Alcobra Ltd. (NASDAQ:ADHD)
June 2015

Dr. Yaron Daniely
President & CEO
Forward-Looking Statements

This presentation includes statements that are, or may be deemed, “forward-looking statements.” In some cases, these forward-looking statements can be identified by the use of forward-looking terminology, including the terms “believes,” “estimates,” “anticipates,” “expects,” “plans,” “intends,” “may,” “could,” “might,” “will,” “should,” “approximately,” “potential” or, in each case, their negative or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. They appear in a number of places throughout this presentation and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, the expected milestones, and the development, of our lead product candidate and its various indications, including the timing of our clinical trials, the potential of MDX to address the market opportunity in ADHD, the potential to use MDX to treat Fragile X Syndrome and our ability to protect our proprietary technology and enforce our intellectual property rights. In addition, historic results of scientific research and clinical and preclinical trials do not guarantee that the conclusions of future research or trials would not suggest different conclusions or that historic results referred to in this press release would not be interpreted differently in light of additional research and clinical and preclinical trials results. By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics, and healthcare, regulatory and scientific developments and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this presentation as a result of, among other factors, the factors referenced in the “Risk Factors” section of our annual report on Form 20-F for the year ended December 31, 2014 filed with the Securities and Exchange Commission. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this presentation, they may not be predictive of results or developments in future periods. Any forward-looking statement that we make in this presentation speaks only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this presentation.
• MDX is a novel **Phase III drug candidate for ADHD**

• Addresses a **clear unmet need** in a large and growing market:
  • A **rapidly effective, non-abusible, non-addictive, safe and tolerable** ADHD drug candidate

• Consistent **pro-cognitive** effect demonstrated in multiple controlled clinical studies

• MDX additionally investigated for treatment of **Fragile X Syndrome**

• **Multiple layers of IP** protection to 2028 and beyond
About Metadoxine Extended Release (MDX)

**MDX**

- MDX is a once-daily, proprietary dual-release formulation of Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate)

**Metadoxine Experience**

- Since the 1980s, Metadoxine has been available in immediate release forms (<1hr t<sub>1/2</sub>) for acute treatment of Alcohol Intoxication and chronic treatment of Alcoholic Liver Disease in Italy, Portugal, Hungary, Russia, India, China, Mexico and Thailand
- An estimate of 13+ million patient days of therapy on Metadoxine (acute/chronic) since its introduction; To our knowledge, in 30+ years of product availability no major safety/tolerability issues have been published
- Multiple peer reviewed papers have been published on the chronic use of Metadoxine at 1000-2000mg levels<sup>(1)</sup>

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1. Caballeria et al (J Hep, 1998) – n=69, 3 months, 1500mg
   Cacciatore et al (Clin Trial J, 1988) – n=30, 300mg IM twice daily for 30 days, then 500mg tablet 3 times a day for 5 months (6 months – 1500mg)
   Bono et al (Int J Clin Pharm Res, 1991) – n=20, 900mg IV twice daily (10 days - 1800mg)
Over 30 submitted patents globally may provide multiple layers of protection to 2028 and beyond:

- **Dual-release composition of MDX** –
  US PATENT #8,476,304 ISSUED JULY 2013
  INTERNATIONAL PATENTS ISSUED(ALLOWED (EU, JP, AU, MX, RU, HK)

- **Use of metadoxine for cognitive disorders and impairments** –
  US PATENT #8,710,067 ISSUED APRIL 2014
  INTERNATIONAL PATENTS ISSUED (NZ, MX, AU)

- **New molecular derivatives of Metadoxine** –
  US PATENT #8,889,715 ISSUED NOVEMBER 2014

- **Combination therapies containing Metadoxine**

- **Metadoxine manufacturing process**
Attention deficit-hyperactivity disorder (ADHD) is a neurobehavioral disorder characterized by difficulty in maintaining attention, hyperactivity and impulsive behavior.

ADHD affects 8-10% of school-aged children and 4-5% of the adult population worldwide.

**Inattention**
- Easily Distracted
- Trouble following direction/completing tasks
- Organizational problems
- Difficulty listening to others
- Forgetful
- Often loses things
- Daydreams

**Hyperactivity**
- Squirms/fidgets in chair
- Doesn’t stay seated
- Restless
- Trouble staying quiet/Talks Excessively

**Impulsivity**
- Has difficulty waiting his turn
- Has difficulty waiting for complete question
- Often interrupts others
Marketed ADHD Treatments

- **Psychostimulants**
  - Ritalin, Concerta, Adderall, Vyvanse
  - Strong Effect
  - Rapid Onset
  - Scheduled Substance
  - Significant Side Effects
  - Titration required

- **Non-stimulants**
  - Strattera, Intuniv, Kapvay
  - Non-Scheduled
  - Moderate Effect
  - Delayed onset
  - Significant Side Effects
  - Titration required

2014 Total ADHD Sales in US = $9 billion; 63M Rx
ADHD Medications have shown Rapid Market Uptake and Revenue Growth
- minimal impact of generics introductions

<table>
<thead>
<tr>
<th>Product (launch)</th>
<th>Class</th>
<th>Owner</th>
<th>Years to Peak Share</th>
<th>Peak Share</th>
<th>Peak Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta (2000)</td>
<td>Stimulant</td>
<td>J&amp;J</td>
<td>2</td>
<td>26%</td>
<td>$1.3 BB</td>
</tr>
<tr>
<td>Adderall XR (2001)</td>
<td>Stimulant</td>
<td>Shire</td>
<td>5</td>
<td>26%</td>
<td>$1.1 BB</td>
</tr>
<tr>
<td>Strattera (2002)</td>
<td>Non-Stimulant</td>
<td>Eli Lilly</td>
<td>2</td>
<td>18%</td>
<td>$739 MM</td>
</tr>
<tr>
<td>Focalin XR (2005)</td>
<td>Stimulant</td>
<td>Novartis</td>
<td>3</td>
<td>6%</td>
<td>$400 MM</td>
</tr>
<tr>
<td>Vyvanse (2007)</td>
<td>Stimulant</td>
<td>Shire ($2.6bn acquisition)</td>
<td>6</td>
<td>17%</td>
<td>$1.5 BB</td>
</tr>
<tr>
<td>Intuniv (2009)</td>
<td>Non-Stimulant</td>
<td>Shire</td>
<td>4</td>
<td>4%</td>
<td>$335 MM</td>
</tr>
</tbody>
</table>

1 US Market
2 Source: Company annual reports; Strattera and Vyvanse sales still growing
## MDX Clinical Studies in ADHD

Comprehensive development history shows consistent pro-cognitive benefits and tolerability

<table>
<thead>
<tr>
<th>Phase of Study</th>
<th>Number of Subjects &amp; Sites</th>
<th>Study Assessments</th>
<th>Study Design &amp; Type of Control</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>16 healthy adult subjects 1 site</td>
<td>Safety, tolerability and PK</td>
<td>Single center, open-label, repeated-dose study</td>
<td>5 days</td>
</tr>
<tr>
<td>Phase IIa</td>
<td>40 adult subjects 1 site</td>
<td>Efficacy, safety and tolerability</td>
<td>Open-label, single-dose, single center study</td>
<td>Single dose</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>120 adult subjects 2 sites</td>
<td>Efficacy, safety and tolerability</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group, multicenter study</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>36 adult subjects 1 site</td>
<td>Efficacy, safety and tolerability of two doses</td>
<td>Randomized, double-blind, placebo-controlled, crossover-comparison, single-center study</td>
<td>Single dose</td>
</tr>
<tr>
<td>Phase III</td>
<td>300 adult subjects 20 sites</td>
<td>Efficacy, safety and tolerability</td>
<td>Randomized, multicenter, double-blind, parallel, fixed-dose Study</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Phase II</td>
<td>82 adolescent subjects 6 sites</td>
<td>Safety, tolerability and PK</td>
<td>Randomized, double-blind, multicenter, fixed dose, single administration study</td>
<td>Single dose</td>
</tr>
</tbody>
</table>

MDX 1st Phase III Study (AL012)

- Multicenter, randomized, double-blind, parallel-group, fixed-dose study of MDX 1400 mg once daily vs placebo (NCT02059642)
  - 300 adults with ADHD enrolled at 20 sites (US, 18; Israel, 2)
  - Randomized 1:1 to receive MDX 1400 mg or Pbo once daily for 6 weeks

<table>
<thead>
<tr>
<th>Screening and Washout Period</th>
<th>Stabilization Interval</th>
<th>Treatment Period (Double-blind, Placebo-controlled)</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–4 Weeks</td>
<td>3 to 10 Days</td>
<td>6 Weeks</td>
<td>2 Weeks</td>
</tr>
</tbody>
</table>

V1 Day −38 to −14

V1a Day −3 to Day −10

V2 Day 0

V3 Day 7

V4 Day 14

V5 Day 28

V6 Day 35

V7 Day 42

V8 Day 49

V9 Day 63

ADHD medication discontinued (28 days for fluoxetine, 14 days for other medications including atomoxetine)

Interim Visit (CAARS-Inv)

Randomization

Matching placebo

MDX 1400 mg once daily

Matching placebo

Termination

Follow-up
### Safety & Tolerability

No statistically or clinically significant differences in adverse events seen between MDX and Placebo

<table>
<thead>
<tr>
<th>AE</th>
<th>MDX 1400 mg/d (n = 152)</th>
<th>Placebo (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of Patients</td>
<td>No. (%) of Patients</td>
</tr>
<tr>
<td>Headache</td>
<td>23 (15.1)</td>
<td>18 (12.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (8.6)</td>
<td>9 (6.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (7.2)</td>
<td>12 (8.2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (5.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

No drug-related serious AEs were reported.

No statistically or clinically significant differences seen between MDX and Placebo on cardiac functions, lab tests, physical exams, etc.
## Primary Efficacy Analysis (CAARS-Inv)

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>Treatment Group</th>
<th>N</th>
<th>n</th>
<th>LS Mean change</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>LS Mean Difference Between Groups</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>148</td>
<td>146</td>
<td>-9.9</td>
<td>-11.89</td>
<td>-7.92</td>
<td>-2.10</td>
<td>.1360</td>
</tr>
<tr>
<td></td>
<td>MDX 1400 mg</td>
<td>152</td>
<td>151</td>
<td>-12.0</td>
<td>-13.95</td>
<td>-10.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CAARS change from baseline*

Week

- **Placebo**
  - Week 1: -8.7
  - Week 2: -5.9
  - Week 3: -6.5
  - Week 4: -9.4
  - Week 5: 10.1
  - Week 6: -9.9

- **MDX 1400 mg**
  - Week 1: -12
  - Week 2: -11
  - Week 3: -12

*P value based on MMRM analysis*
AL012 key lessons

- On **multiple endpoints**, MDX consistently favorable over placebo
- Improvement from baseline of drug treated group **consistent** with previous MDX studies
- Placebo treatment shows unusual magnitude and variability compared to previous MDX studies and other adult ADHD studies

<table>
<thead>
<tr>
<th>MDX Studies</th>
<th>LS Mean ± SD</th>
<th>Atomoxetine (Strattera) Studies</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III MDX Study; N=300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDX</td>
<td>-12.0 ± 12.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-9.9 ± 11.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase IIb MDX Study¹; N=120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDX</td>
<td>-12.5 ± 8.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-8.9 ± 9.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Michelson D et al, 2003²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1 N = 267</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>-9.5 ± 10.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-6.0 ± 9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2 N = 248</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>-10.5 ± 10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-6.7 ± 9.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pivotal adult Phase III study (AL016)

- Lessons from AL012 implemented in design of the pivotal study for MDX in adults
  - Larger study (conservatively powered)
  - Selectivity in site participation; focus on established practitioners with large clinical databases
  - Reduced number of sites/raters for decreased variability
  - Introduce variable placebo period to exclude placebo responders
  - Reduce visit frequency and duration; minimize burden to subject & rater
  - Extend trial duration to allow rebound of placebo response
MDX for ADHD – next steps

- Q1 Meeting with the FDA focused on AL012 results and proposed path to NDA in adults and pediatric ADHD
- FDA concurred that positive efficacy results from a single additional Phase III study in adult ADHD will be sufficient to demonstrate efficacy for approval of MDX in this sub-population
- **AL016, the pivotal adult ADHD study, will launch in Q2 2015, with data reporting by the middle of 2016.**

- FDA further concurred that two positive pediatric studies (one Phase II + one Phase III) will be sufficient to demonstrate efficacy in this sub-population
- The company submitted to FDA a Pediatric Study Plan containing the proposed protocols for pediatric ADHD studies
MDX for treatment of Fragile X Syndrome

- Fragile X Syndrome is a rare neuro-genetic disorder
- Most common known genetic cause of autism
- Most common inherited form of intellectual disability
- Approximately 50,000 Americans affected
- Unmet need: No FDA approved therapies
- MDX Orphan Drug Designation obtained in December 2013

**Rationale for MDX study in Fragile X Syndrome:**

- *Fragile X is associated with GABA transmission imbalance*\(^1\)
- *Pro-cognitive properties of MDX observed in other trials*
- *Significant improvements in working memory, learning and social interaction observed in a pre-clinical animal model of Fragile X (FMR1 KO mouse)*

\(^1\) Berry-Kravis EM et al. Sci Transl Med 2012; 152(4): 1-7
MDX Phase IIb Trial in Fragile X (AL014)

- 6-week, randomized, multicenter, placebo-controlled, double-blind, parallel group, dose-ranging study of MDX once daily in 60 adults and adolescents with FXS (NCT02126995)
- Efficacy assessments:
  - ADHD-RS
  - ABC
  - VABS
  - RBANS
  - KiTAP

Behavioral

Cognitive
MDX for treatment of Fragile X Syndrome

- Completed patient enrollment in AL014
- Data to be announced in 2Q 2015
- If clinical benefit seen on behavioral/cognitive endpoints, meet with FDA to discuss plan for Pivotal study
- Unique MDX formulation/dosing to be used for Fragile X Syndrome (vs. ADHD)
Key 2015/2016 milestones and value catalysts

<table>
<thead>
<tr>
<th>Indication</th>
<th>Milestone</th>
<th>Anticipated Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult ADHD</td>
<td>FDA meeting</td>
<td>1Q 2015</td>
</tr>
<tr>
<td></td>
<td>Initiate 2\textsuperscript{nd} Phase III study</td>
<td>2Q 2015</td>
</tr>
<tr>
<td></td>
<td>Data announcement from 2\textsuperscript{nd}</td>
<td>1H 2016</td>
</tr>
<tr>
<td></td>
<td>Phase III study</td>
<td></td>
</tr>
<tr>
<td>Pediatric ADHD</td>
<td>Data announcement from Phase II study</td>
<td>1Q 2015</td>
</tr>
<tr>
<td></td>
<td>Pediatric Development Plan submission to FDA</td>
<td>2Q 2015</td>
</tr>
<tr>
<td>Fragile X</td>
<td>Complete enrollment in Phase II study</td>
<td>1Q 2015</td>
</tr>
<tr>
<td></td>
<td>Data release from Phase II study</td>
<td>2Q 2015</td>
</tr>
<tr>
<td></td>
<td>Planned FDA meeting</td>
<td>3Q 2015</td>
</tr>
</tbody>
</table>

Jan ‘15 financing provides sufficient capital through 2016
Alcobra Ltd.

NASDAQ:ADHD

http://www.alcobra-pharma.com/