Athira PHARMA

Restoring Lives by Advancing Bold Therapies

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HGF/MET Receptor Agonist NDX-1017 Translational Phase 1a and b Results

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Disclosures

Hans Moebius is an employee and stockholder of Athira Pharma Inc.

About Athira Pharma

Pipeline focused on regeneration of neuronal damage in CNS diseases to restore function

LEAD INDICATION:
Cognitive enhancement in Alzheimer's disease

FOLLOW-ON INDICATIONS:
Parkinson's, ALS, MS, Neuropathies, etc.

Lead asset NDX-1017 with novel regenerative MOA

- Encouraging data in AD patients
- Functional biomarker signal suggests rapid improvement in brain circuitry (EEG/ERP)
  - Substantially greater effect than current marketed products
- Supports CNS penetration and target engagement
- To date, safe and well-tolerated in Phase 1 (88 subjects)

De-risked clinical development strategy

- Cost and time efficient clinical trials
- Established regulatory pathway (marketed AD drugs)
- Additional compounds in preclinical development

Athira's Target:
HGF/MET plays an Important Role in Repairing Neurodegeneration

Hepatocyte* Growth Factor (HGF)/MET Receptor

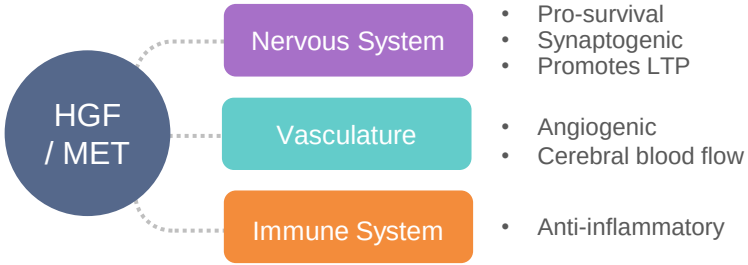
Vital neurotrophic factor system

Critical to neuron function, learning, and memory

Stable expression in healthy CNS

Neuronal MET expression is reduced in Alzheimer's

Beneficial impacts on multiple systems



Demonstrated effects of HGF/MET promotion in animal models of disease

Alleviates Aβ-induced cognitive impairment

Takeuchi, D., et al (2008). Gene Therapy 15, 561-71

Prevents onset of Parkinson's disease

Koike, H., et al (2006). Gene Therapy 13, 1639-44

Prolongs Life Span in a Transgenic Mouse Model of ALS

Sun, W., et al. (2002). Neuroscience 22, 6537-48

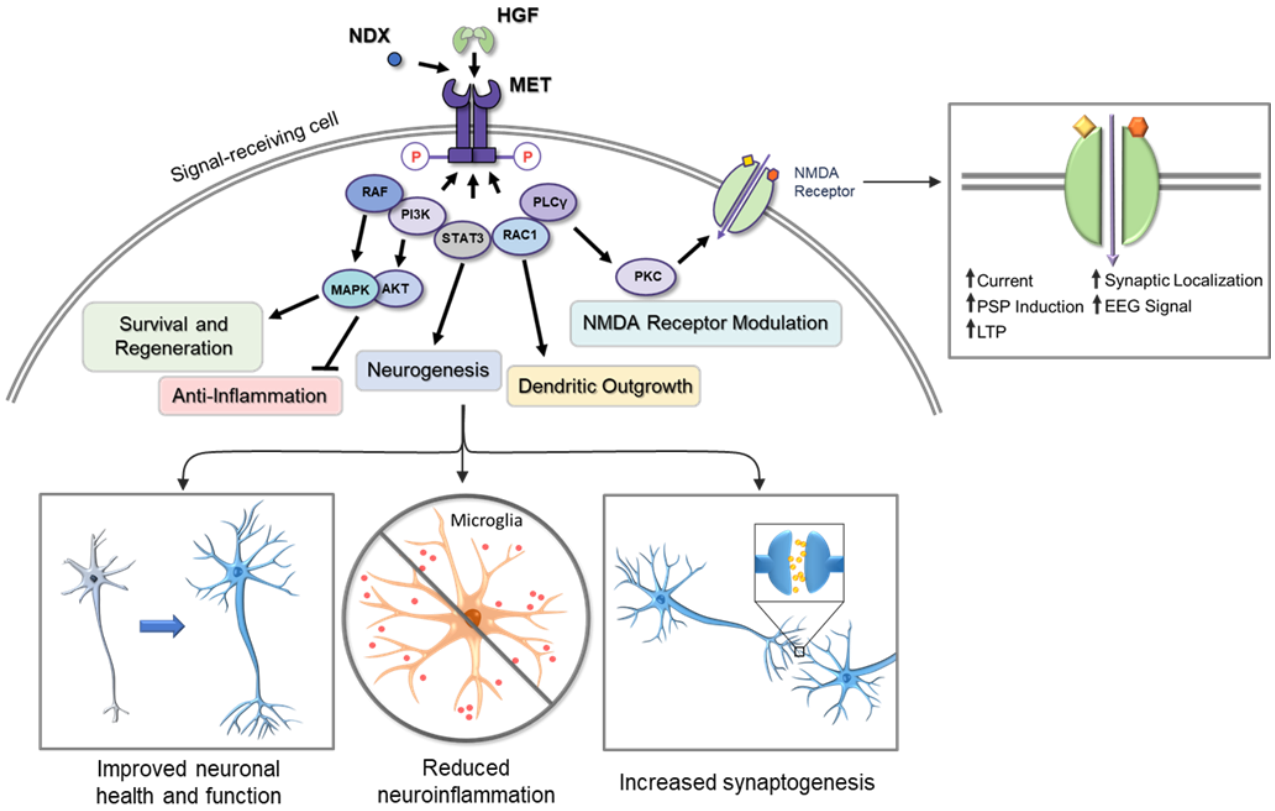
Improves Learning and Memory Dysfunction of Microsphere-Embolized Rats

Date, I., et al. (2004). Neuroscience Research 78, 442-53

*Historically termed

NDX-1017 is a Specific Agonist of the HGF/MET Neurotrophic System with Acute and Sustained Effects on Synaptic and Network Function

- Fast-acting positive modulator
- Protective and regenerative
- **Procognitive (Symptomatic)**
- EEG biomarker



NDX-1017 Product Profile

INDICATIONS

Alzheimer's and Parkinson's disease

DELIVERY MODE

Subcutaneous injection

MOA

Small molecule agonist of HGF/MET

DOSAGE FORM

Prefilled syringes

HALF LIFE

90 min (pulsatile mode of target activation)

REGIMEN

Once per day

NDX-1017: Stage of Development

- Phase 1 clinical trial demonstrated safety, tolerability and PK
- 26-week GLP tox in rats and dogs provided coverage of planned clinical dose(s)
- qEEG biomarker translated from animal to human studies
- ERP P300 biomarker established CNS effect relevant for Alzheimer's
- Kilogram-scale GMP manufacturing

NEXT STEP Phase 2/3 clinical trial starts in **2020**

NDX-1017 Phase 1a/b Trial Overview

Phase 1 (US and France) – active IND and CTA

- Randomized, placebo-controlled, double-blinded, single-ascending dose (A) and multiple-ascending dose (B) (s.c., o.d.)
- *Safety, pharmacokinetics, and pharmacodynamics biomarker, i.e., qEEG/ERP*

STUDY	POPULATION	DOSE	Treatment Day D1	D2	D3	D4	D5	D6	D7	D8	D9	STATUS
Part A: single-dose	48 healthy young (6:2 active vs. placebo)	2-90 mg (6 doses)	●									Complete
Part B: multiple-dose (9 days)	24 healthy elderly (6:2)	20 mg	●	●	●	●	●	●	●	●	●	Complete
		40 mg	●	●	●	●	●	●	●	●	●	
		60 mg	●	●	●	●	●	●	●	●	●	
	5 healthy elderly (4:1)	80 mg	●	●	●	●	●	●	●	●	●	
	11 AD dementia patients (7:4)	40 mg	●	●	●	●	●	●	●	●	●	Complete

NDX-1017 Phase 1a/b Safety and PK Summary

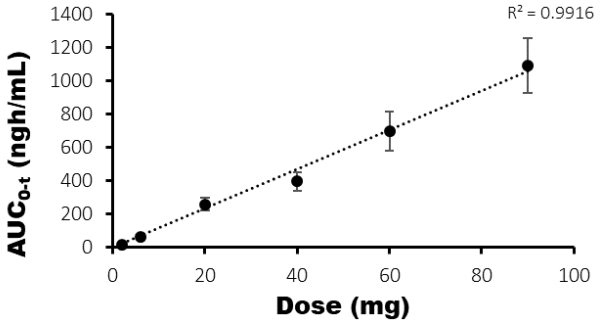
NDX-1017 is safe and well-tolerated

- No serious adverse events (SAE)
- No relevant medical events

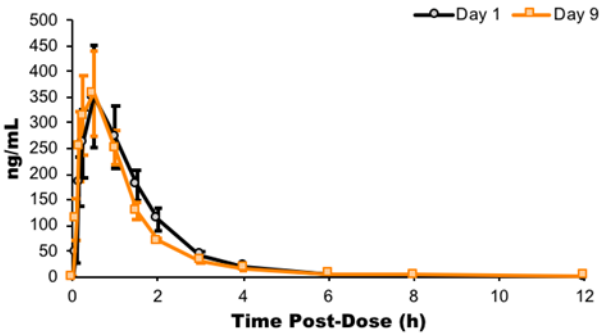
PK Results

- T_{max} = 30 min; $T_{1/2}$ = 1.5 hours
- Dose linear
- No accumulation
- No age or sex effect
- Targeting pulsatile mode of target activation

SAD PK (dose linear)

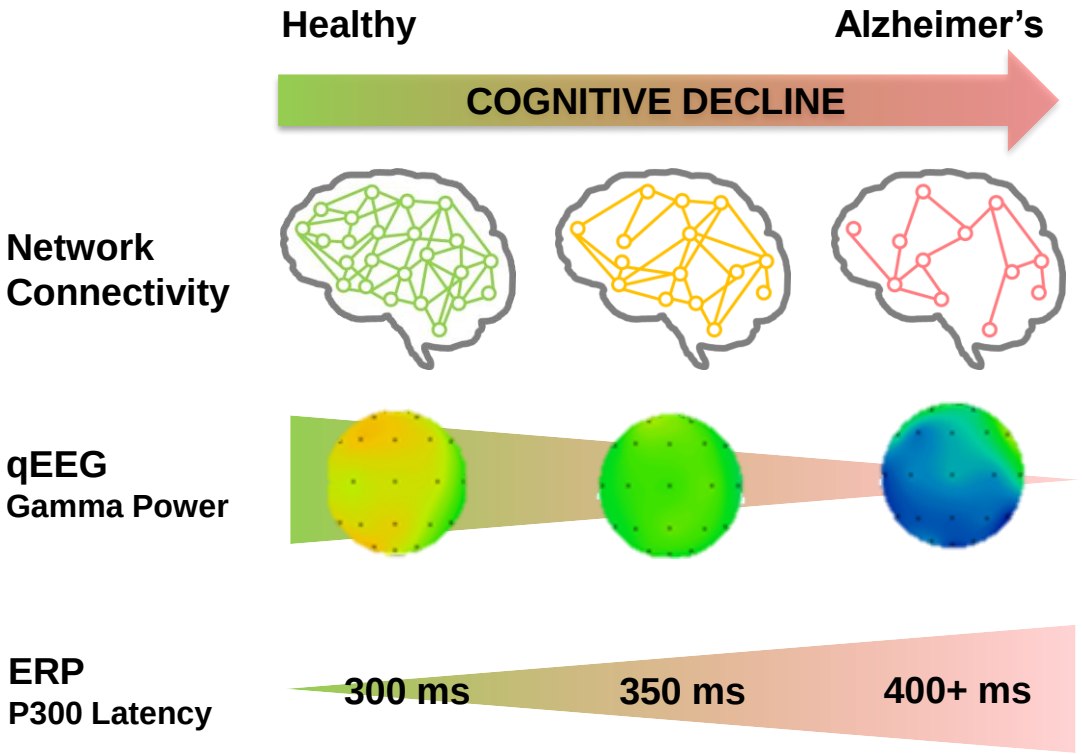


MAD PK (no accumulation)



EEG: Translational Biomarker of Brain Recovery and Function

- **CNS:** EEG provides a direct measure of brain activity
- **Translation:** highly translatable from animals to humans
- **MOA:** NDX-1017's EEG signature is linked to MOA
- **Cognition:** Changes in EEG are reflective of learning, memory and executive functions (i.e., gamma and P300 latency)
- **Neurodegeneration:** Abnormal EEG have been consistently characterized in AD, reflective of neurodegeneration
- **Predictive biomarker:** Normalization of EEG is indicative of network recovery and associated with cognitive improvement in response to treatment



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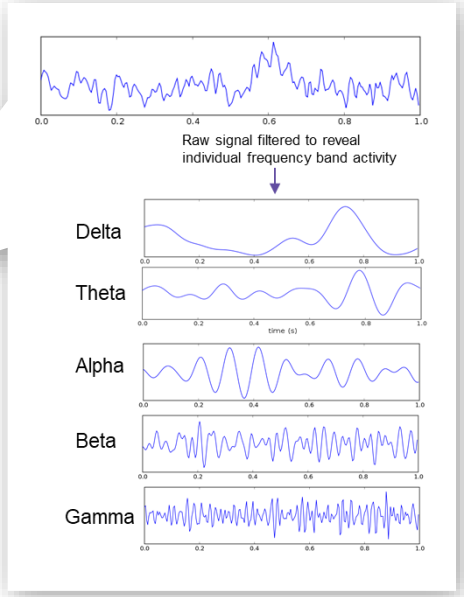
EEG as a Biomarker of Functional Recovery in the Brain

EEG signals reflect synaptic function and network health



- EEG is a direct reflection of brain activity
- EEG is a biomarker of BBB penetration and CNS target engagement
- qEEG describes frequency bands as associated with certain pathologies, tasks or cognitive states
- Gamma power is reflective of learning, memory and executive functions
- Translatable biomarker from animals to humans
- Abnormal qEEG power band patterns have been consistently characterized in AD
- Shift from low to high frequency bands is indicative of network recovery

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SAD (Healthy Young) Shows Induction in Gamma Power

PHASE 1a SAD

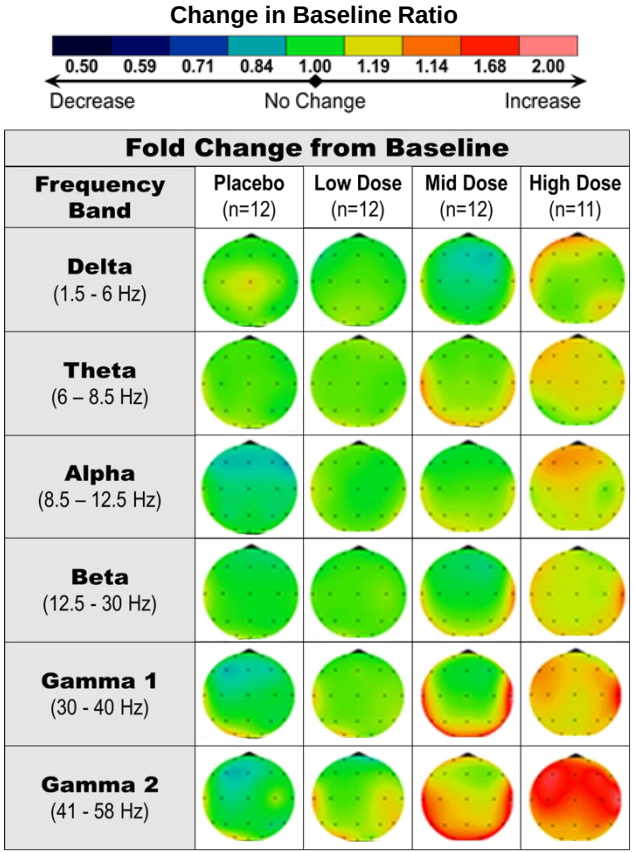
NDX-1017: single dose EEG, 1-hour post-dose

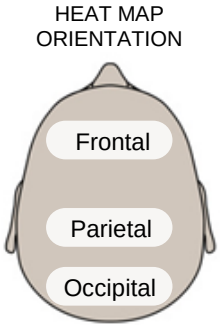
- Placebo, n=12
- Low doses (2 & 6 mg), n=12
- Mid doses (20 & 40 mg), n=12
- High doses (60 & 90 mg), n=11
- Gamma ↑ at 20, 40, 60, 90 mg (>50%)
  - Dose-dependent increase
  - Statistically significant at 90 mg (n=6)
- Indicates CNS penetration and target engagement

PHASE 1a MAD

Phase 1b qEEG in Healthy Elderly Subjects

- Increased gamma power in healthy elderly volunteers treated with NDX-1017 not placebo





Multiple-Dose Study in AD Dementia Patients

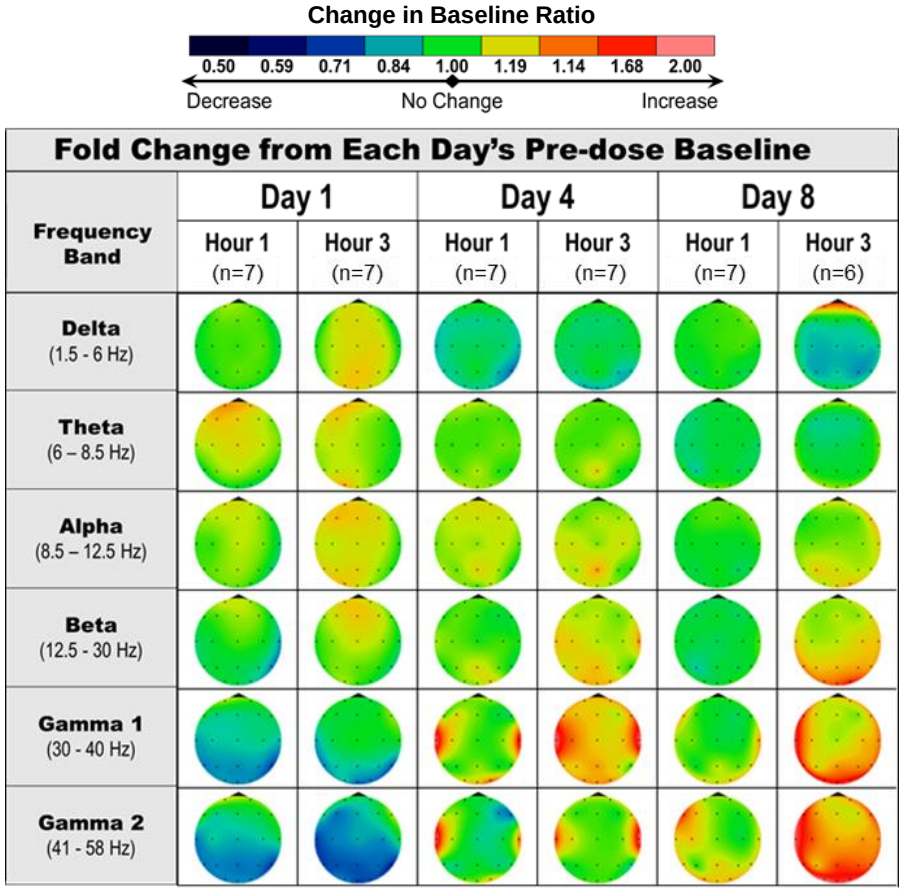
PHASE 1b

NDX-1017 – 40 mg
(s.c., o.d., 9 days, n=7)

- Study Complete
- No SAEs or relevant medical events
- qEEG and ERP were assessed at pre-dose, 1 and 3 hours post-dose at days 1, 4 and 8

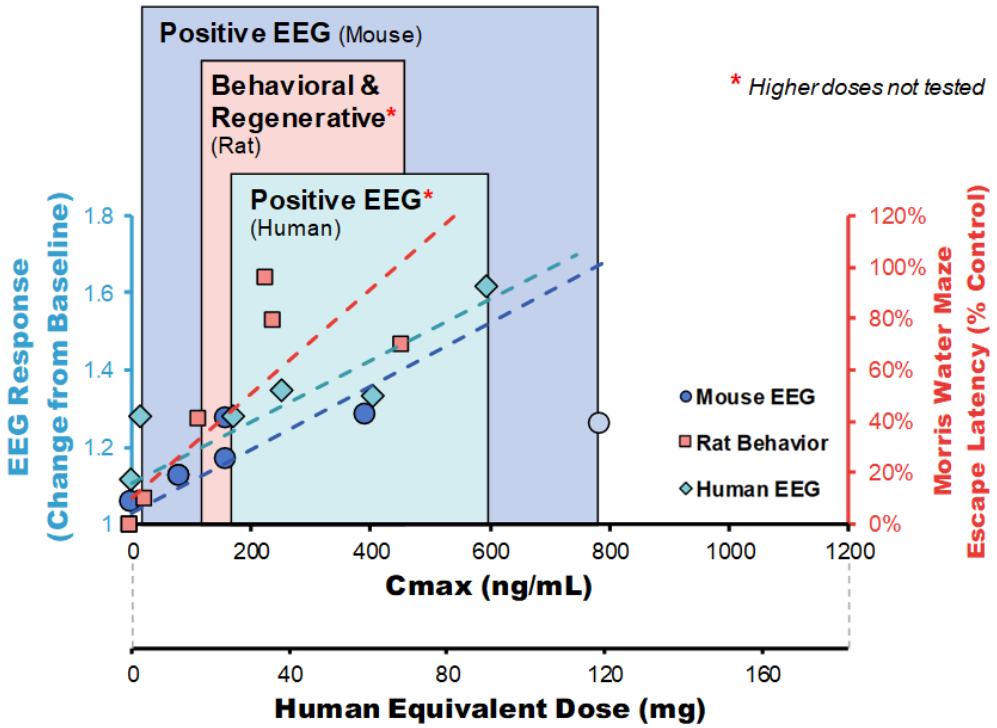
qEEG Observations

- Change from same day's pre-dose recording
- Data is expressed as qEEG relative power
- Gamma power increase on day 4 and 8
- Effect appears to increase with further treatment
  - Effect larger on day 8 vs. 4
  - May be indicative of recovering connectivity



Strong Translation of Preclinical Activity and Exposures Support Clinical Dose Selection

NDX-1017 concentrations that demonstrated pro-cognitive activity in rats overlap with concentrations that stimulate Gamma power increases in mice and humans

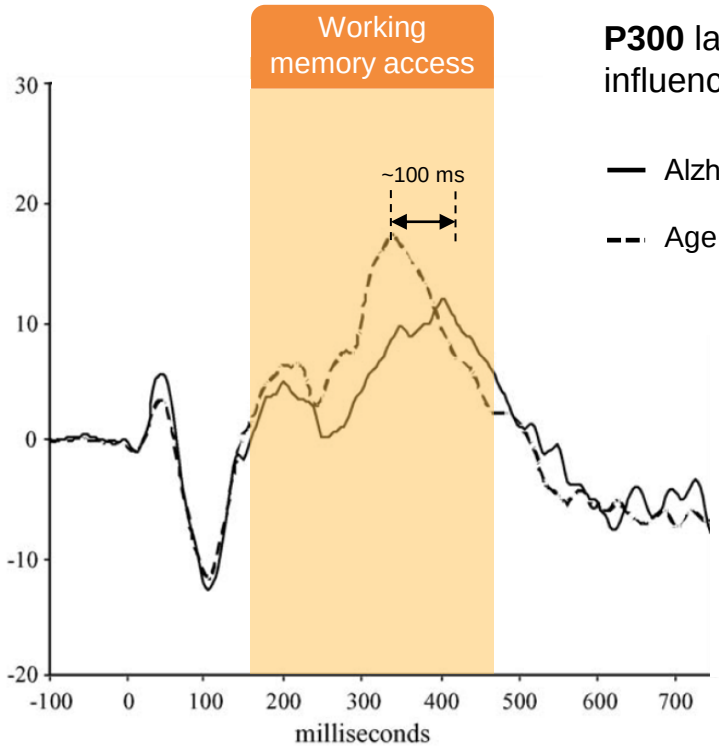


Rat behavioral data are from Morris Water Maze studies across a dose range of 0.05 to 1 mg/kg. The pharmacodynamic response is shown as a percent possible escape latency where animals receiving vehicle + scopolamine have a score of 0% and control animals not receiving scopolamine have a score of 100%.

P300: Immediate Cognitive Processing of a Task Related Event

P300 Latency

- Time to peak positive wave response at ~300 ms
- Functional biomarker, closely related to clinical endpoints
- Measure of cognitive processing (working memory access)
- Correlation with cognition (Ally et al., 2006, Pedroso et al., 2012)
  - Heathy: stable signal, peak ~300 ms
  - Dementia: correlated with cognition decline, peak ~400 ms



P300 latency highly influenced by dementia

— Alzheimer's disease

- - - Age matched controls

Adapted from Ally et al, 2006

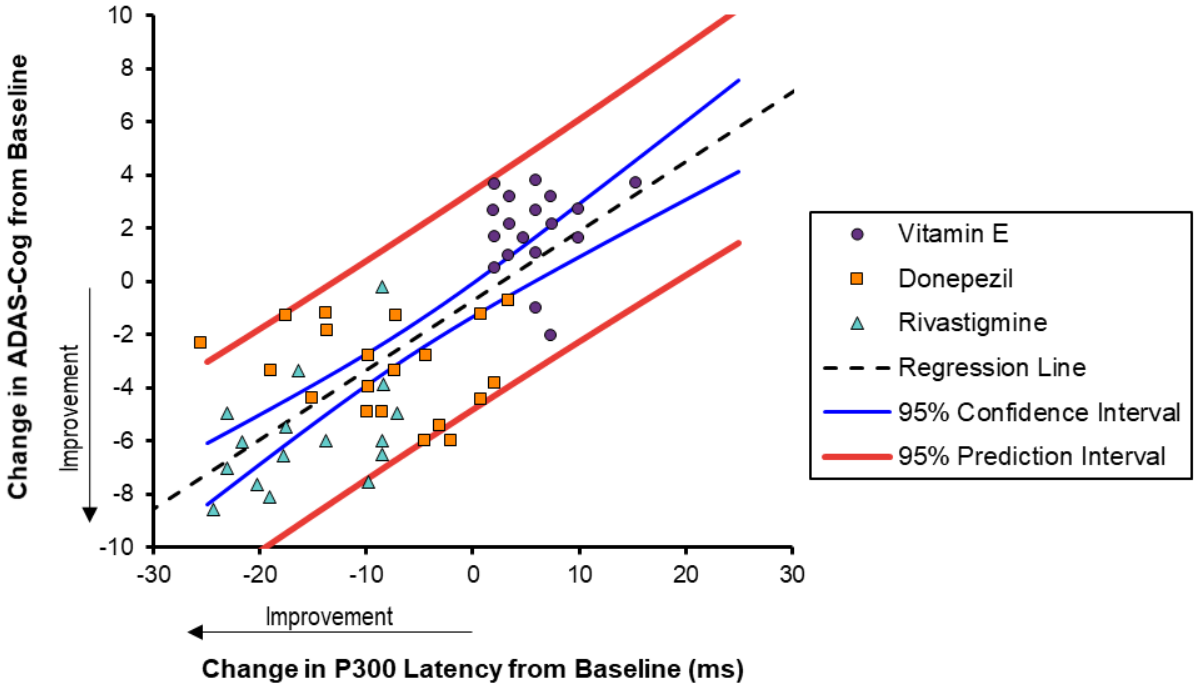
ERP P300 as a Translational Biomarker for AD Clinical Trials

P300 latency is correlated with cognition in AChEI trials

- Donepezil and Rivastigmine
- Improvement in cognition (ADAS-cog ↓) is correlated with reduction in P300 latency (26 weeks db, plc)

Anticholinergic drugs (scopolamine) impair memory and increase P300 latency in humans

- Potter et al., 2000
- Meador et al., 1987



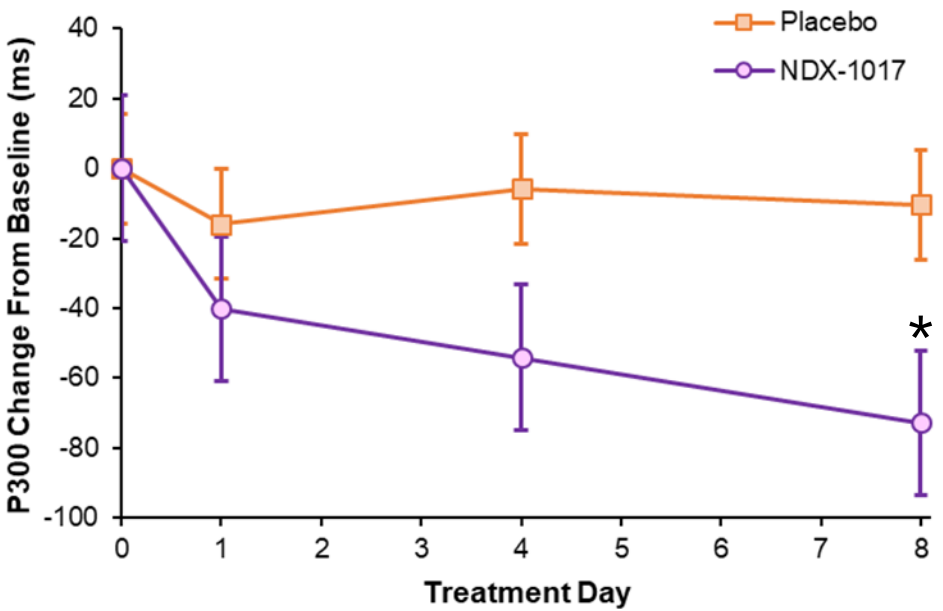
Modified from Thomas et al, 2001

NDX-1017 Improved P300 Latency in AD Dementia Subjects

PHASE 1b

- Group averages of AD subjects receiving NDX-1017 (n=7) show decreasing P300 latency
  - **change from baseline significant on Day 8**
- Latency in AD subjects receiving placebo (n=4) remained unchanged

P300 Latency in NDX-1017 and placebo-treated AD Subjects

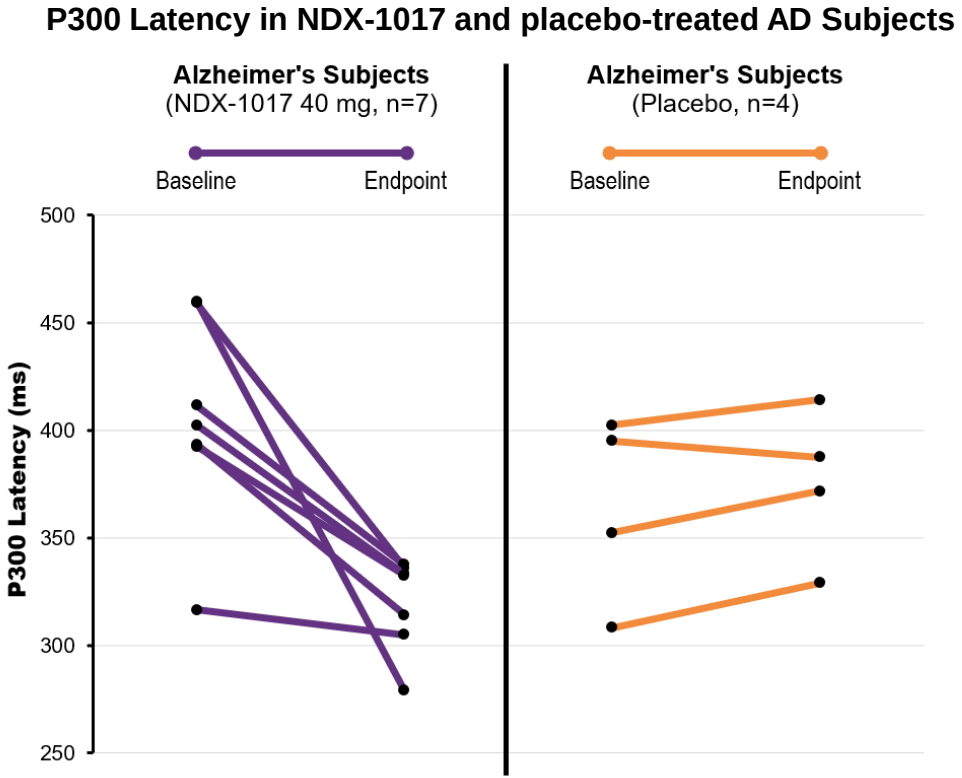


P300 data from FZ, CZ, and PZ electrodes, Data plotted as mean +/- SE.. *p<0.05 with MMRM

NDX-1017 Improved P300 Latency in AD Dementia Subjects

PHASE 1b

- Every AD subject receiving NDX-1017 showed slope to improvement of P300 latency
- AD subjects receiving placebo had no consistent response from baseline to endpoint
- Pathological P300 latencies at BL approached normal ranges after 8 days of NDX-1017

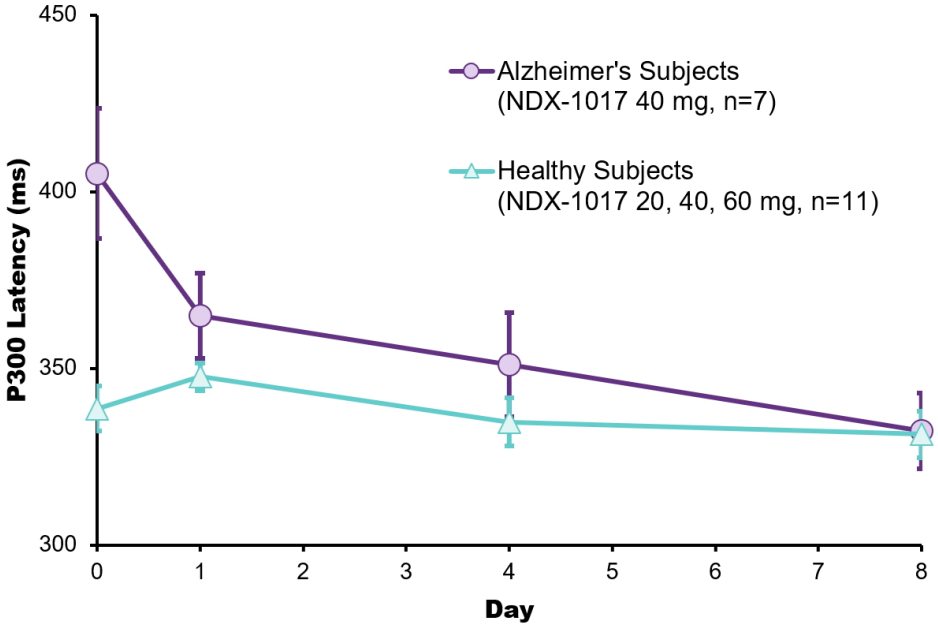


P300 data from FZ, CZ, and PZ electrodes

NDX-1017 Improved P300 Latency in AD Dementia Subjects

PHASE 1b

NDX-1017 treatment reduced P300 latency to normal levels



P300 data from FZ, CZ, and PZ electrodes, Data plotted as mean +/- SEM.

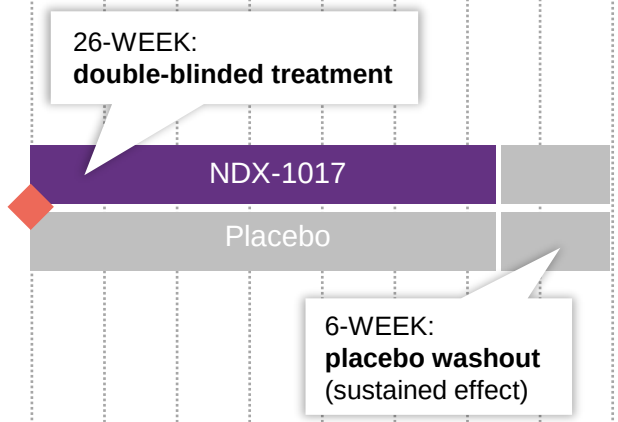
Phase 1ab - Study Goals Achieved

- **NDX -1017 was safe and well-tolerated at therapeutically relevant doses**
- **Ideal PK profile and translation from animal studies**
- **EEG confirms CNS penetration and supports target engagement**
- **ERP P300 latency, an objective measure of cognitive processing, moved towards the normal range within 8 days of NDX-1017 treatment**
- **Enables AD-confirmed dose ranging in Phase 2/3 trials for novel approach**

NDX-1017 Phase 2/3 Study Design – Alzheimer's Disease

POPULATION	TREATMENT DURATION	ENDPOINTS

120 mild-to-moderate AD dementia subjects
(55-85 years;
CDR 1 and 2;
MMSE 14-24 incl.)



PRIMARY ENDPOINT

- **Global Statistical Test (GST, O'Brien 1984)**
- Safety: ECG, safety labs, vitals, injection site, physical and neurological exams

SECONDARY ENDPOINTS WITH HIERARCHY

1. Cognition (key secondary): ADAS-Cog11
2. Global (key secondary): ADCS CGIC - Clinician
3. Function: Disability assessment for dementia (DAD)
4. Behavior: Neuropsychiatric inventory (NPI)
5. Executive memory: Controlled oral word association test (COWAT)

EXPLORATORY ENDPOINTS

- Resource utilization in dementia lite version (RUD-lite)
- Zarit Caregiver Burden (ZBI)
- qEEG and ERP
- Plasma biomarkers and CSF biomarkers sub-study

Athira Pharma Team

Thank you to all volunteers, patients, and their caregivers for your participation in our Phase 1 trial!

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