

Issuer Free Writing Prospectus  
Filed Pursuant to Rule 433  
Registration No. 333-191714  
October 22, 2013



October 22, 2013

ALCOBRA PHARMA

# Forward-Looking Statements

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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 ADHD patient market size and market issuance of patents by the U.S. PTO and other governmental patent agencies adoption of MGO1CI by physicians and patients, the timing and cost of clinical trials plans for MGO1CI or whether such trials will be conducted at all, completion and receiving favorable results of future clinical trials for MGO1CI, the development and approval of the use of MGO1CI for additional indications such as Fragile X Syndrome or in combination therapy, the use of the proceeds from this offering, FDA approval of, or other regulatory action with respect to, MGO1CI, the timing, cost or other aspects of the commercial launch of MGO1CI and the commercial launch and future sales of MGO1CI or any other future products or product candidates. In addition, historic results of scientific research do not guarantee that the conclusions of future research would not suggest different conclusions or that historic results referred to in this press release would be interpreted differently in light of additional research. 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 the prospectus contained in our Amended Registration Statement on Form F-1 filed with the Securities and Exchange Commission on October 22, 2013 (the “Amended Registration Statement”). 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.

You should read carefully the factors described in the “Risk Factors” section of the prospectus contained in the Amended Registration Statement to better understand the risks and uncertainties inherent in our business and underlying any forward-looking statements.

# Free Writing Prospectus Statement

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This presentation highlights basic information about us and the offering. Because it is a summary, it does not contain all of the information that you should consider before investing.

We have filed an amended registration statement (including a prospectus) with the SEC for the offering to which this presentation relates. The amended registration statement has not yet become effective. Before you invest, you should read the prospectus in the amended registration statement (including the risk factors described therein) and other documents we have filed with the SEC for more complete information about us and the offering. You may get these documents for free by visiting EDGAR on the SEC Web site at [www.sec.gov](http://www.sec.gov). The preliminary prospectus, dated October 22, 2013, is available on the SEC Web site at [http://www.sec.gov/Archives/edgar/data/1566049/000114420413056180/v357808\\_f1-a.htm](http://www.sec.gov/Archives/edgar/data/1566049/000114420413056180/v357808_f1-a.htm). Alternatively, we or any underwriter participating in the offering will arrange to send you the prospectus if you contact Stifel, Nicolaus & Company, Incorporated, Attention: Syndicate, One Montgomery Street, Suite 3700, San Francisco, California 94104, by calling (415) 364-2720 or by emailing [SyndicateOps@stifel.com](mailto:SyndicateOps@stifel.com); or Aegis Capital Corp., Prospectus Department, 810 Seventh Avenue, 18th Floor, New York, NY 10019, telephone: 212-813-1010, e-mail: [prospectus@aegiscap.com](mailto:prospectus@aegiscap.com).

# Offering Summary

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Issuer

Alcobra Ltd.

Exchange/Ticker

NASDAQ Capital Market / ADHD

Deal Size

\$30,000,000

Overallotment

15%

Use of Proceeds

Clinical development of MG01CI for Fragile X Syndrome and pediatric ADHD, working capital & general corporate purposes

Book-Runners

Stifel, Aegis Capital Corp.

## Yaron Daniely, PhD MBA – Chief Executive Officer

- Joined Alcobra in 2010 as CEO and director
- Previously CEO of NanoCyte Inc, and VP Business Development of Gamida Cell Ltd
- PhD from NYU School of Medicine, MBA from the Technion

## Jonathan Rubin, MD, MBA – Chief Medical Officer

- Joined Alcobra in August 2013 as CMO
- Formerly Medical Director in Global Medical Affairs supporting multiple products within the ADHD portfolio, Shire Plc
- MD from the University of Connecticut, pediatric residency at Albert Einstein/Montefiore, Ambulatory Pediatric fellowship at Boston Children’s Hospital, MBA from Columbia Business School

## Udi Gilboa – CFO & Co-Founder

- Co-founded Alcobra in 2008 and has served as CFO/CAO since its inception
- Founder and managing partner of Top-Notch Capital, a prominent Israeli life sciences investment bank
- BA and MBA from Tel Aviv University

## Hanna Ron, MSc – SVP, Non-Clinical Development

- Joined Alcobra in 2011 as manager, Non-Clinical Development
- Over 26 years of experience in the pharmaceutical industry as an expert in chemistry, manufacturing and controls
- Previously VP Chemistry, Manufacturing and Controls at NASDAQ:BLRX

### **Board of Directors**

Aharon Schwartz, PhD  
Chairman  
VP Innovative Ventures,  
TEVA (former)

Howard B. Rosen, MBA  
VP Commercial Strategy,  
Gilead (former)

Daniel Geffken, MBA  
CFO, Transkaryotic  
Therapies (Former)

Hadas Gelandar, PhD

Ori Mor, MBA

Dalia Megiddo, MD

Udi Gilboa, MBA

Yaron Daniely, PhD MBA

# Introduction to Alcobra Ltd.

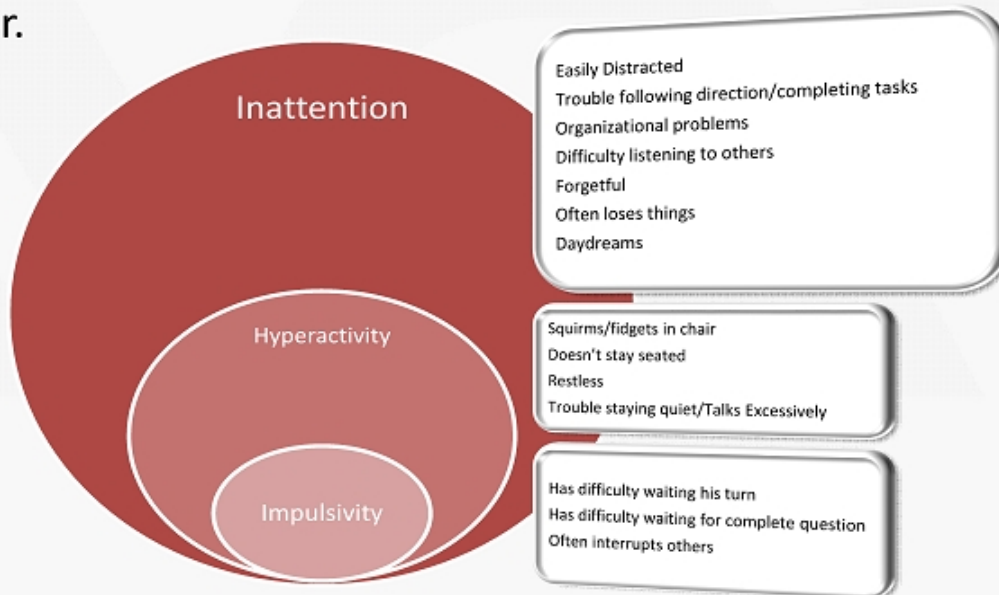
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- Emerging clinical-stage biopharmaceutical company founded in 2008 and headquartered in Tel Aviv, Israel
- Completed IPO on May 21, 2013, raising approximately \$25 million at \$8/share; 11M shares O/S , 12M F/D post-IPO
- Primarily focused on the development and commercialization of a proprietary drug, MG01CI, to treat Cognitive Dysfunctions
- MG01CI addresses significant market opportunities
  - A rapidly effective, non-stimulant with a differentiated mechanism of action for ADHD
  - Possibility to leverage clinical effects on executive functions in other major indications in cognitive impairment such as Fragile X Syndrome, a rare neurogenetic disorder associated with Autism

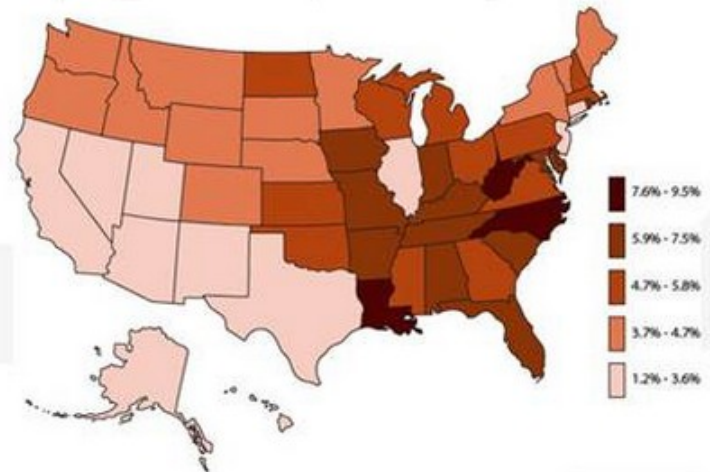
# Definition of ADHD

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



# ADHD – Large & Underpenetrated Market

- Affects 8-10% of school-aged children and about 4-5% of the adult population
- US market valued at US\$3.8bn (accounting for 90% of the global ADHD market)
  - US Market forecast to grow at a CAGR of 7.3% per annum and reach US\$6.3 billion by 2018
- Growth Drivers:
  - Increased disease recognition and awareness in the US (using the DSM V diagnostic criteria), Europe (with entry of new drugs) and ROW
  - Increasing pharmacotherapy adoption rates in children and adolescents in the US



Percent of all children aged 4-17 years currently taking medication for ADHD by state: United States, 2007<sup>1</sup>



# Impact of Untreated / Undertreated ADHD



## Healthcare System

50% ↑ in bike accidents<sup>(1)</sup>  
33% ↑ in ER visits<sup>(2)</sup>  
2-4x more motor vehicle crashes<sup>(3-5)</sup>

## Patient

↑ Criminal activity  
↑ Incarceration

## Family

3-5x ↑ Parental Divorce or Separation<sup>(11, 12)</sup>  
2-4x ↑ Sibling Fights<sup>(13)</sup>

## School and Occupation

46% Expelled<sup>(6)</sup>  
35% Drop Out<sup>(6)</sup>  
Lower Occupational Status<sup>(7)</sup>

## Society

Substance Use Disorders:  
2x Risk<sup>(8)</sup>  
Earlier Onset<sup>(9)</sup>  
Less Likely to Quit in Adulthood<sup>(10)</sup>

## Employer

↑ Parental Absenteeism<sup>(14)</sup>  
And Lower Productivity<sup>(15)</sup>

(1) DiScala et al., 1998

(2) Cuffe et al., 2009

(3) NHTSA, 1997

(4) Cox et al., 2006:

(5) Kieling et al., 2011

(6) Loe & Feldman, 2007

(7) Galera et al., 2012

(8) Molina et al., 2012

(9) Joss et al., 2012

(10) Wilens et al., 1995

(11) Schermerhorn et al., 2012

(12) Wymbs, 2008

(13) Mash & Johnston, 1983

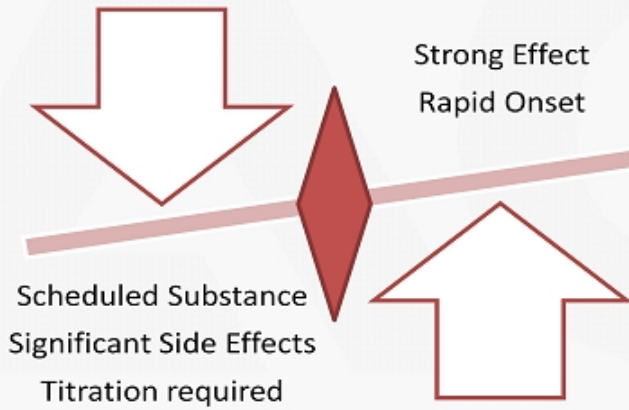
(14) Kupper et al., 2012

(15) Kleinman et al., 2009

# Types of Marketed ADHD Treatments

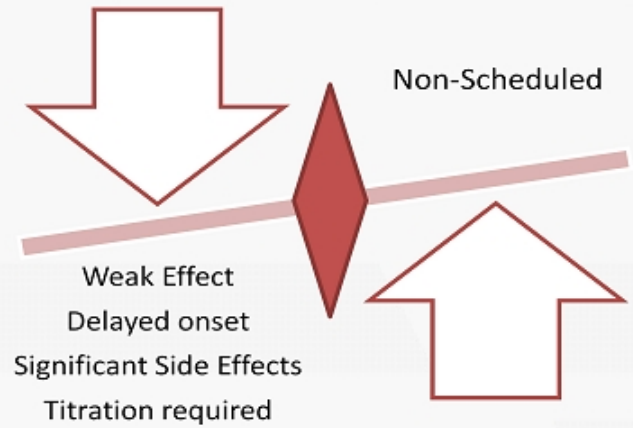
Ritalin, Concerta, Adderall, Vyvanse

## Psychostimulants



Strattera, Intuniv, Kapvay

## Non-stimulants



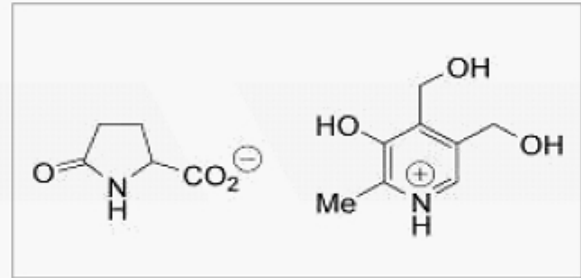
# ADHD – Principal Medications

Brand (launch)	Generic Name	Owner	Class	Peak Sales US\$m
Vyvanse (2008)	Lisdexamfetamine	Shire (\$2.6B M&A)	Stimulant	1,635 (2016E)
Concerta (2000)	Methylphenidate	J&J	Stimulant	1,326 (2009)
Adderall XR (2001)	Amphetamine	Shire	Stimulant	1,102 (2008)
Strattera (2002)	Atomoxetine	Eli Lilly	Non-Stimulant	667 (2004)

# About MG01CI

## MG01CI

- MG01CI contains Pyridoxine Pyroglutamate salt (Metadoxine)
- MG01CI is a proprietary dual-release formulation of Metadoxine



## Metadoxine Safety

- Metadoxine is available (since the 1980's) in immediate release forms for acute treatment of Alcohol Intoxication and chronic treatment of Alcoholic Liver Disease (ALD) in a few countries (Italy, Portugal, Hungary, Russia, India, China, Mexico and Thailand)
- In 30 years of product availability no published safety/tolerability issues to our knowledge
- Papers reporting on treatment with Metadoxine at ~1500mg levels demonstrate safety and tolerability<sup>(1)</sup>

(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)

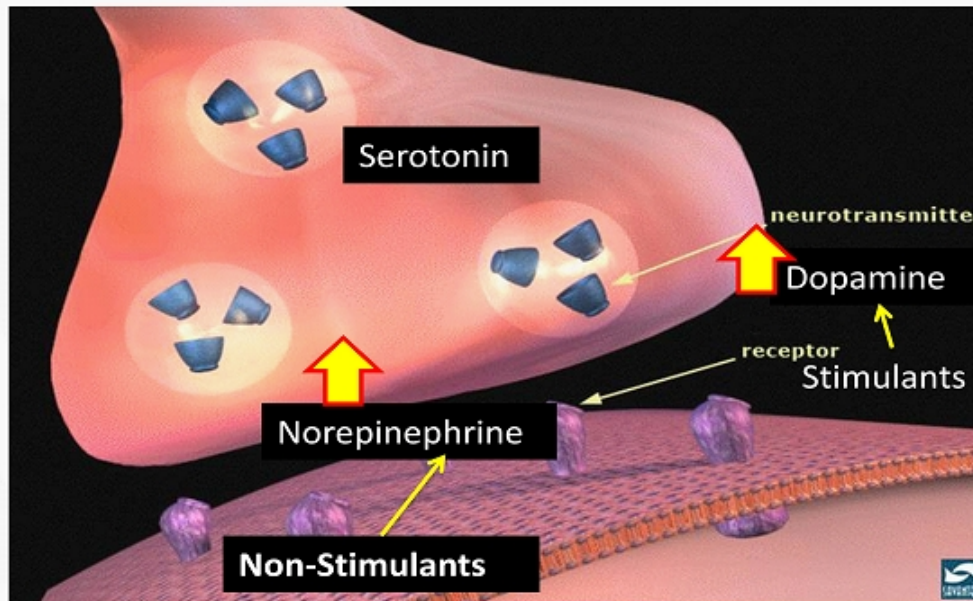
# Intellectual Property

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**Over 30 submitted patents globally may provide multiple layers of protection to 2030 and beyond:**

- Protection of Extended Release/Slow Release formulations of Metadoxine – ***US PATENT #8,476,304 ISSUED JULY 2013***
- Protection of use of any Metadoxine for cognitive disorders and impairments (Important for possible extended indications of Metadoxine)
- Protection of new Metadoxine derivatives
- Protection of combination therapies containing Metadoxine
- Protection of Metadoxine manufacturing process

# ADHD – Underlying Pharmacology



In the ADHD brain, low neurotransmitters levels are modulated by either stimulants or non stimulants

Improvement in ADHD is thought to occur via increased levels of catecholamines, which could lead to elevation of cAMP, PI3K/Akt and ERK signaling pathways

# Metadoxine Proposed MOA

A series of pre-clinical studies conducted by global CROs for Alcobra indicated:

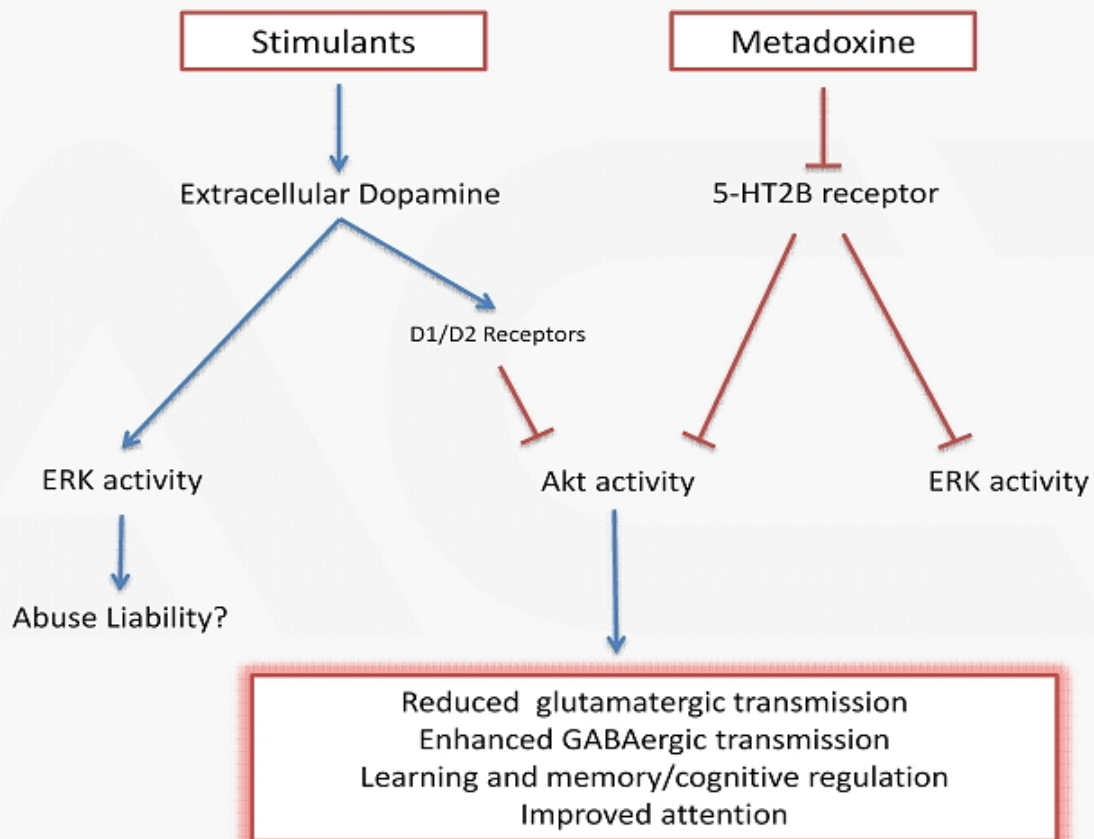
## In contrast to approved ADHD pharmacotherapies:

- Metadoxine shows **no effect on monoamines levels** (DA, NE and 5-HT) in a microdialysis study and **no effect on *in vivo* metabolites** in a 1H-MRS imaging study.
- Metadoxine shows no binding to **DA, NE or 5-HT transporters** *in vitro*.

## BUT:

- Metadoxine (0.5 mg/ml) **binds to the serotonin 5-HT<sub>2B</sub> receptor**, and behaves as an **antagonist** at that receptor.
- Metadoxine **normalizes in a dose-dependent manner** several biochemical markers of neuronal signaling and oxidative stress:
  - **Significantly reduces hyperactivation of ERK and AKT**
  - **Significantly increases GST levels**
  - **Does not affect cAMP/PKA pathway**
 Metadoxine does not induce such effects in WT mice.
- Metadoxine displays a **dose-dependent, reversible reduction in glutamatergic excitatory transmission and enhancement of GABAergic inhibitory transmission** via pre-synaptic modulations in striatal medium spiny neurons.

# Metadoxine Proposed MOA





# MG01CI Phase IIb – Study Design

- Adult, Israeli study (Geha MHC & Rambam MC)
- n = 120
- Design: 6 week randomized, double-blinded parallel comparison 1400mg MG01CI vs. Placebo

## Primary Endpoint

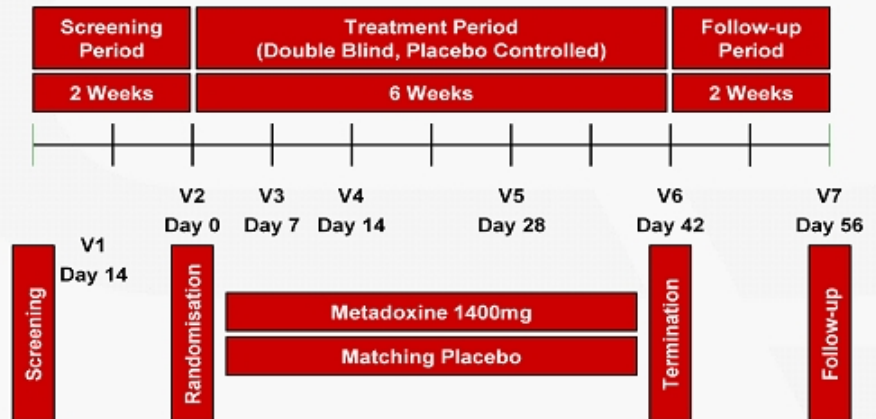
- Prompted CAARS-INV

## Secondary Endpoints:

- Adult ADHD QoL (AAQoL)
- TOVA

## Exploratory Endpoints:

- Rate of AE's
- Discontinuation Rates



# Advisory Board

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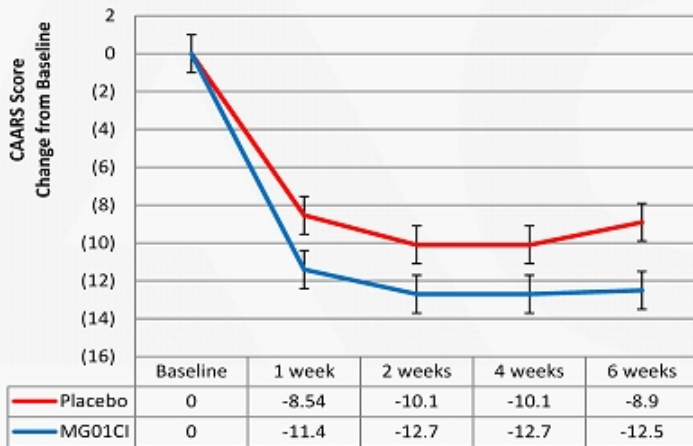


- **Lenard A Adler, MD**, Professor of Psychiatry and Child and Adolescent Psychiatry, New York University Langone Medical Center – **Chair**
- **Richard Weisler, MD**, Adjunct Professor of Psychiatry at the University of NC at Chapel Hill, Adjunct Associate Professor of Psychiatry at Duke University Medical Center, Raleigh, NC
- **Stephen V Faraone, PhD**, Professor of Psychiatry and Behavioral Sciences, State University of New York Upstate
- **Thomas J Spencer, MD**, Associate Professor of Psychiatry, Assistant Director, Pediatric Psychopharmacology Unit, Mass General Hospital
- **Jeffrey Newcorn, MD**, Professor of Psychiatry, Mount Sinai Hospital
- **Mark A Stein, PhD**, Professor, Dept of Psychiatry and Pediatrics, University of Illinois at Chicago
- **Betsy Busch, MD**, Associate Clinical Professor of Pediatrics at the Tufts University School of Medicine
- **Anthony L Rostain, MD**, Professor of Psychiatry and Pediatrics, University of Pennsylvania School of Medicine
- **Phillip Asherson, MB,BS, MRCPsych, PhD**, Professor of Molecular Psychiatry at the MRC Social, Genetic and Developmental Psychiatry centre at the Institute of Psychiatry, King's College London
- **Iris Manor, MD**, Associate Professor of Psychiatry, Director of the ADHD Unit, Geha Mental Health Center

# MG01CI Phase IIb - Efficacy

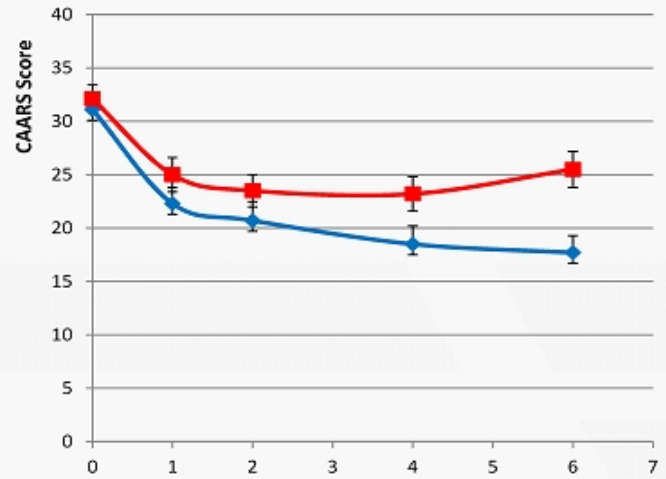
- Statistically Significant Differences Between MG01CI and Placebo Starting Week 2: Primary Endpoint Analysis

CAARS TOTAL SCORE (n=113)



Wilcoxon rank test analysis:  $p < 0.016$   
 Median difference at 6 weeks: 4.0  
**Effect Size: 0.4**

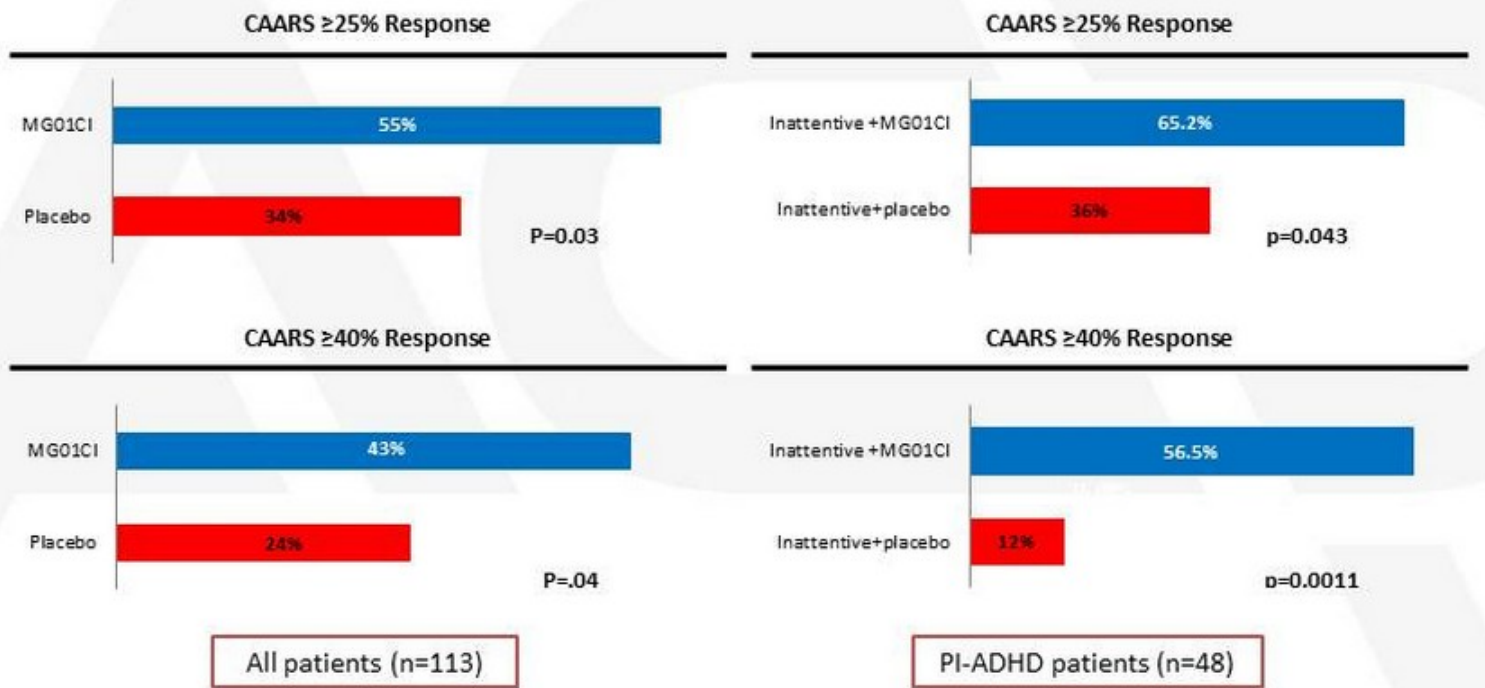
CAARS TOTAL SCORE (n=48) – PI-ADHD Only



Wilcoxon rank test analysis:  $p < 0.05$   
 Median difference at 6 weeks: 10.0  
**Effect Size: 0.9**

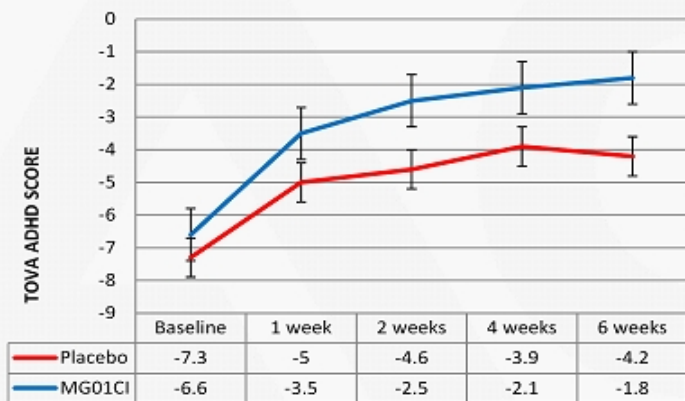
# MG01CI Phase IIb - Efficacy

- Statistically Significant Differences Between MG01CI and Placebo Starting Week 2: Response Rate Analysis

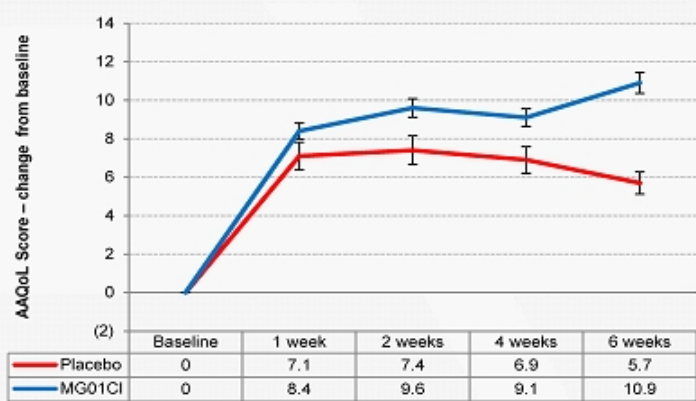


# MG01CI Phase IIb - Efficacy

- Statistically Significant Differences Between MG01CI and Placebo Starting at Week 2: Secondary Endpoint Analyses – TOVA and AAQOL (n=113)



ANOVA T-Test (with adjustments for gender, site, age and baseline scores): **p<0.05 (Week 2+)**



ANOVA T-Test (with adjustments for gender, site and age scores): **p<0.05 (Week 6)**

# MG01CI Phase IIb – Safety Outcomes

- No SAE's related to Study Drug
- No significant change from Placebo in AE profile, with possible exception of Nausea (17%) and Initial Insomnia (5%)
- No statistically significant changes in cardiac function (HR, BP)
- No effect on appetite, mood
- No other changes (ECGs, C-SSRS, CBC, Chem, Urinalysis)

Brand	Generic Name	Class	Common Side Effects
Vyvanse	Lisdexamfetamine	Stimulant	Appetite Suppression; Growth Retardation;
Concerta	Methylphenidate	Stimulant	Mood Disorders; Tics; Cardiovascular effects;
Adderall XR	Amphetamine	Stimulant	Sexual Dysfunction
Strattera	Atomoxetine	Non-Stimulant	Most of the above <b>plus</b> suicidality; liver toxicities

## Overall findings:

- Significant effect size; particularly large on Inattentive patients
- Response rate higher than other non-stimulants
- Response is more rapid than available non-stimulants
- Tolerability appears superior to all approved drugs
- The absence of cardiovascular effects (seen with existing ADHD drugs) is highly meaningful
- Lack of a need for dose titration is advantageous

**Represents The Best Of Both Worlds:  
A Non-Stimulant With Stimulant-Like Efficacy**

# MG01CI – Next Steps

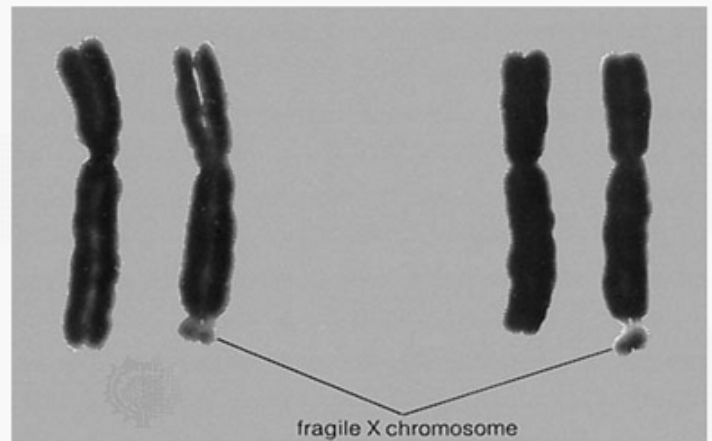
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- Continue discussions with the U.S. FDA to seek approval, via an IND Application submission
  - Conduct a Phase III clinical trial in the United States for the use of MGO1CI to treat ADHD in adults.
  - Conduct one additional clinical trial in order to submit an NDA to the FDA for adult use.
- In addition to the ongoing work in adult ADHD, the Company now plans to complete the necessary work and conduct clinical trials in children with ADHD
  - One Phase I/II dose escalation study to determine effective dose
  - One subsequent Phase III trial required for approval



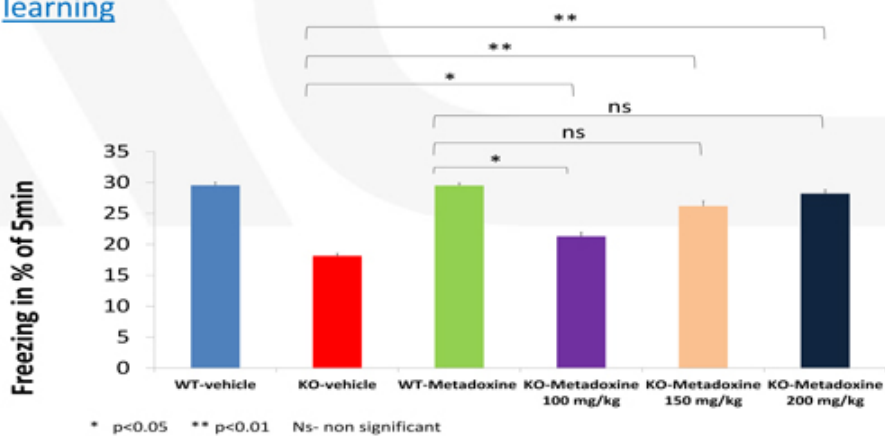
# MG01CI – Significant Upside in Fragile X

- A rare neurogenetic disorder caused by loss of FMR1 protein
- Most common known genetic cause of autism
- Most common inherited form of intellectual disability
- Occurs in 1:4,000 males; 1:8,000 females
- No FDA approved therapies to date



- In a well-validated animal model for Fragile X, Metadoxine showed (in a dose-linear way):
  - Significant improvements in working memory and learning
  - Significant improvements in social interaction
  - Significant changes in biomarkers including pAkt, pERK and GST (but not cAMP/PKA)

## Contextualizing Fear Conditioning: Test of memory and learning



# MG01CI – Significant Upside in Fragile X

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- Company intends to launch Phase IIb studies in adults and children with Fragile X in 2014
- Company to proceed to pivotal studies in adults and children with Fragile X in 2015
- Company submitted request for Orphan Drug Designation
- Unique formulation/dosing possible

# Use of Proceeds

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- The company is engaging in new clinical development activities in order to create new value drivers beyond the adult ADHD opportunity (which is fully funded by our May 2013 IPO proceeds)
  1. Completing Phase II studies in adults and children with Fragile X, followed by Phase III studies for NDA estimated at \$14M
  2. Completing a Phase I/II dose escalation study in children with ADHD, followed by a Phase III study for NDA estimated at \$10M
  3. The remainder will be used for working capital and general corporate purposes.

# Capitalization

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Shares Outstanding*	11.1MM
Options and Warrant Outstanding*	1.1MM
Share Price (NASDAQCM: ADHD)**	\$18.12
Market Cap**	\$201.6MM
Cash and Cash Equivalents***	\$21.6MM

\*As of period ended October 1, 2013

\*\*October 21, 2013

\*\*\*As of period ending June 30, 2013

## Investment Summary

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- MG01CI addresses a significant market opportunity in the ADHD market
  - An rapidly effective non-stimulant with a differentiated mechanism of action and superior tolerability
- Significant pre-clinical findings suggest an opportunity for MG01CI development in Fragile X Syndrome, a rare neurogenetic disease and one of the few known causes of autism
- Proceeds from this offering will be used to fund the company and its advanced clinical trials for MG01CI in pediatric ADHD and Fragile X Syndrome

# Alcobra Ltd.

NASDAQ:ADHD

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

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