# Phase IIb/III ATTENTION-AD Study: Over Three Years of Continuous Treatment with Oral Blarcamesine Continues to Significantly Benefit Early Alzheimer's Disease Patients

AD/PD2025 April 5th, 2025

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# Disclosures

Dr. Grimmer received receiving consulting fees from Acumen, Advantage Ther., Alector, Anavex, Biogen, BMS; Cogthera, Eisai, Eli Lilly, Functional Neuromod., Grifols, Janssen, Neurimmune, Noselab, Novo Nordisk, Roche Diagnostics, and Roche Pharma; lecture fees from Cogthera, Eisai, Eli Lilly, FEO, Grifols, Pfizer, Roche Pharma, Schwabe, and Synlab; and has received grants to his institution from Biogen and Eisai.

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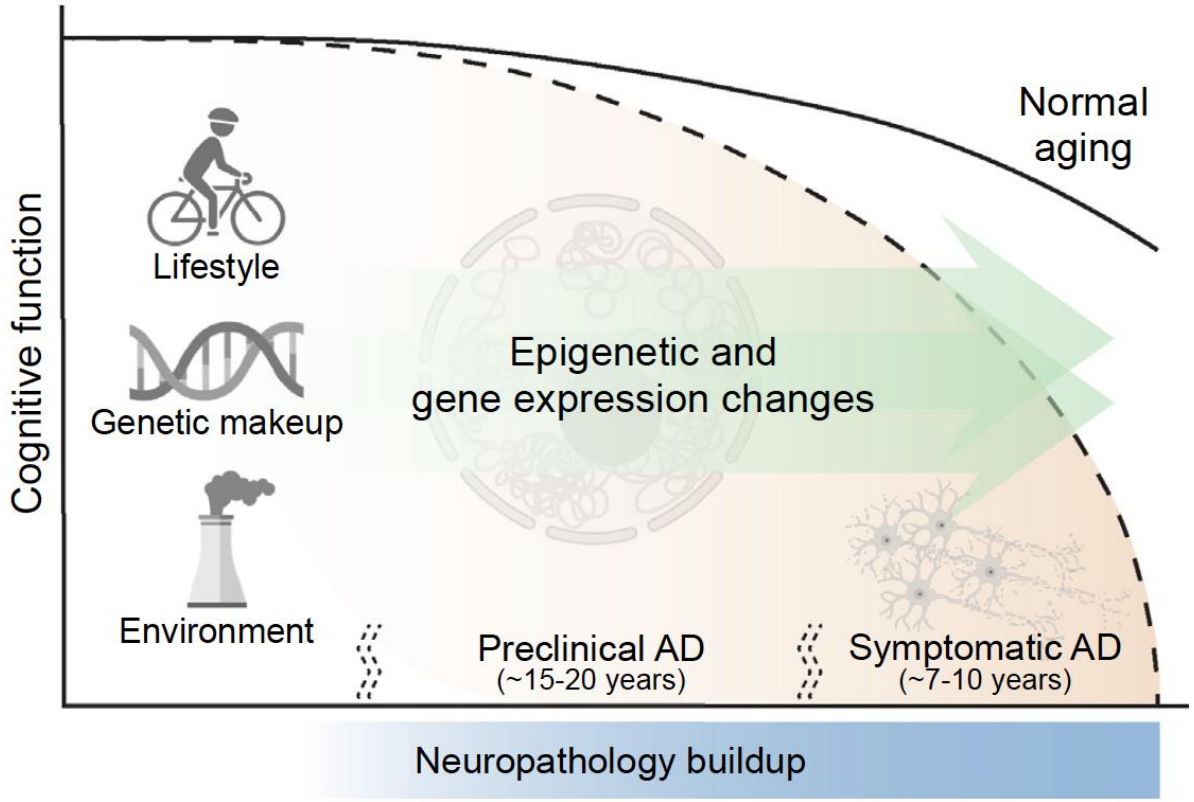
This presentation discusses investigational uses of an agent in development and is not intended to convey conclusions about efficacy or safety. There is no guarantee that any investigational uses of such product will successfully complete clinical development or gain health authority approval.

# Blarcamesine: New Mechanism of Action in Alzheimer’s Disease (AD)

# AD Pathology Is Highly Heterogeneous and Complex




… influenced by genotype, environment, cognitive reserve, and a range of demographic factors

… multiple biologic pathways contribute to AD presentation, including defective amyloid-beta (Aβ) and tau-clearing mechanisms

**Potential solution: activation of an upstream, endogenous pathway for clearing protein aggregates**



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

# Autophagy: An Upstream Compensatory Therapeutic Intervention in AD

**Blarcamesine (Oral drug)**

**SIGMAR1 activation** → **Autophagy** →

**Upstream neuroprotection (remove, repair, regenerate, resilience)**

***Aging*** ⊣ **Survival of brain cells** ⊢ **Neurotoxicity (Aβ, tau)**

**Monoclonal antibodies (IV infusion)** → **Microglial phagocytosis** → **Downstream removal of β-amyloid plaques** → **Neurotoxicity (Aβ, tau)**


Christ, MG, et al. Sigma-1 receptor activation induces autophagy and increases proteostasis capacity in vitro and in vivo. *Cells*. 2019;8(3):211.
Yang H, et al. SIGMAR1/sigma-1 receptor ablation impairs autophagosome clearance. *Autophagy*. 2019;15(9):1539-1557.
Lee JH, et al. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. *Nature Neuroscience*. 2022;25(6):688-701.

# SIGMAR1 Activation has been Shown to Modulate Multiple Broad Aspects of Neurodegenerative Chronic Processes

## SIGMAR1 agonists have been shown to restore neuronal functions in neurodegenerative processes

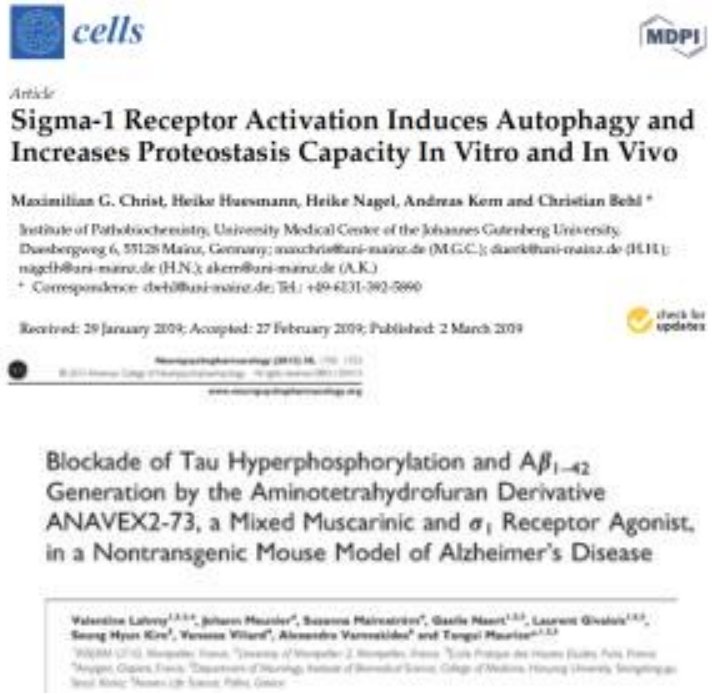

Journal of Pharmacological Sciences

Critical review

Role of sigma-1 receptors in neurodegenerative diseases

Linda Nguyen, Brandon P. Lucke-Wold, Shona A. Mookerjee, John Z. Cavendish, Matthew J. Robson, Anna L. Scandinaro, Rae R. Matsumoto

## Blarcamesine enhances autophagy and alleviates Aβ and Tau pathology in neurodegenerative disease models


cells

MDPI

Article

Sigma-1 Receptor Activation Induces Autophagy and Increases Proteostasis Capacity In Vitro and In Vivo

Maximilian G. Christ, Heike Hussmann, Heike Nagel, Andreas Kern and Christian Behl

Received: 29 January 2019; Accepted: 27 February 2019; Published: 2 March 2019

Blockade of Tau Hyperphosphorylation and $A\beta_{1-42}$ Generation by the Aminotetrahydrofuran Derivative ANAVEX2-73, a Mixed Muscarinic and $\sigma_1$ Receptor Agonist, in a Nontransgenic Mouse Model of Alzheimer's Disease

## SIGMAR1 agonists have a neuroprotective effect in neurodegenerative disease models


REVIEW ARTICLE

Front. Neurosci. | doi: 10.3389/fnins.2019.00862

Neuronal Sigma-1 receptors: signaling functions and protective roles in neurodegenerative diseases

Daniel A. Ryskamp, Svetlana Korban, Vladimir Zhemkov, Nina Kraskovskaya and Ilya Bezprozvanny

Neuroprotective effects of sigma-1 receptor agonists against beta-amyloid-induced toxicity

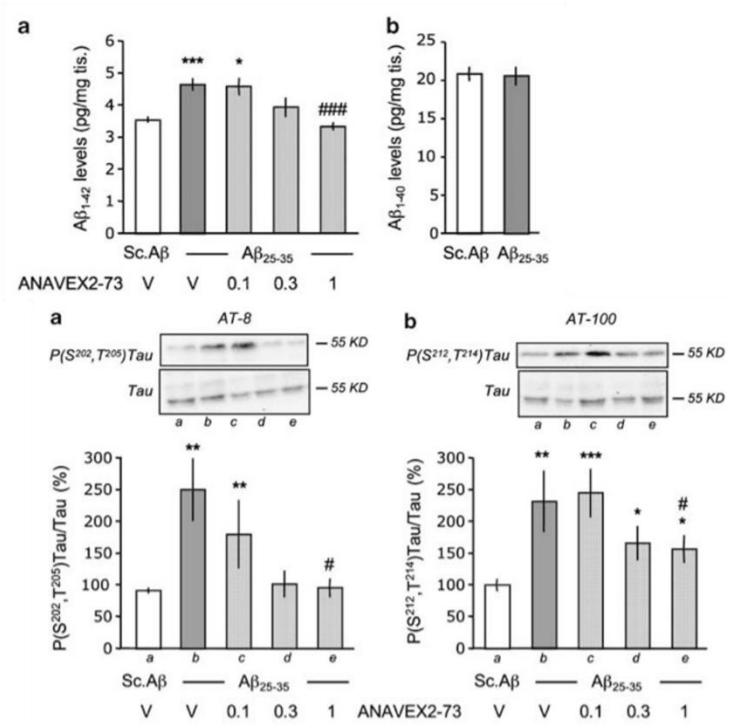
Agostino Marrazzo, Filippo Caraci, Elisa Trovato Salinaro, Tsung-Ping Su, Agata Copani and Giuseppe Ronsisvalle

# Blarcamesine: Clinical Data for the Treatment of Alzheimer’s Disease and Dementia

# Blarcamesine PoC: Previous Preclinical and Clinical ANAVEX2-73-002/3 Phase 2a Studies in AD

Blarcamesine inhibits Aβ1-42 and tau phosphorylation generation and demonstrated exploratory interim proof-of-concept effect on cognition and function over 148 weeks

- Treatment with blarcamesine (ANAVEX®2-73) inhibits amyloid peptide-induced generation of Aβ1-42 (but not Aβ1-40).
- Tau hyperphosphorylation (S202, T205 and S212, T214) is also inhibited in a dose-dependent manner.

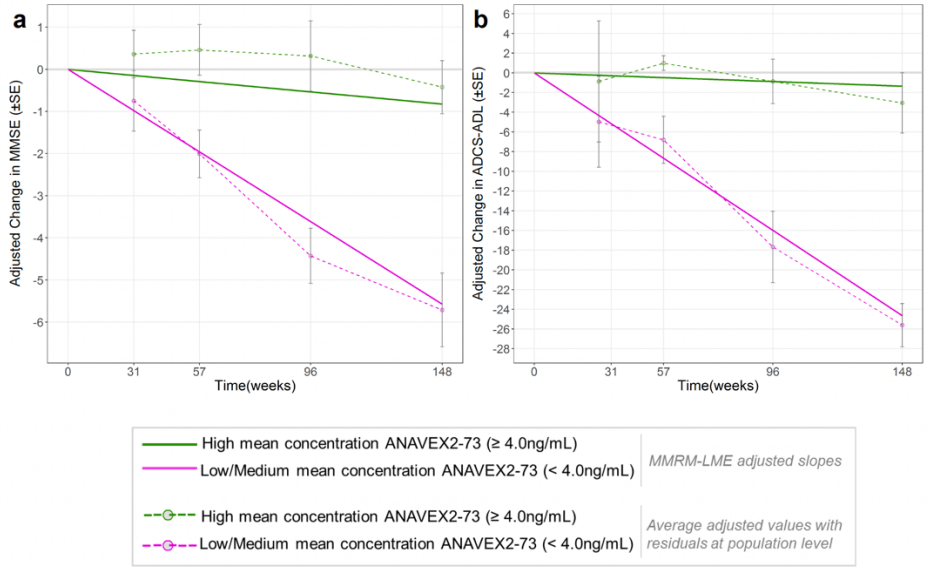



DOI: 10.1002/trc2.12013
RESEARCH ARTICLE
Translational Research & Clinical Interventions

**A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer's disease therapy: Analysis of the blarcamesine (ANAVEX2-73) Phase 2a clinical study**

Harald Hampel[1] | Coralie Williams[2] | Adrien Etcheto[2] | Federico Goodsaid[3] | Frédéric Parmentier[2] | Jean Sallantin[4] | Walter E. Kaufmann[5,6] | Christopher U. Missling[5] | Mohammad Afshar[2]

Linear mixed effect (LME) models of change MMSE and ADCS-ADL over 148 weeks




**Supportive efficacy and safety clinical data**

Lahmy V, et al. *Neuropsychopharmacology*, 2013 Aug;38(9):1706-23.
Hampel H, et al. *Alzheimer's Dement (N Y)*. 2020;6(1):e12013.
PoC, proof of concept; MMSE, Mini-Mental State Examination; ADCS-ADL, Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory.

# Blarcamesine Advantage:

- ✓Oral administration
- ✓Novel upstream target that counters neurodegeneration
- ✓Good 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

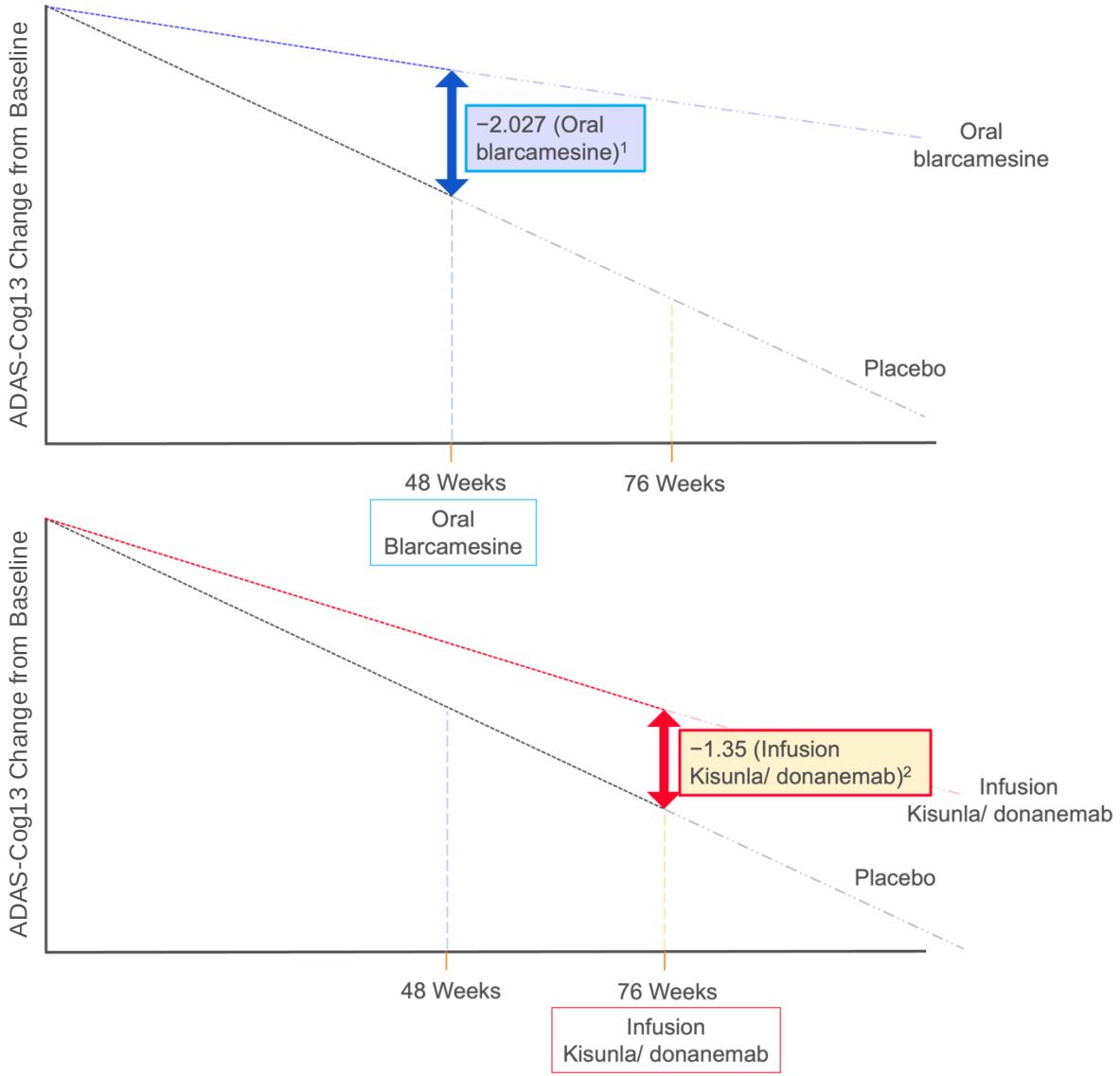
Stephen Macfarlane[a], Timo Grimmer[b], Ken Teo[a], Terence J O'Brien[c], Michael Woodward[d], Jennifer Grunfeld[e], Alastair Mander[f], Amy Brodtmann[g], Bruce J. Brew[h], Philip Morris[i], Cathy Short[j], Susan Kurrle[k], Rosalyn Lai[l], Sneha Bharadwaj[m], Peter Drysdale[n], Jonathan Sturm[o], Simon J.G. Lewis[p], David Barton[q], Chris Kalafatis[r], Saif Sharif[s], Richard Perry[t], Nicholas Mannering[u], J.Emer MacSweeney[v], Stephen Pearson[w], Craig Evans[x], Vivek Krishna[y], Alex Thompson[z], Malathy Munisamy[aa], Neel Bhatt[bb], Aliya Asher[cc], Sandra Connell[dd], Jennifer Lynch[ee], Sterre Malou Rutgers[ff], Paul LJ Dautzenberg[gg], Niels Prins[hh], Patrick Oschmann[ii], Lutz Frölich[jj], Pawel Tacik[kk], Oliver Peters[ll], Jens Wiltfang[mm], Alexandre Henri-Bhargava[nn], Eric Smith[oo], Stephen Pasternak[pp], Andrew Frank[qq], Howard Chertkow[rr], Jennifer Ingram[ss], Ging-Yuek Robin Hsiung[tt], Rodney Brittain[uu], Carmela Tartaglia[vv], Sharon Cohen[ww], Luca M Villa[xx], Elizabeth Gordon[xx], Thomas Jubault[yy], Nicolas Guizard[yy], Amanda Tucker[zz], Walter E Kaufmann[zz], Kun Jin[zz], William R Chezem[zz], Christopher U Missling[zz], Marwan N Sabbagh[ab,*]

# ANAVEX®2-73-AD-004 Program
# Phase IIb/III Trial in Early Alzheimer's Disease with Comparisons

# Numerical Superiority Oral Blarcamesine vs. Infusion Kisunla/ Donanemab

ADAS-Cog13 Efficacy

Numerical Comparison




Schematic representation.

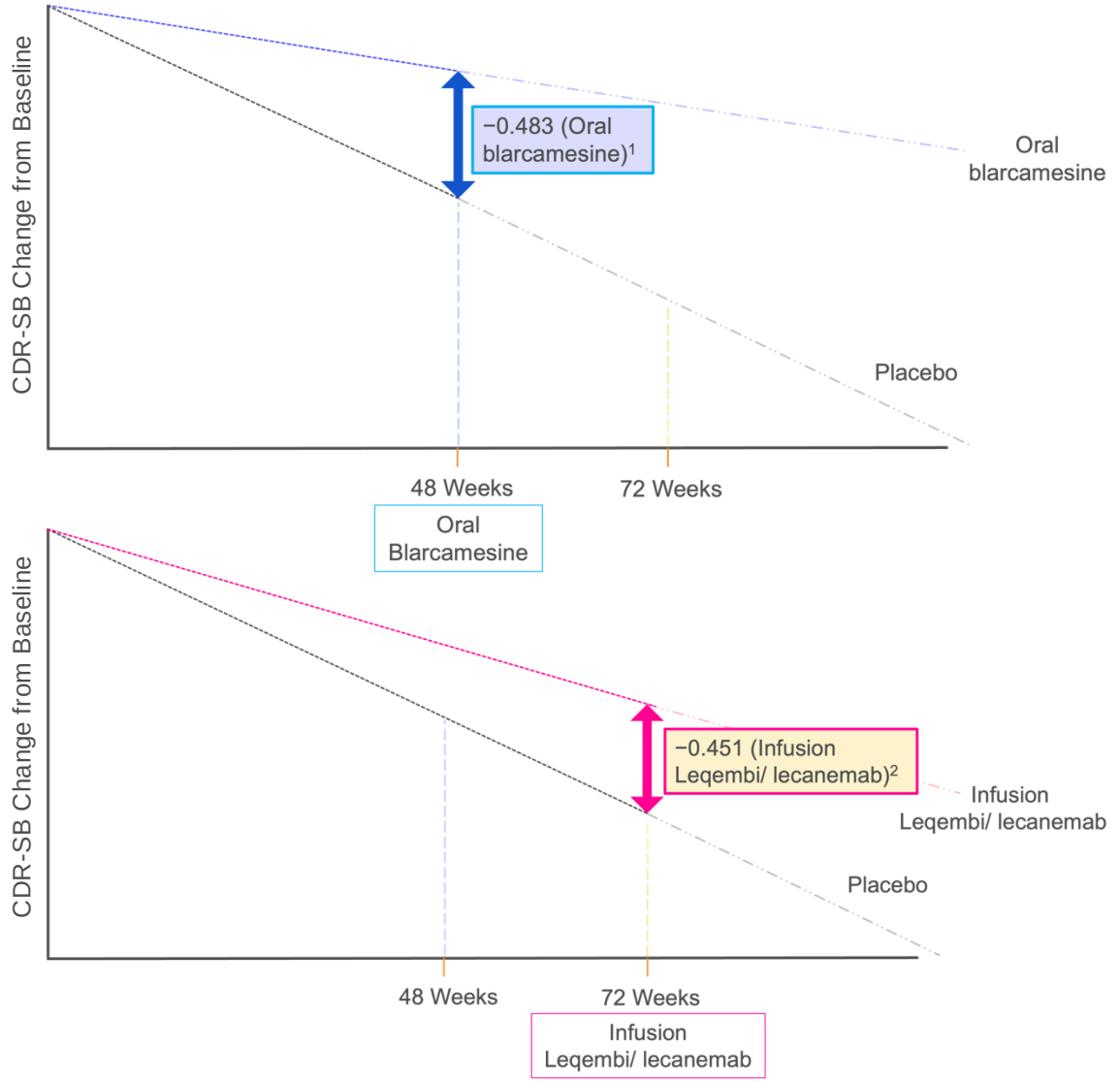
[1] Macfarlane, S. et al. Blarcamesine for the treatment of Early Alzheimer's Disease. J Prev Alzheimers Dis. 2025;12(1):100016

[2] Sims JR et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023; 330(6): 512–27

# Numerical Superiority Oral Blarcamesine vs. Infusion Leqembi/ Lecanemab

CDR-SB Efficacy

Numerical Comparison




Schematic representation.

[1] Macfarlane, S. et al. Blarcamesine for the treatment of Early Alzheimer's Disease. J Prev Alzheimers Dis. 2025;12(1):100016
[2] van Dyck CH et al. Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine. 2023; 388(1): 9–21

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

# ATTENTION-AD ANAVEX®2-73-AD-EP-004 Phase IIb/III Alzheimer's Disease Trial

Global, multicenter, OLE trial (combined 192 Weeks) following randomized, double-blind, placebo-controlled, parallel group, 48-week trial evaluating oral once daily Blarcamesine once daily

## Solid trial design produced reliable and meaningful data

**N=508**

**Early AD patient population**

- Confirmed AD pathology
- Patients aged 60 to 85 years
- MMSE score 20-28

RANDOMIZATION 1:1:1

- Blarcamesine Target 50 mg
- Blarcamesine Target 30 mg
- Placebo

Double-Blind (DB)

Blarcamesine BTD

Open-Label Extension (OLE)

**Delayed-Start Analysis Endpoints***

- ADAS-$Cog_{13}$[1]
- ADCS-ADL[2]

**Other Pre-specified Analyses**

- Genetic variants, including SIGMAR1

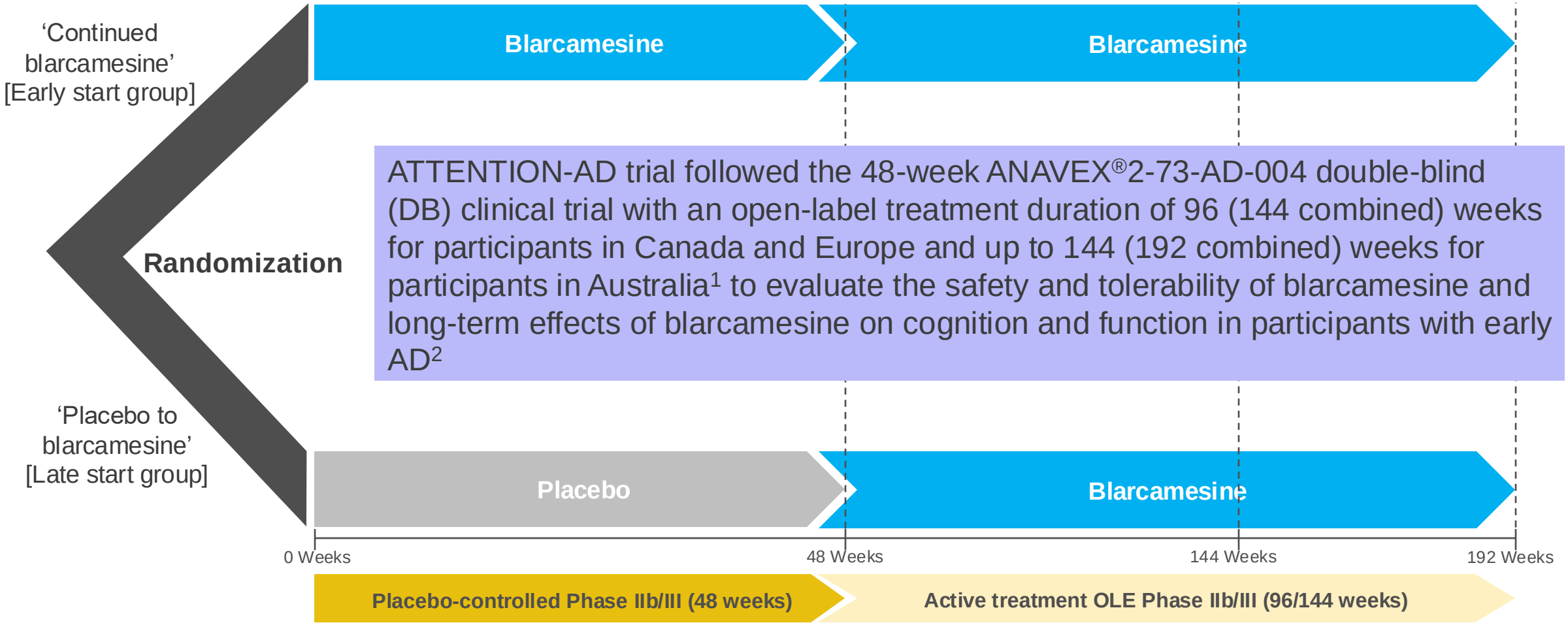
1. AD Assessment Scale-Cognitive subscale
2. AD Cooperative Study-Activities of Daily Living Scale

BTD: Best tolerated dose (up to 50 mg)

* Prespecified MMRM analysis method, same as the primary analysis method in DB

# 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.

# 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)

# Efficacy Results—Delayed-Start Analysis

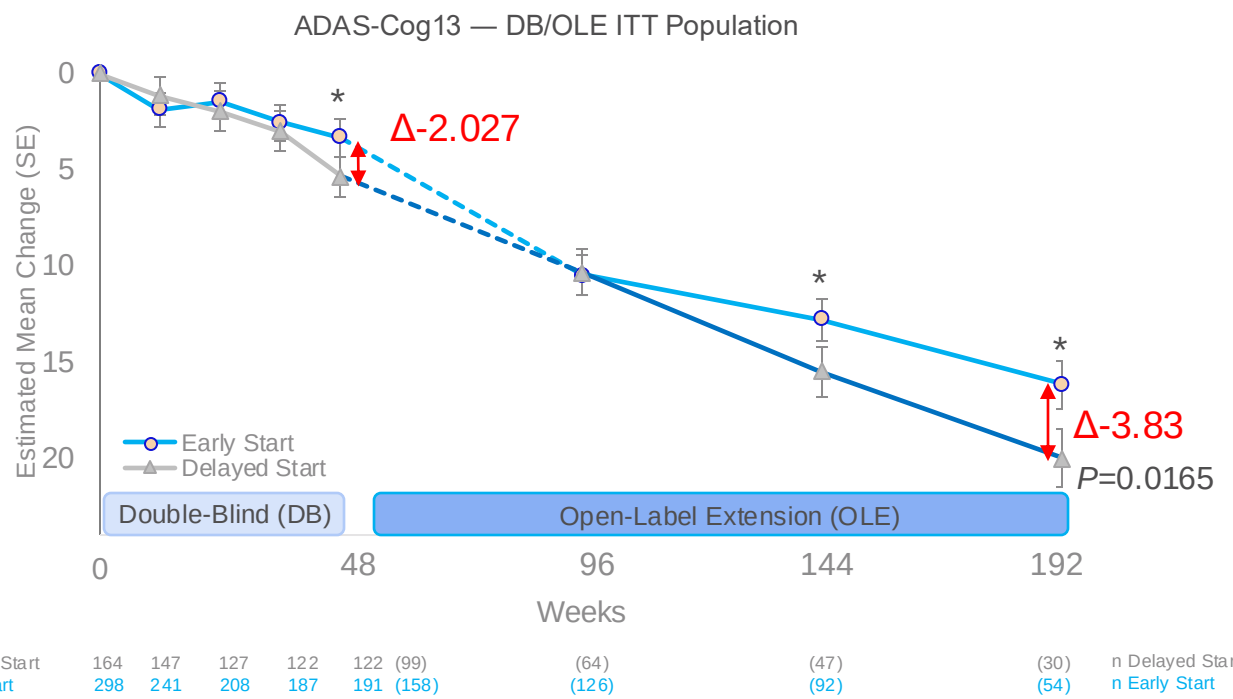
- Due to COVID, OLE (Open-Label-Extension) dosing re-start was variable
- 'No/Short Interruption Population' includes 'continued blarcamesine' participants with few or no interrupted treatment
  - —Resulting in no substantial loss of drug effect due to continued blarcamesine treatment
- The remaining 'continued blarcamesine' participants had a substantially longer drug interruption
  - —Resulting in loss of drug effect due to interruption of continued blarcamesine treatment
- Blarcamesine therapy with few or no interrupted treatment days leads to improved treatment efficacy
- Longer interruption of therapy associated with slightly worse efficacy results

✓Continued blarcamesine treatment—without interruption—is encouraged for more favorable clinical outcome

✓OLE results show the importance of continued long-term blarcamesine treatment and the importance of early intervention that may indicate disease-modifying effect

# Clinical Cognitive Outcome Through 192 Weeks: Early Treatment Significantly Better

OLE results indicate disease-modifying effect and importance of continued long-term blarcamesine treatment

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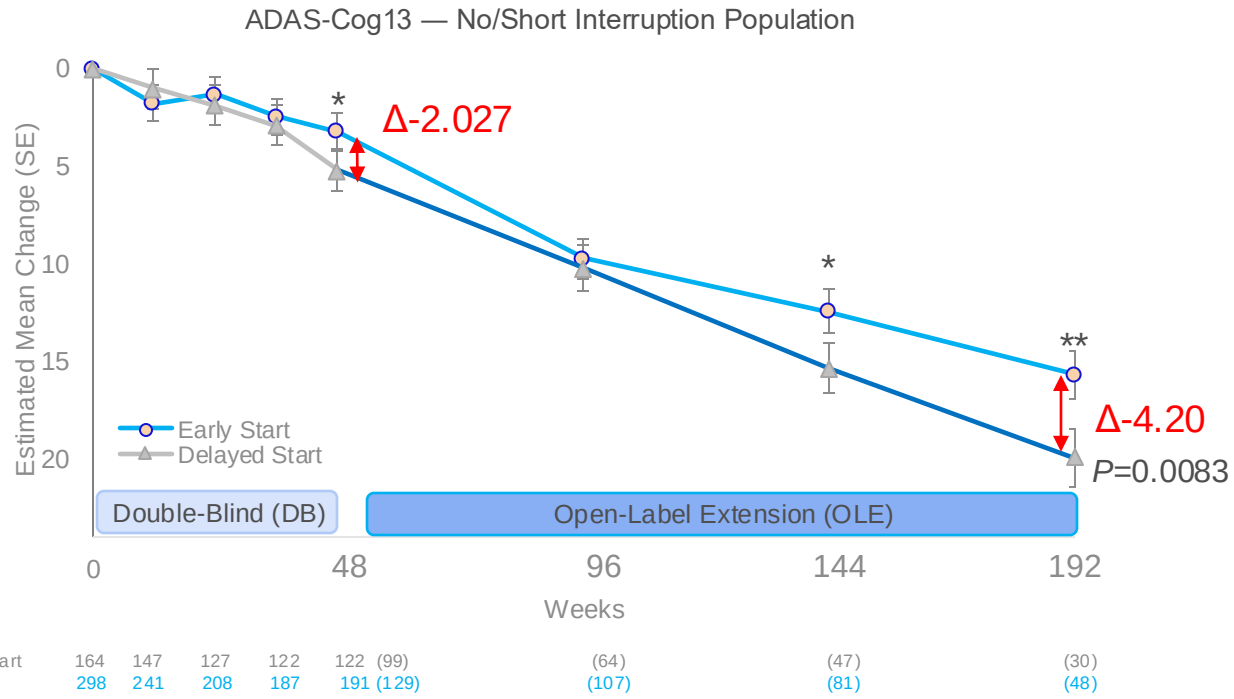
|---|---|---|---|---|---|---|---|---|---|
| n Delayed Start | 164 | 147 | 127 | 122 | 122 (99) | (64) | (47) | (30) |
| n Early Start | 298 | 241 | 208 | 187 | 191 (158) | (126) | (92) | (54) |




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| n Delayed Start | 164 | 147 | 127 | 122 | 122 (99) | (64) | (47) | (30) |
| n Early Start | 298 | 241 | 208 | 187 | 191 (129) | (107) | (81) | (48) |

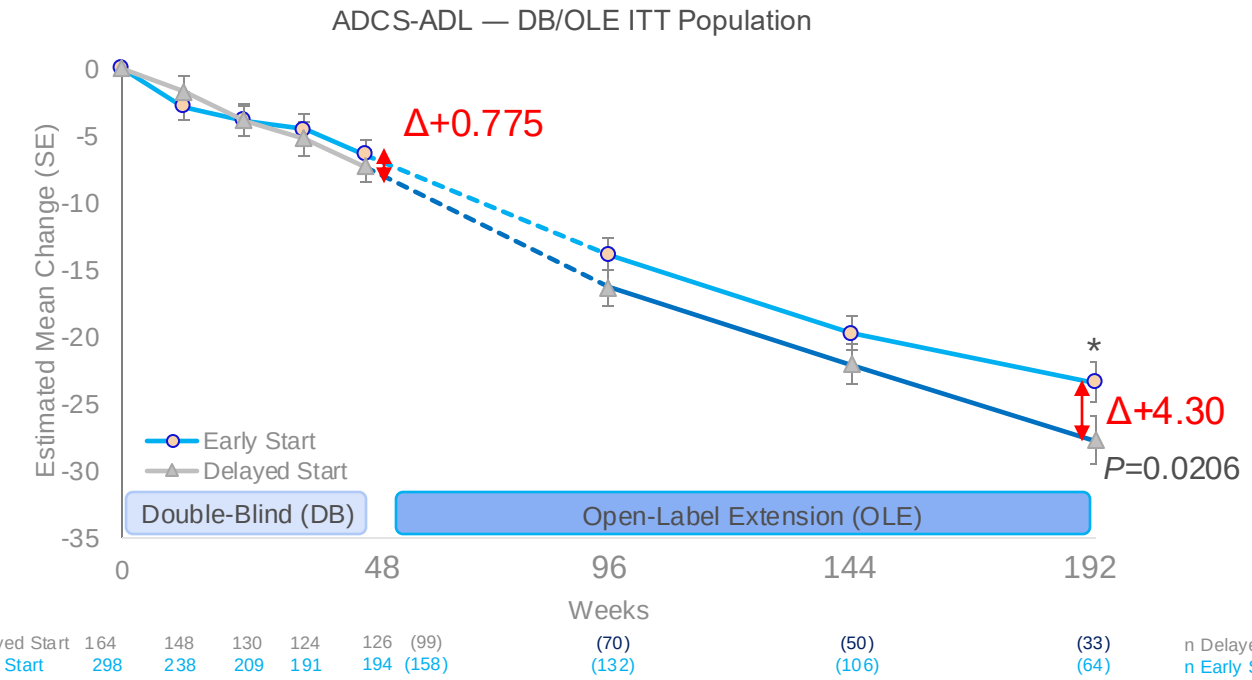
Due to COVID, OLE dosing re-start was variable. OLE re-start was on average (mean) 19 days after end of DB. 'No/Short Interruption Population' includes 'continued blarcamesine' participants with few or no interrupted treatment <19 days (mean 2.5 days). The remaining 'continued blarcamesine' participants (>19 days) had a longer drug interruption (mean 75 days).

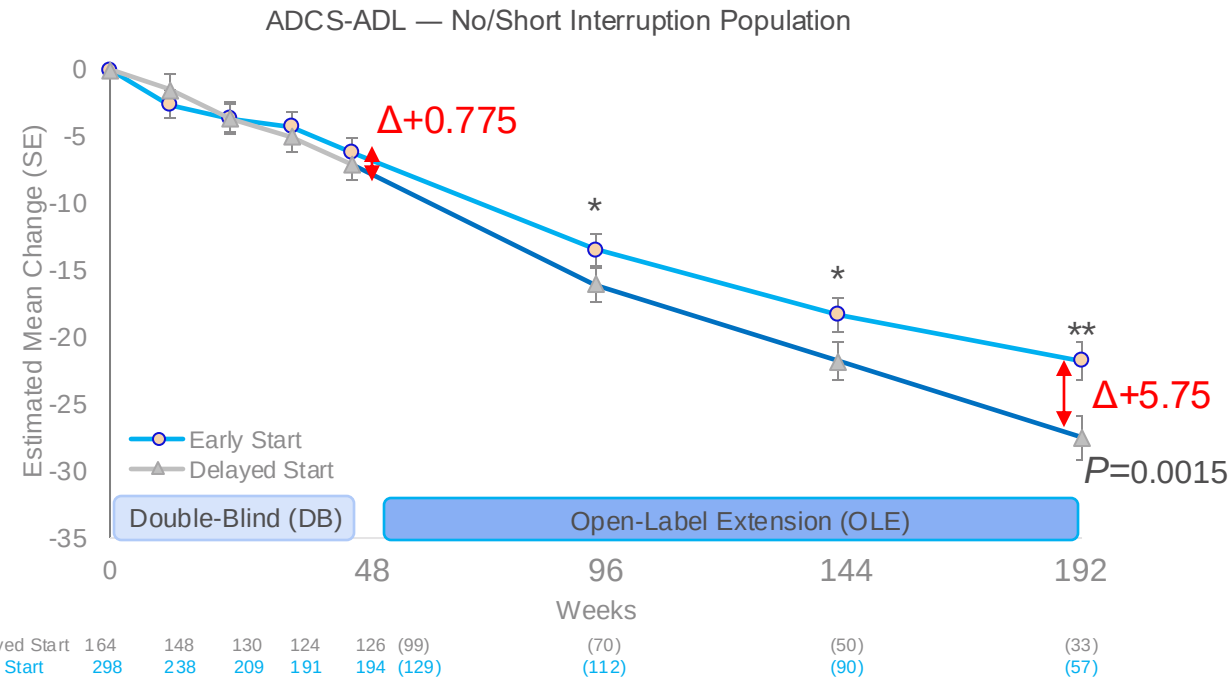
Participants in the OLE started with a 10-week titration phase before reaching respective maintenance dose. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM). Population numbers (n) represent the number of participants with non-missing data and covariates at each time point for DB/OLE ITT population, with OLE time points in parentheses. ADAS-Cog13 = AD Assessment Scale-Cognitive subscale.

*: p<0.05; **: p<0.01

# Clinical Functional Outcome Through 192 Weeks: Early Treatment Significantly Better

OLE results indicate disease-modifying effect and importance of continued long-term blarcamesine treatment

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Participants in the OLE started with a 10-week titration phase before reaching respective maintenance dose. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM). Population numbers (n) represent the number of participants with non-missing data and covariates at each time point for DB/OLE ITT population, with OLE time points in parentheses. ADCS-ADL = AD Cooperative Study-Activities of Daily Living scale.

*: p<0.05; **: p<0.01

# Delayed-Start Analysis ATTENTION-AD and AD-004 Trial

**Summary:**

### Key safety findings

- Consistent safety profile—no new safety findings observed with over four (4) years of treatment with blarcamesine
- Titration adjustment demonstrate manageable nature of the most frequent TEAE (dizziness)
- No deaths related to the study drug

### Key efficacy findings

- Treatment mean difference continued to increase up to Week 192
- ADAS-Cog13 difference: -3.83
  *P* = 0.0165
- ADCS-ADL difference: +4.30
  *P* = 0.0206
- Data indicate disease-modifying effect of oral blarcamesine

### Summary

**Suggests earlier oral blarcamesine treatment initiation may have continued long-term beneficial therapeutic effect**

ADAS-Cog13 differences larger than 2 points are considered clinically meaningful improvements*



* 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. doi:10.1002/alz.13770

# 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 Common SIGMAR1 WT gene carriers (~70% of general population) compared to ITT 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**
- ✓**Long-term (~4 years) promising clinical results: Earlier oral blarcamesine treatment initiation may have continued long-term beneficial therapeutic effect – prespecified ADAS-Cog13 difference: -3.83 (P = 0.0165), ADCS-ADL difference: +4.30 (P = 0.0206)**

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.

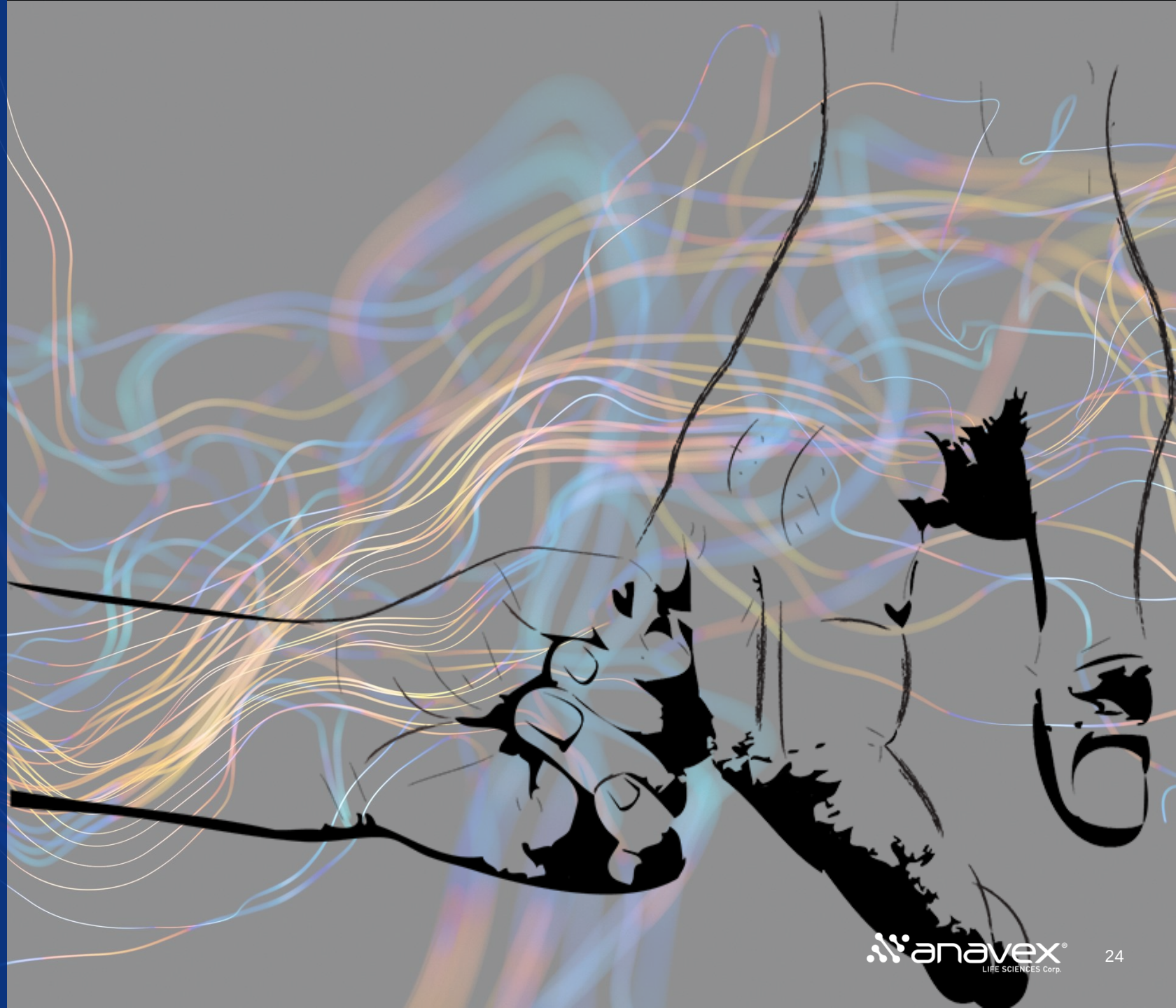
# Acknowledgements

Most of all, we share grateful acknowledgement of the contribution by participating Alzheimer's disease patients and their caregivers.

—Principal Investigators, Clinical Sites' Study Staff, Data Safety Review Committee, and Anavex Scientific Advisory Board

## Anavex's Advantage is Precision Medicine Platform Scalability

## Equitable and Accessible for Diverse Populations, and Maintaining Sustainability within Global Healthcare Systems



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