# Top Line Data of ANAVEX®2-73 (*blarcamesine*) Randomized, Double-blind, Multicenter, Placebo-controlled Phase 2b/3 in Patients with Early Alzheimer's Disease (AD)

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# Disclosures

Stephen Macfarlane:

- Speakers' Honoraria: Eli Lilly, Lundbeck, Janssen
- Advisory Boards: Eli Lilly, Roche, Biogen
- Research funding: Eli Lilly, Roche, Merck, Prana Biotechnology, Novo Nordisk, Janssen, Eisai, Anavex Life Sciences
- Paid stipend: Medical Safety Monitor for Anavex Rett syndrome program

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# Today's Highlights

- A Novel Platform Approach to Address the Complexity of CNS Diseases by Activation of SIGMAR1 by Orally Available Small Molecule (ANAVEX®2-73 – *blarcamesine*)
- ANAVEX®2-73 Phase 2b/3 AD Study Met Primary Endpoints, Showing Statistically Significant Reduction of Clinical Decline In Global Clinical Study of Patients With Early Alzheimer's Disease
- Consistent Scientific Rationale with Correlating Biomarkers with Clinical Outcome Measures by Applying Genetic Precision Medicine
- Confirmed Human Patient Data also in other Disorders of Cognitive Impairment: Rett Syndrome (RTT), Parkinson's Disease Dementia (PDD)

# ANAVEX®2-73 (*blarcamesine*) Mechanism of Action

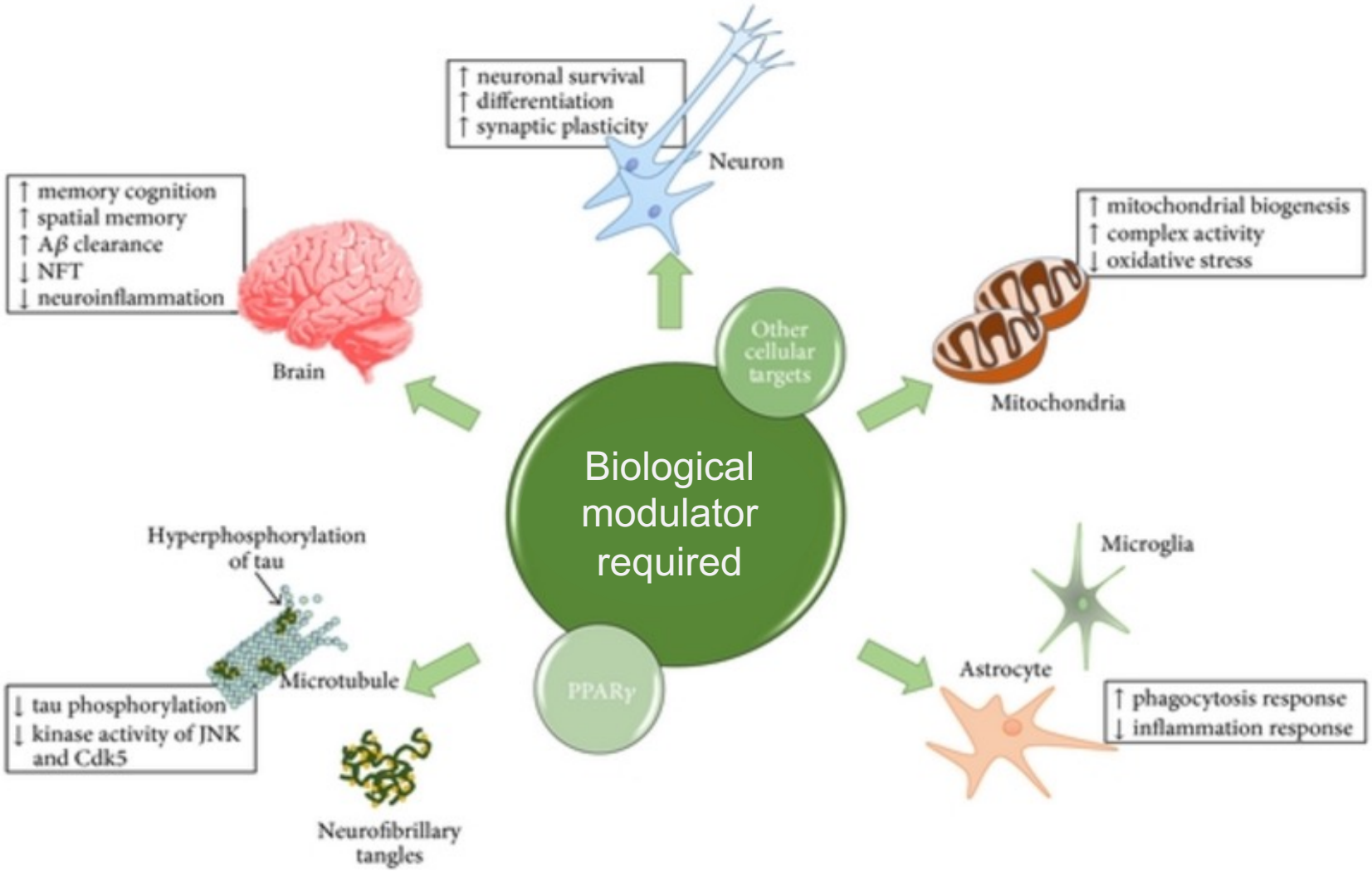
# Alzheimer’s Disease (AD) Pathology is Complex

- Amyloid beta
- Tau hyper-phosphorylation
- Mitochondrial dysfunction
- Inflammation
- Synaptic dysfunction
- Cellular stress / protein misfolding

# AD Pathology is Complex

## Targeting:

- ☑ Amyloid beta
- ☑ Tau hyper-phosphorylation
- ☑ Mitochondrial dysfunction
- ☑ Inflammation
- ☑ Synaptic dysfunction
- ☑ Cellular stress / protein misfolding

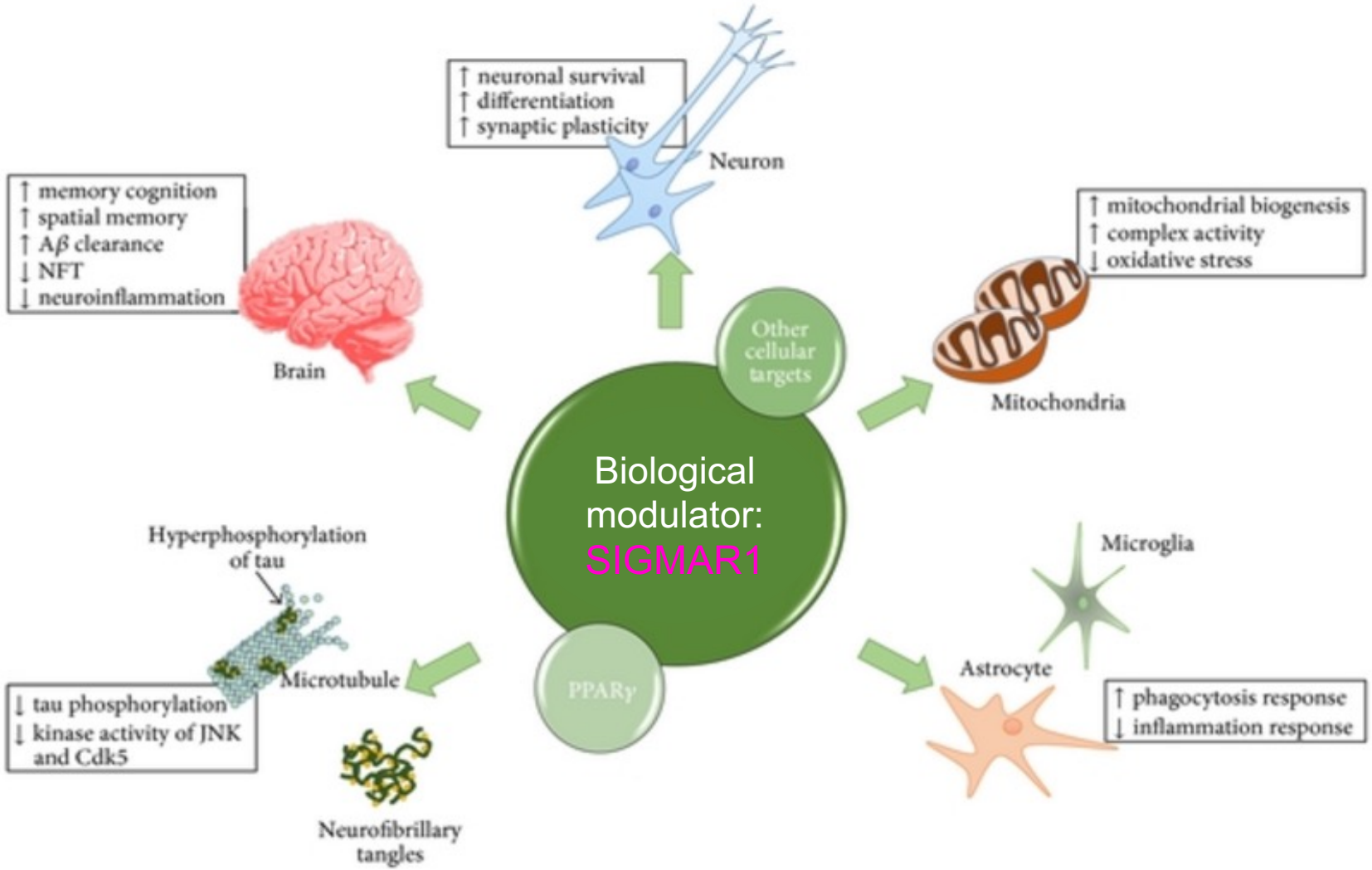



*Adapted from Perez et al., PPAR Res. 2015;2015:957248*

# AD Pathology is Complex … Upstream SIGMAR1 Activation ➔ Right Direction

## Targeting:

- ☑ Amyloid beta
- ☑ Tau hyper-phosphorylation
- ☑ Mitochondrial dysfunction
- ☑ Inflammation
- ☑ Synaptic dysfunction
- ☑ Cellular stress / protein misfolding




*Adapted from Perez et al., PPAR Res. 2015;2015:957248*

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

## Sigma-1 receptor agonists have been shown to restore neuronal functions in neurodegenerative processes

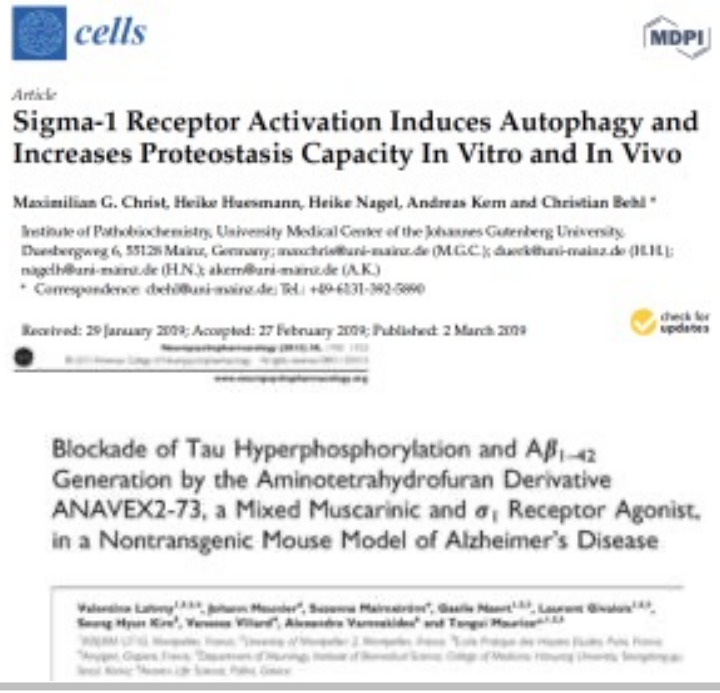
Journal of Pharmacological Sciences

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

## ANAVEX®2-73 enhances autophagy and alleviates 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 Huesmann, 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

## Sigma-1 receptor agonists have a neuroprotective effect in neurodegenerative disease models

REVIEW ARTICLE

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

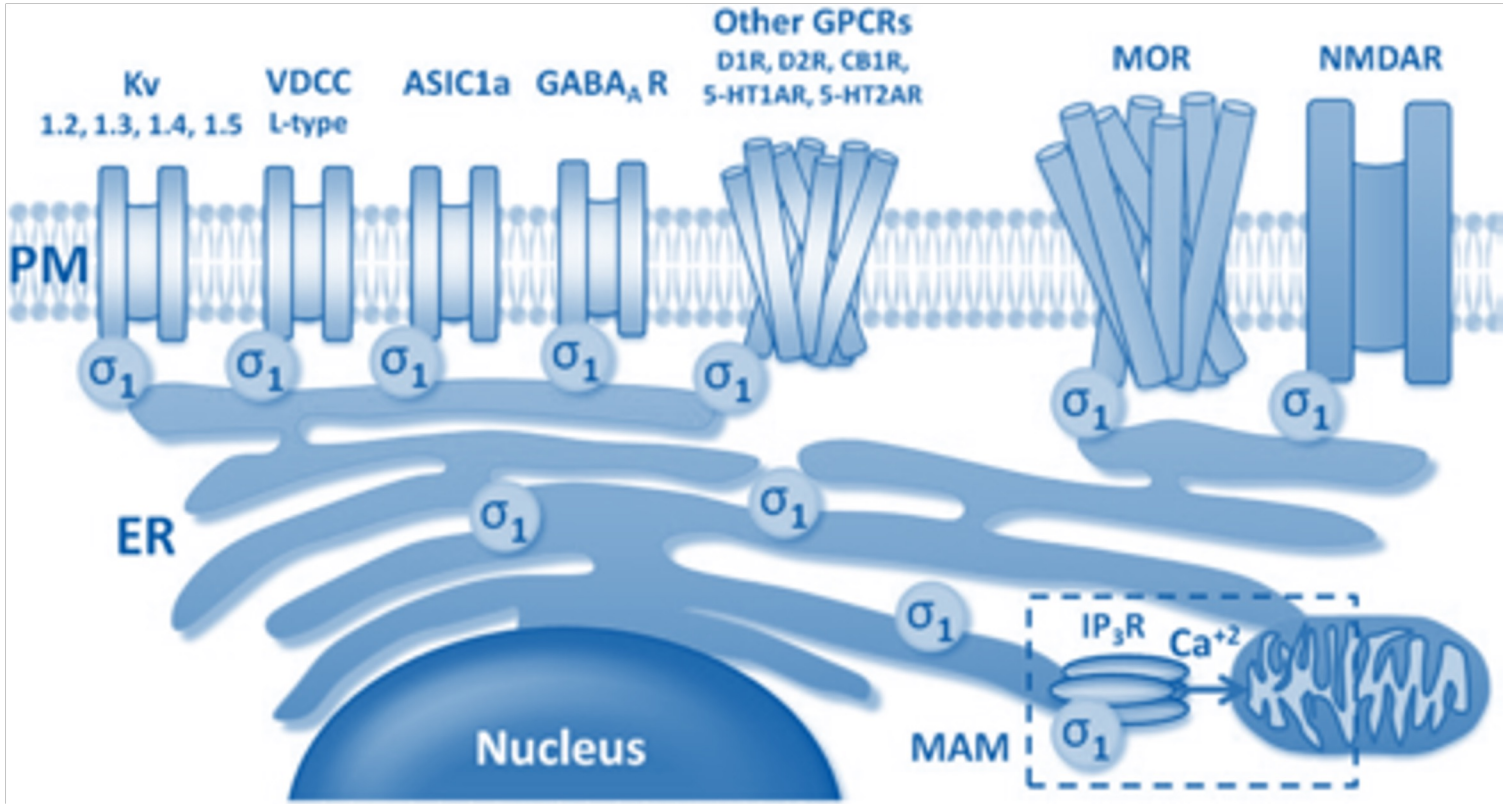
Neuronal Sigma-1 receptors: signaling functions and protective roles in neurodegenerative diseases

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, Teung-Ping Su, Agata Copani and Giuseppe Ronsisvalle

# The SIGMAR1 Receptor is an Integral Membrane Protein Involved in Cellular Homeostasis




Impaired SIGMAR1 function leads to dysfunction in ER-mitochondria crosstalk, calcium homeostasis impairment, and ER stress response

*Source: Figure adapted from Sánchez-Fernández C et al 2017, Fig 9.1*

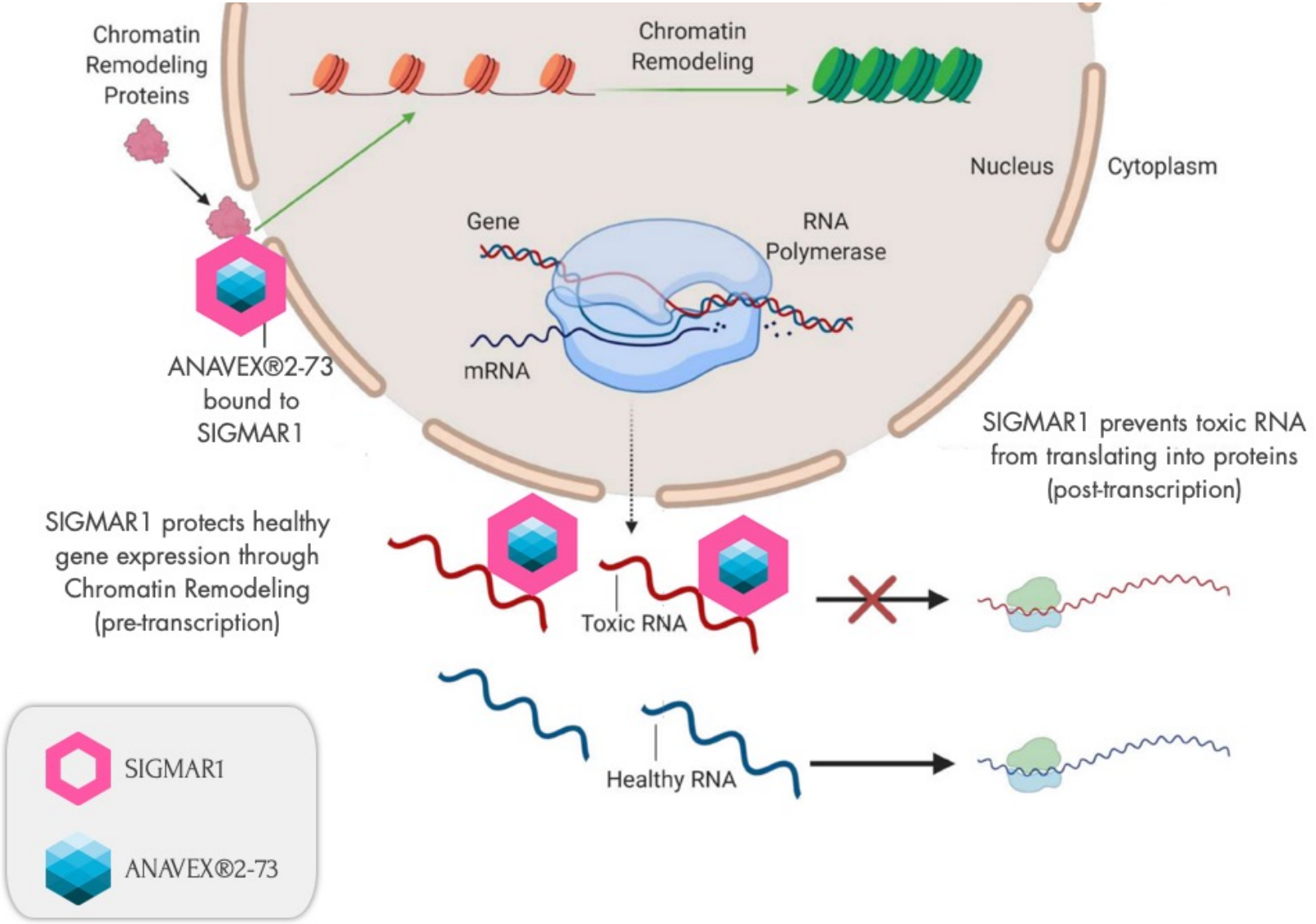
# ANAVEX®2-73 Mechanism of Action for Neurological Diseases

Neurological chronic conditions:
Impaired restoration function and impaired homeostasis

SIGMAR1 activation as compensatory mechanism to chronic CNS diseases[1]

[1] *Brimson JM, et al. "Using Sigma-ligands as part of a multi-receptor approach to target diseases of the brain." Expert opinion on therapeutic targets. 2020*

# ANAVEX®2-73 MoA: SIGMAR1 Activation Prevents Cellular Stress Before *and* After RNA Gene Transcription




*Source: Couly et al., Knocking Out Sigma-1 Receptors Reveals Diverse Health Problems. Cell Mol Neurobiol (2020); Lee et al., Sigma-1 receptor chaperones rescue nucleocytoplasmic transport deficit seen in cellular and Drosophila ALS/FTD models. Nat Commun. 2020 Nov 4;11(1):5580*

# ANAVEX®2-73-AD-004 Study Design

# ANAVEX®2-73 AD-004 Phase 2b/3 Alzheimer's Disease Study Design

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

**N=509**

**Early AD patient population**

- Confirmed AD pathology / amyloid pathophysiology (CSF/amyloid PET)
- Patients aged 60 to 85 years
- MMSE score 20-28
- DNA and RNA sequencing

Randomization 1:1:1

- ANAVEX®2-73 50 mg
- ANAVEX®2-73 30 mg
- Placebo

### Primary Endpoints
- ADAS-Cog
- ADCS-ADL

### Key Secondary Endpoint
- CDR-SB

### Pre-specified Analyses
- Genetic variants SIGMAR1 (rs1800866) exclusion on treatment effect

### Other Analyses
- Structural and functional MRI
- Biomarkers: $Abeta_{40}$/$Abeta_{42}$, T-tau, P-tau, NFL, YKL-40, neurogranin, BACE1

# ANAVEX®2-73-AD-004 Top Line Data

# ANAVEX®2-73-AD-004 Baseline Disease Characteristics

| | Placebo (n=170) | ANAVEX2-73 30mg (n=169) | ANAVEX2-73 50mg (n=169) | ANAVEX2-73 Total (n=338) |
|---|---|---|---|---|
| Age, years, mean (SD) | 73.4 (6.44) | 73.9 (6.76) | 73.9 (6.49) | 73.9 (6.63) |
| Female, n (%) | 83 (48.8) | 83 (49.1) | 77 (45.6) | 160 (47.3) |
| Race, White, n (%) | 163 (95.9) | 165 (97.6) | 164 (97.0) | 329 (97.3) |
| Race, Asian, n (%) | 2 (1.2) | 3 (1.8) | 5 (3.0) | 8 (2.4%) |
| Ethnicity Non-Hispanic or Latino or of Spanish origin, n (%) | 158 (92.9) | 156 (92.3) | 160 (94.7) | 316 (93.5) |
| Use of Alzheimer's Disease Medications[a], n (%) | 111 (66.1) | 109 (65.3) | 109 (64.9) | 218 (65.1) |
| MMSE Score[a], mean (SD) | 23.11 (2.69) | 23.62 (3.10) | 23.52 (2.73) | 23.57 (2.92) |
| ADAS-Cog Total Score[a], mean (SD) | 30.25 (8.39) | 28.43 (8.52) | 29.07 (8.83) | 28.75 (8.67) |
| ADCS-ADL Score[a], mean (SD) | 66.48 (7.08) | 66.59 (7.26) | 66.85 (7.93) | 66.72 (7.59) |
| CDR-SB Total Score[a], mean (SD) | 4.10 (1.76) | 3.82 (1.65) | 3.80 (1.81) | 3.81 (1.73) |

ADAS-Cog: Alzheimer Disease Assessment Scale-Cognition scale; ADCS-ADL: Alzheimer's Disease Cooperative Studies Activities of Daily Living Scale; CDR-SB: Clinical Dementia Rating Scale Sum of Boxes scale; MMSE: Mini-Mental State Examination; [a]Full Analysis Set, incudes 5 subjects not randomized, proportions may be marginally different..

# ANAVEX®2-73 Phase 2b/3 Alzheimer's Disease Study

## Primary and Key Secondary Efficacy Endpoints

### Primary Endpoints

ADAS-Cog (Alzheimer Disease Assessment Scale-Cognition)

Reduction in cognitive decline assessed from baseline over 48 weeks all patients with ANAVEX®2-73 compared to placebo using the Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog) scale

ADCS-ADL (Activities of Daily Living)

Reduction in decline of the ability to perform daily activities assessed from baseline over 48 weeks all patients with ANAVEX®2-73 compared to placebo using the Activities of Daily Living (ADCS-ADL) scale

### Key Secondary Endpoint

CDR-SB (Clinical Dementia Rating Scale Sum of Boxes)

Reduction in cognitive decline assessed from baseline over 48 weeks all patients with ANAVEX®2-73 compared to placebo using the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB)

# ANAVEX®2-73-AD-004 Top Line Data - Efficacy

# ANAVEX®2-73-AD-004 Primary Endpoint – ADAS-Cog

- **ANAVEX®2-73 treatment was 84% more likely to improve cognition compared to placebo, by ADAS-Cog score change of -0.50 points or better at 48 weeks**
- **Among patients, who improved with ANAVEX®2-73 treatment, Mean ADAS-Cog score improvement -4.03 points**

| Treatment Group | [a]Odds Ratio | P-value | 90% CI | 95% CI |
|---|---|---|---|---|
| Placebo | 1.0 (reference) | - | - | - |
| ANAVEX®2-73 | | | | |
| ITT Population | 1.839 | 0.015 | (1.17, 2.94) | (1.07, 3.22) |

[a]Analysis method: logistic regression
ITT: Intent-to-treat

# ANAVEX®2-73-AD-004 Primary Endpoint – ADCS-ADL

- **ANAVEX®2-73 treatment was 167% more likely have improve function compared to placebo, at clinically significant ADCS-ADL score change of +3.5 points or better at 48 weeks**
- **Clinically significant response categorization in function defined as ADCS-ADL ≥ +3.5-point change from baseline**

| Treatment Group | [a]Odds Ratio | P-value | 90% CI | 95% CI |
|---|---|---|---|---|
| Placebo | 1.0 (ref.) | - | - | - |
| ANAVEX®2-73 | | | | |
| ITT Population | 2.67 | 0.0255 | (1.17, 6.13) | (1.00, 7.18) |

[a]Analysis method: logistic regression
ITT: Intent-to-treat

# ANAVEX®2-73-AD-004 Primary Endpoint – ADAS-Cog

- **ANAVEX®2-73 treatment slowed cognitive decline by 45% compared to placebo at 48 weeks**
- **Mean difference in ADAS-Cog score change of -1.85 points**

| Treatment Group | ADAS-Cog Score, Mean (SE) | | | [b]Relative Reduction in Decline (%) | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 48 | [a]Mean Change | Mean | 95% CI | [a]P-value |
| **Intent-to-treat (ITT) Population** | | | | | | |
| Placebo | 29.18 (0.61) | 33.26 (0.98) | 4.11 (0.86) | Ref. | - | - |
| ANAVEX®2-73 | 27.62 (0.50) | 30.36 (0.83) | 2.26 (0.51) | 45.02 | (43.68, 48.24) | **0.033** |

Ref.: Reference
[a]Analysis method: t-test on change from baseline at the end of treatment (week 48) on subjects with available scores at week 48.
Mean change from baseline obtained from an average of ADAS-Cog score change for each subject.
Mean of change from baseline not equivalent to subtracting mean baseline scores from mean end of treatment scores when all subjects do not have both measures.
[b]Relative Reduction in Decline = (1- [mean change in active/mean change in placebo])*100

# ANAVEX®2-73-AD-004 Secondary Endpoint – CDR-SB

- **ANAVEX®2-73 treatment slowed clinical decline in cognition and function assessed by 27% compared to placebo**
- **ANAVEX®2-73 treatment difference in mean score change of -0.42 points**

| Treatment Group | CDR-SB, Mean (SE) | | | [b]Relative Reduction in CDR-SB Decline (%) | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 48 | [a]Mean Change | Mean | 95% CI | [a]P-value |
| **Intent-to-treat (ITT) Population** | | | | | | |
| Placebo | 4.11 (0.14) | 5.61 (0.26) | 1.52 (0.19) | *Ref.* | - | - |
| ANAVEX®2-73 | 3.78 (0.10) | 4.89 (0.17) | 1.11 (0.14) | 27.23 | (26.33, 27.76) | **0.040** |

Ref.: Reference
[a]Analysis method: t-test on change from baseline at the end of treatment (week 48) on subjects with available scores at week 48.
Mean change from baseline obtained from an average of CDR-SB score change for each subject.
Mean of change from baseline not equivalent to subtracting mean baseline scores from mean end of treatment scores when all subjects do not have both measures.
[b]Relative Reduction in Decline = (1- [mean change in active/mean change in placebo])*100

# ANAVEX®2-73-AD-004 Top Line Data - Safety

# ANAVEX®2-73-AD-004 Patient Disposition and Drug Titration Status

| | Placebo (n=170) | ANAVE®X2-73 Total (n=338) |
|---|---|---|
| Subjects Up Titrated[a] to 30mg or 50mg n (%) | 148 ( 88.1) | 287 ( 85.7) |
| Subjects with no Up Titration[a] to 30mg or 50mg n (%) | 20 ( 11.9) | 48 ( 14.3) |
| Subjects with no Down Titration[a], n (%) | 166 ( 98.8) | 263 ( 78.5) |

- Study design allowed up titration to target dose with provision for down titration based on tolerability
- Similar proportion of patients in placebo and ANAVEX®2-73 treatment groups did not up titrate
- Therefore, ANAVEX®2-73 treatment groups were combined in primary analyses (all exposed to ANAVEX®2-73)

[a]Titration Phase; excludes 5 subjects not randomized; proportions may be marginally different.

# ANAVEX®2-73-AD-004 Summary of Adverse Events

- Similar TEAE rates in Active and Placebo arms
- Adverse Events ≥7.5% were predominantly mild or moderate
- No clinically significant changes in vital signs, lab values and ECG parameters in Active and Placebo groups
- Dizziness consistent with CNS drug effects. Will be mitigated in the future by bedtime dosing
- Safety findings are consistent with the known safety profile of ANAVEX®2-73

| [a]Safety Population | Placebo (n=161) | ANAVEX®2-73 Total (n=301) |
|---|---|---|
| | n (%) | n (%) |
| Any TEAE | 113 (70.2) | 248 (82.4) |
| Serious TEAE | 15 (9.3) | 47 (15.6) |
| Deaths (unrelated to treatment)* | 1 ( 0.6) | 1 ( 0.3) |
| **Adverse Events ≥ 7.5%** | | |
| Dizziness | 9 (5.6) | 76 (25.2) |
| Confusional State | 4 (2.5) | 40 (13.3) |
| Fall | 16 (9.9) | 21 (7.0) |

[a] Maintenance phase of trial

[*] Unrelated to treatment. Placebo arm: worsening posterior cortical atrophy; Active arm: Urinary tract infection resulting in urosepsis

# ANAVEX®2-73-AD-004 Drug Modifications Due to AEs

| | Placebo (n=161) | ANAVEX®2-73 Total (n=301) |
|---|---|---|
| [a]**Safety Population** | **n (%)** | **n (%)** |
| Dizziness | 5 ( 3.1) | 58 ( 19.3) |
| Dose Changed | 1 ( 0.6) | 33 ( 11.0) |
| Drug Interrupted | 4 ( 2.5) | 23 ( 7.6) |
| Drug Withdrawn | 1 ( 0.6) | 11 ( 3.7) |
| | | |
| Confusional State | 2 ( 1.2) | 36 ( 12.0) |
| Dose Changed | 2 ( 1.2) | 20 ( 6.6) |
| Drug Interrupted | 0 | 11 ( 3.7) |
| Drug Withdrawn | 0 | 6 ( 2.0) |

- ANAVEX®2-73 was well tolerated
- Most frequent adverse events (dizziness and confusion) led to drug withdrawal in <6%

[a] Maintenance phase of trial

# Summary

# Summary

- ANAVEX®2-73 treatment slowed decline of cognition and function in patients with early Alzheimer's disease over 48 weeks
- Patients on ANAVEX®2-73 treatment were 84% more likely to improve cognitively compared to placebo, by ADAS-Cog score threshold change of -0.50 points or better
- ANAVEX®2-73 treatment slowed cognitive decline by 45% compared to placebo at 48 weeks
- At clinically significant levels of improvement in function (ADCS-ADL score threshold change of +3.5 points or better), ANAVEX®2-73 treatment was 167% more likely to improve function compared to placebo
- Compared to placebo, ANAVEX®2-73 reduced clinical decline of cognition and function by 27% as measured by the CDR-SB
- ANAVEX®2-73 was safe and well tolerated

# ANAVEX®2-73 Phase 2b/3 Results Consistent with Previous Phase 2a Study in Alzheimer's Disease

DOI: 10.1002/trc2.12013

RESEARCH ARTICLE

Alzheimer's & Dementia
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]

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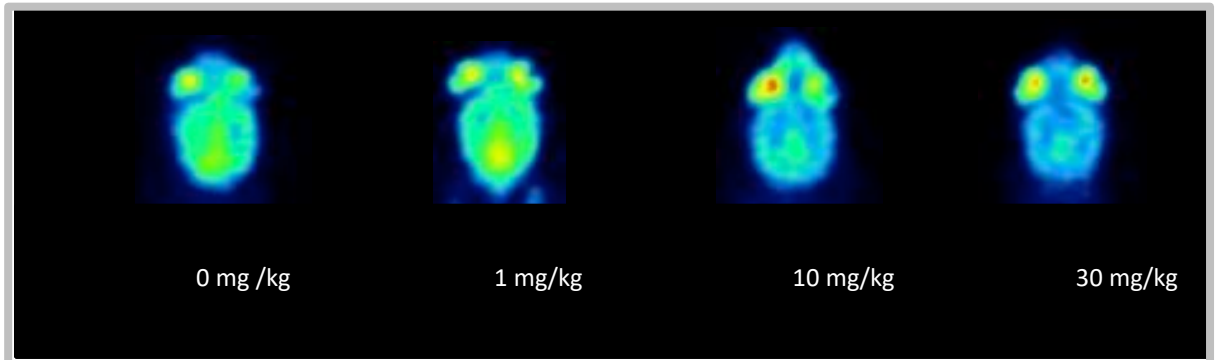
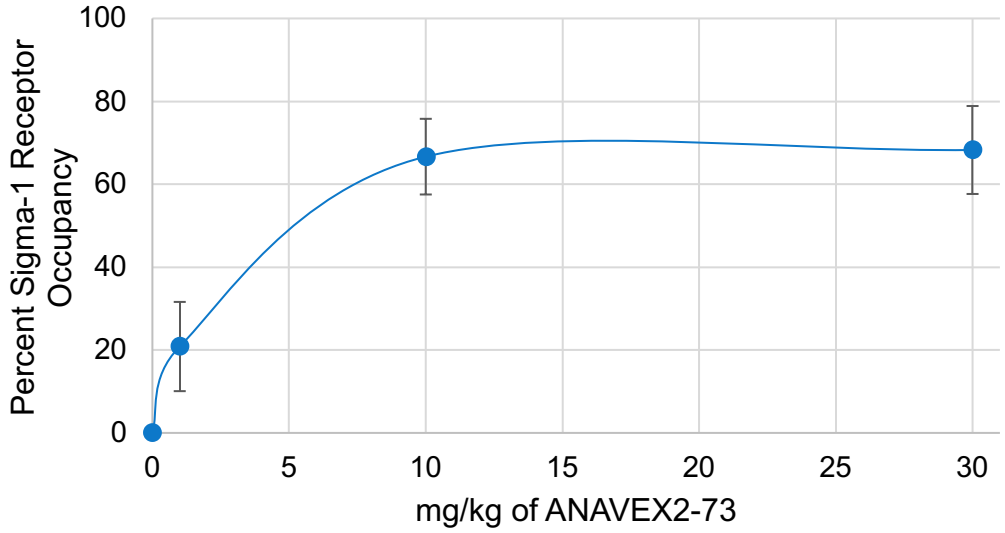
Phase 2b/3 ANAVEX®2-73 results complement and are consistent with findings from the previously completed Alzheimer's disease Phase 2a ANAVEX®2-73 trial, which also demonstrated therapeutic effect on cognition and function over 148 weeks

*Source: Hampel et al. 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. Alzheimer's Dement. 2020;00:1–14*

# ANAVEX®2-73 Established SIGMAR1 Target Activation

## 2D [18F]FTC-146-PET imaging of ANAVEX®2-73: Dose-dependent ANAVEX®2-73 Target Engagement




*Reyes S et al., Sci Rep. 2021 Aug 25;11(1):17150*

# Next Steps

# Next Steps

- The full analyses, including prespecified biomarkers of response as well as Whole Exome Sequencing DNA data and full RNA exome expression data collection data on biomarkers of neurodegeneration, will be published in a peer-reviewed medical journal
- The open-label extension study ATTENTION-AD will continue to follow participants over 96 weeks
- Plan to meet with regulatory authorities to determine next steps

# Acknowledgements


- Principal Investigators & clinical sites' study staff
- Data safety review committee
- Anavex SAB
- Most of all, grateful acknowledgement of the contribution of the participating AD patients and their caregivers

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