

## ORIGINAL ARTICLE

# Ifenprodil for the treatment of methamphetamine use disorder: An exploratory, randomized, double-blind, placebo-controlled trial

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## Abstract

**Aim:** No effective pharmacological interventions have been developed for patients with methamphetamine use disorder. Ifenprodil is a blocker of G protein-activated inwardly rectifying potassium channels, which play a key role in the mechanism of action of addictive substances. We conducted a randomized, double-blind, exploratory, dose-ranging, placebo-controlled trial to examine the clinical efficacy of ifenprodil for the treatment of methamphetamine use disorder.

**Methods:** Participants were assigned to three groups: placebo, 60 mg/d ifenprodil, or 120 mg/d ifenprodil. The drug administration period was 84 days. The primary outcome was the use or nonuse of methamphetamine during the drug administration period in the placebo group vs 120 mg/d ifenprodil group. We also assessed drug use status, relapse risk based on the Stimulant Relapse Risk Scale (SRRS), drug craving, and methamphetamine in urine as secondary outcomes. We further evaluated drug

**Abbreviations:** AE, adverse event; CRC, Clinical Research Coordinator; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EP, emotionality problem; GIRK, G protein-activated inwardly rectifying potassium; NRS, Numerical Rating Scale; SRRS, Stimulant Relapse Risk Scale; TLFB, Timeline Follow-back.

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use status and SRRS subscale scores in patients who were not taking addiction medications during the study.

**Results:** Ifenprodil did not affect the primary or secondary outcomes. However, the additional analyses showed that the number of days of methamphetamine use during the follow-up period and scores on the emotionality problems subscale of the SRRS improved in the 120 mg/d ifenprodil group. The safety of ifenprodil was confirmed in patients with methamphetamine use disorder.

**Conclusion:** The present findings did not confirm the efficacy of ifenprodil for methamphetamine use disorder treatment based on the primary or secondary outcomes, but we found evidence of its safety and efficacy in reducing emotionality problems.

**Clinical trial registration:** The study was registered at the University Hospital Medical Information Network Clinical Trial Registry (no. UMIN000030849) and Japan Registry of Clinical Trials (no. jRCTs031180080). The main registration site is jRCT (<https://jrct.niph.go.jp/>).

#### KEYWORDS

days of methamphetamine use, G protein-activated inwardly rectifying potassium channel, ifenprodil, methamphetamine use disorder, randomized-controlled trial

## 1 | INTRODUCTION

Methamphetamine is an addictive psychostimulant drug that causes aberrant physiological and psychological status.<sup>1</sup> In East Asia, South-East Asia, and North America, methamphetamine dominates drug markets. Methamphetamine use significantly increased between 2013 and 2016 in North America.<sup>2</sup> In Japan, methamphetamine is the most popular psychostimulant. Approximately 80% of drug-related crimes are associated with methamphetamine.<sup>3,4</sup> Effective pharmacological interventions for methamphetamine use disorder have not yet been developed.

G protein-activated inwardly rectifying potassium (GIRK) channels are implicated in the mechanisms of action of various addictive substances. Functional GIRK channel subunits have four heterotetramers.<sup>5-7</sup> GIRK1, GIRK2, and GIRK3 subunits have been shown to be expressed in brain regions that are associated with addiction in rodents.<sup>8,9</sup> GIRK channels are activated by the activation of G protein-coupled receptors that couple with  $G_{\alpha i/o}$  proteins<sup>10,11</sup> and are important for regulating cellular activity. Alcohol can directly open GIRK channels without the participation of G protein-coupled receptors.<sup>12</sup> *Weaver* mutant mice with a missense mutation at the channel pore in the GIRK2 subunit did not exhibit methamphetamine-induced conditioned place preference or priming effects.<sup>13</sup> A single nucleotide polymorphism of the *Kcnj6* gene, which encodes GIRK2, could serve as a marker to predict susceptibility to nicotine dependence in humans.<sup>14</sup> Therefore, GIRK channels are crucial in the mechanism of action of addictive substances.

Ifenprodil is a blocker of  $\alpha_1$ -adrenergic and GluN2B subunit-containing N-methyl-D-aspartate receptors<sup>15,16</sup> and inhibits GIRK channels.<sup>17</sup> Ifenprodil is approved as a treatment for dizziness after

brain ischemia ( $\leq 60$  mg/d).<sup>18</sup> High-dose ifenprodil is used as an analgesic in Japan.<sup>19</sup> Pretreatment with ifenprodil reduced morphine-induced conditioned place preference in mice,<sup>20</sup> and ifenprodil inhibited amphetamine-induced potentiation of excitatory postsynaptic currents in rat midbrain dopamine neurons.<sup>21</sup> Ifenprodil (60 mg/d) treatment for 3 months improved alcohol use scores in patients with alcohol dependence.<sup>22</sup> Ifenprodil (120 mg/d) also suppressed craving in a patient who was addicted to the cough medicine Bron<sup>®</sup> and a patient with alcohol dependence.<sup>23</sup> Fluoxetine and paroxetine have been reported to inhibit GIRK channels.<sup>24</sup> Ifenprodil does not have serious adverse effects.<sup>25</sup> Paroxetine can cause several serious adverse effects, such as serotonin syndrome,<sup>26</sup> and fluoxetine use is not yet approved in Japan. These studies suggest that ifenprodil may be an effective treatment for substance use disorder. We conducted an exploratory, randomized, double-blind, placebo-controlled trial to investigate the clinical safety and efficacy of ifenprodil for the treatment of methamphetamine use disorder in Japanese patients. The study protocol was previously published as a protocol article.<sup>27</sup>

## 2 | METHODS

### 2.1 | Trial design

This randomized, double-blind, exploratory, dose-ranging, placebo-controlled trial was conducted in a single center (National Centre Hospital, National Centre of Neurology and Psychiatry [NCNP], Japan). Patients were randomly assigned to the following three groups: placebo, 60 mg/d ifenprodil, and 120 mg/d ifenprodil (1:1:1 allocation ratio). The patients orally took either placebo or ifenprodil



over the 84-day administration period and were followed up for 84 days. The study was performed according to the tenets of the Declaration of Helsinki<sup>28</sup> and approved by the Ethics Committee of NCNP and Tokyo Metropolitan Institute of Medical Science. All patients provided written informed consent. Further methodological details of the protocol were published previously.<sup>27</sup> The following can be found in the Appendix S1: blood tests, dropout criteria, data management, access to data, harms, data monitoring, and data auditing.

## 2.2 | Eligibility criteria and participant recruitment

Outpatients were recruited at the National Centre Hospital, NCNP, from January 2018 to March 2019. The inclusion criteria were the following: (a) outpatients who were diagnosed with methamphetamine use disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5),<sup>1</sup> (b) outpatients who used methamphetamine in the past year, and (c) outpatients who were >20 years old when informed consent was obtained. The exclusion criteria were the following: (a) patients with severe physical diseases, (b) patients with a high risk of suicide, (c) patients with severe symptoms of substance-induced psychotic disorder, (d) patients with impairments in cognitive function, (e) patients who did not wish to be notified of their functional magnetic resonance imaging results, (f) patients who were determined to be ineligible to participate in the study by their attending psychiatrists, and (g) patients who took the GIRK channel blocker paroxetine. We screened for eligible patients who met the inclusion criteria using the in-hospital computer system.

## 2.3 | Patient schedule and assessments

The clinical research coordinator (CRC) and authors of the present study explained the study in detail to the participants and obtained informed consent from all patients, stating that participation was voluntary and that participants could withdraw from the study at any time. The CRC and authors of the present study collected information about sociodemographic characteristics, self-reported drug use status using a self-report calendar format based on the timeline follow-back (TLFB) method, relapse risk based on the Stimulant Relapse Risk Scale (SRRS),<sup>29</sup> and drug craving based on a numerical rating scale (NRS) after patients signed the informed consent form. The NRS consisted of a numerical rating scale from 0 to 10. Higher scores indicated a greater magnitude of craving for methamphetamine. These self-administered questionnaires were applied at baseline and during visits every 4 weeks until day 168 (ie, the end of the study period). On day 0, all participants underwent urine and blood tests. The urine tests were conducted at all visits. The blood tests were conducted on days 0, 28, and 84 to monitor safety. The primary physicians, CRC, and authors of the present study checked for adverse events (AEs) at all visits.

## 2.4 | Interventions

We used Cerocral fine granules 4% (20 mg ifenprodil tartrate/0.5 g; SANOFI-Nichi-Iko) as the study medication. Placebo consisted of granules without ifenprodil tartrate. Cerocral granules were ground to a consistency that was similar to fine lactate in the Pharmaceutical Department at NCNP. Patients received the medication during the drug administration period three times daily.

## 2.5 | Randomization and blinding

Patients were randomized to the three groups using the minimization method at the Translational Medical Centre (TMC), NCNP. The following prognostic factors were considered: sex, DSM-5 diagnostic criteria met (<4 criteria = mild, ≥4 criteria = moderate to severe), and methamphetamine use within the past 28 days. The allocation staff at the TMC received information from the CRC via a password-protected email, and they sent the allocation results to unblinded pharmacists via a password-protected email. The primary physicians, CRC, patients, and authors of the present study were blinded.

## 2.6 | Study outcomes

### 2.6.1 | Primary outcome

We assessed the use vs nonuse of methamphetamine during the 84-day ifenprodil or placebo administration period in the placebo and 120 mg/d ifenprodil groups as the primary outcome. A self-monitoring calendar format, based on the TLFB method, was used to evaluate methamphetamine use over the past 28 days at baseline and the follow-up assessments, every 28 days. The patients checked one of three categories (0, 1, or 2) in the self-monitoring calendar format. The categories represented the participants' drug use status: 0 (no drug use), 1 (use of other drugs and/or alcohol, absence of methamphetamine use), and 2 (methamphetamine use). When the category 2 was checked during the administration period, we defined that methamphetamine was used (ie, the presence of methamphetamine use) and calculated the ratio of patients who used methamphetamine during the administration period in both the placebo and 120 mg/d ifenprodil groups.

### 2.6.2 | Secondary outcomes

We also assessed the use vs nonuse of methamphetamine during the 84-day ifenprodil or placebo administration period in the placebo vs 60 mg/d ifenprodil groups and in the 60 mg/d ifenprodil vs 120 mg/d ifenprodil groups as secondary outcomes. We set the days of methamphetamine use during the drug administration period and follow-up period in the placebo and 120 mg/d ifenprodil groups, in the placebo vs 60 mg/d ifenprodil groups, and in the 60 mg/d ifenprodil



vs 120 mg/d ifenprodil groups as secondary outcomes. The days of methamphetamine use during the drug administration and follow-up periods were calculated using the TLFB method. The days when category 2 of the TLFB was selected were defined as days of methamphetamine use. The number of days of methamphetamine use that was calculated for each patient was cumulated in each group, and comparisons were made among groups. The positivity rate of urine methamphetamine (ie, percentage of those who had at least one positive urine test, number of positive urine tests) during the 84-day administration period was assessed. Relapse risk during the 84-day administration period was assessed using the SRRS. The SRRS was composed of the following five subscales: anxiety and intention to use the drug (AI), emotionality problem (EP), compulsivity for drug use (CD), positive expectancies and a lack of control over drug use (PL), and a lack of negative expectancy for drug use (NE). The total score ranged from 30 to 90. Subscale scores ranged from 8 to 24 for AI, 8 to 24 for EP, 4 to 12 for CD, 6 to 18 for PL, and 4 to 12 for NE. Higher total and subscale scores indicated a higher relapse risk. Finally, drug craving during the 84-day administration period was assessed using the NRS. For the above parameters, the following comparisons were performed: placebo vs 120 mg/d ifenprodil groups, placebo vs 60 mg/d ifenprodil groups, and 60 mg/d ifenprodil vs 120 mg/d ifenprodil groups.

## 2.7 | Statistical analysis

All *P*-values were two-tailed. The 95% confidence interval (CI) was computed along with *P*-values.

### 2.7.1 | Primary analysis

We evaluated the primary outcome according to a per-protocol analysis. The frequency of methamphetamine use during the drug administration period in the placebo vs 120 mg/d ifenprodil groups was compared using Fisher's exact test. If there were no missing values, then point estimates and their standard errors (or CIs) were calculated. If there were missing values, then multiple datasets were created, and missing values were completed according to the multiple imputation method. The *chi-squared* test was performed for each dataset, and combined *chi-squared* values were tested using *D*<sub>2</sub> statistics.<sup>30</sup>

### 2.7.2 | Secondary analysis

Each secondary endpoint was analyzed in the placebo vs 120 mg/d ifenprodil groups, placebo vs 60 mg/d ifenprodil groups, and 60 mg/d ifenprodil vs 120 mg/d ifenprodil groups after the drug administration period using Fisher's exact test for categorical variables and Welch's *t* test for continuous variables. These statistical test results were interpreted using Bonferroni-Holm adjustment for

multiple comparisons. Multiple comparison tests were conducted twice for the presence or absence of methamphetamine use during the drug administration period. Multiple comparison tests were also conducted three times for the days of methamphetamine use during the drug administration period. If necessary, then Box-Cox data transformation was performed.

Secondary outcomes during the follow-up period were compared between groups as in the drug administration period using Fisher's exact test for categorical variables and Welch's *t* test for continuous variables. These statistical test results were interpreted using Bonferroni-Holm adjustment for multiple comparisons. Multiple comparison tests were conducted twice for the presence or absence of methamphetamine use during the follow-up period. Multiple comparison tests were also conducted three times for the days of methamphetamine use during the follow-up period. Box-Cox data transformation was performed when appropriate. All statistical analyses were conducted on a per-protocol basis.

## 2.8 | Patient characteristics at the baseline assessment and safety evaluation

Patient characteristics at baseline and safety data were assessed among groups using one-way analysis of variance (ANOVA). The frequency and proportion of each AE in the three groups were recorded.

## 2.9 | Sample size

The sample size was calculated using *G\*power* 3.1.<sup>31</sup> The settings for the analysis of covariance were the following: effect size = 0.4,  $\alpha = 0.05$ ,  $1 - \beta = 0.8$ , number of groups = 3. These numbers were based on a previous study that investigated ifenprodil treatment in patients with alcohol dependence.<sup>22</sup> This analysis showed that the required number of patients in the present study was 52. A sample size of 80 was considered appropriate based on the number of patients at the NCNP. The number of new outpatients who were examined for drug dependence at the NCNP for 1 year was 60-90. We expected 20 patients to drop out based on the dropout rate of 10%-30% that was reported in previous studies.<sup>32-38</sup> The administration and follow-up periods in these previous studies ranged from 10 days to 36 weeks. We expected that the ratio of informed consent would be 50%, and 60 patients were expected to be analyzed.

## 2.10 | Additional analyses

For better analytical accuracy, we excluded patients who took other medications for addiction during the study. Two patients took varenicline (smoking-cessation aid), and one patient took Cerocral (ie, ifenprodil). The subsequent analysis included the following patient groups: placebo (*n* = 9), 60 mg/d ifenprodil (*n* = 11), and 120 mg/d

ifenprodil ( $n = 10$ ). We focused on the following outcomes: days of methamphetamine use and interindividual SRRS subscale scores. The sample size in the categories varied because we excluded the patients with missing data. The days and percentage of days of methamphetamine use during the drug administration and follow-up periods were calculated using the TLFB method. The ratio of days of methamphetamine use was calculated by using the days of the administration and follow-up periods (each period was 84 days) in each group as the denominator and the number of days of methamphetamine use as the numerator.

### 3 | RESULTS

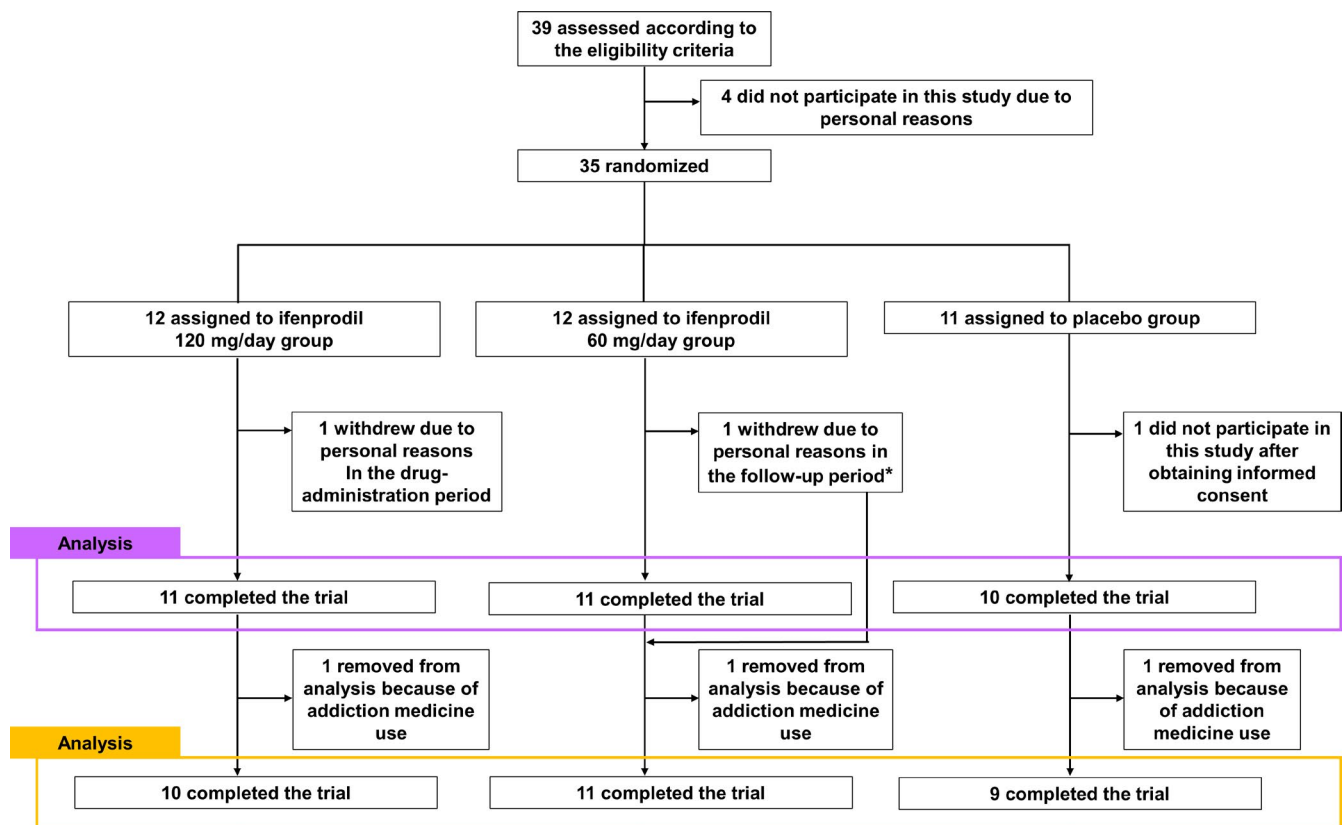
#### 3.1 | Participants

Figure 1 shows the results of study-arm (group) assignment and retention. Thirty-nine patients met the eligibility criteria, of which four did not participate in the present study because of personal reasons. Thirty-five patients were randomized and assigned to the three groups. One patient who was assigned to the placebo group did not

participate after providing informed consent. One patient who was assigned to the 120 mg/kg ifenprodil group withdrew because of personal reasons. Similarly, one patient who was assigned to the 60 mg/kg ifenprodil group withdrew because of personal reasons. In the primary and secondary analyses, the number of participants was the following: placebo group ( $n = 10$ ), 60 mg/d ifenprodil group ( $n = 11$ ), and 120 mg/d ifenprodil group ( $n = 11$ ). For the safety data, we included the one patient who had withdrawn because of personal reasons. Therefore, the number of patients per group was the following: placebo group ( $n = 10$ ), 60 mg/d ifenprodil group ( $n = 12$ ), and 120 mg/d ifenprodil group ( $n = 12$ ). There were no significant differences in patient characteristics (Table 1). All patients were diagnosed with either moderate or severe methamphetamine use disorder.

#### 3.2 | Primary outcome

We evaluated the presence or absence of methamphetamine use during the drug administration period between the placebo and 120 mg/d ifenprodil groups as the primary outcome. Table 2 lists



**FIGURE 1** Flow chart of participants. Thirty-nine patients were assessed according to the eligibility criteria. Thirty-five patients were randomly assigned to the following three groups: placebo ( $n = 11$ ), 60 mg/d ifenprodil ( $n = 12$ ), and 120 mg/d ifenprodil ( $n = 12$ ). In the placebo and 120 mg/d groups, one patient did not attend the study after providing informed consent, and two patients withdrew from participation because of personal reasons, respectively. Ten patients in the placebo group, 12 patients in the 60 mg/d ifenprodil group, and 11 patients in the 120 mg/d ifenprodil group were analyzed for the primary and secondary outcomes (purple box). For the additional analyses, patients who took other medications for addiction were removed from each group (orange box). \*The patient in the 60 mg/d ifenprodil group was included in the additional analysis because she completed the drug administration period

TABLE 1 Patient characteristics at baseline assessment

		120 mg/d ifenprodil (n = 11)	60 mg/d ifenprodil (n = 12)	Placebo (n = 10)	<i>f</i>	<i>P</i>
Age (SD)		41.7 (9.2)	43.5 (5.8)	43.4 (5.0)	0.200	.820
Sex	Male	10	11	9	0.008	.992
	Female	1	1	1		
Marital status	Currently married	1	2	0	0.107	.899
	Never married	8	9	9		
	Divorced	2	0	1		
	Widowed	0	1	0		
Education	Junior high school	1	3	1	0.640	.534
	High school	3	3	2		
	Vocational school	2	2	2		
	College or higher	5	4	5		
Job	Full-time	4	6	5	0.240	.788
	Part-time	1	0	1		
	Unemployed	2	4	2		
	On leave	2	0	0		
	Housewife/ other	2	2	2		
Substance use disorder severity (DSM-5)	4 items or more (Moderate, Severe)	11	12	10	-	-
	3 items or less (Mild)	0	0	0		
Number of patients who used methamphetamine in past 28 d		4	4	4	0.048	.953
Total score of SRRS		72 (2.3)	70.5 (3.5)	73.5 (2.6)	0.251	.780
NRS		6.3 (0.8)	5.5 (1.0)	8 (0.4)	2.072	.144

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; NRS, Numerical Rating Scale; SRRS, Stimulant Relapse Risk Scale.

the primary and secondary outcomes. We calculated the ratio of patients who used methamphetamine during the administration period in both the placebo and 120 mg/d ifenprodil groups (Table 2, primary outcome). The percentage of patients who used methamphetamine was 25% in the placebo group (of the 10 patients in the placebo group: presence [ $n = 2$ ], absence [ $n = 6$ ], unknown [ $n = 2$ ]), and 44.4% in the 120 mg/d ifenprodil group (of the 11 patients in the 120 mg/kg ifenprodil group: presence [ $n = 4$ ], absence [ $n = 5$ ], unknown [ $n = 2$ ]). No significant differences in the primary outcome were found between the placebo and 120 mg/d ifenprodil groups ( $P = .353$ ).

### 3.3 | Secondary outcomes

#### 3.3.1 | Presence or absence of methamphetamine use during the drug administration period

The  $P$ -values of secondary outcomes that are shown are adjusted values in Table 2. The percentage of the presence of methamphetamine use was 58.3% in the 60 mg/d ifenprodil group (presence [ $n = 7$ ], absence [ $n = 5$ ], unknown [ $n = 0$ ]). No significant differences

were found between the placebo and 60 mg/d ifenprodil groups (presence [ $n = 2$ ], absence [ $n = 6$ ], unknown [ $n = 2$ ];  $P = .394$ ) or between the 120 mg/d ifenprodil group (presence [ $n = 4$ ], absence [ $n = 5$ ], unknown [ $n = 2$ ]) and 60 mg/d ifenprodil group ( $P = .670$ ).

#### 3.3.2 | Days of methamphetamine use during the drug administration and follow-up periods

No significant differences in the days of methamphetamine use (ie, total methamphetamine use days) were found between the placebo and 120 mg/d ifenprodil groups during the drug administration period (28 days in placebo group, 22 days in 120 mg/d ifenprodil group;  $P = .497$ ). No difference was found between the placebo and 60 mg/d ifenprodil groups (28 days in placebo group, 20 days in 60 mg/d ifenprodil group;  $P = .422$ ) or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = .876$ ). In the follow-up period, no significant differences in the days of methamphetamine use were found between the placebo and 120 mg/d ifenprodil groups (21 days in placebo group, 8 days in 120 mg/d ifenprodil group,  $P = .435$ ). Significant differences were found between the placebo and 60 mg/d ifenprodil groups (21 days in placebo group, 62 days

TABLE 2 Results of primary and secondary outcomes

	Groups	Numerical value	Significance	P
Primary outcome				
The presence or absence of methamphetamine use during the drug administration period	Placebo vs 120 mg/d	Placebo: 25%, 120 mg/d: 44.4%	n.s.	.353
Secondary outcomes				
The presence or absence of methamphetamine use during the drug administration period	Placebo vs 60 mg/d	Placebo: 25%, 60 mg/d: 58.3%	n.s.	.394
	120 mg/d vs 60 mg/d	120 mg/d: 44.4%, 60 mg/d: 58.3%	n.s.	.670
The days of methamphetamine use during the drug administration period	Placebo vs 120 mg/d	Placebo: 28, 120 mg/d: 22	n.s.	.497
	Placebo vs 60 mg/d	Placebo: 28, 60 mg/d: 20	n.s.	.422
	120 mg/d vs 60 mg/d	120 mg/d: 22, 60 mg/d: 20	n.s.	.876
The days of methamphetamine use during the follow-up period	Placebo vs 120 mg/d	Placebo: 21, 120 mg/d: 8	n.s.	.435
	Placebo vs 60 mg/d	Placebo: 21, 60 mg/d: 62	s.	<.001
	120 mg/d vs 60 mg/d	120 mg/d: 21, 60 mg/d: 62	s.	<.001
Positive urine for methamphetamine (positive/negative) during the drug administration period	Placebo vs 120 mg/d	Placebo: 14.3%, 120 mg/d: 22.2%	n.s.	1.000
	Placebo vs 60 mg/d	Placebo: 14.3%, 60 mg/d: 44.4%	n.s.	.923
	120 mg/d vs 60 mg/d	120 mg/d: 22.2%, 60 mg/d: 44.4%	n.s.	1.000
Positive urine for methamphetamine (positive/negative) during the follow-up period	Placebo vs 120 mg/d	Placebo: 12.5%, 120 mg/d: 20.0%	n.s.	1.000
	Placebo vs 60 mg/d	Placebo: 12.5%, 60 mg/d: 28.6%	n.s.	1.000
	120 mg/d vs 60 mg/d	120 mg/d: 20.0%, 60 mg/d: 28.6%	n.s.	1.000
Positive urine for methamphetamine (number of positive urine test) during the drug administration period	Placebo vs 120 mg/d	Placebo: 14.3%, 120 mg/d: 7.4%	n.s.	.975
	Placebo vs 60 mg/d	Placebo: 14.3%, 60 mg/d: 11.1%	n.s.	1.000
	120 mg/d vs 60 mg/d	120 mg/d: 7.4%, 60 mg/d: 11.1%	n.s.	1.000
Positive urine for methamphetamine (number of positive urine test) during the follow-up period	Placebo vs 120 mg/d	Placebo: 2.1%, 120 mg/d: 3.3%	n.s.	1.000
	Placebo vs 60 mg/d	Placebo: 2.1%, 60 mg/d: 9.5%	n.s.	.542
	120 mg/d vs 60 mg/d	120 mg/d: 3.3%, 60 mg/d: 9.5%	n.s.	.787
Change of the SRRS total score from baseline to the end of drug administration period	Placebo vs 120 mg/d	Placebo: 53.1 (6.64), 120 mg/d: 50.7 (13.26)	n.s.	1.000
	Placebo vs 60 mg/d	Placebo: 53.1 (6.64), 60 mg/d: 51.9 (12.47)	n.s.	1.000
	120 mg/d vs 60 mg/d	120 mg/d: 50.7 (13.26), 60 mg/d: 51.9 (12.47)	n.s.	1.000
Change of the SRRS total score from baseline to the end of follow-up period	Placebo vs 120 mg/d	Placebo: 51.3 (8.85), 120 mg/d: 49.4 (13.26)	n.s.	1.000
	Placebo vs 60 mg/d	Placebo: 51.3 (8.85), 60 mg/d: 51.7 (14.89)	n.s.	1.000
	120 mg/d vs 60 mg/d	120 mg/d: 49.4 (13.26), 60 mg/d: 51.7 (14.89)	n.s.	1.000
Change of NRS from baseline to the end of drug administration period	Placebo vs 120 mg/d	Placebo: 5.1 (3.16), 120 mg/d: 4.6 (3.97)	n.s.	1.000
	Placebo vs 60 mg/d	Placebo: 5.1 (3.16), 60 mg/d: 3.9 (3.46)	n.s.	1.000
	120 mg/d vs 60 mg/d	120 mg/d: 4.6 (3.97), 60 mg/d: 3.9 (3.46)	n.s.	1.000
Change of NRS from baseline to the end of follow-up period	Placebo vs 120 mg/d	Placebo: 5.6 (4.42), 120 mg/d: 4.8 (3.97)	n.s.	1.000
	Placebo vs 60 mg/d	Placebo: 5.6 (4.42), 60 mg/d: 4.0 (3.46)	n.s.	1.000
	120 mg/d vs 60 mg/d	120 mg/d: 4.8 (3.97), 60 mg/d: 4.0 (3.46)	n.s.	1.000

Note: All P-values in the secondary outcomes were adjusted.

Blue letters: data not showing therapeutic effects of ifenprodil.

Abbreviations: NRS, Numerical Rating Scale; n.s., not significant; s, significant; SD, standard deviation; SRRS, Stimulant Relapse Risk Scale.



in 60 mg/d ifenprodil group;  $P < .001$ ) and between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P < .001$ ).

### 3.3.3 | Urine positivity for methamphetamine (percentage of patients with at least one positive urine test) during the drug administration and follow-up periods

No significant differences in the ratio of urine positive for methamphetamine were found between the placebo and 120 mg/d ifenprodil groups (14.3% vs 22.2%, respectively;  $P = 1.000$ ), between the placebo and 60 mg/d ifenprodil groups (14.3% vs 44.4%, respectively;  $P = .923$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = 1.000$ ) during the drug administration period. In the follow-up period, no significant differences in the ratio of urine positive for methamphetamine were found between the placebo and 120 mg/d ifenprodil groups (12.5% vs 20.0%, respectively;  $P = 1.000$ ), between the placebo and 60 mg/d ifenprodil groups (12.5% vs 28.6%, respectively;  $P = 1.000$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = 1.000$ ).

### 3.3.4 | Urine positive for methamphetamine (number of positive urine tests) during the drug administration and follow-up periods

In the administration period, no significant differences in the number of positive urine tests were found between the placebo and 120 mg/d ifenprodil groups (6 vs 4, respectively;  $P = .974$ ), between the placebo and 60 mg/d ifenprodil groups (6 vs 6, respectively;  $P = 1.000$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = 1.000$ ). In the follow-up period, no significant differences in the number of positive urine tests were found between the placebo and 120 mg/d ifenprodil groups (1 vs 1, respectively;  $P = 1.000$ ), between the placebo and 60 mg/d ifenprodil groups (1 vs 4, respectively;  $P = .542$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = .787$ ).

### 3.3.5 | Total SRRS scores during the drug administration and follow-up periods

In the administration period, no significant differences in total SRRS scores were found between the placebo and 120 mg/d ifenprodil groups (53.1 [SD = 6.6] vs 50.7 [SD = 13.2], respectively;  $P = 1.000$ ), between the placebo and 60 mg/d ifenprodil groups (53.1 [SD = 6.6] vs 51.9 [SD = 12.4], respectively;  $P = 1.000$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = 1.000$ ). In the follow-up period, no significant differences in total SRRS scores were found between the placebo and 120 mg/d ifenprodil groups (51.3 [SD = 8.8] vs 49.4 [SD = 13.2], respectively;  $P = 1.000$ ), between the placebo and 60 mg/d ifenprodil groups (51.3 [SD = 8.8] vs

51.7 [SD = 14.8], respectively;  $P = 1.000$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = 1.000$ ).

### 3.3.6 | Numerical rating scale scores (drug craving) during the drug administration and follow-up periods

In the administration period, no significant differences in NRS scores were found between the placebo and 120 mg/d ifenprodil groups (5.1 [SD = 3.1] vs 4.6 [SD = 3.9], respectively;  $P = 1.000$ ), between the placebo and 60 mg/d ifenprodil groups (5.1 [SD = 3.1] vs 3.9 [SD = 3.4], respectively;  $P = 1.000$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = 1.000$ ). In the follow-up period, no significant differences in NRS scores were found between the placebo and 120 mg/d ifenprodil groups (5.6 [SD = 4.4] vs 4.8 [SD = 3.9], respectively;  $P = 1.000$ ), between the placebo and 60 mg/d ifenprodil groups (5.6 [SD = 4.4] vs 4.0 [SD = 4.5], respectively;  $P = 1.000$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = 1.000$ ).

## 3.4 | Results of the additional analyses

### 3.4.1 | Days of methamphetamine use during the drug administration and follow-up periods

Table 3 shows the results of the additional analyses. There were no significant differences in the frequency of days of methamphetamine use during the drug administration period between the placebo and 120 mg/d ifenprodil groups (2.4% vs 3.3%, respectively;  $P = .952$ ), between the placebo and 60 mg/d ifenprodil groups (2.4% vs 2.2%, respectively;  $P = 1.000$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = .952$ ). For this outcome, the analysis included the following groups: placebo ( $n = 7$ ), 60 mg/d ifenprodil ( $n = 8$ ), and 120 mg/d ifenprodil ( $n = 8$ ). The sample size varied because patients with missing data were excluded.

Significant differences in the ratio of days of methamphetamine use during the follow-up period were found between the placebo and 120 mg/d ifenprodil groups (3.1% vs 0.0%, respectively;  $P < .001$ ), between the placebo and 60 mg/d ifenprodil groups (3.1% vs 5.8%, respectively;  $P = .016$ ), and between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P < .001$ ). For this outcome, the analysis included the following groups: placebo ( $n = 8$ ), 60 mg/d ifenprodil ( $n = 9$ ), and 120 mg/d ifenprodil ( $n = 4$ ). The sample size varied because patients with missing data were excluded.

### 3.4.2 | Intraindividual changes in SRRS EP subscale scores from baseline to the end of the drug administration and follow-up periods

Table 3 shows these results. There were no significant differences in intraindividual changes in EP subscale scores from baseline to the





end of the drug administration period in the placebo and 60 mg/d ifenprodil groups (placebo:  $-1.56$  [SD = 4.6],  $P = .347$ ; 60 mg/d ifenprodil:  $-1.18$  [SD = 2.0],  $P = .084$ ). There was a significant difference in intraindividual changes in EP subscale scores from baseline to the end of the drug administration period in the 120 mg/d ifenprodil group ( $-4.33$  [SD = 4.6],  $P = .022$ ). For this outcome, the analysis included the following groups: placebo ( $n = 9$ ), 60 mg/d ifenprodil ( $n = 11$ ), and 120 mg/d ifenprodil ( $n = 9$ ). The sample size varied because patients with missing data were excluded. There were no significant differences in intraindividual changes in EP subscale scores from baseline to the end of the follow-up period in the placebo and 60 mg/d ifenprodil groups (placebo:  $-0.75$  [SD = 3.1],  $P = .516$ ; 60 mg/d ifenprodil group:  $-1.78$  [SD = 2.7],  $P = .086$ ). A significant difference in intraindividual changes was found in the 120 mg/d ifenprodil group ( $-4.88$  [SD = 2.9],  $P = .002$ ). For this outcome, the analysis included the following groups: placebo ( $n = 8$ ), 60 mg/d ifenprodil ( $n = 9$ ), and 120 mg/d ifenprodil ( $n = 8$ ). The sample size varied because patients with missing data were excluded.

### 3.4.3 | Group differences in changes in SRRS EP subscale scores from baseline to the end of the drug administration and follow-up periods

Table 3 shows these results. There were no significant group differences in changes in EP subscale scores from baseline to the end of the drug administration period between the placebo and 120 mg/d ifenprodil groups ( $P = .222$ ), between the placebo and 60 mg/d ifenprodil groups ( $P = .827$ ), or between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = .084$ ). Significant group differences in interindividual changes in EP subscale scores from baseline to the end of the follow-up period were found between the placebo and 120 mg/d ifenprodil groups ( $P = .017$ ) and between the 120 mg/d ifenprodil and 60 mg/d ifenprodil groups ( $P = .043$ ). No significant group differences were found between the placebo and 60 mg/d ifenprodil groups ( $P = .482$ ). Additional analyses of other outcomes are reported in the Details of the Results of Additional Analyses in the Appendix S1 (Table S1).

### 3.5 | Safety data

Table 4 shows the AEs that occurred in two or more patients in the three groups. Data from one patient in the 120 mg/d ifenprodil group who dropped out of the study because of personal reasons are included. No significant differences were found among the three groups. The most common AE during the study period was common cold symptoms. Importantly, the AEs were not associated with the administration of ifenprodil or placebo, as assessed by primary physicians. There were two cases with severe AEs (ie, hospitalization because of disturbances of consciousness after brotizolam overdose and because of nasal septum deviation) that were reported to the Institutional Review Board (Table S2). For the case of brotizolam

overdose, the primary physician found no causal relationship between ifenprodil/placebo administration and hospitalization. This patient presented with insomnia because of strong craving for methamphetamine and took brotizolam. The patient who was hospitalized because of nasal septum deviation had been scheduled for this hospitalization before study enrollment. The other AEs and severe AEs were listed in Table S2.

## 4 | DISCUSSION

The present findings showed that ifenprodil is safe for the treatment of methamphetamine use disorder, but we found no evidence of efficacy with regard to the primary or secondary outcomes. Nonetheless, the additional analyses showed that the days of methamphetamine use during the follow-up period were lower and SRRS EP subscale scores improved after treatment with 120 mg/d ifenprodil compared with both placebo and 60 mg/d ifenprodil. These results suggest that beneficial outcomes can be achieved with ifenprodil for the treatment of methamphetamine use disorder.

We set the use vs nonuse of methamphetamine, days of methamphetamine use, urine positivity, SRRS scores, and NRS scores as primary and secondary outcomes, but none of these outcomes supported the efficacy of ifenprodil for the treatment of methamphetamine use disorder. Although these outcomes have been previously used to investigate the efficacy of drug treatment and cognitive therapy for methamphetamine use disorder,<sup>30,39,40</sup> these outcomes may have been insufficient to assess efficacy in the present study. In the additional analyses, we excluded patients who were on other medications to treat addiction during the study to eliminate possible confounding effects. Interestingly, we found that 120 mg/d ifenprodil improved the days of methamphetamine use during the follow-up period.

Emotionality problems on the SRRS include anxiety, loneliness, and irritability. Glasner-Edwards et al reported that negative affective states (eg, anxiety and depression) increased relapse risk in patients with methamphetamine use disorder.<sup>41,42</sup> A recent study reported that COVID-19 pandemic-related stress (eg, anxiety and loneliness that were attributable to being unable to go out) was associated with the relapse of methamphetamine use.<sup>43</sup> These previous studies demonstrate that emotional states are important in methamphetamine use disorder. Previous studies showed that ifenprodil treatment was effective in the context of impairments in cognitive function. For example, ifenprodil-treated rats exhibited a decrease in depressive-like behavior.<sup>44</sup> Clinical case reports showed that ifenprodil treatment was effective for patients with posttraumatic stress disorder.<sup>45,46</sup> In the present study, we found that treatment with 120 mg/d ifenprodil improved EPs, including anxiety, loneliness, and irritability, in the context of methamphetamine use disorder. However, the sample size in this additional analysis was small because we excluded patients who used other medications to treat addiction or who had missing data at the study visits where we collected self-administered questionnaires. Further studies are needed

TABLE 3 Results of additional analyses

	Groups: the days of methamphetamine use/total days, (%)	Significance	P
The days of methamphetamine use during the drug administration period			
Placebo vs 120 mg/d ifenprodil	Placebo: 14/588, 2.4% 120 mg ifenprodil: 22/672, 3.3%	n.s.	.952
Placebo vs 60 mg/d ifenprodil	Placebo: 14/588, 2.4% 60 mg ifenprodil: 15/672, 2.2%	n.s.	1.000
120 mg/d ifenprodil vs 60 mg/d ifenprodil	120 mg ifenprodil: 22/672, 3.3% 60 mg ifenprodil: 15/672, 2.2%	n.s.	.952
The days of methamphetamine use during the follow-up period			
Placebo vs 120 mg/d ifenprodil	Placebo: 21/672, 3.1% 120 mg ifenprodil: 0/336, 0.0%	s.	<.001
Placebo vs 60 mg/d ifenprodil	Placebo: 21/672, 3.1% 60 mg ifenprodil: 44/756, 5.8%	s.	.016
120 mg/d ifenprodil vs 60 mg/d ifenprodil	120 mg ifenprodil: 0/336, 0.0% 60 mg ifenprodil: 44/756, 5.8%	s.	<.001
	Score difference (SD)	Significance	P
Emotionality problems; intraindividual variation from baseline to day 84			
Placebo	-1.56 (4.0)	n.s.	.347
120 mg/d ifenprodil	-4.33 (4.6)	s.	.022
60 mg/d ifenprodil	-1.18 (2.0)	n.s.	.084
Emotionality problems; intraindividual variation from baseline to day 168 (follow-up)			
Placebo	-0.75 (3.1)	n.s.	.516
120 mg/d ifenprodil	-4.88 (2.9)	s.	.002
60 mg/d ifenprodil	-1.78 (2.7)	n.s.	.086
	Score difference	Significance	P
Group differences of Emotionality problems from baseline to day 168 (follow-up)			
Placebo vs 120 mg/d ifenprodil	-0.75 vs -4.88	s.	.017
Placebo vs 60 mg/d ifenprodil	-0.75 vs -1.78	n.s.	.483
120 mg/d ifenprodil vs 60 mg/d ifenprodil	-4.88 vs -1.78	s.	.043

Abbreviations: n.s., not significant; s., significant; SD, standard deviation.

Red letters: data showing therapeutic effects of ifenprodil; Blue letters: data not showing therapeutic effects of ifenprodil.

TABLE 4 Adverse events that occurred in two or more patients in the three groups during the study period

	120 mg/d ifenprodil (n = 12)	60 mg/d ifenprodil (n = 12)	Placebo (n = 10)	f	P
Common cold	8	5	4	1.003	.378
Diarrhea	2	2	0	0.912	.412
Headache	2	1	0	0.912	.412
Cough	2	0	0	2.006	.152
Syphilis	0	0	2	2.735	.081
Constipation	1	1	0	0.414	.664
Shoulder pain	1	0	1	0.560	.577
Hay fever	1	1	0	0.414	.664
Low back pain	0	1	1	0.560	.577
Allergic rhinitis	0	1	1	0.560	.577

to verify the efficacy of ifenprodil in improving EPs in patients with methamphetamine use disorder.

To our knowledge, this was the first randomized-controlled trial on a pharmacotherapy for the treatment of methamphetamine use disorder in Japan. Japan is an ideal location to evaluate specifically methamphetamine use disorder because of the relatively low number of multidrug abusers compared with other countries.<sup>47</sup> Previous

clinical studies for patients with methamphetamine use disorder reported dropout rates of 10%–30%.<sup>32–38</sup> One of our concerns was that patients who resumed methamphetamine use would not return for follow-up visits, possibly because of their fear of imprisonment.<sup>27</sup> However, only three of the 35 participants in this study dropped out. This dropout rate suggests our study protocol was appropriate for these patients with methamphetamine use disorder.



The present study has limitations. First, the number of patients was low, and the target sample size was not achieved. It is difficult for patients with methamphetamine use disorder to access medical institutions in Japan. Future studies should have a longer recruitment period to study larger cohorts. Second, self-administered questionnaires and self-reports of methamphetamine use were not objective indicators. Third, we conducted this study in a single center in Japan. Multicenter studies are needed that include a larger number of patients.

Overall, this was the first clinical trial on the treatment of methamphetamine use disorder with ifenprodil. Our findings confirmed the safety of ifenprodil, and ifenprodil at the highest dose exerted slight efficacy. Future studies with more patients are needed to further compare the effects of placebo and 120 mg/d ifenprodil to more definitively determine whether ifenprodil is effective for the treatment of methamphetamine use disorder.

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## CONFLICT OF INTERESTS

Kazutaka Ikeda received speaker's fees from Sumitomo Dainippon Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo, Eisai Co., Ltd., MSD KK, and TV Asahi Productions Co., Ltd. Kazutaka Ikeda received consulting honoraria from Sumitomo Dainippon Pharma Co., Ltd., Atheneum Partners, Nippon Chemiphar, and VistaGen Therapeutics, Inc, and research grants from Asahi Kasei Pharma Corporation. Tsuyoshi Sasaki received speaker's fees from Eisai, Otsuka, Kyowa, Towa, GlaxoSmithKline, Shionogi, Shire, Daiichi Sankyo, Taisho, Dainippon Sumitomo, Tanabe Mitsubishi, Eli Lilly, Novartis, Nobel Pharma, Meiji Seika, and Janssen. Tsuyoshi Sasaki received research grants from Otsuka, Shionogi, Taisho, Dainippon Sumitomo, and Novartis. The other authors report no financial relationships with commercial interests. None of the authors have financial disclosures with regard to the subject of this work.

## AUTHOR CONTRIBUTIONS

KI was the principal investigator who conceived this study. TM was the principal investigator and primary physician. AT, HK-M, and YO designed the original protocol for this study. HK-M and KI drafted the manuscript. HK-M, EB, and MK participated in data collection and patient recruitment. DF, YT, TM, TS, and HO participated in refinements of the protocol. AT, HT, and KM decided which statistical methods should be used. SH, TK, and YT conducted the statistical analyses. All authors read and approved the final manuscript to be published.

## APPROVAL OF RESEARCH PROTOCOL BY INSTITUTIONAL REVIEWER BOARD

The Institutional Review Board of the National Center of Neurology and Psychiatry and Tokyo Metropolitan Institute of Medical Science approved the study.

## INFORMED CONSENT

All participants provided written informed consent.

## DATA AVAILABILITY STATEMENT

We do not share individual de-identified participant data. All data generated or analyzed during this study are included in this published article and its supplementary information file Data S1.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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