UNITED STATES

SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 6-K

Report of Foreign Private Issuer
Pursuant to Rule 13a-16 or 15d-16
under the Securities Exchange Act of 1934

For the month of: October 2014 (Report No. 2)

ALCOBRA LTD.
(Translation of registrant's name into English)

Amot Investment Building
2 Weizman St. 9th Floor
Tel Aviv 6423902 Israel
(Address of principal executive offices)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F.

Form 20-F x Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulations S-T Rule 101(b)(1):_____

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulations S-T Rule 101(b)(7):_____

Indicate by check mark, whether the registrant by furnishing the information contained in this Form is also thereby furnishing the information to the Commission pursuant to Rule 12g3-2(b) under the Securities Exchange Act of 1934.

Yes ☐ No ☒

If "Yes" is marked, indicate below the file number assigned to the registrant in connection with Rule 12g3-2(b): ___

Alcobra Ltd. has posted a presentation to its website. A copy of the presentation is furnished with this Report of Foreign Private Issuer on Form 6-K as Exhibit 99.1 and is incorporated herein by reference.

Forward Looking Statements

The presentation attached hereto as Exhibit 99.1 may contain forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995 and other Federal securities laws. Because such statements deal with future events and are based on Alcobra's current expectations, they are subject to various risks and uncertainties and actual results, performance or achievements of Alcobra could differ materially from those described in or implied by the statements in such presentation. For example, 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 such presentation would not be interpreted differently in light of additional research and clinical and preclinical trials results. The forward-looking statements contained or implied in such presentation are subject to other risks and uncertainties, including those discussed under the heading "Risk Factors" in Alcobra Ltd.'s Annual Report on Form 20-F filed with the Securities and Exchange Commission ("SEC") on March 28, 2014, and in subsequent filings with the SEC. Except as otherwise required by law, Alcobra disclaims any intention or obligation to update or revise any forward-looking statements, which speak only as of the date hereof, whether as a result of new information, future events or circumstances or otherwise.

Exhibit No.

99.1	Presentation

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Alcobra Ltd.
(Registrant)

By /s/ Dr. Yaron Daniely
Name: Dr. Yaron Daniely

Chief Executive Officer and President

Date: October 22, 2014

Randomized Controlled Trials of Metadoxine Extended Release in Adults With Attention-Deficit/Hyperactivity Disorder

Lenard Adler, MD

October 22, 2014

AACAP's 61st Annual Meeting

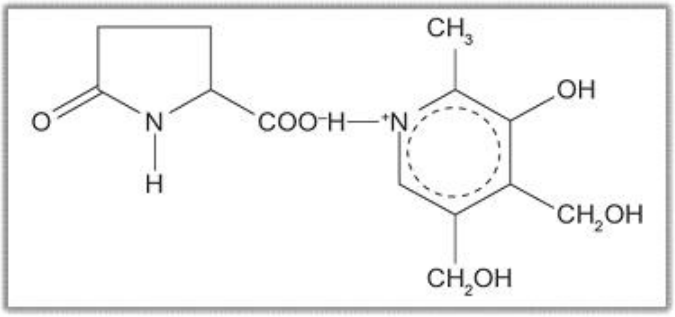
NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Disclosures of Potential Conflict: Lenard A Adler, MD

Commercial Interest	What Was Received?	For What Role?
Alcobra Ltd	Honoraria	Consulting, Advisory Board
Shire Pharmaceuticals	Honoraria Research Support	Consulting, Advisory Board, Conduct of Clinical Trial
NYU School of Medicine	License Fees	License of Adult ADHD Training Materials
SUNY Upstate	Consulting	Consulting on ADHD Trial
APSARD/Pond Foundation	Research Support	Conduct of Clinical Trial
National Football League	Honoraria	Consulting
Major League Baseball	Honoraria	Consulting
Major League Baseball Players Association	Honoraria	Consulting
Novartis Bioventures	Honoraria	Consulting
Theravance	Honoraria Research Support	Consulting, Advisory Board, Conduct of Clinical Trial
US Department of Veterans Affairs Cooperative Studies Program	Research Support	Conduct of Clinical Trial
Sunovion	Honoraria, Research Support	Consulting, Advisory Board, Conduct of Clinical Trial
Purdue Pharma	Research Support	Conduct of Clinical Trial
Heptares	Honoraria	Consulting

Metadoxine Extended Release (MDX)

MDX is a proprietary dual-release formulation of metadoxine, an ion-pair salt of pyridoxine (vitamin B_6) and 2-pyrrolidone-5-carboxylate (PCA, also known as L-PGA)



Metadoxine Safety (ex-US)

- Metadoxine is available in immediate-release form 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 metadoxine was 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 tolerability[1-3]

1. Caballeria et al. *J Hepatology*. 1996;28:54-60. N = 69, 3 months of metadoxine 1500 mg/d.
2. Cacciatore 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/d.
3. Bono et al. *Int J Clin Pharm Res*. 1991;11:35-40. N = 20, metadoxine 900 mg IV twice daily (1800 mg/d) for 10 days.

Metadoxine Has a Novel Mechanism of Action (MOA)

Available preclinical data suggest that metadoxine has a novel MOA characterized by:

1. A monoamine-independent GABAergic transmission modulation, and
2. Antagonism of the 5-HT_{2B} receptor

Rubin J, et al. Poster 1364 presented at: Society of Biological Psychiatry 69th Annual Scientific Meeting; May 10, 2014; New York, NY.

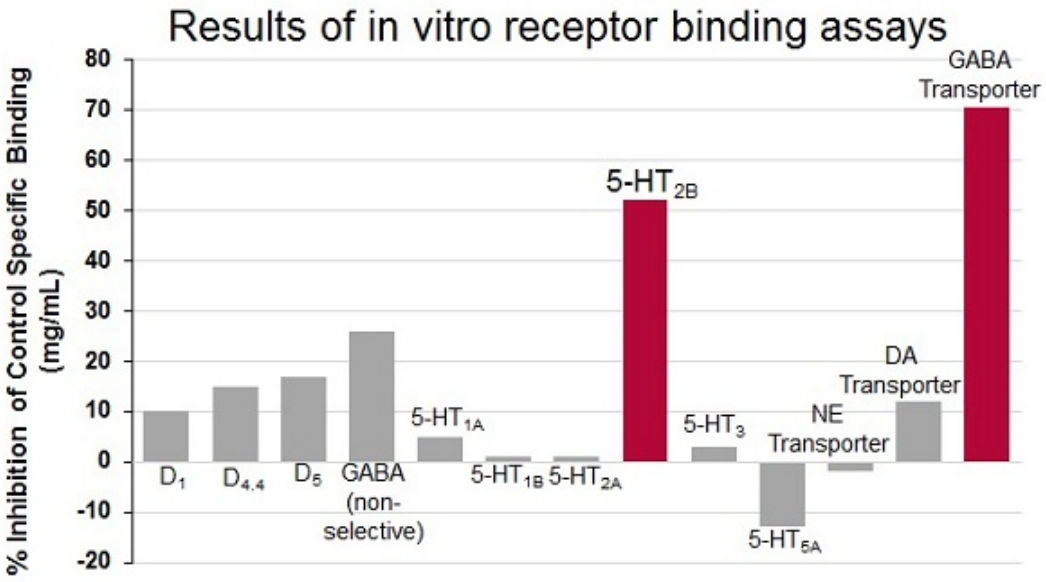
Metadoxine Has Little Effect on Dopamine, Norepinephrine, or Serotonin in vivo

In a microdialysis study, single-dose administration of metadoxine 150 and 300 mg/kg orally had no statistically significant effect on DA, 5-HT, or NE levels in the frontal cortex or on DA or 5-HT in the striatum of freely moving rats

A single oral dose of metadoxine 70 mg/kg or 140 mg/kg had no effect on in vivo ^{1}H-MRS metabolite levels or on striatal neurotransmitter levels in rats

Rubin J, et al. Poster 1364 presented at: Society of Biological Psychiatry 69th Annual Scientific Meeting; May 10, 2014; New York, NY.

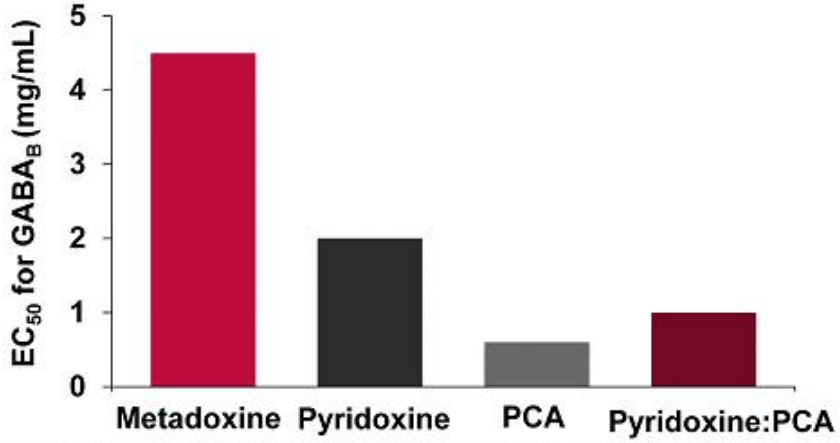
Metadoxine Binds to the 5-HT$_{2B}$ Receptor and GABA Transporter



Rubin J, et al. Poster 310 presented at: 27th Annual US Psychiatric & Mental Health Congress; September 20–23 , 2014; Orlando, FL.

Metadoxine Has $GABA_B$ Agonist-Like Activity That Differs From Components

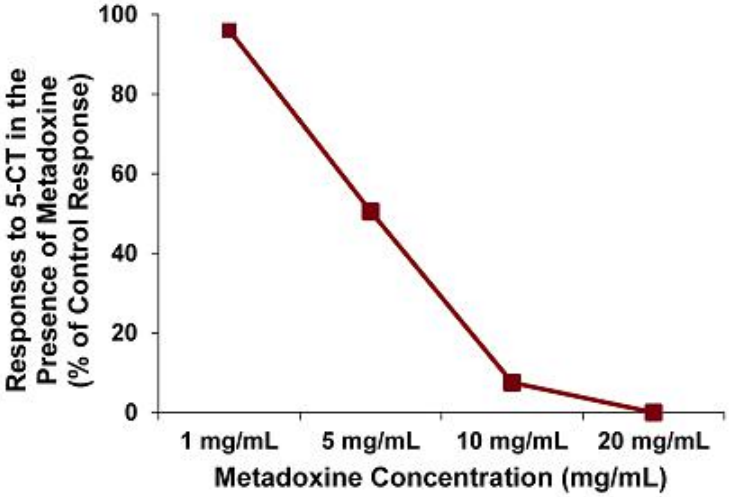
The pharmacologic activity of metadoxine and its 2 components (pyridoxine and PCA separately and as a 1:1 mixture) differ in the $GABA_B$ receptor assay



Rubin J, et al. Poster 1364 presented at: Society of Biological Psychiatry 69th Annual Scientific Meeting; May 10, 2014; New York, NY.

Metadoxine Acts as a 5-HT_{2B} Antagonist

Metadoxine demonstrated selective concentration-dependent inhibition of rat stomach fundus contraction induced by the 5-HT_{2B} agonist 5-CT



Rubin J, et al. Poster 1364 presented at: Society of Biological Psychiatry 69th Annual Scientific Meeting; May 10, 2014; New York, NY. 5-CT = 5-carboxamidotryptamine.

MDX Clinical Trial Updates

Randomized, Placebo-Controlled, Multiple-Dose Phase IIb Study

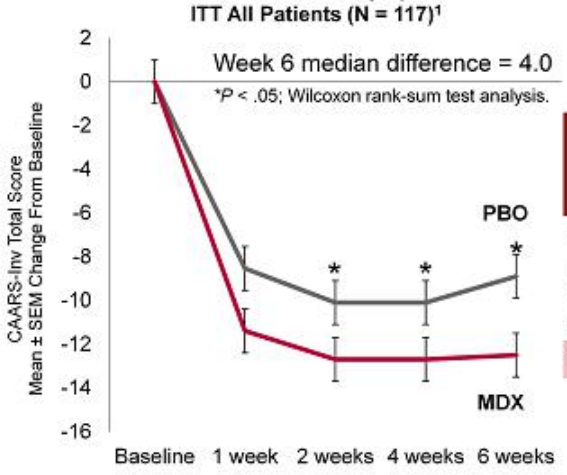
- Adult multiple-dose study (2 centers in Israel)
  - N = 120 adults with ADHD
  - Design: 6-week randomized, double-blind, parallel group comparison of MDX 1400 mg once daily vs placebo
- Primary endpoint
  - Conners' Adult ADHD Investigator Rating Scale with adult prompts (CAARS-Inv)
- Secondary endpoints
  - Response rates for CAARS-Inv
  - Test of Variables of Attention (TOVA®) ADHD score
  - Adult ADHD Quality of Life Score (AAQoL)
- Exploratory endpoints
  - Adverse event (AE) rates
  - Discontinuation rates

Manor I, et al. *J Clin Psychiatry*. 2012;73:1517-1523.

Multiple-Dose 6-Week Phase IIb Study: CAARS-Inv Score

Statistical separation of MDX and placebo effect starting at week 2 (ITT)

CAARS-Inv Total ADHD Symptom Score
ITT All Patients (N = 117)[1]



CAARS-Inv Total ADHD Symptom Score
By ADHD Subtypes[2]

	CT-ADHD (N=69)		PI-ADHD (N=49)	
	Placebo (N=33)	MDX 1400 mg (N=36)	Placebo (N=26)	MDX 1400 mg (N=23)
Baseline	40.9 ± 7.8	41.1 ± 7.9	32.1 ± 6.7	31.1 ± 5.0
Week 6	30.1 ± 13.2	29.8 ± 10.1	25.5 ± 8.3	17.7 ± 7.5
Mean change	-10.8±6.8	-11.3±8.9	-6.6±10.7	-13.4±10.2
P Value	0.61		<0.05	

Analysis using 2-sample *t* test.

1. Manor I, et al. *J Clin Psychiatry*. 2012;73:1517-1523. 2. Manor I, et al. *Postgrad Med.* 2013;125:181-190.

Multiple-Dose 6-Week Phase IIb Study: Safety

- No serious AEs related to study drug
- No clinically significant differences compared with placebo in AE profile, with possible exception of nausea (17%) and initial insomnia (5%)
- No statistically significant changes in cardiac function (heart rate, blood pressure)
- No effect on appetite or mood
- No other changes in safety assessments
  - Electrocardiograms
  - Columbia-Suicide Severity Rating Scale
  - Complete blood count
  - Blood chemistry
  - Urinalysis

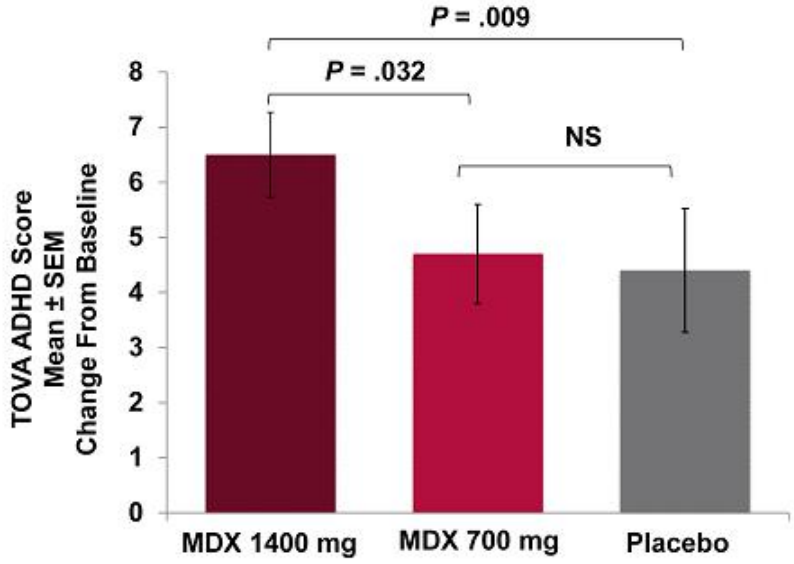
Manor I, et al. *J Clin Psychiatry*. 2012;73:1517-1523.

Randomized, Placebo-Controlled, Single-Dosing, Crossover Phase IIb Study

- Adult single-center study (1 site in Israel)
  - N = 36 adults with PI-ADHD
  - Design: Randomized, double-blind, placebo-controlled, single-dosing, crossover comparison of 2 MDX doses (700 and 1400 mg once daily) and placebo
  - Each patient received each dose of each treatment 1 week apart
- Primary endpoint
  - TOVA ADHD score
- Secondary endpoints
  - TOVA subscores and TOVA response rates
- Exploratory endpoints
  - AE rates and discontinuation rates

Manor I, et al. *Postgrad Med.* 2014;126:7-16.

Single-Dosing Crossover Phase IIb Study: TOVA ADHD Score (ITT)



P values based on paired *t* tests. NS = not significant.
Manor I, et al. *Postgrad Med.* 2014;126:7-16.

Single-Dosing Crossover Study: Adverse Events

AE	No. (%) of Patients		
	MDX 1400 mg (n = 34)	MDX 700 mg (n = 36)	Placebo (n = 35)
Total AEs	11 (32.4)	6 (16.7)	11 (31.4)
Fatigue	5 (14.7)	0 (0)	4 (11.4)
Headache	4 (11.8)	2 (5.6)	4 (11.4)

Severity of AEs:

- 3 moderate AEs of headache
  - 2 on MDX 700 mg, 1 on placebo
- Remaining AEs were mild in severity
- 1 discontinuation due to an AE of dermatitis treated with a prohibited concomitant medication

Manor I, et al. *Postgrad Med.* 2014;126:7-16.

6-Week Multicenter 300 Patient Phase III Study: Overview

- 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 placebo once daily for 6 weeks
  - Randomization stratified to ensure ≥ 33% of patients in each group had PI-ADHD

- Baseline and efficacy assessments review
  - Rater training and certification was conducted as per published methodology at baseline and once during trial[1]
  - Integrity of rater monitoring of the Adult Clinician Diagnostic Scale (ACDS) v1.2, prompted CAARS-Inv, and CGI was assessed via remote inspection of case report forms (CRFs) by blinded observer
    - 36% of all baseline ratings were examined

1. Adler LA, et al. *J Atten Disord*. 2005;8(3):121-126.

Study Assessments

Primary efficacy assessment

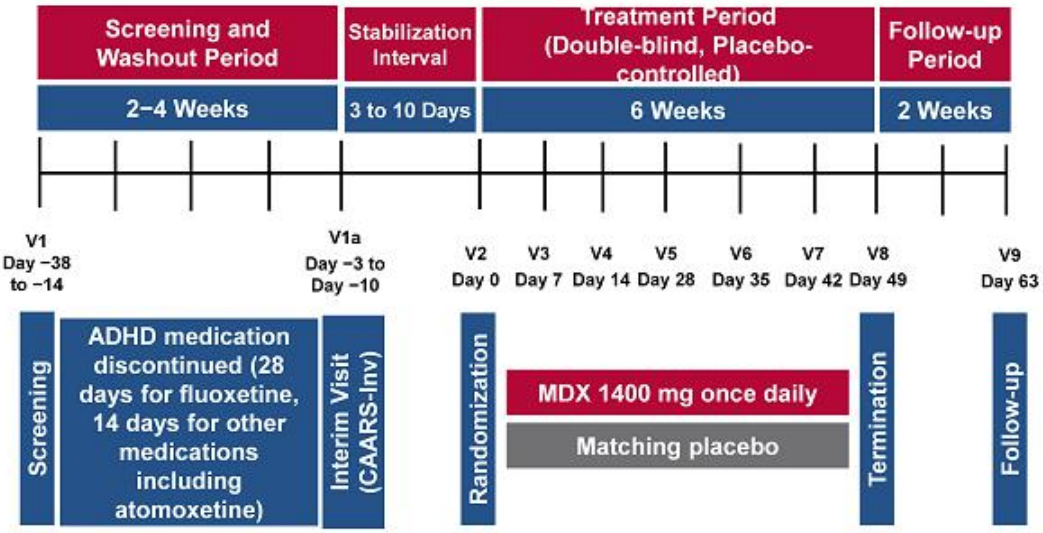
- Total ADHD symptom score of the CAARS-Inv with adult prompts

Secondary assessments

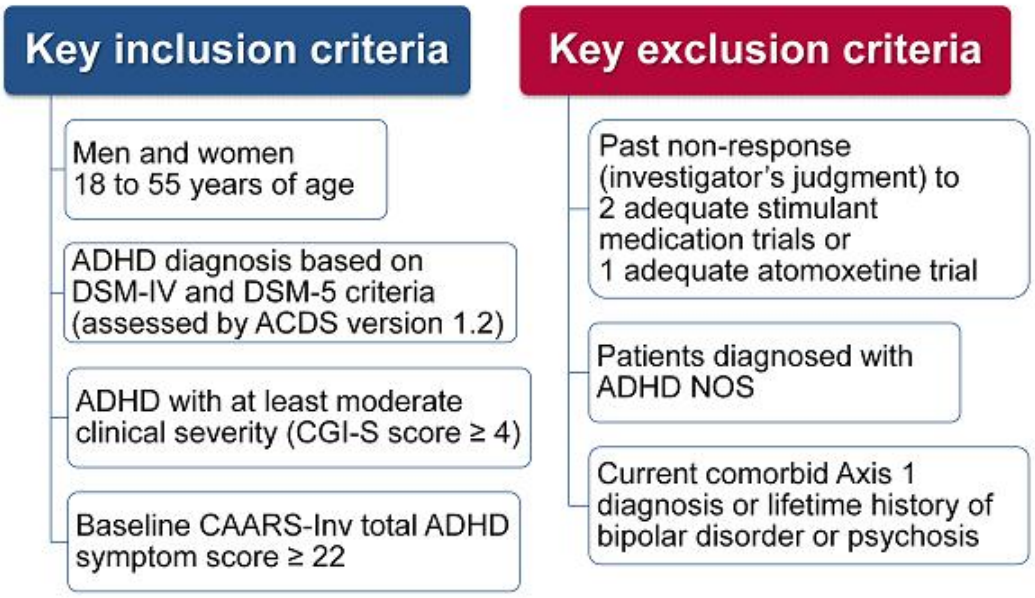
- Clinical Global Impression-Severity (CGI-S)
- Clinical Global Impression-Improvement (CGI-I)
- Adult ADHD Self-Report Scale (ASRS-Self)
- Barkley Functional Impairment Scale (BFIS)*
- Behavior Rating Inventory of Executive Function (BRIEF-A)*
- Adult ADHD Quality of Life Questionnaire (AAQoL)*
- Safety: Adverse events, vital signs, electrocardiogram, laboratory evaluation, physical and neurological examination, Columbia Suicide Severity Rating Scale (C-SSRS)

*Data still being analyzed

Study Design

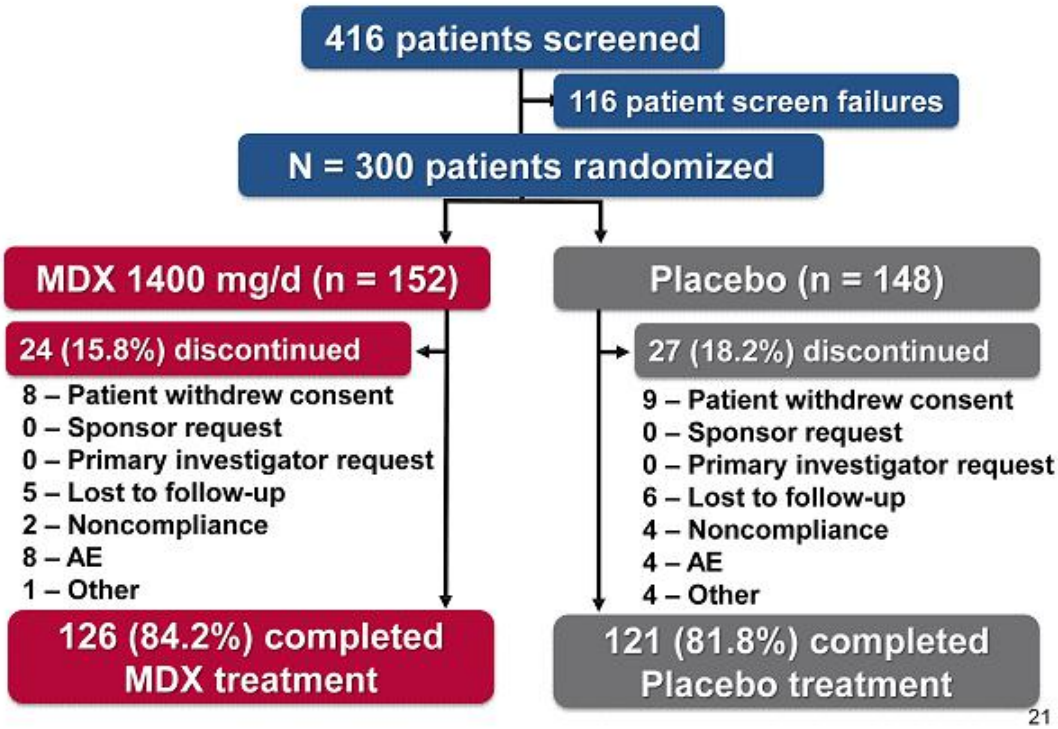


Inclusion/Exclusion Criteria



ACDS = Adult ADHD Clinical Diagnostic Scale; NOS = not otherwise specified.

Patients Disposition



Patient Baseline Demographics

Characteristic	MDX 1400 mg/d (n = 152)	Placebo (n = 146)
Age, mean (range), y	35.1 (18 – 55)	35.6 (18 – 55)
Sex, n (%)		
Female	79 (52)	79 (54)
Male	73 (48)	67 (46)
Race, n (%)		
White	128 (84.2)	130 (89.0)
Black	17 (11.2)	14 (9.6)
Asian	4 (2.6)	0
Ethnicity		
Hispanic or Latino	10 (6.6)	15 (10.3)
Not Hispanic or Latino	141 (92.8)	131 (89.7)
Weight, mean ± SD (range), kg	82.1 ± 19.8 (44 – 138)	82.3 ± 21.1 (47 –150)

Baseline demographic data are calculated from Safety Population (all patients who received at least 1 dose of study medication)

Baseline Clinical Characteristics

Characteristic	MDX 1400 mg/d (n = 152)	Placebo (n = 146)
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, mean ± SD (range)	38.5 ± 8.1 (22 – 54)	38.2 ± 8.0 (22 – 53)
CAARS-Inv inattentive symptom score (subset A)	21.5 ± 4.1 (8.0 – 27.0)	21.8 ± 4.0 (10.0 – 27.0)
CAARS-Inv hyperactive-impulsive symptom score (subset B)	17.0 ± 6.1 (0.0 – 27.0)	16.4 ± 6.0 (0.0 – 27.0)
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
Total Adult ADHD Self-Report Scale (ASRS), mean ± SD (range)	48.1 ± 10.7 (20.0 – 70.0)	47.5 ± 11.0 (21.0 – 72.0)

Baseline demographic data are calculated from Safety Population (all patients who received at least 1 dose of study medication)

Pre-specified Primary Analyses

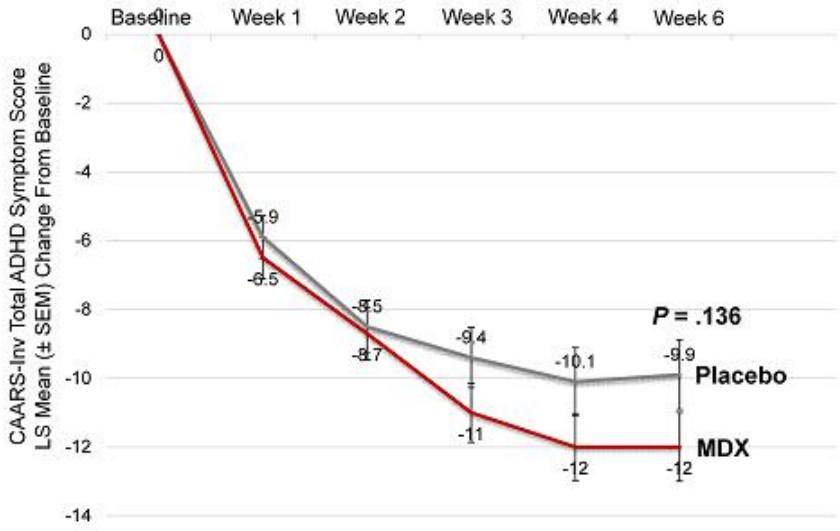
- A mixed-effect model repeated measures (MMRM) analysis was used for all primary analyses (the CAARS-Inv total ADHD symptom score).
- The **ITT** analysis compared the estimated least-square (LS) mean difference from baseline to week 6 (or early termination) between treatment groups.
- A **pre-specified** modified intention-to-treat (mITT) analysis employed the same comparison after omitting any patient who had a week 6 outcome that was ≥ 3 standard deviations (SD) from the within treatment average change.

Post-hoc Analyses

- A **post-hoc analysis** was performed on the ITT population excluding patients with major entry criteria violations[1]
  - Major entry criteria violations were identified prior to unblinding of randomization codes by an adult ADHD expert
- A combination of the pre-specified mITT analysis and the post-hoc analysis was also performed as **an additional post-hoc analysis**

[1] ICH E9 Guideline: "Statistical Principles for Clinical Trials".

Primary Efficacy Analysis Results
CAARS-Inv: ITT (n = 297[1])



P values based on MMRM analysis. Week 6 SD for MDX = 12.5 and for PBO = 11.8

[1] 3 patients enrolled in the study did not have any post-baseline efficacy assessment

Other Efficacy Analyses on Primary Measure (CAARS-Inv)

- 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
- The **post-hoc** mITT cohort (n=289), derived from excluding patients with major entry criteria violations at baseline by a blinded expert, resulted in the exclusion of 8 patients from the ITT population
  - Reasons for exclusion:
    - 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 (Chlordiazepoxide)
    - Patient was a close family member of a rater in the study

Summary of Efficacy Analyses on Primary Measure (CAARS-Inv)

Analysis Population	Treatment Group	N	n	LS Mean change	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 Major Entry Criteria Violations (n = 289)	Placebo	148	141	-9.6	-11.60	-7.54	-2.41	.0927
	MDX 1400 mg	152	148	-12.0	-13.96	-10.0		
Post-hoc mITT Excluding Entry Criteria 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		

P values based on MMRM analysis.

Summary of Efficacy Analyses on CAARS-Inv Subscales

Inattentive Score (A)	Treatment Group	N	n	LS Mean change	Lower 95% CI	Upper 95% CI	LS Mean Difference	*P* Value
ITT Population (n = 297)	Placebo	148	146	-5.7	-6.85	-4.53	-1.13	.1708
	MDX 1400 mg	152	151	-6.8	-7.95	-5.68		
Pre-specified mITT Excluding ≥ 3 SD Outliers (n = 295)	Placebo	146	144	-5.4	-6.52	-4.21	-1.43	.0805
	MDX 1400 mg	152	151	-6.8	-7.92	-5.67		
Post-hoc mITT Excluding Major Entry Criteria Violations (n = 289)	Placebo	148	141	-5.5	-6.71	-4.34	-1.37	.1005
	MDX 1400 mg	152	148	-6.9	-8.04	-5.74		
Post-hoc mITT Excluding Entry Criteria Violations and ≥ 3 SD Outliers (n = 287)	Placebo	146	139	-5.3	-6.42	-4.08	-1.63	.0479
	MDX 1400 mg	152	148	-6.9	-8.01	-5.75		

Hyperactive/Impulsive Score (B)	Treatment Group	N	n	LS Mean change	Lower 95% CI	Upper 95% CI	LS Mean Difference	*P* Value
ITT Population (n = 297)	Placebo	148	146	-4.2	-5.18	-3.26	-1.00	.1435
	MDX 1400 mg	152	151	-5.2	-6.17	-4.27		
Pre-specified mITT Excluding ≥ 3 SD Outliers (n = 295)	Placebo	146	144	-3.8	-4.78	-2.89	-1.25	.0628
	MDX 1400 mg	152	151	-5.1	-6.01	-4.16		
Post-hoc mITT Excluding Major Entry Criteria Violations (n = 289)	Placebo	148	141	-4.1	-5.05	-3.09	-1.04	.1339
	MDX 1400 mg	152	148	-5.1	-6.07	-4.15		
Post-hoc mITT Excluding Entry Criteria Violations and ≥ 3 SD Outliers (n = 287)	Placebo	146	139	-3.8	-4.79	-2.85	-1.29	.0594
	MDX 1400 mg	152	148	-5.1	-6.05	-4.17		

P values based on MMRM analysis.

Clinical Global Impression (CGI) – ITT population

CGI-Severity (CGI-S)			
Group	n/N	Odds Ratio for MDX vs PBO (95% CI)	***P* Value**
MDX	24/134	2.07 (0.98, 4.38)	.0569
PBO	14/126		

CGI-Improvement (CGI-I)			
Group	n/N	Odds Ratio for MDX vs PBO (95% CI)	***P* Value**
MDX	52/134	1.76 (1.03, 3.00)	.0384
PBO	34/126		

Summary statistics and p-values are from a logistic regression model at the week6 visit. The model includes treatment group and pooled site as categorical effects and baseline value as a continuous covariate. Odds ratios of CGI-S < 2 or CGI-I < 2 for MDX relative to Placebo

Adult ADHD Self-Report Scale (ASRS-Self) - ITT population

ASRS-Self Total ADHD Symptom Score week 6								
Analysis Population	Treatment Group	N	n	LS Mean change	Lower 95% CI	Upper 95% CI	LS Mean Difference Between Groups	*P* Value
ITT Population (n = 297)	Placebo	148	126	-9.9	-12.32	-7.51	-2.64	.122
	MDX 1400 mg	152	134	-12.6	-14.92	-10.20		

ASRS-Self Subscales Symptom Score week 6								
ASRS-Self Inattentive Subscale (ITT, n = 297)	Placebo	148	126	-5.0	-6.30	-3.63	-1.48	.117
	MDX 1400 mg	152	134	-6.4	-7.75	-5.14		
ASRS-Self Hyperactive-Impulsive Subscale (ITT, n = 297)	Placebo	148	126	-5.0	-6.19	-3.80	-1.13	.185
	MDX 1400 mg	152	134	-6.1	-7.30	-4.95		
ASRS-Self Executive Function Subscale (ITT, n = 297)	Placebo	148	126	-5.0	-6.33	-3.66	-0.95	.315
	MDX 1400 mg	152	134	-5.9	-7.25	-4.63		
ASRS-Self Emotional Control Subscale (ITT, n = 297)	Placebo	148	126	-2.3	-2.91	-1.78	-0.35	.382
	MDX 1400 mg	152	134	-2.7	-3.25	-2.14		
ASRS-Self Impulsivity Subscale (ITT, n = 297)	Placebo	148	126	-1.2	-1.55	-0.86	-0.21	.367
	MDX 1400 mg	152	134	-1.4	-1.75	-1.10		

P values based on MMRM analysis.

ASRS-Self - Other populations

ASRS-Self Total Score	Treatment Group	N	n	LS Mean change	Lower 95% CI	Upper 95% CI	LS Mean Difference	*P* Value
ITT Population (n = 297)	Placebo	148	126	-9.9	-12.32	-7.51	-2.64	.122
	MDX 1400 mg	152	134	-12.6	-14.92	-10.20		
Pre-specified mITT Excluding ≥ 3 SD Outliers (n = 295)	Placebo	146	124	-9.4	-11.77	-7.02	-3.16	.061
	MDX 1400 mg	152	134	-12.6	-14.87	-10.24		
Post-hoc mITT Excluding Major Entry Criteria Violations (n = 289)	Placebo	148	123	-9.9	-12.33	-7.48	-2.89	.092
	MDX 1400 mg	152	132	-12.8	-15.17	-10.43		
Post-hoc mITT Excluding Entry Criteria Violations and ≥ 3 SD Outliers (n = 287)	Placebo	146	121	-9.4	-11.76	-6.97	-3.43	.043
	MDX 1400 mg	152	132	-12.8	-15.12	-10.47		

ASRS-Self Inattentive Subscale	Treatment Group	N	n	LS Mean change	Lower 95% CI	Upper 95% CI	LS Mean Difference	*P* Value
ITT Population (n = 297)	Placebo	148	126	-5.0	-6.30	-3.63	-1.48	.117
	MDX 1400 mg	152	134	-6.4	-7.75	-5.14		
Pre-specified mITT Excluding ≥ 3 SD Outliers (n = 295)	Placebo	146	124	-4.7	-5.97	-3.34	-1.79	.054
	MDX 1400 mg	152	134	-6.4	-7.72	-5.17		
Post-hoc mITT Excluding Major Entry Criteria Violations (n = 289)	Placebo	148	123	-5.0	-6.30	-3.61	-1.61	.090
	MDX 1400 mg	152	132	-6.6	-7.87	-5.25		
Post-hoc mITT Excluding Entry Criteria Violations and ≥ 3 SD Outliers (n = 287)	Placebo	146	121	-4.6	-5.95	-3.31	-1.93	.038
	MDX 1400 mg	152	132	-6.6	-7.84	-5.28		

P values based on MMRM analysis.

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%)
- 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

Vital Signs

Vital Sign	MDX 1400 mg/d (n = 152) Mean ± SD	Placebo (n = 146) Mean ± SD
Systolic blood pressure, mm Hg		
Baseline	118.7 ± 12.7	118.1 ± 13.6
Change at week 6	−1.7 ± 10.4	−1.7 ± 10.1
Diastolic blood pressure, mm Hg		
Baseline	75.3 ± 9.0	74.7 ± 10.3
Change at week 6	−1.6 ± 8.2	−1.7 ± 9.0
Pulse rate, bpm		
Baseline	71.1 ± 10.7	70.6 ± 11.7
Change at week 6	−2.0 ± 10.0	−0.2 ± 10.2

ECG Parameters

Vital Sign	MDX 1400 mg/d (n = 152) Mean ± SD	Placebo (n = 146) Mean ± SD
QT duration, msec		
Baseline	387.8 ± 25.8	388.3 ± 26.3
Change at week 6	6.8 ± 21.7	5.0 ± 21.0
QTc Bazett's correction, msec		
Baseline	409.2 ± 20.7	407.5 ± 20.7
Change at week 6	−2.0 ± 17.6	−2.5 ± 18.5
QTc Fridericia's correction, msec		
Baseline	401.5 ± 17.3	400.5 ± 16.9
Change at week 6	1.0 ± 14.0	0.2 ± 14.3
PR duration, msec		
Baseline	150.2 ± 20.7	152.1 ± 18.1
Change at week 6	0.8 ± 11.0	0.3 ± 10.9
QRS duration, msec		
Baseline	91.6 ± 8.1	92.5 ± 9.0
Change at week 6	0.8 ± 5.0	0.4 ± 5.2

Adverse Events

Adverse Events in ≥ 5% of Patients in Any Group

AE	MDX 1400 mg/d (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

No drug-related serious AEs were reported.

Adult ADHD Trials: Placebo and SD Results in Context

Study		Mean ± SD
Michelson D et al, 2003[1]		
Study 1 N = 267	Atomoxetine	−9.5 ± 10.1
	Placebo	−6.0 ± 9.3
Study 2 N = 248	Atomoxetine	−10.5 ± 10.9
	Placebo	−6.7 ± 9.3
Medori R et al, 2012[2]; N=401		
OROS MPH 72 mg arm		−13.7 ± 11.1
Placebo		−10.6 ± 10.3
Manor I et al, 2013[3]; N=120		
MDX		−12.0 ± 9.7
Placebo		−8.9 ± 9.3
Phase III MDX Study; N=300		
MDX		−11.8 ± 12.6
Placebo		−9.7 ± 11.4

1. Michelson D, et al. *Biol Psychiatry*. 2003;52:112-120. 2. Medori R, et al. *Biol Psychiatry*. 2008;63:981-989.
3. Manor I, et al. *J Clin Psychiatry*. 2012;73:1517-1523

Reducing the Placebo Response and Variability

- Patient selection
  - Suggestibility of patients
  - Severity of patients
- Monitoring
  - Central rater
  - Real-time monitoring of rater and patient integrity
  - Monitoring ratings during trial
- Study design
  - Placebo lead-in
  - Sequential parallel comparison design[1]

1. Fava M, et al. *Psychother Psychosom*. 2003;72:115-127.

Conclusions

- Based upon analysis to date, MDX appears to be well tolerated
- ITT analysis of Phase III adult ADHD study yielded a non-significant positive trend showing consistent drug effect with previously reported phase 2b study[1], but a larger placebo effect than previously reported prior MDX[1] and other studies with ADHD pharmacotherapies[2,3]
- 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
- Further analyses from this study, including ADHD subtype analyses and evaluation of additional secondary efficacy endpoints, are ongoing
- A Phase II safety and PK study of MDX once daily in 82 adolescents with PI-ADHD is ongoing (NCT02189772)
- A phase 2b study of MDX in 60 adults and adolescents with Fragile X Syndrome is ongoing (NCT02126995)

1. Manor I, et al. *J Clin Psychiatry*. 2012;73:1517-1523. 2. Michelson D, et al. *Biol Psychiatry*. 2003;52:112-120.
3. Medori R, et al. *Biol Psychiatry*. 2008;63:981-989.