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

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Disclosures

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

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*

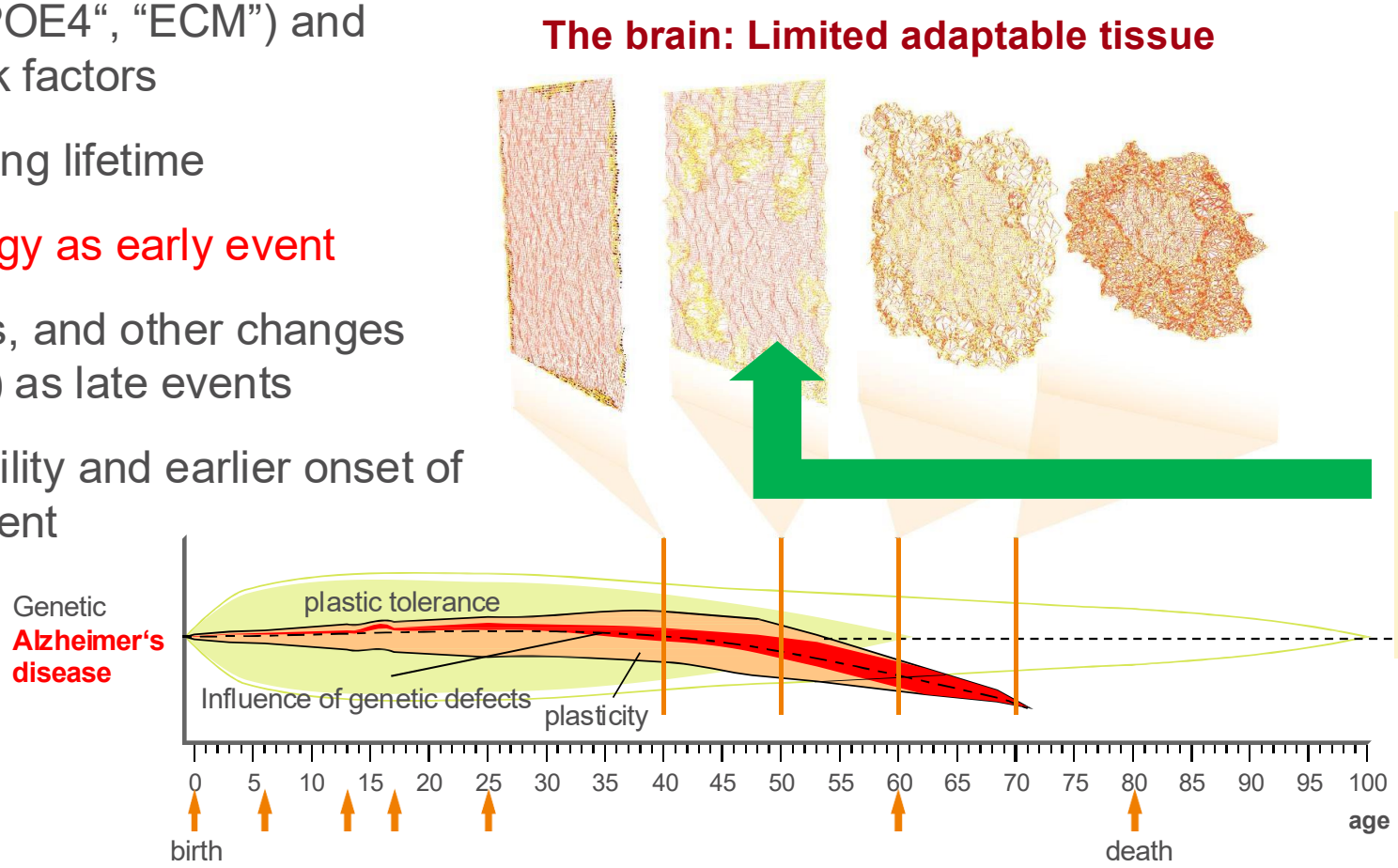
Tau Tangles
- *Microtubule Destabilization*

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).

Brain At Risk - Individual Genetic Risk Factors and Lifetime Challenges Determines Chronic AD: The Need for Protective Measures

- Genetic (e.g., “APOE4“, “ECM”) and environmental risk factors
- Low plasticity during lifetime
- Impaired autophagy as early event
- Plaques & tangles, and other changes (mixed pathology) as late events
- Reduced adaptability and earlier onset of cognitive impairment



Restoring autophagy via SIGMAR1 activation

Re-normalization of:

- ✅ **neural function**
- ✅ **neuronal survival**

High risks for chronic Alzheimer‘s:

Limited resolution over time

Adapted from: Yang et al. “Decoding extracellular matrix-lysosome cross-talk and its implications for neurodegenerative diseases.” Science signaling vol. 18,890 (2025): eadt1936.

APOE4 = APOE gene encodes for apolipoprotein E, a protein involved in lipid (fat) transport and metabolism in the brain. APOE4 is the strongest genetic risk factor for late-onset Alzheimer's disease

ECM = Extracellular Matrix

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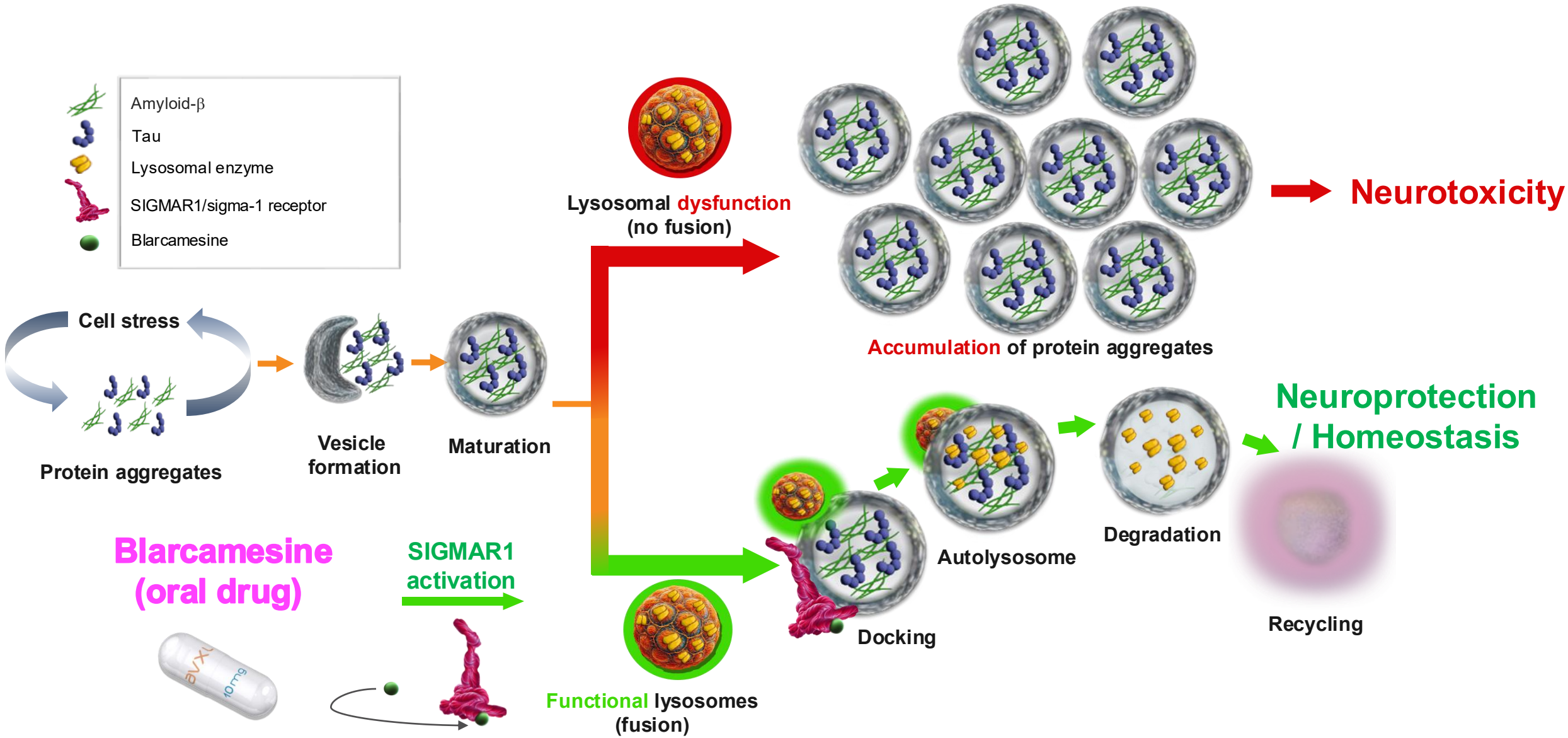
Blarcamesine Restoring Autophagy and Homeostasis



Schematic representation.

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.

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

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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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

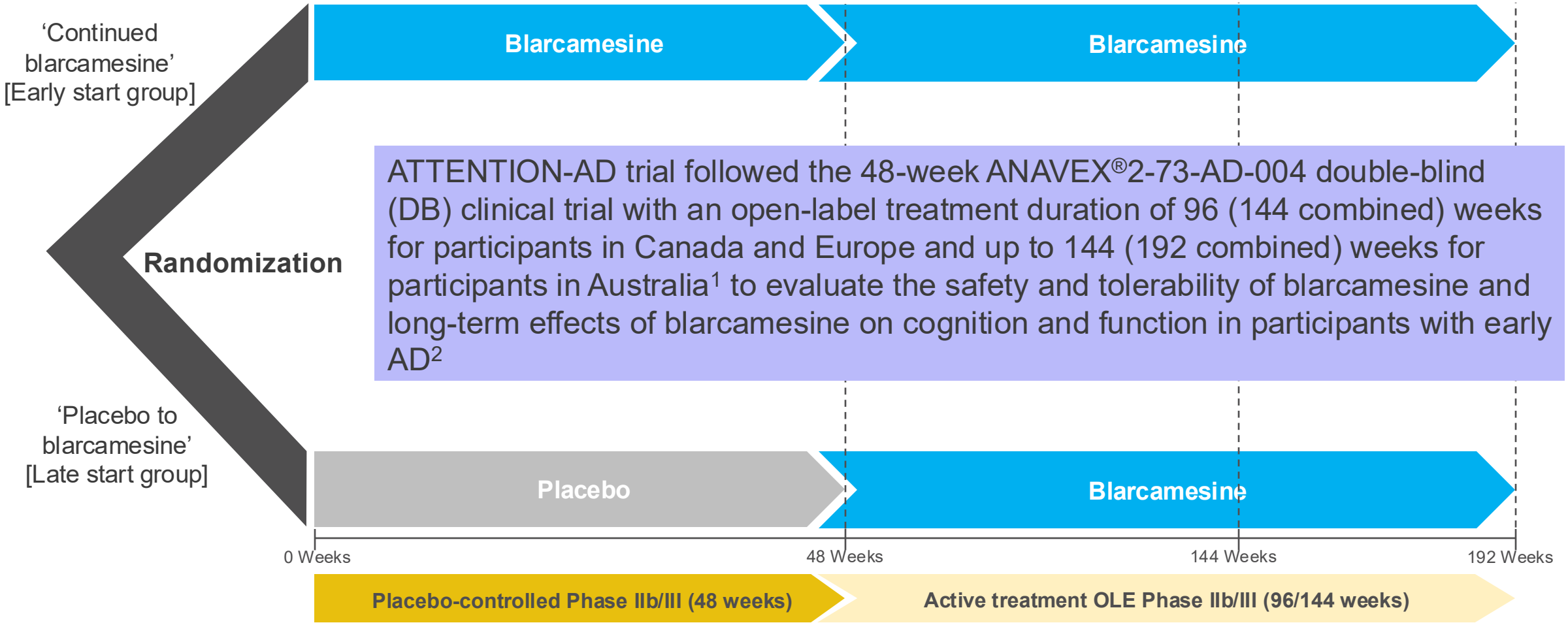
1. AD Assessment Scale-Cognitive subscale
2. AD Cooperative Study-Activities of Daily Living Scale

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

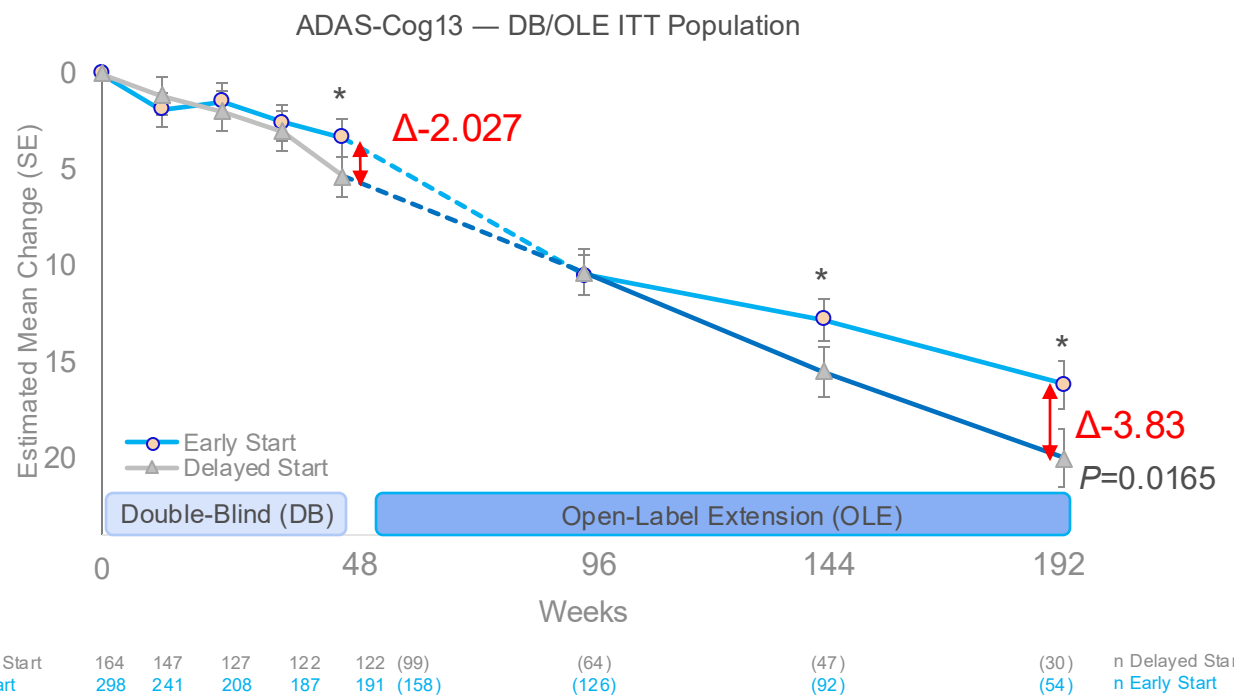
- Due to COVID, OLE (Open-Label-Extension) dosing re-start was variable
- 'No/Short Interruption Population' includes 'continued blarcamesine' participants with few or no interrupted treatment
  - —Resulting in no substantial loss of drug effect due to continued blarcamesine treatment
- The remaining '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

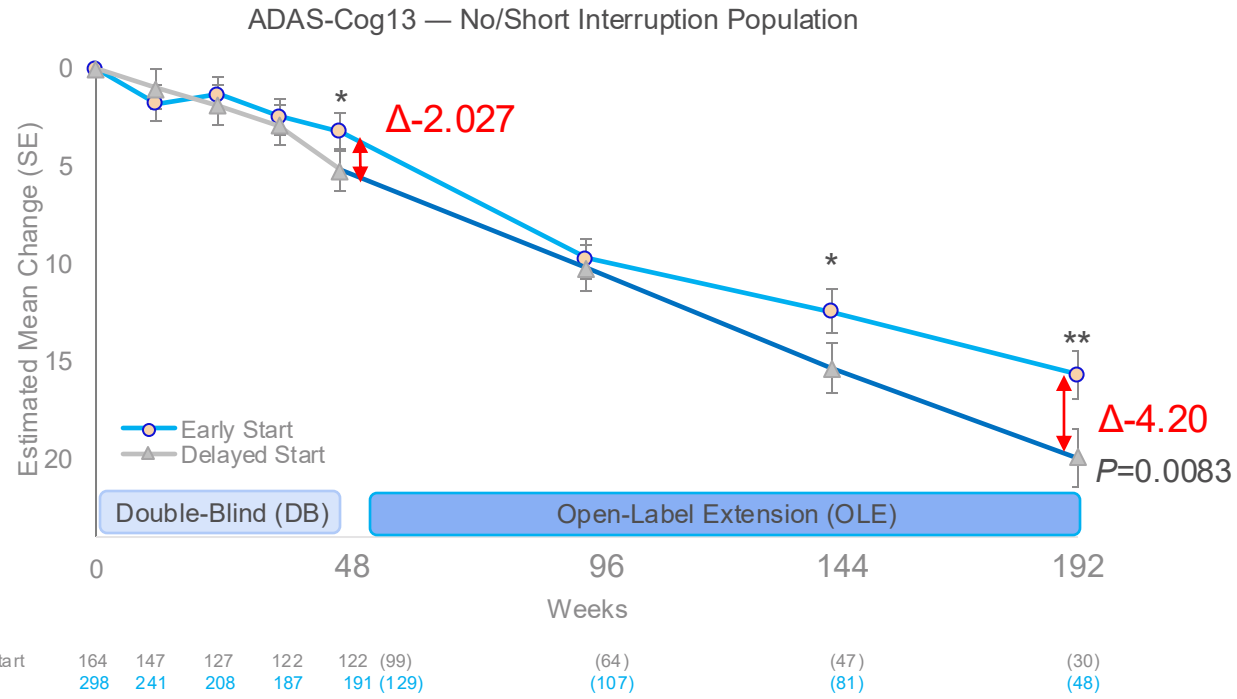
✓OLE results show the importance of continued long-term blarcamesine treatment and the importance of early intervention that may indicate disease-modifying effect

Clinical Cognitive Outcome Through 192 Weeks: Early Treatment Significantly Better

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



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)

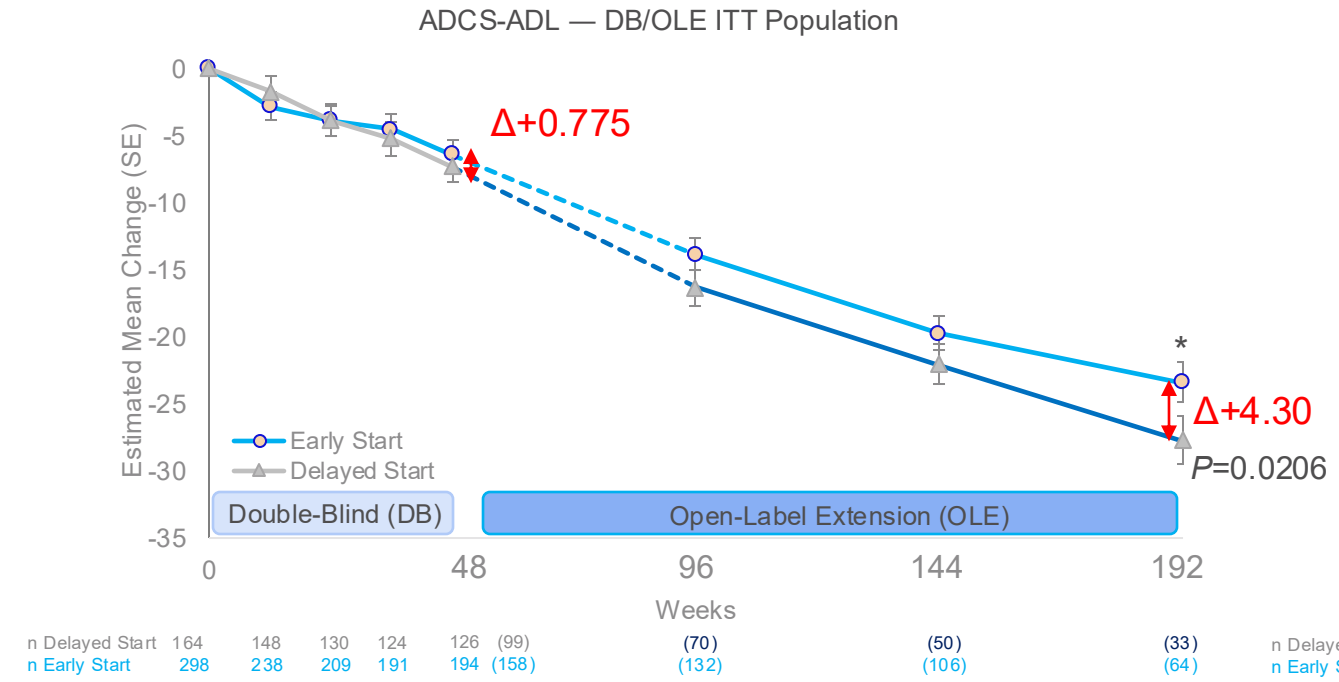
Due to COVID, OLE dosing re-start was variable. OLE re-start was on average (mean) 19 days after end of DB. 'No/Short Interruption Population' includes 'continued blarcamesine' participants with few or no interrupted treatment <19 days (mean 2.5 days). The remaining 'continued blarcamesine' participants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

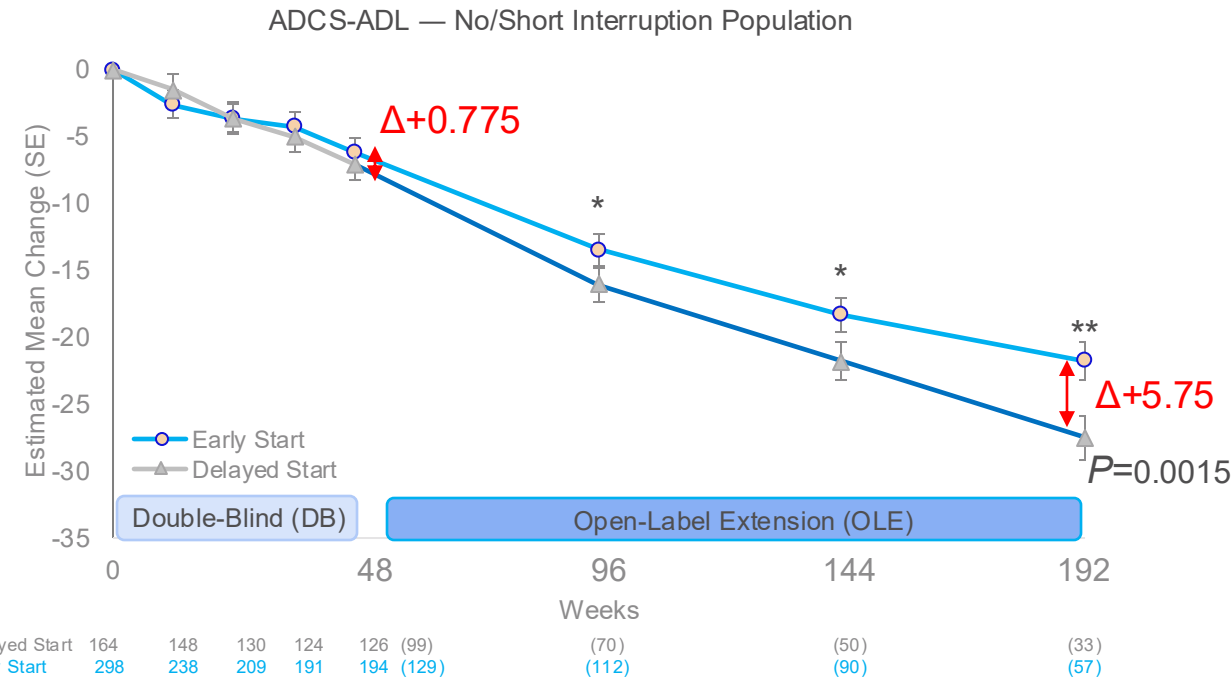
Participants in the OLE started with a 10-week titration phase before reaching respective maintenance dose. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM). Population numbers (n) represent the number of participants with non-missing data and covariates 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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*: 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*

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* 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

Precision Medicine Delayed-Start Analysis ATTENTION-AD and AD-004 Trial

Global Frequency of ABCLEAR2* Population: ~71.7%**

Further improved efficacy for ABCLEAR2 Population

- Treatment mean difference continued to further increase up to Week 192
- ADAS-Cog13 difference: -5.43
  P = 0.0035
- ADCS-ADL difference: +9.50
  P < 0.0001
- Data indicate disease-modifying effect of oral blarcamesine

Time Saved Analysis

Up to 84.6 Weeks (19.5 Months) saved by Early Start

* GWAS-identified population ABCLEAR2 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variant non-carrier population
** Source: https://www.ncbi.nlm.nih.gov/snp/

Conclusions

Blarcamesine once daily, orally 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 ITT population ADAS-Cog13 difference: -3.83 (P = 0.0165), ADCS-ADL difference: +4.30 (P = 0.0206) and and ABCLEAR2 population ADAS-Cog13 difference: -5.43 (P = 0.0035), ADCS-ADL difference: +9.50 (P < 0.0001)**

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.

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