Phase 2/3 trials of ATH-1017, a novel treatment approach for mild-to-moderate Alzheimer's disease: updates and baseline data

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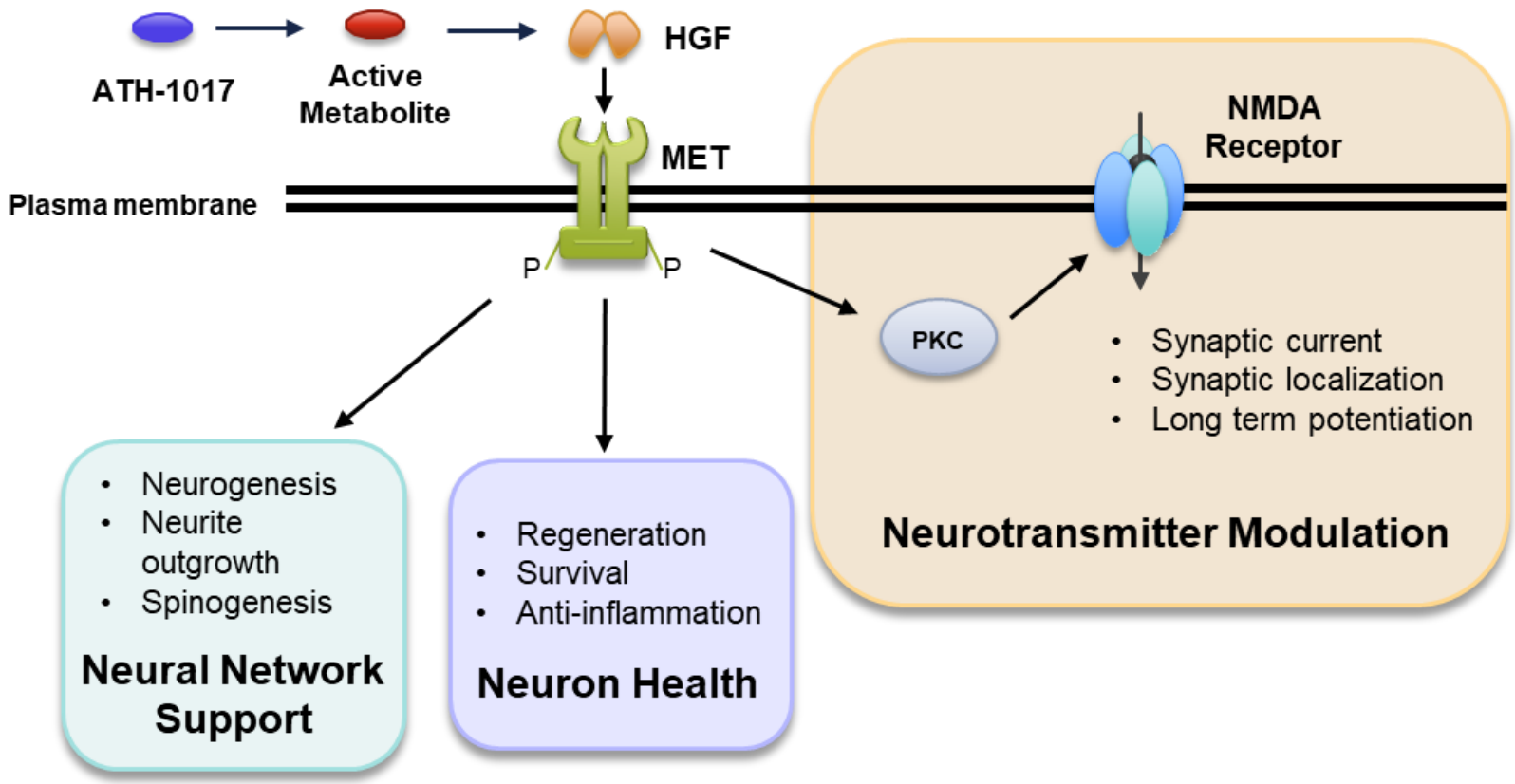
Disclosures

- Xue Hua, Kevin Church, Kai-Bin Ooi, Joyce Maalouf, William Walker, and Hans J. Moebius are all employees of Athira Pharma, Inc., with salary and stock compensation
- 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
- Larry Ereshefsky is a paid advisor to Athira, with cash and stock compensation

ATH-1017 is a Positive Modulator of the HGF/MET Neurotrophic System

ATH-1017:

- Administered via 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



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

Athira's approach to ATH-1017 clinical development in AD

Long-term toxicity

- Early initiation of long-term toxicity studies

Phase 1

- Larger Phase 1 than usual
- Included functional biomarker
- Included AD cohort
- Reassured dose range

Phase 2
(6 month double-blind)

ActAD

Phase 2/3
(6 month double-blind)

LiftAD

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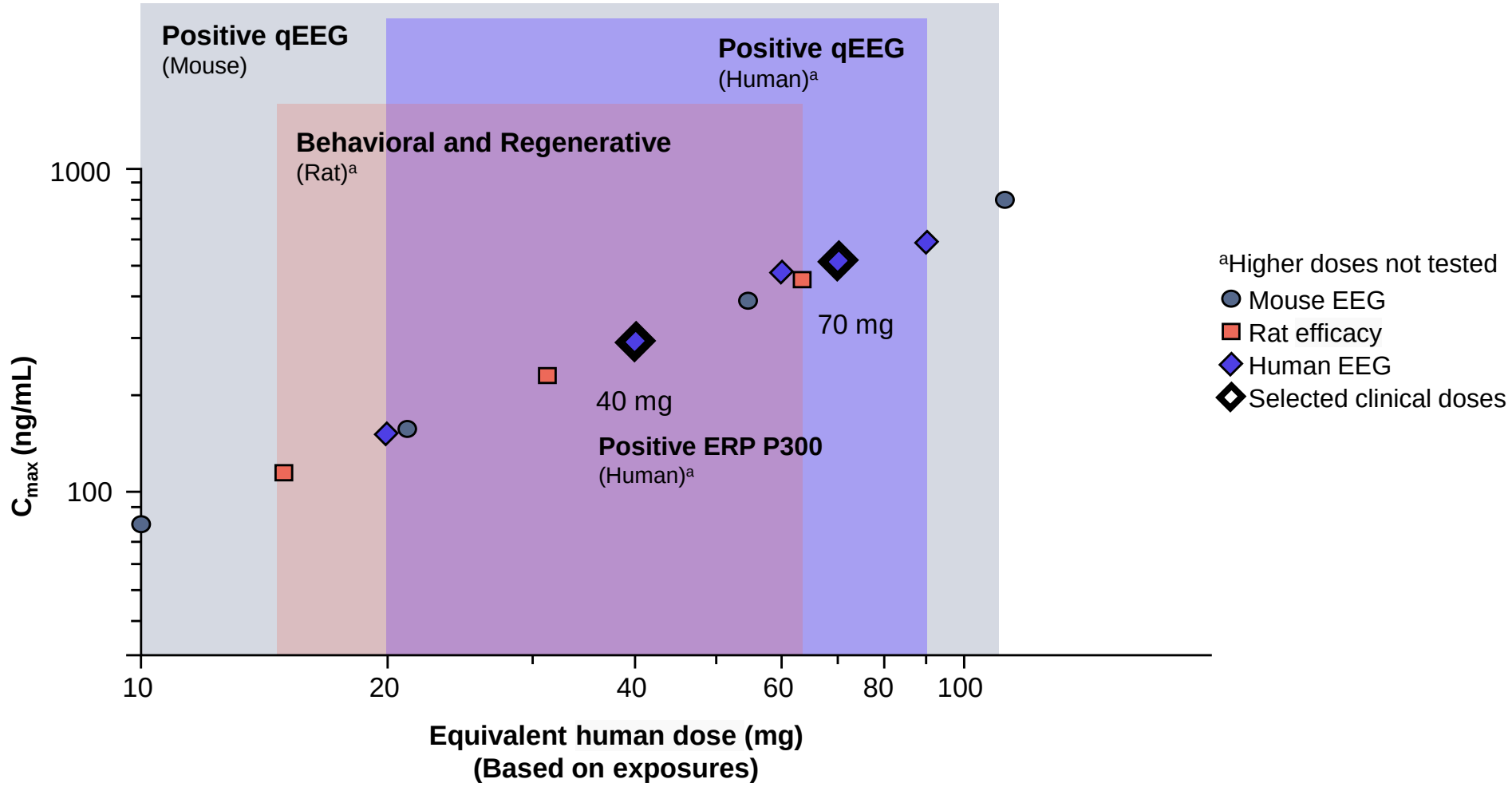
AD, Alzheimer's disease.

ATH-1017: Translational evidence for dose range selection



C_{max}, maximum serum concentration; EEG, electroencephalogram.

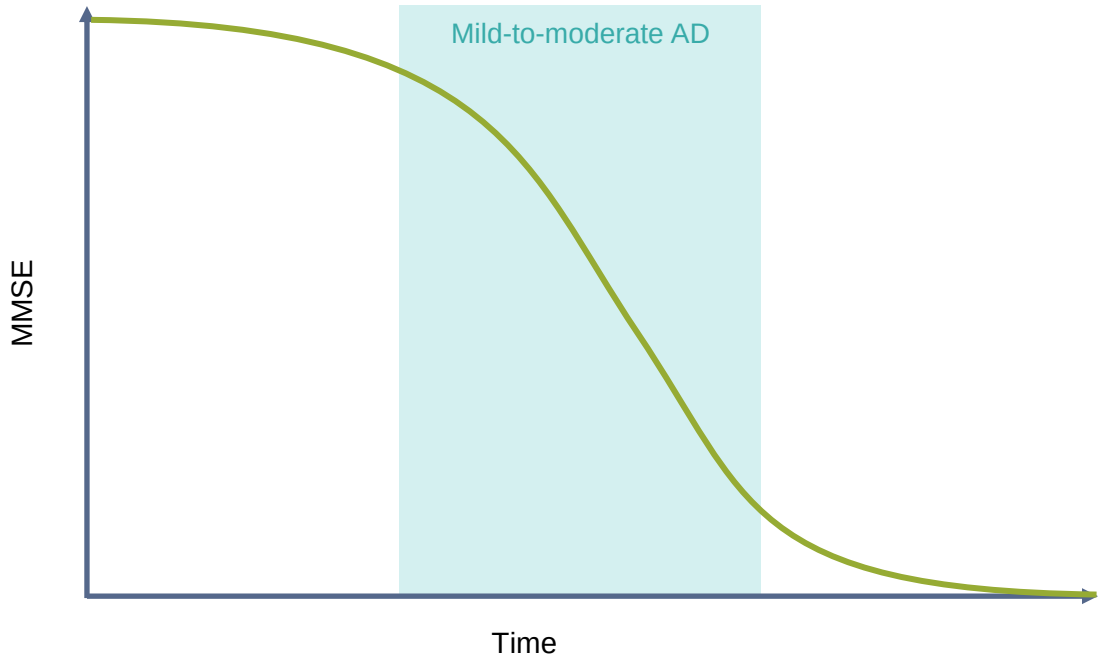
Why first address mild-to-moderate AD instead of pre-dementia?

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)



AD, Alzheimer's disease.

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.

Ongoing clinical trials: overview – mild to moderate Alzheimer's

ActAD

26-week double-blind duration

Final enrollment: 77

1:1:1 placebo, 40 mg/d or 70 mg/d ATH-1017

Dual severity criteria: MMSE, CDR

Estimated topline results: First half of 2022

LiftAD

26-week double-blind duration

Preliminary target enrollment: 300

1:1:1 placebo, 40 mg/d or 70 mg/d ATH-1017

Dual severity criteria: MMSE, CDR

Designed to provide primary evidence on efficacy

6-month open-label extension

GST, global statistical test.

Ongoing clinical trials LIFT-AD and ACT-AD: common IC/EC

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 before 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

Aβ and tau agnostic approach

Aβ, amyloid-β; AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CT, computed tomography; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer's Association.

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

Ongoing clinical trials: outcomes

Primary endpoints

- ERP P300 latency
- Adverse events

- GST[a]
- Adverse events

Secondary endpoints

- GST[a]
- Change from baseline to week 26 in:
  - ADAS-Cog$_{11}$
  - ADCS-CGIC
  - ADCS-ADL23
- Plasma PK
- Correlation of ERP P300 latency and cognition/ executive memory function

- Change from baseline to week 26 in:
  - ADAS-Cog$_{11}$
  - ADCS-CGIC
  - ADCS-ADL23

  } Key co-secondary endpoints
- Plasma PK

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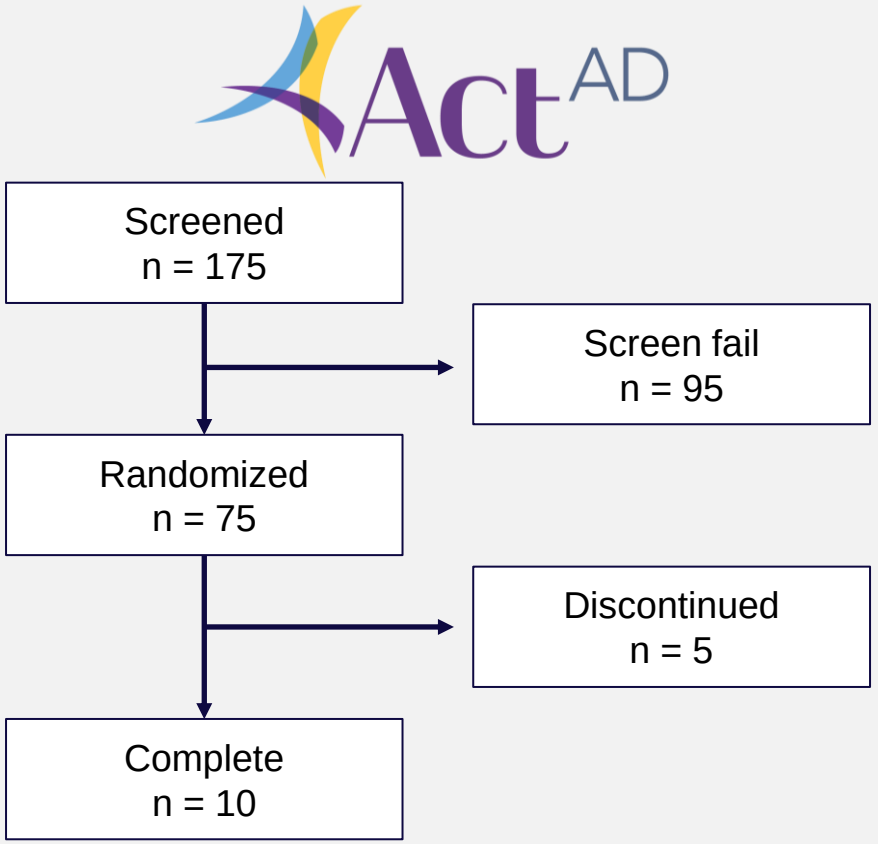
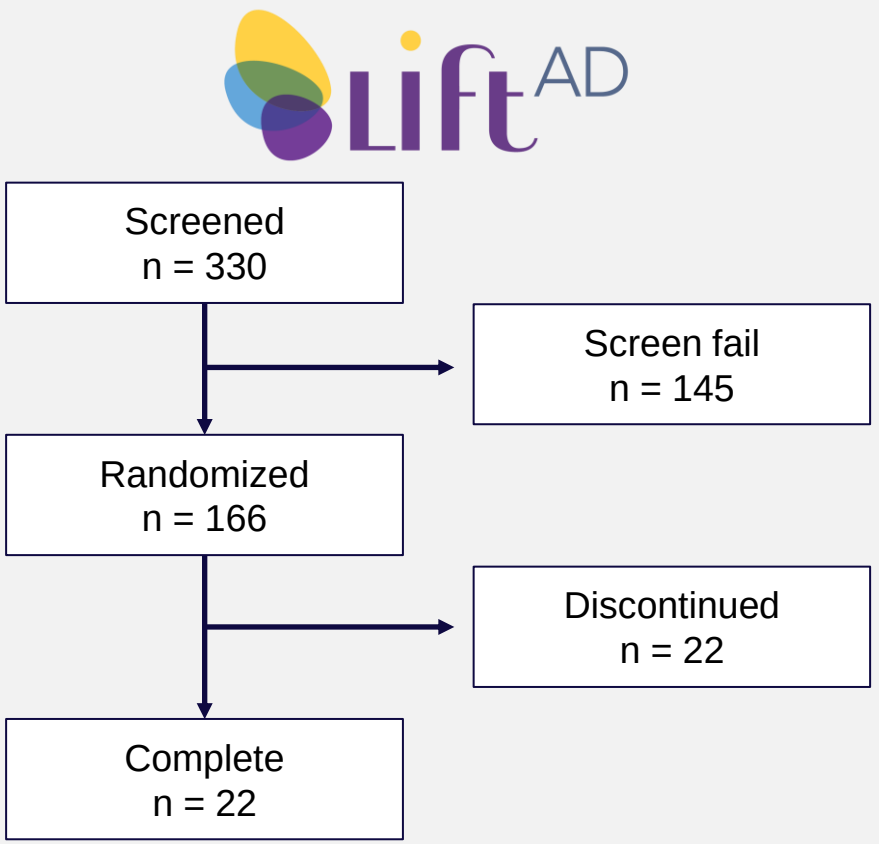
[a]The GST combines scores from cognition (ADAS-Cog$_{11}$) and global impression of change (ADCS-CGIC).
ADAS-Cog$_{11}$ Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCD-CGIC, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change ERP, event-related potential; GST, global statistical test; PK, pharmacokinetics.

Ongoing clinical trials: enrollment status



Enrollment at data cutoff: 75



Preliminary target enrollment: 300

Ongoing clinical trials: baseline demographics

	Act AD — Enrollment complete			Lift AD — Currently enrolling		
Disease severity[a]	**Mild *(n=29)***	**Moderate *(n=42)***	**Overall (n=75)**	**Mild (n = 79)**	**Moderate (n = 87)**	**Overall (n = 166)**
Age at informed consent (years); mean (SD)	73.1 (7.2)	70.6 (7.4)	71.6 (7.3)	72.9 (7.0)	72.1 (7.6)	72.5 (7.3)
Body mass index (kg/m^2), mean (SD)	25.8 (3.9)	25.6 (3.3)	25.4 (3.7)	27.2 (4.0)	25.4 (4.2)	26.2 (4.2)
Sex, n (%)						
Female	12 (41.4)	22 (52.4)	38 (50.7)	33 (41.8)	51 (59.3)	84 (50.9)
Male	17 (58.6)	20 (47.6)	37 (49.3)	46 (58.2)	35 (40.7)	81 (49.1)
Years of education, mean (SD)	15.4 (2.8)	14.6 (2.8)	14.9 (2.8)	15.0 (2.8)	15.3 (3.2)	15.1 (3.0)
Baseline MMSE, mean (SD)	21.2 (2.7)	18.2 (2.5)	19.5 (2.9)	21.9 (2.4)	17.2 (3.1)	19.4 (3.7)
Pending data readout, n (%)	*0 (0)*	*0 (0)*	4 (5.3)	0 (0)	0 (0)	0 (0)
APOε4 genotype, n (%)						
$\varepsilon4^{-/-}$	11 (37.9)	21 (50.0)	32 (45.1)	30 (38.0)	36 (41.4)	66 (39.8)
$\varepsilon4^{-/+}$	13 (44.8)	13 (31.0)	26 (36.6)	37 (46.8)	37 (42.5)	74 (44.6)
$\varepsilon4^{+/+}$	5 (17.2)	8 (19.0)	15 (20.0)	12 (15.2)	12 (13.8)	24 (14.5)
Pending data readout, n (%)	*0 (0)*	*0 (0)*	2 (2.7)	0 (0)	2 (2.3)	2 (1.2)

[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.

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; SD, standard deviation.

Ongoing clinical trials: early termination rates

	ActAD Enrollment complete (N=77)	LiftAD Currently enrolling
Randomized (at data cut off)	**75**	**166**
Completed	10	22
Early termination (ET rate %)	5 (6.7%)	22 (13.3%)
Due to AEs	**4 (5.3%)**	**11 (6.6%)**
Withdrawal	1 (1.3%)	6 (3.6%)
Other/TBD	0	5 (3.0%)
TEAEs leading to study drug withdrawal/ET by primary system organ class	(Out of 4 ET due to AE)	(Out of 11 ET due to AE)
General disorders and administration site conditions	3	5
Injury, poisoning and procedural complications	0	2
Nervous system disorders	0	2
Blood and lymphatic system disorders	0	1
Musculoskeletal and connective tissue disorder	0	1
Information pending	1	0

Novel, specific, and multipronged

Potential for tangible *clinical* benefit

Orthogonal to marketed therapies

Accessible

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