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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 $\geq$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 $\pm$ 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

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Item                                               (N=45)
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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<br>  Preferred Term | ATMX<br>(N=45)<br>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

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┌─────────────────────────────────────┐
│ 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                         │
└─────────────────────────────────────┘
```