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An Open-Label, Dose-Titration Tolerability Study of Atomoxetine Hydrochloride in Japanese Adults with Attention-Deficit/Hyperactivity Disorder

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Abstract

Aims: The main purpose of this first atomoxetine study in Japanese adults with Attention-Deficit/Hyperactivity Disorder (ADHD) was to investigate the tolerability of an 8 week treatment regimen.

Methods: This was an open-label, dose escalation study conducted in 45 Japanese patients aged at least 18 years with DSM-IV-defined ADHD. Patients received atomoxetine orally for 8 weeks. Atomoxetine administration was started at 40 mg/day (7 days), and subsequently increased to a maximum dose of 120 mg/day. Tolerability was assessed by discontinuation rate due to adverse events. Adverse events, laboratory tests, vital signs and electrocardiograms were collected. In addition, ADHD symptoms were

assessed by using the Japanese version of the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV) scores.

Results: 39 patients completed the study period. Atomoxetine was well tolerated with a 6.7% (3/45) discontinuation rate due to nausea, malaise and anorexia. The most commonly reported adverse events were nausea, nasopharyngitis and headache; there were no unexpected safety concerns. No deaths or serious adverse events were reported. Mean CAARS-Inv:SV-J total ADHD symptom scores decreased in a time-dependent manner; the mean change from baseline to endpoint was -15.0 ($p<0.001$).

Conclusions: This study showed that atomoxetine was well tolerated in these patients and suggested that atomoxetine at a maximum dose of 120 mg/day would be safe in Japanese ADHD patients.

Key Words: atomoxetine, safety, tolerability, Japanese adult, ADHD

Running Title: Atomoxetine in Japanese adults with ADHD

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is a chronic neurodevelopmental disorder with onset typically prior to 7 years of age. The predominant symptoms involve problems of inattention, hyperactivity and impulsivity. ADHD had been thought to be a specific disorder of children, and therefore was not considered to be observed in adults for a long time.[1] However, multiple lines of research have demonstrated that ADHD is a chronic disorder with onset in childhood that persists into adulthood in 30 to 80% of all children with ADHD. [2,3,4] Awareness of adult ADHD was low, and ADHD symptoms in adulthood include poor planning and organization, poor memory, difficulty in finishing daily jobs, lower academic achievement, distractibility and restlessness.[5,6] Accordingly, some adult patients find it difficult to cope in their work and life. In addition, ADHD is known to be associated with various comorbid disorders.[7] Although psycostimulants and atomoxetine are available for adult ADHD patients in some other countries, there is no approved medication for Japanese adult patients. [8] Therefore, medication in adults is considered necessary for treatment of ADHD symptoms.

Atomoxetine hydrochloride (hereafter referred to as atomoxetine) is a selective inhibitor of the presynaptic norepinephrine transporter, with little affinity for other neurotransmitter transporters or receptors.[9] Atomoxetine is classified as a non-stimulant and has a very low risk of abuse.[10]

Atomoxetine is known to be metabolized by cytochrome P450 2D6 (CYP2D6) predominantly.[11,12] It is reported that few people are classified as poor metabolizers (PM), that is some CYP2D6 gene mutations or deletions associated with defective CYP2D6 metabolism. Shimizu et al reported that there was racial differences in the frequency of PM on CYP2D6; 1.9% of Asian and 7.7% of Caucasians.[13]

In a placebo-controlled, double-blind trial of atomoxetine in Japanese children and adolescents with ADHD aged from 6 to 17 years, atomoxetine was shown to be generally well tolerated with no safety concerns.[14] Atomoxetine was also found in that study to be effective at reducing ADHD symptoms as shown by decreases in ADHD RS-IV-J:I total score (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored, translated and validated in Japanese). As of February 2009, atomoxetine has been approved for children and adolescents with ADHD in 84 countries and regions.

While there are a number of studies of atmoxetine treatment in child and adolescent ADHD patients, few studies have been reported in adult ADHD patients. However, these studies have also demonstrated that atomoxetine was safe and efficacious in adults with ADHD[15,16] and at present atomoxetine has been approved for adult use in more than 39 countries including the United States. On the other hand, currently there are no data available regarding the safety and efficacy of atomoxetine in Asian adult patients with ADHD.

As a first step in this patient group, the present study investigated the tolerability of atomoxetine in Japanese adults with ADHD to obtain a preliminary assessment of safety in these patients. In addition, changes in ADHD symptoms following atomoxetine treatment were assessed by using the Japanese version of the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV-J; Multi-Health System Inc, North Tonawanda , NY, U.S.A.).[17]

METHODS

Patients

This study included 45 Japanese adult ADHD patients aged 18.5 to 59.4 years from

19 study sites in Japan. All study sites and principle investigators were as follows: Hokkaido University Hospital (Ichiro Kusumi), Fukushima Medical University Hospital (Shinichi Niwa), Saitama Medical University Hospital (Fujio Yokoyama), Kounodai Hospital, International Medical Center of Japan (Tetsuro Enomoto), NIippon Medical School Hospital (Takuya Saito), Sakurai Clinic (Kimiko Sakurai), Tokyo Metropolitan Children's Medical Center (Satoru Yamada), Nihon University Nerima Hikarigaoka Hospital (Kentaro Ohga), National Center For Child Health and Development (Masutomo Miyao), Tokai University Hospital (Hideo Matsumoto), Kanazawa University Hospital (Toshio Munesue), Chiba University Hospital (Michiko Nakazato), Myojinshita Clinic (Shusuke Yoneda), Toho University Omori Medical Center (Masafumi Mizuno), Nagoya University Hospital (Norio Ozaki), Taguchi Clinic (Takashi Taguchi), Nagamineminami Clinic (Takaaki Okano), Kyoto University Hospital (Takashi Okada), Nara Medical University Hospital (Miyuki Sadamatsu). All investigators were well-trained experienced psychiatrists, receiving specific training for the use and evaluation of CAARDID, CAARS Inv:SV-J and CAARS S-SV-J before participating a trial study. Eli Lilly Japan KK obtained the permission to use CAARS-J for this study and the CAARS-J validation study from Multi Health System Inc. Linguistic validation was conducted by Multi Health System Inc.; CAARS-J was generated by translation into Japanese from the original English version, followed by back-translation into English by Multi-Health System Inc. The reliability and validity of

the CAARS Inv:SV-J was validated by evaluating internal consistency, the capability of distinguishing between ADHD patients and healthy adults, and the correlation with other rating scales.[18]

At study entry, patients had to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV™) criteria for current ADHD and have a historical diagnosis of ADHD during childhood based on the Conners' Adult ADHD Diagnositic Interview (CAADID). Patients had a score ≥ 2 on at least 6 items of either the inattentive symptom or hyperactive/impulsive symptom subscales on the Conners' Adult ADHD Rating Scales-Investigator Rated: Screening Version (CAARS-Inv:SV-J). Their total score on all 18 items of the CAARS-Inv:SV-J scale (sum of the inattention and hyperactivity/impulsivity subscales) was ≥20, and their CGI-ADHD-S score was 4 (moderate symptoms) or higher.

Patients who met the following DSM-IV™ diagnostic criteria were excluded from the study: current major depressive disorder, current anxiety disorder requiring anti-anxiety drug therapy except for those taking benzodiazepines analogues, either alcohol dependence or alcohol abuse, or either drug dependence or drug abuse. Patients with organic brain disease, or a history of bipolar disorder, schizophrenia, psychotic disorder or pervasive developmental disorder (DSM-IV™) were also excluded.

All patients underwent full clinical and laboratory screening; information on patient medical and psychiatric history was collected, and all previous therapy for ADHD was noted. Additionally, blood samples were drawn at the initial study visit and analyzed for CYP2D6 genotype to categorize patients into extensive metabolizers (EM) or poor metabolizers (PM). If patients had two nonfunctional alleles, a PM genotype was assigned; otherwise, an EM genotype was assigned.

Written informed consent was obtained from each participant prior to beginning the procedures for this study. Each site's institutional review board approved the conduct of the study, which was developed in accordance with good clinical practice (GCP) and the ethical principles in Declaration of Helsinki.

Study Design

This was an open-label, dose escalation study that consisted of 3 study periods (Figure 1). Study Period I was an assessment and washout period to collect baseline measures prior to administration of atomoxetine. If it was determined at Visit 1 that the patient was taking an excluded drug, this drug was discontinued and a washout period conducted before giving atomoxetine to the patient at Visit 2. Study Period II was an 8 week, dose escalation atomoxetine treatment period. Patients started once daily oral administration of atomoxetine at 40 mg/day for 7 days. This was followed

by stepwise titration to a maximum of 120 mg/day （Figure 1） unless there was a tolerability issue. However, if the investigator determined there was a safety concern and it was difficult to increase or maintain the dose, the dose was either maintained at the current level or reduced to the next lowest level, respectively. Study Period II was followed by a 2-week observational period after study drug withdrawal (Study Period III).

Tolerability and Safety

The primary objective of this study was to assess tolerability, as measured by the discontinuation rate due to adverse events, in doses up to 120 mg/day. An adverse event was defined as any unfavorable medical event, newly emerged or the deterioration of a preexisting condition, that occurred in a patient after administration of atomoxetine, without regard to the possibility of a causal relationship. Adverse events, laboratory tests, vital signs, weight and electrocardiograms (ECG) were collected in Study Periods II and III. For analysis of ECG results, the Fridericia corrected QT interval (QTcF) was preferred because the Bazett method of correction is known to over-correct heart rate effects, and is therefore not appropriate when assessing safety in a drug that increases heart rate.

ADHD Symptoms and other Efficacy Measures

ADHD symptoms were assessed by using the 18 items of CAARS-Inv:SV-J scale, the Japanese version of the Conners' Adult ADHD Rating Scale- Investigator Rated: Screening Version.[17] This scale contains two 9 item symptom-related subscales: inattention and hyperactivity-impulsivity. The investigators met with patients at biweekly study visits to discuss their symptoms during the previous week and evaluated each CAARS-Inv:SV-J item using a 4-point scale. The change from baseline to endpoint in the 18 item total ADHD symptom score (sum of the inattention and hyperactivity/impulsivity subscales) was used to measure changes in ADHD symptoms. The mean change from baseline to endpoint in the inattention and hyperactivity/impulsivity subscales was also assessed. Severity of ADHD was further evaluated using the CGI-ADHD-S score based on a 7 item scale.[19,20]

In addition, CAARS-S:SV-J total ADHD symptoms score (self-check), Hamilton Depression Rating Scale 17 (HAMD-17) for depression, Hamilton Anxiety Rating Scale 14 (HAMA-14) for anxiety, Short Form-36 version 2 (SF-36v2) for health-related QOL and Stroop Color Word test for cognitive function were also measured.

Statistical Analyses

Analyses were performed separately for Study Period II and Study Period III on patients in the Full Analysis Set (FAS). This included patients who enrolled in the study and received at least one dose of atomoxetine. The purpose of the analyses in Study Period II (FAS Study Period II) was to assess the safety of atomoxetine treatment and the changes in CAARS-Inv:SV-J and CGI-ADHD-S scores. Analyses in Study Period III (FAS Study Period III) assessed safety after completion/discontinuation of atomoxetine treatment. Baselines in the Study Period II and Study Period III analyses were defined as the last non-missing observation of Visit 1 and Visit 2, and the last available observation in Study Period II, respectively. To summarize the data, descriptive statistics were used for continuous variables. Both frequency counts and percentages were used for categorical variables. All statistical tests were performed based on a two-sided significance level of 0.05 unless otherwise specified.

Adverse events and vital sign values were summarized with frequency and percentage. Terms for adverse events were coded by MedDRA version 11.0. The discontinuation rate due to adverse events was summarized using the frequency, percentage and the 2-sided 95% confidence interval based on the binomial distribution. Descriptive statistics of baseline values, post-baseline values, and changes from baseline were summarized by visit for the continuous safety variables and all efficacy variables (i.e., variables used to measure changes in CAARS-Inv:SV-

J and CGI-ADHD-S scores). Descriptive statistics of endpoint values (last observation carried forward [LOCF]) and their changes from baseline were also summarized. A paired t-test for efficacy variables and the Wilcoxon signed rank test for safety variables were performed to evaluate changes from baseline. Data were analyzed by the SAS version 8.02 of WINDOWS edition.

RESULTS

Patients

Informed consent was obtained from 64 patients, of whom 45 were enrolled into the study and received at least one dose of atomoxetine. The reason and the number of exclusion with 19 patients as screening failure was as follows: subject decision: withdrawal of informed consent (1); patient's own reason (1); difficult to wash out methlyphenidate (1); wish for discontinuation (1), did not met inclusion criteria (11), met exclusion criteria (4). Of which two patients were excluded by screening who met exclusion criteria of commodities related to major depressive disorder and seriously suicidal. Patient disposition is shown in Figure 2: 39 patients (86.7%) completed Study Period II and 6 patients discontinued from the study before beginning Study Period III. The reasons for discontinuation were as follows: adverse events (3 patients); protocol violation, subject decision, physician decision (1 patient each). Two patients decided to withdraw during Study Period III.

Patient characteristics for the FAS analysis are shown in Table 1. The mean age was 33.12 years with the inattentive ADHD subtype being most prevalent at 62.2% (28/45). The CYP2D6 phenotype test showed that 44 patients were classified as EMs and one patient as a PM. The mean CAARS-Inv:SV-J total ADHD symptom score was 31.2 at baseline (range 20-49). CGI-ADHD-S scores indicated that 51.1% (23/45) of patients were markedly ill, and all patients were at least moderately ill in terms of ADHD severity.

The proportion of compliant patients at each visit was between 93.2% and 100.0%. Compliance was defined as having taken atomoxetine on at least 70% of the days between one visit and the next. At Visit 5, when according to the protocol the patient was able to be prescribed the maximum dose of 120 mg/day, the mean dose was close to the maximum (Visit 5: 113.0 mg/day and Visit 6: 113.8 mg/day; median 120.0 mg/day at both visits). In addition, the proportion of patients taking the maximum dose at Visits 5 and 6 was high (78.0% and 75.0%, respectively).

Discontinuation rate due to adverse events

The tolerability of atomoxetine was assessed by the discontinuation rate due to adverse events. Three patients discontinued at Visit 4 (Study Period II) due to adverse events resulting in an overall discontinuation rate of 6.7% (3/45

[95% CI = 1.4-18.3]). Adverse events that led to discontinuation were nausea, malaise and anorexia (1 patient each), all of which were considered by the investigator to be possibly related to atomoxetine. At the time of these events, atomoxetine doses were between 80 mg/day and 105 mg/day. No patients discontinued due to an adverse event while on a dose of 120 mg/day. Fourteen (31.1%) patients did not progress to a higher dose of study drug at the prescribed time due to adverse events. Nausea and malaise were the two most commonly reported events that prevented an increase in dose or led to a dose reduction.

Adverse events

Table 2 summarizes adverse events that occurred in at least 5% of patients in Study Period II. Frequently occurring adverse events were nausea (46.7%), nasopharyngitis (35.6%), headache (24.4%), somnolence (20.0%), anorexia (20.0%), and thirst (20.0%). While one patient experienced severe anorexia which led to discontinuation from the study, all other adverse events were mild or moderate. During Study Period III, the most frequently occurring adverse event was headache (24.4%); all adverse events were mild or moderate.

Laboratory tests, vital signs, weights and ECGs

Statistically significant mean decreases were seen for alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), chloride and cholesterol. With the exception of cholesterol, these changes did not involve high or low abnormal values in individual patients. Four clinically significant laboratory abnormalities (1 patient for each) were reported: increased blood urea, increased blood uric acid, increased blood thyroid stimulating hormone and decreased white blood cell count. All were mild in intensity.

There were statistically significant increases from baseline in mean pulse ($p<0.001$, at all visits), and mean diastolic blood pressure at all visits ($p=0.031$, 0.003, <0.001, 0.026 and 0.007 for at visit 3, 4, 5, 6 and endpoint, respectively). Mean pulse increased by 12.8 bpm from baseline to endpoint (LOCF) and mean diastolic blood pressure by 4 mmHg. Mean values for diastolic / systolic blood pressure and pulse returned to near baseline levels in Study Period III.

Changes in mean weight from baseline at each visit were statistically significant ($p<0.001$). Mean weight decreased from baseline to endpoint (LOCF) by 1.6 kg.

A statistically significant increase in mean QT interval from baseline to endpoint (LOCF) was observed using the Bazett correction (12.8 ms: $p<0.001$), however, no statistically significant change was seen in the preferred QTcF interval (2.1 msec : $p=0.349$). While four patients had a QTcF interval increase of more than 30 msec

from baseline in Study Period II, no patients showed an increase from baseline of more than 60 msec.

ADHD Symptoms and other Efficacy Measures

A statistically significant ($p<0.001$) decrease of -15.0 from baseline to endpoint (LOCF) was observed in the mean CAARS-Inv:SV-J total ADHD symptom score (Figure 3). The mean CAARS-Inv:SV-J total ADHD symptom score decreased incrementally at each visit (Visit 3 to Visit 6, all $p<0.001$). Similar statistically significant results were seen at all time points for the CAARS-Inv:SV-J inattentive and hyperactive/impulsive subscale scores ($p<0.001$). Changes from baseline to endpoint were -9.9 for inattentive and -5.0 for hyperactive/impulsive symptoms (Figure 4). Statistically significant decreases were also observed in the mean CGI-ADHD-S score from a baseline value of 5.0 to 3.7 at endpoint ($p<0.001$).

The mean change from baseline to endpoint in CAARS-S:SV-J was -11.9 ($p<0.001$). Statistically significant improvement was observed in the mean Stroop color-word score from baseline to endpoint ($p=0.003$) as well as in word test ($p=0.005$) and color test ($p<0.001$). Mean changes from baseline to endpoint in HAMD-17 and HAMA-14 score were small with 0.2 and -0.1, respectively, and were not statistically significant. . The mean changes in the all SF-36v2™ subdomains

from baseline to endpoint showed a small improvement numerically without statistical significance except for physical functioning.

DISCUSSION

The present study is the first investigation of the tolerability of atomoxetine in Japanese adult ADHD patients. The results suggested that atomoxetine was well tolerated and suggested that it would be safe in these patients. Furthermore, a decrease in CAARS-Inv:SV-J scores was observed following administration of atomoxetine.

Of the 45 patients enrolled in this study, 39 patients completed Study Period II with 8 weeks of atomoxetine treatment. The discontinuation rate due to adverse events was 6.7%. This was almost similar to the rates, 7.8 % and 9.3 %, observed in two large-scale, placebo-controlled studies completed in the U.S. in adult ADHD patients.[15] In addition, the proportion of compliant patients at each visit was more than 93.2%. These results suggest that treatment with atomoxetine was well tolerated in Japanese adults with ADHD.

There were no unexpected adverse events observed in these Japanese patients. The most commonly reported adverse events were nausea, headache, anorexia and somnolence, all of which have been reported in previous overseas studies with atomoxetine.[15,21,22] Statistically significant changes were seen in some laboratory tests, vital signs and ECGs, however, these changes were small and were not considered clinically significant. The increase in heart rate, significant changes in

diastolic blood pressure were not unexpected from pharmacologic action of atomoxetine. The Fridericia correction of the QT interval (QTcF) was the preferred method of assessment, and no statistical significance was observed in the mean change from baseline to endpoint in QTcF interval. Michelson et al. reported that no serious safety concerns were observed during a 10-week treatment period in two placebo-controlled, double-blind studies with adult ADHD patients in the U.S., while modest mean increases in blood pressures and heart rate appeared to be associated with atomoxetine.[15] These results suggested that the Japanese adult ADHD patients in this study had a similar safety profile to that seen in US studies with adult ADHD patients. However, further study will be required to investigate tolerability and safety more thoroughly because of the small size and open-label design of this study.

A proportion of PM patients was 2.2% (1/45) in our study. Shimizu et al reported that racial differences in the frequency of PM on CYP2D6 was 1.9% of Asian and 7.7% of Caucasians.[13] From these results, PM frequency in Japanese patients in our study was almost consistent with the previous report and was not unexpected, although number of patients in our study was small and there is a limitation to interpret this data.

Atomoxetine has been approved for the treatment of children and adolescents with ADHD in Japan in April 2009. In a placebo-controlled, double-blind study in 245 Japanese children and adolescents with ADHD, two patients in the atomoxetine

treatment groups discontinued from the study due to adverse events. Importantly, adverse events reported at least 5% of patients were nasopharyngitis, headache, decreased appetite, somnolence and nausea, vomiting, abdominal pain and diarrhea[14]. There were no major differences in the safety profiles between the Japanese adult ADHD patients in this study and Japanese pediatric ADHD patients reported in the previous study.

This study also took a preliminary look at how ADHD symptoms changed in these patients during a course of atomoxetine administration. Symptoms were evaluated by using a Japanese version (CAARS-SV-J) of the Conners Adult ADHD Rating Scale-Screening Version (CAARS-SV). Treatment with atomoxetine for 8 weeks showed statistically significant decreases in CAARS-Inv:SV-J total ADHD symptoms scores in a time-dependent manner from baseline to the last observational visits. This result was similar to previous studies showing that atomxetine improved ADHD symptoms in adults as measured by CAARS-Inv:SV-J total score.[15,20]. Although further study to evaluate ADHD symptoms in Japanese adults will be required, these results suggest that atomoxetine would be expected to be efficacious and safe in Japanese adults with ADHD as has been shown in other countries.

Limitations

Since this was an open-label study with a small number of patients and a limited treatment period, the results of efficacy and safety in this study was suggestive for treatment with atomoxetine in Japanese adult patients, however, we can not conclude definitely, Therefore, safety and efficacy need to be confirmed in a larger scale, placebo-controlled study in Japanese adult patients with ADHD. Such a study, along with a long term treatment study, is now being conducted to achieve these objectives.

CONCLUSION

This first Asian open-label study with 45 Japanese adults with ADHD showed that treatment with atomoxetine for 8 weeks was well tolerated in these patients. The most commonly reported adverse events were nausea, nasopharyngitis, headache , somnolence, anorexia and thirst, and most of these events were mild or moderate. The results of this study suggest that atomoxetine would be expected to be efficacious and safe in Japanese adults with ADHD, although a placebo-controlled study will be required for further demonstration..

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Figure Legends

Figure 1 Study Design

Figure 2 Overview of Patient Disposition

Figure 3 CAARS-Inv:SV-J Total ADHD Symptom Score by Visit for Full Analysis Set in Study Period II

Values are mean ± SD. Patient numbers are 45, 45 44, 41 and 40 at baseline, Visit 3, Visit 4, Visit 5 and Visit 6, respectively. **p<0.001, compared with baseline by paired t-test. CAARS-Inv:SV-J = Japanese version of the Conners' Adult ADHD Rating Scales-Investigator Rated: Screening Version.

Figure 4 CAARS-Inv:SV-J Subscale Scores at Baseline and Endpoint for Full Analysis Set in Study Period II

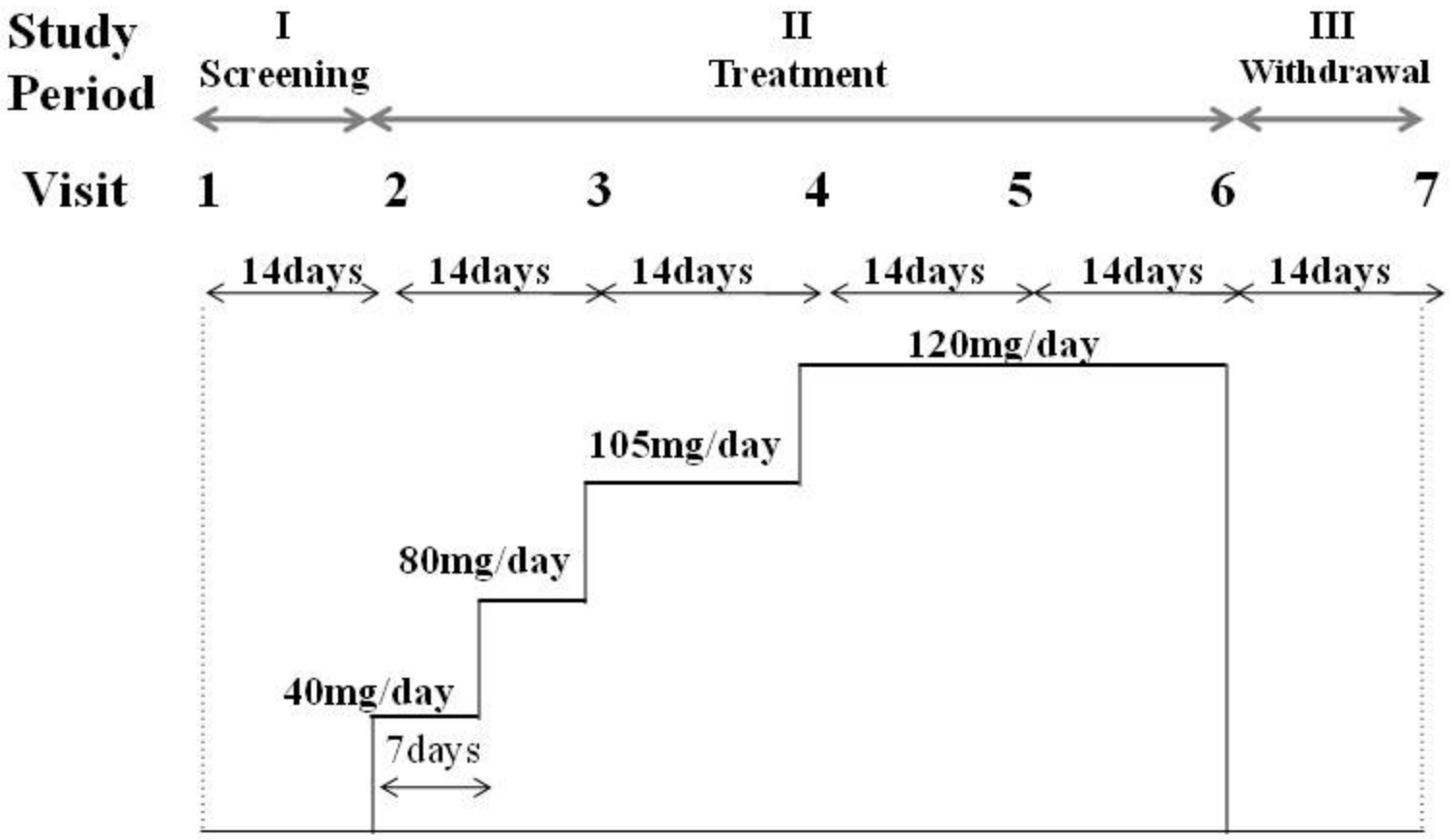
Values are mean + SD. Patient numbers are 45. **p<0.001, compared with baseline by paired t-test. CAARS-Inv:SV-J = Japanese version of the Conners' Adult ADHD Rating Scales-Investigator Rated: Screening Version.

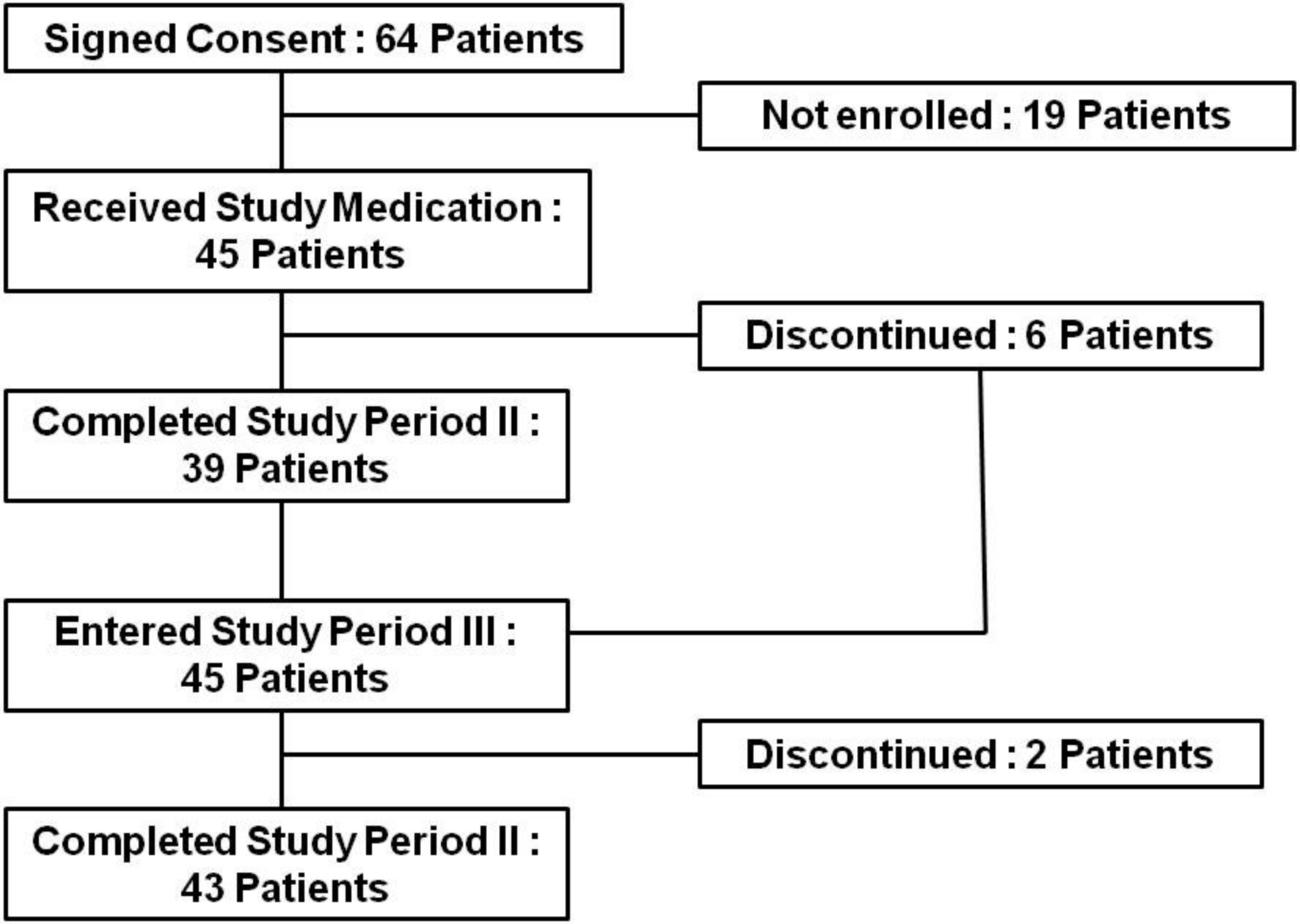
Table 1 Summary of Demographics and Other Clinical Chracteristics at Baseline for Full Analysis set

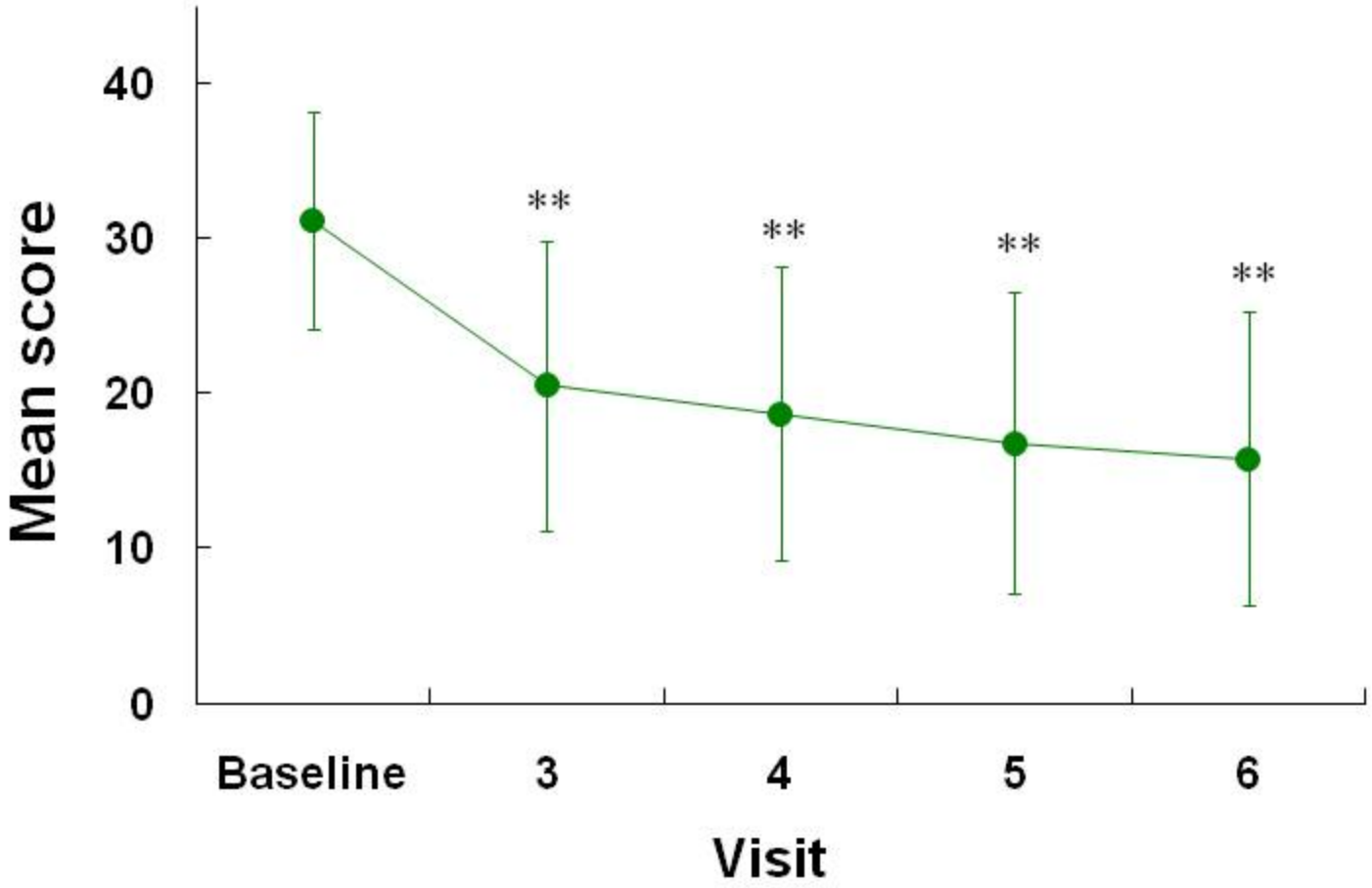
Item	(N=45)
Gender, No.	45
Female, n (%)	26 (57.8)
Male, n (%)	19 (42.2)
Age (yrs), No.	45
Mean	33.12
S.D.	8.97
Min	18.5
Median	32.44
Max	59.4
Age (yrs), No.	45
<40, n (%)	33 (73.3)
>=40, n (%)	12 (26.7)
AD/HD Subtype Current, No.	45
Inattentive, n (%)	28 (62.2)
Hyperactive/Impulsive, n (%)	1 (2.2)
Mixed, n (%)	16 (35.6)
CAARS-Inv:SV-J Total Symptoms Score, No.	45
Mean	31.2
S.D.	7.0
Median	31.0
CGI-ADHD-S, No.	45
Normal, not at all ill, n (%)	0
Borderline ill, n (%)	0
Mildly ill, n (%)	0
Moderately ill, n (%)	12 (26.7)
Markedly ill, n (%)	23 (51.1)
Severely ill, n (%)	9 (20.0)
Among the most extremely ill subjects, n (%)	1 (2.2)
Prior Stimulant Exposure, No.	42
No, n (%)	12 (28.6)
Yes, n (%)	30 (71.4)
CYP2D6 Phenotype (EM/PM), No.	45
EXTN, n (%)	44 (97.8)
SLOW, n (%)	1 (2.2)

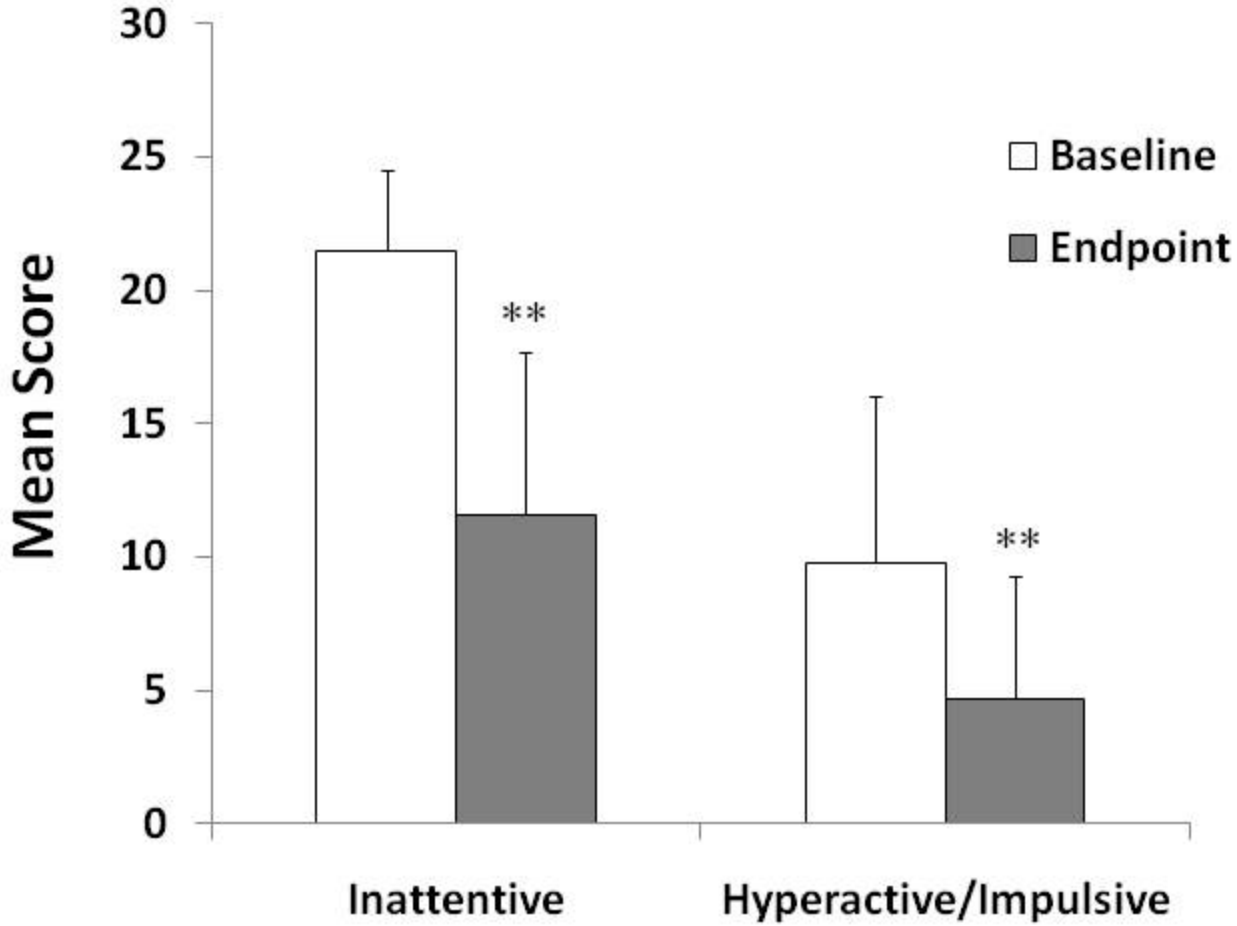
Table 2 Adverse Events with Overall Frequency of >5% in Study Period II

System Organ Class Preferred Term	ATMX (N=45) n (%)
Patients with >= 1 TEAE	45 (100.0)
Gastrointestinal disorders	32 (71.1)
Nausea	21 (46.7)
Constipation	7 (15.6)
Dry mouth	4 (8.9)
Dyspepsia	4 (8.9)
Stomach discomfort	3 (6.7)
Nervous system disorders	25 (55.6)
Headache	11 (24.4)
Somnolence	9 (20.0)
Dizziness	4 (8.9)
Dysgeusia	3 (6.7)
Tremor	3 (6.7)
General disorders and administration site conditions	21 (46.7)
Thirst	9 (20.0)
Malaise	6 (13.3)
Pyrexia	3 (6.7)
Infections and infestations	20 (44.4)
Nasopharyngitis	16 (35.6)
Investigations	13 (28.9)
Weight decreased	6 (13.3)
Electrocardiogram QT prolonged	3 (6.7)
Metabolism and nutrition disorders	13 (28.9)
Anorexia	9 (20.0)
Decreased appetite	4 (8.9)
Psychiatric disorders	12 (26.7)
Middle insomnia	4 (8.9)
Insomnia	3 (6.7)
Reproductive system and breast disorders	10 (22.2)
Dysmenorrhoea	6 (13.3)
Cardiac disorders	8 (17.8)
Palpitations	7 (15.6)
Vascular disorders	7 (15.6)
Hot flush	7 (15.6)
Renal and urinary disorders	4 (8.9)
Dysuria	4 (8.9)


Study Period
I
Screening
II
Treatment
III
Withdrawal
Visit
1
2
3
4
5
6
7
14days
14days
14days
14days
14days
14days
120mg/day
105mg/day
80mg/day
40mg/day
7days


Signed Consent : 64 Patients
Not enrolled : 19 Patients
Received Study Medication : 45 Patients
Discontinued : 6 Patients
Completed Study Period II : 39 Patients
Entered Study Period III : 45 Patients
Discontinued : 2 Patients
Completed Study Period II : 43 Patients


Mean score
40
30
20
10
0
**
**
**
**
Baseline
3
4
5
6
Visit


30
25
20
15
10
5
0
Mean Score
Baseline
Endpoint
**
**
Inattentive
Hyperactive/Impulsive