What's on the Horizon? Research Advances

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Disclosures

- Grants
  - NIH P30 AG072946, U24 AG057437, R01 AG053798, R01 AG063689, U19 AG010483, R01 AG054029, R01 AG061848, R01AG061146, UF1 NS125488, R01 AG061111, U19 NS120384, R01 AG065248, R01 AG068324, P01 AG078116, R01 NS116058, U54 TR001998, U13 AG067696, U19 AG024904
- Contract Research (No personal reimbursement)
  - Alnylam, Cognition therapeutics, **Eisai, NovoNordisk,** ONO
- Unpaid Leadership Roles
  - Alzheimer's Association ALZ-NET, ACTC, ADCS, NIH/NIA ADRC Clinical Task Force & Clinical Core Steering Committees, NIH/NINDS MarkVCID

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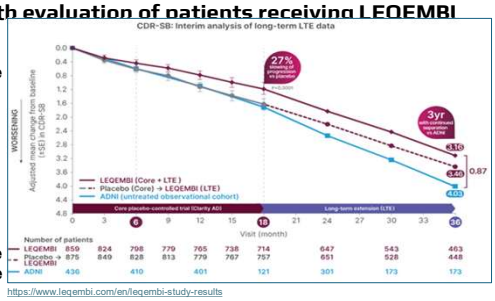
Clarity AD ongoing long-term extension (LTE)

36-month evaluation of patients receiving LEQEMBI

- **Benefits of Leqembi maintenance dosing include increased separation of the curves**
- **UK has had folks on maintenance dosing since 2013**



https://www.leqembi.com/en/leqembi-study-results

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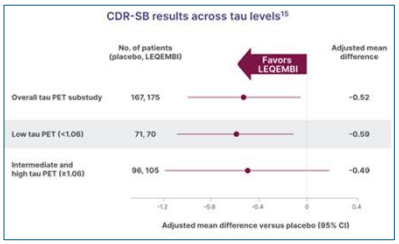
Effects based on tau (tangles)

- Increased benefits in those with low tau
- Earlier treatment is just better
- We really need to get folks identified on board early to maximize benefits



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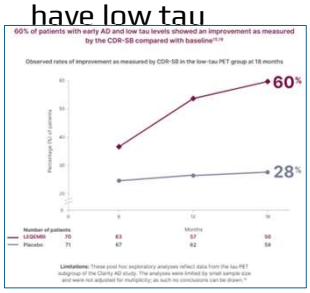
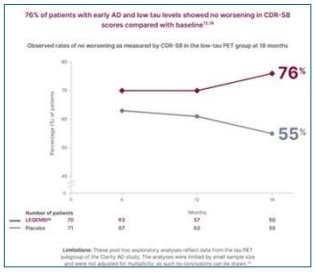
Many patients may actually improve or remain stable without decline if they have low tau





https://www.leqembi.com/en/leqembi-study-results

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Two agents: Leqembi & Kisunla

Lecanemab (Leqembi®)

- 18 months of treatment
- Benefits of maintenance treatment are clear

Donanemab (Kisunla®)

- 18 months of treatment
- No maintenance treatment supported by available data

- How do we reconcile this?
- The data suggest two different paths to treatment?
- I suspect Kisunla just doesn't have the data yet because of the studies they have done?

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf

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Lecanemab (Leqembi®) autoinjector for maintenance dosing

- UK has had patients using the autoinjector since 2001
- No difference in maintenance benefits were seen between IV (infusions once monthly at an infusion center) and home administration (weekly home injections)
- Fewer systemic reactions were seen in the autoinjector group
- No difference otherwise in safety profile
- Our patients love this option!

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf

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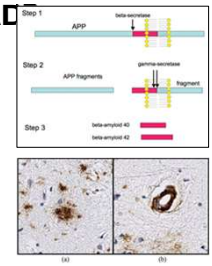
How about vaccines for AD?

- ABvac40 is an investigational active vaccine for early-stage Alzheimer's disease (AD) that targets the amyloid-beta 40 (Aβ40) peptide
- In contrast to therapies targeting Aβ42, which mostly accumulates in the brain tissue, ABvac40 targets Aβ40, which primarily deposits in the walls of cerebral blood vessels in a condition known as cerebral amyloid angiopathy (CAA).
- The vaccine is designed to offer a different approach to modifying the disease

Pascual-Lucas et al., Alzheimers Dement. 2025 Oct;21(10):e70776.



AB 42 & 40 **AB 40**

Amin et al., (2023) Scientific Reports. 13

8

ABvac40 study results: Safety

- The safety profile was benign
- More TEAEs & TESAEs were seen in placebo than on treatment
- Higher rates of ARIA-H were seen in placebo for ApoE negative and heterozygotes (e3/e4)
- Higher rates were seen for treatment in homozygotes (e4/e4)

TEAEs, n (%)	ABvac40 (N = 64)	Placebo (N = 60)
Any TEAE	58 (90.6)	56 (93.3)
Any treatment-related TEAE	29 (45.3)	26 (43.3)
Any TEAEs leading to treatment discontinuation	4 (6.3)	7 (11.7)
Any TEAE leading to death.*	1 (1.6)	1 (1.7)
Any TESAE	17 (26.6)	16 (26.7)
Any treatment-related TESAE	3 (4.7)	8 (13.3)
Any TESAE leading to treatment discontinuation	2 (3.1)	4 (6.7)
Any TESAE leading to death.*	1 (1.6)	1 (1.7)
Any TESAESI	8 (12.5)	9 (15.0)
Aseptic meningoencephalomyelitis	0 (0.0)	0 (0.0)
ARIA-E	0 (0.0)	0 (0.0)
ARIA-H	8 (12.5)	9 (15.0)
ARIA-H leading to treatment discontinuation	0 (0.0)	2 (3.3)
ARIA-H by *APOE* ε4 carrier status		
Non-carrier	4/25 (16.0)	4/23 (17.4)
Heterozygous carrier	3/30 (10.0)	5/32 (15.6)
Homozygous carrier	1/9 (11.1)	0/5 (0.0)

Pascual-Lucas et al., Alzheimers Dement. 2025 Oct;21(10):e70776.

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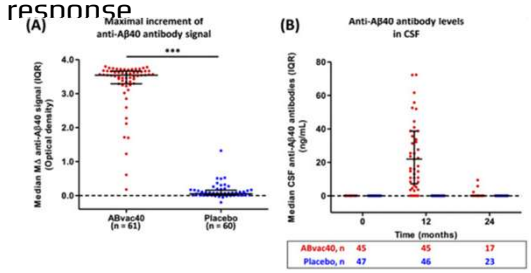
ABvac40 study results: Antibody response



Pascual-Lucas et al., Alzheimers Dement. 2025 Oct;21(10):e70776.

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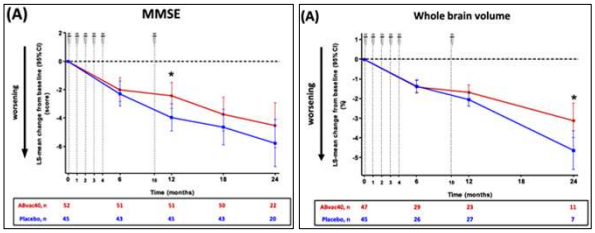
ABvac40 study results: Clinical & Imaging



Pascual-Lucas et al., Alzheimers Dement. 2025 Oct;21(10):e70776.

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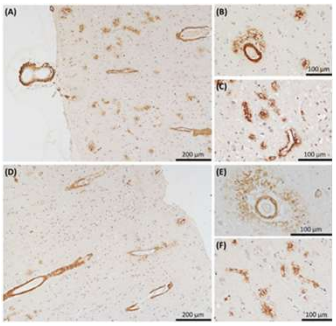
What's next for ABvac40?

- This vaccine is moving into phase 3 clinical trials currently
- It may also be a new effective treatment for CAA, not just for AD
- Many other promising vaccines are on the



Pascual-Lucas et al., Alzheimers Dement. 2025 Oct;21(10):e70776.

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What about the new blood tests for AD?

Fujirebio Lumipulse
- measures a ratio of p-tau217 and amyloid-beta (42/40)
- Received FDA clearance in May 2025
- Can both positively identify and rule out Alzheimer's pathology
- Able to both positively test for and rule out the presence of Alzheimer's pathology
- Many (~30%) may have an inconclusive test

Roche Elecsys
- measures levels of the p-tau181 protein alone
- Received FDA clearance in October 2025
- Can rule out Alzheimer's 97.9% of the time.
- The test uses a negative predictive value and helps to rule out Alzheimer's in individuals
- Many (~30%) may have an inconclusive test

https://www.nature.com/articles/d41586-025-03394-w

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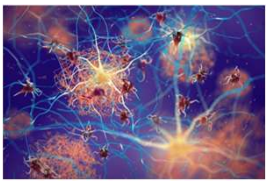
How will these blood tests change our care?

- Currently, about 92% of adults with mild cognitive impairment might go undiagnosed
- Neurologists have hailed the new blood tests that measure biomarkers of Alzheimer's to be a major turning point for diagnosing the disease and distinguishing it from other conditions related to cognitive decline



https://www.nature.com/articles/d41586-025-03394-w

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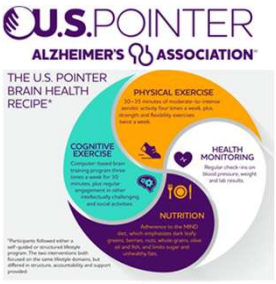
U.S. POINTER

- National data indicate that up to 35% of older adults do not meet physical activity guidelines
- 81% consume suboptimal diets
- 55% meet criteria for metabolic syndrome (≥3 risks)
- These estimates highlight the prevalence of eligibility-targeted characteristics and support generalizability to the broader US population.



Baker et al., JAMA. 2025 Aug 26;334(8):681-691

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U.S. POINTER

QUESTION Can multidomain lifestyle interventions improve or protect cognitive function in older adults at risk of cognitive decline and dementia?

CONCLUSION Among older adults at risk of cognitive decline and dementia, a structured, higher-intensity intervention had a greater benefit on global cognition than a self-guided, low-intensity intervention.

POPULATION

1455 Women
656 Men

Adults aged 60 to 79 years with sedentary lifestyle, suboptimal diet, and at least 2 other cognitive decline and dementia risk factors

Mean age: 68 years

LOCATIONS

5 Clinical sites in the US

INTERVENTION

2111 Participants randomized

1056 **Structured**
Promotion of increased physical and cognitive activity, healthy diet, social engagement, and cardiovascular monitoring via 38 team meetings with navigators and interventionists; activity plans with quantifiable adherence metrics

1055 **Self-guided**
Six peer team meetings; publicly available education materials and encouragement of lifestyle changes

PRIMARY OUTCOME

Annual rate of change in global cognitive function using a composite measure of executive function, episodic memory, and processing speed, assessed over 2 years

FINDINGS

Mean rate of change per year in global cognitive function

Structured	Self-guided
0.243 SD (95% CI, 0.227 to 0.258)	0.213 SD (95% CI, 0.198 to 0.229)

The structured intervention significantly improved global cognitive function:
Between-group difference in mean rate of change per year,
0.029 SD
(95% CI, 0.008 to 0.050); $P = .008$

© AMA

Baker LD, Espeland MA, Whitmer RA, et al. Structured vs self-guided multidomain lifestyle interventions for global cognitive function: the US POINTER randomized clinical trial. *JAMA*. Published online July 28, 2025. doi:10.1001/jama.2025.12923

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What was the intervention?

B Overview of multidomain interventions

INTERVENTION DURATION: 2 YEARS

Structured lifestyle intervention: 38 facilitated peer team meetings over 2 years, with education, goal-setting, and accountability to support the health behaviors below

Physical exercise:	Nutrition:	Cognitive and social challenge:	Guideline-based health coaching:
Aerobic, resistance, and stretching and balance exercise primarily at a community facility, with support through facilitated peer group meetings	Encouragement to follow the MIND diet, with support through peer group meetings and telephone contacts with the interventionist	Computer cognitive training at home and regular participation in intellectually and socially engaging activities through peer group meeting support	Medical advisor appointments every 6 months to review monthly pressure monitoring results, blood laboratory results provided at clinic visits, and goal-setting

Self-guided lifestyle intervention: 6 facilitated peer team meetings over 2 years to provide the support below

Education | Tangible tools to facilitate self-guided plans | General support to encourage physical activity, a healthy diet, and cognitive and social stimulation

Blood laboratory results and blood pressure measurements are provided at clinic assessment visits.

- Intervention: Costly gym membership, dietary restrictions, costly computerized memory & thinking programs, health coaching beyond your PCP
- Placebo: Health literacy and education and then pick your own approach

Baker et al., JAMA. 2025 Aug 26;334(8):681-691

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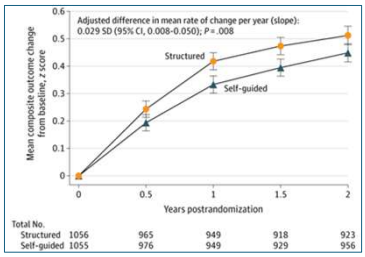
Change From Baseline in Global Cognitive Function Composite Score (Primary Outcome) by Structured vs Self-Guided Lifestyle Interventions

- Bothe the treatment and intervention arms improved over time
- The intervention was statistically better
- The difference was actually quite small
- Let's try to put the benefit in context…



Baker et al., JAMA. 2025 Aug 26;334(8):681-691

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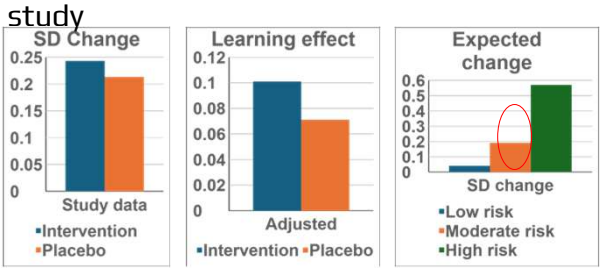
We need to understand average decline, learning effects, and change due to the study



Hayden et al., Age and Ageing, Volume 40, Issue 6, November 2011, Pages 684–689
Wilson et al., Neurobiology of Aging, Volume 66, 2018, Pages 122-130,

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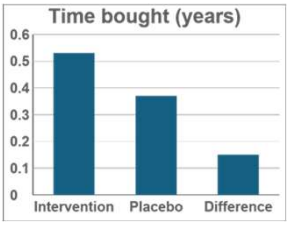
We can use this to inform on the clinical meaningfulness of the study changes seen

- If we use moderate change given a high-risk group was enrolled this is 0.19/year
- Using learning effect adjusted scores at 0.101 & 0.071
- We can then convert this to an annual time interval
- This could buy up to ½ a year for every year we engage in healthy activities
- The difference between structured vs, on your own is about 8 weeks per year



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So, let's get started today with a brain health program!

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What about DLB?

Four Symptom Domains Drive Lewy Body Disease Burden

"A multifactorial disease with a buffet of symptoms"

	Behavior	Cognition	Function	Movement
Patient symptom	Hallucinations, anxiety, delusions	Memory and problem solving	Bathing, toileting, shopping, meal preparation	Standing, maintaining balance
Assessment tool	Neuropsychiatric Inventory (NPI) Care Partner's NPI of "Distress"	Cognitive Drug Research (CDR) System Montreal Cognitive Assessment (MoCA)	ADCS-Activities of Daily Living (ADL) Clinician Assessment of Fluctuation (CAF)	MDS-Unified Parkinson's Disease Rating Scale (UPDRS)

Slides from Dr. Galvin, CTAD 2024: https://ir.cogrx.com/wp-content/uploads/2025/01/2025-ILBDC-Galvin-SHIMMER-Conf-Slides.pdf

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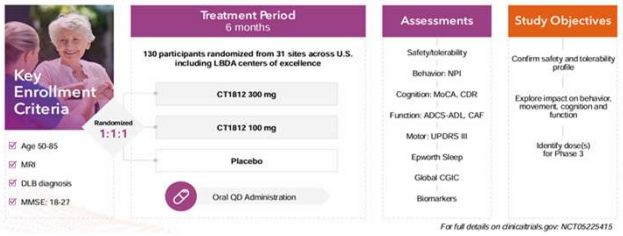
Study Design

SHIMMER Study Designed to Assess Multifactorial Burden

Conducted in Collaboration with LBDA Centers of Excellence, Academic Centers and Industry
Partially funded by NIA (R01AG071643)



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Top-line results

SHIMMER COG1201

The Phase 2 SHIMMER study on CT1812 for dementia with Lewy bodies (DLB)

Cognitive function: There was a 91% reduction in cognitive fluctuations (a hallmark of DLB) compared to placebo.

Behavioral symptoms: Patients treated with CT1812 showed an 86% improvement in neuropsychiatric symptoms, with particularly strong reductions in anxiety and hallucinations.

Functional ability: Participants preserved 52% more of their functional ability compared to the placebo group, as measured by their ability to perform daily living activities.

Motor function: A 62% slowing in the progression of motor decline was observed in the treatment group versus placebo.

Caregiver impact: Caregiver distress caused by behavioral symptoms was also shown to improve in the treatment group.

https://www.neurologylive.com/view/ct1812-meets-primary-end-point-phase-2-shimmer-study-dementia-lewy-bodies

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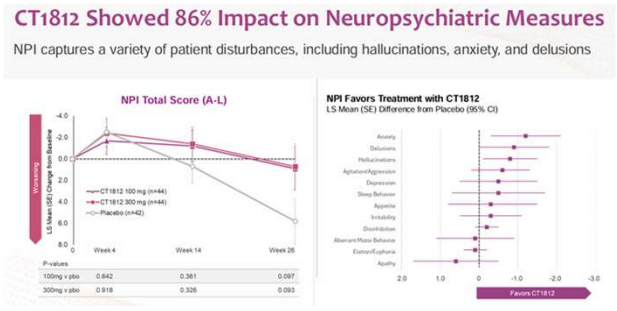

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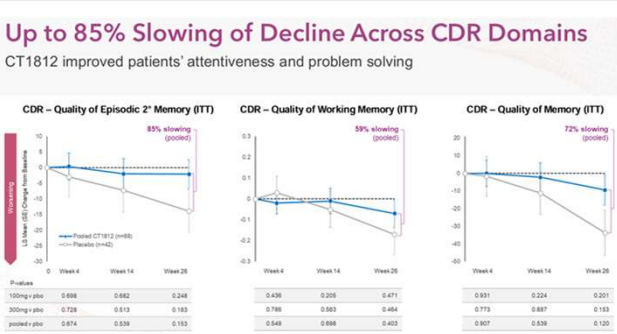

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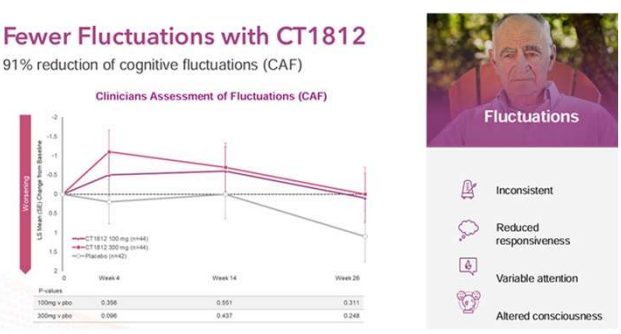

Slides from Dr. Galvin, CTAD 2024: https://ir.cogrx.com/wp-content/uploads/2025/01/2025-ILBDC-Galvin-SHIMMER-Conf-Slides.pdf

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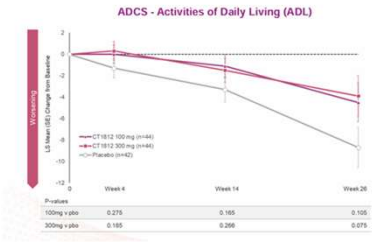
People on CT1812 Maintained ADLs

52% preservation in activities of daily living (ADL) with p=0.05



Slides from Dr. Galvin, CTAD 2024: https://ir.cogrx.com/wp-content/uploads/2025/01/2025-ILBDC-Galvin-SHIMMER-Conf-Slides.pdf

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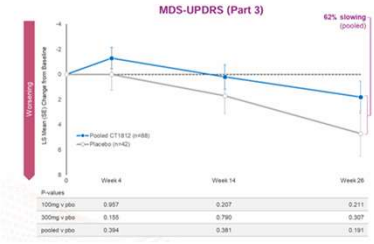
People on CT1812 Maintained Motor Function

62% preservation in measures of movement



Slides from Dr. Galvin, CTAD 2024: https://ir.cogrx.com/wp-content/uploads/2025/01/2025-ILBDC-Galvin-SHIMMER-Conf-Slides.pdf

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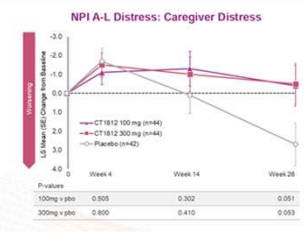
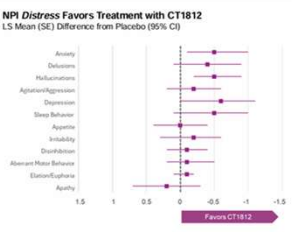
CT1812 Reduced Caregiver Distress

'NPI Distress' measures levels of care partner distress in DLB (p=0.025)





Slides from Dr. Galvin, CTAD 2024: https://ir.cogrx.com/wp-content/uploads/2025/01/2025-ILBDC-Galvin-SHIMMER-Conf-Slides.pdf

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Strong Early Data Supporting CT1812 for DLB

Safety and efficacy to be confirmed in phase 3 trials

- SHIMMER suggests CT1812 can slow progression in DLB
- Evidence across multiple endpoints
- Safe and well tolerated*
- Results support advancement of CT1812 into late-stage trials

*CT1812 has not been approved for any use by the FDA or other health authority; nor have regulators reviewed plans for subsequent clinical trials

Slides from Dr. Galvin, CTAD 2024: https://ir.cogrx.com/wp-content/uploads/2025/01/2025-ILBDC-Galvin-SHIMMER-Conf-Slides.pdf

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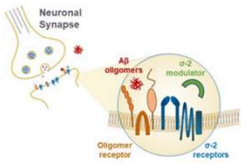
What is CT1812?

CT1812: A Synaptoprotective Approach to Alzheimer's Disease



- CT1812 penetrates the blood brain barrier and binds selectively to the σ-2 receptor
- By modulating σ-2, CT1812 displaces and prevents oligomers from binding to neurons and clears them into CSF
- Prevents synaptotoxicity and facilitates restoration of neuronal function

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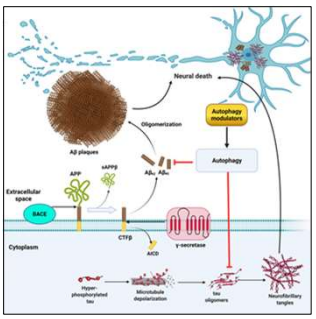
What else does it do

- Autophagy influences dementia by clearing cellular waste, including toxic protein aggregates like amyloid-beta and tau, that are hallmarks of diseases like Alzheimer's
- When autophagy is impaired, these proteins build up, and damaged organelles are not cleared, leading to neuronal dysfunction, inflammation, and disease progression
- Targeting and enhancing autophagy is therefore being explored as a potential therapeutic strategy to slow dementia.



Eshraghi et al., Pharmacology & Therapeutics, Volume 237, 2022, 108171

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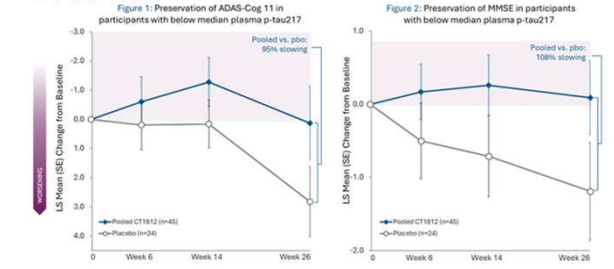
SHINE: Cognitive outcomes in AD with CT1812



https://ir.cogrx.com/press_releases/cognition-therapeutics-announces-results-of-pre-specified-analysis-of-shine-study-data-presented-at-ctad/

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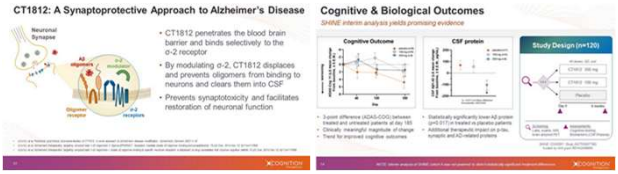
START Currently underway nationally!



- Encourages those that have been on lecanemab for > 6 months to join as well as those that do not want or are ineligible
- Works through a different pathway that may augment response with a combination therapy approach

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Top line results coming out on semaglutide…

- These will be presented at CTAD 2025 in early December

Risk of first–time diagnosis of Alzheimer's disease in patients with type 2 diabetes (comparison between matched semaglutide vs other antidiabetes medications groups)

Size/Group	Exposure group	Comparison group	Exposure Group Cases (overall risk)	Comparison Group Cases (overall risk)	HR (95% CI)
17,087	Semaglutide	Insulin	27 (0.16%)	73 (0.43%)	0.33 (0.21 to 0.51)
17,080	Semaglutide	Metformin	27 (0.16%)	68 (0.40%)	0.38 (0.24 to 0.59)
15,878	Semaglutide	DPP–4i	27 (0.17%)	62 (0.39%)	0.40 (0.26 to 0.63)
15,288	Semaglutide	SGLT2i	26 (0.17%)	40 (0.26%)	0.60 (0.37 to 0.98)
16,503	Semaglutide	SU	27 (0.16%)	80 (0.49%)	0.31 (0.20 to 0.48)
10,847	Semaglutide	TZD	24 (0.22%)	51 (0.47%)	0.43 (0.26 to 0.70)
17,029	Semaglutide	Other GLP–1RAs	27 (0.16%)	44 (0.26%)	0.59 (0.37 to 0.95)

0.10 0.20 0.40 0.70 2.0 3.00 5.00 8.00

Hazard ratio (HR)

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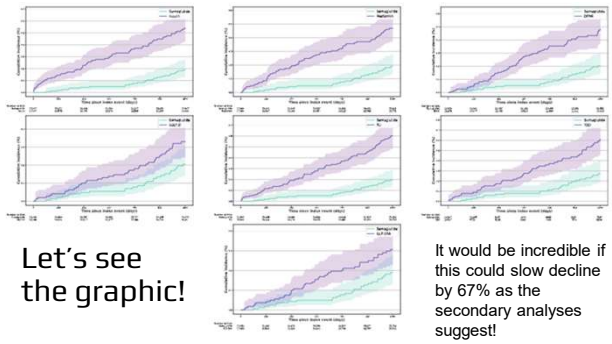

Let's see the graphic!

It would be incredible if this could slow decline by 67% as the secondary analyses suggest!

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Stay tuned…

It's an exciting time for us all!

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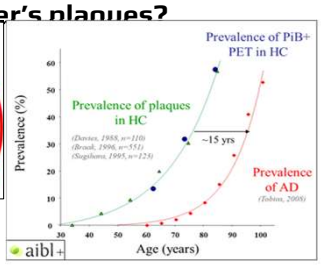
What about opening the use of anti-amyloid therapies to the 1/3 of memory normal persons that are already building up Alzheimer's plaques?



- **Trailblazer 3**
- **AHEAD**

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Trailblazer 3: results out May 2026 (NCT05738486)

- This double-blind, placebo-controlled trial used a plasma phosphorylated tau-217 (p-tau217) assay to detect AD pathology for eligibility and a decentralized design to enhance screening and enrollment
- After nine monthly infusions, clinical assessments continue every 6 months with a time-to-event primary outcome. A sub-study will evaluate longitudinal changes in amyloid and tau positron emission tomography (PET).
- Participants 55–80 years of age were screened (N = 63,124).
- Plasma p-tau217-eligible participants were enrolled (N = 2196), with Clinical Dementia Rating (CDR) scale-Global score (CDR-GS) of 0 (n = 1202) and 0.5 (n = 664).
- Plasma p-tau217 eligibility increased with age, differing across races and ethnicities.

Yaari et al., 2025; 21:e70662. https://doi.org/10.1002/alz.70662

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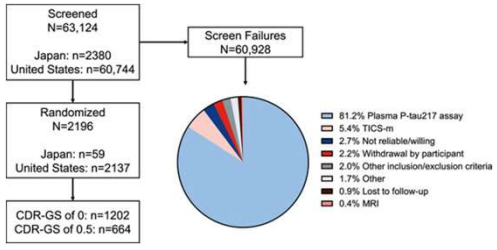
Trailblazer 3 eligibility?



Yaari et al., 2025; 21:e70662. https://doi.org/10.1002/alz.70662

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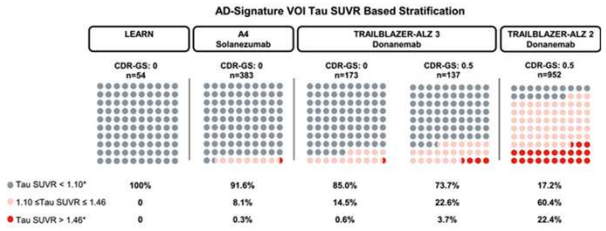
Trailblazer 3 stage of biological disease (tau)



Yaari et al., 2025; 21:e70662. https://doi.org/10.1002/alz.70662

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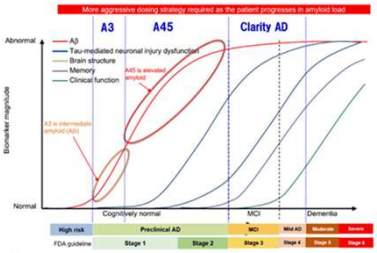
AHEAD: results out in January 2031
(probably sooner in summer/fall 2028)

- Using Leqembi in persons with amyloid that do not yet have cognitive decline
- Confirm or extend Trailblazer 3 results
- Both could be positive or negative, or they could differ?



Rafii et al., Alzheimers Dement. 2023 Apr;19(4):1227-1233.

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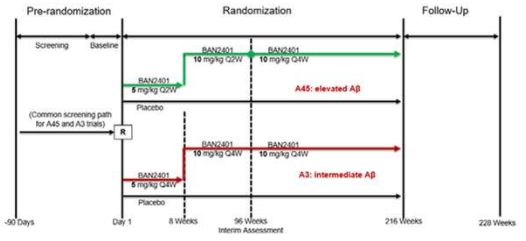
AHEAD study: treatment regim



Rafii et al., Alzheimers Dement. 2023 Apr;19(4):1227-1233.

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Baseline data should be out this December 2025 at CTAD

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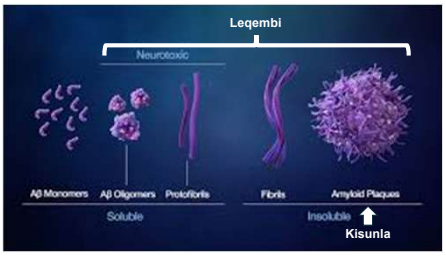
But, will only one work? Will they both work? Will both fail? They do different things…

- Lecanemab targets oligomers, protofibrils, fibrils and plaques
- Donanemab only targets plaques
- Will it make a difference?



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What does the science say?

AHEAD (Lecanemab)	Trailblazer 3 (Donanemab)
• Targets an earlier stage of amyloid accumulation	• More effectively targets a later stage of amyloid plaques
• Removes plaques in 12-18 months	• Removes plaques in 6-12 months
• Needs to be continued for maximal benefit (oligomers?)	• Once the plaques are removed it may longer be effective?
• Small substudy showed no decline in CDR-SOB at 18 mos in low tau persons	• Slowing in 36% of low/moderate and only 29% combined population in CDR-SB

Direct comparisons cannot be made as the studies used different populations that were characterized in different ways

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There is much, much, much more to come!!!

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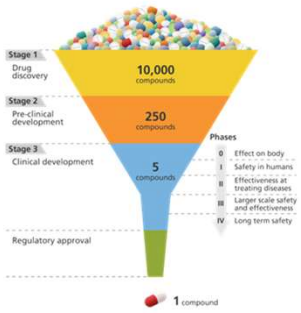
Remember that better medicines & an eventual cure may take thousands of more compounds, tens of thousands of more willing research participants, & hundreds of billions of more funding!



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Let's talk…

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