report describes a randomized controlled study to investigate the safety, efficacy, and outcomes of ifenprodil treatment for methamphetamine dependence. The patients were randomly allocated to one of three groups: placebo, 60 mg/d ifenprodil (normal dose), and 120 mg/d ifenprodil (high dose). This article describes the study protocol according to SPIRIT guidelines.[39]

2 | METHODS

2.1 | Study design

The present study is a randomized, double-blind, exploratory, dose-ranging, placebo-controlled, single-center (National Center Hospital, National Center of Neurology and Psychiatry, Japan) clinical trial. Patients will be randomized into three arms (1:1:1 allocation ratio): placebo, 60 mg/d ifenprodil, and 120 mg/d ifenprodil. Placebo or ifenprodil will be taken orally for 84 days (3 months). Follow-up assessments will then be conducted for 3 months after the drug administration period.

2.2 | Eligibility criteria

Study participants will be solely recruited from the National Center Hospital, National Center of Neurology and Psychiatry (NCNP). The following inclusion criteria will be applied to patients with methamphetamine use disorder: (a) outpatients who are diagnosed with methamphetamine use disorder by the DSM-5, (b) those who used methamphetamine in the past year, and (c) those who are age 20 years old or over at obtaining of informed consent. Exclusion criteria will include the following: (a) patients with severe physical diseases, (b) patients with a high suicide risk, (c) patients with severe symptoms of substance-induced psychotic disorder, (d) patients with impairments in cognitive function, (e) patients who do not wish to be notified of the functional magnetic resonance imaging examination results, (f) patients who are judged to be ineligible to participate in the study by their attending psychiatrist, and (g) patients who take paroxetine, a GIRK channel blocker.

2.3 | Participant recruitment

Promotion of this study will be done through notices that are placed within the hospital.

Additionally, the researchers will search for eligible patients who meet the study's inclusion criteria using hospital computer systems and report the information (ID in an electronic medical record and name) of eligible patients to each primary physician. This study has three primary physicians. If a primary physician determines that the patient can participate in the study, then the primary physician will introduce this study to the patient with an explanation leaflet. If patients show interest in participating in this study, then (a) they will be requested to send a blank e-mail to the study's e-mail address, or (b) they will write their e-mail address on a form, and the primary physician will collect the form and give it to the Clinical Research Coordinator (CRC) and researchers. The CRC and researchers will receive the blank e-mail from the patients (in the case of [a]) or send an e-mail to the patients (in the case of [b]) and set a day and time to explain the study to the patient and to obtain informed consent (see Table 1, Day −7). The overall procedures for the trial are shown in Figure 1.

2.4 | Participant timeline and schedule of assessments

The study scheme is outlined in Table 1. The CRC and researchers will obtain informed consent from all eligible and consenting patients who are introduced by their primary physicians (Day −7). Signed consent forms will be obtained from all study participants as follows. The CRC or researchers will first explain that participation in the study is voluntary, and the participants can withdraw from the study at any time after the study begins. The CRC or researchers will explain the purpose of the study, the study timeline, intervention methods, random allocation to three groups, evaluation methods, protection of personal information, publication of study results, compensation for participation (prepaid cards), and contact address for complaints. After explaining the study, the patients will decide whether to participate. When they sign the informed consent form, their participation begins. After the patients sign the informed consent form, the following information will be gathered to obtain sociodemographic profiles (ie, sex, age, residence, marital status, house mate, education history, employment status, and alcohol use status), self-reported drug use status (self-report calendar format based on the Timeline Follow-back [TLFB] method),[40,41] relapse risk (Stimulant Relapse Risk Scale [SRRS]),[42] and drug craving (Numerical Rating Scale [NRS]).[43] The TLFB (self-reported drug use status), SRRS (relapse risk), and NRS (drug craving) will be applied on Days −7, 28, 56, 84, 112, 140, and 168 (ie, after Day −7, every 4 weeks). The study participants will be assigned to one of three groups between Day −7 and Day 0. Examinations by the primary physician will be conducted at all visits until Day 168. The participants will undergo a urine test and blood test on Day 0. Blood tests will be conducted on Days 0, 28, and 84. Urine tests will be conducted at all visits until Day 168. Placebo or ifenprodil will be administered from Day 0 to Day 84 (administration period). Determinations of adverse events (AEs) will be made by the primary physicians at all visits until Day 168. The CRC will send an e-mail to confirm AEs and compliance with ifenprodil or placebo administration every 2 weeks (ie, weeks without examinations by primary physicians) until Day 168. The criterion for dropping out based on the lack of drug administration will be the following: The patient has not taken placebo or ifenprodil for a total of 25 days of the 84 day administration period. If the patients take placebo or ifenprodil on a particular day even once, then that day is considered a medication day. When participants drop out

TABLE 1 Study schedule and outcome measurement

	Pre-administration period		Administration period							Post administration period					
	Visit 1														
Timepoint Day (D)	Enrolment D −7	Allocation	Visit 2 D 0	Visit 3 D14	Visit 4 D 28	Visit 5 D 42	Visit 6 D 56	Visit 7 D 70	Visit 8 D 84	Visit 9 D 98	Visit 10 D 112	Visit 11 D 126	Visit 12 D 140	Visit 13 D 154	Visit 14 D 168
Enrollment															
Informed consent	X														
Sociodemographic profile	X														
Allocation		X													
Clinical examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments															
Self report calender format based on TLFB	X				X		X		X		X		X		X
SRRS	X				X		X		X		X		X		X
NRS	X				X		X		X		X		X		X
Urine test			X	X	X	X	X	X	X	X	X	X	X	X	X
fMRI			X						X		X				
Vital signs															
Blood test			X		X				X						
Medical treatment															
Ifenprodil/Placebo			→	→	→	→	→	→	→						

fMRI, functional magnetic resonance imaging; NRS, Numerical Rating Scale; SRRS, Stimulant Relapse Risk Scale; TLFB, Timeline Flow-Back.

from the study during the administration period based on drug discontinuation, then the assessment which is given on Day 84 for the patients who do not drop out will be given to the dropout participants. The CRC and researchers will record the participants' prescribed concurrent medications, psychosocial therapies, and complications at all visits until Day 168. The participants will receive 2000-yen prepaid cards (as a gratuity for each questionnaire application and blood test). In cases of hospitalization, if the patients express a desire and intention to continue to participate in the study and if their primary physicians permit continued participation in the study, then the patient can continue participation in the study. The researchers and CRC will manage the participants' progress and completion of ifenprodil or placebo treatment and the follow-up assessments. They will also share information about recruitment progress and data collection.

2.5 | Interventions

This study will use Cerocral fine granule 4%® (20 mg ifenprodil tartrate/0.5 g [ifenprodil tartrate and excipient]; Sanofi K.K. [Tokyo, Japan], Nichi-Iko Pharmaceutical Co., Ltd [Toyama, Japan]). The placebo will be composed of lactate only. Cerocral fine granule is ground down to be similar to fine lactate. Cerocral fine granule and fine lactate will be identical in appearance (Figure 2). The placebo in the placebo group will consist of fine lactate only (1 g/pack). The drug in the 60 mg/d ifenprodil group will consist of 0.5 g fine lactate and 0.5 g Cerocral fine granule (1 g/pack). The drug in the 120 mg/d ifenprodil group will consist of Cerocral fine granule only (1 g/pack). The CRC or researchers will give the drugs that are dispensed every 4 weeks to the study participants on Days 0, 28, and 56 (Table 1). The participants will be asked to take three packs per day after meals for 84 days. The CRC or researchers will remind the participants by e-mail to take their medications every 2 weeks (ie, weeks without examinations by primary physicians).

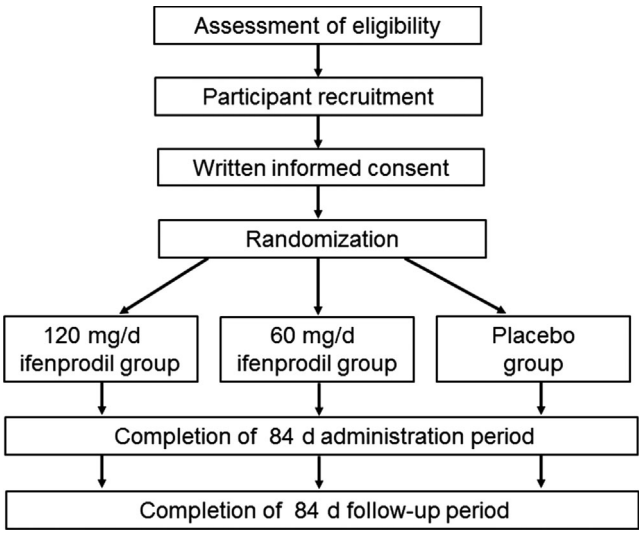

FIGURE 1 Study design and participant flow

2.6 | Randomization and blinding

The participants will be informed that they will be allocated to one of three groups (120 mg/d ifenprodil, 60 mg/d ifenprodil, and placebo) on Day −7. After baseline assessment on Day −7, the participants will be randomly assigned to one of these three groups based on dynamic allocation using the minimization method in the Translational Medical Center (TMC). Prognostic factors, including sex (male or female), DSM-5 score (<4 or ≥4), and the presence or absence of methamphetamine use in the past 4 weeks, will be used to ensure the balance of participants among groups. The CRC will send the allocation information by e-mail with a password to the allocation staff at the TMC. The allocation staff will give the results of the allocation to unblinded pharmacists by e-mail with a password. The CRC, researchers, and primary physicians who work as recruiting staff and the study participants will be blinded to group allocation.

2.7 | Study outcomes

2.7.1 | Primary outcome

The primary outcome will be the presence or absence of methamphetamine use during the 84-day ifenprodil or placebo administration period. A self-monitoring calendar format, based on TLFB methods,[41] will be used to assess methamphetamine use over the past 28 days at the baseline and follow-up assessments every 4 weeks. The participants will select and check one of three numbers (0, 1, or 2), and that

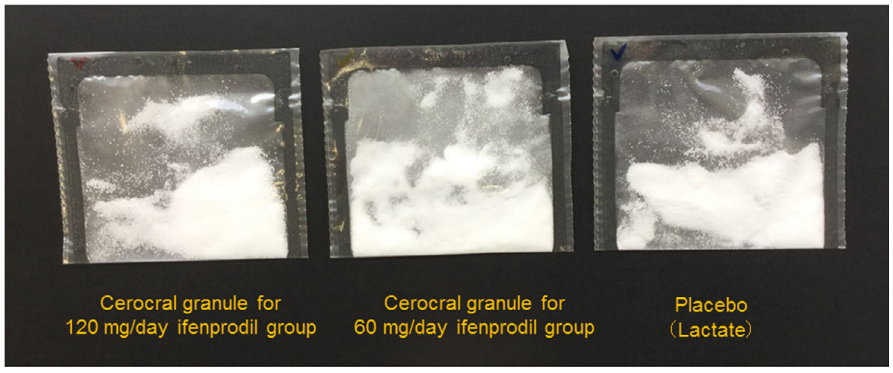

FIGURE 2 Appearance of Cerocral granule 4%® (ifenprodil) and placebo used in this study

number will be written on each date. The numbers represent the participants' drug use status: 0 (no drug or alcohol use), 1 (use of other drugs and/or alcohol), and 2 (methamphetamine use).

2.7.2 | Secondary outcomes

The days and percentage of days of abstinence from methamphetamine use during the 84-day administration period will be evaluated. The days and percentage of days of methamphetamine use during the 84-day administration period will also be evaluated. The days of abstinence and days of methamphetamine use will be assessed using a self-reported calendar format based on the TLFB method. Positive urine for methamphetamine (positive/negative, number of times, ratio) during the 84-day administration period will be assessed. Urine samples will be taken at every visit. The urine tests will be analyzed using AccuSign® MET (Princeton BioMeditech Corporation, Princeton, NJ) by staff of the clinical laboratory department. In cases of difficulty obtaining a clear positive or negative result, the staff will reexamine the urine samples using Triage DOA® (Abbott, Chiba, Japan). The final judgment of positive or negative will be made by the primary physicians.

Relapse risk during the 84-day administration period will be assessed by the SRRS. The SRRS was developed to measure various aspects of stimulant relapse risk and consists of 35 items that are measured on a 3-point Likert scale.[40] The SRRS is composed of five subscales: anxiety and intention to use drug, emotionality problems, compulsivity for drug use, positive expectancies, and lack of control over drug use and lack of negative expectancy for drug use.[40] A higher average total score and higher subscale score indicate higher relapse risk.[37,40]

Drug craving during the 84-day administration period will be assessed by the NRS. A previous study used visual analog scales (VASs) to assess craving for drugs.[44,45] Because the application of VASs is inconvenient, we adopted the NRS for the present study. The NRS includes a numerical scale from 0 to 10: 0 ("I do not want any drugs at all") to 10 ("I want drugs very much").

We will analyze data on days of abstinent, urine test results, relapse risk, and drug craving after the administration period to evaluate the stability of effects of ifenprodil.

Blood tests will be conducted to monitor safety. The following blood test parameters will be evaluated: aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), creatine kinase (CK), urea nitrogen (UN), creatinine (Cr), natrium (Na), kalium (K), chloride (Cl), tocopherol (TC), triglyceride (TG), glucose (Glu), white blood cells (WBC), red blood cell (RBCs), hematocrit (Ht), and hemoglobin (Hb). The CRC and researchers will report any abnormal variables for each item in the blood test to the primary physicians.

2.8 | Statistical analysis

All P values will be two-tailed. Values of $P < 0.05$ will be considered statistically significant.

2.9 | Primary analysis

The primary outcome will be assessed according to a per-protocol analysis. Frequencies of the presence of methamphetamine use during the 84-day administration period in the 120 mg/d ifenprodil group vs placebo group will be compared using Fisher's exact test.

2.10 | Secondary analysis

The primary outcome (ie, frequency of the presence of methamphetamine use during the 84-day administration period) will also be evaluated in the 60 mg/d ifenprodil group vs placebo group and in the 60 mg/d ifenprodil group vs 120 mg/d ifenprodil group using Fisher's exact test.

Each secondary endpoint will be analyzed in the 120 mg/d ifenprodil group vs placebo group, 60 mg/d ifenprodil group vs placebo group, and 60 mg/d ifenprodil group vs 120 mg/d ifenprodil group after the 84-day administration period using Fisher's exact test for categorical variables and Welch's t test for continuous variables. These statistical tests will be interpreted using Bonferroni-Holm adjustment for multiple comparisons. Box-Cox data transformation will be performed when appropriate.

Each primary and secondary outcome during the follow-up period will be compared between each group (ie, 120 mg/d ifenprodil group vs placebo group, 60 mg/d ifenprodil group vs placebo group, and 60 mg/d ifenprodil group vs 120 mg/d ifenprodil group) using Fisher's exact test for categorical variables and Welch's t test for continuous variables. These statistical tests will be interpreted using Bonferroni-Holm adjustment for multiple comparisons. Box-Cox data transformation will be performed when appropriate. All of the statistical analyses described above will be performed on a per-protocol basis.

For continuous variables for the primary and secondly outcomes, changes in these outcomes over time will be assessed using mixed-effect models for repeated measures. In this model, the between-subjects factor will be treatment group (120 mg/d ifenprodil, 60 mg/d ifenprodil, and placebo), and the within-subjects factor will be measurement time-point. These statistical analyses will be performed on an intention-to-treat basis.

2.11 | Descriptive statistics

Descriptive statistics will be calculated for each endpoint (including primary and secondary outcomes) in each group to confirm associations between improvement and patient characteristics. We will examine appropriate endpoints in a future clinical trial for this study based on these descriptive statistics.

2.12 | Safety evaluation

We will report the frequencies and proportions of each AE in the 120 mg/d ifenprodil group, 60 mg/d ifenprodil group, and placebo

group. We will also create cross tabulations between AEs and patient characteristics (background, compliance with drug administration, comorbidities, and co-administered drugs) to examine associations between them.

2.13 | Sample size

We set the sample size at 80 based on the study period, the number of new patients with methamphetamine use disorder for 1 year at NCNP, attrition rates that are reported in previous studies, and the expected participation rate. The number of new outpatients for 1 year is ~60-90. Because previous studies revealed dropout rates of 10%-30%,[44–50] we expect that 20 patients may drop out. We expect that the ratio of informed consent will be 50%, and 60 patients are expected to be analyzed (20 patients/group).

2.14 | Data management and access to data

The researchers and CRC will collect the raw data from the assessments and tests and transcribe the raw data to Case Report Forms (CRFs). Researchers and the CRC will also submit CRFs to the data manager at the Data Management Section, Department of Epidemiology, TMC. The data manager will review the data according to the data checklist and will send data queries to the researchers and CRC. After data cleaning with regard to the answers to queries, the data manager will fix the data temporally and enter the data into a database system for case conference. After the case conference, the data will be finally fixed. The researchers will analyze the data that are blinded under the tutorage of a responsible investigator for statistical analysis.

2.15 | Harms

Adverse events include any untoward signs, symptoms, or diseases that occur during or after drug administration in this clinical trial. The primary physicians will confirm AEs for the participants in this study in an examination that is performed every 2 weeks. The CRC or researchers will send an e-mail to the participants to confirm details about AEs every 2 weeks (ie, weeks without examinations by primary physicians). All AEs that occur during this trial will be documented, including the date of occurrence, degree of severity, existence or non-existence of treatment for AEs, and date of recovery from AEs. When serious AEs (in cases of death, threat to life, hospitalization for treatment of some disease/injury, disability or dysfunction, transmitting birth defects to descendants) occur during this study, a principal investigator (TM) will provide required treatment immediately and report the occurrence of a serious AE to the president of NCNP. The principal investigator (TM) will report the researchers who are involved in this research and share information on the AEs. Furthermore, the president of NCNP will report the occurrence of the AEs to the Ministry of Health, Labour and Welfare as necessary and publish correspondence and results about the AEs.

2.16 | Data monitoring

A monitor at the Department of Clinical Research Support in the TMC will systematically verify that the reported data are accurate and verifiable from source documents and that this study is in compliance with the approved protocol. The monitor will immediately start data monitoring after the first case registration. The monitor will verify electronic medical records and CRFs for each participant from source documents and ensure that written informed consent is obtained before participation in the trial. CRFs include the following information: informed consent, case registration, visit schedule, status of drug administration, questionnaires for assessment, results of urine tests and blood tests, concurrent medications, combined therapies, complications, and AEs.

2.17 | Auditing

CMIC Co., Ltd (Tokyo, Japan), will audit this study to ensure data quality and completeness. The audit will intend to review the systems that are utilized in this study and the participants' medical records.

3 | ETHICS AND DISSEMINATION

3.1 | Research ethics approval

Ethical approval for this study has been granted by the Ethics Committee of the NCNP and Tokyo Metropolitan Institute of Medical Science. The purpose and potential risks of this clinical trial will be fully explained to the participants before obtaining consent. The participants will be informed that their participation in this study can be withdrawn at any time. This study has been registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR; no. UMIN000030849).

3.2 | Confidentiality

Identification records of the participants will be kept confidential for 5 years after the end of the clinical trial. After 5 years, all documents for this study will be discarded. All documents that are related to the trial, including CRFs, will be recorded and labeled with participant identification codes and will not show the name of the participant. All participant data will be digitized by the data manager. Raw data (CRFs) will be stored in a locked cabinet.

3.3 | Declaration of interests

The authors declare no conflict of interest.

3.4 | Dissemination of research findings

The findings of the study will be disseminated via publications in peer-reviewed international journals. We will also present the findings at relevant research conferences, local academic symposia, and seminars.

4 | DISCUSSION

The present study has two strong points. First, this study is the first clinical trial of ifenprodil treatment for patients with methamphetamine dependence in a double-blind, placebo-controlled trial. Because the previous study of ifenprodil treatment for patients with alcohol dependence was conducted with a prospective, randomized, controlled, rater-blinded design,[37] the patients were able to recognize which drug they received (ifenprodil [Cerocral] or control drug [Cinal]) based on the receipt they received at the time of accounting in the healthcare system in Japan. Thus, we presumed that this previous study may not be sufficient to assess the efficacy of ifenprodil treatment. The present study employs a double-blind, placebo-controlled design, which is a research design that can examine the efficacy of ifenprodil treatment more objectively and accurately. Second, the patient sample in the present study is not limited to patients who can be prescribed with ifenprodil based on insurance coverage. The subjects in the previous study were limited to patients with alcohol dependence who were suspected of having mild cognitive deficiency or brain damage because these patients can be prescribed with ifenprodil based on insurance coverage.[37] These limited inclusion criteria in the previous study may have precluded an accurate evaluation of the efficacy of ifenprodil treatment.

Some difficulties in conducting this study with patients with methamphetamine dependence can be predicted. The use of methamphetamine is subject to criminal penalties, and a government crackdown on methamphetamine use has been prioritized over the treatment of patients with methamphetamine dependence in Japan.[51] Thus, it is highly likely that the patients who participate in this study have been previously imprisoned, and the patients who resume methamphetamine use will not attend follow-up visits during the study period because they are afraid of being imprisoned. These characteristics of patients with methamphetamine dependence may make the continuation of treatment difficult compared with patients with other psychiatric disorders. Many patients with methamphetamine dependence receive cognitive behavioral therapies and self-help group therapies. Thus, active information exchange among patients in the present study is expected to occur. We will need to pay close attention to prevent incorrect information from spreading so that accurate information about this study can be conveyed to the patients.

4.1 | Study status

This study is ongoing. The first participant was recruited into the trial in January 2018. Recruitment is scheduled to be completed by April 2019. The follow-ups and data collection are scheduled to be completed by September 2019.

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CONFLICT OF INTEREST

Nothing declared.

DATA REPOSITORY

As this paper is clinical trial protocol and the trial is ongoing, we do not have the data to be disclosed.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The Institutional Review Board of the NCNP and Tokyo Metropolitan Institute of Medical Science approved the study.

INFORMED CONSENT

All of the participants will provide written informed consent.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

This clinical trial was registered in the UMIN clinical trial registry (UMIN0000030849).

AUTHOR CONTRIBUTIONS

KI is the principal investigator who conceived this study. TM is a principal investigator and primary physician. AT, HK-M, and YO designed the original protocol of this study. AT, HK-M, YO, HT, and KI drafted the manuscript. HK-M and ST will participate in data collection and participant recruitment. MM, DF, YT, TM, TS, and HO participated in refinements of the protocol. AT, HT, and KM decided which statistical methods should be used. All of the authors read and approved the final manuscript to be published.

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