Metadoxine Extended Release in Adults With Predominantly Inattentive Attention-Deficit/Hyperactivity Disorder: A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Crossover Trial

Iris Manor, MD

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Disclosures
Iris Manor has received grant/research support from Alcobra Ltd, participated in advisory boards for Janssen-Cilag Pty Limited and Novartis Pharmaceutical Corporation, and acted as a consultant for Enzymotec Ltd, Janssen-Cilag Pty Limited, Novartis Israel, and Teva Pharmaceuticals Industries, Ltd.
Metadoxine Extended Release (MDX)

MDX (previously MG01Cl)
- MDX contains pyridoxine pyroglutamate salt (metadoxine)
- MDX is a proprietary dual-release formulation of metadoxine

Metadoxine safety (ex-US)
- Metadoxine is available in immediate-release forms for acute treatment of alcohol intoxication and chronic treatment of alcoholic liver disease (ALD) in select countries (Italy, Portugal, Hungary, Russia, India, China, Mexico, and Thailand) since the 1980s
- An estimated 13+ million patient days on therapy since first introduced
  - In >30 years of product availability, no published safety or tolerability issues to our knowledge
  - Published reports of metadoxine treatment ~1500 mg/d demonstrate safety and tolerability1-3

2Cacciatore L, et al. Clin Trial J. 1988;25:220-226. N = 30, metadoxine 300 mg IM twice daily for 30 days, then a 500-mg tablet 3 times a day for 5 months, for a total of 6 months of metadoxine 1500 mg/day.
Metadoxine Proposed Mechanism of Action

**Metadoxine is a monoamine-independent GABA/glutamate modulator**

- Monoamine-independent mechanism of action
  - Metadoxine shows **no effect on dopamine, norepinephrine or serotonin levels** in vivo\(^1\)
  - Metadoxine shows **no binding to dopamine, norepinephrine, or serotonin transporters** in vitro\(^2\)
- GABA/glutamate modulator
  - Metadoxine displays a dose-dependent, reversible **reduction in basal transmission** and **enhancement of GABAergic inhibitory transmission** via presynaptic modulations in striatal medium spiny neurons\(^2\)
- Metadoxine **normalizes** some biochemical markers of neuronal signaling
  - Metadoxine significantly reduces hyperactivation of **Akt and ERK\(^1,3,4\)**
- Metadoxine is a serotonin 5-HT\(_{2B}\) receptor antagonist\(^1\)

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\(^1\)Rubin J, et al. Poster 1364 presented at: Society of Biological Psychiatry 69th Annual Scientific Meeting; May 10, 2014; New York, NY.
\(^2\)Data on file. Alcobra Ltd. Tel Aviv, Israel.
\(^3\)Cogram P, et al. Poster presented at: FRAXA Investigators Meeting; September 29, 2013; Southbridge, MA.
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Objective of the Study</th>
<th>Study Design and Type of Control</th>
<th>Test Product; Dosage Regimen; Route of Administration</th>
<th>Number of Subjects</th>
<th>Healthy Subjects or Diagnosis of Patients</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>AL006</td>
<td>To evaluate efficacy, safety and tolerability of a single dose of metadroxine extended release formulation for the treatment of adults diagnosed with ADHD</td>
<td>Open-label, single-dose, single center study in adult subjects with ADHD. The study was comprised of main study and two sub-studies</td>
<td>IR and SR metadroxine tablets; 700, 1400, 2100 mg/day</td>
<td>40 enrolled, 38 dosed</td>
<td>Adults diagnosed with ADHD</td>
<td>Single dose</td>
</tr>
<tr>
<td>Phase 2</td>
<td>AL008</td>
<td>To evaluate efficacy, safety and tolerability of metadroxine extended release formulation for the treatment of adults diagnosed with ADHD</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group, multicenter study in adult subjects with ADHD. Eligible subjects were randomly assigned in a 1:1 ratio to one of two treatment groups, 1400 mg/day MG01CI or placebo</td>
<td>IR and SR metadroxine tablets; 1400 mg/day; oral administration</td>
<td>120 randomized, 113 completed</td>
<td>Adults diagnosed with ADHD</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>
MDX Phase 2b (AL011): Study Design

- **Adult Israeli single-center study (Geha Mental Health Center)**
  - N = 36 adults with predominantly inattentive attention-deficit/hyperactivity disorder (PI-ADHD)
  - Design: Randomized, double-blind, placebo-controlled, single-dose, crossover comparison of 2 MDX doses (700 and 1400 mg once daily)

- **Primary endpoint**
  - Test of Variables of Attention (TOVA®) ADHD score

- **Secondary endpoints**
  - TOVA subscores
  - Response rates
  - CANTAB (Cambridge Neuropsychological Test Battery)

- **Exploratory endpoints**
  - Adverse event (AE) rates
  - Discontinuation rates
SELECTION OF SUBJECTS: KEY INCLUSION/EXCLUSION CRITERIA

• Adult men and women, 18 to 55 years old, inclusive, at screening visit
• Diagnosed with PI-ADHD based on DSM-IV criteria for ADHD as assessed by the Adult ADHD Clinician Diagnostic Scale (ACDS V1.2);
• Clinical severity of at least a moderate level (Clinical Global Impression score of 4 or above)
• TOVA ADHD score of -1.8 or below at Screening /Baseline

KEY INCLUSION

• Subjects with ADHD not otherwise specified (NOS) diagnosis
• Subjects with combined type or predominantly hyperactive impulsive ADHD diagnoses
• Subjects with current Axis I diagnosis on SCID
• Subjects with lifetime bipolar or psychosis
• Subjects in treatment for Axis I disorders, even if the disorder is remitted
• Subjects who were non-responders to at least two adequately administered ADHD treatments
• Subjects with any medical or psychiatric condition that may preclude safe and complete study participation

KEY EXCLUSION

### MDX Phase 2b (AL011): Study Design

<table>
<thead>
<tr>
<th>Treatment Week</th>
<th>Sequence 1 (n = 12)</th>
<th>Sequence 2 (n = 12)</th>
<th>Sequence 3 (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MDX 1400 mg</td>
<td>MDX 700 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>2</td>
<td>MDX 700 mg</td>
<td>Placebo</td>
<td>MDX 1400 mg</td>
</tr>
<tr>
<td>3</td>
<td>Placebo</td>
<td>MDX 1400 mg</td>
<td>MDX 700 mg</td>
</tr>
</tbody>
</table>

**Screening Period**
- **1 Week**

**Treatment Period** (Double-blind, Placebo-controlled)
- **3 Weeks**

**Follow-up Period**
- **1 Week**

**V1 to V6**
- **Day −7 to −1**: Screening
- **Day 0**: Randomization
- **Day 7**: Single Dosing
- **Day 14**: Single Dosing
- **Day 21**: Single Dosing
- **Day 28**: Follow-up

**Washout**
- After V1
- After V2
- After V5
57 subjects screened

21 subjects screen failures

36 subjects randomized

2 subjects discontinued
1 – Sponsor request
1 - Non-compliance

Double Blind Phase
34 subjects completed treatment with all 3 periods
## Patient Demographics

<table>
<thead>
<tr>
<th>Randomized patients</th>
<th>N</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Mean (± SD)</td>
<td>31.9 (6.7)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>52.8%</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>47.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 years</td>
<td>29.2%</td>
<td></td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>77.8%</td>
<td></td>
</tr>
<tr>
<td><strong>ADHD onset</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 7 years</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 7 years</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Global Impression-Severity (CGI-S)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately ill</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Markedly ill</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Severely ill</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation.
TOVA ADHD Score (ITT)

Mean ± SEM Change From Baseline

MDX 1400 mg

MDX 700 mg

Placebo

P = .009

P = .032

NS

P values based on paired t tests. NS = not significant.
MDX Phase 2b (AL011): Secondary Endpoint

TOVA Response Rates (ITT)

- **MDX 1400 mg**: 97.1%
- **MDX 700 mg**: 77.8%
- **Placebo**: 71.4%

- **P = .028** for MDX 1400 mg vs MDX 700 mg and placebo.
- **P = .006** for MDX 700 mg vs placebo.

*P values based on Fisher exact test for MDX 1400 mg vs MDX 700 mg and placebo; Chi-square test for MDX 700 mg vs placebo.*
TOVA Response Time Variability Subscore (ITT)
Baseline and 3 to 5 Hours Post-Dose

$P = .022$

$P = .018$

NS

$P$ values based on paired $t$ tests. NS = not significant.
### MDX Phase 2b (AL011): Adverse Events

#### No. (%) of Patients

<table>
<thead>
<tr>
<th>AE</th>
<th>MDX 1400 mg (n = 34)</th>
<th>MDX 700 mg (n = 36)</th>
<th>Placebo (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
<td>11 (32.4)</td>
<td>6 (16.7)</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (14.7)</td>
<td>0 (0)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (11.8)</td>
<td>2 (5.6)</td>
<td>4 (11.4)</td>
</tr>
</tbody>
</table>

#### Severity of AEs
- 3 moderate AEs of headache
- 2 on MDX 700 mg, 1 on placebo
- Remaining AEs were mild in severity

**Only 1 discontinuation due to an AE**
Overall, both doses of MDX (700 mg and 1400 mg) demonstrated a favorable safety profile.

Efficacy was demonstrated in adults with PI-ADHD following a single dose of 1400-mg MDX, but not after a single dose of 700-mg MDX, as measured 3 to 5 hours post-dose.

- The mean increase in TOVA ADHD score from baseline was 4.7 following a single MDX 700-mg dose and 6.5 following a single 1400-mg MDX dose ($P = .032$).

This study is the second placebo-controlled phase 2b study to demonstrate efficacy of MDX in adults with ADHD.

- MDX treatment has been consistently associated with significant improvements in TOVA ADHD scores in adults with PI-ADHD.
- In the 6-week randomized controlled study of MDX that included 48 patients with PI-ADHD, the mean increase in TOVA ADHD score from baseline to endpoint was 6.7 points.
תודה לך
THANK YOU