Oral Blarcamesine Phase IIb/III Trial Confirms Identified Precision Medicine Patient Population – Significant Broad Clinical and Quality of Life Improvements for Early Alzheimer's Disease Patients

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Disclosures

Dr. Sabbagh discloses ownership interest (stock or stock options) in uMethod Health, Athira, Lighthouse Pharmaceuticals, Alzheon; consulting in Roche-Genentech, Eisai, Lilly, Synaptogenix, NeuroTherapia, Signant Health, Novo Nordisk, Prothena, Anavex, Cognito Therapeutics, GSK, AbbVie; and board of directors' membership in EIP Pharma/CervoMed.

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Blarcamesine: Convenience of Blarcamesine in Alzheimer’s Disease (AD)

Blarcamesine:

- ✓**Once-daily, oral** administration
- ✓Novel upstream target that **counters neurodegeneration** (**less brain volume loss**)
- ✓**Favorable comparative safety** profile (no ARIA, i.e., no potentially fatal brain bleeding or brain swelling)
- ✓**No deaths** related to study drug

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Original Article

Blarcamesine for the treatment of Early Alzheimer's Disease: Results from the ANAVEX2-73-AD-004 Phase IIB/III trial

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Oral Blarcamesine Precision Medicine

Alzheimer's Disease Progression

Impairment of autophagy precedes both amyloid beta and tau tangles, and therefore anticipates the neurodegenerative process in Alzheimer's disease[1]

Impaired Autophagy
- *Lysosomal and Synaptic Dysfunction*

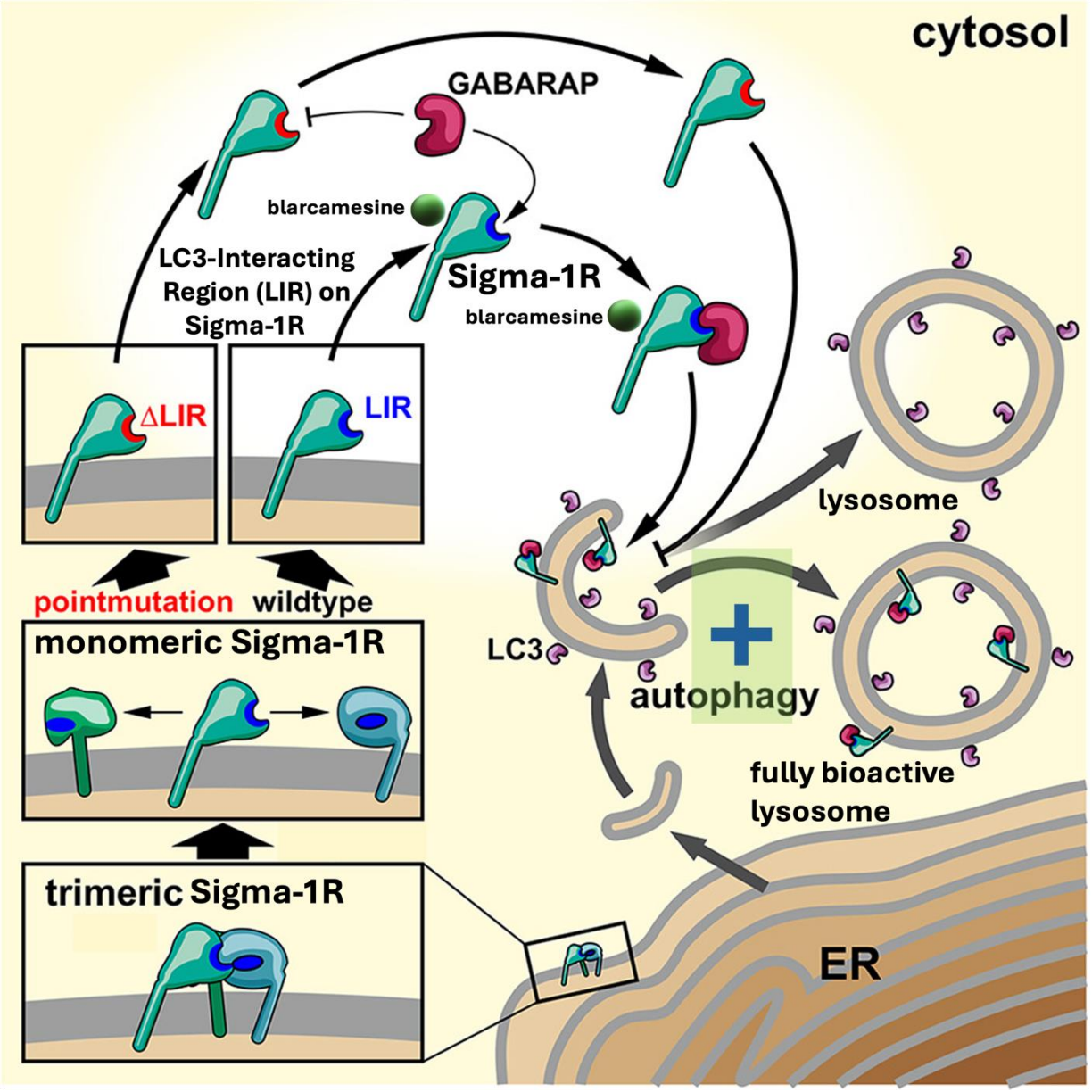
Amyloid Beta Accumulation
- *APP Processing*

Tau Tangles
- *Microtubule Destabilization*

Neurodegeneration
- *Synaptic Loss and Neuronal Death*

[1] Christ MG, Clement AM, Behl C. The Sigma-1 Receptor at the Crossroad of Proteostasis, Neurodegeneration, and Autophagy. Trends Neurosci. 2020 Feb;43(2):79-81; Chen, J., He, HJ., Ye, Q. et al. Defective Autophagy and Mitophagy in Alzheimer's Disease: Mechanisms and Translational Implications. Mol Neurobiol 58, 5289–5302 (2021).

Blarcamesine – MoA: Enhanced-Restored Autophagy



GABARAP: key autophagy protein

LC3: key autophagy protein

blarcamesine

LC3: microtubule-associated protein 1 light chain 3

LIR: LC3-Interacting Region

ΔLIR: pointmutation of LIR

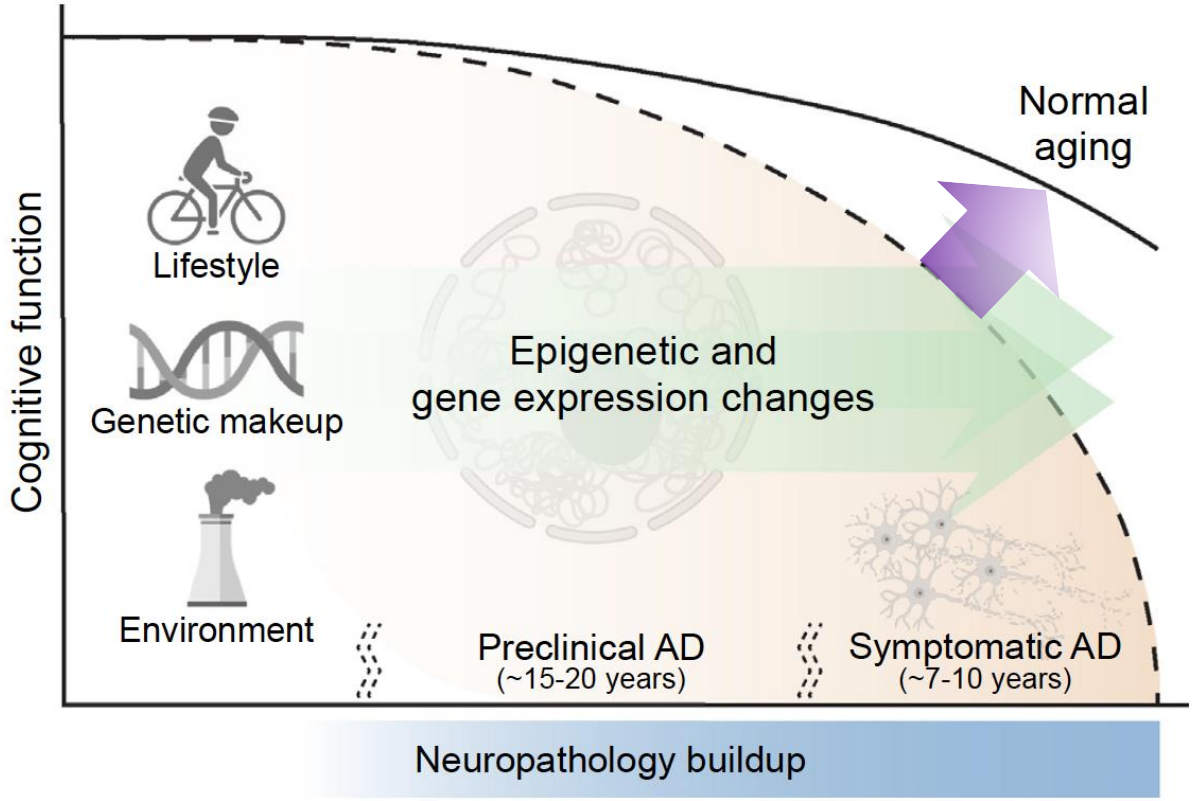
ER: Endoplasmic Reticulum

+: Switch-on of autophagy with blarcamesine activated Sigma-1R (SIGMAR1)

RESTORED – ENHANCED AUTOPHAGY

Source: Baeken, MW et al. "Conserved LIR-specific interaction of Sigma-1 receptor and GABARAP." iScience vol. 28,9 113287. 5 Aug. 2025.

New Precision Medicine Paradigm: Blarcamesine's Potential Ability to Approximate Expected Course of Cognitive Decline in Healthy Aging Adults



Restoring autophagy via SIGMAR1 activation

Re-normalization of:

- ✅ neural function
- ✅ neuronal survival

Highly Heterogeneous and Complex Alzheimer's Pathology Requires Precision Medicine Benefiting up to ~70% of the AD Population

Gouveia Roque C, Phatnani H, Hengst U. The broken Alzheimer's disease genome. *Cell Genom.* 2024;4(5):100555.

New Precision Medicine Paradigm: Blarcamesine's Potential Ability to Match Barely Detectable Prodromal AD Decline

	Baseline	
	ADAS-Cog13, mean [SD]	CDR-SB, mean [SD]
Blarcamesine ABCLEAR3 population*	28.4 [9.10]	4.02 [1.853]
Prodromal population[1]	23.22 [6.79]	2.11 [0.97]

	Change from Baseline	
	ADAS-Cog13	CDR-SB
Blarcamesine ABCLEAR3 population*, 48 weeks	0.853	0.465
Prodromal population, 52 weeks[1]	1.26	0.56

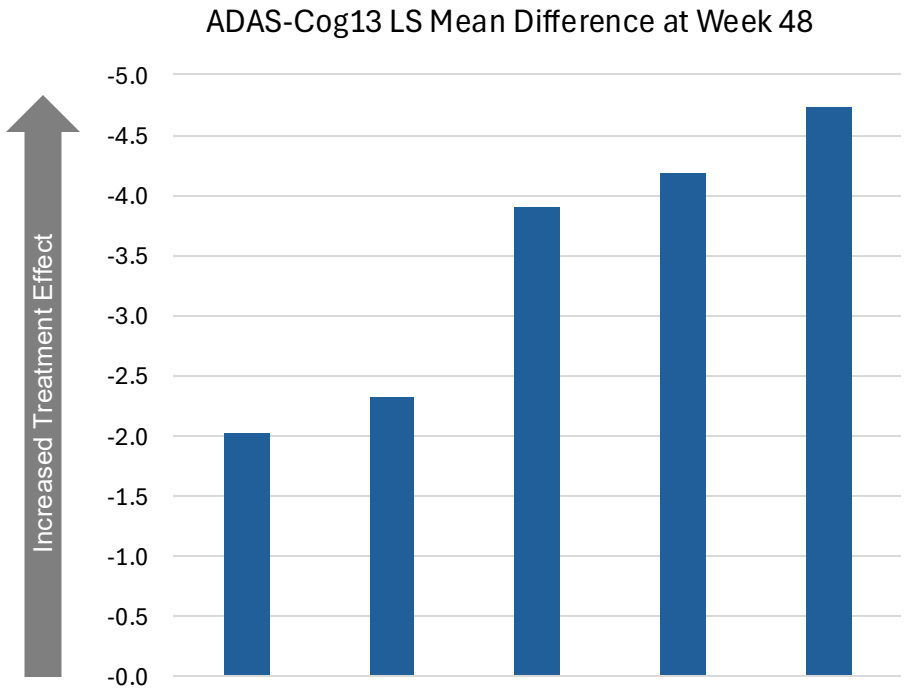
Blarcamesine data are similar to referenced barely detectable prodromal AD decline, in spite of the more advanced stage of AD impairment at baseline of the blarcamesine population

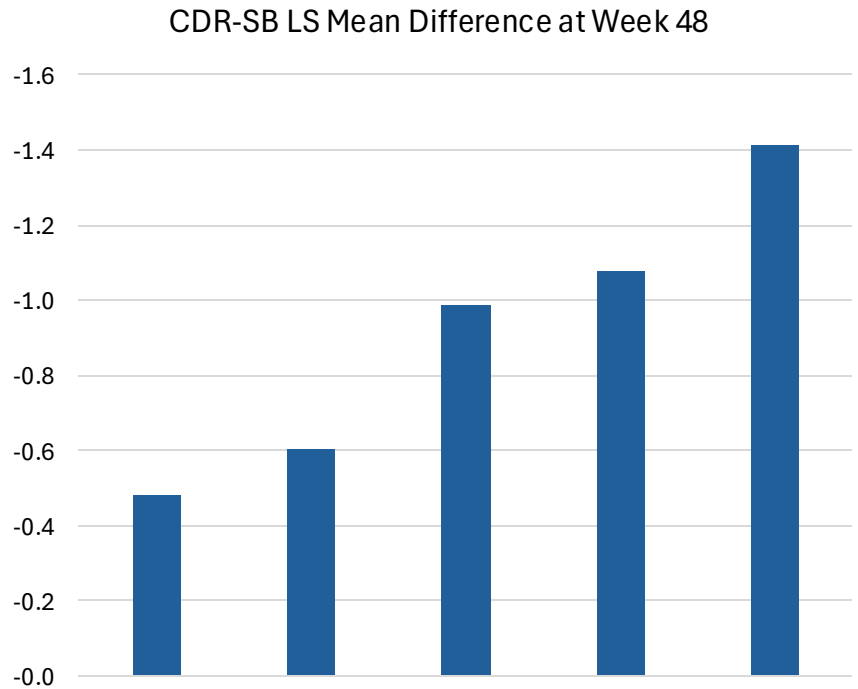
Cognitive outcomes observed in the oral blarcamesine 30 mg Precision Medicine cohort move toward normal aging profiles across validated clinical scales, reaching up to **84.7% clinical benefit** compared to placebo supporting its relevance in early-stage Alzheimer's care

Blarcamesine: Oral convenient scalable potential treatment

* ABCLEAR3 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variants non-carrier population (SIGMAR1 wild type [WT]/COL24A1 wild type [WT]).
1. McDougall, F et al. "Psychometric Properties of the Clinical Dementia Rating- Sum of Boxes and Other Cognitive and Functional Outcomes in a Prodromal Alzheimer's Disease Population." JPAD. vol. 8,2 (2021): 151-160.

Precision Medicine: Unprecedented Blarcamesine Effect Size Over Placebo for Cognition and Cognition-Function





	Blarcamesine Total ITT Population	Blarcamesine Total ABCLEAR1 Population	Blarcamesine Total ABCLEAR2 Population	Blarcamesine Total ABCLEAR3 Population	Blarcamesine 30mg ABCLEAR3 Population
Difference from Placebo	-2.027	-2.317	-3.901	-4.179	-4.739
P Value	0.0079	0.0149	<0.0001	0.0005	0.0004
% Difference	36.3%	49.8%	59.8%	75.9%	84.7%

	Blarcamesine Total ITT Population	Blarcamesine Total ABCLEAR1 Population	Blarcamesine Total ABCLEAR2 Population	Blarcamesine Total ABCLEAR3 Population	Blarcamesine 30mg ABCLEAR3 Population
Difference from Placebo	-0.483	-0.601	-0.986	-1.076	-1.414
P Value	0.0104	0.012	<0.0001	0.0002	<0.0001
% Difference	27.6%	33.7%	47.6%	57.0%	75.2%

ITT = Intent-to-Treat population (100% population)
ABCLEAR1 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variant non-carrier population (SIGMAR1 wild type [WT]) (~70% population)
ABCLEAR2 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variant non-carrier population (COL24A1 wild type [WT]) (~71% population)
ABCLEAR3 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variants non-carrier population (SIGMAR1 wild type [WT]/COL24A1 wild type [WT]) (~50% population)

Importance of Self-assessed Quality Of Life (QoL-AD) for Individuals with Alzheimer's Disease

QoL-AD: What it measures:

Physical health: Overall physical well-being.

Energy: Level of energy and vitality.

Mood: Emotional state and feelings.

Living situation: Satisfaction with where the person lives.

Memory: Cognitive function and memory abilities.

Family: Quality of relationships with family members.

Marriage/Significant other: Satisfaction with the relationship with a partner.

Friends: Quality of social relationships with friends.

Self as a whole: Overall self-perception and self-esteem.

Ability to do chores: Capacity to perform household tasks.

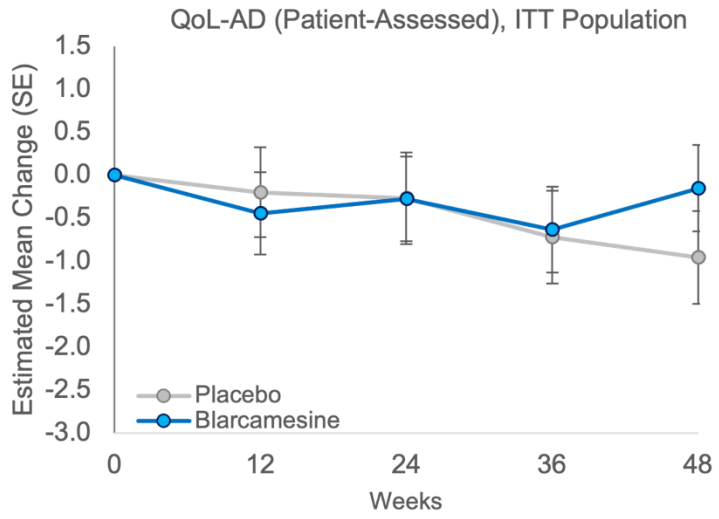
Ability to do things for fun: Enjoyment of leisure activities.

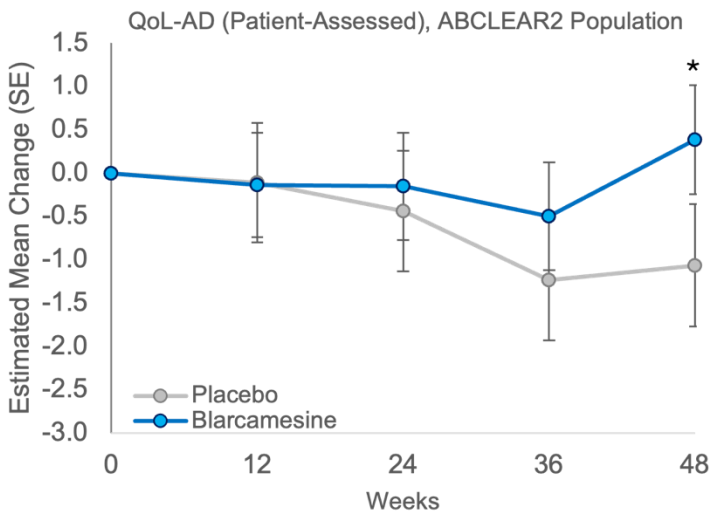
Money: Financial well-being.

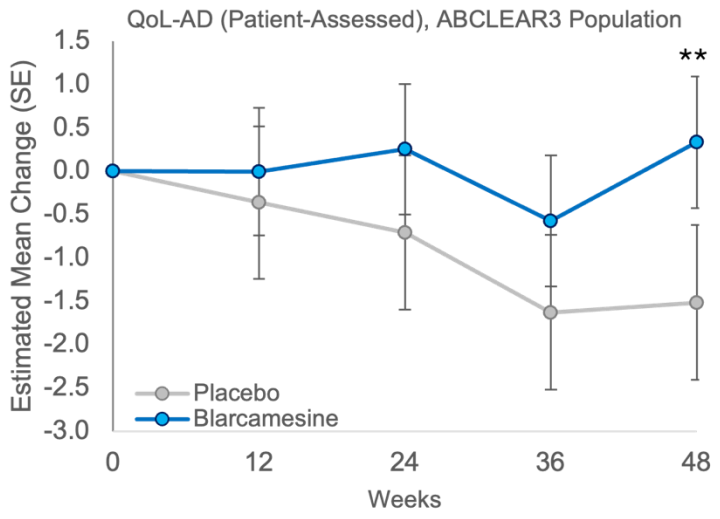
Life as a whole: Overall satisfaction with life.

Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC5312555/

Significant Improvement in Self-assessed Quality Of Life (QoL-AD) Indicating Reversal of Negative Trajectory For Alzheimer's Disease







Blarcamesine (n)	298	239	206	191	194	(n)	228	184	155	149	150	(n)	156	129	113	109	108
Placebo (n)	164	146	129	123	123	(n)	108	93	87	84	82	(n)	66	62	58	57	56

ITT = Intent-to-Treat population (100% population)
ABCLEAR1 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variant non-carrier population (SIGMAR1 wild type [WT]) (~70% population)
ABCLEAR2 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variant non-carrier population (COL24A1 wild type [WT]) (~71% population)
ABCLEAR3 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variants non-carrier population (SIGMAR1 wild type [WT]/COL24A1 wild type [WT]) (~50% population)

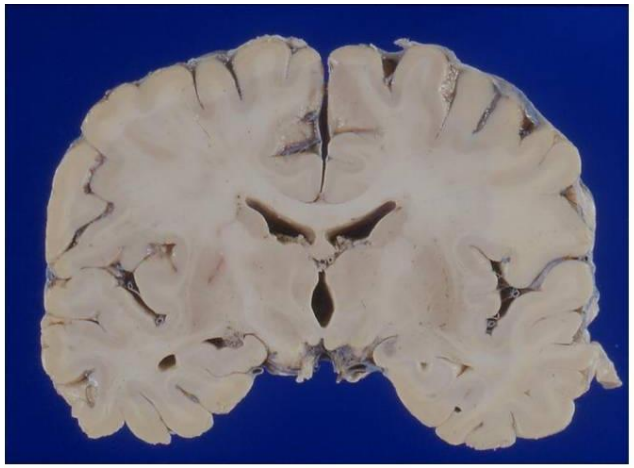
Clinical efficacy endpoints were analyzed using mixed model for repeated measures (MMRM) estimates for the least-squares mean change from baseline at 12, 24, 36, and 48 weeks, with error bars representing standard error (SE). The number of trial participants with analyzed results at each visit is noted beneath the x axis. Asterisks indicate statistically significant differences, where *: $p < 0.05$; **: $p < 0.01$.

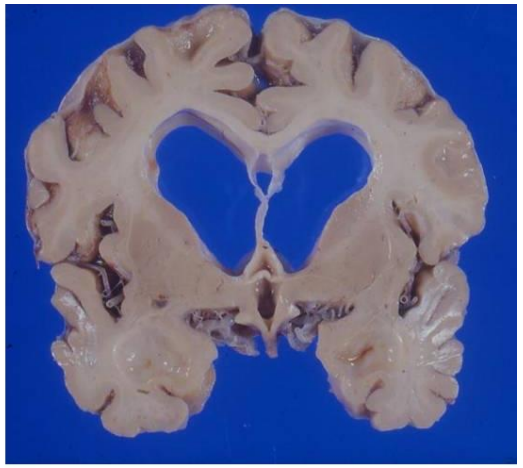
Blarcamesine: Efficacy Confirmed with Surrogate Biomarker Data

Reduced Atrophy of the Brain in Blarcamesine-Treated Patients

Brain volume loss (atrophy) in Alzheimer's disease[1]

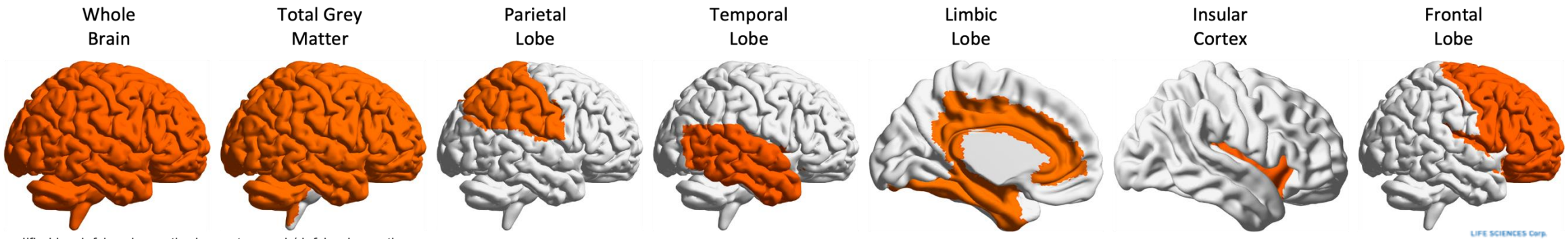
Significantly slowed atrophy in brain regions after 48 weeks of treatment compared to placebo[2]





NORMAL **AD**

$p < 0.05$ $p < 0.0001$

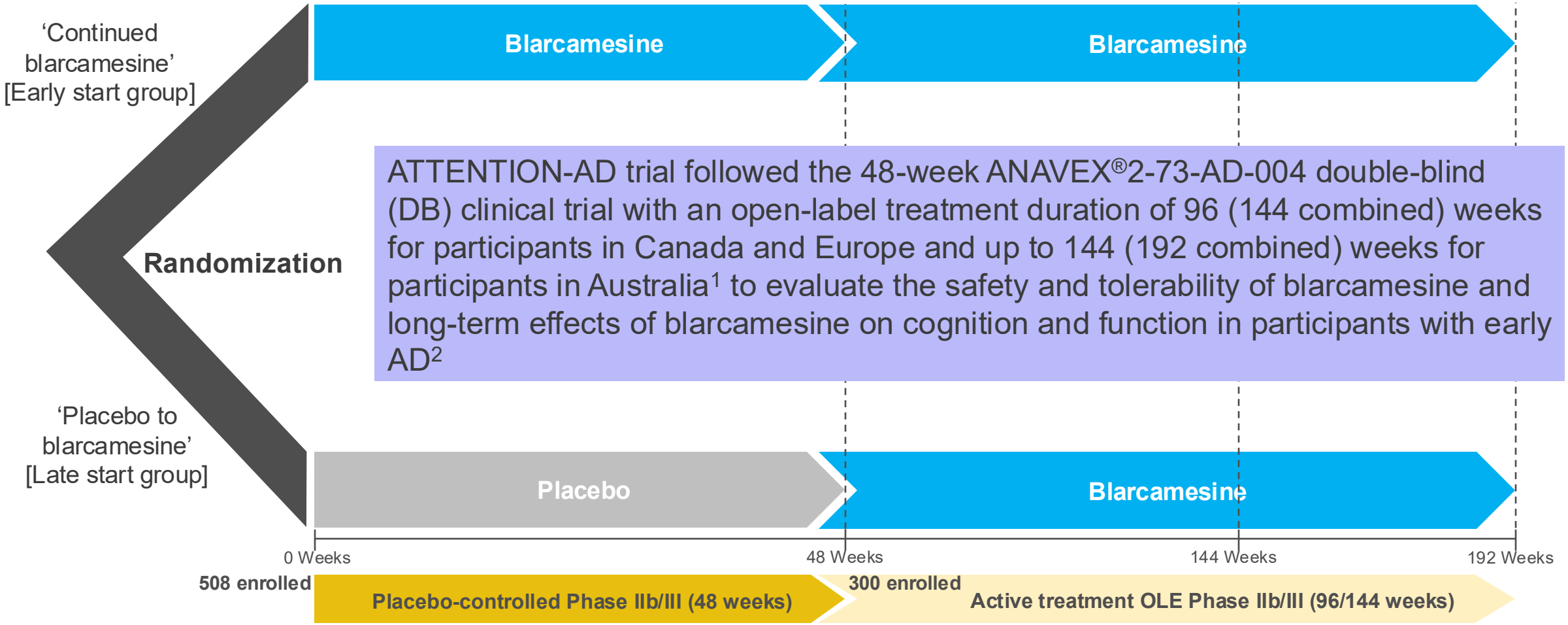


1. Exemplified by defying dementia. lancaster.ac.uk/defyingdementia
2. Data on file. Anavex Life Sciences Corp. https://www.anavex.com/post/anavex-sphase2b-3trialofblarcamesine-anavex-2-73-inpatientswithalzheimer-sdisease

Blarcamesine: Earlier Treatment Initiation with Continued Long-term Beneficial Therapeutic Effect

ATTENTION-AD AD-004 OLE Phase IIb/III Early Alzheimer's Disease

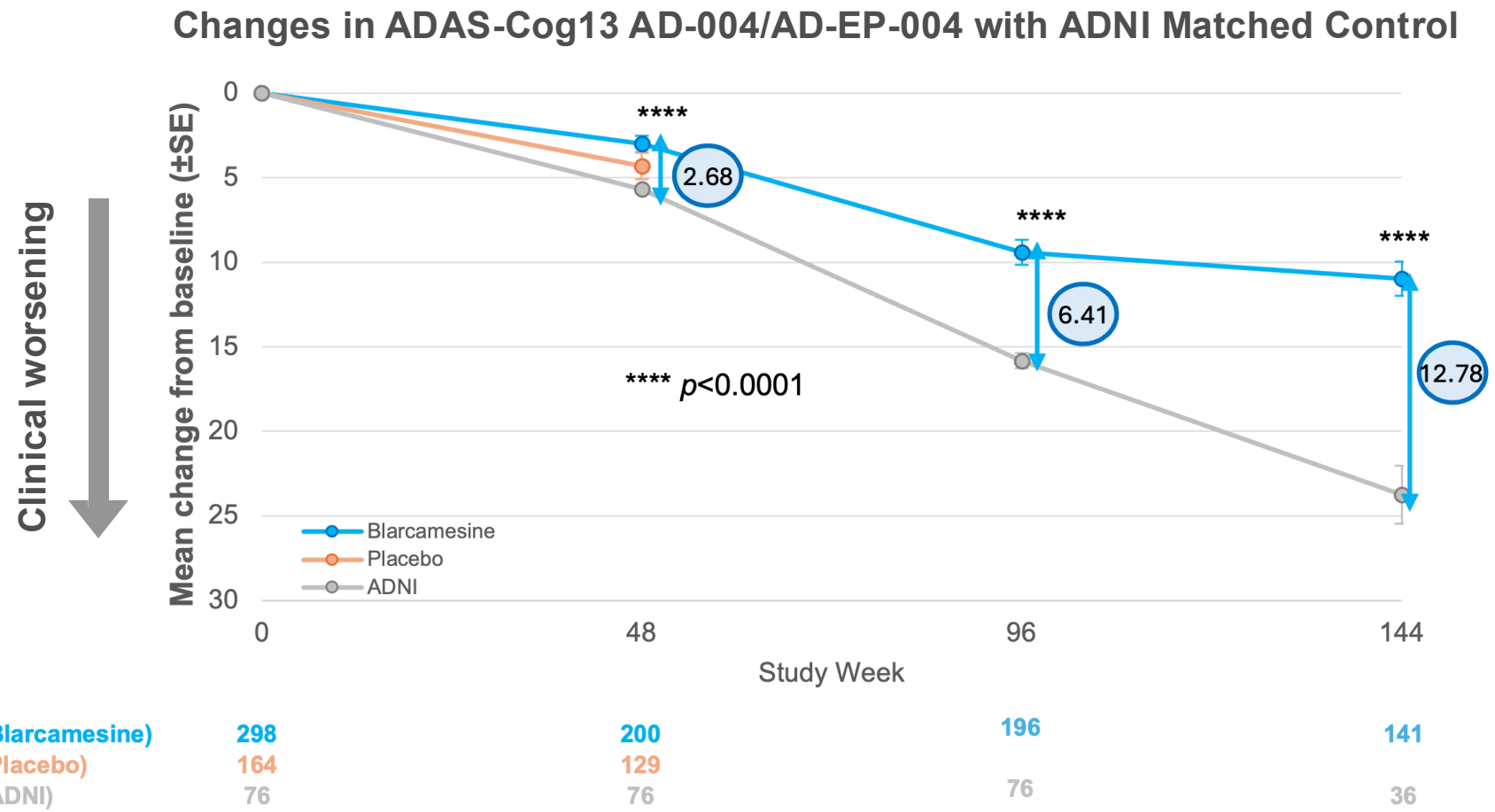
Global, multicenter, randomized, Open-Label-Extension (OLE), 96/144-week trial evaluating Blarcamesine (ANAVEX®2-73) once-daily oral capsules, following placebo-controlled 48-week trial[1]



1. The preceding double-blind study (ANAVEX®2-73-AD-004) had started in Australia before the other regions (Europe and North America). This did not allow time for the other regions to also participate in the additional OLE extension beyond the initial 96 Weeks OLE period, which was extended to 144 Weeks upon investigators request in Australia.

2. The scheduled visits were [OLE Week 0 = Combined Week 48], [OLE Week 48 = Combined Week 96], [OLE Week 96 = Combined Week 144] and [OLE Week 144 = Combined Week 192]; Combined = OLE (open-label-extension) + DB (double-blind) studies.

Significant Beneficial Therapeutic Effect of Blarcamesine Compared to Decline Observed in the ADNI Control Group



77.4 Weeks (17.8 Months = 1.5 years) time saved with oral blarcamesine allowing for longer independence

Mean +/- SE of Change from Baseline ADAS-Cog13 Total Score DB/OLE ITT Population and Alzheimer's Disease Neuroimaging Initiative (ADNI) Matched Control

Safety Results

- Long-term (192 weeks, approx. 4 years) treatment with oral blarcamesine appeared to be safe
- Most TEAEs were mild or moderate (Grade 1 or 2), and predominantly linked to the initial titration phase—could be managed with adjusted titration schedules
- No signs of brain swelling, hemorrhage or ARIA
- There were no deaths related to the study drug
- No adverse effects on liver enzymes, vital signs, ECGs, or physical/neurological examination findings
- Manageability of the most commonly reported drug-related treatment emergent adverse event (TEAE) dizziness, which was generally transient in duration (approx. 7-11 days): Noticeably reduced during the maintenance phase vs. titration phase, indicating these events are manageable and suggesting improved tolerability over time:
  - —Markedly lower frequency of dizziness from previously 25.2% in the ANAVEX®2-73-AD-004 trial (2-3 weeks titration) to 9.6% in the ATTENTION-AD trial (10 weeks titration)—demonstrating the manageable nature of the most frequent TEAE (dizziness)

Extending the Dignity of Aging

Impact on Daily Life:

- Promising clinical results (numerically superior to injectable infusion mAbs)
- Improved self-assessed Quality of Life (QOL-AD)
- Clinical meaningful treatment effect, also on predesignated biomarkers

Extended Time Saved:

- Allowing for longer independence of loved ones

Convenient Alzheimer's treatment - safer and better outcome

Conclusions

Blarcamesine once orally daily restores autophagy through SIGMAR1 activation -> corroborated MoA by pre-specified SIGMAR1 gene analysis: Greater significant clinical benefit, - ADAS-Cog13 at 48 Weeks by 49.8% - experienced by ~70% of general population (Macfarlane, S. et al. JPAD 2025. *Blarcamesine for the treatment of Early Alzheimer's Disease: Results from the ANAVEX2-73-AD-004 Phase IIb/III trial*).[1]

In the Phase IIb/III clinical trial, blarcamesine also demonstrated:

- ✓**Good comparative safety** profile (no ARIA)
- ✓**Improvements** in ADAS-Cog13 and CDR-SB efficacy endpoints
- ✓**Clinical meaningful** treatment effect[2], supported by predesignated biomarkers within the A/T/N spectrum; further enhanced responses in ABCLEAR2 and ABCLEAR3 populations[3]
- ✓**Long-term (~4 years)** promising clinical results: Earlier oral blarcamesine treatment initiation with continued long-term beneficial therapeutic effect - ADAS-Cog13 difference: -3.83 (P = 0.0165), ADCS-ADL difference: +4.30 (P = 0.0206) and up to **17.8 months saved** with ADAS-Cog13 difference: **-12.78 (P < 0.0001)** compared to ADNI matched control

1. Macfarlane, S. et al. Blarcamesine for the treatment of Early Alzheimer's Disease. J Prev Alzheimers Dis. 2025;12(1):100016.
2. Muir RT, Hill MD, Black SE, Smith EE. Minimal clinically important difference in Alzheimer's disease: Rapid review. Alzheimers Dement. 2024;20(5):3352-3363.
3. medRxiv 2025.09.27.25336656; doi: https://doi.org/10.1101/2025.09.27.25336656

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