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# A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Metadoxine Extended Release 1400 mg Compared With Placebo Once Daily in 300 Adults With Attention-Deficit/Hyperactivity Disorder

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## BACKGROUND

- Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neuropsychiatric condition affecting 4.4% of adults in the United States[1]
- ADHD is associated with serious and diverse life impairments in adults, including higher rates of substance abuse, increased driving violations and accidents, employment difficulties, and marital problems[2–4]
- Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is an ion-pair salt of pyridoxine (vitamin $B_6$) and 2-pyrrolidone-5-carboxylate (PCA, also known as L-PGA) that has been used in an immediate-release form for more than 30 years to treat acute alcohol intoxication, alcohol withdrawal syndrome, and chronic alcoholic liver disease[5]
- Metadoxine extended release (MDX) is a modulator of GABAergic transmission with a monoamine-independent mechanism of action in clinical development for the treatment of ADHD[6]
- In clinical trials of adults with ADHD, MDX has demonstrated significant improvement in ADHD symptoms, neuropsychological test performance, and quality of life with a rapid onset of action[5,7]
  - A double-blind, placebo-controlled, 6-week study of MDX 1400 mg in 120 adults with ADHD demonstrated significant improvement in ADHD symptoms compared with placebo[5]
  - A placebo-controlled crossover study demonstrated that a single dose of MDX 1400 mg significantly improved sustained and selective attention in adults with PI-ADHD within 3 to 5 hours post-dose[7]
- MDX has been well tolerated in clinical trials of adults with ADHD, with no clinically significant cardiovascular or other significant side effects[5,7]
- To further investigate the safety and efficacy of MDX, a 6-week, multicenter, randomized, double-blind, parallel-group, fixed-dose study of MDX 1400 mg once daily compared with placebo in 300 adults with ADHD (NCT02059642) was completed

## METHODS

### Participants

- 300 men and women 18 to 55 years of age were enrolled at 20 sites (18 in the United States and 2 in Israel)
- Patients were included if they had a diagnosis of ADHD based on *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV)* and DSM-5 criteria, as assessed by the Adult ADHD Clinical Diagnostic Scale (ACDS, version 1.2)
- Patients had ADHD with at least moderate clinical severity (Clinical Global Severity of Illness [CGI-S] score of ≥ 4)
- Patients had a baseline Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version with adult ADHD prompts (CAARS-Inv) total ADHD symptom score of ≥ 22
- Patients who did not respond in the past to 2 adequate trials of stimulant medications or 1 adequate trial of atomoxetine (as defined by investigator judgment) were excluded from study participation, as were patients with a diagnosis of ADHD not otherwise specified

### Study Design and Treatment

- This was a 6-week, multicenter, randomized, double-blind, parallel-group, fixed-dose study of MDX 1400 mg once daily compared with placebo
- Patients were randomized 1:1 to receive MDX 1400 mg or placebo once daily for 6 weeks **(Figure 1)**
  - Randomization was stratified to ensure that at least 33% of patients in each group had PI-ADHD
- Following a screening visit, eligible patients discontinued ADHD medications for a washout period of 14 days (for psychotropic medications other than fluoxetine, including atomoxetine) or 28 days (for fluoxetine) before randomization
  - Patients requiring a washout period had an interim visit (off drug) between day –10 and day –3 for CAARS-Inv assessment after the washout period
  - The baseline CAARS-Inv was completed on day 0
    - If there was a ≥ 25% change in the CAARS-Inv result between the interim visit and the baseline visit for patients requiring a washout period (or between the screening visit and the baseline visit for patients who did not require a washout period), then the patient was not randomized

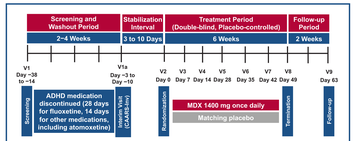


**Figure 1. Study Design.** Patients were randomized 1:1 to receive MDX 1400 mg once daily or placebo for 6 weeks following a screening and washout period.

### Assessments

#### *Efficacy Assessments*

- Primary efficacy measure
  - Total ADHD symptom score of the CAARS-Inv with adult prompts for the intention-to-treat (ITT) population
    - The CAARS-Inv was assessed at baseline (day 0) and at weeks 1, 2, 3, 4, and 6
- All investigators received rater training to administer the CAARS-Inv with adult prompts
- Clinical monitoring of baseline ratings occurred as per standard clinical trial methodology
  - This report will focus on the primary efficacy measure. Secondary efficacy measures are currently being analyzed

#### *Safety Assessments*

- Safety assessments included
  - Adverse event reports
  - Study discontinuations
  - Columbia Suicide Severity Rating Scale (C-SSRS)
  - Electrocardiograms (ECG)
  - Vital signs
  - Laboratory assessments (chemistry panel, complete blood count, urinalysis)
  - Physical examination
  - Neurological examination

### Statistical Analysis

- Assuming a difference between groups of 3.1 units on the mean change in CAARS-Inv total ADHD symptom score from baseline to endpoint, and a standard deviation of 9.29, a sample size of 150 patients per treatment group was required to detect a statistically significant difference at $\alpha = .05$ (2-sided) with a power of 82.1%
- The ITT population included all patients who were randomized and had at least 1 valid post-baseline measurement of CAARS-Inv total ADHD symptom score
- The safety population included all patients who received at least 1 dose of study medication
- A mixed-effect model repeated measures (MMRM) analysis was used to compare the estimated least-square (LS) mean difference from baseline to week 6 (or early termination) in the CAARS-Inv total ADHD symptom score between treatment groups in the ITT population
- A **pre-specified** modified intention-to-treat (mITT) analysis using MMRM compared the estimated LS mean difference from baseline to week 6 (or early termination) in the CAARS-Inv total ADHD symptom score between treatment groups after omitting patients who had a change from baseline to week 6 on the CAARS-Inv score that was ≥ 3 standard deviations (SD) from the within treatment average change from baseline to week 6
- A **post-hoc analysis** was performed on the ITT population excluding patients with major protocol violations related to inclusion and exclusion criteria at baseline. Protocol violations were identified prior to unblinding of the randomization codes. An expert in adult ADHD (LAA) reviewed the protocol violations while unblinded to patient treatment assignment and outcomes, and selected patients with major protocol violations related to baseline inclusion and exclusion criteria that could confound the assessment of the primary measure
- An additional **post-hoc analysis** was performed on the ITT population excluding major protocol violations related to inclusion and exclusion and additionally excluding any outliers identified by the **pre-specified** ≥ 3 SD analysis
- All tests were 2-tailed, and *P* values of ≤ .05 were considered statistically significant
- Data were analyzed using SAS® version 13.1 (SAS Institute, Cary, NC)

## RESULTS

### Patient Disposition and Demographics

- Patient disposition
  - Of 416 patients screened for participation, 300 were randomized to receive MDX 1400 mg/d (n = 152) or placebo (n = 148)
  - The number of patients discontinuing from the study and the reasons for discontinuation are shown in **Figure 2**
  - The number of patients withdrawing from either group due to noncompliance with study medication and adverse events is low, though more patients in the placebo group withdrew because of noncompliance and more patients in the MDX 1400-mg group withdrew because of adverse events

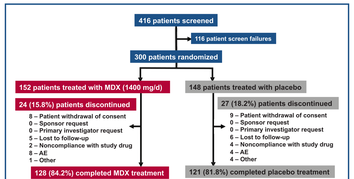


**Figure 2. Patient Disposition.** Of the 300 patients randomized, 152 were treated with MDX 1400 mg once daily and 148 were treated with placebo. A similar number of patients in each treatment group completed the 6-week randomized treatment period (128 in the MDX 1400-mg group vs 121 in the placebo group).

- Patient demographics and baseline characteristics
  - 300 adults with ADHD were enrolled (297 patients with ADHD by DSM-IV criteria and 3 patients with ADHD by DSM-5 criteria), with approximately 70% of patients enrolled in the US (n = 215)
  - The safety population (all patients who received at least 1 dose of study medication) included 152 patients in the MDX 1400-mg group and 146 patients in the placebo group
  - Patients had a mean ± SD age of 35.4 ± 10.16 years, 53% (n = 158) were female, and 86.6% (n = 258) were white **(Table 1)**
  - The mean baseline CAARS-Inv total ADHD symptom score for the safety population was 38.3 ± 8.07
  - Additional baseline characteristics are summarized in **Table 1**

**Table 1. Baseline Patient Demographics and Baseline Characteristics (Safety Population)**

| Characteristic | MDX 1400 mg (N = 152) | Placebo (N = 146) |
|---|---|---|
| Mean age (range), y | 35.1 (18–55) | 35.6 (18–55) |
| Sex, n (%) | | |
| Female | 79 (52) | 79 (54.1) |
| Male | 73 (48) | 67 (45.9) |
| Weight, mean ± SD (range), kg | 82.1 ± 19.8 (44–138) | 82.3 ± 21.1 (47–150) |
| Race, n (%) | | |
| White | 128 (84.2) | 130 (89.0) |
| Black | 17 (11.2) | 14 (9.6) |
| Asian | 4 (2.6) | 0 |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 10 (6.6) | 15 (10.3) |
| Not Hispanic or Latino | 141 (92.8) | 131 (89.7) |
| DSM-IV adult ADHD subtype, n (%) | | |
| Predominantly inattentive | 59 (38.8) | 55 (37.7) |
| Hyperactive-impulsive | 2 (1.3) | 2 (1.4) |
| Combined | 91 (59.9) | 89 (61.0) |
| CAARS-Inv total ADHD symptom score (ranging 0–54), mean ± SD (range) | 38.5 ± 8.13 (22–54) | 38.2 ± 8.03 (22–53) |
| CGI-S score, n (%) | | |
| 4 (moderately ill) | 57 (37.5) | 60 (41.1) |
| 5 (markedly ill) | 73 (48.0) | 74 (50.7) |
| 6 (severely ill) | 21 (13.8) | 12 (8.2) |
| 7 (extremely ill) | 1 (0.7) | 0 |
| AAQoL Total Score (ranging 0–100), mean ± SD (range) | 50.96 ± 15.81 (12.07–95.69) | 50.20 ± 14.07 (17.24–87.50) |

AAQoL = Adult ADHD Quality of Life Scale.

### Efficacy

- Primary efficacy
  - The ITT population included 297 patients (n = 151 in the MDX 1400-mg group and n = 146 in the placebo group). Three patients enrolled in the study did not have a post-baseline efficacy assessment
  - In the ITT analysis (n = 297), the LS mean (95% CI) change from baseline to week 6 in the CAARS-Inv score was –12.0 (–13.95, –10.06) for the MDX group vs –9.9 (–11.89, –7.92) for the placebo group (*P* = .136) **(Figure 3)**
  - The **pre-specified** mITT cohort (n = 295) was derived from an outlier analysis applied to both placebo and MDX groups that resulted in exclusion of 2 patients who had a change from baseline to week 6 on the CAARS-Inv score that was ≥ 3 SD from the within treatment average change
  - In the **pre-specified** mITT derived from the outlier analysis, the LS mean (95% CI) change from baseline to week 6 in the CAARS-Inv score was –12.0 (–13.90, –10.10) for the MDX group vs –9.4 (–11.36, –7.46) for the placebo group (*P* = .0606)
  - The **post-hoc** mITT cohort, derived from excluding patients with major protocol violations at baseline, resulted in the exclusion of 8 patients from the ITT population (n = 289)
    - Elevated HgbA1c beyond protocol established cut-off
    - Lack of DSM-IV diagnosis
    - Assignment of wrong kit at baseline
    - Administration of prohibited concomitant medication at baseline and throughout study (Librium®)
    - Patient was a close family member of a rater in the study
  - In the **post-hoc** mITT derived from excluding patients with major protocol violations at baseline, the LS mean (95% CI) change from baseline to week 6 in the CAARS-Inv score was –12.0 (–13.96, –10.00) for the MDX group vs –9.6 (–11.60, –7.54) for the placebo group (*P* = .0927)
  - Analysis of the cohort derived from both the pre-specified exclusion of 3 SD outliers and the post-hoc exclusion of patients with major protocol violations at baseline (n = 287) resulted in a LS mean (95% CI) change from baseline to week 6 in the CAARS-Inv of –12.0 (–13.89, –10.02) for the MDX group vs –9.0 (–11.03, –7.04) for the placebo group (*P* = .0383)
  - A summary of the primary efficacy analyses is presented in **Table 2**

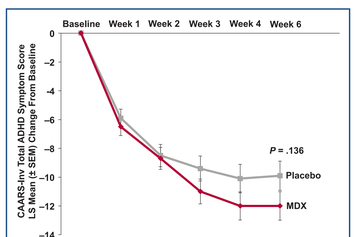


**Figure 3. Mean Change ± SEM in CAARS-Inv Total ADHD Symptom Score From Baseline to Week 6 for the ITT Population (n = 297).**
The ITT analysis of 297 patients yielded a positive trend toward statistical significance (12.0-point improvement from baseline to week 6 in the MDX group vs a 9.9-point improvement in the placebo group, *P* = .136 based on MMRM analysis).

**Table 2. Summary of Primary Efficacy Analyses**

| Analysis Population | Treatment Group | N | n | LS Mean | Lower 95% CI | Upper 95% CI | LS Mean Difference Between Groups | *P* Value |
|---|---|---|---|---|---|---|---|---|
| ITT Population (n = 297) | Placebo | 148 | 146 | –9.9 | –11.89 | –7.92 | –2.10 | .1360 |
| | MDX 1400 mg | 152 | 151 | –12.0 | –13.95 | –10.06 | | |
| Pre-specified mITT Excluding ≥ 3 SD Outliers (n = 295) | Placebo | 146 | 144 | –9.4 | –11.36 | –7.46 | –2.59 | .0606 |
| | MDX 1400 mg | 152 | 151 | –12.0 | –13.90 | –10.10 | | |
| Post-hoc mITT Excluding Baseline Protocol Violations (n = 289) | Placebo | 148 | 141 | –9.6 | –11.60 | –7.54 | –2.41 | .0927 |
| | MDX 1400 mg | 152 | 148 | –12.0 | –13.96 | –10.00 | | |
| Post-hoc mITT Excluding Baseline Protocol Violations and ≥ 3 SD Outliers (n = 287) | Placebo | 146 | 139 | –9.0 | –11.03 | –7.04 | –2.92 | .0383 |
| | MDX 1400 mg | 152 | 148 | –12.0 | –13.89 | –10.02 | | |

### Safety

- Treatment with MDX 1400 mg once daily was well tolerated
- The number of patients reporting AEs was similar between the MDX and placebo treatment groups
- The most common AEs were headache (15.1% in the MDX group vs 12.3% in the placebo group), nausea (8.6% vs 6.2%), and fatigue (7.2% vs 8.2%)
- All AEs reported by ≥ 5% of patients in either treatment group are shown in **Table 3**
- No drug-related serious AEs were reported
- No clinically significant abnormalities in laboratory values, vital sign measurements, ECG parameters, C-SSRS, or findings during clinical examination, including neurological examination, were observed

**Table 3. Adverse Events Reported by ≥ 5% of Patients in Either Treatment Group**

| Adverse Event | MDX 1400 mg (n = 152) No. (%) of Patients | Placebo (n = 146) No. (%) of Patients |
|---|---|---|
| Headache | 23 (15.1) | 18 (12.3) |
| Nausea | 13 (8.6) | 9 (6.2) |
| Fatigue | 11 (7.2) | 12 (8.2) |
| Decreased appetite | 8 (5.3) | 0 |

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## CONCLUSIONS

- Based upon preliminary analysis, MDX appeared to be well tolerated and led to an effect on reducing overall ADHD symptoms. The ITT analysis of 297 adults with ADHD yielded a non-significant positive trend (12.0-point LS mean improvement from baseline to week 6 in the MDX group vs a 9.9-point LS mean improvement in the placebo group, *P* = .136, n = 297).
  - The magnitude of the MDX change is consistent with previously reported data in a prior MDX phase 2b study (N = 120 patients)[5]
  - The magnitude of the placebo change is larger than previously reported data in a prior MDX phase 2b study[5] and in other studies with ADHD pharmacotherapies[8,9]
- A **pre-specified** mITT analysis identified and removed 2 patients with ≥ 3 SD changes at week 6. Both patients were in the placebo group; no such outliers were identified in the MDX group.
  - This mITT analysis noted effects on CAARS-Inv total ADHD symptom scores at a positive trend (*P* = .0606 level, n = 295), just missing significance.
- A **post-hoc** mITT analysis excluded 8 patients with major protocol violations at baseline.
  - This mITT analysis also noted effects on CAARS-Inv total ADHD symptom scores at a positive trend (*P* = .0927 level, n = 289).
- Treatment with MDX 1400 mg once daily was well tolerated.
  - The most common AEs were headache (15.1% in the MDX group vs 12.3% in the placebo group), nausea (8.6% vs 6.2%), and fatigue (7.2% vs 8.2%).
  - No drug-related serious AEs were reported.
- While the study was carefully conducted and monitored, results from the ITT and mITT analyses suggest that both a small number of issues with patient selection and a few significant outliers had effects on the outcome of the study. A future study, with more rigorous monitoring of patient selection and greater efforts to reduce placebo response is planned to further demonstrate the effects of MDX in ADHD patients.
- Results from these analyses provide a signal of efficacy of MDX in adults with ADHD, supporting the evidence of efficacy seen in previous placebo-controlled studies of MDX.[5,7]
- Further analyses from this study, including ADHD subtype analyses and additional efficacy endpoints, are currently underway to examine potential contributions to the response to MDX and placebo and to evaluate other endpoints.
- A safety and PK study of MDX 1400 mg once daily in 82 adolescents with PI-ADHD is ongoing (NCT02189772).

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