Advancing Alzheimer's Disease Care: Convenience for *Both* Patients and Families with Oral Blarcamesine

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Disclosures

Dr. Grimmer received consulting fees and lecture fees from Anaxex.

Outside the submitted work Dr. Grimmer reported receiving consulting fees from Acumen, Advantage Ther, Alector, 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, Eisai and Eli Lilly.

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The Journey of an Alzheimer's Patient

Inconvenient and Challenging…

Credit: Susan Gregg / UW Medicine

For the Patient:

- ✕ Currently no new convenient *patient-centric* disease-modifying treatments are approved for Alzheimer's disease
- ✕ No oral treatment
- ✕ Requirement of complex logistical resources
- ✕ Added personnel for drug administration
- ✕ Expensive safety monitoring (ARIA)
- ✕ Most-in-need patients (APOE E4 homozygous carriers) *excluded* (!)

"The journey is tough, but no one should walk it alone."

… Emotional and Social Impact

For the Patient:

- Feelings of isolation and helplessness

For the Family:

- Emotional toll, caregiver stress, financial strain
- Importance of community and support groups

“The journey is tough, but no one should walk it alone.”

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

The Journal of Prevention of Alzheimer's Disease 12 (2025) 100016

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

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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Key Advantages of Oral Blarcamesine: Tailored to Individual Needs

- **Orally**-administered **convenient once-daily** blarcamesine (ANAVEX®2-73):
  - ✓Taken once daily by mouth, **easy treatment** for patients
  - ✓**Enhanced patient access** and minimizing disparities in European/UK healthcare delivery
  - ✓Allows for affordability and **accessibility** within Europe/UK without complex logistics and without frequent MRI examinations
- Blarcamesine is a **scalable** potential **therapeutic solution** for AD by:
  - ✓**Countering** neurodegeneration (improved retention of brain volume)
  - ✓**Improving autophagy**—a key **upstream clearance mechanism** that removes protein aggregates and misfolded proteins
  - ✓Market Authorisation Application (MAA) currently under review by EMA for Alzheimer's disease

The Blarcamesine Advantage

Patients *and* Families Continue to be the Center and Focus

Advantage For the Patient:

- Proven protocol and assessments allowing for quicker time-sensitive access to new oral treatment
- Continued focus on individual patient
- No logistical barriers to treatment
- No need to arrange or schedule complex PET, lumbar puncture (spinal tap) or repeated MRIs

Continued patient *and* family-centric care with ability to augment with supplemental support (diet, sleep, social activities, etc.)

More “Family Time” Together

Advantage For the Family:

- Less caregiver stress, and likely less financial strain
- No need to arrange for constant transportation
- No impact on own work schedule
- Being able to help timely without delays and constrains by cumbersome and limiting inconvenient complex logistical challenges

Family members are able to help with less distraction

Accurate Diagnosis by Physician—Fast And Convenient Access to Study Drug

Advantage For the Physician:

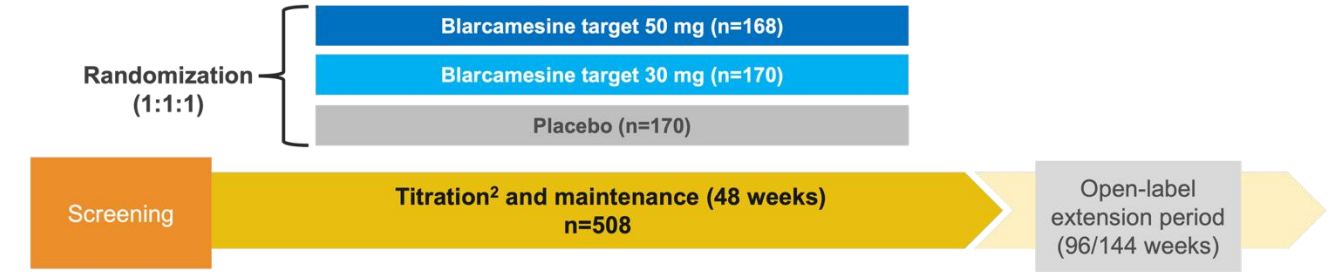
- No disruption of proven workflow
- No logistical barriers to treatment
- No need to arrange or schedule complex PET, lumbar puncture (spinal tap) or repeated MRIs
- Proven protocol and assessments allowing for quicker time-sensitive access to new oral treatment
- Continued focus on individual patient

Without the need for logistical challenging administration and cumbersome follow up: No PET scan or lumbar puncture (spinal tap) or repeated MRIs required

Blarcamesine: Clinical Data and Precision Medicine

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

Global, multicenter, randomized, double-blind, placebo-controlled, parallel group, 48-week trial evaluating blarcamesine (ANAVEX®2-73) once-daily oral capsules



Key eligibility criteria:
- Met the NIA-AA 2011 criteria for diagnosis of early-stage mild dementia or MCI due to AD
- Aged 60 to 85 years
- MMSE score 20-28
- Confirmation of AD via amyloid or FDG PET, CT, or MRI scan, or CSF (amyloid or tau)[1]

Coprimary endpoints*
- ADAS-Cog13
- ADCS-ADL

Key secondary endpoint
- CDR-SB

Other endpoints
- Structural and functional MRI
- Biomarkers: $A\beta_{42}/A\beta_{40}$, p-tau (181), p-tau (231), Nf-L
- CGI-I
- SIGMAR1 gene variant and GWAS analysis

*Published scientific evidences about ADCS-ADL, e.g. Teng et al. 2023, and March 2024 FDA Guidance for Early AD and respective EMA Guideline, a sole cognitive measure can serve as the primary endpoint for early AD trials

Relevant For the Patient:

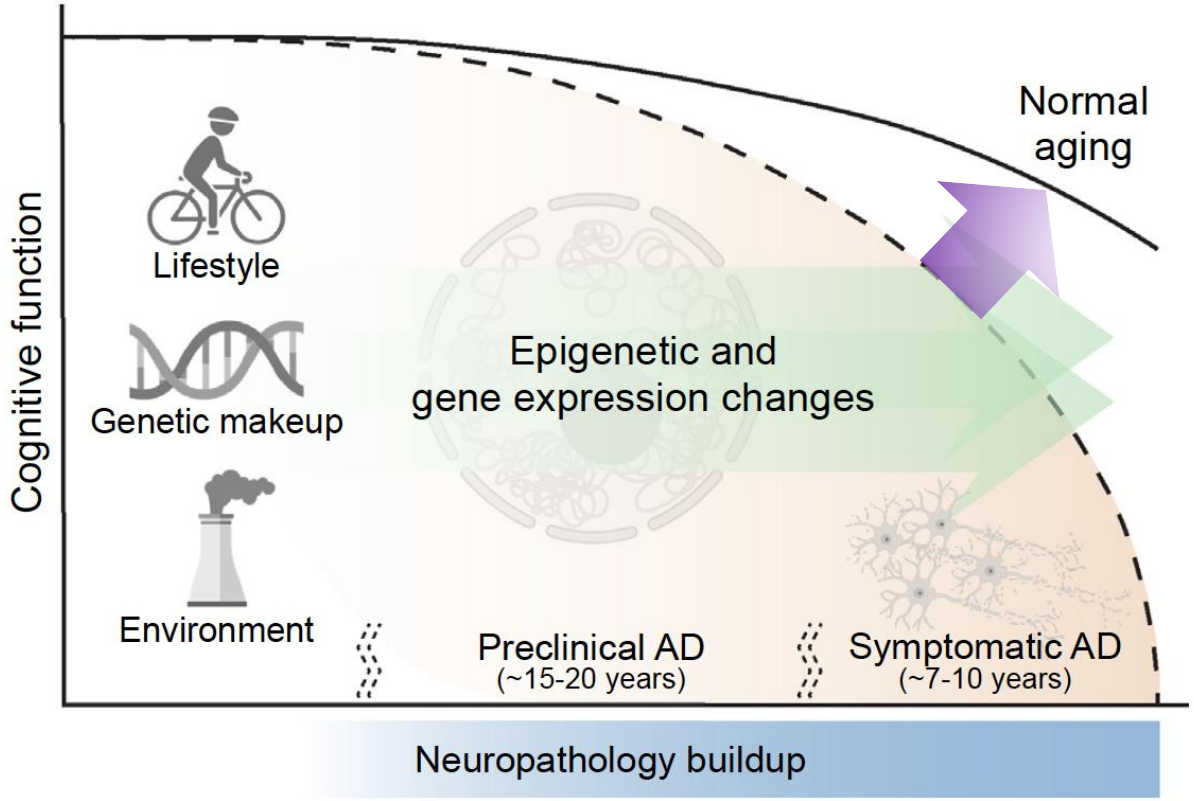
- The trial inclusion requirements were readily manageable for both the patients and the families
- With no mandatory invasive assessments
- The emphasis was on the National Institute on Aging (NIA)–AA 2011 criteria for diagnosis of early-stage MCI and mild-dementia due to AD
- The same accommodating procedures would be followed upon potential market approval

[1]AD status supported by the elevated baseline levels of plasma p-tau(181) and p-tau(231).

[2]Titration occurred from days 1-21.

AD, Alzheimer's disease; ADAS-Cog13, a 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-ADL, AD Cooperative Study-Activities of Daily Living Scale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NIA-AA, National Institute on Aging-Alzheimer's Association; Nf-L, neurofilament light chain.

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.

Blarcamesine Precision Medicine Data Findings: Potential Ability to Match Barely Detectable Prodromal Alzheimer's 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 Alzheimer's disease (AD) decline, in spite of the more advanced stage of AD impairment at baseline of the blarcamesine population

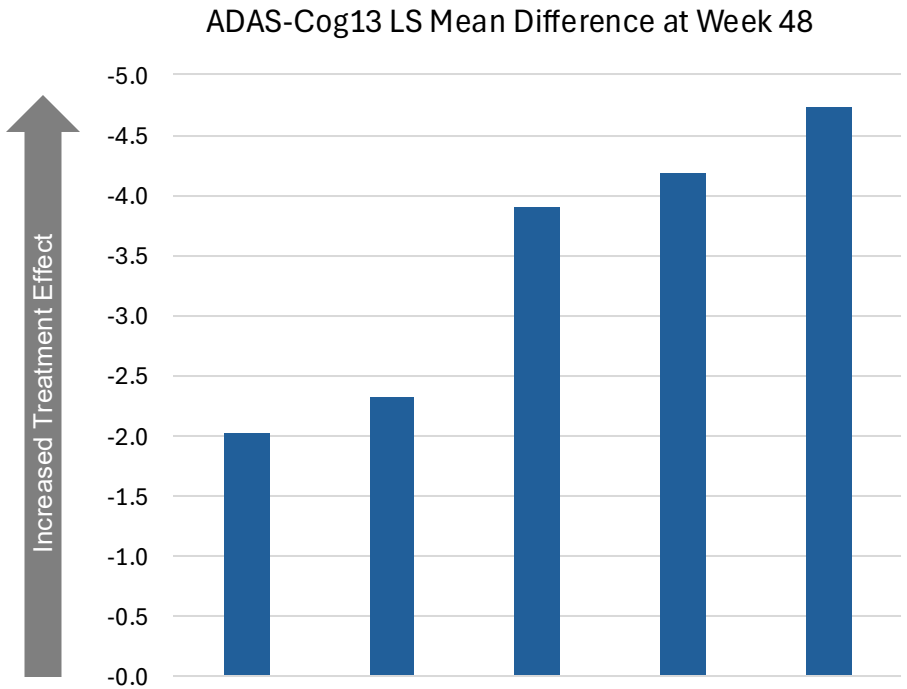
Cognitive outcomes observed in the oral blarcamesine 30 mg Precision Medicine cohort move toward normal aging profiles across validated clinical scales, supporting its relevance in early-stage Alzheimer's care

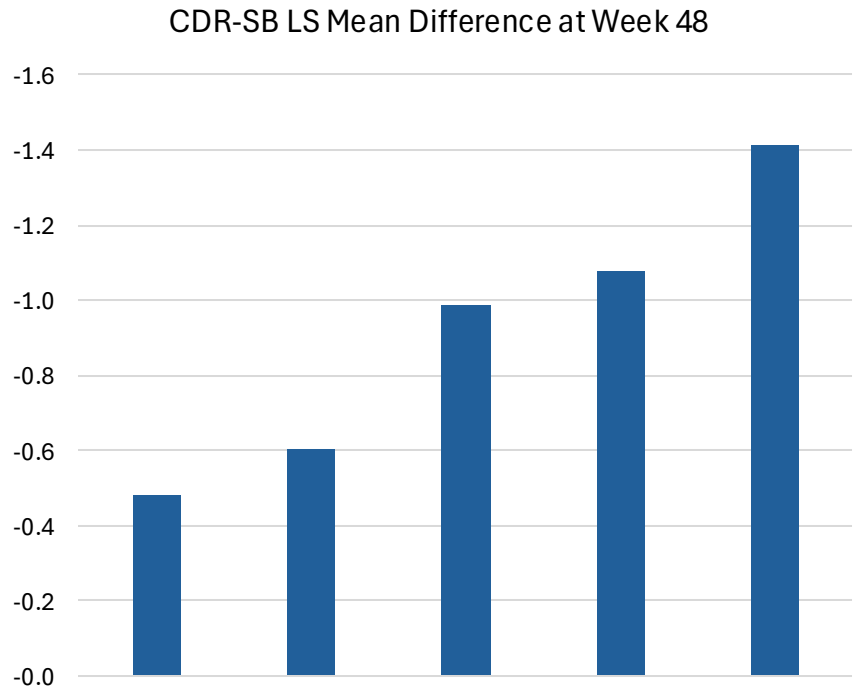
Blarcamesine: Oral convenient scalable potential treatment

* 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

	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

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.

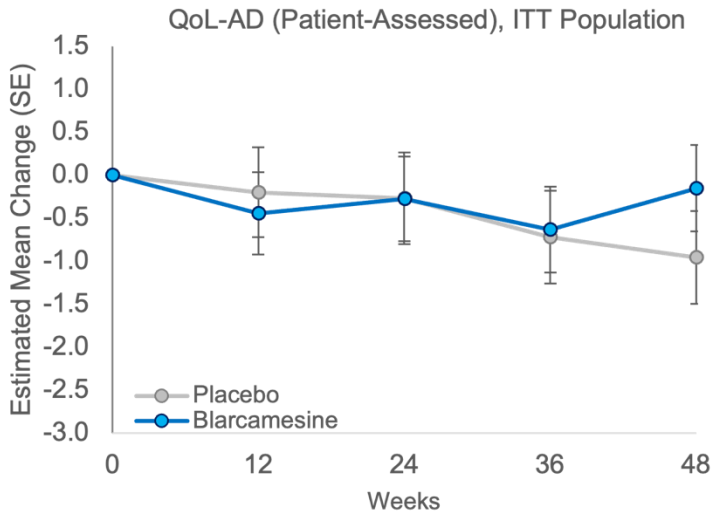
Ability to do things for fun: Enjoyment of leisure activities.

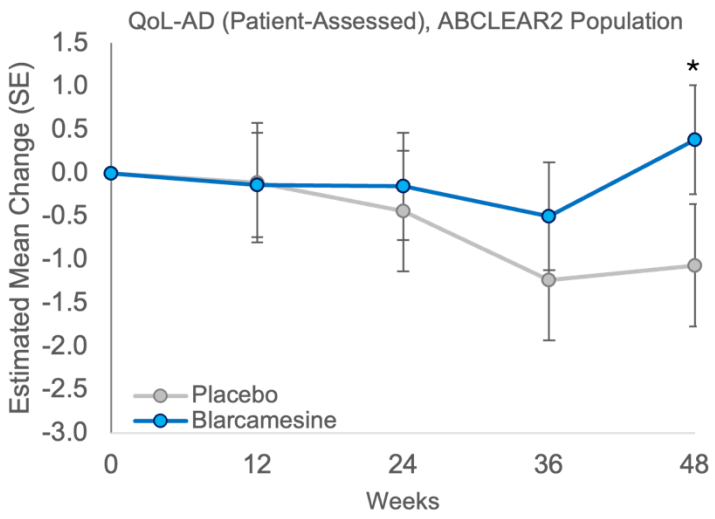
Money: Financial well-being.

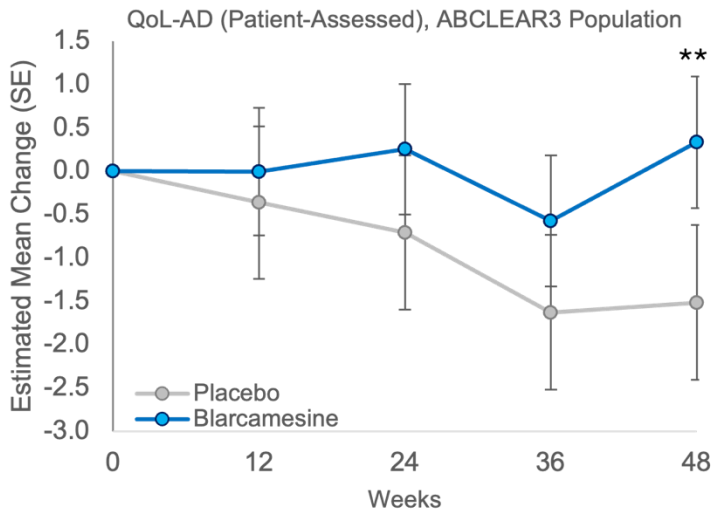
Life as a whole: Overall satisfaction with life.

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

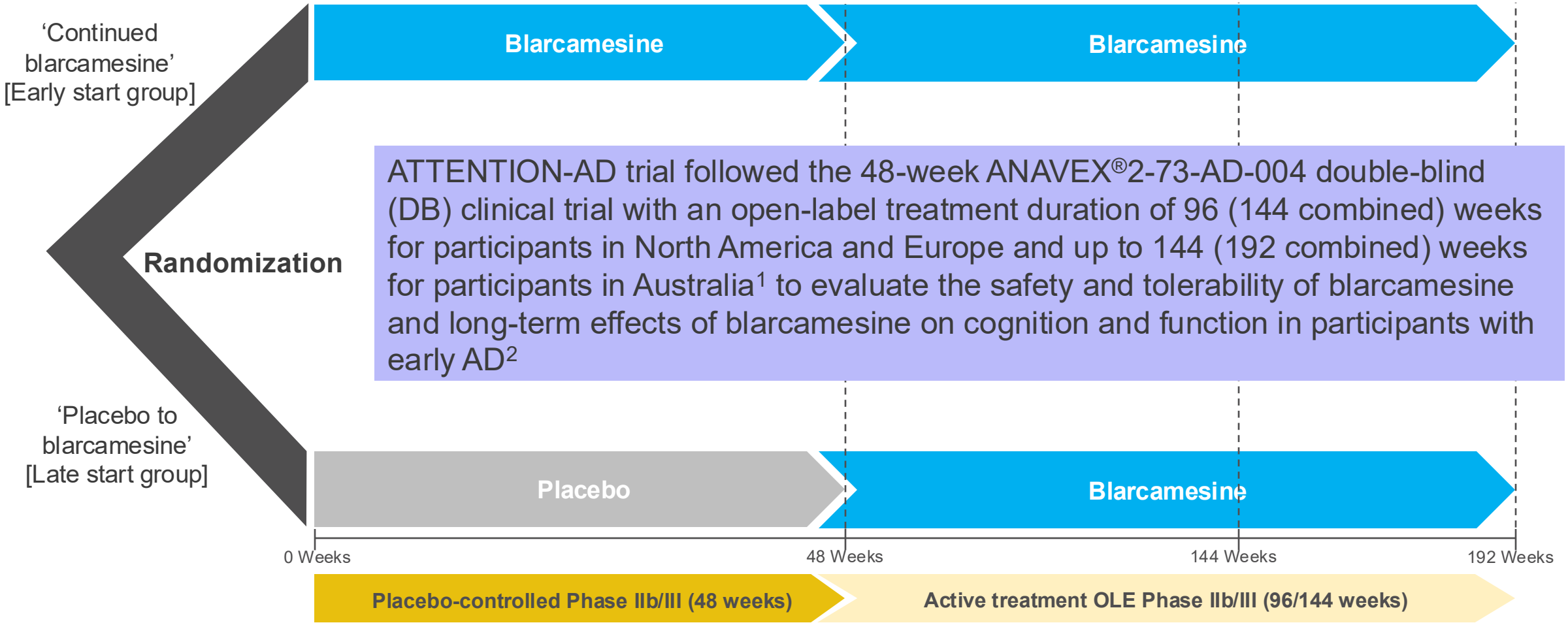
ITT = Intent-to-Treat population (100% population)
ABCLEAR1 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variant non-carrier population (SIGMAR1 wild type [WT]) (~70% population)
ABCLEAR2 = Alzheimer's Blarcamesine Cognition Efficacy and Resilience gene variant non-carrier population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

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/

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)

Blarcamesine Once Daily Orally Significantly Slowed Brain Volume Loss

Countering Neurodegeneration:

- Blarcamesine significantly slowed brain volume loss in the whole brain, total grey matter, and lateral ventricles
- Clinical outcomes were also corroborated by biomarkers from the A/T/N spectrum, including a significant increase in plasma Aβ 42/40 ratio (mean increase 0.013)

Blarcamesine safe to use with no neuroimaging-related side effect

Extending the Dignity of Aging

Impact on Daily Life:

- Promising clinical results (numerically superior to injectable infusion mAbs)
- 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

“Oral Blarcamesine: Convenient for Both Patients *and* Caregivers.”

Summary:

- The impact on daily life is extended by time saved with oral Alzheimer's treatment blarcamesine
- Allowing for longer independence of loved ones with safer and better outcome
- While allowing efficiency, accessibility, and ease for patients and families

Understanding that Alzheimer’s disease is not the end …

Conclusions

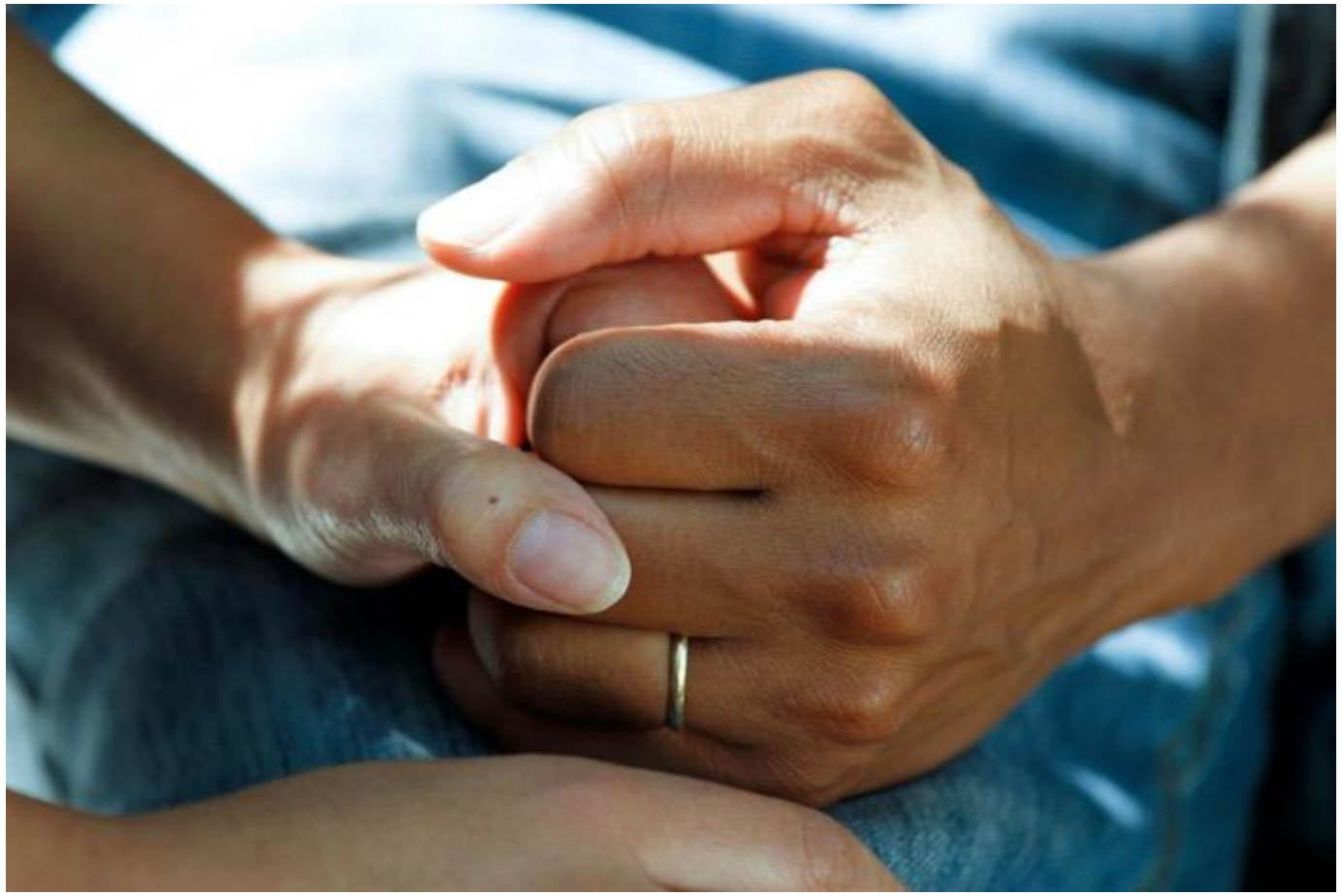
Blarcamesine once daily, orally restores autophagy through SIGMAR1 activation -> corroborated MoA by pre-specified SIGMAR1 gene analysis: Greater significant clinical benefit, — ADAS-Cog13 at 48 Weeks by 49.8% — experienced by Common SIGMAR1 WT gene carriers (~70% of general population) compared to ITT 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.

… We Want To Walk The Journey With You



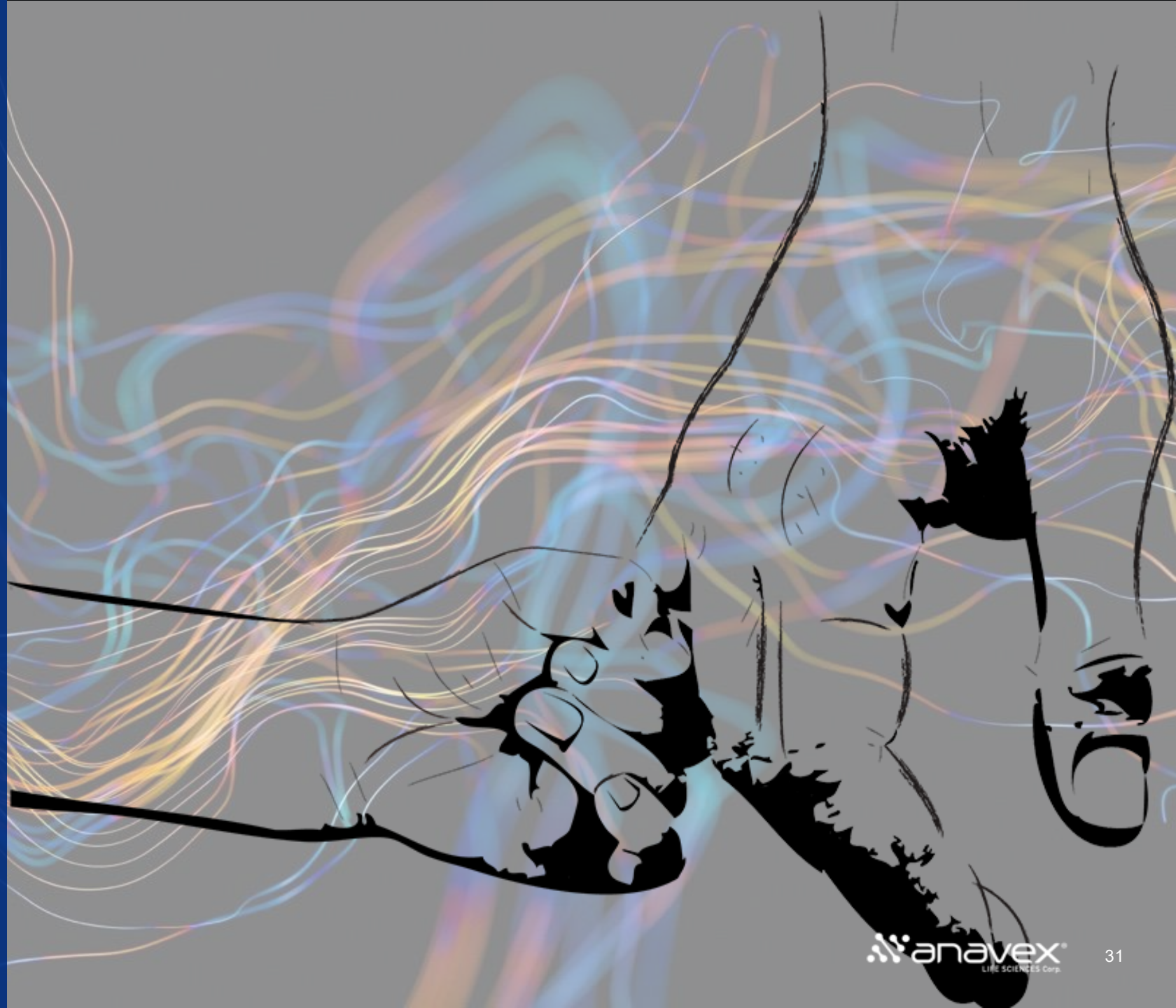
Acknowledgements

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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