anavex® LIFE SCIENCES Corp.

Blarcamesine in Early Alzheimer's Disease: Phase IIb/III Randomized Clinical Trial

Marwan Noel Sabbagh MD, FAAN, FANA

Moreno Family Chair for Alzheimer's Research
Vice Chairman for Research and Professor
Department of Neurology
Barrow Neurological Institute

Forward Looking Statements

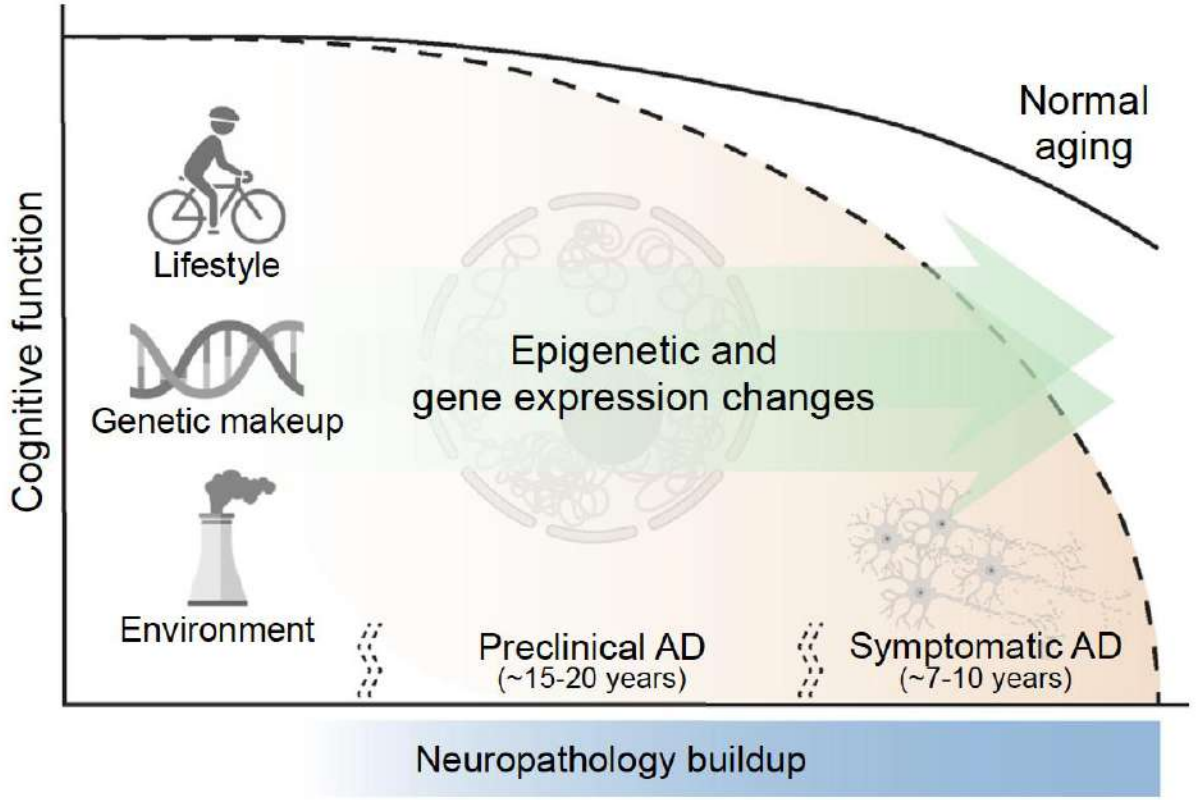
This presentation contains forward-looking statements made within the meaning of the Private Securities Litigation Reform Act of 1995 by Anavex® Life Sciences Corp. and its representatives. These statements can be identified by introductory words such as “expects,” “plans,” “intends,” “believes,” “will,” “estimates,” “forecasts,” “projects,” or words of similar meaning, and by the fact that they do not relate strictly to historical or current facts. Forward-looking statements frequently are used in discussing potential product applications, potential collaborations, product development activities, clinical studies, regulatory submissions and approvals, and similar operating matters. Many factors may cause actual results to differ from forward-looking statements, including inaccurate assumptions and a broad variety of risks and uncertainties, some of which are known and others of which are not. Known risks and uncertainties include those identified from time to time in reports filed by Anavex Life Sciences Corp. with the Securities and Exchange Commission, which should be considered together with any forward-looking statement. No forward-looking statement is a guarantee of future results or events, and one should avoid placing undue reliance on such statements. Anavex Life Sciences Corp. undertakes no obligation to update publicly any forward-looking statements, whether as a result of new information, future events or otherwise. Anavex Life Sciences Corp. cannot be sure when or if it will be permitted by regulatory agencies to undertake clinical trials or to commence any particular phase of any clinical trials. Because of this, statements regarding the expected timing of clinical trials cannot be regarded as actual predictions of when Anavex Life Sciences Corp. will obtain regulatory approval for any “phase” of clinical trials. We also cannot be sure of the clinical outcome for efficacy or safety of our compounds. Potential investors should refer to the risk factors in our reports filed on Edgar.

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.

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

AD Pathology Is Highly Heterogeneous and Complex



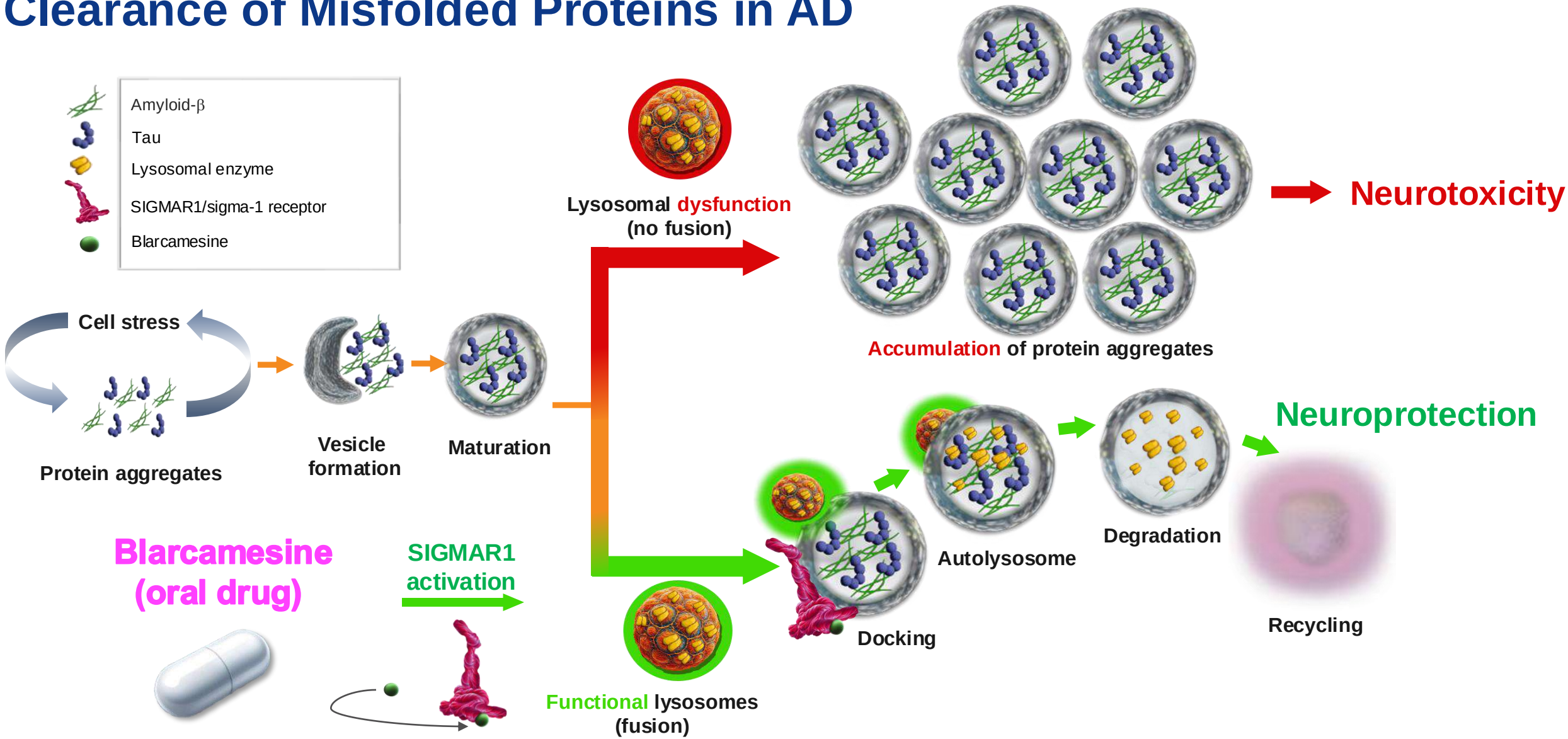
… influenced by genotype, environment, cognitive reserve, and a range of demographic factors

… 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.

Blarcamesine Improves Upstream Autophagy and Clearance of Misfolded Proteins in AD



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.

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**

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.

- Orally-administered blarcamesine (ANAVEX®2-73) is a novel, investigational small molecule that activates an upstream compensatory process: autophagy through SIGMAR1 activation

- Blarcamesine is a scalable potential therapeutic solution for AD by:

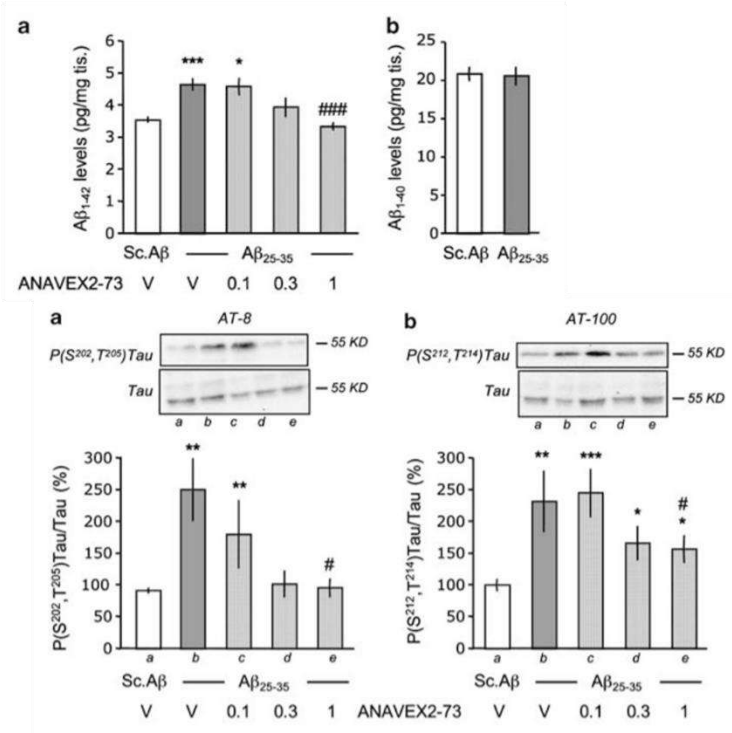
  ✓Countering neurodegeneration

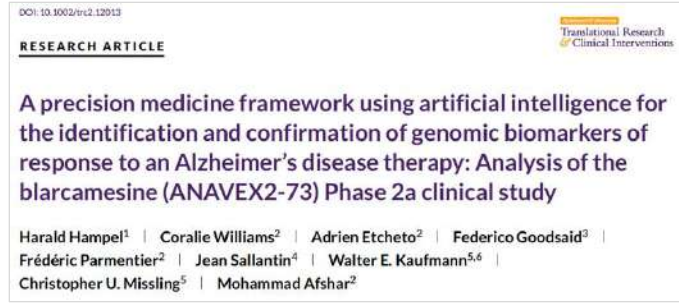
  ✓Improving autophagy—a key clearance mechanism that removes protein aggregates and misfolded proteins

Blarcamesine PoC: Previous Preclinical and Clinical ANAVEX®2-73-002/3 Phase 2a Studies in Alzheimer's Disease

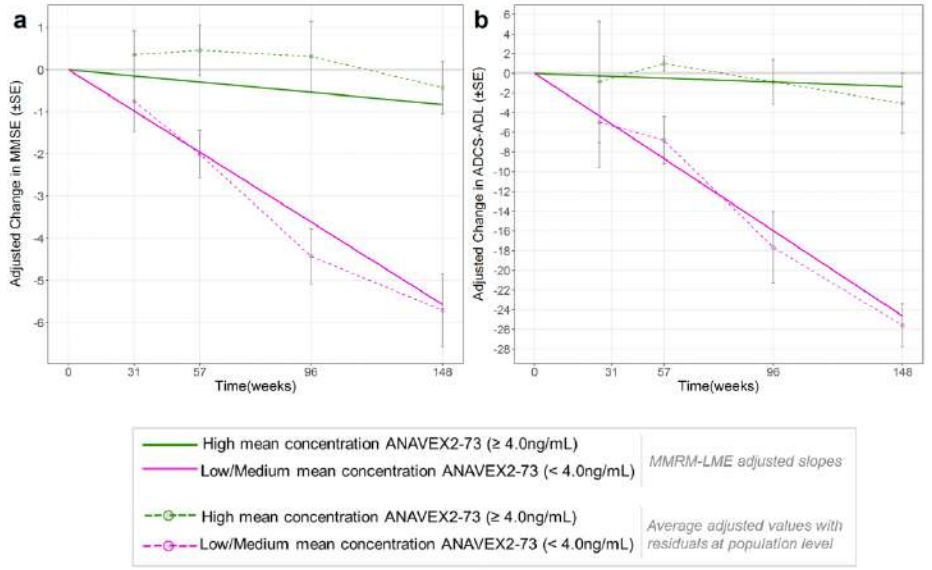
Blarcamesine inhibits Aβ1-42 and tau phosphorylation generation and demonstrated exploratory interim proof-of-concept effect on cognition and function over 148 weeks

- Treatment with blarcamesine (ANAVEX2-73) 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.





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

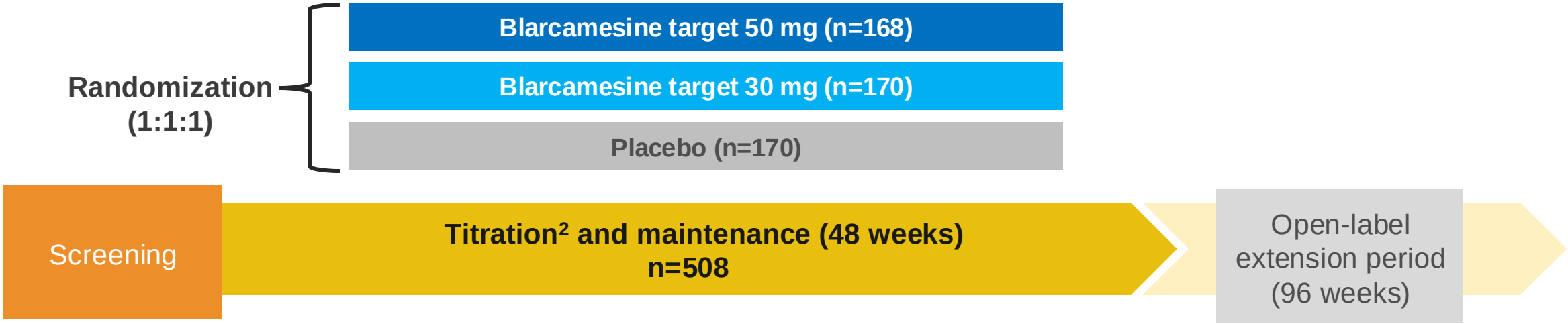


Lahmy V, et al. *Neuropsychopharmacology*, 2013 Aug;38(9):1706-23.
Hampel H, et al. *Alzheimer's Dement (N Y)*. 2020;6(1):e12013.
PoC, proof of concept; MMSE, Mini-Mental State Examination; ADCS-ADL, Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory.

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

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

ATTENTION-AD study

*With the March 2024 FDA Guidance for Early AD, a sole cognitive measure can serve as the primary endpoint for early AD trials

[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.

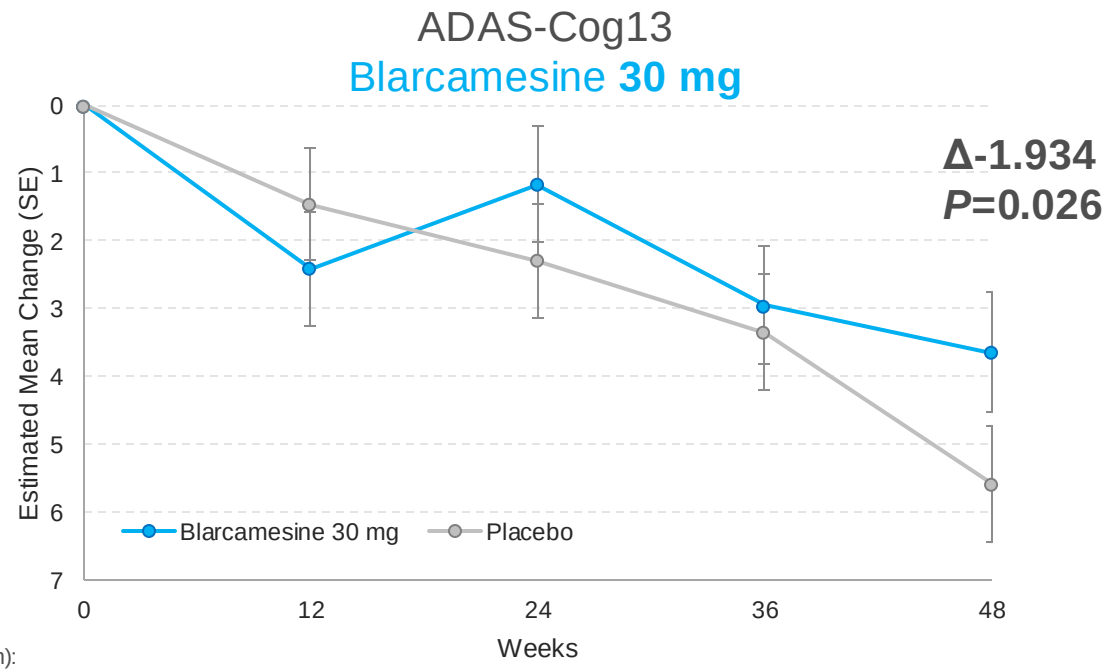
Baseline Demographics

Demographic Characteristics	Blarcamesine 30 mg (n=154)	Blarcamesine 50 mg (n=144)	Blarcamesine Pooled (n=298)	Placebo (n=164)
Sex, n (%)				
Female	74 (48.1)	69 (47.9)	143 (48.0)	82 (50.0)
Male	80 (51.9)	75 (52.1)	155 (52.0)	82 (50.0)
Age, Mean (SD)	73.7 (6.6)	74.1 (6.3)	73.9 (6.5)	73.5 (6.3)
Race, n (%)				
Asian	3 (1.9)	4 (2.8)	7 (2.3)	2 (1.2)
Black or other African American	0 (0)	0 (0)	0 (0)	2 (1.2)
Other	1 (0.6)	0 (0)	1 (0.3)	3 (1.8)
White	150 (97.4)	140 (97.2)	290 (97.3)	157 (95.7)
Ethnicity, n (%)				
Hispanic or Latino/a or of Spanish origin	5 (3.2)	2 (1.4)	7 (2.3)	1 (0.6)
Not disclosed	7 (4.5)	6 (4.2)	13 (4.4)	8 (4.9)
Not Hispanic or Latino/a or of Spanish origin	142 (92.2)	136 (94.4)	278 (93.3)	155 (94.5)
APOE ε4 genotype, n (%)				
Noncarrier	47 (30.5)	47 (32.6)	94 (31.5)	46 (28.0)
Carrier	99 (64.3)	89 (61.8)	188 (63.1)	106 (64.6)
Heterozygotes	69 (44.8)	65 (45.1)	134 (45.0)	76 (46.3)
Homozygotes	30 (19.5)	24 (16.7)	54 (18.1)	30 (18.3)
Missing	8 (5.2)	8 (5.6)	16 (4.0)	12 (7.3)

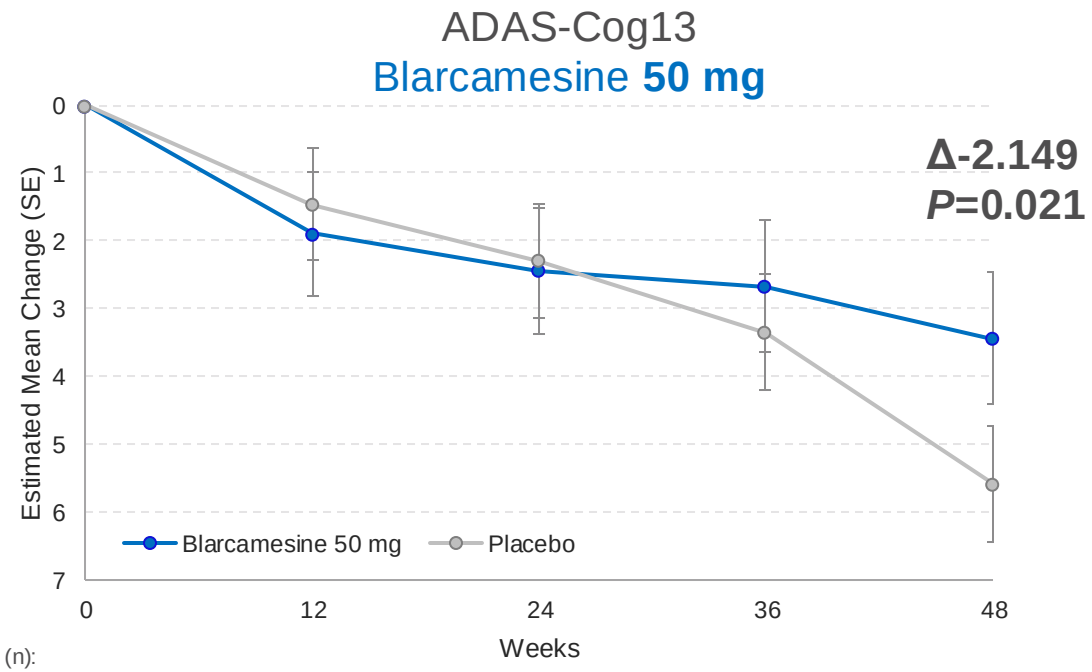
Baseline Clinical Characteristics

Characteristic	Blarcamesine 30 mg (n=154)	Blarcamesine 50 mg (n=144)	Blarcamesine Pooled (n=298)	Placebo (n=164)
Baseline Clinical Scores, Mean (SD)				
ADAS-Cog13	28.4 (8.4)	28.9 (9.1)	28.5 (8.5)	30.4 (8.4)
ADCS-ADL	66.7 (7.4)	67 (7.9)	66.9 (7.6)	66.4 (7.1)
CDR-SB	3.8 (1.6)	3.8 (1.8)	3.8 (1.7)	4.1 (1.8)
MMSE	23.6 (3.1)	23.6 (2.8)	23.6 (2.9)	23.0 (2.7)
Baseline CDR-Global scores, n (%)				
0	0 (0)	1 (0.7)	1 (0.3)	0 (0)
0.5	98 (63.6)	96 (66.7)	194 (65.1)	94 (57.3)
1.0	54 (35.1)	45 (31.3)	99 (33.2)	68 (41.5)
2.0	1 (0.6)	2 (1.4)	3 (1.0)	2 (1.2)
3.0	1 (0.6)	0 (0)	1 (0.3)	0 (0)
MMSE score at baseline, n (%)				
<20	11 (7.1)	9 (6.3)	20 (6.7)	10 (6.1)
≥20	143 (92.9)	135 (93.8)	278 (93.3)	154 (93.9)
Concomitant AD medication, n (%)				
Cholinesterase inhibitors (ChEIs)	102 (66.2)	104 (72.2)	206 (69.1)	108 (65.9)
Memantine	19 (12.3)	17 (11.8)	36 (12.1)	18 (11.0)
Baseline Plasma p-tau (181)				
No. of participants evaluated at baseline	145	132	277	153
Baseline mean (SD), pg/mL	61.88 (25.44)	62.62 (25.75)	62.23 (25.54)	65.42 (28.04)
Baseline Plasma p-tau (231)				
No. of participants evaluated at baseline	102	97	199	123
Baseline mean (SD), pg/mL	29.02 (29.55)	34.19 (50.76)	31.54 (41.24)	27.08 (34.58)

Coprimary Endpoint: ADAS-Cog13



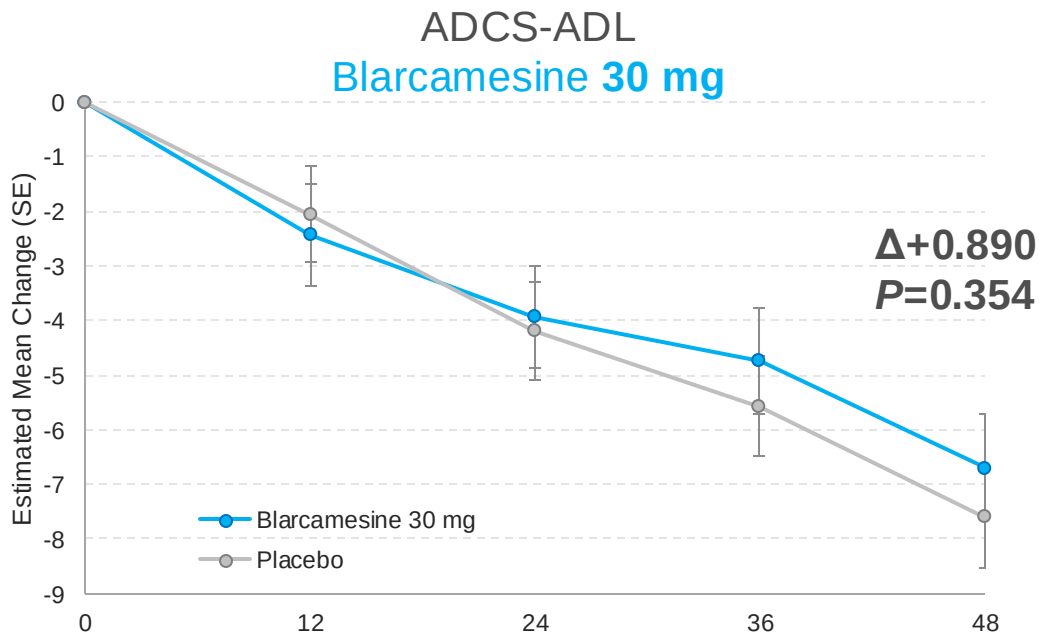
Participants (n):					
Blarcamesine 30 mg	154	130	117	108	108
Placebo	164	147	127	122	122



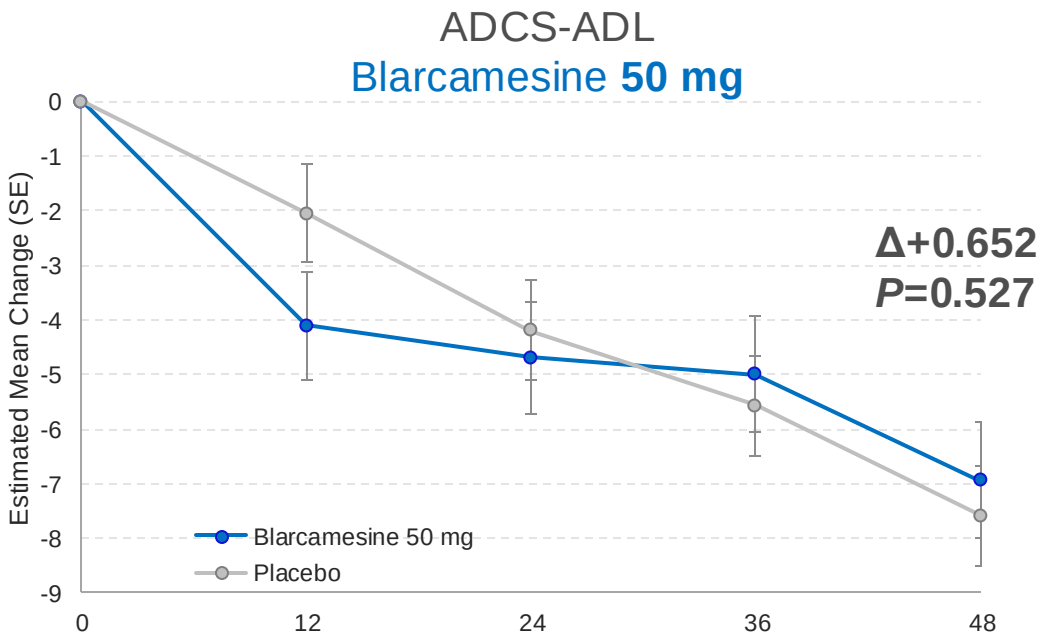
Participants (n):					
Blarcamesine 50 mg	144	111	91	79	83
Placebo	164	147	127	122	122

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).

Coprimary Endpoint: ADCS-ADL



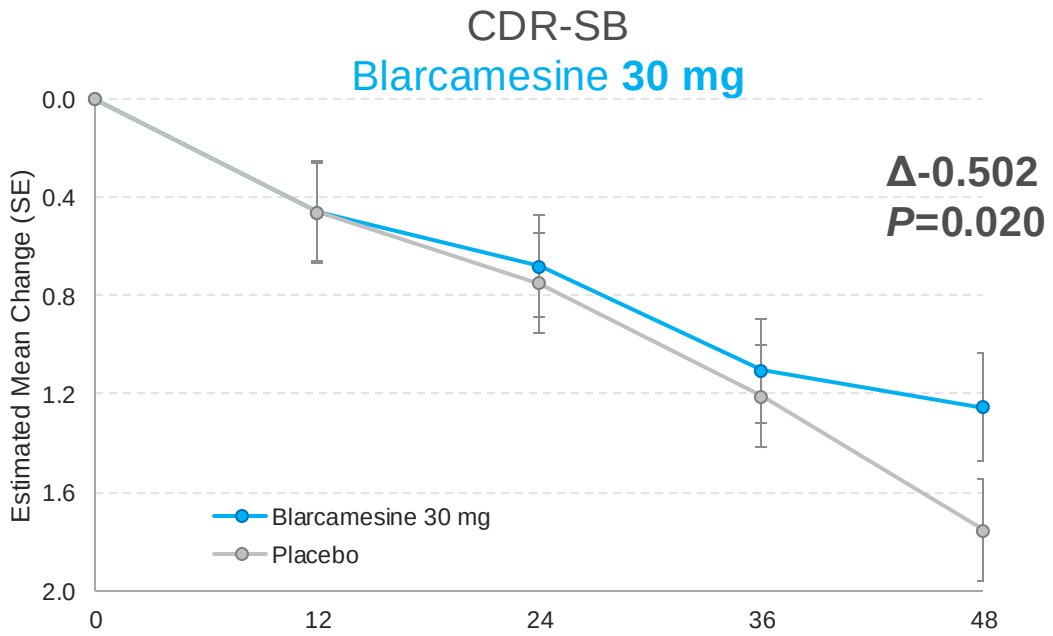
Participants (n):					
Blarcamesine 30 mg	154	127	118	109	109
Placebo	164	148	130	124	126



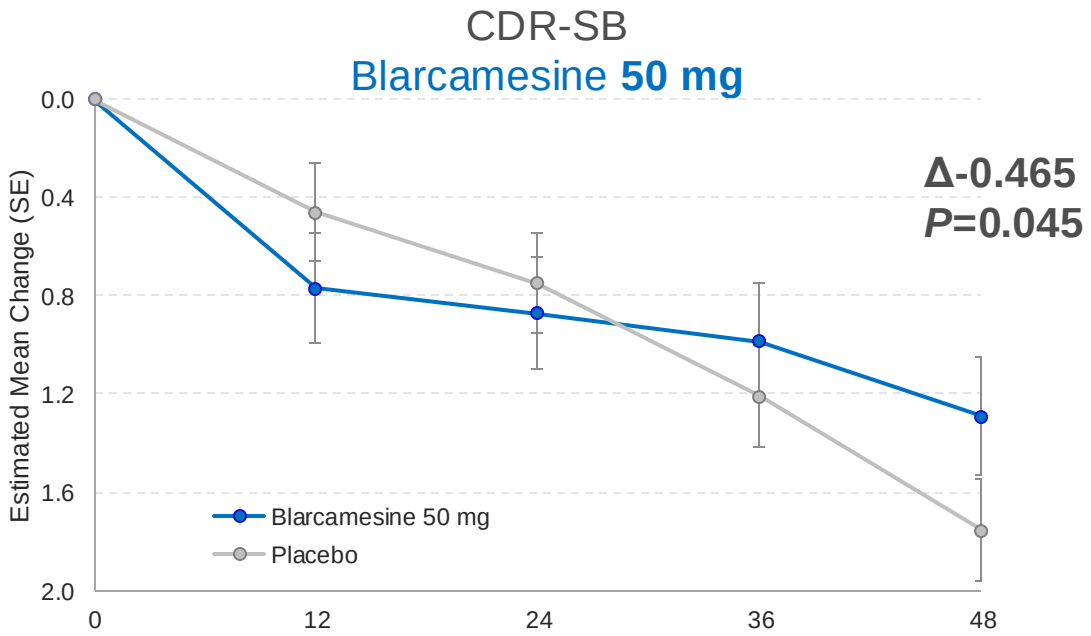
Participants (n):					
Blarcamesine 50 mg	144	111	91	82	85
Placebo	164	148	130	124	126

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).

Key Secondary Endpoint: CDR-SB



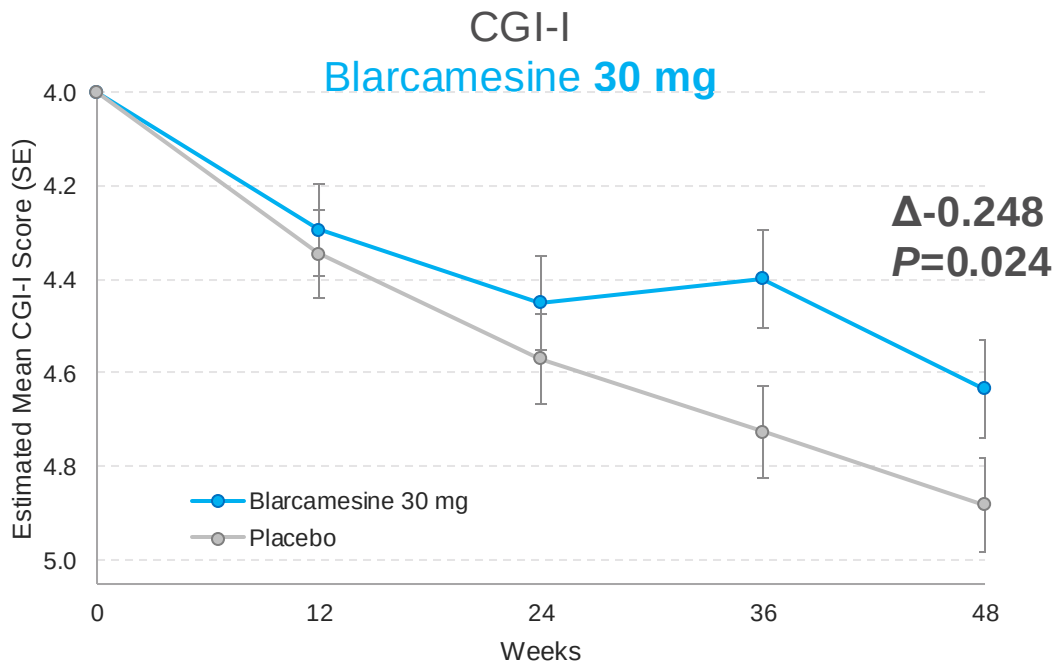
Participants (n):					
Blarcamesine 30 mg	154	128	117	108	107
Placebo	164	146	128	121	126



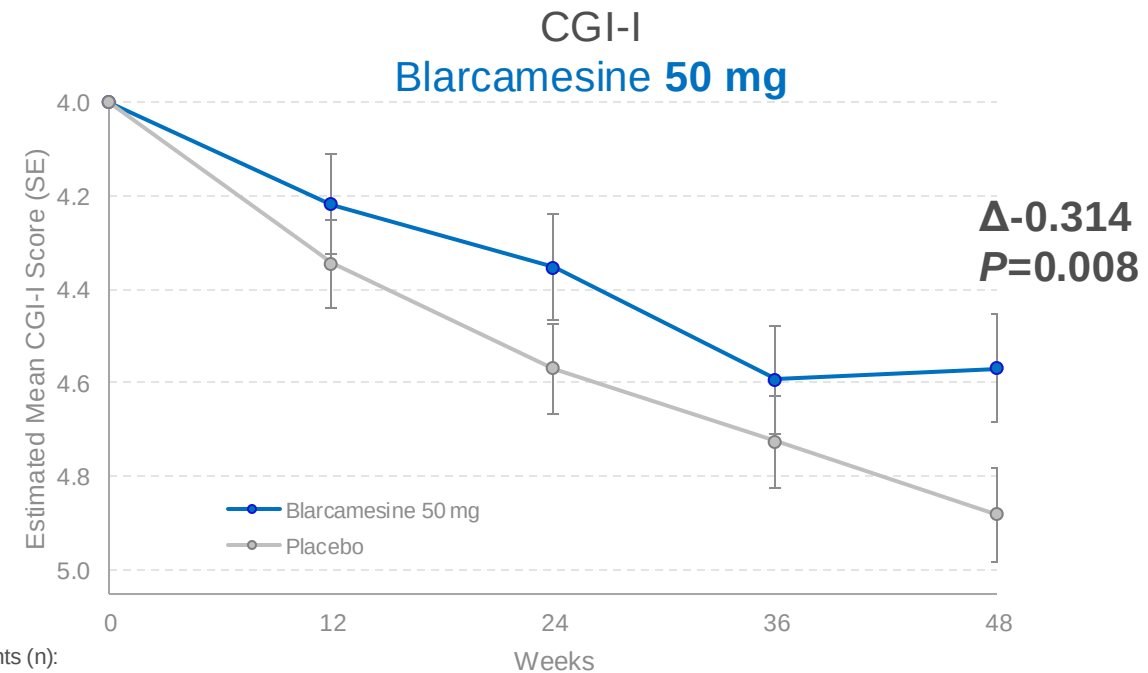
Participants (n):					
Blarcamesine 50 mg	144	108	91	81	84
Placebo	164	146	128	121	126

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).

Exploratory Endpoint: CGI-I



Participants (n):					
Blarcamesine 30 mg	153	130	118	104	107
Placebo	163	146	129	123	125



Participants (n):					
Blarcamesine 50 mg	143	107	89	82	83
Placebo	163	146	129	123	125

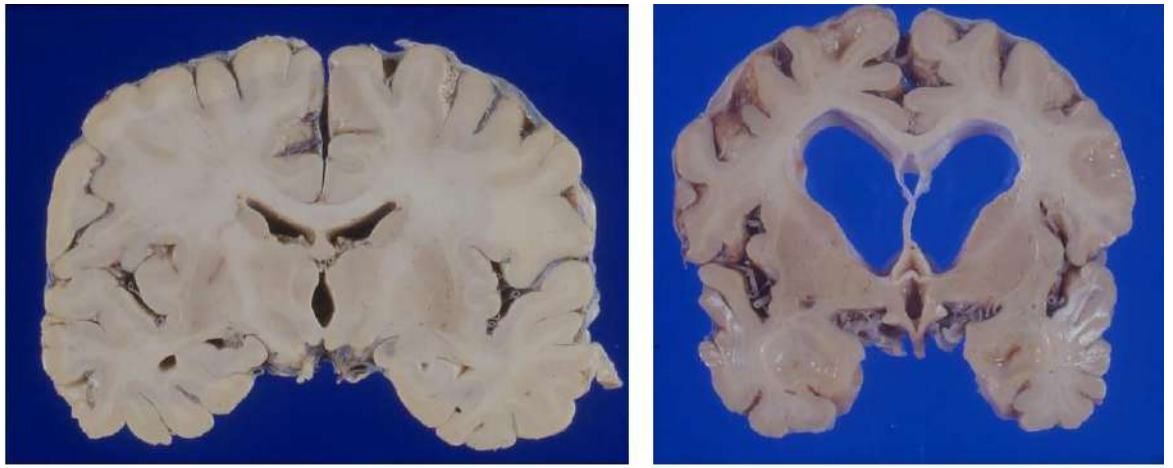
Clinical efficacy endpoints were analyzed using mixed model for repeated measures (MMRM) estimates for the least-squares mean change from baseline at 12, 24, 36, and 48 weeks, with error bars representing standard error (SE).

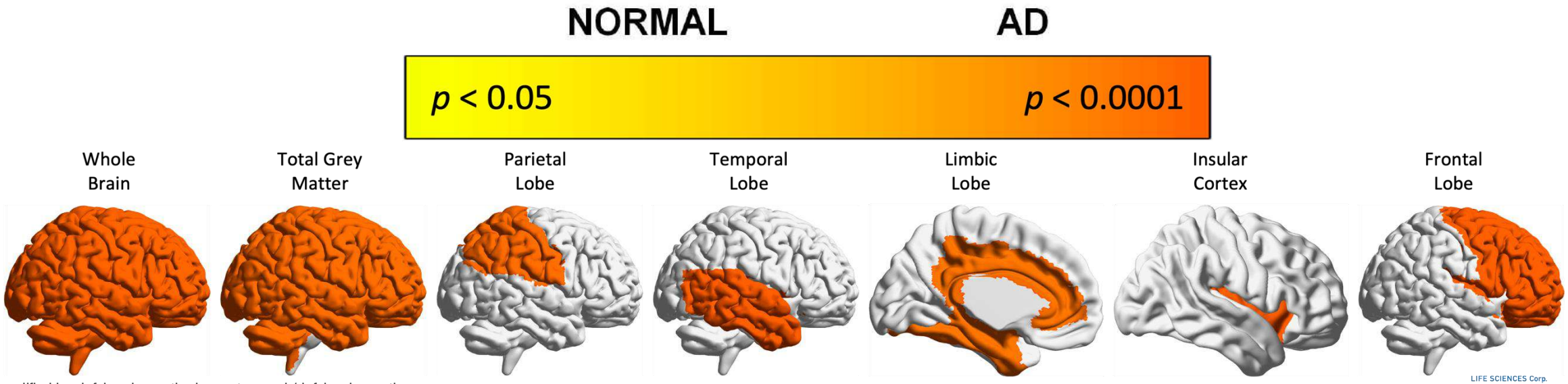
Clinical Global Impression – Improvement scale (CGI-I). CGI-I baseline is represented as a score of 4, which represents “no change” in clinical improvement.

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]

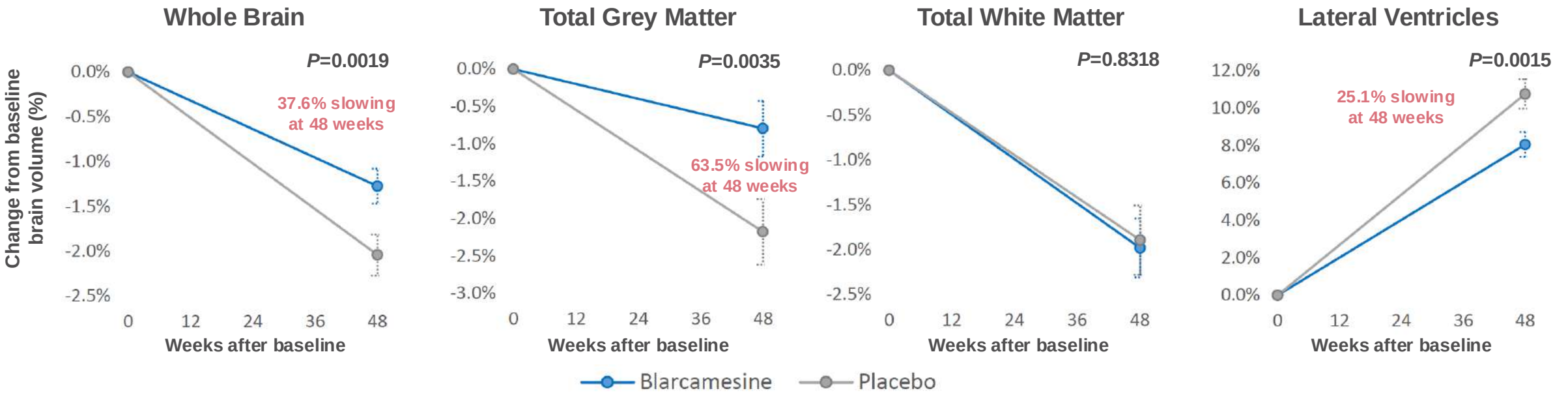




1. Exemplified by defying dementia. lancaster.ac.uk/defyingdementia
2. Data on file. Anavex Life Sciences Corp. https://www.anavex.com/post/anavex-sphase2b-3trialofblarcamesine-anavex-2-73-inpatientswithalzheimer-sdisease

Reduced Brain Atrophy in Blarcamesine-Treated Patients Compared to Placebo

Annualized percent change in volumetric MRI at 48 weeks, pooled blarcamesine vs placebo

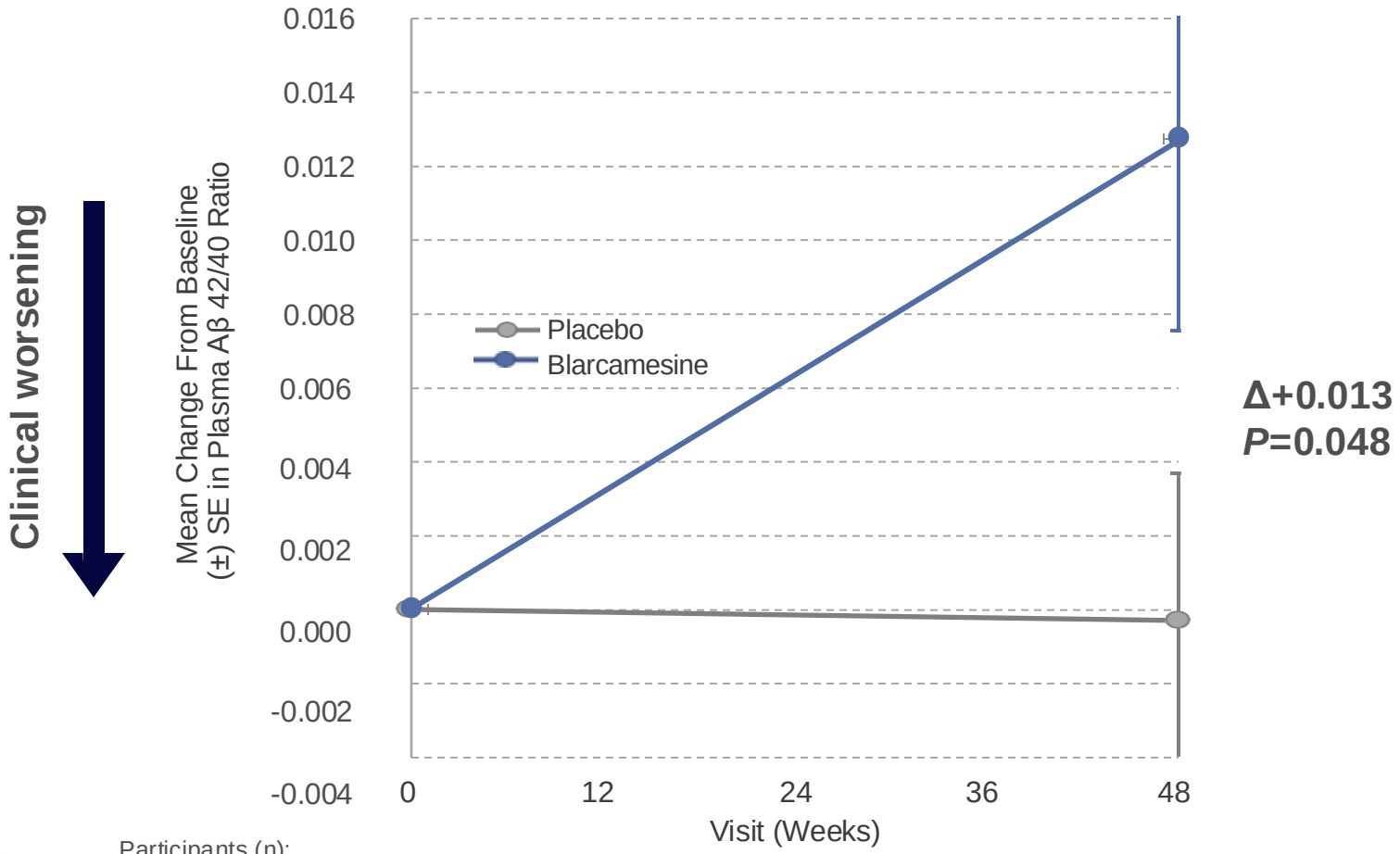


Whole Brain		Total Grey Matter		Total White Matter		Lateral Ventricles	
Participants (n)		Participants (n)		Participants (n)		Participants (n)	
Blarcamesine Week 0 (298)	Week 48 (165)	Blarcamesine Week 0 (298)	Week 48 (165)	Blarcamesine Week 0 (298)	Week 48 (166)	Blarcamesine Week 0 (298)	Week 48 (166)
Placebo Week 0 (164)	Week 48 (100)	Placebo Week 0 (164)	Week 48 (100)	Placebo Week 0 (164)	Week 48 (100)	Placebo Week 0 (164)	Week 48 (100)

Pooled blarcamesine 30 mg and 50 mg results. Results are based on linear modeling using treatment group, baseline volume, and baseline MMSE status (<20 or >20) as covariates.

Exploratory Outcome: Plasma Amyloid Beta 42/40

Plasma amyloid beta 42/40 ratio significantly increased in blarcamesine-treated patients compared to placebo at 48 weeks.

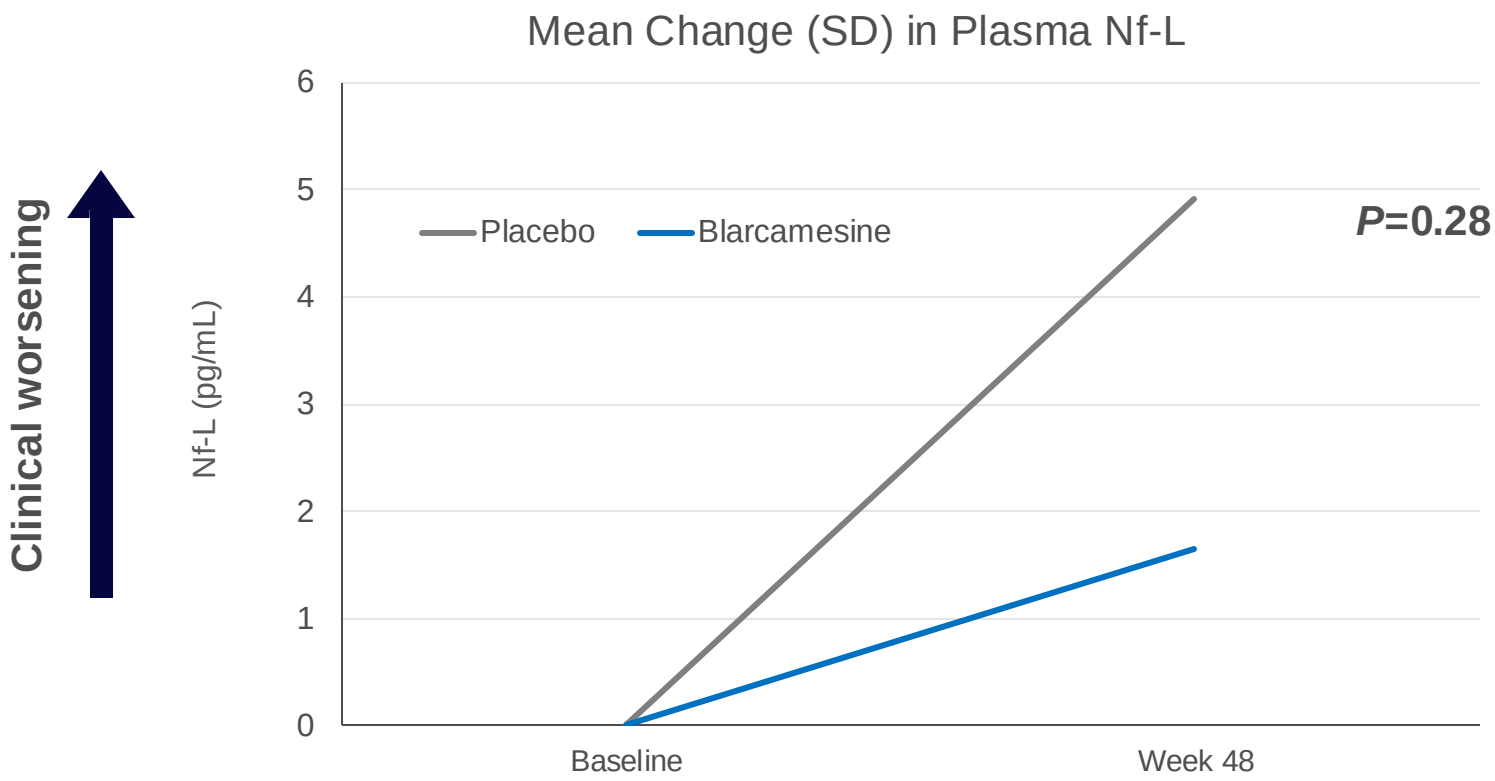


Pooled blarcamesine 30 mg and 50 mg results.

AB, amyloid beta; SE, standard error.

Participants (n):			
Blarcamesine	298		119
Placebo	164		78

Exploratory Outcome: Plasma Biomarkers (Nf-L)



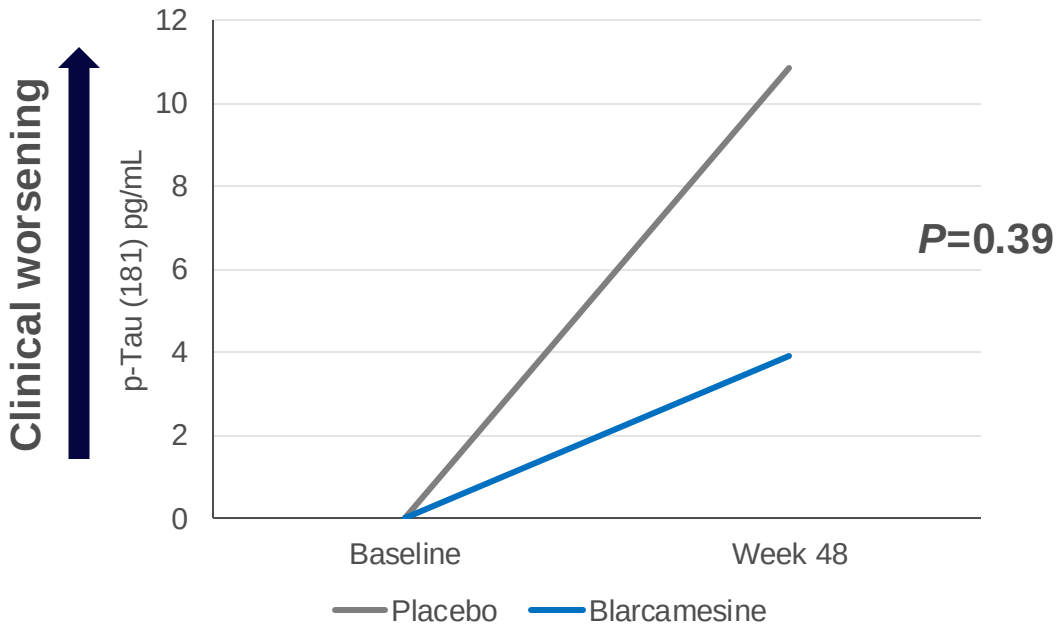
Participants (n):		
Blarcamesine	298	182
Placebo	164	122

Pooled blarcamesine 30 mg and 50 mg results.

Nf-L, neurofilament light chain; mL, milliliter; pg, picogram; SD, standard deviation.

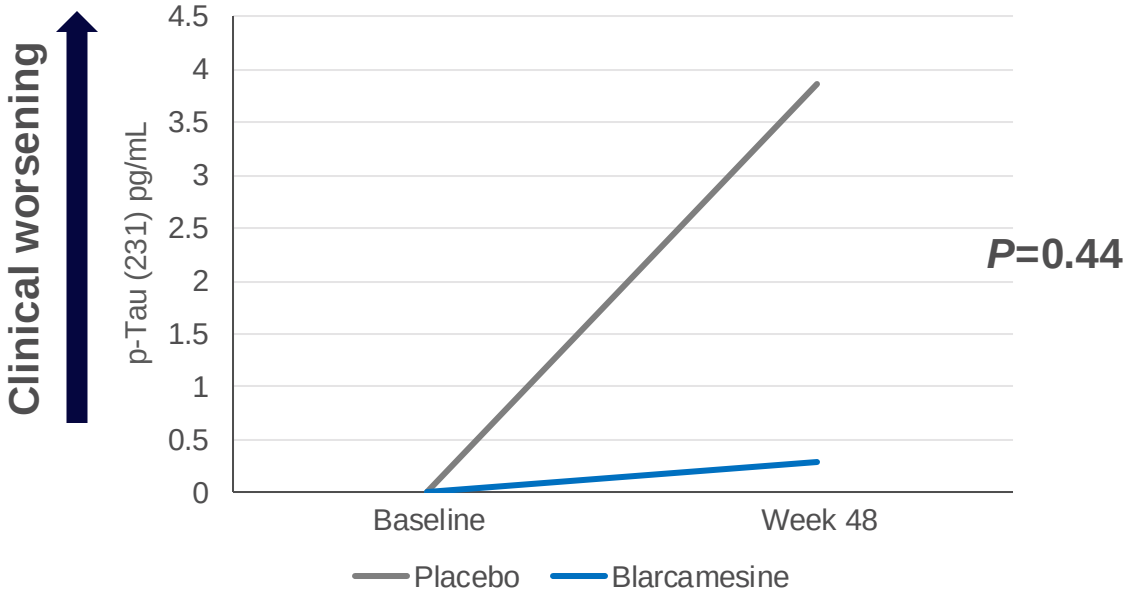
Exploratory Outcome: Plasma Biomarkers (p-Tau)

Mean Change (SD) in Plasma p-Tau (181)



Participants (n):		
Blarcamesine	298	165
Placebo	164	117

Mean Change (SD) in Plasma p-Tau (231)



Participants (n):		
Blarcamesine	298	105
Placebo	164	83

Pooled blarcamesine 30 mg and 50 mg results.

Nf-L, neurofilament light chain; mL, milliliter; pg, picogram; SD, standard deviation.

Adverse Events Summary, Full Safety Population

Adverse Events Summary	Blarcamesine 30 mg	Blarcamesine 50 mg	Blarcamesine	Placebo
Patients, n	167	168	335	168
Death, n (%)	0	1 (0.6)	1 (0.3)	1 (0.6)
Death considered related to treatment	0	0	0	0
Participants with ≥1 serious TEAEs, n (%)	25 (15.0)	31 (18.5)	56 (16.7)	17 (10.1)
TEAE, n (%)	159 (95.2)	165 (98.2)	324 (96.7)	129 (76.8)
TEAE leading to treatment and study discontinuation, n (%)	41 (24.6)	67 (39.9)	108 (32.2)	12 (7.1)
Blarcamesine titration AE ≥5%, n (%)	167	168	335	168
Dizziness	53 (31.7)	67 (39.9)	120 (35.8)	10 (6.0)
Confusional state	24 (14.4)	24 (14.3)	48 (14.3)	1 (0.6)
Balance disorder	12 (7.2)	13 (7.7)	25 (7.5)	1 (0.6)
Fatigue	9 (5.4)	10 (6.0)	19 (5.7)	0
Anxiety	8 (4.8)	10 (6.0)	18 (5.4)	0
Nausea	8 (4.8)	13 (7.7)	21 (6.3)	8 (4.8)
Blarcamesine Maintenance TEAE ≥5.0%, n (%)	148	153	301	161
Dizziness	28 (18.9)	48 (31.4)	76 (25.2)	9 (5.6)
Confusional state	16 (10.8)	24 (15.7)	40 (13.3)	4 (2.5)
Fall	12 (8.1)	9 (5.9)	21 (7.0)	16 (9.9)
Depressed mood	8 (5.4)	7 (4.6)	15 (5.0)	3 (1.9)
Headache	8 (5.4)	11 (7.2)	19 (6.3)	6 (3.7)
Anxiety	6 (4.1)	11 (7.2)	17 (5.6)	6 (3.7)
Balance disorder	5 (3.4)	11 (7.2)	16 (5.3)	2 (1.2)

AEs including dizziness were transient and are manageable.

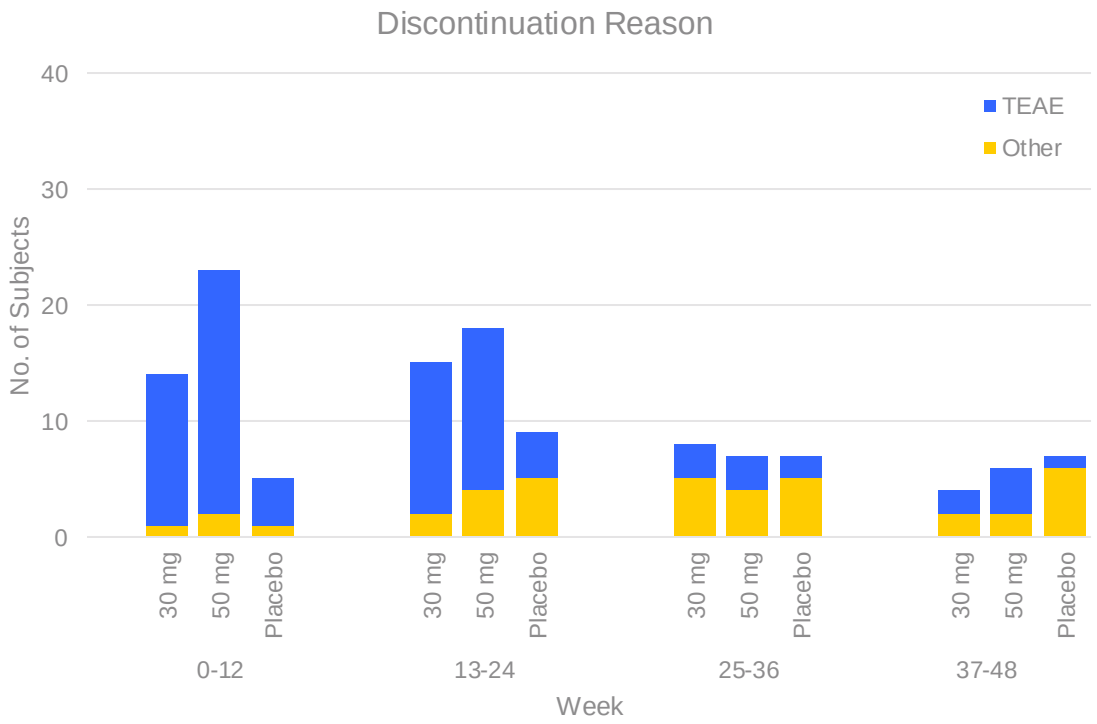
TEAEs tend to occur in first 24 weeks and might be related to titration schedule.

Summary: Safety Population

- TEAEs tend to occur in first 24 weeks and related to titration schedule
- AEs including dizziness:
  - Mostly Grade 1 or 2 (mild)
  - Transient (approx. 7-11 days)
  - Manageable by adjusting titration and dosing time

Early Discontinuations (Due to Titration Schedule)

- Early discontinuations due to TEAE (**blue**) before Week 24 might be related to up-titration of blarcamesine to the target doses coupled with administration early in the morning
- These events can be addressed by adjusting titration schedule to slower titration and nighttime dosing, as has been positively observed in the blarcamesine compassionate use program
- The low dropouts for non-TEAE reasons, 'Other' (**yellow**) are consistent across blarcamesine and placebo groups, which suggests that there are no dropouts due to lack of efficacy in the blarcamesine group
- There is no evidence that early discontinuations introduced a bias in favor of blarcamesine



Blarcamesine 30 mg group and 50 mg group results.

TEAE, Treatment Emergent Adverse Events.

Summary: Blarcamesine AD-004 Phase IIb/III Study in Early Alzheimer's Disease

- Blarcamesine once daily orally significantly slowed clinical decline:
  - ✓ ADAS-Cog13 at 48 Weeks: by **38.5%** (50-mg group) and by **34.6%** (30-mg group).
  - ✓ Key Secondary Endpoint CDR-SB at 48 Weeks: by **26.5%** (50-mg group) and by **28.6%** (30-mg group).
- ADCS-ADL was trending positive but did not reach significance at Week 48.
- Blarcamesine significantly slowed brain atrophy in key regions of interest, including 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 was relatively safe and no associated neuroimaging adverse events.

Conclusions

Blarcamesine once orally daily restores autophagy through SIGMAR1 activation.

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

- ✓**Good comparative safety profile (no ARIA)**
- ✓**Improvement in ADAS-Cog13 coprimary efficacy endpoint**
- ✓**Meaningful treatment effect on predesignated biomarkers within the A/T/N spectrum**
- ✓**Promising clinical results:**

  The positive results from this trial are encouraging as the recent FDA guidance to consider approval may be based on a single cognitive endpoint (like ADAS-Cog) in Early Alzheimer's disease trials[1]

1. US Food and Drug Administration. Early Alzheimer's Disease: Developing Drugs for Treatment: Guidance for Industry. Accessed July 2, 2024. https://www.fda.gov/media/110903/download

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