New Research in Treatment for Cognitive Impairment in Fragile X Syndrome

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FRAXA

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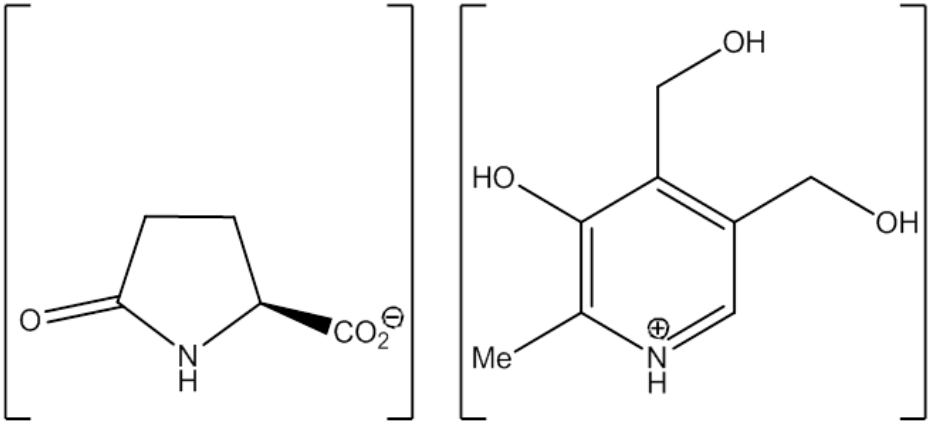
Overview

- Introduction to metadoxine
- Proposed mechanism of action (MOA) of metadoxine
- Metadoxine extended release (MDX) in patients with attention-deficit/hyperactivity disorder (ADHD); MDX as a procognitive agent that may help with thinking and attention
- Metadoxine in a mouse model of Fragile X (*fmr1* KO mice)
- Phase 2 clinical trial of MDX in patients with Fragile X syndrome (FXS)

Metadoxine

- Metadoxine: ion base pair salt of pyridoxine (vitamin B_6) and L-pyroglutamic acid (L-PGA)
- MDX: immediate-release and slow-release formulations in a single bilayer tablet

L-PGA Pyridoxine



Metadoxine

Metadoxine Proposed Mechanism of Action

Metadoxine is a monoamine-independent GABA transmission modulator

- **Monoamine-independent**
  - Metadoxine is a 5-HT2B receptor antagonist
  - Most ADHD medications (stimulants and Strattera) work by increasing monoamines (dopamine, norepinephrine, serotonin) in the brain
  - Metadoxine shows no effect on dopamine, norepinephrine, or serotonin levels in vivo
  - Metadoxine shows no binding to dopamine, norepinephrine, or serotonin transporters in vitro
- **GABA transmission modulator**
  - Metadoxine binds the GABA transporter
  - Metadoxine displays a dose-dependent, reversible enhancement of GABAergic inhibitory transmission via presynaptic mechanisms in a type of neurons called striatal medium spiny neurons
  - Metadoxine does not work via the metabotropic glutamate receptor (mGluR)

Rubin J, et al, US Psychiatric & Mental Health Congress; September 20–23 , 2014; Orlando, FL.

Clinical Trials of MDX in Adult Subjects with ADHD

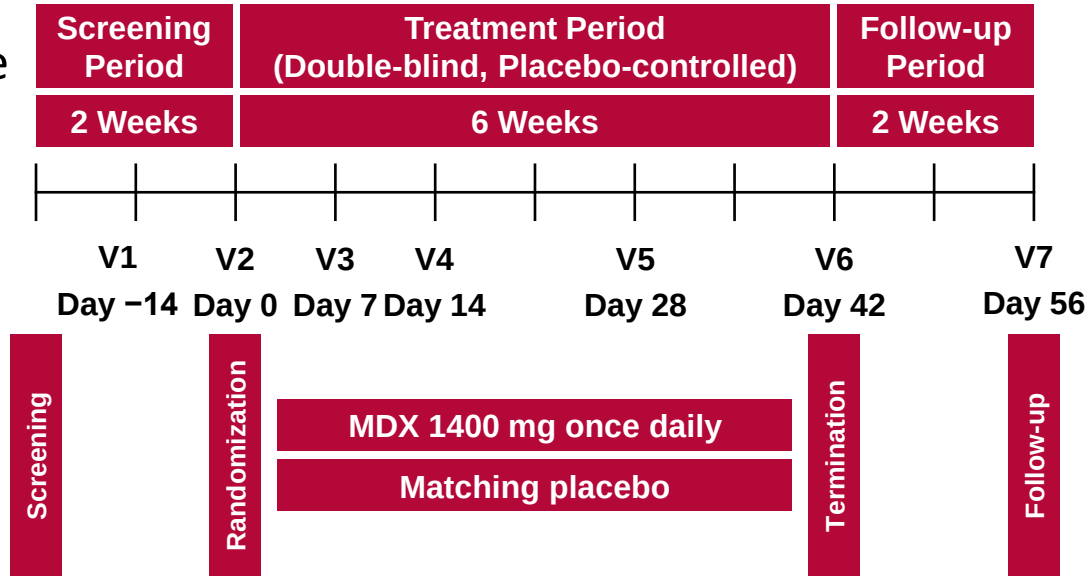
MDX Phase 2a Proof-of-Concept Study in ADHD

- Phase 2a open-label proof-of-concept study of 38 adults with ADHD
- Demonstrated efficacy on procognitive measures[1]
  - Improvement on the Test of Variables of Attention (TOVA) ADHD score
  - Improvement on TOVA subscores of errors of commission, omission, and response time variability
  - Improvement on several subscales of the Wechsler Adult Intelligence Scale – Revised

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

MDX Phase 2b: Study Design

- Adult study (Geha Mental Health Center/Rambam Health Care Center, 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
  - Prompted CAARS-INV (interview about ADHD symptoms)
- Secondary endpoints
  - AA Quality of life measure
  - TOVA
- Exploratory endpoints
  - Adverse event (AE) rates
  - Discontinuation rateS



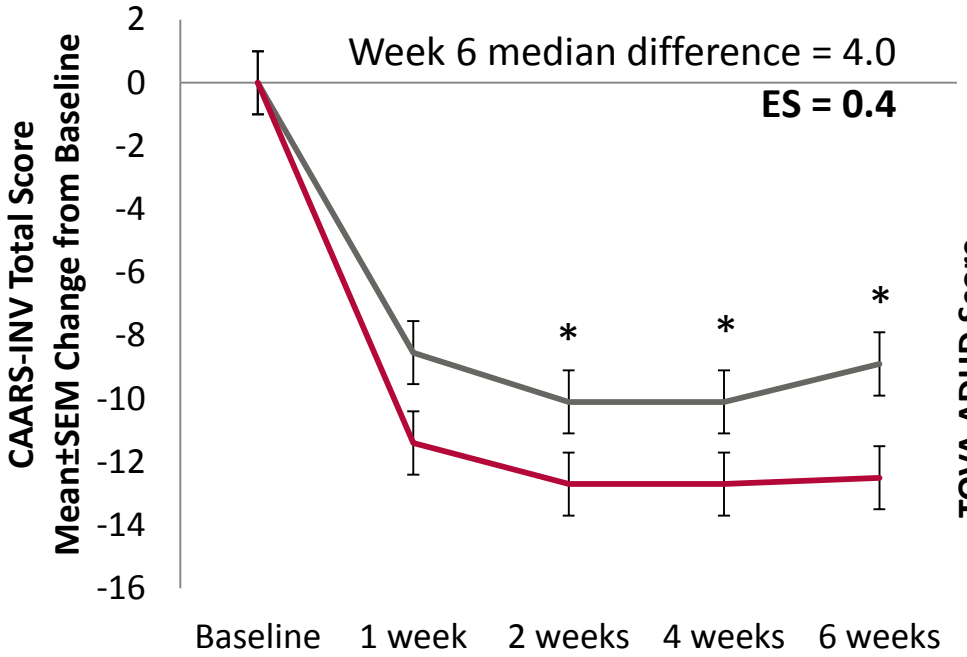
CAARS-INV = Conners Adult ADHD Rating Scale-Investigator; AAQoL = Adult ADHD Quality of Life Scale.

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

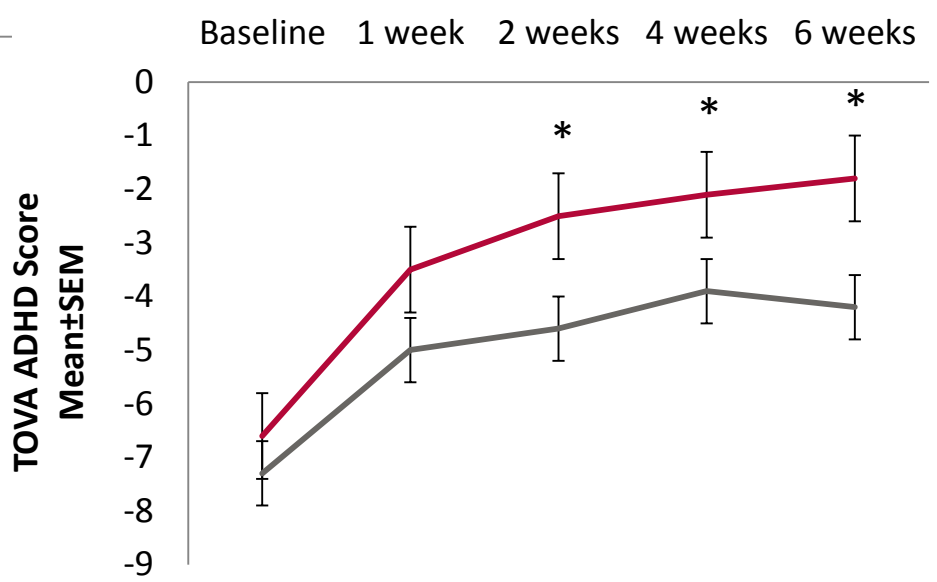
MDX Phase 2b: Primary Endpoint Analyses

MDX Placebo

CAARS-INV TOTAL SCORE (N = 113)[1]



TOVA ADHD SCORE (N = 113)[1]



*P < .05; Wilcoxon rank-test analysis.

ITT = intention to treat; PI = predominantly inattentive.

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

MDX Phase 2b: Safety Outcomes

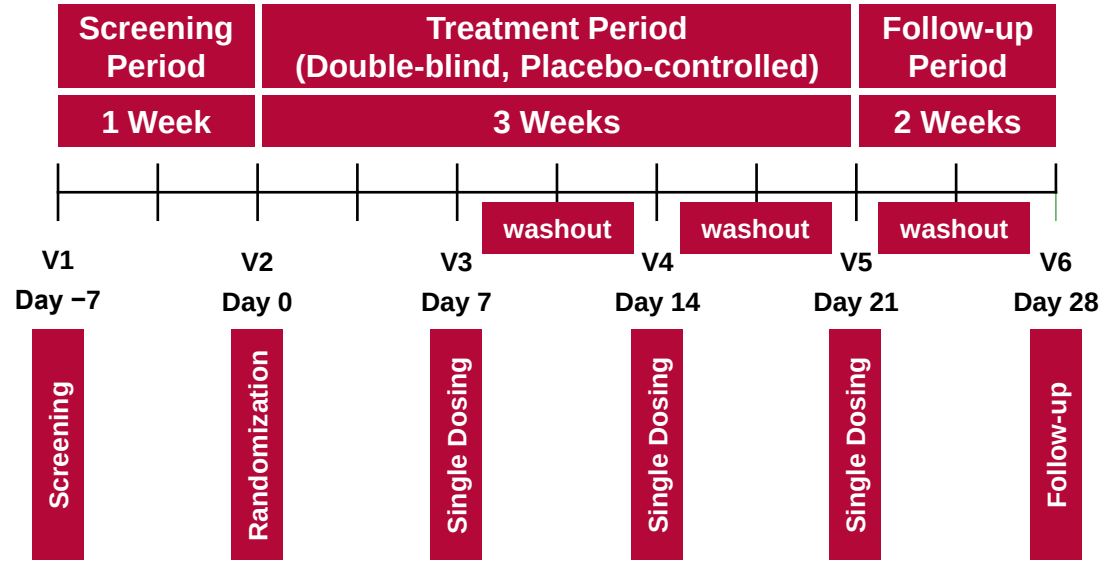
- No serious AEs related to study drug
- No clinically significant differences compared with placebo in AE profile, with possible exception of nausea (17%) and initial insomnia (5%)
- No statistically significant changes in cardiac function (heart rate, blood pressure)
- No effect on appetite or mood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

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

MDX Phase 2b (single center): Study Design

- Adult single-center study (Geha Mental Health Center, Israel)
  - N = 36 adults with primarily inattentive ADHD
  - Design: Randomized, double-blind, placebo-controlled, *single-dosing,* crossover comparison of 2 MDX doses (700 and 1400 mg once daily)
- Primary endpoint
  - TOVA ADHD Score
- Secondary endpoints
  - TOVA subscores
  - Response rates
  - CANTAB
- Exploratory endpoints
  - AE rates
  - Discontinuation rates

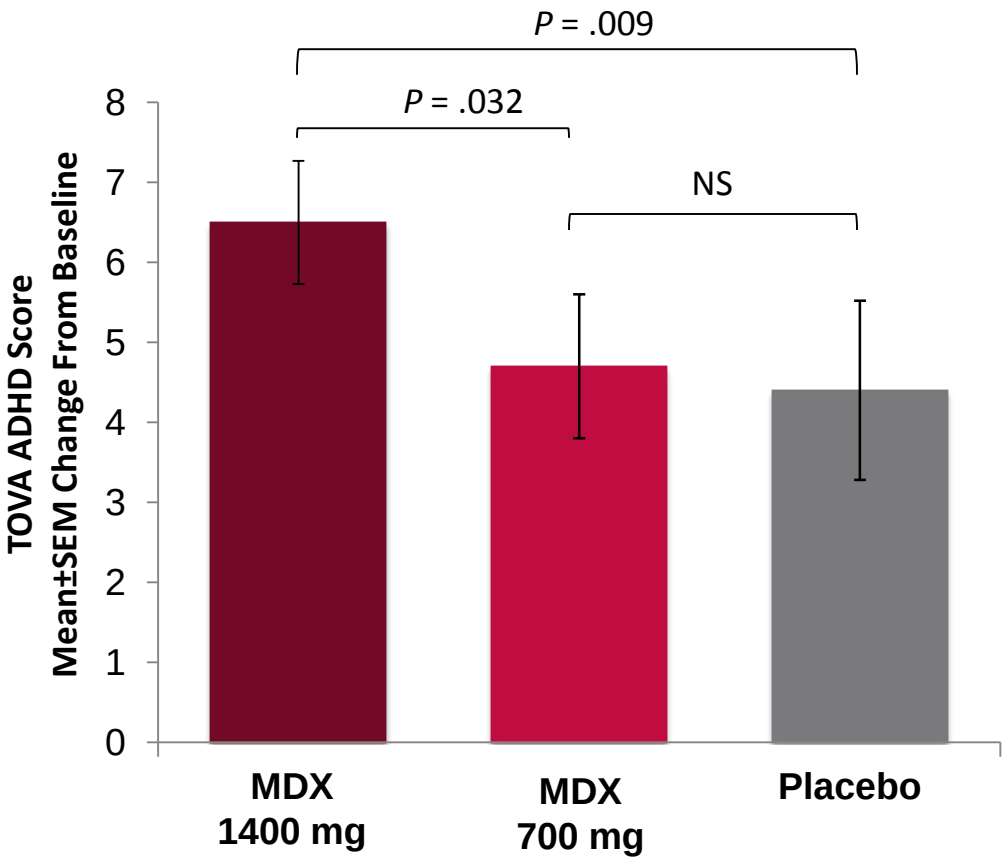
Treatment Week	Sequence 1 (n = 12)	Sequence 2 (n=12)	Sequence 3 (n=12)
1	MDX 1400 mg	MDX 700 mg	Placebo
2	MDX 700 mg	Placebo	MDX 1400 mg
3	Placebo	MDX 1400 mg	MDX 700 mg



CANTAB = Cambridge Neuropsychological Test Battery. Rubin J, et al. Poster NR6-021 presented at: American Psychiatric Association 167th Annual Meeting; May 5, 2014; New York, NY.

MDX Phase 2b (single center): Key Efficacy and Safety Data

TOVA ADHD Score (ITT)



P values based on paired *t* tests. NS = not significant.

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

Rubin J, et al. Poster NR6-021 presented at: American Psychiatric Association 167th Annual Meeting; May 5, 2014; New York, NY.

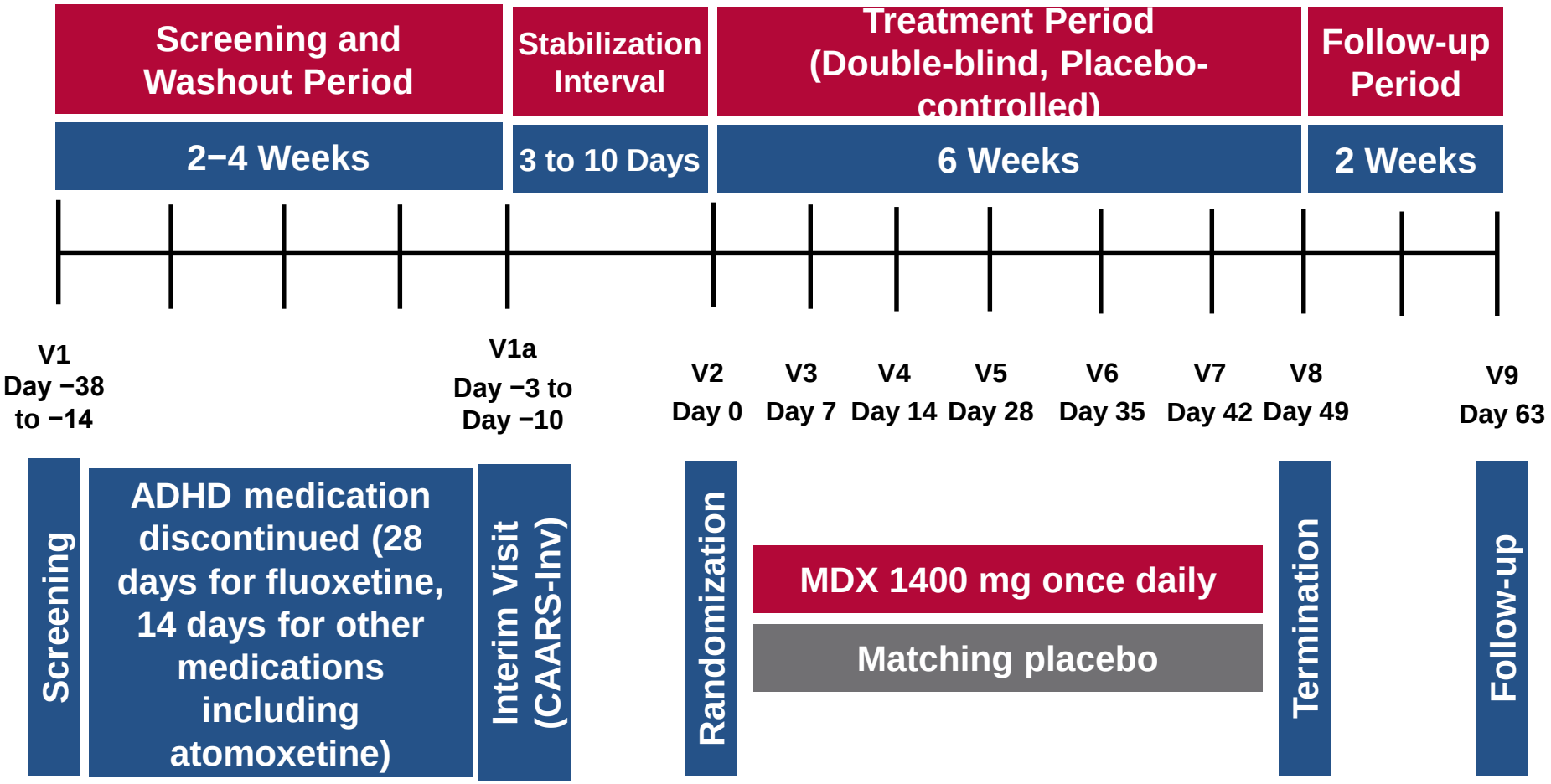
MDX Phase 3: Study Overview

- 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 primarily inattantive ADHD

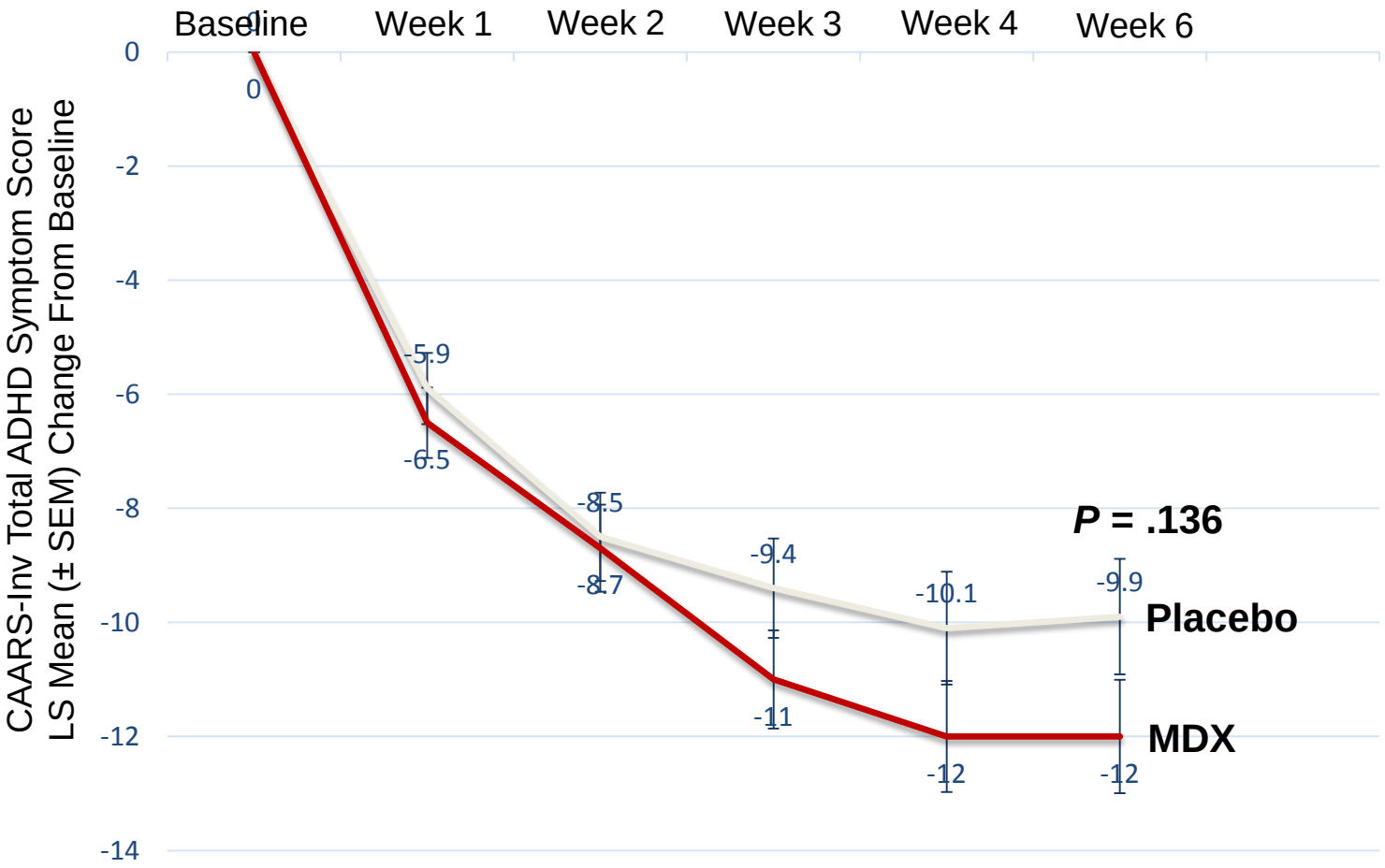
- Baseline and efficacy assessments review
  - Rater training and certification was conducted as per published methodology at baseline and once during trial[1]
  - Integrity of rater monitoring of the Adult Clinician Diagnostic Scale (ACDS) v1.2, prompted CAARS-Inv, and CGI was assessed via remote inspection 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.

MDX Phase 3: Study Design



MDX Phase 3: Primary Efficacy Analysis Results CAARS-Inv: ITT (n = 297[1,2])



P values based on MMRM analysis. [1] 3 patients enrolled in the study did not have any post-baseline efficacy assessment

[2]Adler L et al. Oral Presentation at AACAP 2014 meeting. October 22, 2014, San Diego, CA.

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

Summary of MDX ADHD Clinical Studies

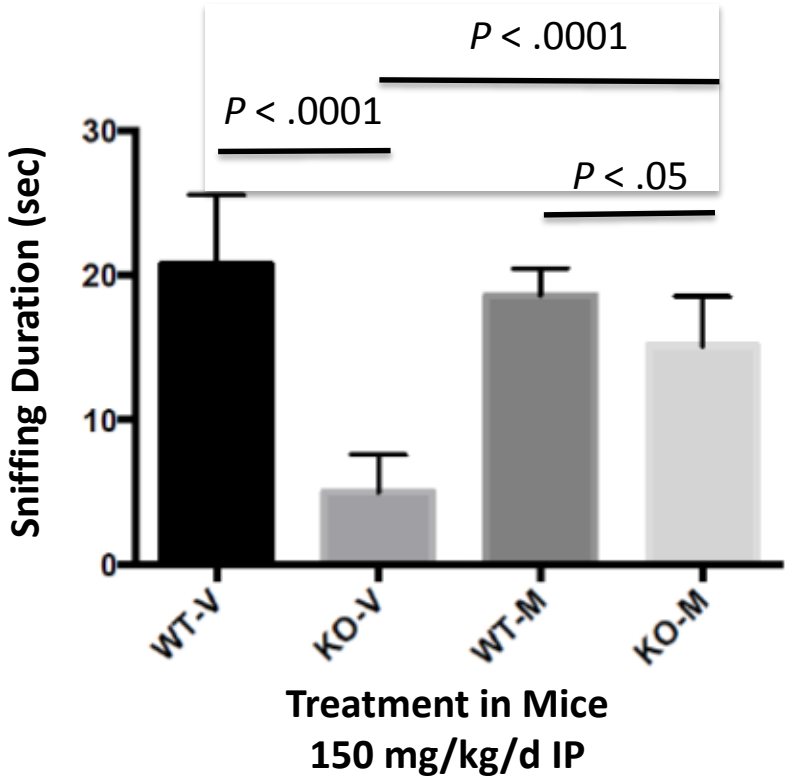
Overall findings to date:

- Efficacy signal in multiple, placebo-controlled trials
- Analysis of secondary endpoints and sub-scales suggest impact on attention and executive function
- Rapid response, within first day, as demonstrated on objective performance tests
- Favorable tolerability
- No effect on appetite, mood
- Absence of cardiovascular effects
- No potential for abuse or addiction seen
- Fixed dose (no need for dose titration)

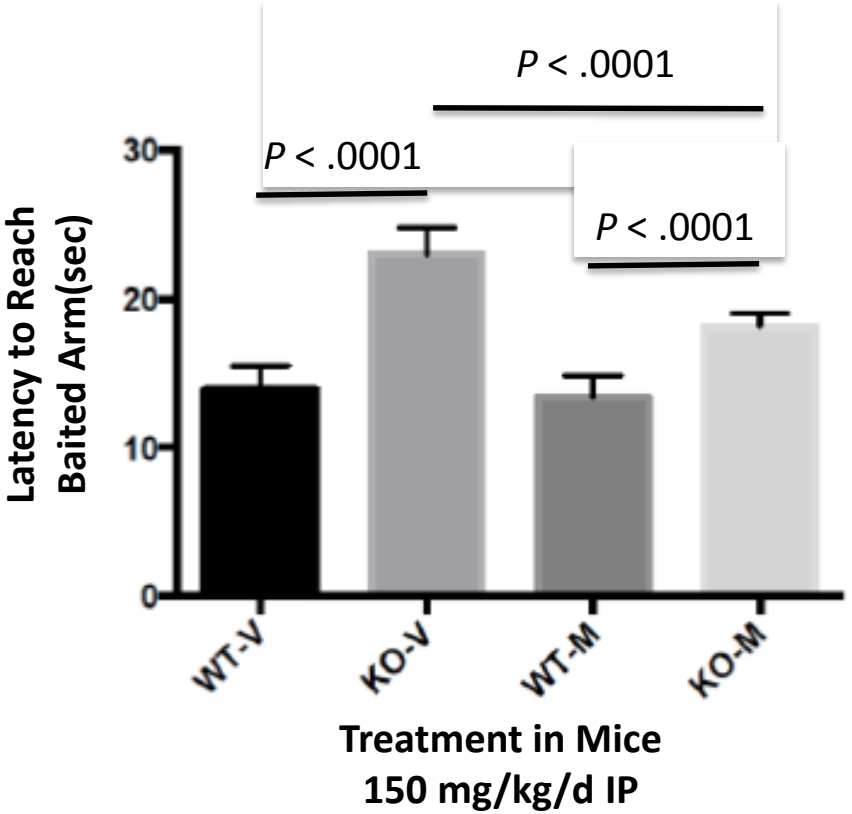
Pre-clinical Data for FXS

fmr1 KO Mouse Study 1 (Juvenile Mice – 2 Months Old): Behavioral Effects of Metadoxine

Social Approach

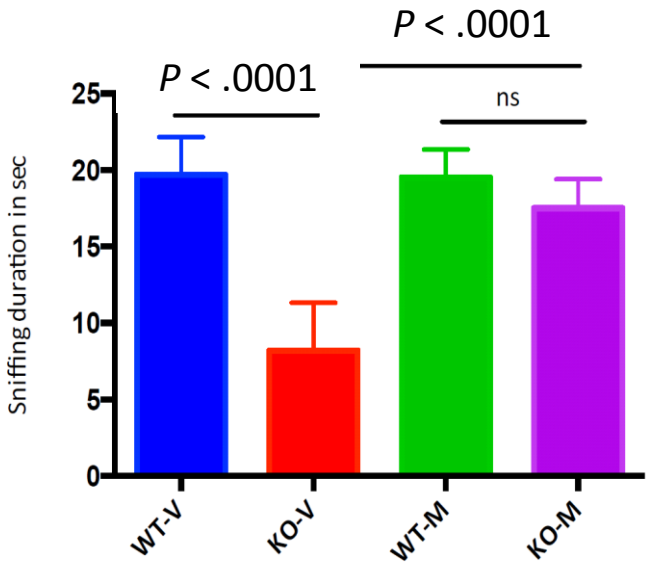


Spatial Working Memory Skills (T-Maze)



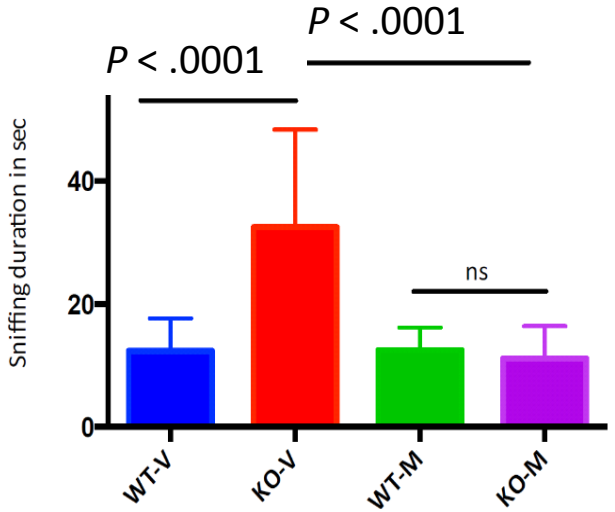
fmr1 KO Mouse Study 2A (Adult Mice-6 Months Old): Behavioral Effects of Metadoxine

Social Approach



Treatment in Mice
150 mg/kg/d IP

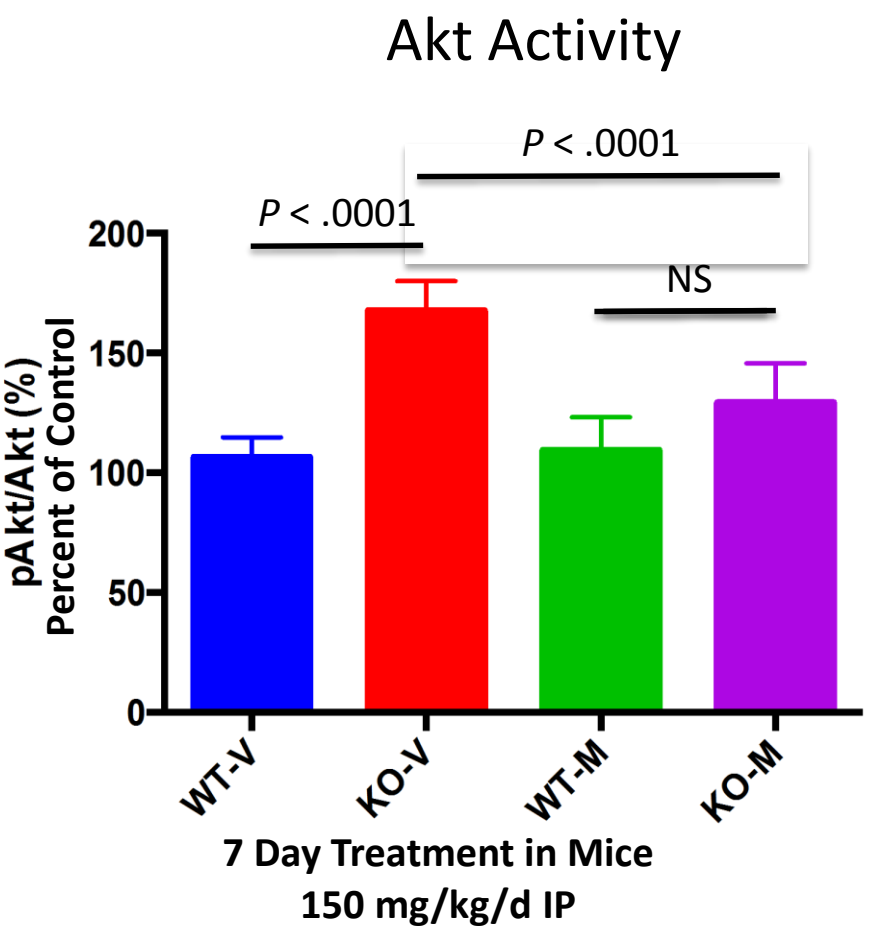
Social Memory

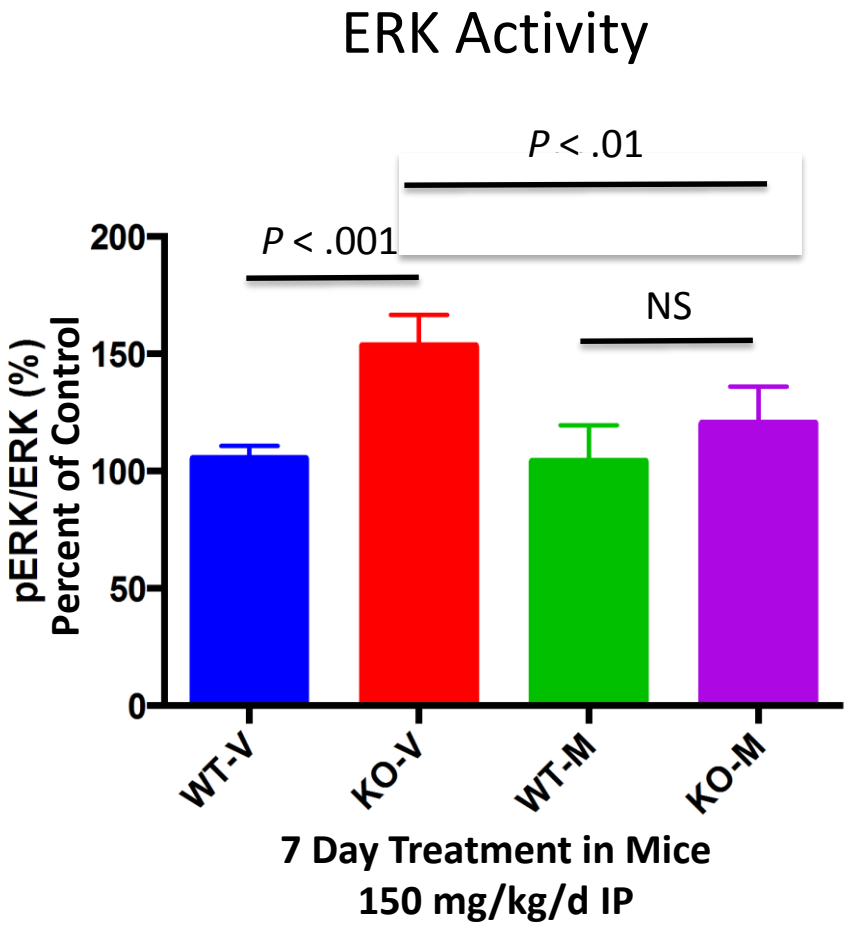


Treatment in Mice
150 mg/kg/d IP

Schumann J, et al. Poster presented at: Fragile X and Autism-Related Disorders Gordon Research Conference; June 2, 2014; West Dover, VT.

fmr1 KO Mouse Study 1 (Juvenile Mice – 2 months old): Whole Brain Biomarker Effects of Metadoxine



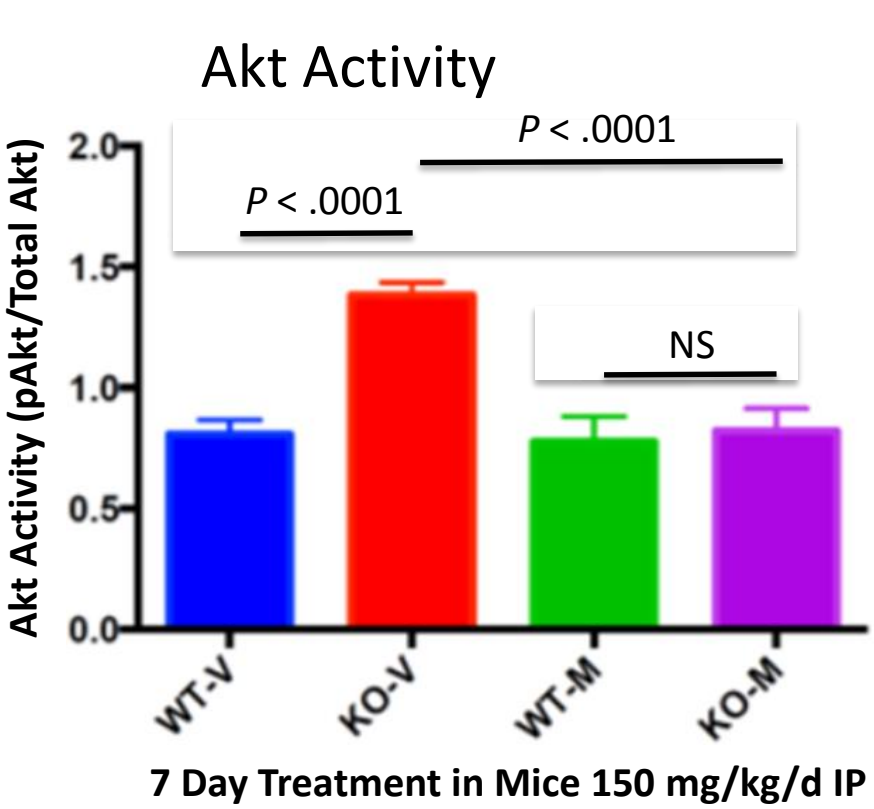


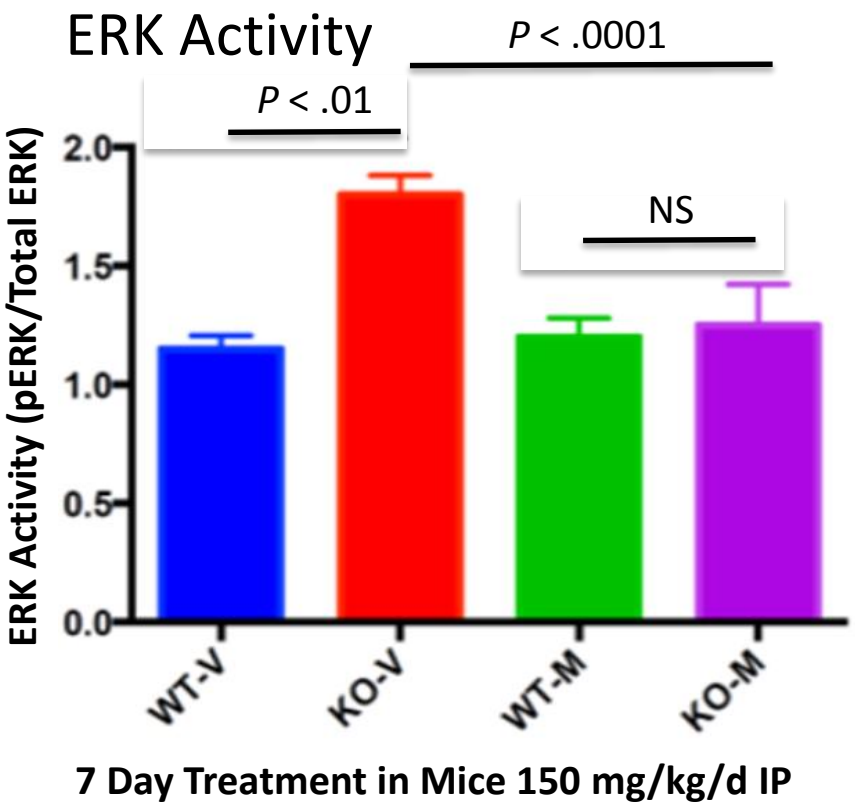
NS = not significant.

Cogram P, et al. Poster presented at: FRAXA Investigators Meeting; September 29, 2013; Southbridge, MA.

fmr1 KO Mouse Study 2A (Adult Mice – 6 months old): Whole Brain Biomarker Effects of Metadoxine

ERK, Akt also normalized by metadoxine in multiple separate brain regions and in lymphocytes from Fmr1 k/o mouse

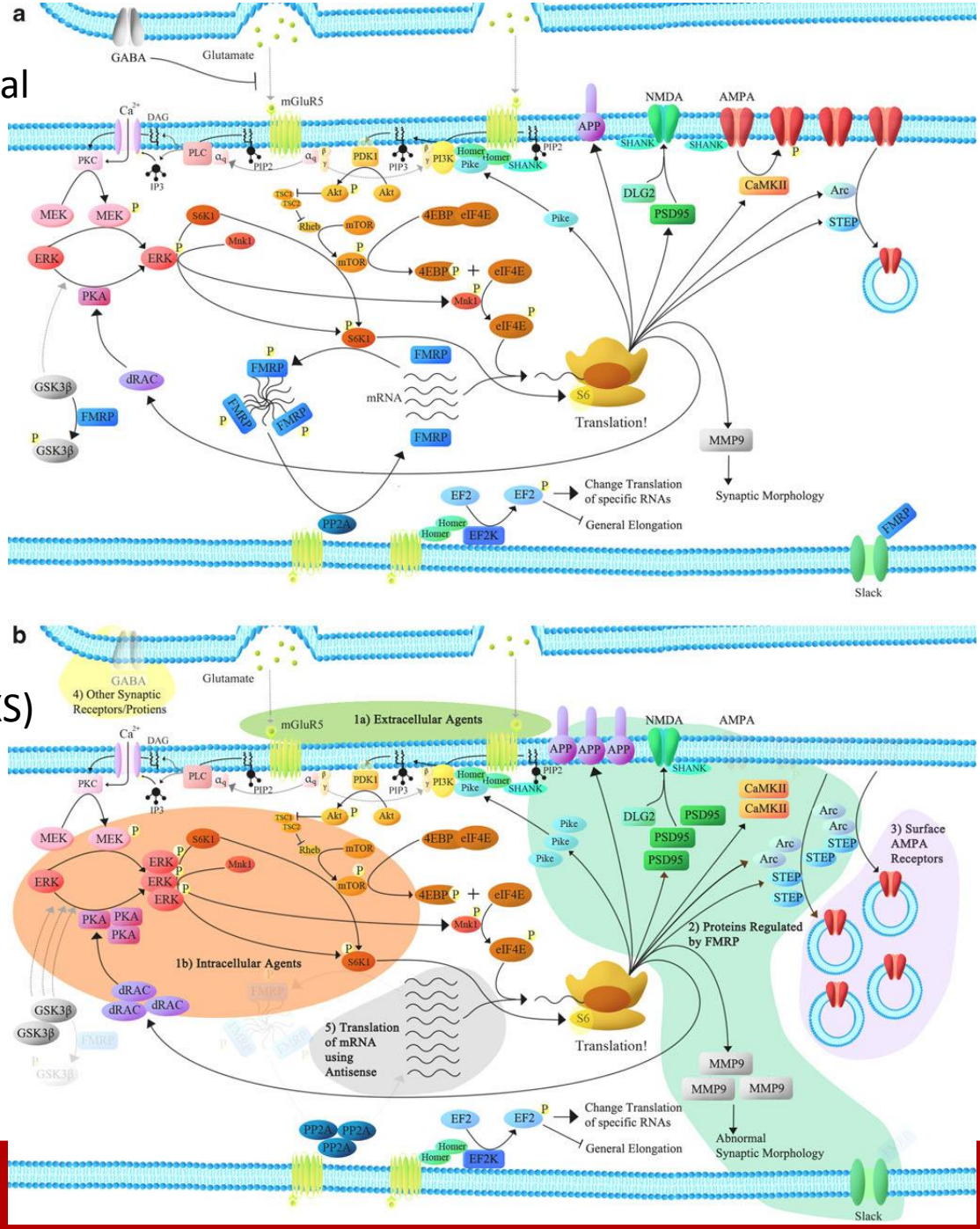




Neuronal Signaling Pathways in Translational Regulation

Normal

Absent FMRP (FXS)



Berry-Kravis et al. JND 2012

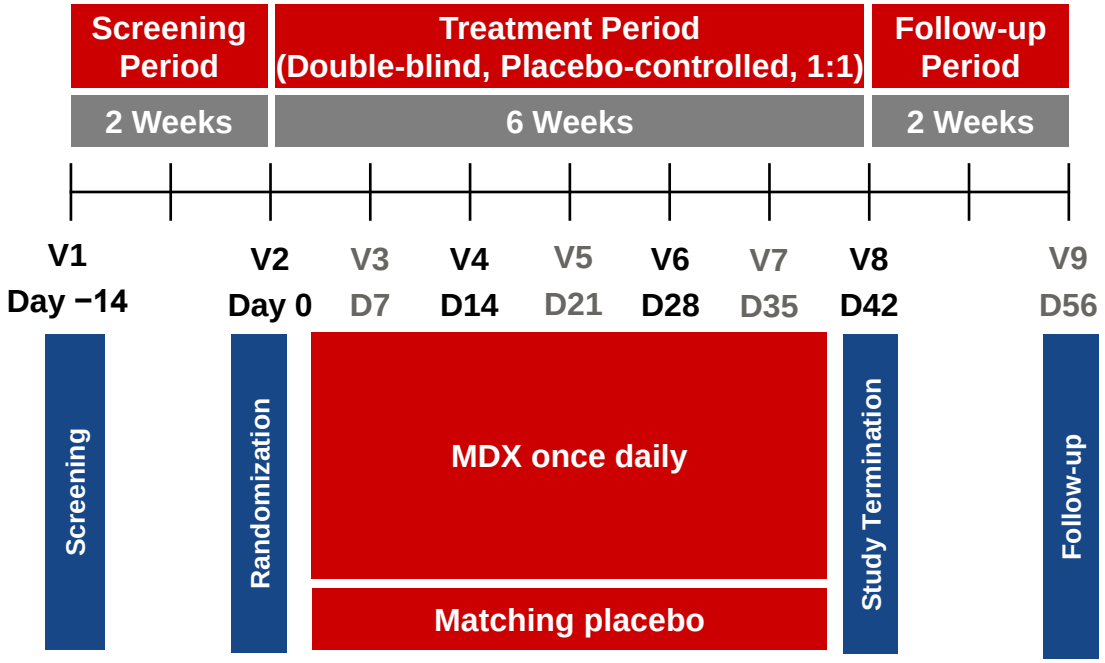
Phase 2 Clinical Study of MDX in Adolescents and Adults with Fragile X Syndrome

Rationale for a Study in Patients With FXS

- Findings in the adult ADHD studies suggest that MDX is a procognitive drug that might improve attention and cognition in patients with FXS
- Findings in *fmr1* KO mice suggest that metadoxine has procognitive effects in several tests
- Metadoxine mechanism of action
  - Akt and ERK findings in *fmr1* KO mice are consistent with reported clinical findings as well as what is known about the pathophysiology of FXS (hyperactivity of both pathways)
  - Enhanced GABAergic inhibitory transmission might be beneficial in patients with FXS (FXS is associated with excitatory/inhibitory transmission imbalance)

MDX Ongoing Phase II Clinical Trial in Fragile X (AL014)

- Phase 2, 6-week, randomized, multicenter, placebo-controlled, double-blind, parallel group, study of MDX once daily in adults and adolescents with FXS
- 60 adults and adolescents (Age 15-55), 13 study sites (12 in US)
- Primary endpoint: Inattentive subscale of ADHD RS-IV
- Secondary endpoints include several efficacy and safety measures



FXS Clinical Trial: Objectives

- Primary objective
  - To evaluate the efficacy of MDX once daily compared with placebo in the treatment of FXS symptoms in adolescents and adults as measured by the inattentive subscale of the ADHD Rating Scale-IV (as rated by the investigator in a clinical interview of the caregiver)
- Secondary objectives
  - To evaluate the efficacy of MDX once daily compared with placebo in the treatment of FXS symptoms in adolescents and adults as measured by the ADHD-RS IV total score
  - To evaluate the efficacy of once-daily MDX treatment on the basis of ADHD, behavior rating, neurocognitive, and functional rating scales and to evaluate the safety and tolerability of once-daily MDX treatment on the basis of AEs, laboratory test results, ECG parameters, and vital sign measurements

ADHD RS-IV = ADHD Rating Scale-IV.

FXS Clinical Trial: Patients

- 60 adults and adolescents with FXS
  - Men and women aged 15 to 55 years
  - Molecular confirmation of full *FMR1* mutation (≥ 200 CGG repetitions)
- Score of ≥12 on the inattentive subscale of the ADHD RS-IV
- Current treatment with ≤ 3 prescribed psychotropic medications
- Behavioral treatments (excluding psychotherapy) must be stable for 4 weeks before screening and through study period

FXS Clinical Trial: Study Requirements

- 6 study visits including screening over about 10 weeks
- 3 visits conducted as phone calls during 10 weeks
- Blood tests 3 times (screening, week 2, week 6)
- EKGs 4 times
- Answering forms, interviews, attention/cognitive measures – all visits during study
- Travel paid upon approval
- US Sites: Southwest Autism Research & Resource Center (Phoenix), UC Davis MIND Institute (Sacramento), Rush University Medical Center (Chicago), Children's Hospital Colorado (Denver), Kennedy-Krieger (Baltimore), Duke (Durham, NC), Boston Children's (Boston), University of Massachusetts (Worcester MA), Cincinnati Children's (Cincinnati), Suburban Research (Media, PA), Baylor (Houston), University of Washington (Seattle)

FXS Clinical Trial: Endpoints

- Primary endpoint: change from baseline at week 6 in ADHD RS-IV inattentive subscale
- Secondary endpoints: change from baseline in
  - ADHD RS-IV total score
  - Test of Attentional Performance for Children (KiTAP)
  - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
  - Aberrant Behavior Checklist (ABC)
  - Vineland Adaptive Behavior Scales (VABS) (Daily Living Skills and Socialization domains)
  - Pediatric Anxiety Rating Scale-Revised (PARS-R)
  - Clinical Global Impression of Improvement (CGI-I)
  - Clinical Global Impression of Severity (CGI-S)
- Safety endpoints
  - AEs, discontinuations, vital signs, clinical chemistries, hematology, urinalysis, ECGs, physical and neurologic examinations, and assessment of suicidal ideation/behavior

FXS Clinical Trial: KiTAP

- Developed to analyze different aspects of attention and cognition for children and adults
  - Specialized version for younger children (KiTAP[1]) assures high motivation of participants by provided in stimuli and tasks suitable for children
- Previously studied in an FXS population 7 to 50 years of age[2]
  - Based on previous findings, only tests of alertness, distractibility, flexibility, and go/no go to be done in MDX trial

alertness

distractibility

flexibility

1. Psychologische Testsysteme. KiTAP Test of Attentional Performance for Children. 2011.
2. Knox A, et al. *J Neurodev Disord*. 2012;4:2. doi: 10.1186/1866-1955-4-2.

FXS Clinical Trial: RBANS

- Brief neurocognitive battery with 4 alternate forms
- Overall test measures immediate and delayed memory, attention, language, and visuospatial skills
- List Learning subtest
  - List of 10 unrelated words
  - Read for immediate recall over 4 trials
  - Maximum possible score = 40
  - Words are of moderate-high imagery and low age-of-acquisition (reducing possible education effects on performance and easing translation)

Randolph C. *Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).* San Antonio, TX: Harcourt, The Psychological Corporation; 1998.

FXS Clinical Trial: Biomarker Assessments

- Blood biomarkers (pAkt/Akt, pERK/ERK) will be assessed at baseline, week 2, and week 6
- Hyperactivation of Akt and ERK pathways in FXS clinical trials
  - Hoefer[1] examined phosphorylation levels in patients with FXS and typically developing controls
    - Elevation in Akt and ERK phosphorylated/unphosphorylated ratios in blood lymphocytes of 38 patients with FXS as compared with ratios in 14 typically developing controls
    - Elevation in Akt phosphorylation levels in the autopsied brains of 4 patients with FXS as compared with ratios in 4 controls; no difference was found with ERK
  - Wang[2] found increased ERK phosphorylation and increased pERK/ERK in the autopsied brains of 4 patients with FXS as compared to 7 age-matched controls

1. Hoeffer CA, et al. *Genes Brain Behav*. 2012; 11:332-341.
2. Wang X, et al. *J. Neurochem*. 2012; 121: 672-679.

Summary

- MDX has demonstrated procognitive properties in multiple ADHD studies
- Metadoxine improved behavioral and biochemical outcomes in a mouse model of Fragile X
- Metadoxine is a GABA modulator, and it reduces Akt and ERK hyperactivation
- These findings suggest the therapeutic potential of MDX for the treatment of FXS
- A phase 2 placebo-controlled study of MDX in adults and adolescents with FXS is currently enrolling subjects

Participating Sites

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Questions????

www.thefragilexstudy.com

ClinicalTrials.gov study link:

http://clinicaltrials.gov/ct2/show/NCT02126995?term=metadoxine&rank=8