



# Corporate Presentation

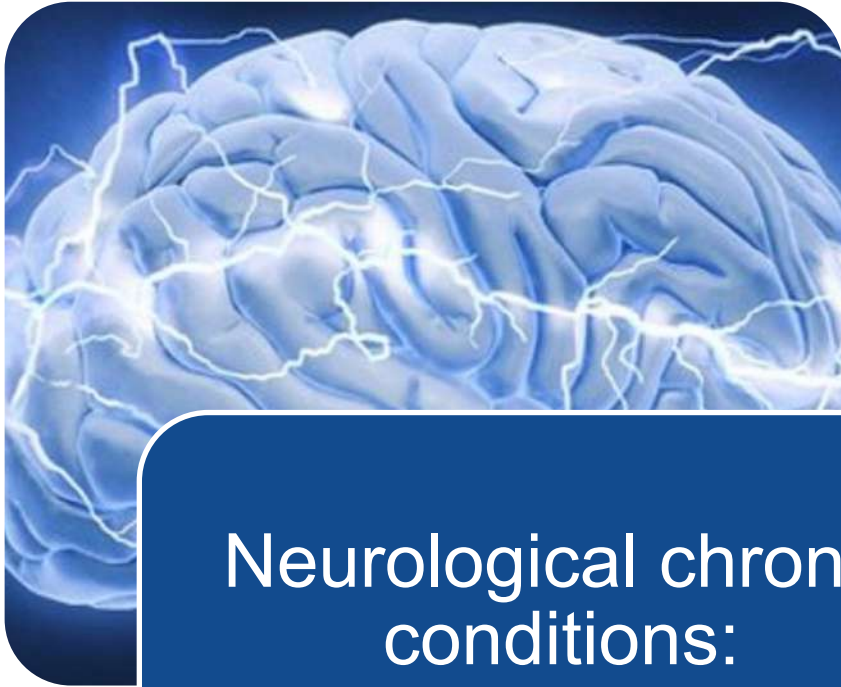
Christopher U Missling, PhD | President & CEO

Nasdaq: AVXL | December 2021

# Forward Looking Statement

This presentation contains forward-looking statements made within the meaning of the Private Securities Litigation Reform Act of 1995 by Anavex<sup>®</sup> 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.

# ANAVEX Platform for Neurological Diseases



Neurological chronic conditions:  
Impaired housekeeping function and impaired homeostasis

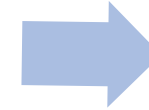
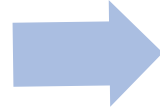


SIGMAR1 activation  
as compensatory  
mechanism to chronic  
CNS diseases<sup>1</sup>

<sup>1</sup> Brimson JM, Brimson S, Chomchoei C, et al. Using Sigma-ligands as part of a multi-receptor approach to target diseases of the brain. Expert opinion on therapeutic targets. 2020



# Large Markets by Applying Precision Medicine Platform



## Today

- SIGMAR1 activation established as a **New Platform Class**
- ANAVEX®2-73 (*blarcamesine*)  
Clinical study results in broad CNS indications confirm SIGMAR1 technology

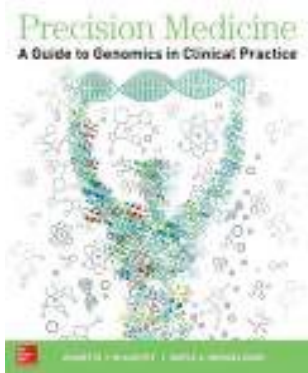
## Tomorrow

- SIGMAR1 technology to **Succeed Traditional Modalities**
  - Alzheimer's disease
  - Parkinson's disease
  - Rett syndrome
  - Fragile X syndrome
  - Other rare diseases

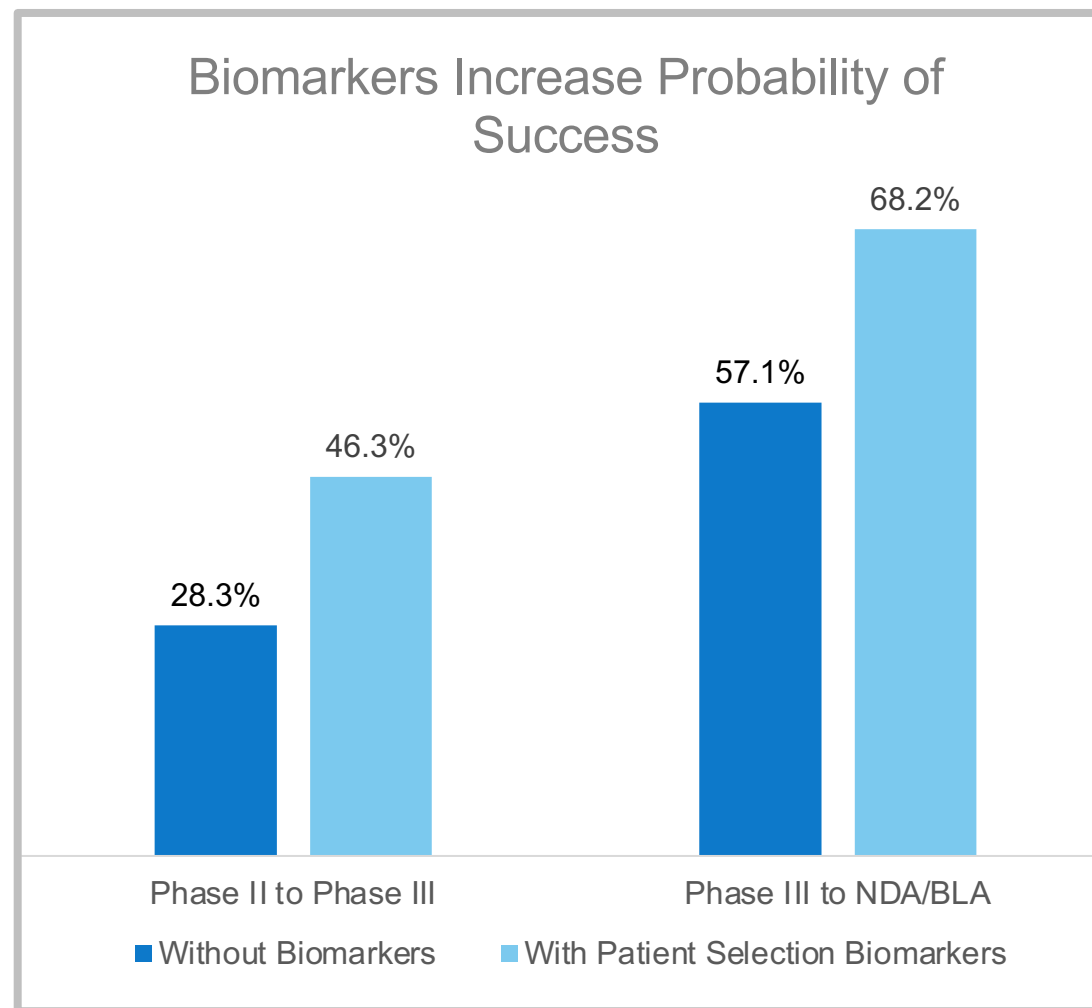
## The Future

- SIGMAR1 to open up new opportunities **Beyond the Horizon**
  - Expanded CNS indications
  - Regenerative medicine<sup>1</sup>
  - Disease prevention<sup>2</sup>

<sup>1</sup> K. Ruscher, T. Wieloch, The involvement of the sigma-1 receptor in neurodegeneration and neurorestoration, *Journal of Pharmacological Sciences*, Volume 127, Issue 1, 2015, Pages 30-35, ISSN 1347-8613, <https://doi.org/10.1016/j.jphs.2014.11.011>. <sup>2</sup> L. Nguyen et al., Role of sigma-1 receptors in neurodegenerative diseases, *Journal of Pharmacological Sciences*, Volume 127, Issue 1, 2015, Pages 17-29, ISSN 1347-8613, <https://doi.org/10.1016/j.jphs.2014.12.005>.



# Precision Medicine

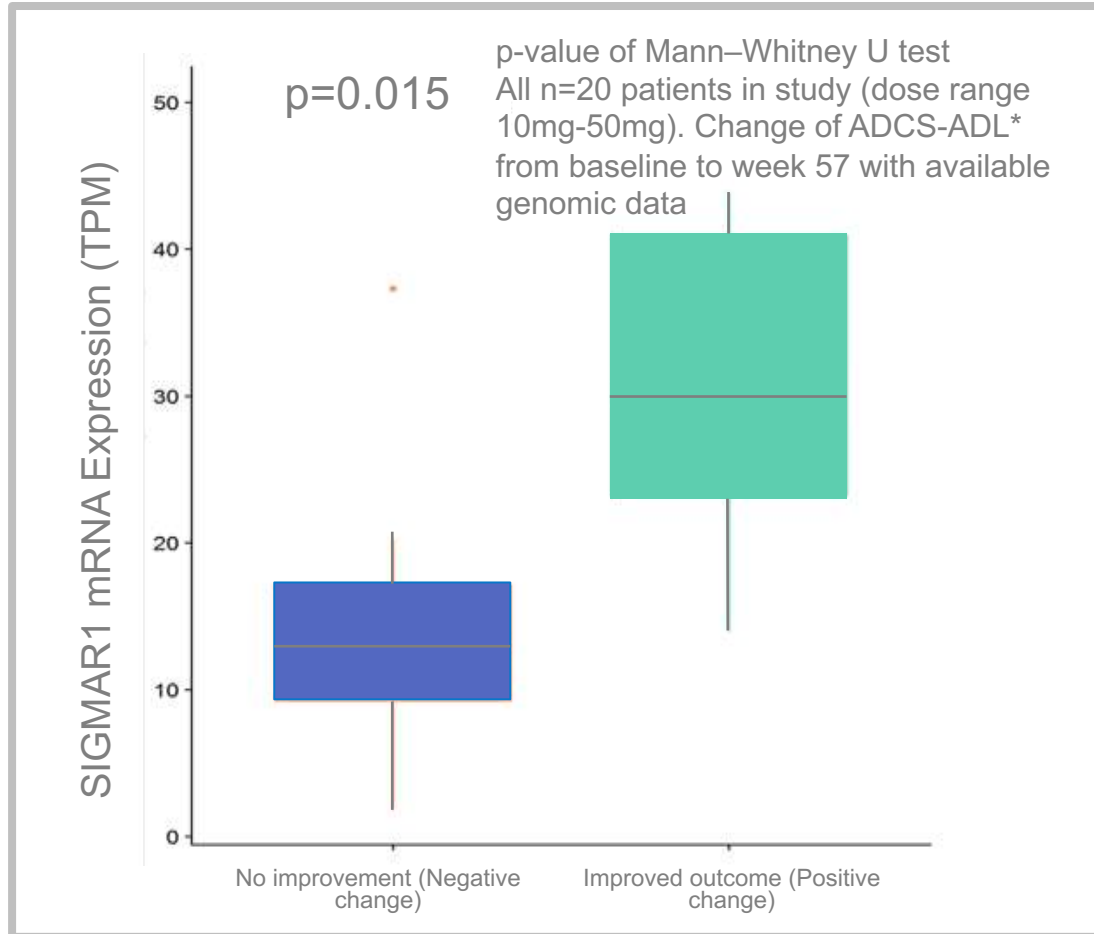


- Patient selection biomarkers
- Higher therapeutic response
- Lower variability in the target population

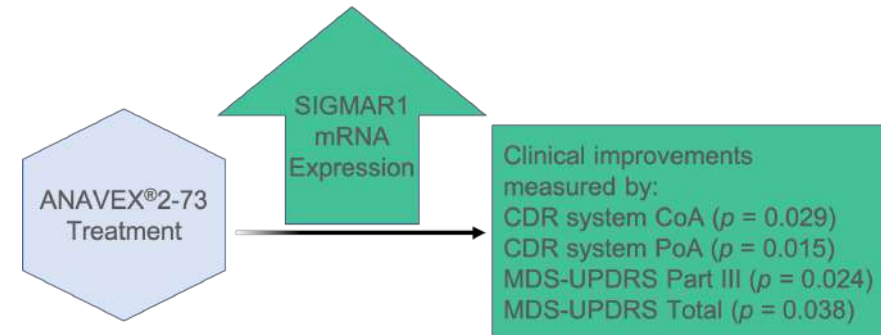
Thomas DW et al. Clinical Development Success Rates 2011-2020. BIO | QLS Advisors | Informa UK Ltd 2021

# ANAVEX®2-73 Establishes SIGMAR1 mRNA Predictive Biomarker of Efficacy in Alzheimer's, Parkinson's and Rett Syndrome

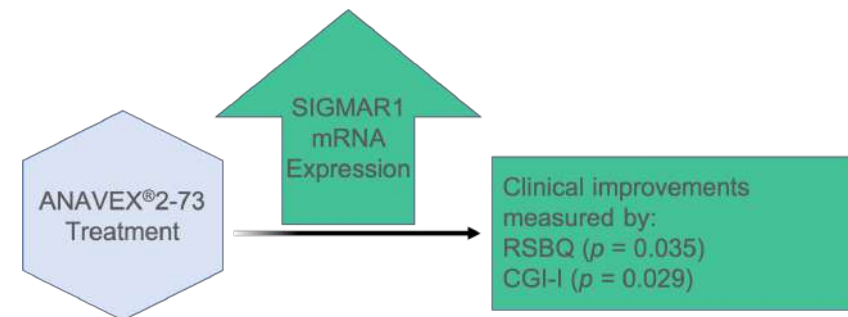
ANAVEX®2-73 improves functional (ADCS-ADL\*) outcome in Alzheimer's disease patients correlating with SIGMAR1 mRNA levels



ANAVEX®2-73 positive response in functional outcome in patients with Parkinson's disease correlate with SIGMAR1 mRNA levels



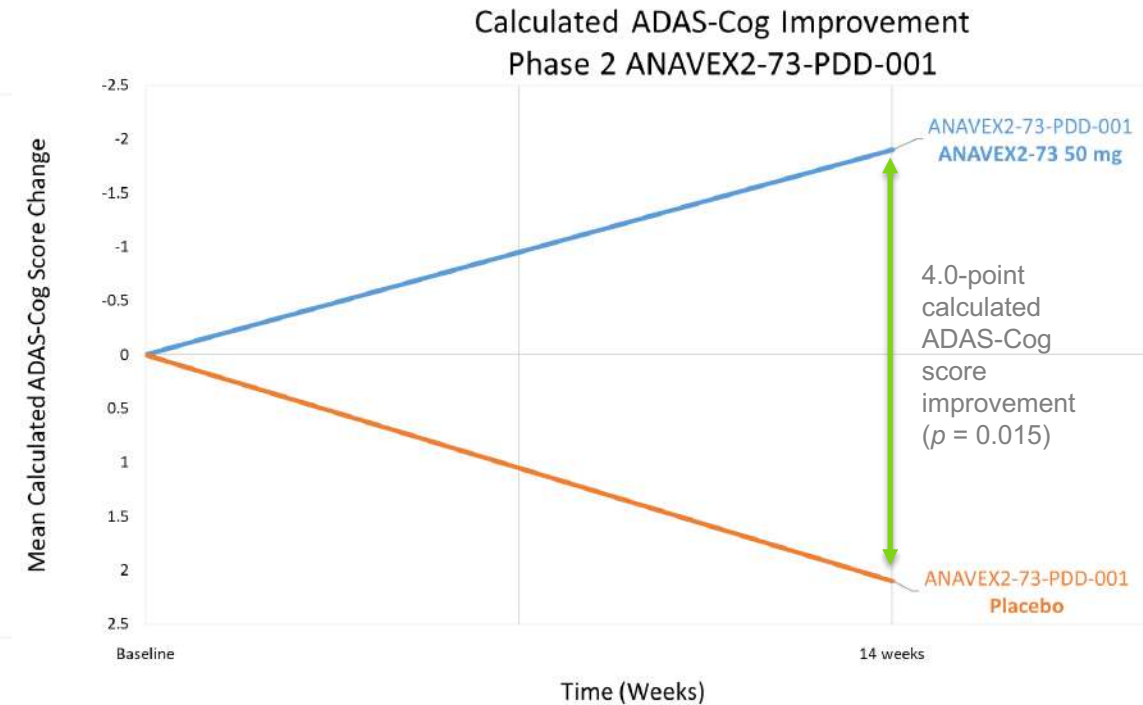
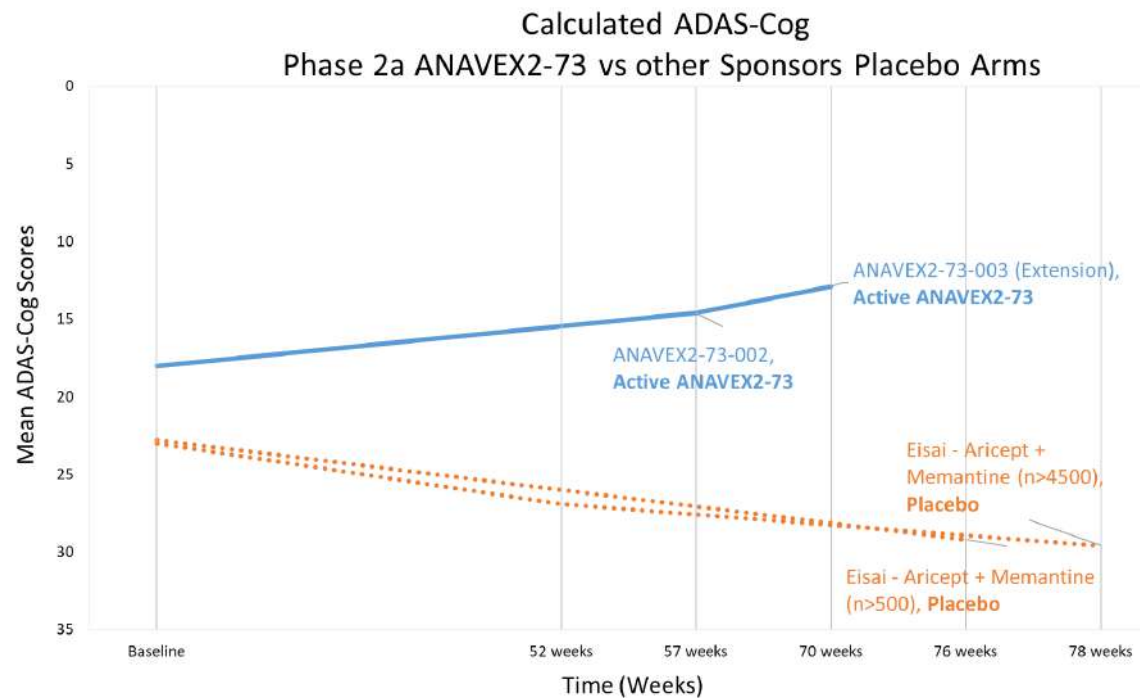
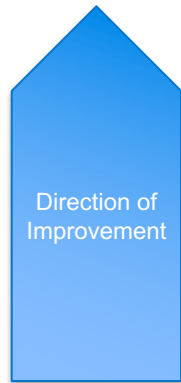
ANAVEX®2-73 positive response in functional outcome in patients with Rett syndrome correlate with SIGMAR1 mRNA levels



# Aiming to Change the Course of Dementia ...

... Dementia is progressive and over time a patient's cognition will worsen

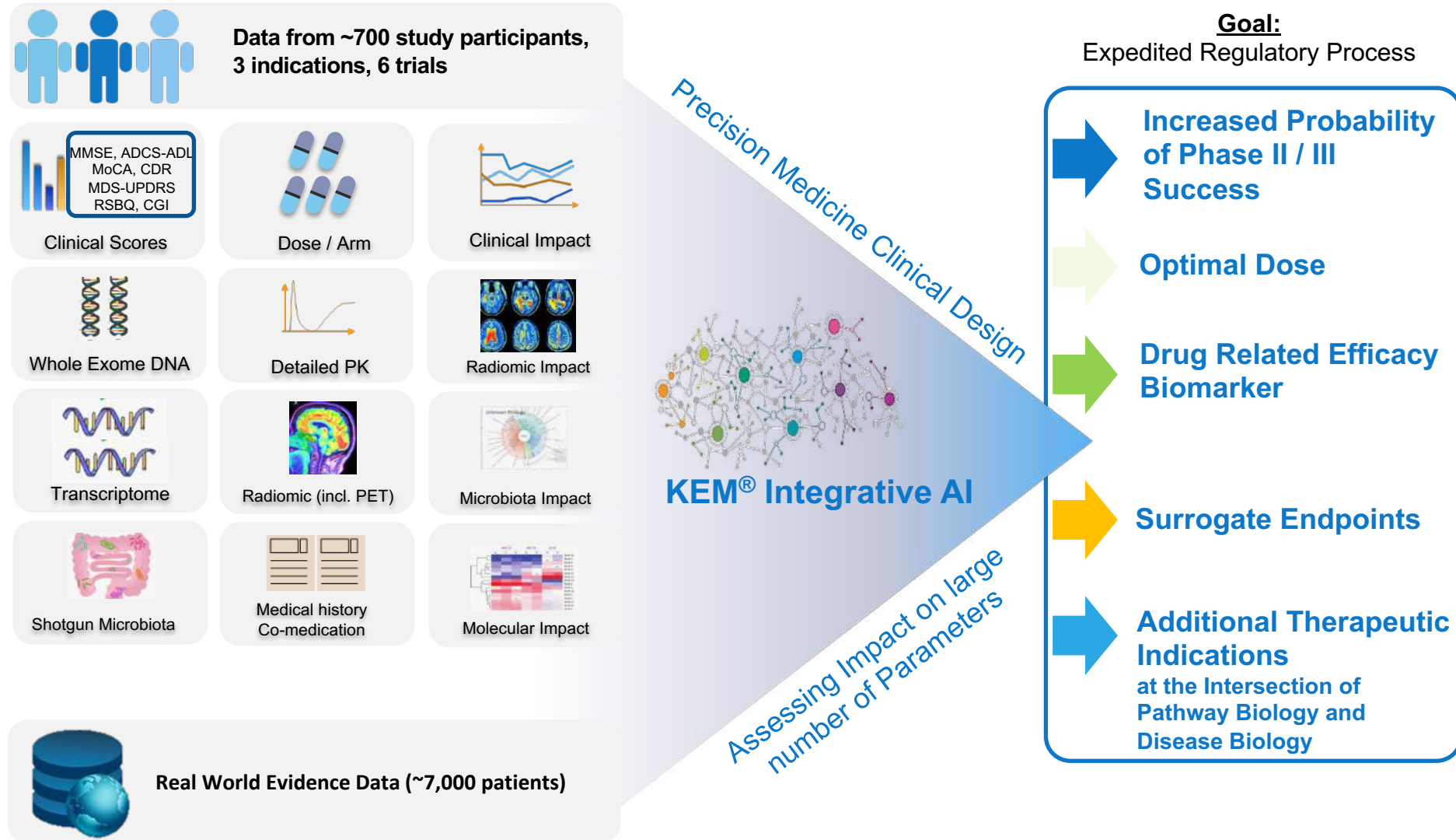
► Trajectory changed with ANAVEX®2-73



Visualize the improvement in calculated ADAS-Cog scores in Alzheimer's patients treated with ANAVEX®2-73, relative to the placebo arms of other sponsors' trials

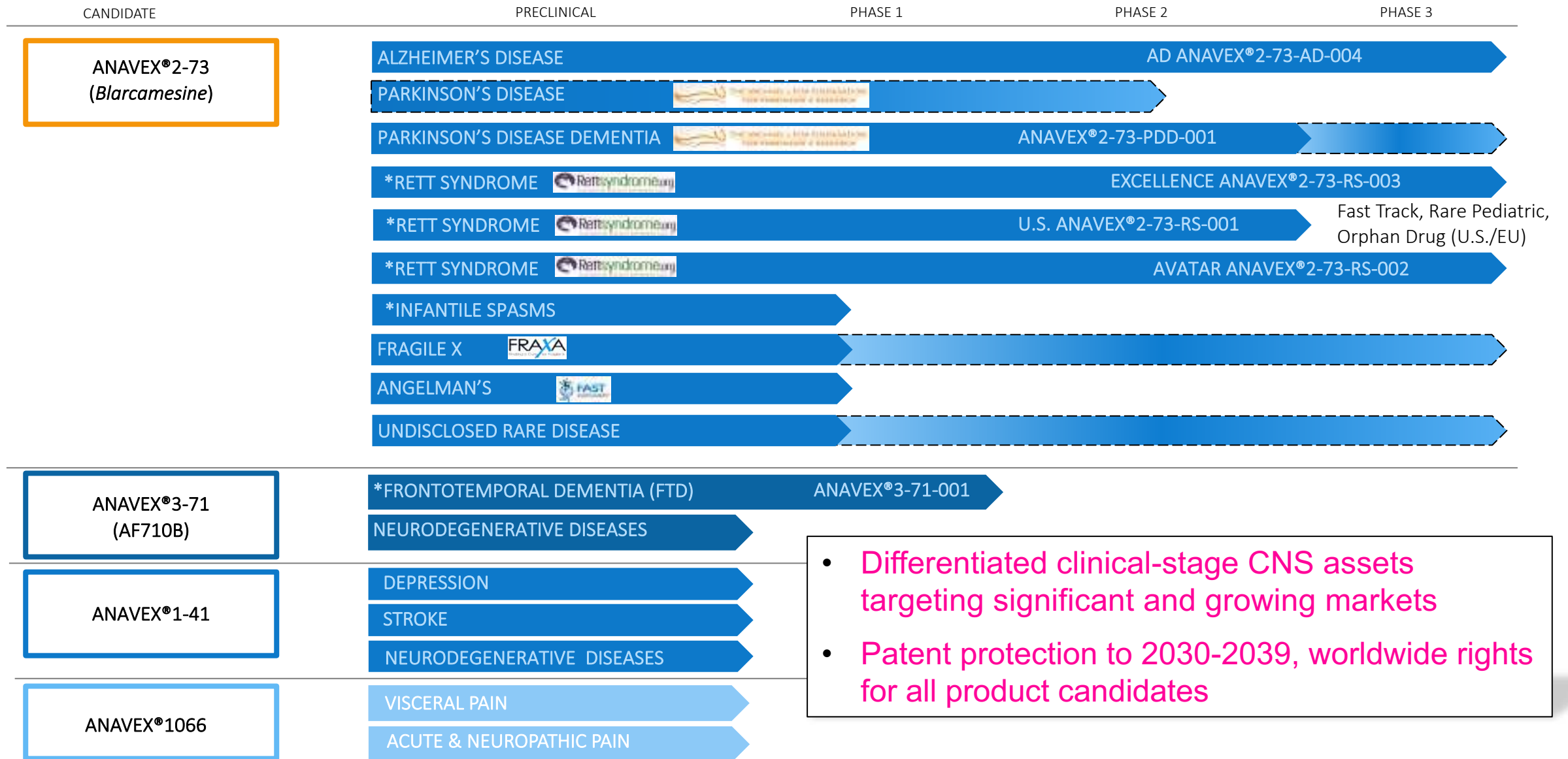
Parkinson's disease dementia (PDD) patients improved with ANAVEX®2-73 in calculated corresponding ADAS-Cog scores from baseline to 14 weeks

# AI Powered, Biomarker Driven, Accelerated Development Built on in-depth Molecular Understanding of SIGMAR1 Pathway





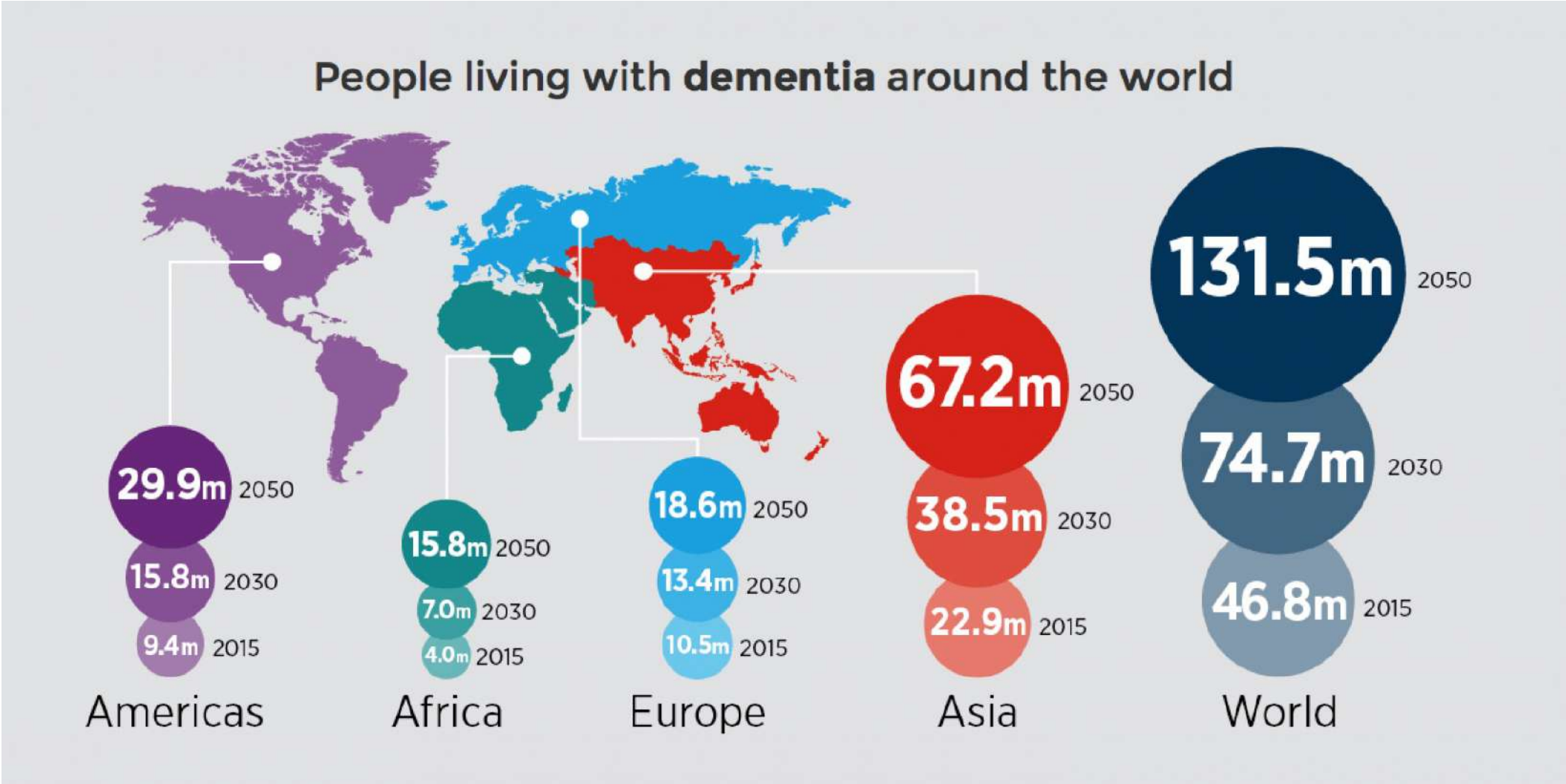
# Broad SIGMAR1 Platform Targeting Significant Unmet Medical Need



\* = Orphan Drug Designation by FDA; Dashed lines indicate planned clinical studies

# Worldwide Dementia Cases Projected to Grow to Over 130M by 2050

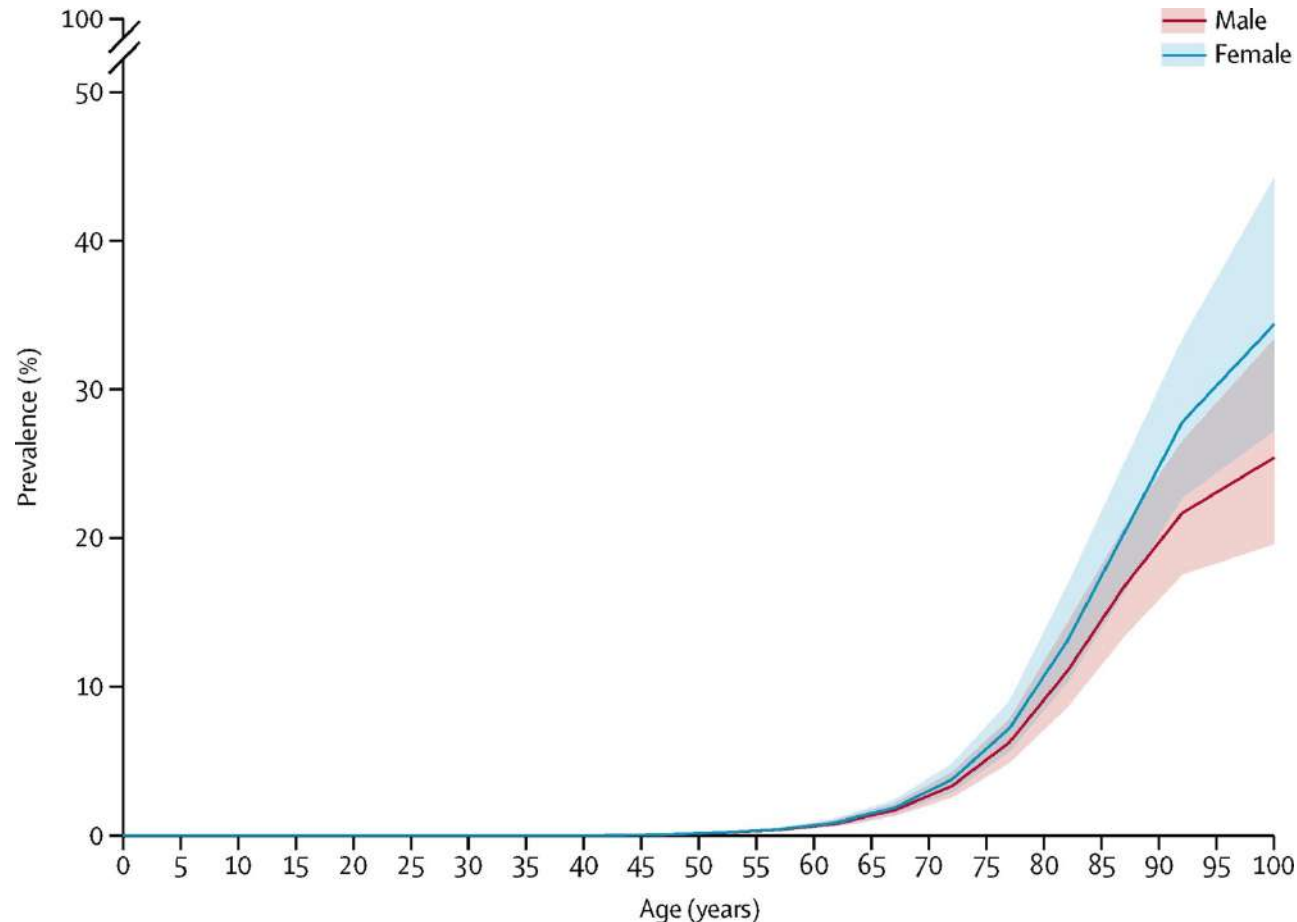
Targeting Large Market: Global Dementia



Source: World Alzheimer's Report

# Costs Associated with Alzheimer's Treatment and Care in the U.S. are Unsustainable

## Age Prevalence of Global Alzheimer's Disease and Dementias



**>\$20 trillion**

Cumulative costs of Alzheimer's and dementia care from 2015 to 2050

**1 in 3**

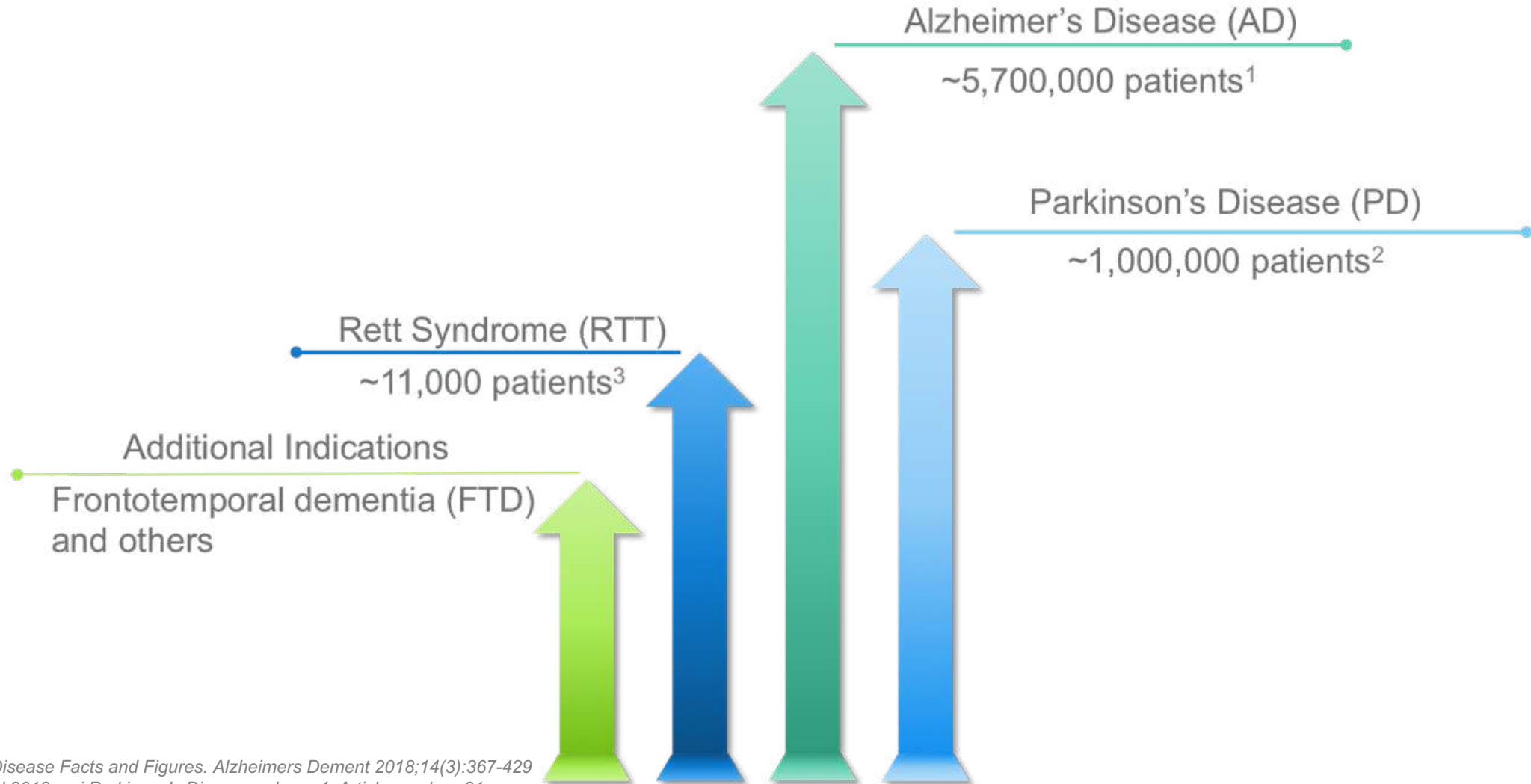
Medicare dollars will be spent on people living with Alzheimer's and other dementias in 2050

**>11 million**

The number of Americans providing unpaid care for people with Alzheimer's or other dementias

# Targeting Large Market Opportunities with Significant Unmet Medical Need

## All U.S. Patient Numbers



1) Alzheimer's Disease Facts and Figures. *Alzheimers Dement* 2018;14(3):367-429

2) Marras C et al 2018. *npj Parkinson's Disease* volume 4, Article number: 21

3) Based on prevalence number on orphaned



# Anavex's Transformative Precision Medicine Platform

- › ANAVEX®2-73 (*Blarcamesine*) **Rett Syndrome** Program Received **Fast Track** Designation and is Eligible for **Pediatric Priority Review Voucher**
- › Pursuing Large Markets with High Unmet Need by Applying **Genetic Precision Medicine**
- › Novel **Upstream** CNS Mechanism of Action for both Neurodevelopment and Neurodegeneration
- › **Compelling Human Patient Data** in Rett Syndrome (**RTT**), Parkinson's Disease Dementia (**PDD**) and Alzheimer's Disease (**AD**)
- › Sufficient Cash for >5 Years To Achieve Key Milestones — Including non-dilutive Cash from Michael J Fox Foundation, International Rett Syndrome Foundation and Australian Government



## **Continued Significant Value-creating Pipeline Expansion Opportunities for ANAVEX®2-73:**

- › Novel approach of targeting SIGMAR1 using precision medicine with potential for biomarker-focused pivotal Fragile X and Parkinson's disease dementia clinical trials

# Catalysts to Drive Value

## The company has multiple clinical milestones

- ✓ Complete data ANAVEX<sup>®</sup>2-73 U.S. Rett syndrome Phase 2 study
- ✓ Complete data ANAVEX<sup>®</sup>2-73 Parkinson's disease dementia (PDD) Phase 2 study
- › Top-line data AVATAR: Potentially pivotal Phase 2/3 adult RTT clinical trial – expected YE 2021
- › Top-line data Phase 1 ANAVEX<sup>®</sup>3-71 clinical trial – expected YE 2021
- › Top-line data EXCELLENCE: Potentially pivotal Phase 2/3 pediatric RTT clinical trial – expected 1H 2022\*
- › Top-line data ANAVEX<sup>®</sup>2-73-AD-004: Potentially pivotal Phase 2b/3 AD clinical trial – expected 2H 2022
- › Initiation of ANAVEX<sup>®</sup>2-73 imaging-focused Parkinson's disease clinical trial – expected 1H 2022
- › Pipeline expansion opportunities for ANAVEX<sup>®</sup>2-73
  - › Initiation of potentially pivotal Phase 2/3 Fragile X clinical trial – expected 1H 2022
  - › Initiation of potentially pivotal Phase 2/3 clinical trial for the treatment of a new, rare disease indication – expected 1H 2022

\* Increased patient study participants to 84 from 69



## Clinical Trials

### Mechanism of Action (MoA) and Clinical Data:

- Rett Syndrome (RTT)
- Parkinson's Disease Dementia (PDD)
- Alzheimer's Disease (AD)

# 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



ANAVEX®2-73 enhances autophagy and alleviates Tau pathology in neurodegenerative disease models



Blockade of Tau Hyperphosphorylation and Aβ<sub>1-42</sub> Generation by the Aminotetrahydrofuran Derivative ANAVEX2-73, a Mixed Muscarinic and σ<sub>1</sub> Receptor Agonist, in a Nontransgenic Mouse Model of Alzheimer's Disease

Valentine Labrecque<sup>1,2,3,4</sup>, Johanne Massier<sup>1</sup>, Suzanne Malvestrum<sup>1</sup>, Gaëlle Naud<sup>1,2,3</sup>, Laurent Gauthier<sup>1,2,3</sup>, Seung Hyun Kim<sup>1</sup>, Veronique Vilard<sup>1</sup>, Alexandre Vasselin<sup>1</sup> and Tongyi Maurice<sup>1,2,3,4</sup>

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

REVIEW ARTICLE **Neuroprotective effects of sigma-1 receptor agonists against beta-amyloid-induced toxicity**

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

Daniel A. Ryskamp<sup>1</sup>, Svetlana Korban<sup>2</sup>, Vladimir Zhemkov<sup>2</sup>, Nina Kravkovskaya<sup>2</sup> and Ilya Bezprozvanny<sup>1,2</sup>

<sup>1</sup>Department of Physiology, UT Southwestern Medical Center, United States

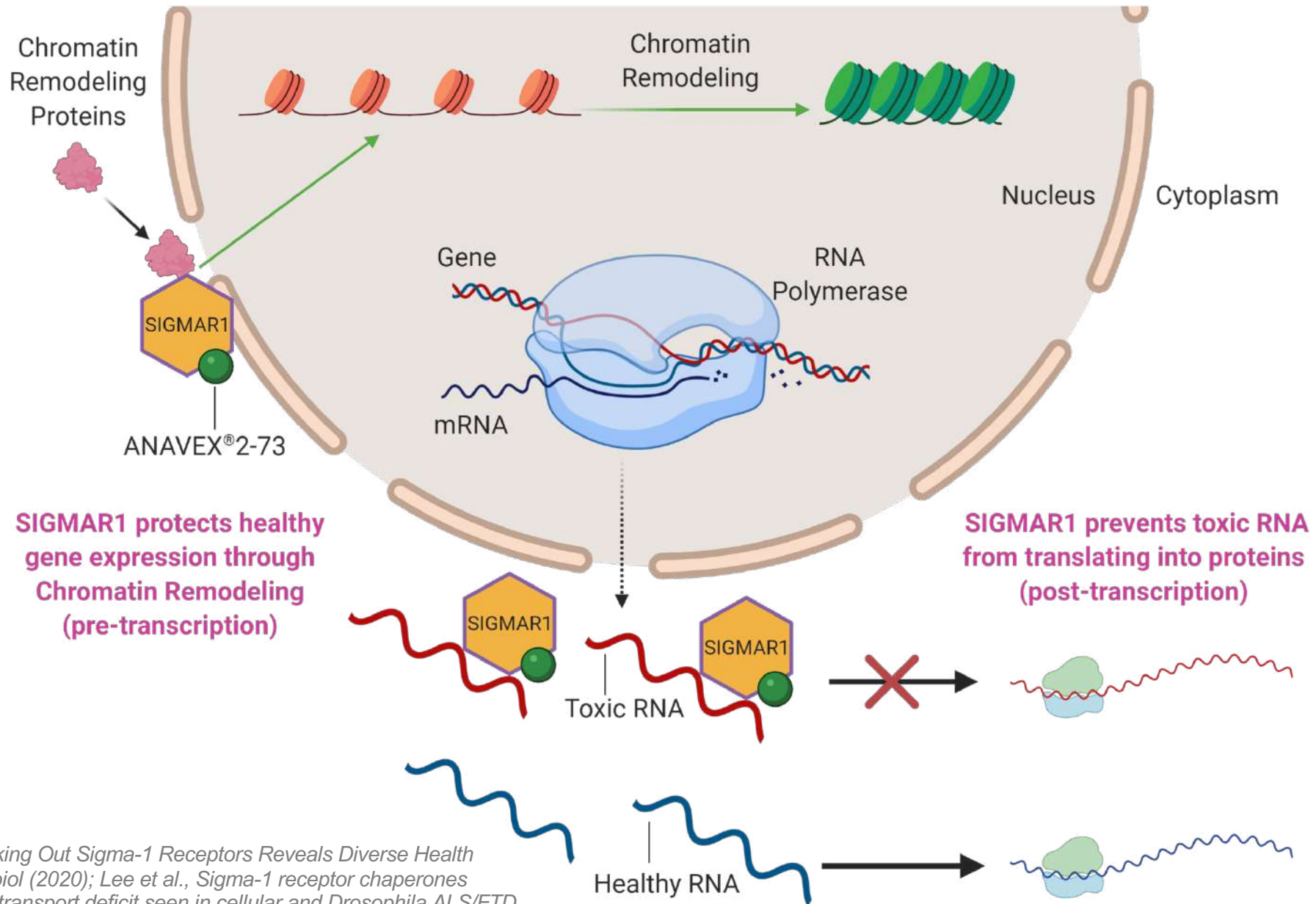
<sup>2</sup>Laboratory of Molecular Neurodegeneration, Saint Petersburg State Polytechnical University, Russia

Neuroprotective effects of sigma-1 receptor agonists against beta-amyloid-induced toxicity

Agostino Marras<sup>1</sup>, Filippo Carai<sup>1</sup>, Elia Trovati Sileari<sup>2</sup>, Tung-Ping Su<sup>3</sup>, Agata Copani<sup>1,2,4</sup> and Giuseppe Ransmayr<sup>1</sup>



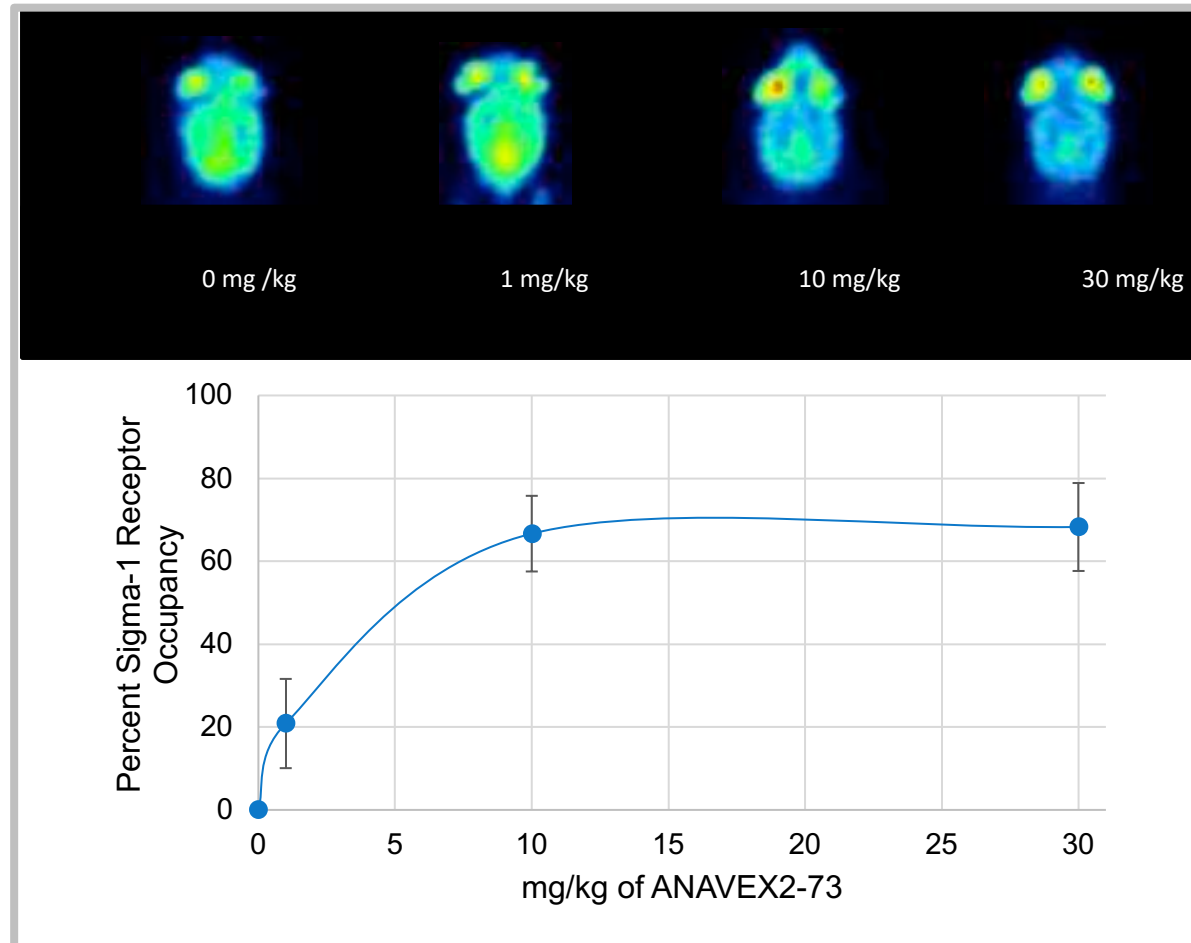
# ANAVEX®2-73 MoA: SIGMAR1 Activation Prevents Cellular Stress Before *and* After RNA Gene Transcription



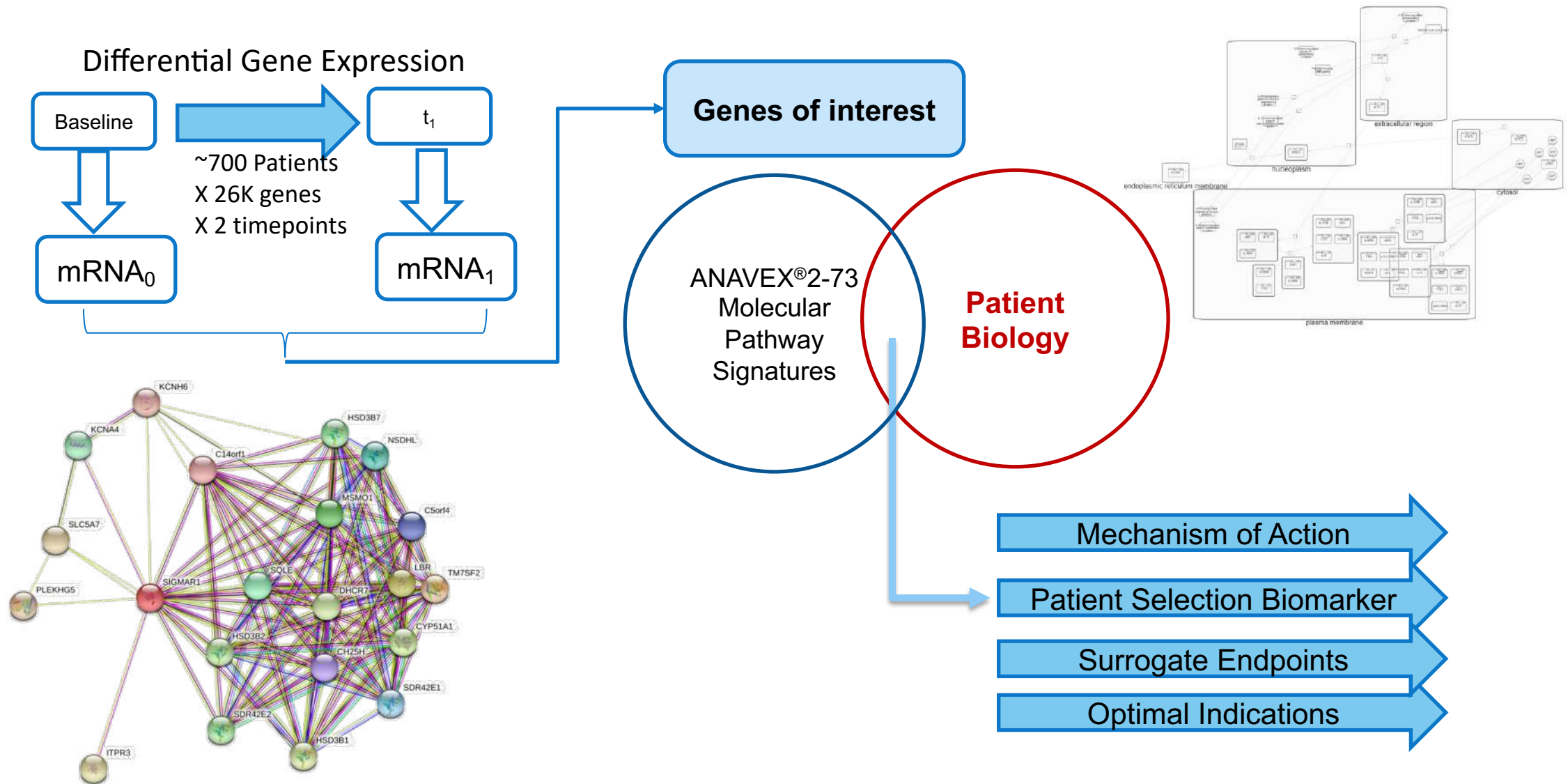
Source: Couly et al., Knocking Out Sigma-1 Receptors Reveals Diverse Health Problems. *Cell Mol Neurobiol* (2020); Lee et al., Sigma-1 receptor chaperones rescue nucleocytoplasmic transport deficit seen in cellular and *Drosophila* ALS/FTD models. *Nat Commun.* 2020 Nov 4;11(1):5580

# ANAVEX<sup>®</sup>2-73 Establishes Proof-of-Concept and SIGMAR1 Target Occupancy

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



# Interface of ANAVEX<sup>®</sup>2-73-activated Pathway Analysis and Disease Biology Using mRNA Differential Gene Expression with Focus on SIGMAR1 Pathway



# What is Rett Syndrome?

Devastating neuro-developmental disease in girls with both movement impairment and cognitive impairment

## Rett Syndrome (RTT)

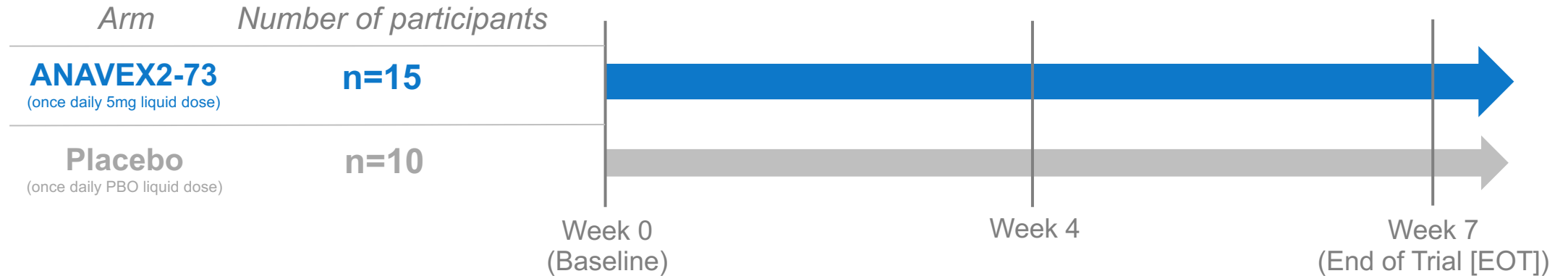
- **Non-inherited genetic postnatal disorder caused by mutations in the MECP2 gene**
  - Occurs almost exclusively in girls
  - Leads to severe impairments, affecting nearly every aspect of the child's life
  - Impairment includes ability to speak, walk, eat and even breathe easily
  - Hallmark of RTT is near constant repetitive hand movements while awake
  - Occurs worldwide in approximately one in every 10,000 to 15,000 live female births
  - The population of patients with Rett syndrome is estimated to be ~11,000 patients in the U.S.
  - There is currently no cure for Rett syndrome





# Rett Syndrome U.S. ANAVEX<sup>®</sup>2-73-RS-001 Phase 2 Trial Design Overview

Randomized, Double-blind, Placebo-controlled Clinical Trial



## Efficacy Assessments:

- Primary: RSBQ (Rett Syndrome Behaviour Questionnaire), CGI-I (Clinical Global Impression – Improvement)
- Secondary: Behavior (ADAMS), Sleep (CSHQ), VAS (top caregiver concerns), Seizure diary
- Biomarkers of response and/or surrogate endpoints: Genomic biomarker: DNA & mRNA profiles; Glutamate, GABA
- *SIGMAR1* variants: Prespecified analyses of population with wild type (WT) variant (n = 14)

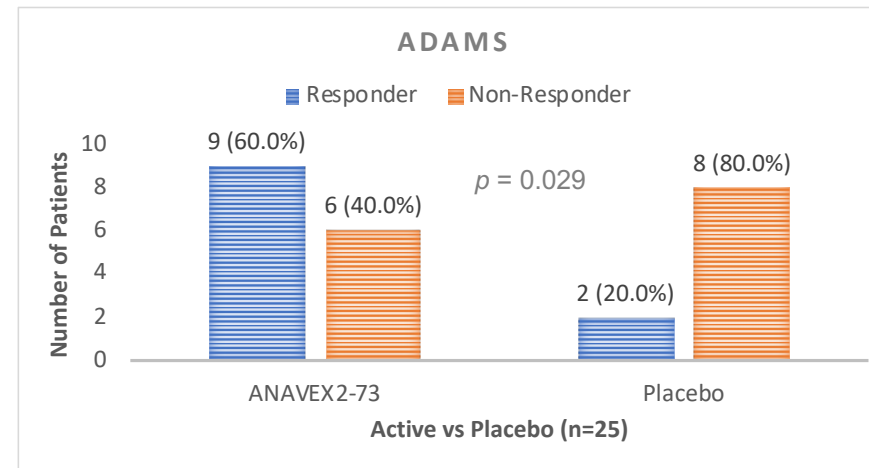
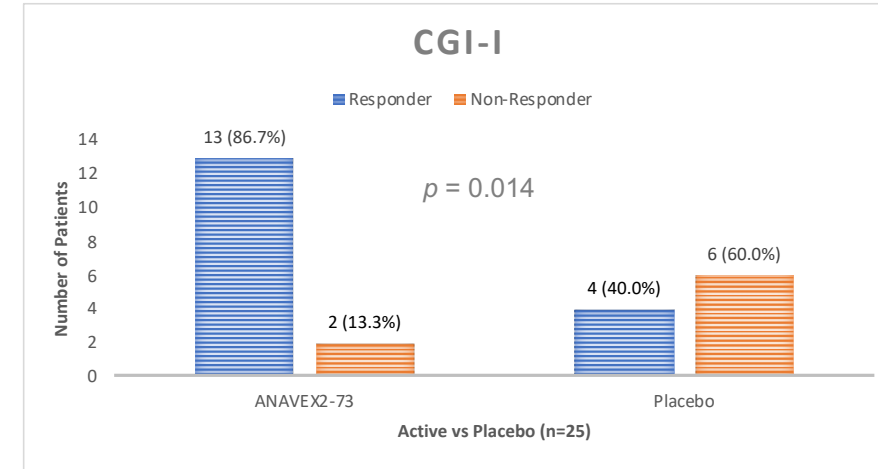
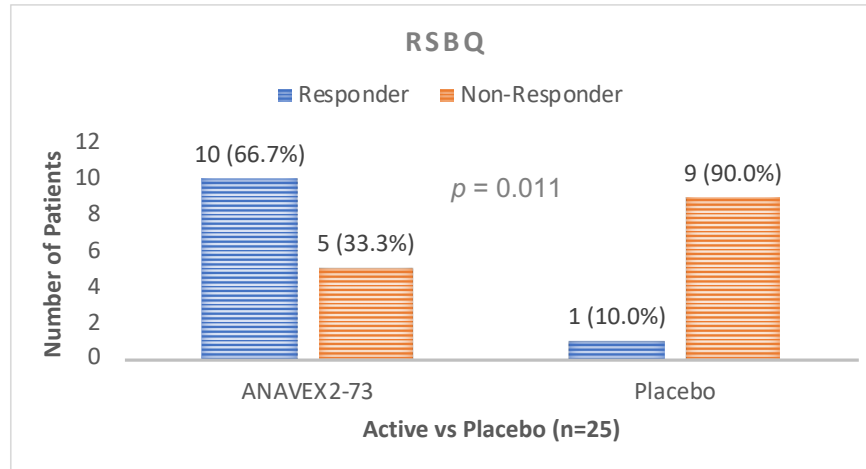
ClinicalTrials.gov: NCT03758924

Separate patient cohort (n=6) underwent a 7-week intensive pharmacokinetic (PK) assessment with safety, tolerability, pharmacokinetic and efficacy evaluation of ANAVEX<sup>®</sup>2-73  
Open-label-extension after End of Trial for at least 36 weeks

anavex

# Phase 2: Improvement in All Key Domains

ANAVEX<sup>®</sup>2-73 Treatment Resulted in a Statistically Significant Improvement for All Patients with Rett Syndrome in the RTT-Relevant Endpoints RSBQ, CGI-I, ADAMS



All participants ITT (n = 25: 15 on ANAVEX2-73 and 10 on Placebo)

Responder analysis capturing the progression of the disease and treatment effect over the course of the study

Improvements in this adult population with Rett syndrome are considered clinically meaningful according to published criteria applied to neurodevelopmental disorders (Chatham et al. Adaptive behavior in autism, Autism Res. 2018;11(2):270-283; Luu et al. Response to Placebo in Fragile X Syndrome Clinical Trials, Brain Sci. 2020 Sep 11;10(9):629

# Favorable Efficacy Already at Low ANAVEX<sup>®</sup>2-73 Doses

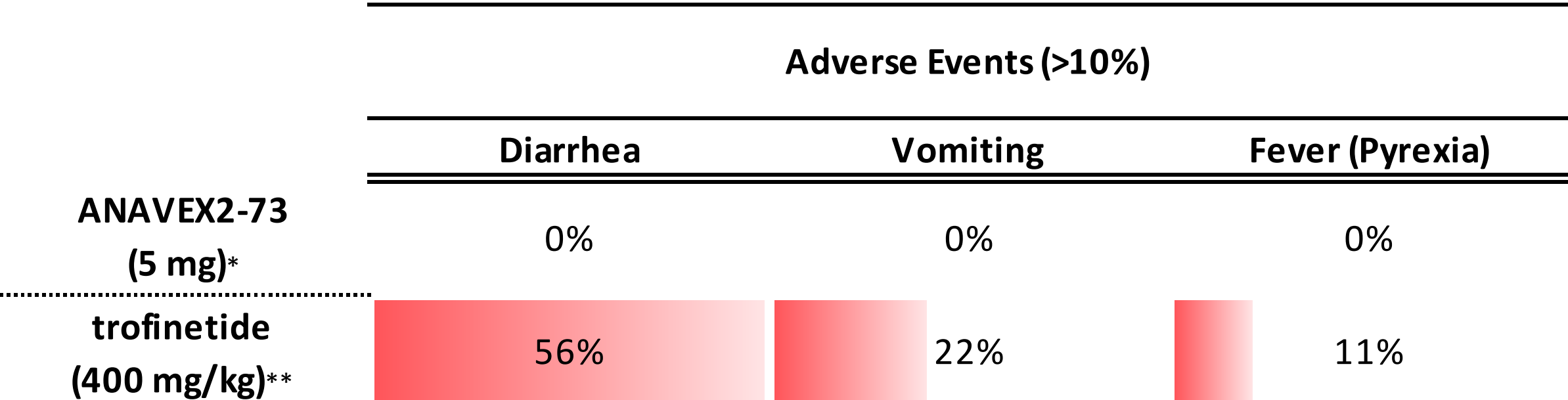
	Estimated Difference between Active and Placebo	Age, y median	Weight, kg median
	RSBQ Total Score		
<b>ANAVEX2-73 <i>low</i> dose (5 mg)*</b>	-14.5	24.00	45.10
<b>trofinetide <i>high</i> dose (400 mg/kg)**</b>	-4.4	9.41	23.05

ANAVEX<sup>®</sup>2-73 Phase 2 RSBQ Total Score compares favorably with other published historical trial  
— despite lower dose and older patient cohort

\* Prespecified WT SIGMAR1 population (n = 14)

\*\* Glaze DG, Neul JL, Kaufmann WE, Berry-Kravis E, Condon S, Stoms G, Oosterholt S, Della Pasqua O, Glass L, Jones NE, Percy AK; Rett 002 Study Group. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. *Neurology*. 2019 Apr 16;92(16):e1912-e1925. doi: 10.1212/WNL.0000000000007316. Epub 2019 Mar 27. PMID: 30918097; PMCID: PMC6550498

# Favorable Adverse Event Profile of ANAVEX<sup>®</sup>2-73



ANAVEX<sup>®</sup>2-73 Phase 2 Adverse Event profile compares favorably with other published historical trial

\* All participants ITT

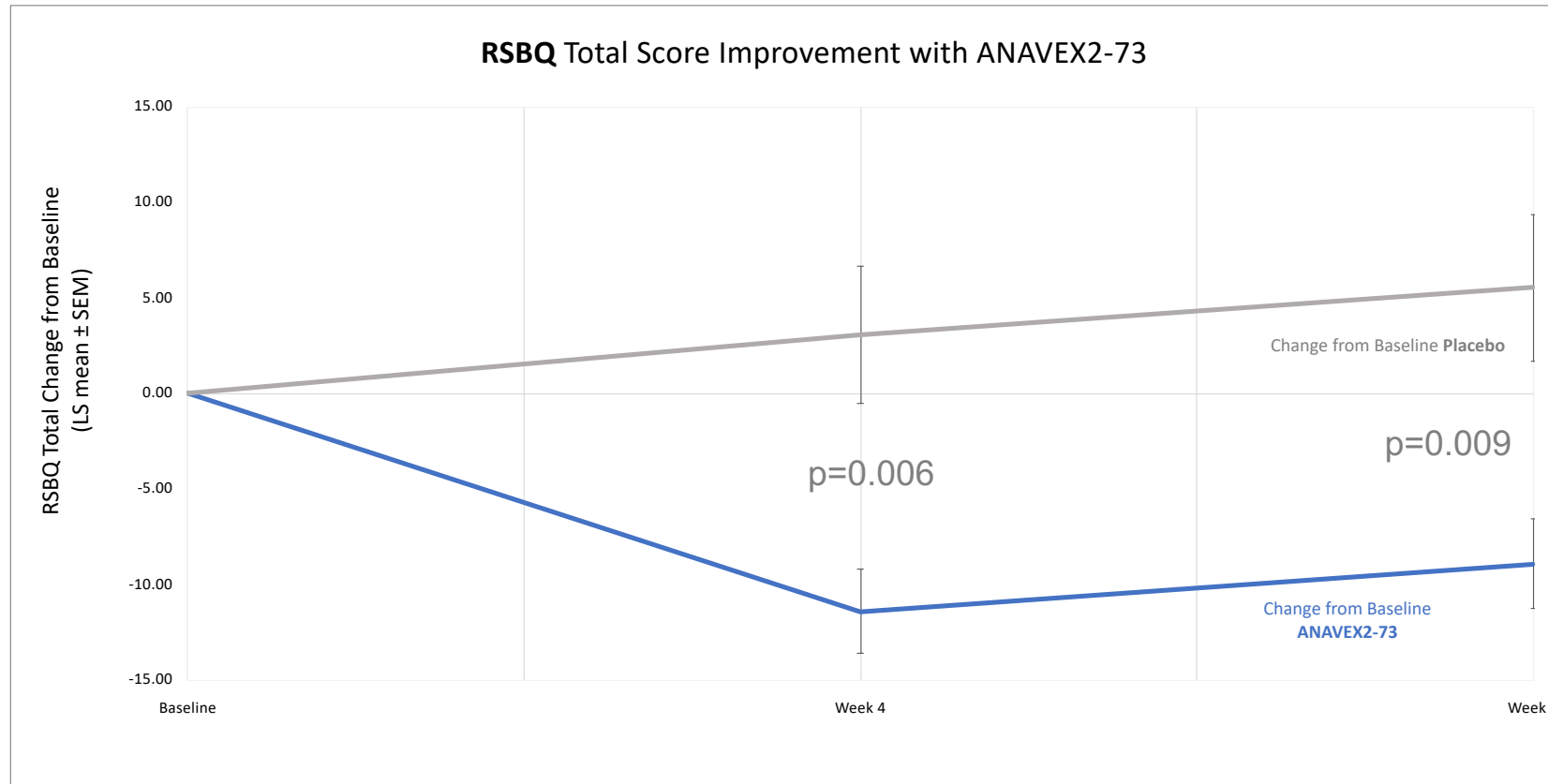
\*\* Glaze DG, Neul JL, Kaufmann WE, Berry-Kravis E, Condon S, Stoms G, Oosterholt S, Della Pasqua O, Glass L, Jones NE, Percy AK; Rett 002 Study Group. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. *Neurology*. 2019 Apr 16;92(16):e1912-e1925. doi: 10.1212/WNL.0000000000007316. Epub 2019 Mar 27. PMID: 30918097; PMCID: PMC6550498

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# Rett Syndrome Behaviour Questionnaire (RSBQ) Total Score

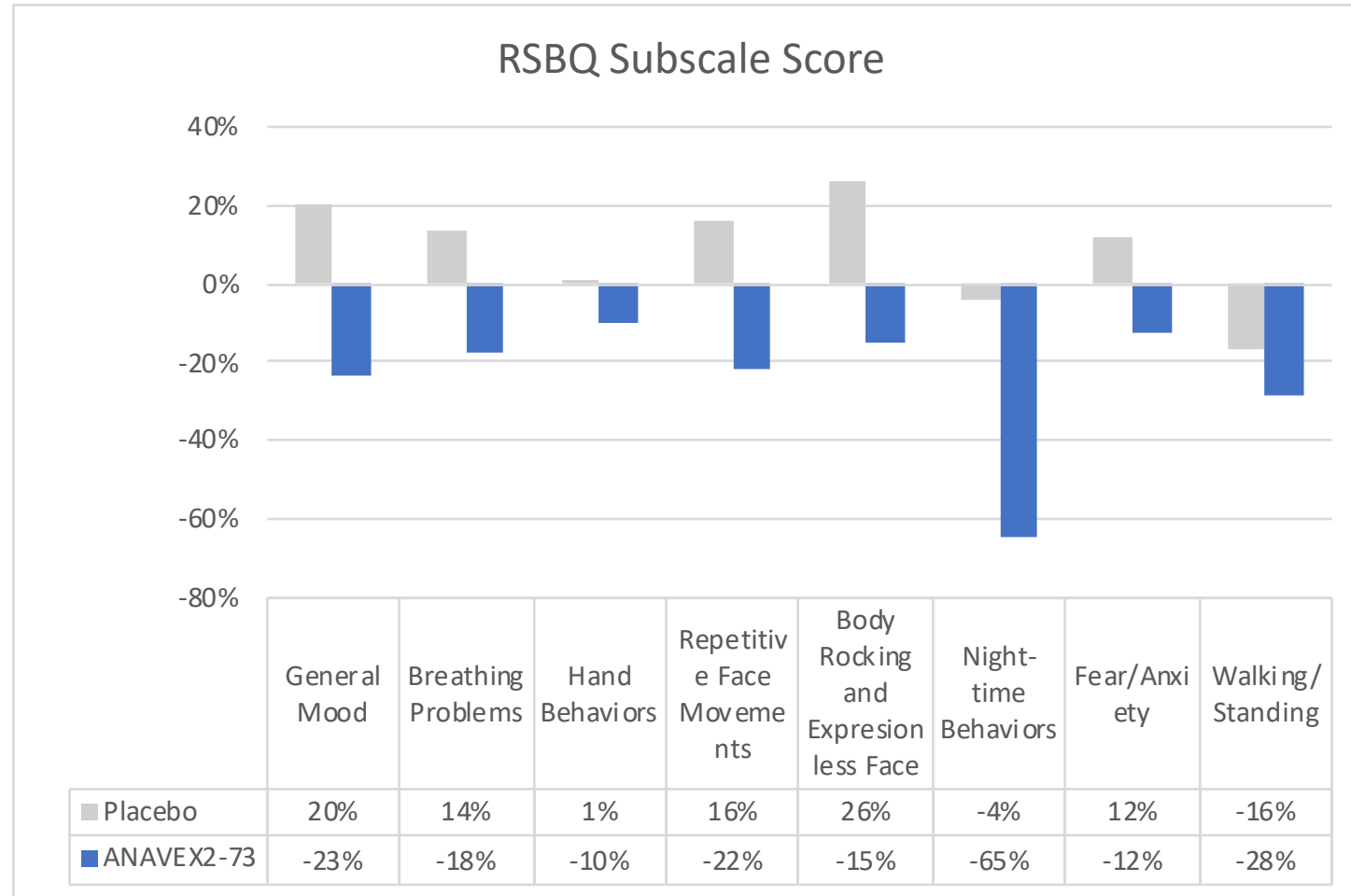
## Prespecified Primary Efficacy Endpoint



- Clinically meaningful and statistically significant Improvement for ANAVEX<sup>®</sup>2-73 treated adult patients with Rett syndrome vs placebo
- 14.5-point improvement at Week 7 with p=0.009 (-8.92 ANAVEX<sup>®</sup>2-73 vs. 5.56 placebo)
- Statistical separation at every assessed time point

# RSBQ Subscale Scores

Significant and Balanced Improvements across all Subscales (observed at End of Trial)

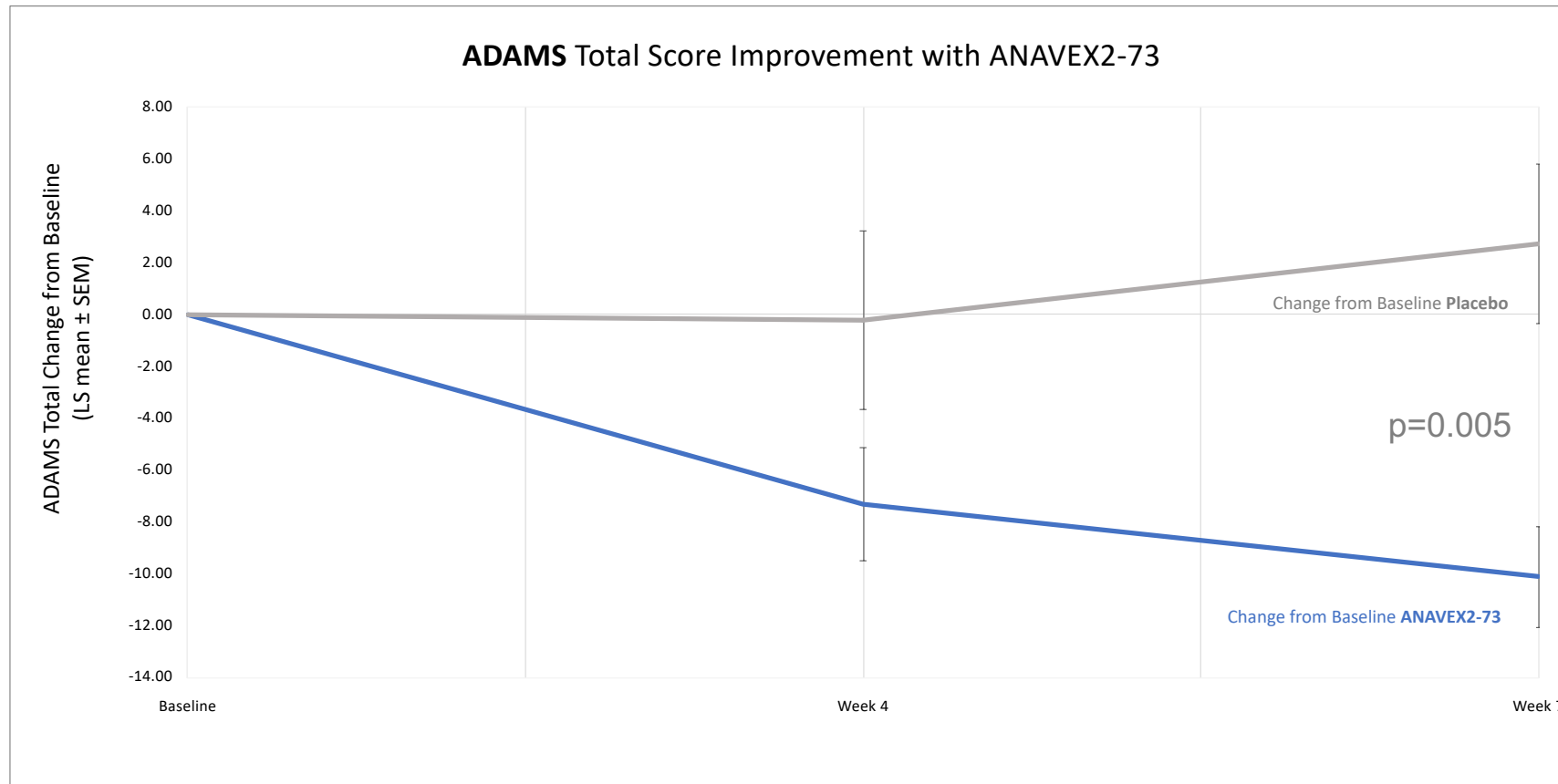


- Cohen's d effect size of 1.11

# ADAMS Total Score

## Clinically Validated Efficacy Endpoint

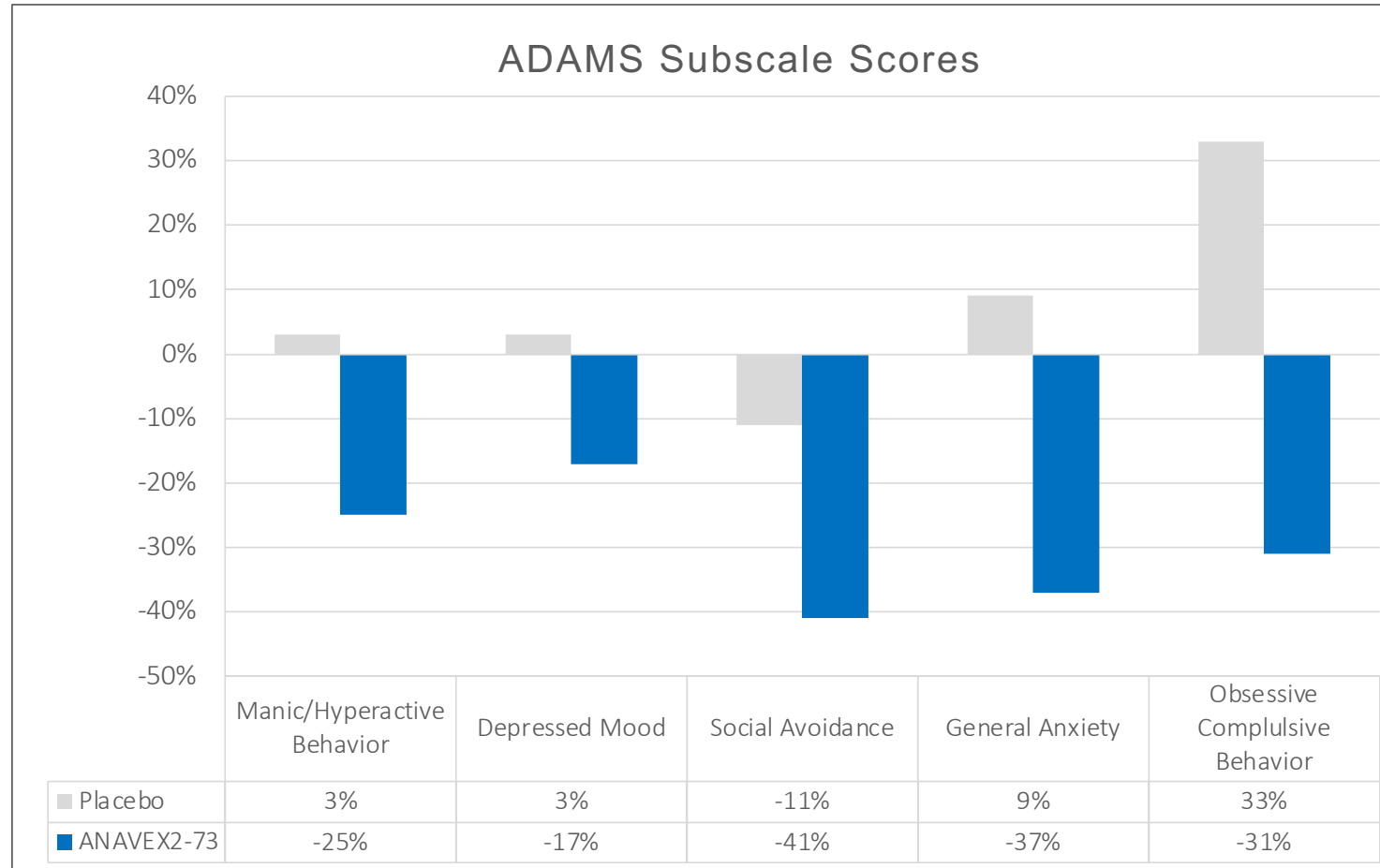
### ADAMS Total Score Improvement with ANAVEX2-73



- Clinically meaningful and statistically significant Improvement for ANAVEX<sup>®</sup>2-73 treated adult patients with Rett syndrome vs placebo
- 12.9-point improvement at Week 7 with p=0.005 (-10.10 ANAVEX<sup>®</sup>2-73 vs. 2.75 placebo)

# ADAMS Subscale Scores

Significant and Balanced Improvements across all Subscales (observed at End of Trial)



- Cohen's d effect size of 1.31

# ANAVEX<sup>®</sup>2-73-RS-002 Phase 2/3 Rett Syndrome AVATAR Study

N=33\*



**7 WEEK STUDY**

... and Open Label Extension (OLE) **48 weeks**

## RTT patient population

- Diagnosis of confirmed RTT
- Patients age >18
- DNA and RNA sequencing

Randomization  
3:2

ANAVEX<sup>®</sup>2-73  
Active dose<sup>#</sup>

Placebo

ClinicalTrials.gov: NCT03941444

### Primary and Secondary Endpoints

- RSBQ, CGI-I
- ADAMS, Sleep function
- Seizure activity
- Safety and tolerability of ANAVEX<sup>®</sup>2-73
- Glutamate biomarker

### Pre-specified Analysis

- Excluding genetic variants SIGMAR1 (rs1800866), COMT (rs113895332/rs61143203) with influence on treatment effect

\* Includes a 3 patient cohort undergoing a 3-week pharmacokinetic (PK) assessment with safety, tolerability, pharmacokinetic and efficacy evaluation of ANAVEX<sup>®</sup>2-73

<sup>#</sup> Oral liquid solution once daily; Dose restricted to maintain complete blinding



# ANAVEX<sup>®</sup>2-73-RS-003 Phase 2/3 Rett Syndrome EXCELLENCE Study

## N=84



## 12 WEEK STUDY

... and Open Label Extension (OLE) 48 weeks

### RTT patient population

- Diagnosis of confirmed RTT
- Patients age 5-18
- DNA and RNA sequencing

Randomization  
2:1

ANAVEX<sup>®</sup>2-73  
Active dose<sup>#</sup>

Placebo

ClinicalTrials.gov: NCT04304482

### Primary and Secondary Endpoints

- RSBQ, CGI-I
- ADAMS, Sleep function
- Seizure activity
- Safety and tolerability of ANAVEX<sup>®</sup>2-73
- Glutamate biomarker

### Pre-specified Analysis

- Excluding genetic variants SIGMAR1 (rs1800866), COMT (rs113895332/rs61143203) with influence on treatment effect

# Parkinson's Disease Dementia (PDD)

Up to 80 percent of those with Parkinson's disease eventually experience Parkinson's disease dementia

## Parkinson's Disease Dementia

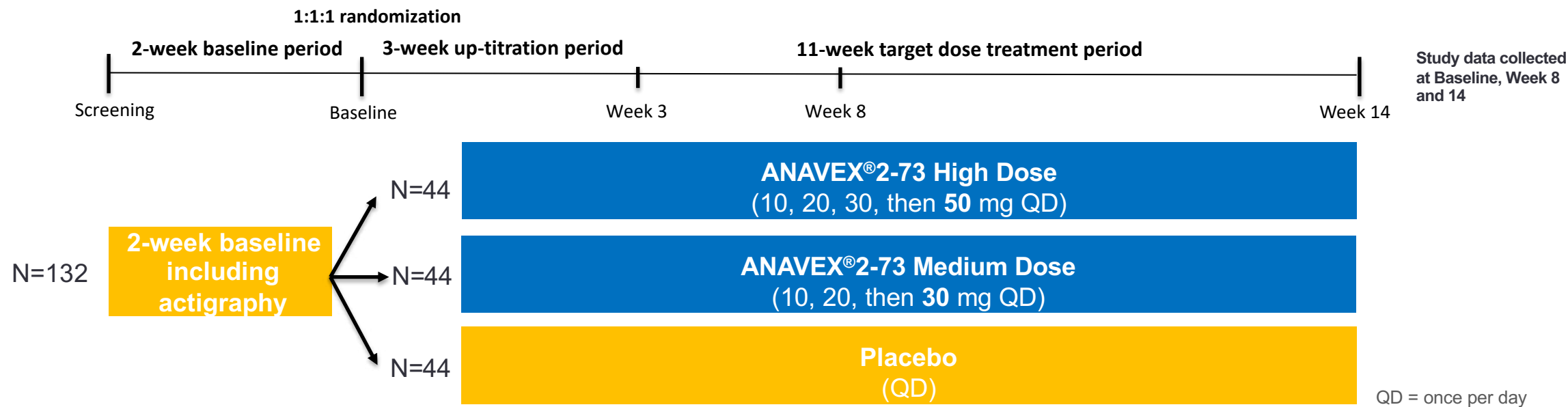
- **Parkinson's disease is a fairly common neurological disorder in older adults, estimated to affect nearly 2 percent of those older than age 65**
  - PD prevalence in US: ~1,000,000
  - The brain changes caused by Parkinson's disease begin in a region that plays a key role in movement
  - Highly heterogeneous multisystem disorder
  - Etiology of cognitive impairment in PD has not yet been fully elucidated
  - As Parkinson's brain changes gradually spread, they often begin to affect mental functions, including memory and the ability to pay attention, make sound judgments and plan the steps needed to complete a task



Source: Aarsland D, Creese B, Politis M, Chaudhuri KR, Ffytche DH, Weintraub D, Ballard C. Cognitive decline in Parkinson disease. *Nat Rev Neurol*. 2017 Apr;13(4):217-231. doi: 10.1038/nrneurol.2017.27. Epub 2017 Mar 3. PMID: 28257128; PMCID: PMC5643027; [www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/parkinson-s-disease-dementia](http://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/parkinson-s-disease-dementia)

# ANAVEX<sup>®</sup>2-73 PoC Phase 2 PDD Study Design

A Phase 2 trial to Assess the Safety, Tolerability and Efficacy of ANAVEX<sup>®</sup>2-73 (*blarcamesine*) Oral Capsules in the Treatment of Parkinson's Disease Dementia



## • PDD Patient Population

- Diagnosis of probable Parkinson's disease dementia
- Diagnosis of idiopathic Parkinson's disease
- Patients aged ≥ 50 years
- MoCA score 13-23

## • Key Primary and Secondary Endpoints

- Safety and tolerability
- CDR Cognitive Domain of Attention
- Sleep function
- MDS-UPDRS
- Actigraphy (24-hour monitoring)
- Entire DNA and RNA sequencing

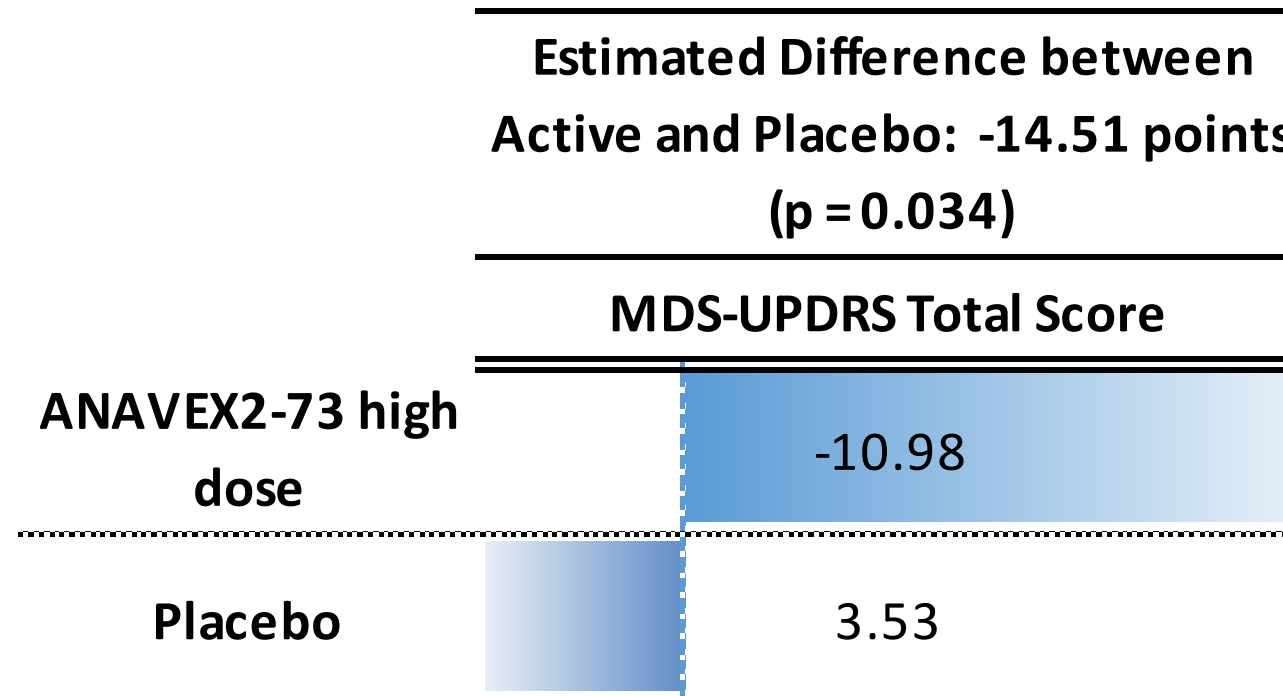
## • Pre-specified Endpoints

- Genetic variants SIGMAR1 (rs1800866),
- COMT(rs113895332/rs6114320 3) with influence on treatment effect

ANAVEX<sup>®</sup>2-73-PDD-001 is a Proof of Concept (PoC) Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-arm, 14-week study

# ANAVEX<sup>®</sup>2-73 Improved MDS-UPDRS Total Score in Placebo-Controlled Parkinson's Disease Dementia Phase 2 Study

**MDS-UPDRS Total score -14.51 improvement is clinically relevant and corresponds to a relative improvement of 18.9 % over 14 weeks**



- Randomized, double-blind, placebo-controlled Phase 2 trial that randomized 132 patients with Parkinson's disease dementia equally (ratio of 1:1:1) to target doses of 30mg (medium), 50mg (high) ANAVEX<sup>®</sup>2-73 or placebo

# Key Cognitive Domains

## Key cognitive features addressed by ANAVEX<sup>®</sup>2-73 (*blarcamesine*)

The criteria from the National Institute on Aging and Alzheimer's Association (NIA-AA) workgroup mention the following five cognitive domains when diagnosing MCI-AD:

Addressed in PoC  
Phase 2 PDD Study

(a) Episodic memory

Episodic memory



(b) Attention

Choice reaction time



(c) Language

Word recognition



(d) Visuospatial skills

Picture recognition



(e) Executive functions

Numeric working memory

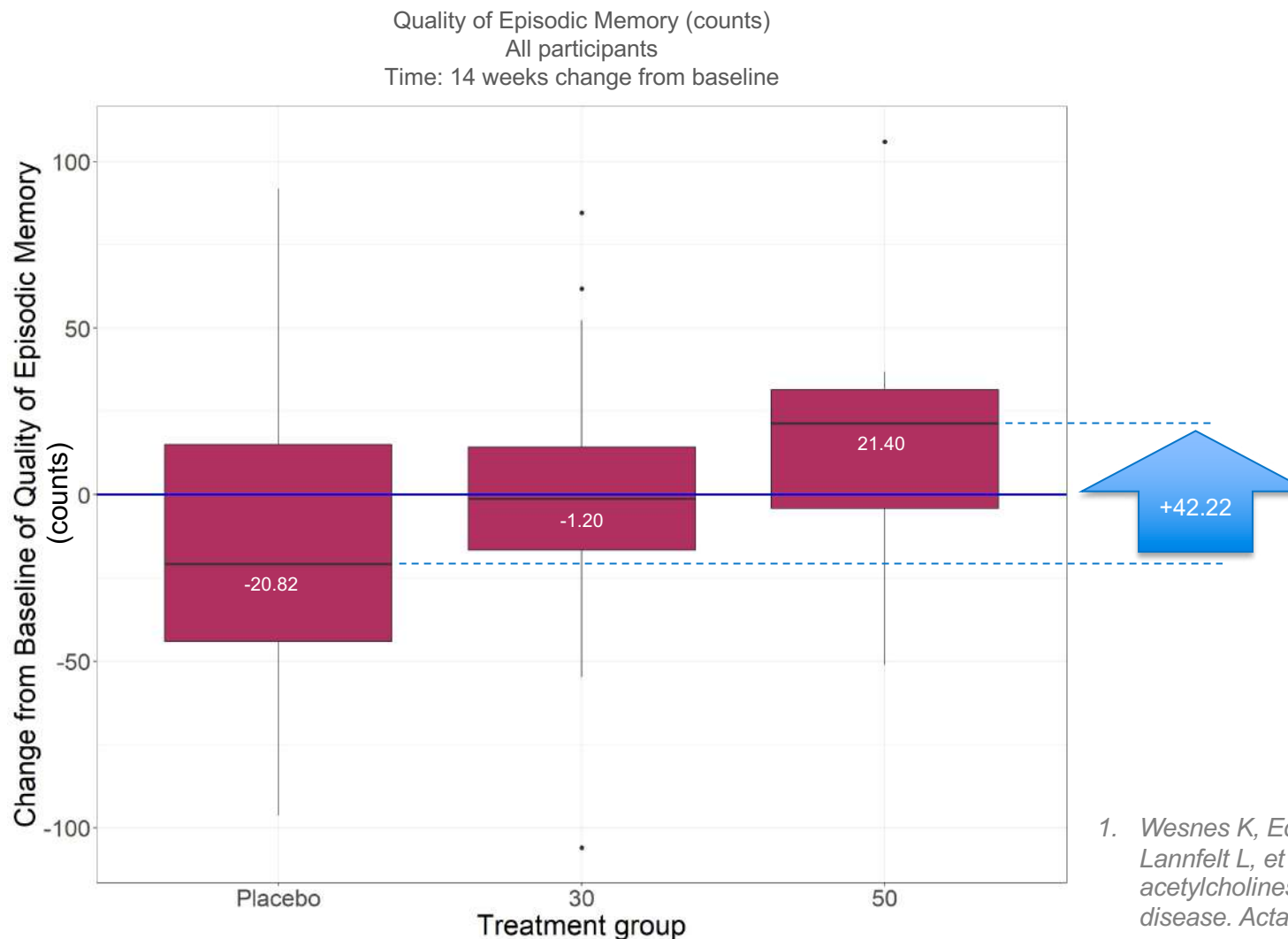


Related CDR  
system  
domains



# Significant Improvements in Episodic Memory with Increased Dose

ANAVEX®2-73-PDD-001 Study: Dose-dependent, statistically significant improvement of Quality of Episodic Memory with ANAVEX®2-73 (*blarcamesine*)



- A high score reflects ability to store, hold and retrieve information of an episodic nature (e.g., an event or name)
- CDR system Quality of Episodic Memory highly correlated (70%) with ADAS-Cog ( $r = 0.7$ )<sup>1</sup>

1. Wesnes K, Edgar C, Andreasen N, Annas P, Basun H, Lannfelt L, et al. Computerized cognition assessment during acetylcholinesterase inhibitor treatment in Alzheimer's disease. *Acta Neurol Scand* 2010; 122:270-7

# Summary of Topline Results:

## Broad and Significant Effects with ANAVEX<sup>®</sup>2-73 (*blarcamesine*) in PDD Patients

- ANAVEX<sup>®</sup>2-73 (*blarcamesine*): a novel, oral, investigational sigma-1 receptor (Sig-1R / SIGMAR1) agonist with multimodal activity
- Data confirm SIGMAR1 as gene “signature” biomarker of response to ANAVEX<sup>®</sup>2-73 (*blarcamesine*) confirming SIGMAR1 activation as mechanism of action
- Broad and statistically significant improvements in CDR system Cognitive Domain of Attention assessed by Choice Reaction Time ( $p = 0.039$ ) and Digital Vigilance ( $p = 0.008$ ) and CDR system Episodic Memory ( $p = 0.047$ ), representing complex cognitive tasks with impact on quality of life such as making a choice between similar objects and remembering daily personal experiences, which are mostly impaired in both PD and AD<sup>1</sup>
- Statistically significant dose-dependent ( $p = 0.003$ ) improvement of CDR system Episodic Memory, which has been shown to be highly correlated (70%) with the Alzheimer’s Disease Assessment Scale–Cognitive score (ADAS-Cog;  $r = 0.7$ )<sup>2</sup>
- ANAVEX<sup>®</sup>2-73 (*blarcamesine*) does not impair sleep and has a positive effect on REM sleep behavior disorder
- ANAVEX<sup>®</sup>2-73 (*blarcamesine*) was generally safe, well tolerated, and improved safety profile compared to dementia drugs associated with typical adverse effects
- These results support continued development in PDD / PD as well as currently ongoing Phase 2 and Phase 2/3 clinical studies with ANAVEX<sup>®</sup>2-73 (*blarcamesine*) in Rett syndrome<sup>3</sup> and Alzheimer’s disease<sup>4</sup>
- Data will be submitted to the U.S. Food and Drug Administration to seek regulatory guidance

1. Mahurin, R. K., & Pirozzolo, F. J. (1993). Application of Hick’s law of response speed in Alzheimer and Parkinson diseases. *Perceptual and Motor Skills*, 77(1), 107–113

2. Wesnes K, Edgar C, Andreasen N, Annas P, Basun H, Lannfelt L, et al. Computerized cognition assessment during acetylcholinesterase inhibitor treatment in Alzheimer’s disease. *Acta Neurol Scand* 2010; 122:270–7

3. ClinicalTrials.gov Identifiers: NCT03758924, NCT03941444, NCT04304482

4. ClinicalTrials.gov Identifiers: NCT03790709, NCT02756858

# Alzheimer's Disease (AD)

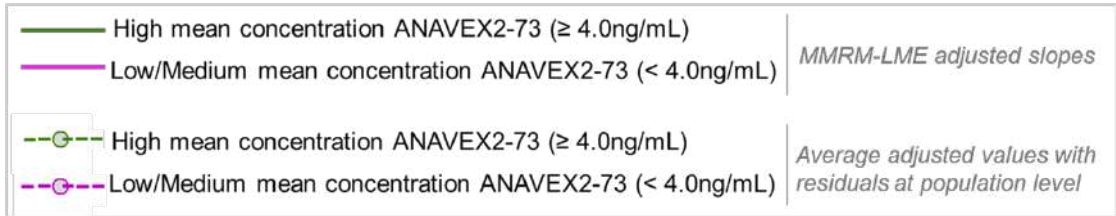
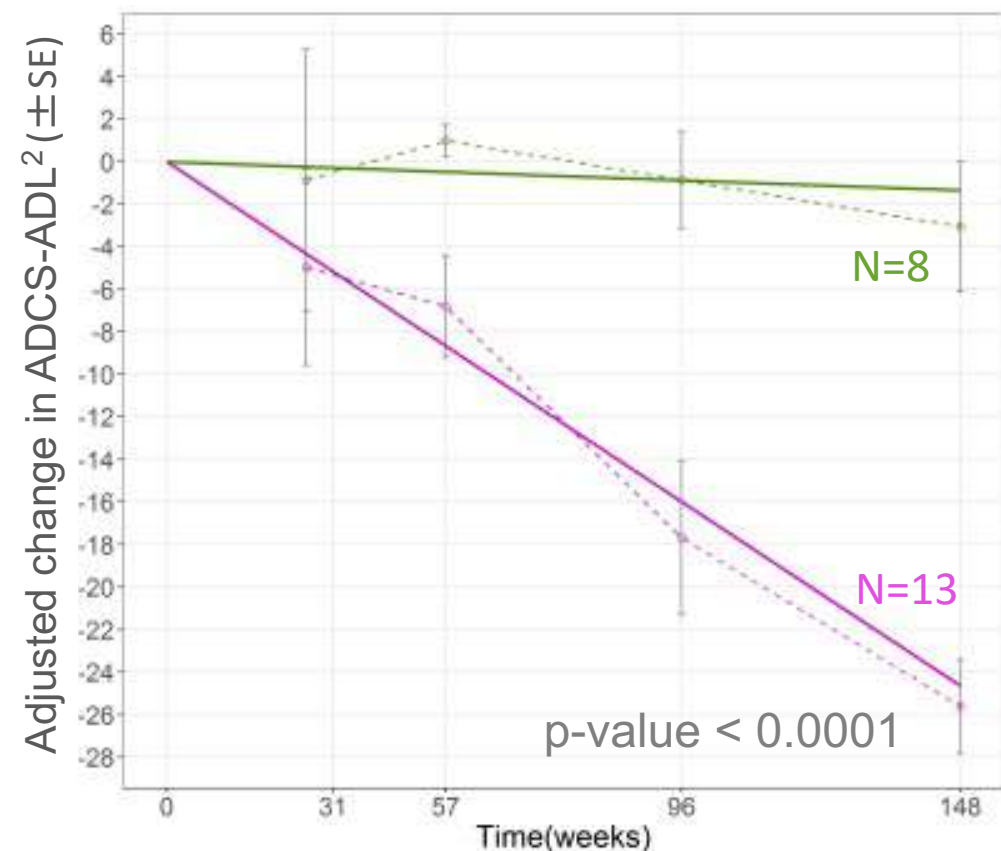
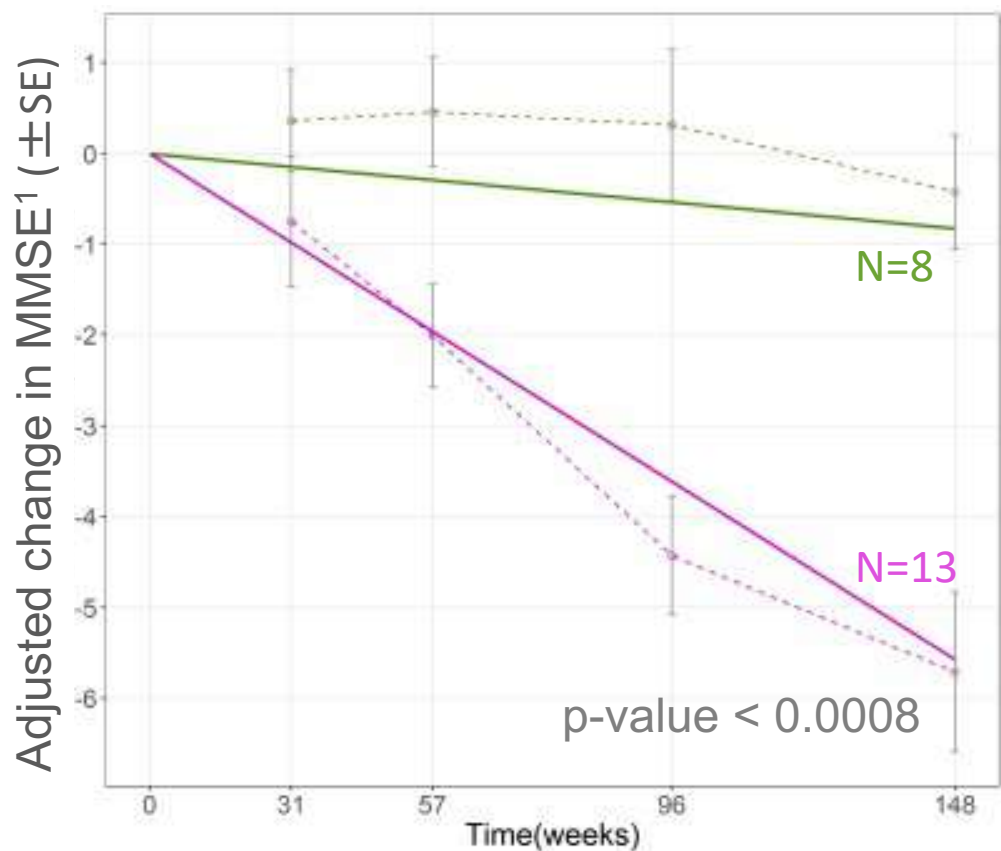
Alzheimer's disease is a progressive, irreversible neurological disease and the most common cause of dementia

## Alzheimer's Disease (AD)

- **Alzheimer's disease incidence highly correlates with age**
  - AD prevalence in US: ~5,700,000
  - Estimated 50 million people live with dementia worldwide
  - Today, there are no commercially available therapies to address the underlying cause of Alzheimer's
  - The current annual cost of dementia is estimated at \$1 trillion, a figure set to double by 2030



# ANAVEX<sup>®</sup>2-73 Demonstrated Improved MMSE<sup>1</sup> and ADCS-ADL<sup>2</sup> Scores in Phase 2a AD Study through 148 Weeks



Dose range 10mg-50mg ANAVEX<sup>®</sup>2-73 oral once daily.

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*

<sup>1</sup> Mini Mental State Examination (MMSE)  
<sup>2</sup> Alzheimer's Disease Cooperative Study Group - Activities of Daily Living Inventory (ADCS-ADL)

# ANAVEX<sup>®</sup> 2-73 Biomarker Driven Development Strategy in Alzheimer's Disease

## Patient Clinical Data



Cognitive Scores

Sleep Questionnaires

Other Scores

Dose, PK

## Genomic Data



DNA

RNA

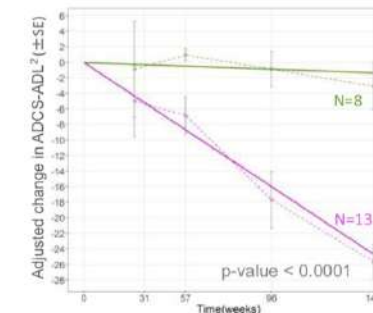
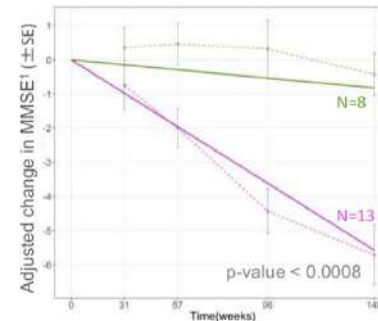
Microbiota

Real World Evidence Data  
(~ 7,000 patients)

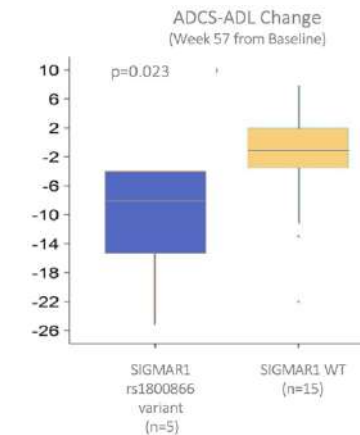
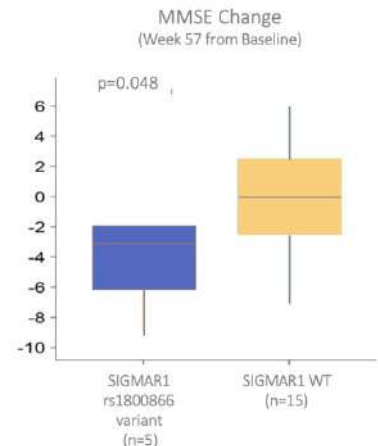


KEM<sup>®</sup> Integrative AI

Demonstrated Improved MMSE and ADCS-ADL through 148 weeks for *all* patients



Novel Genomic Biomarkers of Response Identified in Phase 2a AD study -> Pre-specified Efficacy Endpoints in *all* ANAVEX<sup>®</sup> 2-73 studies (AD, PDD, RTT)



Applied to Phase 2b/3 Alzheimer's disease (AD) study and other indications: Parkinson's disease dementia (PDD) and Rett syndrome (RTT)



# ANAVEX<sup>®</sup>2-73 Phase 2b/3 Alzheimer's Disease and ATTENTION-AD OLE Study

N=509 

## Early AD patient population

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

Randomization  
1:1:1

ANAVEX<sup>®</sup>2-73  
High dose<sup>#</sup>

ANAVEX<sup>®</sup>2-73  
Medium dose<sup>#</sup>

Placebo

**48** WEEK  
STUDY  
... and Open Label Extension (OLE) **96** weeks

ClinicalTrials.gov: NCT03790709

### Primary Endpoints

- ADAS-Cog
- ADCS-ADL
- Safety and tolerability

### Key Secondary Endpoints

- CDR-SB
- Structural and functional MRI
- Biomarkers: Abeta<sub>40</sub>/Abeta<sub>42</sub>, T-tau, P-tau, NFL, YKL-40, neurogranin, BACE1

### Pre-specified Analysis

- Excluding genetic variants SIGMAR1 (rs1800866), COMT (rs113895332/rs61143203) with influence on treatment effect

<sup>#</sup> Oral capsule once daily; Dose restricted to maintain complete blinding

Anavex is pursuing **Large Markets** by Applying **Precision Medicine Platform** to Develop Treatments for *both* **Global Aging** CNS diseases (Alzheimer's, Parkinson's), as well as **catastrophic Orphan Genetically caused** diseases, Rett Syndrome with High Unmet Needs

**\$ 277B**

**Economic burden**

*2018 Alzheimer's Association*

#### OVERARCHING MESSAGE

A **novel platform approach** to address the totality of CNS diseases



#### PRECISION MEDICINE PLATFORM IMPROVES CHANCE OF CLINICAL SUCCESS

Testing for biomarkers demonstrated improved clinical response to ANAVEX®2-73 in Rett syndrome, Parkinson's and Alzheimer's patients correlated with mRNA SIGMAR1 gene expression



#### NOVEL CNS MECHANISM OF ACTION

ANAVEX®2-73, an orally available SIGMAR1 agonist, is upstream of neurodevelopment and neurodegeneration and has been shown to restore homeostasis



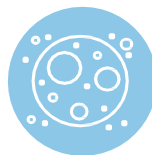
#### COMPELLING INITIAL HUMAN DATA

ANAVEX®2-73 Phase 2 in Rett syndrome, Phase 2 in Parkinson's disease dementia and Phase 2a trial in Alzheimer's with favorable safety and initial efficacy results through 148 weeks



#### WORLDWIDE COMMERCIAL RIGHTS AND STRONG IP FOUNDATION

We retain global commercial rights to all of our product candidates and our lead product candidate, ANAVEX®2-73, including patent protection to 2030-2039



#### SUFFICIENT CASH TO ACHIEVE KEY MILESTONES

Sufficient cash for >5 years to achieve key milestones, including non-dilutive cash from Michael J Fox Foundation, International Rett Syndrome Foundation, Australian government

# Anavex Life Sciences Expertise

## Management Team

**Christopher U. Missling PhD** - President & CEO

**Walter E Kaufmann, MD** - Chief Medical Officer

**Stephan Toutain, MS, MBA** – Chief Operating Officer

**Emmanuel O Fadiran, RPh, PhD** - SVP of Regulatory Affairs

**Daniel Klamer, PhD** - VP of Business Development & Scientific Strategy



## Scientific Advisory Board Members

**Jeffrey Cummings, MD**



**Paul Aisen, MD**



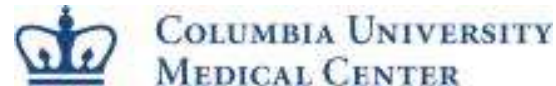
**Corinne Lasmezas, PhD**



**Norman Relkin, MD, PhD**



**Ottavio Arancio, MD, PhD**



**Jacqueline French, MD**



**Andrew Cole, MD**



**Dag Aarsland, MD, PhD**



**Daniel Weintraub, MD**



**Tangui Maurice, PhD**





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