Phase IIb/III Trial of Blarcamesine in Early Alzheimer Disease Demonstrates Pre-specified Clinical Efficacy Through Upstream SIGMAR1 Activation

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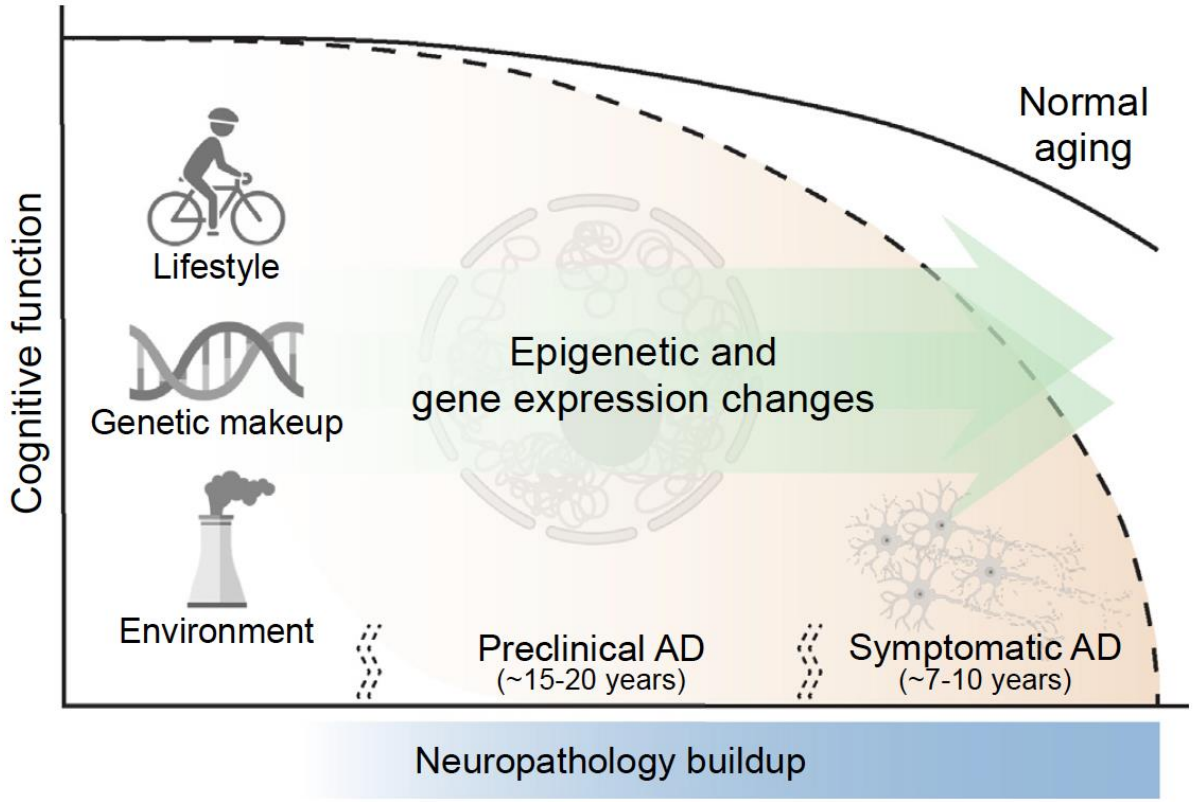
Blarcamesine: Mechanism of Action in Alzheimer’s Disease (AD)

AD Pathology Is Highly Heterogeneous and Complex



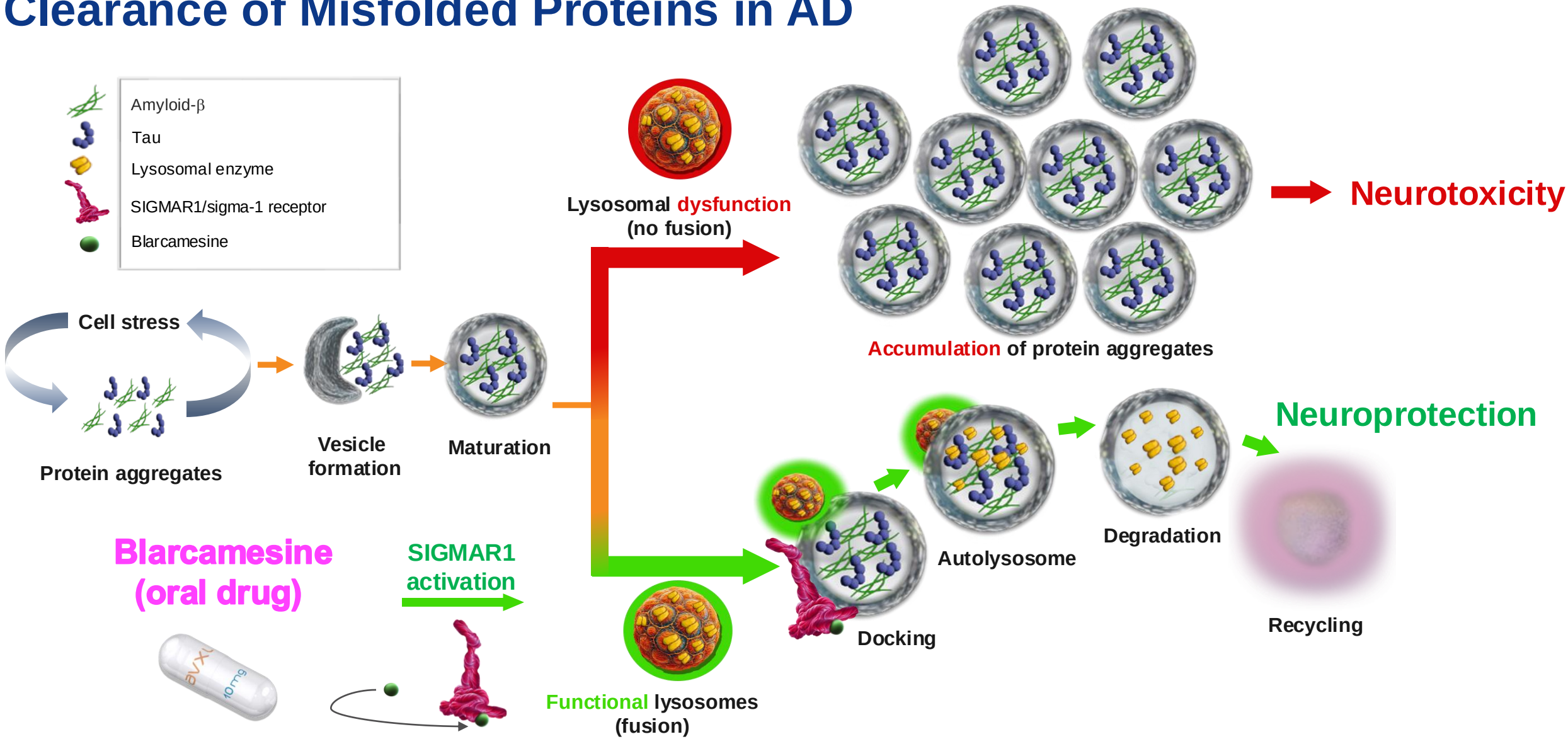
… influenced by genotype, environment, cognitive reserve, and a range of demographic factors

… 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.
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- 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:

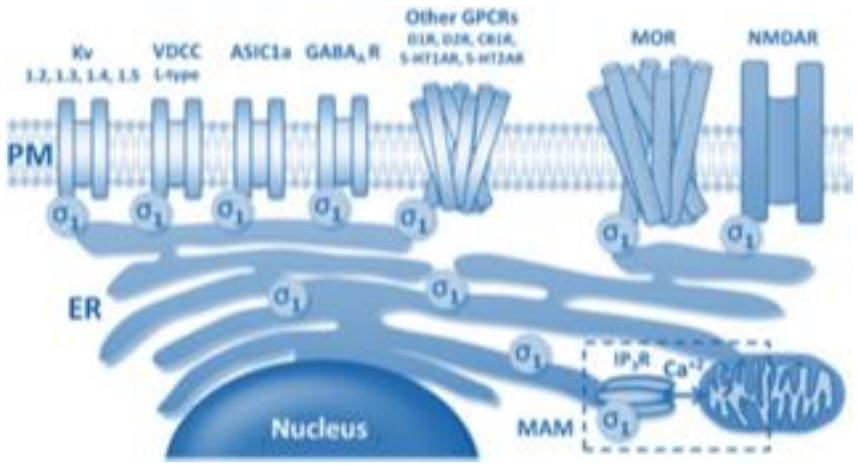
  ✓Countering neurodegeneration

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

Blarcamesine MoA: Confirmation of Upstream SIGMAR1 Activation

Genetic SIGMAR1 Mutations (Variants) Linked to Suboptimal Function

SIGMAR1 is an integral membrane protein involved in restoration of cellular homeostasis
It activates an upstream compensatory process: Autophagy through SIGMAR1 activation



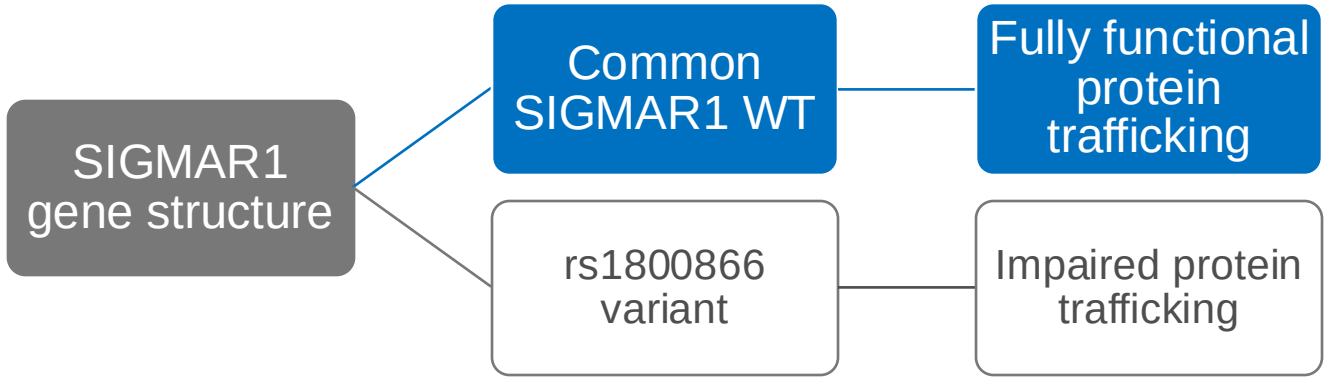
- In Alzheimer's disease patients, mutations (variants) of the SIGMAR1 gene have been identified*
- Impaired SIGMAR1 function (gene mutation, variants) leads to suboptimal function
- Patients who carry the Common SIGMAR1 wild type (WT)** gene are expected to have stronger response to blarcamesine than patients with the mutation (variant)

** Feher A et al 2012. Neurosci Lett; 517: 136-139.*

*** WT = homozygous dominant (TT)*

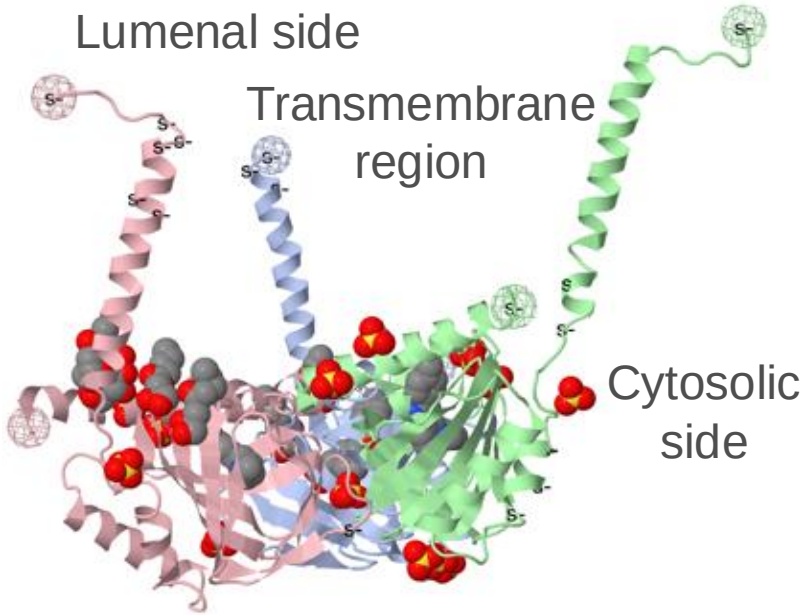
Blarcamesine MoA: Confirmation of Upstream SIGMAR1 Activation

SIGMAR1 Gene Plays a Key Role in Protein Trafficking



~70% of population → greater benefit

~30% of population → benefit



- Majority of the general population (~70%) carries Common SIGMAR1 WT* gene
- Common SIGMAR1 WT gene carriers (~70% of general population) are expected to experience greater benefit from SIGMAR1 activation with blarcamesine

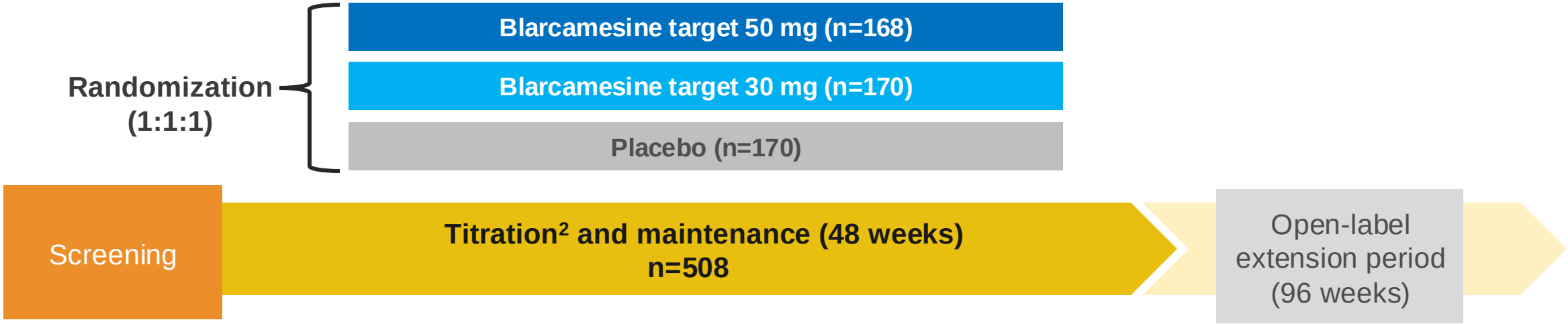
Adapted from: Laurini E., Marson D., Fermeglia M., Pricl S. (2017) 3D Homology Model of Sigma1 Receptor. Evolution of the Concept of Sigma Receptors. Handbook of Experimental Pharmacology, vol 244. Springer, Cham; Schmidt H.R. et al, Nature. 2016 Apr 28; 532(7600): 527–530

** WT = homozygous dominant (TT)*

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
- SIGMAR1 gene variant analysis

ATTENTION-AD study

*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

[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.

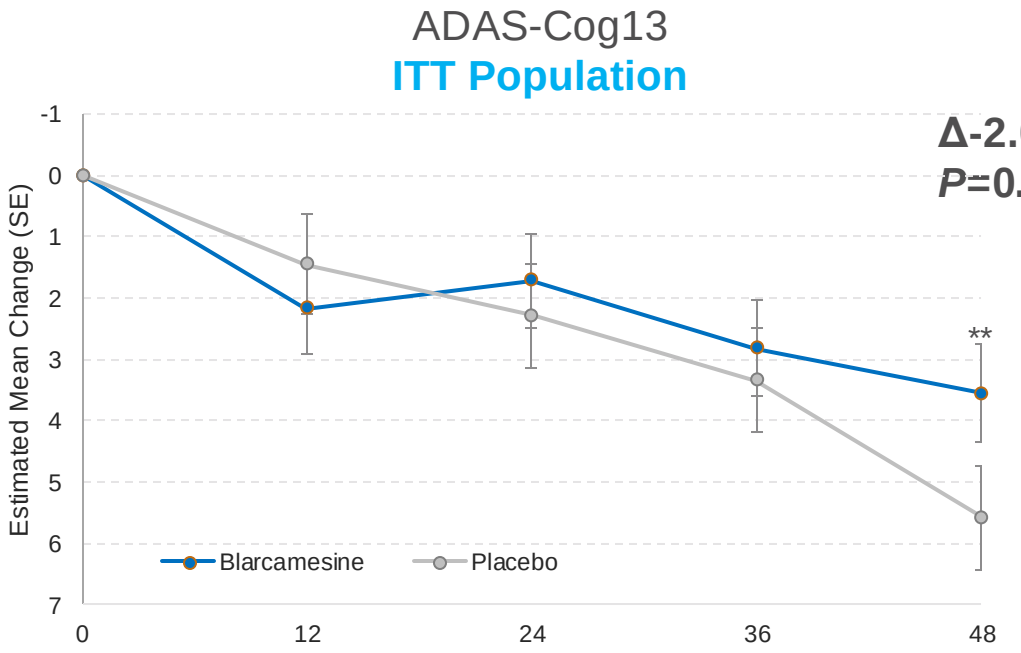
Baseline Demographics

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)

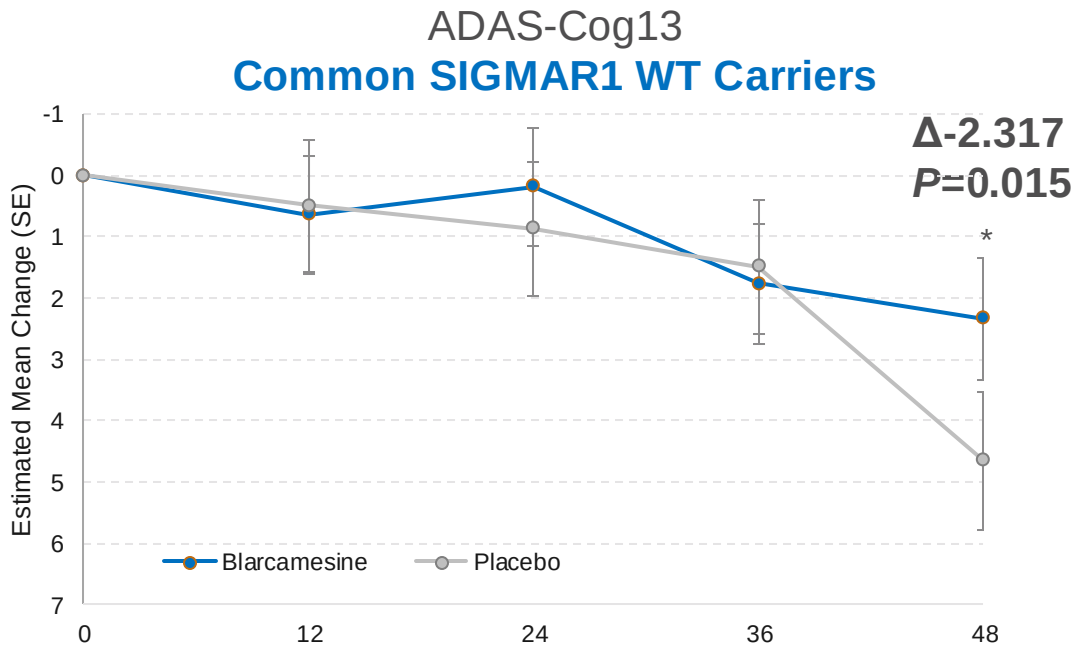
Baseline Clinical Characteristics

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	298	241	208	187	191
Placebo	164	147	127	122	122



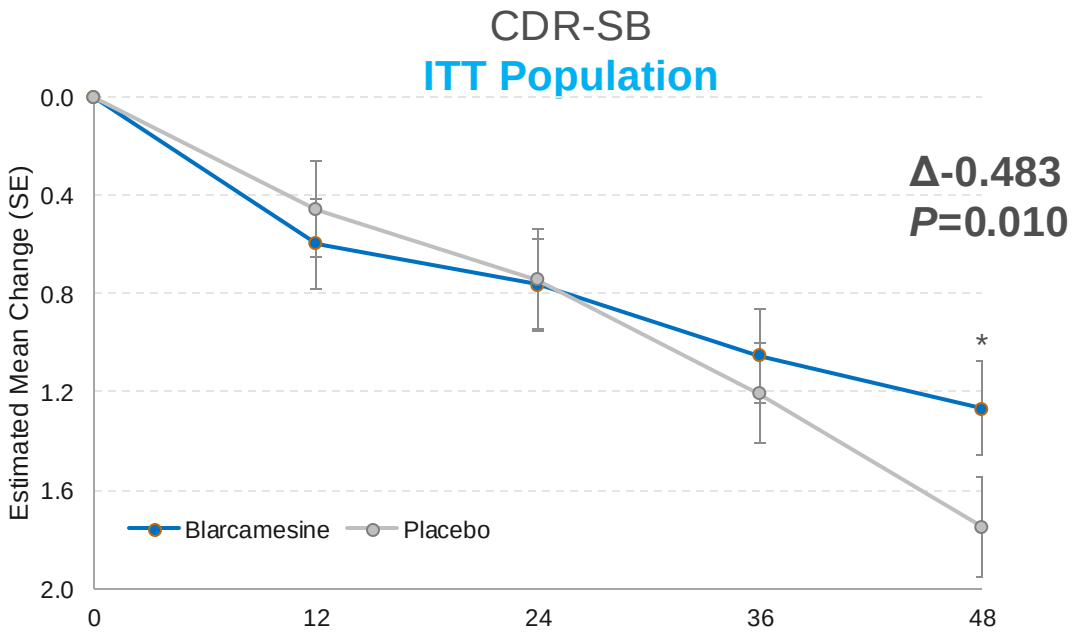
Participants (n):					
Blarcamesine	199	168	150	137	137
Placebo	101	94	84	80	81

- Clinical meaningful outcome (ADAS-Cog delta is >2.0)*

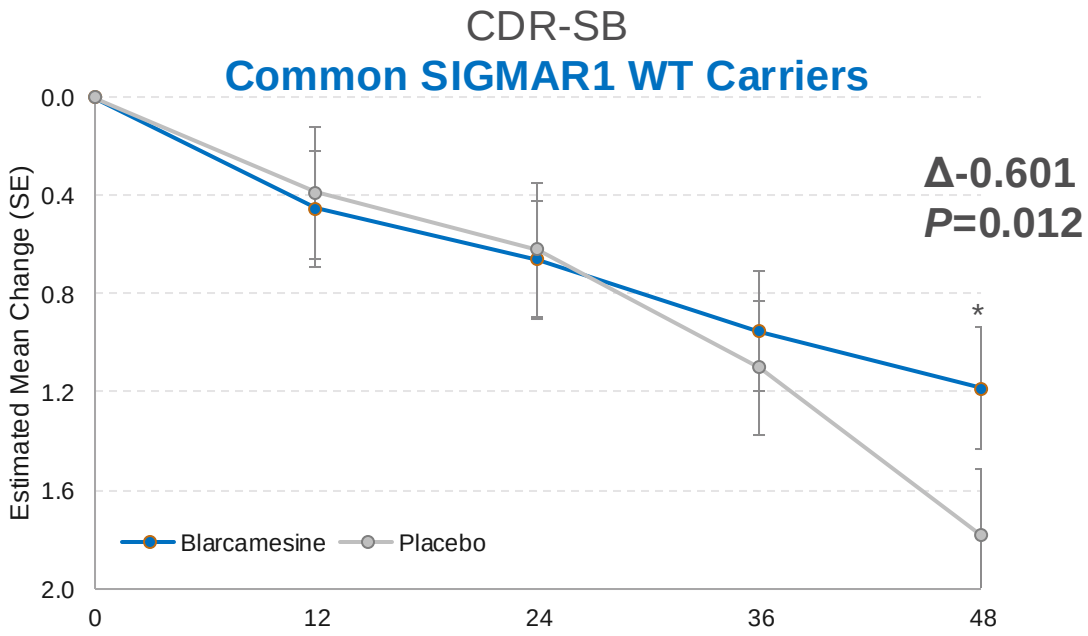
Clinical efficacy endpoints were analyzed using mixed model for repeated measures (MMRM) estimates for the least-squares mean change from baseline at 12, 24, 36, and 48 weeks, with error bars representing standard error (SE). Intent-to-treat (ITT) population which is defined as all randomized patients who received at least 1 dose of double-blind study drug and have at least 1 post-baseline efficacy assessment. Participant numbers (n) below the plot represent subjects with non-missing data at each study visit. *: $p < 0.05$; **: $p < 0.01$

** Muir RT et al. 2024 Alzheimers Dement. 20:3352–3363*

Key Secondary Endpoint: CDR-SB



Participants (n):					
Blarcamesine	298	236	208	189	191
Placebo	164	146	128	121	126



Participants (n):					
Blarcamesine	198	164	150	139	137
Placebo	101	93	84	79	85

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). Intent-to-treat (ITT) population which is defined as all randomized patients who received at least 1 dose of double-blind study drug and have at least 1 post-baseline efficacy assessment. Participant numbers (n) below the plot represent subjects with non-missing data at each study visit. *: $p < 0.05$; **: $p < 0.01$

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

Clinical Data Evidence with Blarcamesine in Alzheimer's Disease

- Blarcamesine once daily orally significantly slowed clinical decline in ITT population:
  - ✓ ADAS-Cog13 at 48 Weeks: by **36.3%**
  - ✓ Key Secondary Endpoint CDR-SB at 48 Weeks: by **27.6%**

Confirmation of beneficial clinical effect through upstream SIGMAR1 activation:

- Blarcamesine once daily orally significantly slowed clinical decline with greater clinical benefit in pre-specified Common SIGMAR1 wild-type (WT) carrier population:*
  - ✓ ADAS-Cog13 at 48 Weeks: by **49.8%**
  - ✓ Key Secondary Endpoint CDR-SB at 48 Weeks: by **33.7%**

- 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

* ~70% of the general population

Conclusions

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

[Macfarlane, S. et al. (submitted). *Blarcamesine for the treatment of Early Alzheimer's Disease: Results from the ANAVEX2-73-AD-004 Phase IIb/III trial*] In the Phase IIb/III clinical trial, blarcamesine also 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