Study Design and Participant Characteristics of a Phase 2 Trial of Fosgonimeton, a Novel Treatment for Mild to Moderate Alzheimer's Disease

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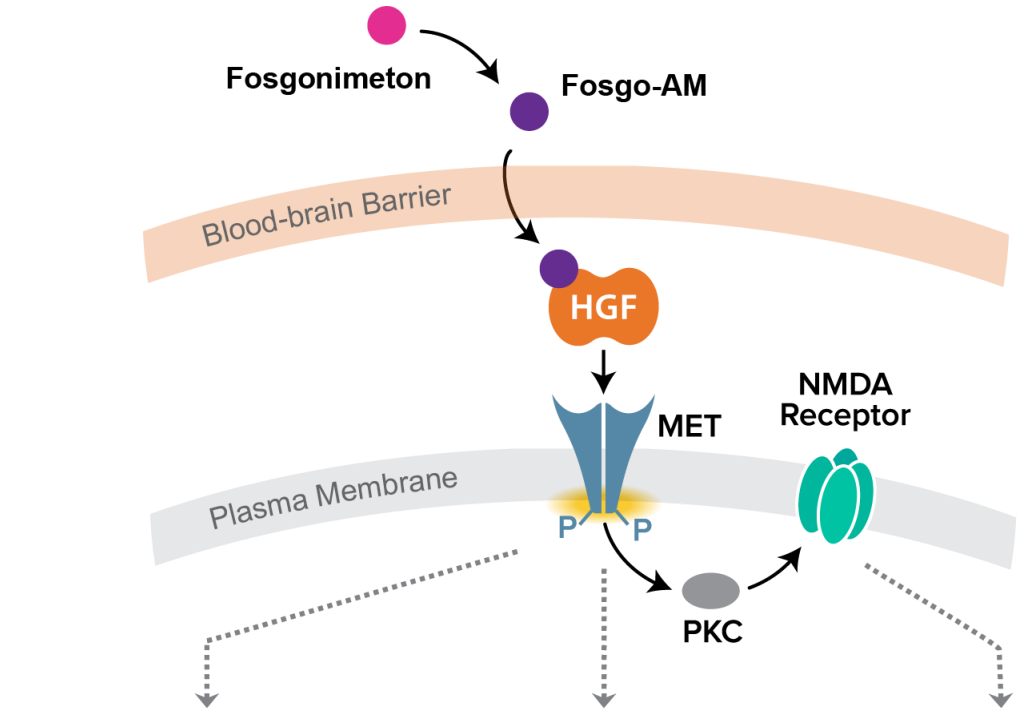
Disclosures

- Hans J. Moebius, Kevin Church, Kai-Bin Ooi, Joyce Maalouf, and William Walker are all employees of Athira Pharma, Inc., with salary and stock compensation
- Xue Hua was an employee of Athira Pharma, Inc.
- Charles Bernick is a principal investigator on Athira clinical studies and is a clinical professor at University of Washington, Department of Neurology
- Sam Dickson and Suzanne Hendrix are both employees of Pentara Corporation

Fosgonimeton (ATH-1017) is a positive modulator of the HGF/MET neurotrophic system

Fosgonimeton:

- Is administered via once-daily subcutaneous injection
- Is a small-molecule prodrug that is immediately converted to an active metabolite in plasma
- Crosses the blood-brain barrier
- Positively modulates HGF/MET



Neural Network Support	Neuron Health	Neurotransmitter Modulation
Synaptogenesis	Regeneration	Synaptic current
Neurogenesis	Survival	Synaptic localization
Neurite outgrowth	Anti-inflammation	Long-term potentiation

Multimodal, protective, and regenerative

HGF/MET signaling and downstream effects described in:
Desole et al, *Frontiers in Cell and Developmental Biology.* 2021
Funakoshi and Nakamura, *Current Signal Transduction Therapy.* 2011
HGF, hepatocyte growth factor; MET, mesenchymal epithelial transition; NMDA, N-methyl D-aspartate; PKC, protein kinase C.

Athira's accelerated approach to fosgonimeton development in AD

Long term toxicology

- Long term GMP tox trials started early and at risk
- Completion to coincide with and allow start of 6-month double blind trials

Phase 1

- Larger than usual
- Included a cohort of subjects with AD
- Included functional biomarkers qEEG and ERP P300
- Confirmed dose range

Phase 2 and 3

- Parallel initiation of Phase 2 and 3 in mild to moderate subjects with AD
- 6-month double blind studies
- Validated endpoints
- Comparable patient demographics and secondary endpoints
- Phase 2 functions as an interim analysis for Phase 3 without statistical penalty or operational complexity

Open Label Extension

- Offered 6-month open label extension to both Phase 2 and 3 subjects
- Subjects and investigators remain blinded to prior treatment assignment

AD, Alzheimer's disease; ERP, event-related potential; GMP, good manufacturing practice; qEEG, quantitative electroencephalogram.

Differential requirements for AD diagnosis early vs later

A/T/N Classification System[1]

- Aß biomarker:
  - Amyloid PET
    OR
  - CST $Aß_{42}$
- Tau pathology biomarker
  - CSF p-tau
    OR
  - Tau PET
- Neurodegeneration biomarker
  - CSF t-tau
    OR
  - FDG-PET
    OR
  - MRI

Resource intensive
&
Low accessibility

Revised National Institute on Aging-Alzheimer's Association criteria[2]

- Probable AD dementia
  - Meets core criteria for dementia
  - Insidious onset
  - Clear history of worsening cognition
  - Most prominent cognitive deficits are in one of the following:
    - Amnestic presentation (most common)
    - Language presentation
    - Visuospatial presentation
    - Executive dysfunction
  - No evidence of:
    - Substantial cerebrovascular disease
    - Prominent features of other dementias
    - Evidence for other neurological disease
    - Non-neurological comorbidity that could affect cognition
    - Use of medication that could affect cognition

Accessible
&
Affordable
&
Real life

1. Jack CR, et al. *Neurology.* 2016; 87(5): 539–547.
2. McKhann GM, et al. *Alzheimers Dement.* 2011; 7(3):263-269.

Aβ, amyloid-β; AD, Alzheimer's disease; CSF, cerebro-spinal fluid; CST, cognitive stimulation therapy; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

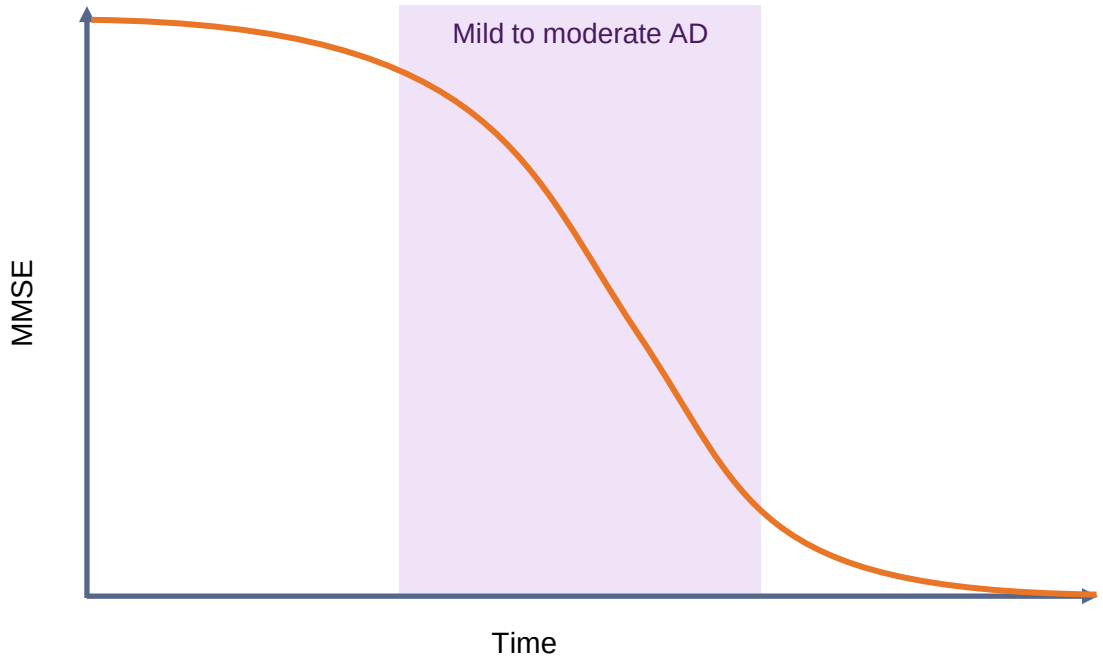
Why first address mild to moderate AD instead of pre-dementia?

Medical need:

- The point of most accelerated disease progression[1,2]
- Currently marketed drugs in mild to moderate space have only modest effects[3]
- Higher financial burden than pre-dementia[4]

Reduced development risk:

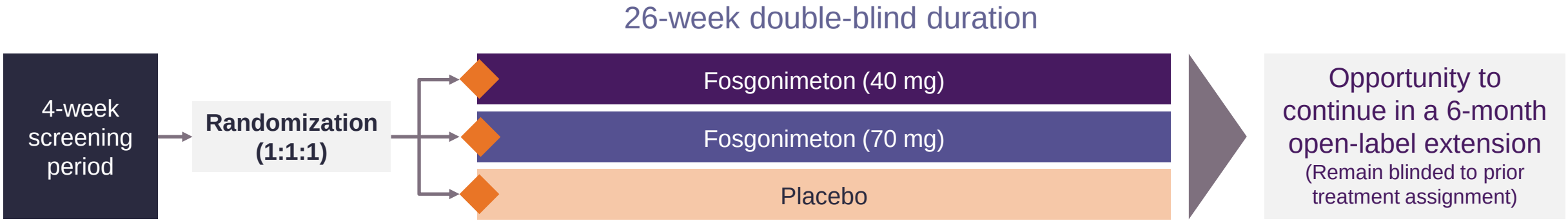
- Clinical, syndromal diagnosis is possible[5]
- Increased likelihood of tangible placebo decline
- Established regulatory path (AChEis, memantine)



1. Ower AK, et al. *Eur J Epidemiol*. 2018;33:657–666.
2. Caroli A, et al. *Neurobiol Aging*. 2010;31(8):1263–1274.
3. Fink HA, et al. *Ann Intern Med*. 2020;172(10):656–668.
4. Cerejeira J, et al., *Front Neurol*. 2012; 3:73.
5. de Aquino CH, et al. *Front Neurol*. 2021;12:694329.

AChEi, acetylcholinesterase inhibitor; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.

Phase 2 ACT-AD: mild to moderate Alzheimer's



Final enrollment: 77

Treatment: 40 mg/d or 70 mg/d fosgonimeton or placebo, daily subcutaneous injection

Age range: 55-85 years

Dual severity criteria for inclusion: MMSE 14-24, CDR 1 and 2

CDR, clinical dementia rating; MMSE, Mini-Mental State Examination.

Athira's ACT-AD trial is supported by a grant from the National Institute on Aging of the National Institutes of Health under Award Number R01AG06268. The information presented at the AD/PD Congress is solely the responsibility of Athira and does not necessarily represent the official views of the National Institutes of Health.

Phase 2 ACT-AD: inclusion and exclusion criteria

Key inclusion criteria

- Aged 55–85 years
- Subjects with mild to moderate AD dementia:
  - MMSE score of 14 to 24 inclusive at screening
  - CDR scale global score of 1 or 2 at screening
- **Clinical diagnosis of <u>probable</u> AD dementia with documented decline** within 12 months before screening, by the revised NIA-AA criteria[1]
  - Onset of symptoms at least 12 months prior to screening
  - MRI or CT within 12 months before screening, with findings that are consistent with the diagnosis of dementia due to AD, without any other significant comorbid CNS pathologies
- Treatment-naïve *OR* receiving stable AChEi treatment

Key exclusion criteria

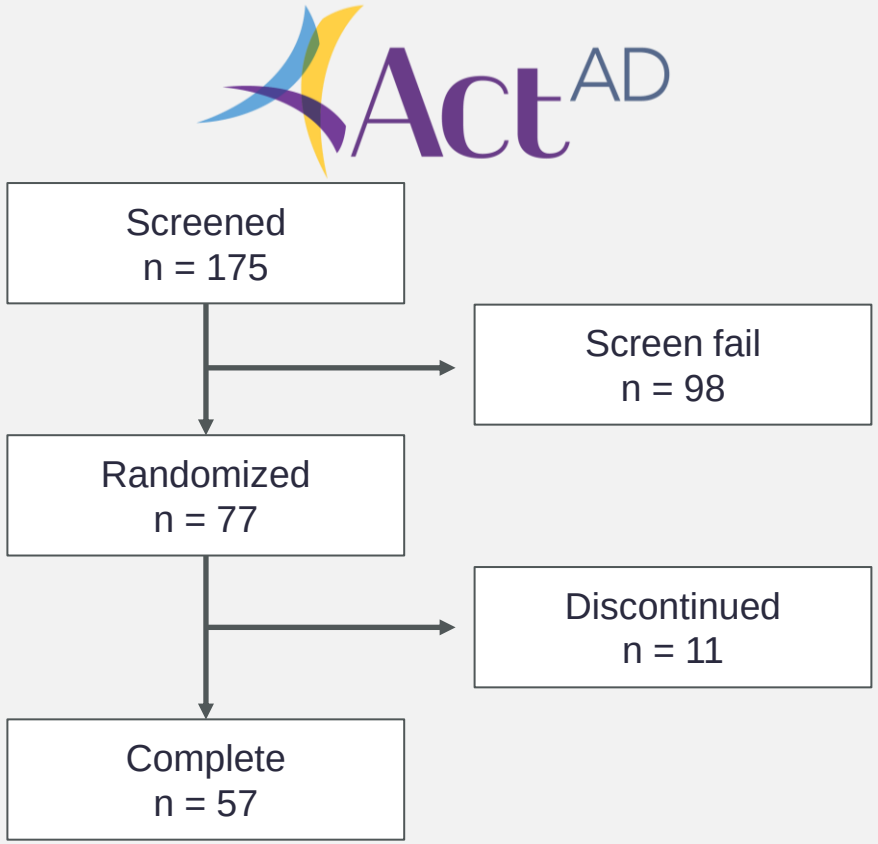
- History of significant neurologic disease
- Atypical variant presentation of AD
- Diagnosis with current symptoms of severe major depressive disorder and/or significant suicide risk
- History of psychosis within 2 years of screening
- Clinically significant cardiac abnormalities
- Hepatic impairment or renal insufficiency
- Memantine treatment

Aβ and tau agnostic approach

1. McKhann GM, et al. *Alzheimer's Dement.* 2011;7(3):263–269.

Aβ, amyloid-β; AChEi, acetylcholinesterase inhibitor; AD, Alzheimer's disease; CDR, clinical dementia rating; CNS, central nervous system; CT, computed tomography; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer's Association.

Phase 2 ACT-AD: current patient disposition



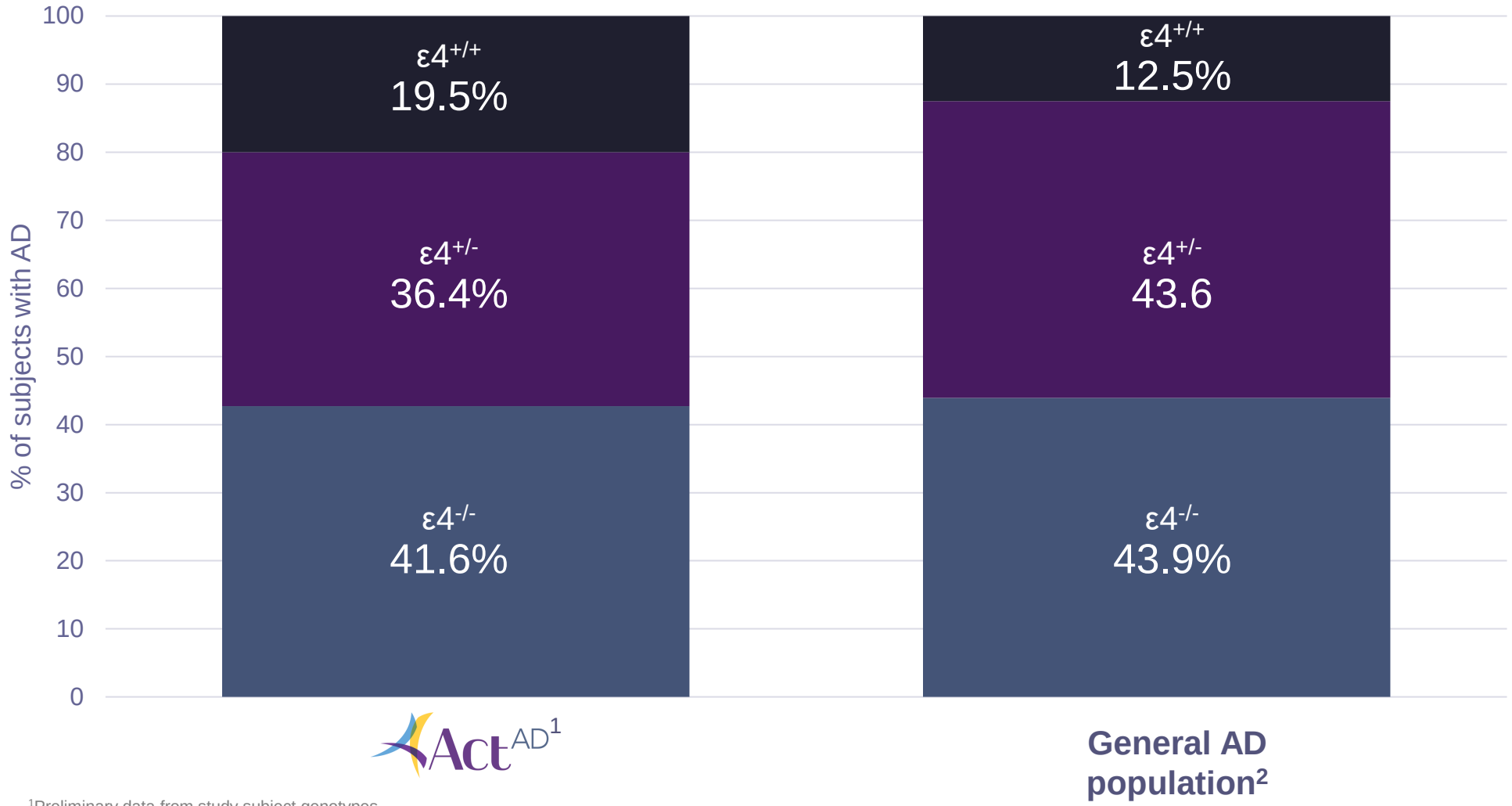
Enrollment: N = 77

Phase 2 ACT-AD: baseline demographics

Disease severity[a]	Mild (n = 31)	Moderate (n = 46)	Overall[b] (N = 77)
Age at informed consent (years); mean (SD)	73.1 ± 7.0	70.5 ± 7.2	71.4 ± 7.3
Body mass index (kg/m^2), mean (SD)	25.8 ± 3.9	25.3 ± 3.5	25.4 ± 3.7
Sex, n (%)			
Female	13 (41.9%)	26 (56.5%)	39 (50.6%)
Male	18 (58.1%)	20 (43.5%)	38 (49.4%)
Years of education, mean (SD)	15.5 ± 2.8	14.5 ± 2.8	14.9 ± 2.8
Baseline MMSE, mean (SD)	21.8 ± 1.9	17.5 ± 1.6	19.3 ± 2.7
Currently taking an AChEi, n (%)	16 (51.6%)	30 (65.2%)	46 (59.7%)

[a]Mild AD was defined as MMSE score of 20–24 at screening; Moderate AD was defined as MMSE score of 14–19 at screening.
[b]MMSE assessment at screening was missing for one subject.
AChEi, acetylcholinesterase inhibitor; AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; SD, standard deviation.

Phase 2 ACT-AD: APOε4 allele frequency



[1]Preliminary data from study subject genotypes.
[2]Calculated from APOε4 genotypes reported in individuals diagnosed with Alzheimer's disease at the initial visit in the National Alzheimer's Coordinating Center database. Total N = 11,663. Data query made March 1, 2022.
AD, Alzheimer's disease; APO, apolipoprotein.

Phase 2 ACT-AD endpoints

Primary

- Safety
- ERP P300 latency

Secondary

- Cognition: ADAS-Cog$_{11}$
- Global clinical change: ADCS CGIC - Clinician
- Function: ADCS-ADL$_{23}$
- Plasma PK

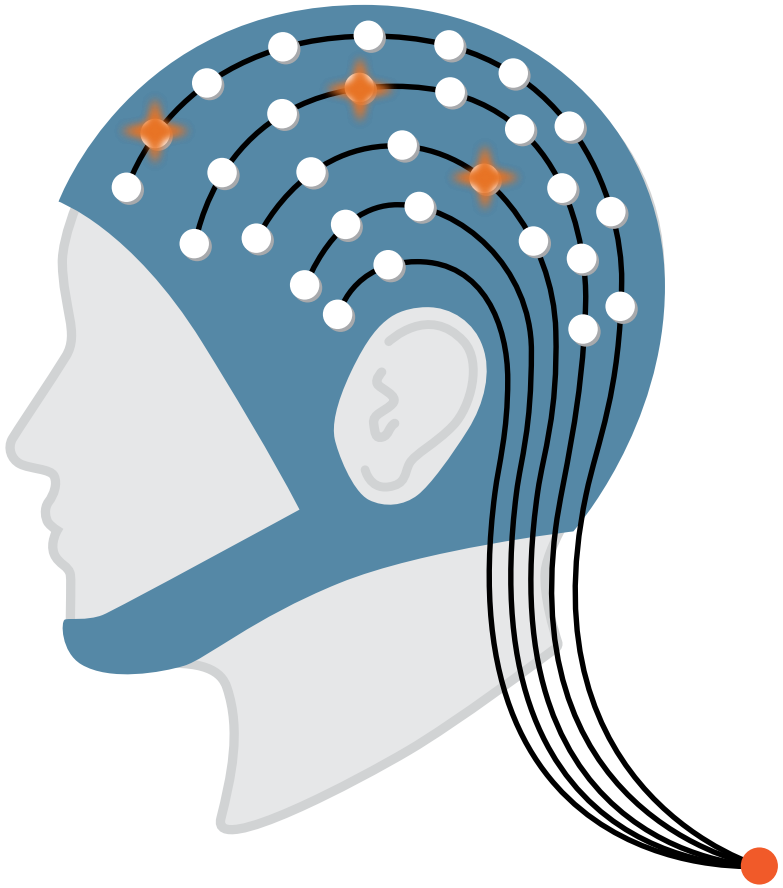
Exploratory

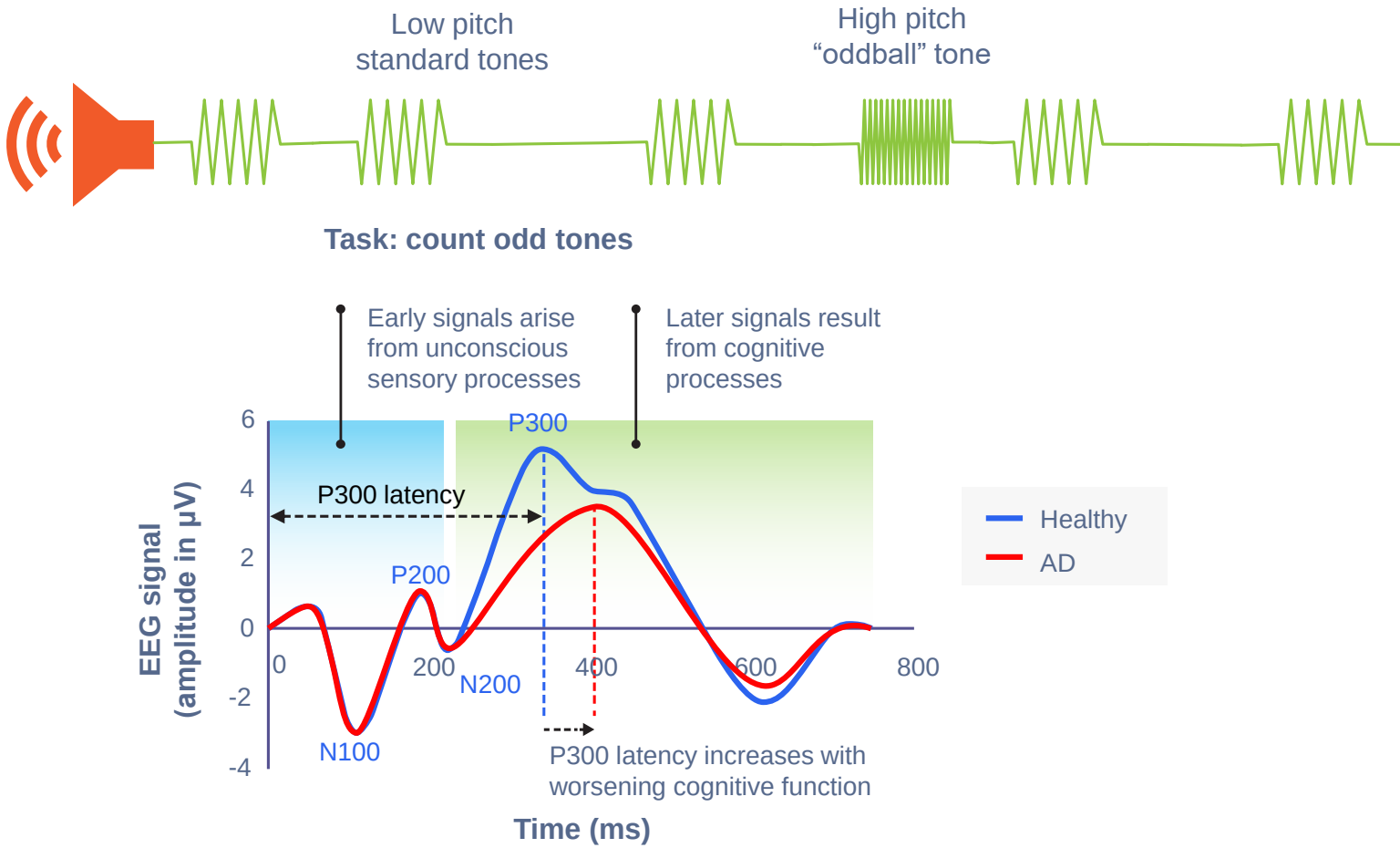
- COWAT
- NPI
- ZBI
- RUD-lite
- EQ-5D-5L
- qEEG spectral power

ADAS-Cog$_{11}$, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL$_{23}$, 23-item Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADCD-CGIC, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; COWAT, Controlled Oral Word Association Test; EQ-5D-5L, EuroQol-5 dimension-5 level; ERP, event-related potential; NPI, Neuropsychiatric inventory; PK, pharmacokinetics; qEEG, quantitative electroencephalogram; RUD, Resource Utilization in Dementia; ZBI, Azrit Burden Interview.

Measuring ERP P300 latency

Auditory ERP Stimulus

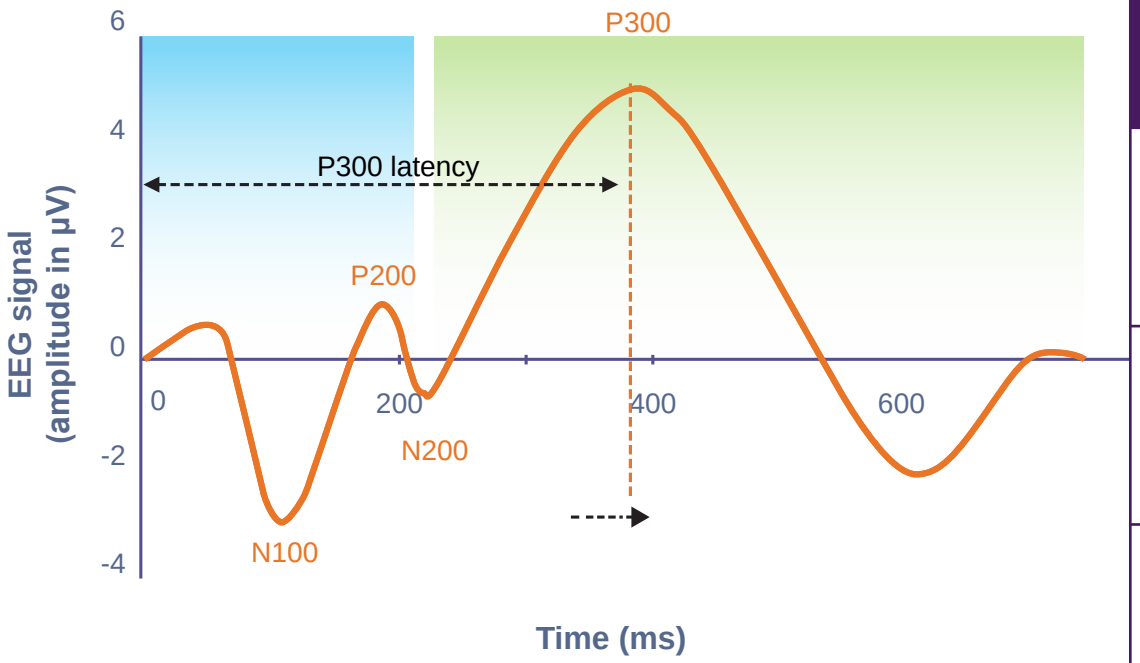




Average response to oddball tone recorded via EEG electrodes

Animations are illustrative. Source: Athira Pharma, Inc.
AD, Alzheimer’s disease; EEG, electroencephalogram; ERP, event-related potential.

ERP P300 latency in the AD population



Population	Age (years, mean)	Baseline P300 latency (msec, mean ± SE)	Δ in P300 latency from baseline (msec, mean ± SE)	Baseline MMSE
Thomas et al, 2001[1] Probable AD donepezil treated (n = 20)	66.5	383 ± 3.4		Mean: 16

Diagram is illustrative and does not represent actual EEG data. Source: Athira Pharma, Inc.

AD, Alzheimer's disease; EEG, electroencephalogram; ERP, event-related potential; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; SE, standard error.

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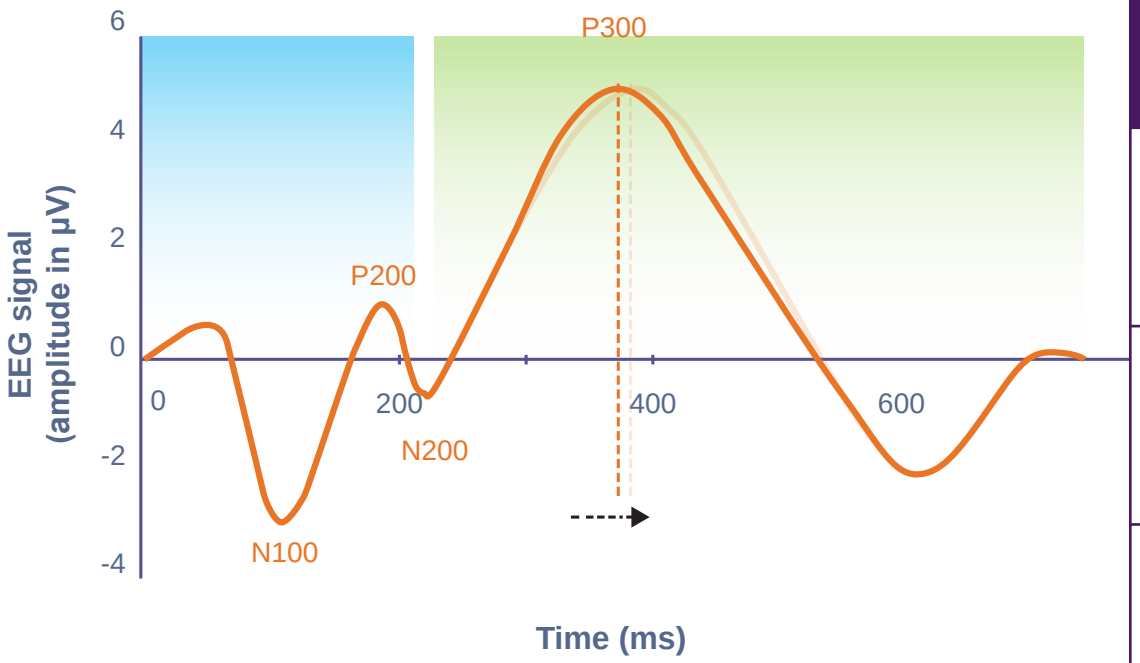

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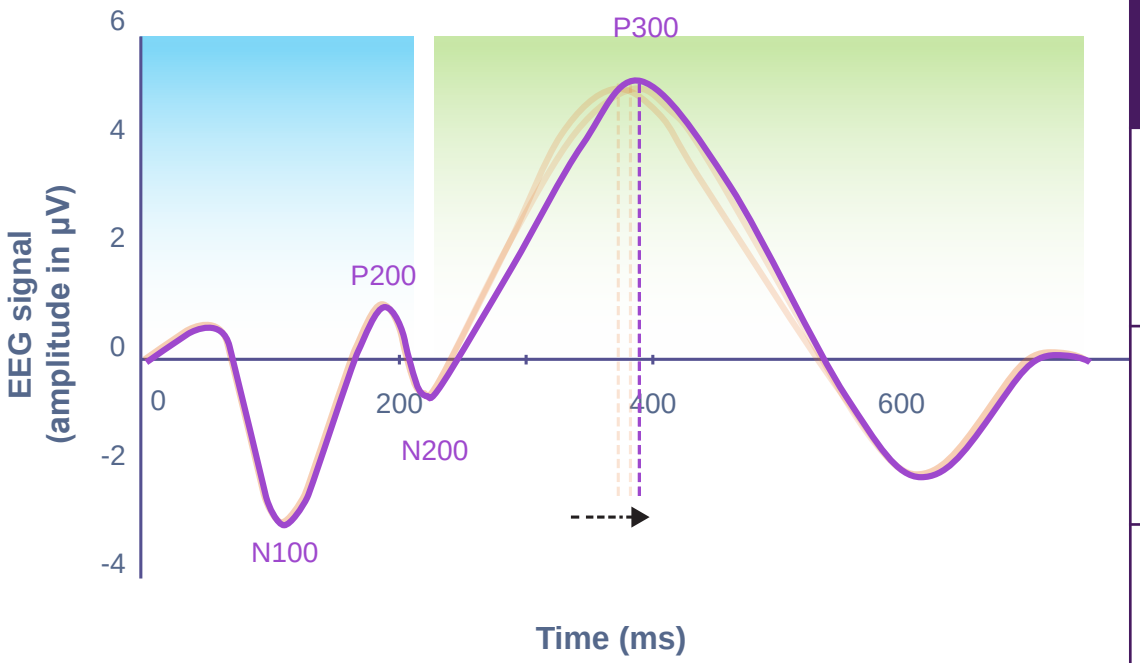

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Phase 1[2,3] AD subjects (n = 11)	69.2	390 ± 14.8		Median: 20

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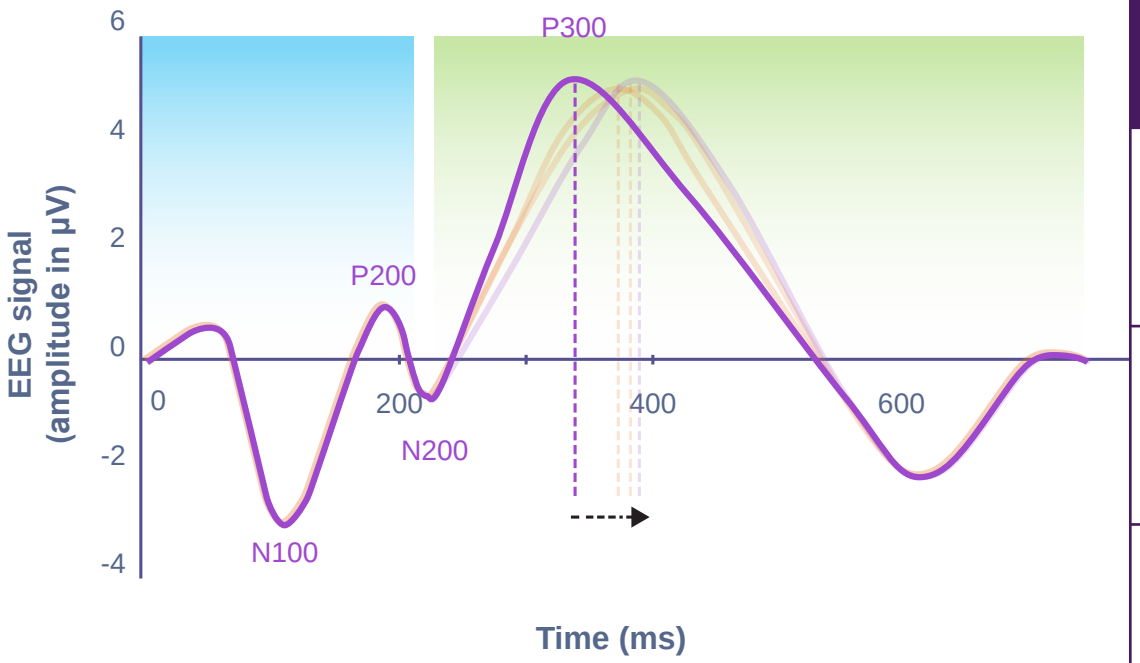

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Phase 1[2,3] AD subjects (n = 11)	69.2	390 ± 14.8	8 days treatment with fosgonimeton: -73 ± 18.4 p = 0.027[a]	Median: 20

[a]MMRM analysis vs placebo
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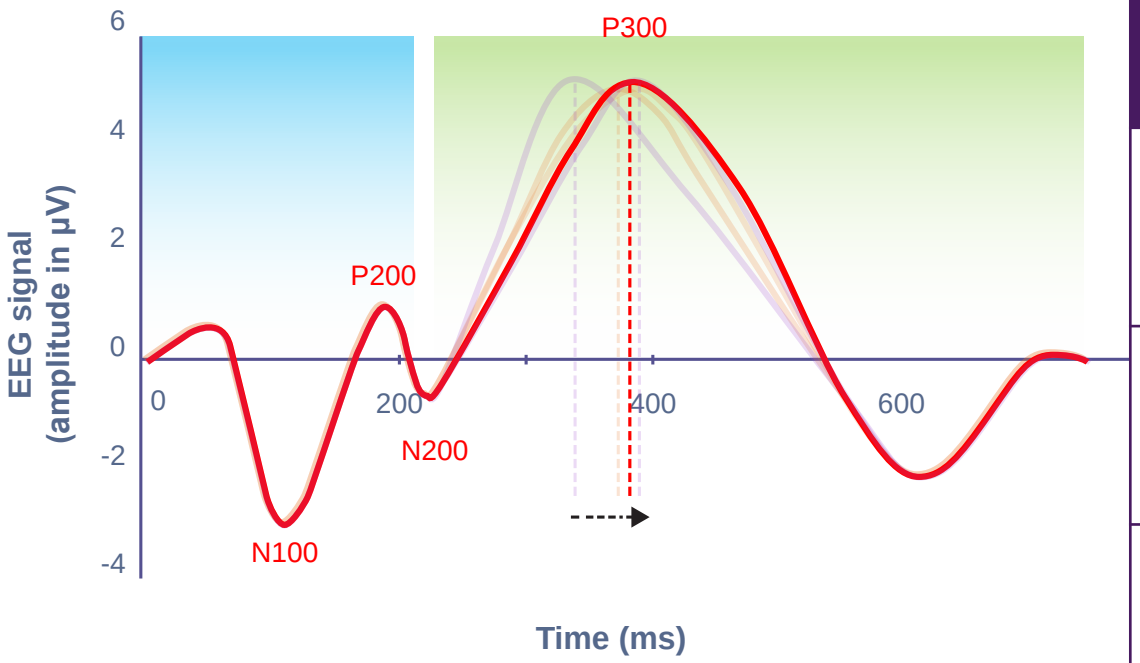
Baseline ERP P300 latency in the ACT-AD population



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Phase 1[2,3] AD subjects (N = 11)	69.2	390 ± 14.8	8 days treatment with fosgonimeton: -73 ± 18.4 p = 0.027[a]	Median: 20
ActAD (N = 77)	71.4	381 ± 4.1[b]	Results available Q2 2022	Mean: 19

[a]MMRM analysis vs placebo; [b]Preliminary.
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AD, Alzheimer's disease; EEG, electroencephalogram; ERP, event-related potential; MMRM, mixed model for repeated measures; MMSE, Mini-Mental State Examination; SE, standard error.

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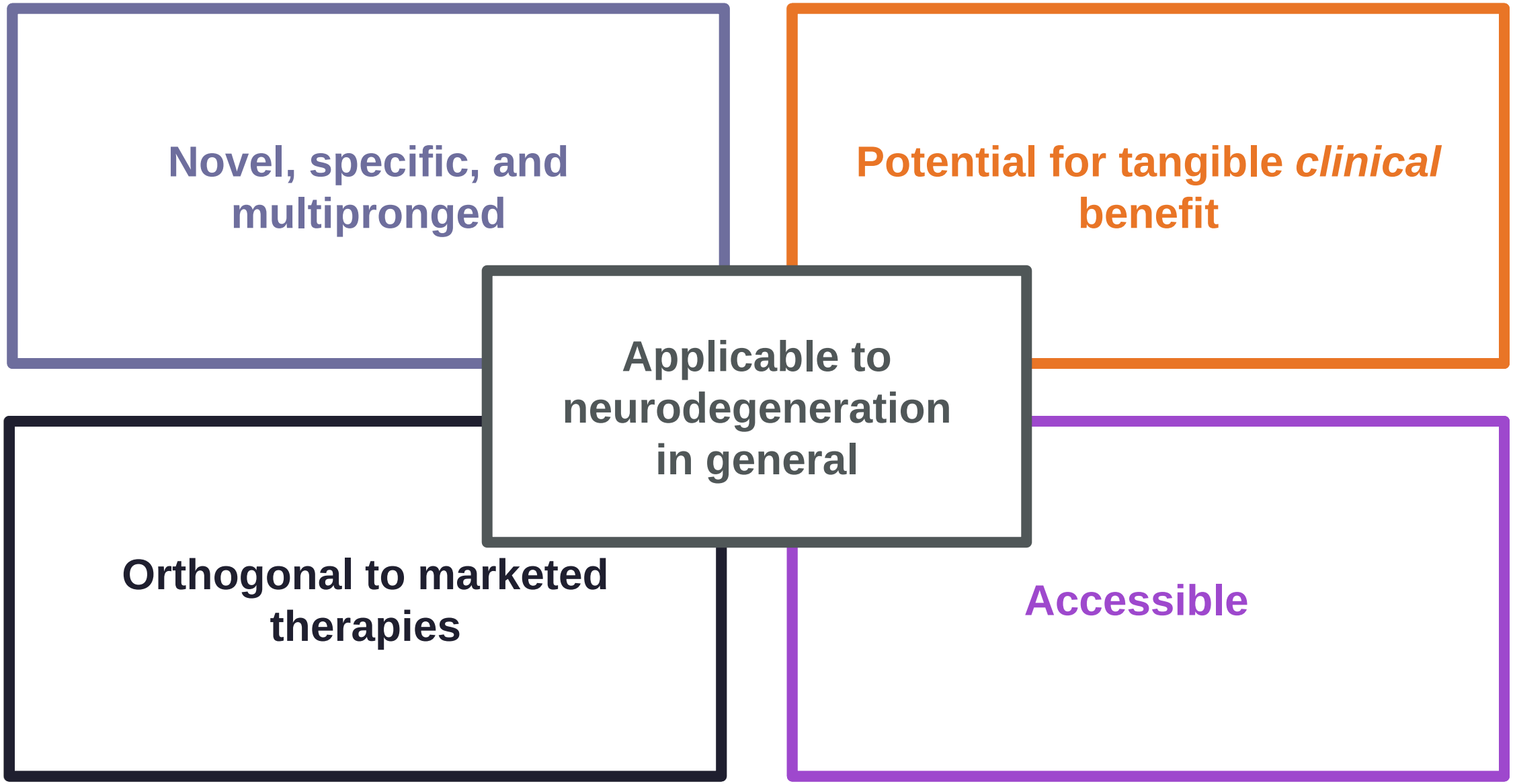
3. Athira Pharma, Inc. Data on file, 2022.

ACT-AD: early termination rate

	ACT AD
Randomized (at data cut off)	77
Completed	57
Early termination (ET, rate %)	11 (14.3%)
Due to AEs	7 (9.1%)
Withdrawal	4 (5.2%)
Other/TBD	0
TEAEs leading to study drug withdrawal/ET by primary system organ class	(Out of 7 ETs due to AE)
General disorders and administration site conditions	4
Injury, poisoning and procedural complications	0
Nervous system disorders	2
Blood and lymphatic system disorders	0
Musculoskeletal and connective tissue disorders	1

AE, adverse event; ET, early termination; TEAE, treatment-emergent adverse event.



Phase 3 in mild to moderate Alzheimer's disease
Currently recruiting

Phase 2 in Parkinson's disease dementia and Dementia with Lewy bodies
Currently recruiting

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Thank you!