



anavex[®]

LIFE SCIENCES Corp.

Corporate Presentation

Christopher U Missling, PhD | President & CEO

Nasdaq: AVXL | March 2019

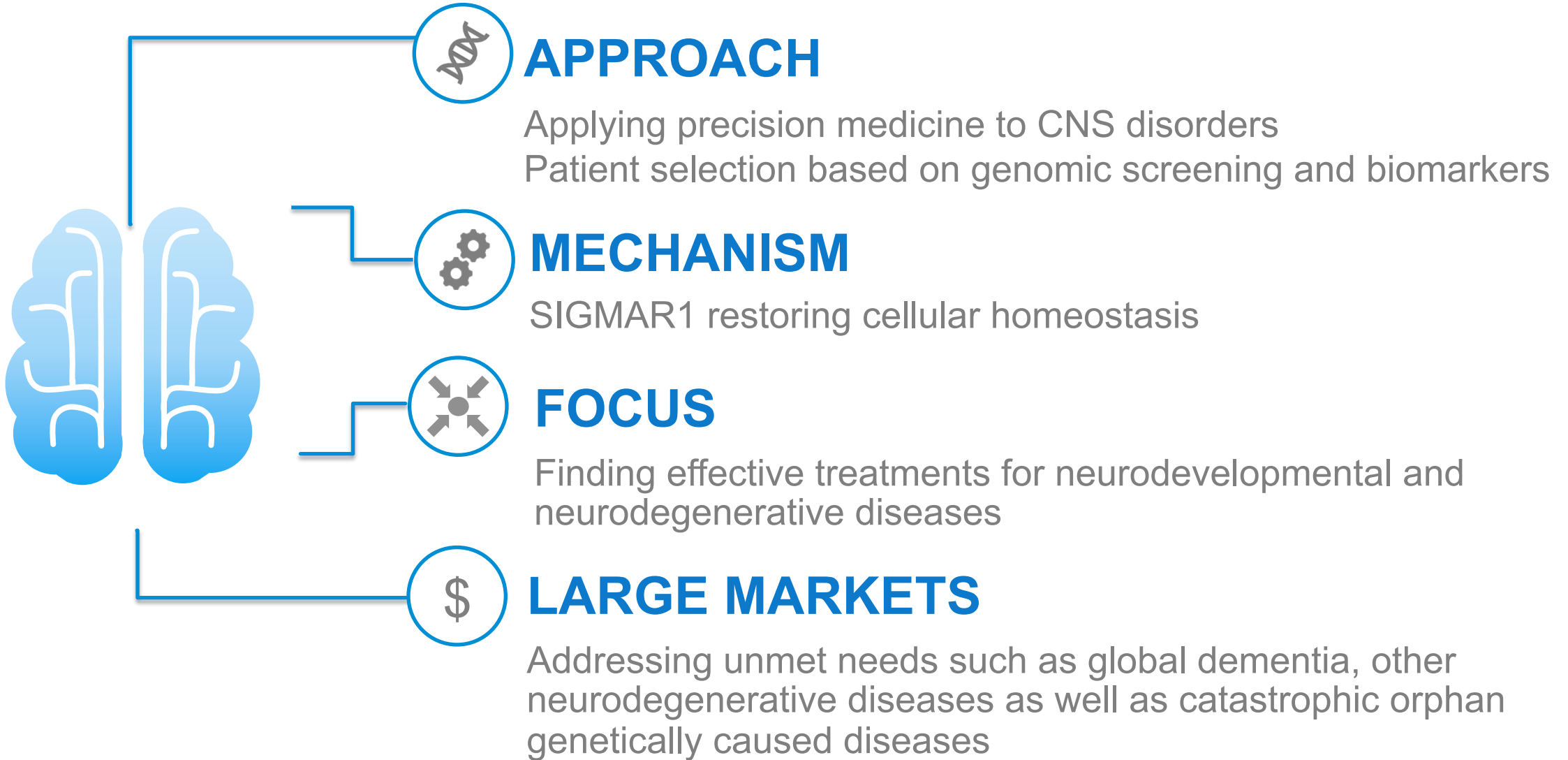
SAFE HARBOR

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New Therapeutic Strategy to Treat CNS Disorders

- Anavex utilizes **genomic biomarkers** in **precision medicine** to treat severe and devastating neurological disorders
- Anavex is focusing on **rare diseases** with no available therapy (Rett syndrome) and **high risk CNS** patient populations (Alzheimer's disease, Parkinson's disease)

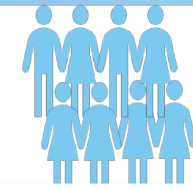
Anavex at a Glance



Overview ANAVEX®2-73 Ongoing Precision Medicine Clinical Trials

PHASE 2 PARKINSON'S
DISEASE DEMENTIA

14 WEEK
STUDY



120

ANAVEX®2-73-PDD-001 STUDY (NCT03774459)*

PHASE 2b/3
ALZHEIMER'S DISEASE

48 WEEK
STUDY

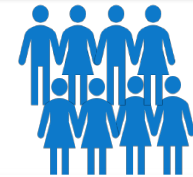


450

ANAVEX®2-73-AD-004 STUDY (NCT03790709)*

PHASE 2
RETT SYNDROME**

7 WEEK
STUDY



15

ANAVEX®2-73-RS-001 STUDY (NCT03758924)*

PHASE 2a
ALZHEIMER'S DISEASE

208 WEEK
STUDY



32

ANAVEX®2-73-AD-002/3 STUDY (NCT02244541/NCT02756858)*

- Sufficient cash including non-dilutive grant and governmental third party support to fund objectives for the next 2 years

*ClinicalTrials.gov Identifier; **FDA granted ANAVEX®2-73 Orphan Drug Designation (ODD) for Rett syndrome

Catalysts to Drive Value

The company is well positioned to achieve key clinical readouts

- Phase 2a – Reported 148-week data at CTAD 2018 scientific meeting
- Phase 2b/3 clinical trial in Alzheimer's disease – ongoing
- Phase 2 clinical trial in Parkinson's disease dementia (PDD) – ongoing
- Initiate Phase 2 clinical trial in Rett syndrome (RTT)
- Topline data Phase 2 Parkinson's disease dementia (PDD)
- Topline data Phase 2 Rett syndrome (RTT)
- Clinical data publications in 2019
- New indications and licensing opportunities

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



Critical review
Role of sigma-1 receptors in neurodegenerative diseases

Linda Nguyen^{a,b,c}, Brandon P. Lucke-Wold^d, Shona A. Mookerjee^e, John Z. Cavendish^f, Matthew J. Robson^g, Anna L. Scandinaro^{a,b,c}, Rae R. Matsumoto^{a,b,c,d,g}

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ANAVEX[®]2-73 alleviates Tau pathology in neurodegenerative disease models

Neuropharmacology (2013) 36, 1156–1171
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www.elsevier.com/locate/neuropharm

Blockade of Tau Hyperphosphorylation and A β _{1–42} Generation by the Aminotetrahydrofuran Derivative ANAVEX2-73, a Mixed Muscarinic and σ_1 Receptor Agonist, in a Nontransgenic Mouse Model of Alzheimer's Disease

Valentine Lahmy^{1,2,3,4}, Johann Meunier⁵, Susanna Malmström⁶, Gaelle Naert^{1,3}, Laurent Givalois^{1,3}, Seung Hyun Kim⁷, Vanessa Vilard⁸, Alexandre Varvakides⁹ and Tanguy Maurice^{1,2,3}
¹INSERM U1170, Montpellier, France; ²University of Montpellier 2, Montpellier, France; ³Centre Pasteur des Maladies d'Alzheimer, Paris, France; ⁴Amyloid, Orléans, France; ⁵Department of Neurology, Institute of Biomedical Sciences, College of Medicine, Hanyang University, Seoul, Korea; ⁶Norges ELSI, Oslo, Norway; ⁷Seoul, Korea; ⁸Nantes ELSI, Nantes, France; ⁹Seoul, Korea

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

NEUROPHARMACOLOGY AND NEUROTOXICOLOGY NEUROREPORT

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

Agostino Marrazzo¹, Filippo Caraci¹, Elisa Trovato Salinaro¹, Tsung-Ping Su², Agata Copani^{1,2,3,4} and Giuseppe Ransisvalle¹

Autophagy as Key Protein Clearance Process: New Pharmacological Target in Neurodegeneration – achieved through SIGMAR1 Activation



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 *

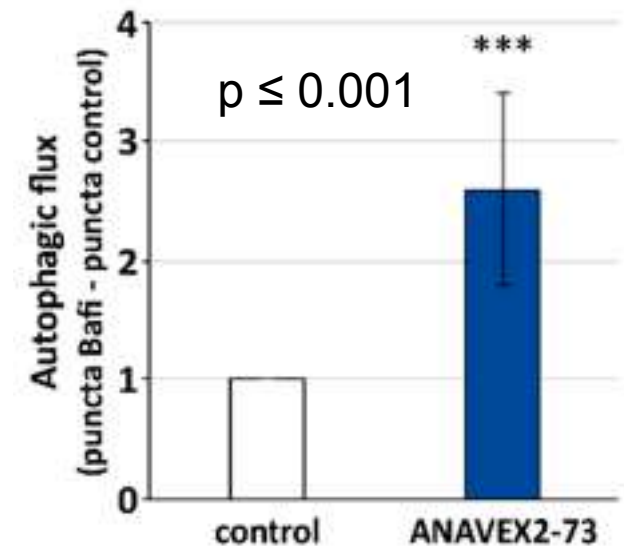
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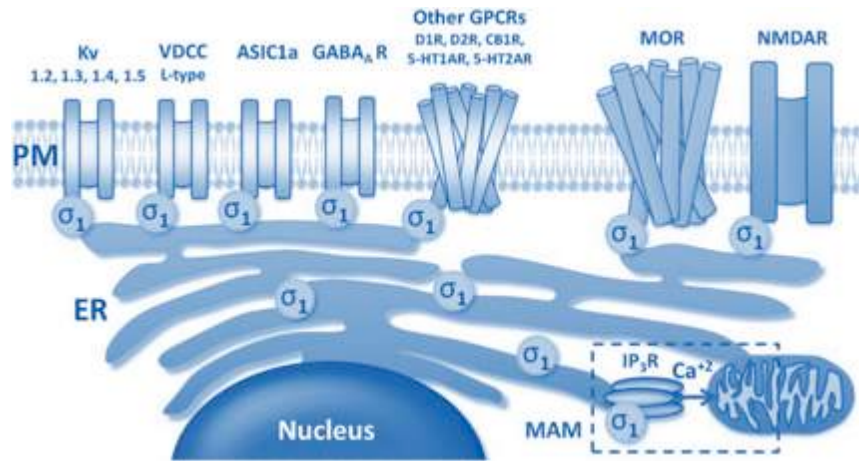


Sigma-1 receptor activation by ANAVEX2-73 enhances autophagy in *C. elegans*



Genetic SIGMAR1 Variations Linked to Neurological Disorders

The SIGMAR1 receptor is an integral membrane protein involved in cellular homeostasis which targets restoration of neuroplasticity and cellular stress response



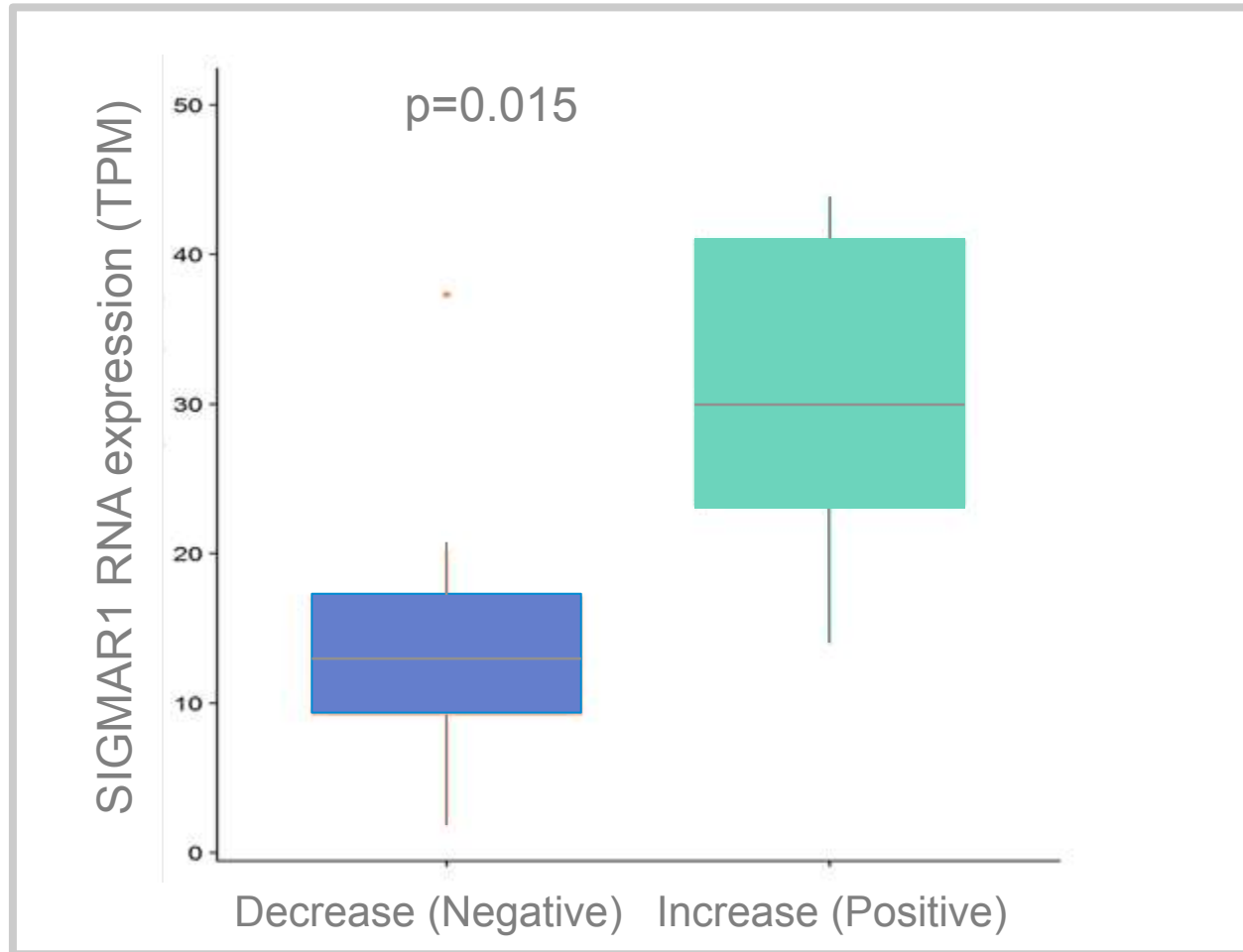
Impaired SIGMAR1 function leads dysfunction in ER-mitochondria crosstalk, calcium homeostasis impairment, ER stress activation

- SIGMAR1 null mice display muscle weakness, axonal degeneration and motor neuron loss¹
- Mutations in SIGMAR1 have been identified in
 - frontotemporal lobar degeneration co-occurring with ALS (FTLD-ALS)²
 - juvenile ALS³
 - the rare neuromuscular disorder distal hereditary motor neuropathy (dHMN)^{4, 5, 6, 7}
 - In Alzheimer's disease, variants of the SIGMAR1 have been shown to be a risk factor⁸

1) Bernard-Marissal N et al 2015. *Brain*. Apr;138(Pt 4):875-90L.; 2) Luty AA et al 2010. *Ann Neurol*. Nov;68(5):639-49; 3) Al-Chalabi A et al 2011. *Ann Neurol*. Dec;70(6):913-9; 4) Li X et al 2015. *Neurology*. Jun 16;84(24):2430-7.; 5) Gregianin E et al 2016. *Hum Mol Genet*. Sep 1;25(17):3741-3753.; 6) Nandhagopal R et al 2018. *Eur J Neurol*. Feb;25(2):395-403.; 7) Almendra L et al 2018. *Acta Myol*. May 1;37(1):2-4.; 8) Feher A et al 2012. *Neurosci Lett*; 517: 136-139.

Patients Improvement Correlates with ANAVEX[®]2-73 and SIGMAR1 RNA Expression

Activities of Daily Living (ADCS-ADL)* Slope from Baseline to Week 57

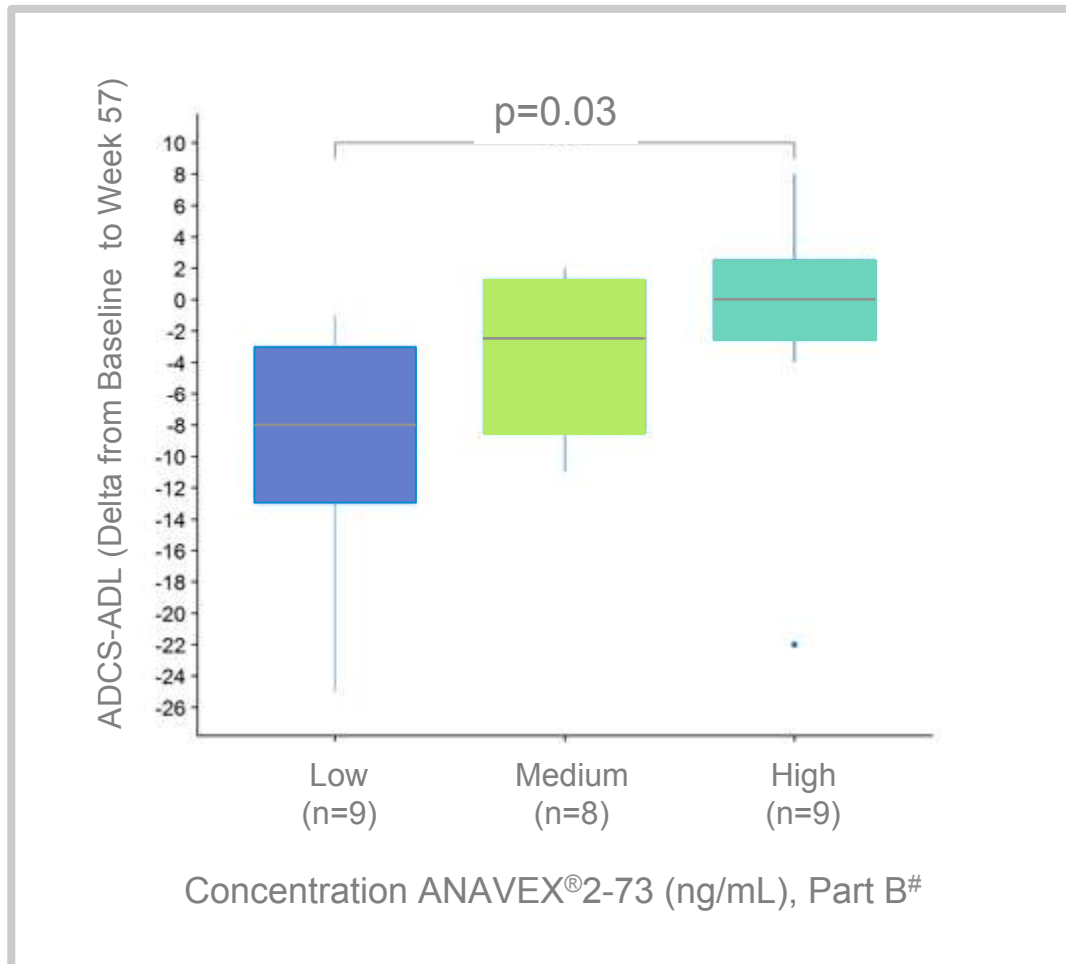


ANAVEX[®]2-73 positive response in functional (ADCS-ADL) outcomes in Alzheimer's disease patients correlate with SIGMAR1 mRNA levels

*p = p-value of Mann-Whitney U test
All n=20 patients in study at week 57
with available genomic data*

Significant Relationship between ANAVEX[®]2-73 Concentration and Patients Response

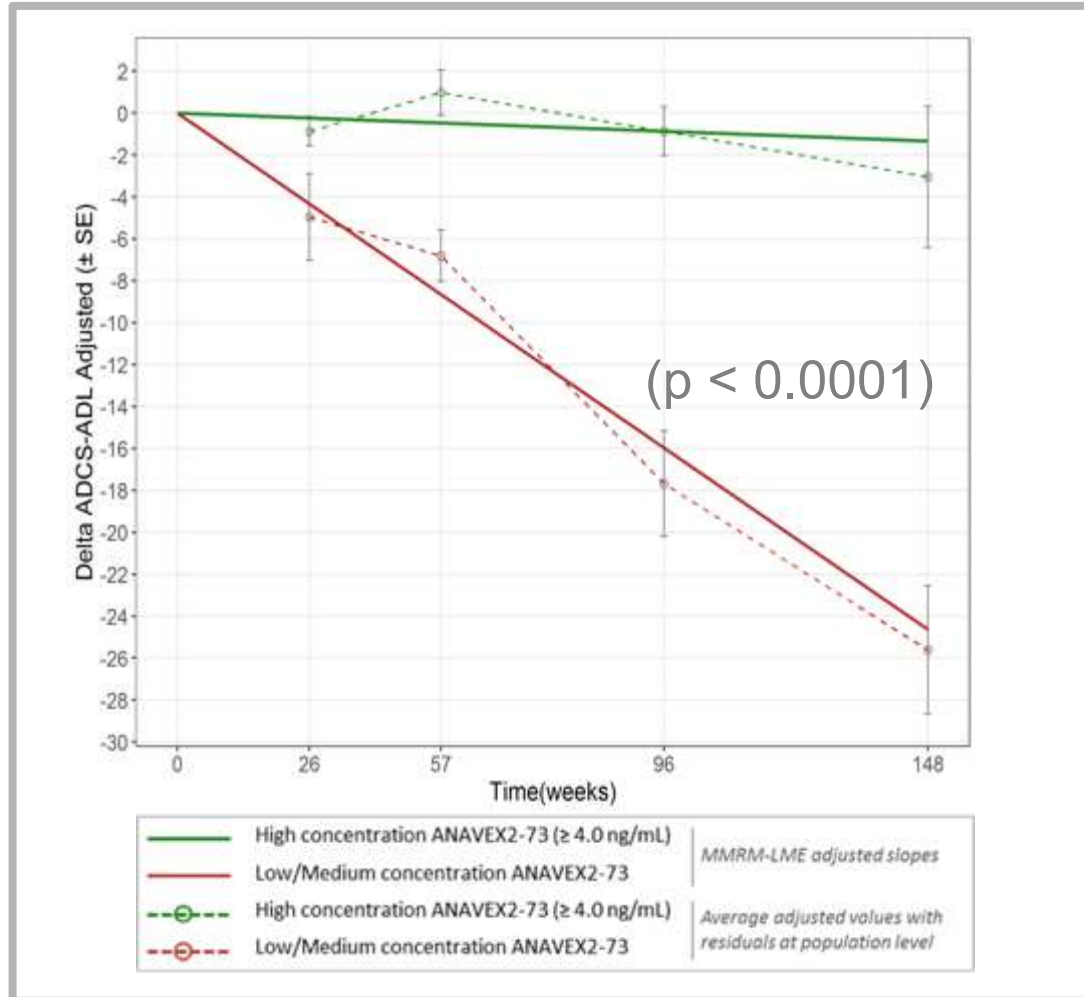
Activities of Daily Living (ADCS-ADL)*



- High Concentration of ANAVEX[®]2-73 => High Delta ADCS-ADL (improved response)
- # Plasma concentration of ANAVEX[®]2-73 is correlated with the administered dose
 - All n=26 patients in study at week 57
 - p = p-value of Mann–Whitney U test

Patients Treated with Higher ANAVEX[®]2-73 Concentration Maintain ADCS-ADL* Performance vs Lower Concentration Cohort

High Concentration cohort shows 88 % difference to low concentration cohort

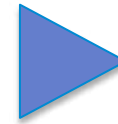
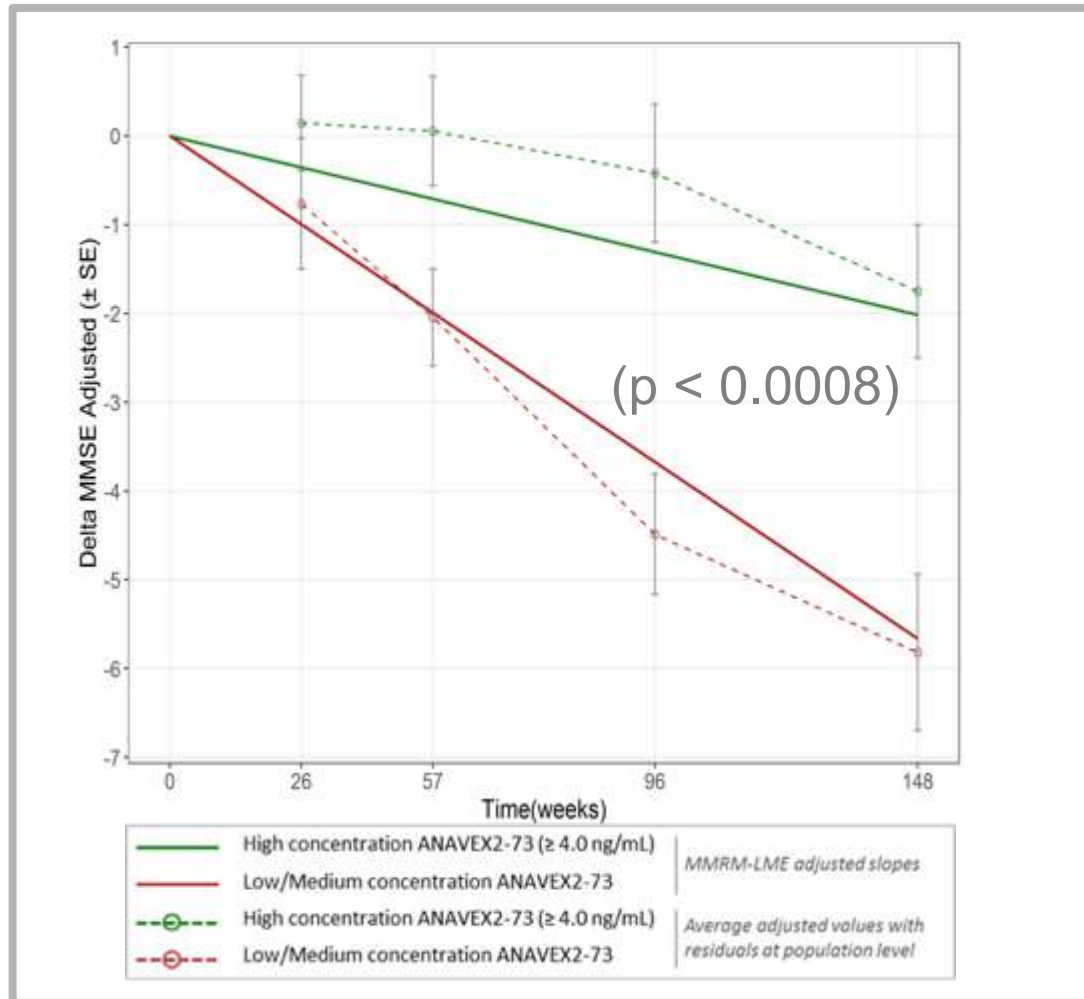


- High plasma concentration of ANAVEX[®]2-73 [>4.0 ng/ml] is correlated with the clinically administered dose
- In addition to concentration, the significant covariates identified in MMRM-LME model are:
 - **SIGMAR1** ($p < 0.0080$),
 - **COMT** ($p < 0.0014$)

The covariates that are included in the MMRM-LME model for ADCS-ADL change are: time as continuous, AV2-73 concentration group (High and Low/Med), sex, APOE $\epsilon 4$ status, age (Low, High), baseline MMSE score, ongoing Donepezil treatment, SIGMAR1-Q2P, COMT-L146FS variants, interactions between time and concentration group, time and APOE $\epsilon 4$ status, time and SIGMAR1, time and COMT, concentration group and APOE $\epsilon 4$ status, and concentration group and SIGMAR1 variant.

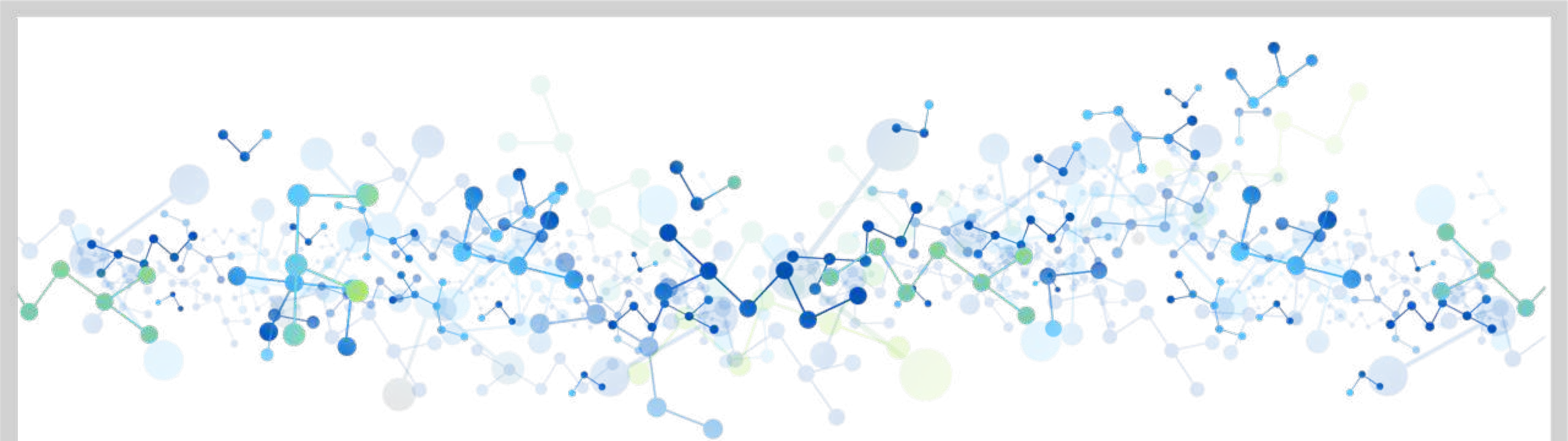
Patients Treated with Higher ANAVEX[®]2-73 Concentration Show Higher MMSE* Performance Compared to Lower Concentration

High Concentration cohort shows 64 % less decline than low concentration cohort



- High plasma concentration of ANAVEX[®]2-73 [>4.0 ng/ml] is correlated with the clinically administered dose

Covariates included in the MMRM-LME model for MMSE change are: time as continuous, AV2-73 concentration group (High and Low/Med), APOE $\epsilon 4$ status, age (Low, High), baseline MMSE score, SIGMAR1-Q2P variant, interactions between time and concentration group, time and APOE $\epsilon 4$ status, time and SIGMAR1, and concentration group and SIGMAR1 variant.



Precision Medicine

Precision Medicine

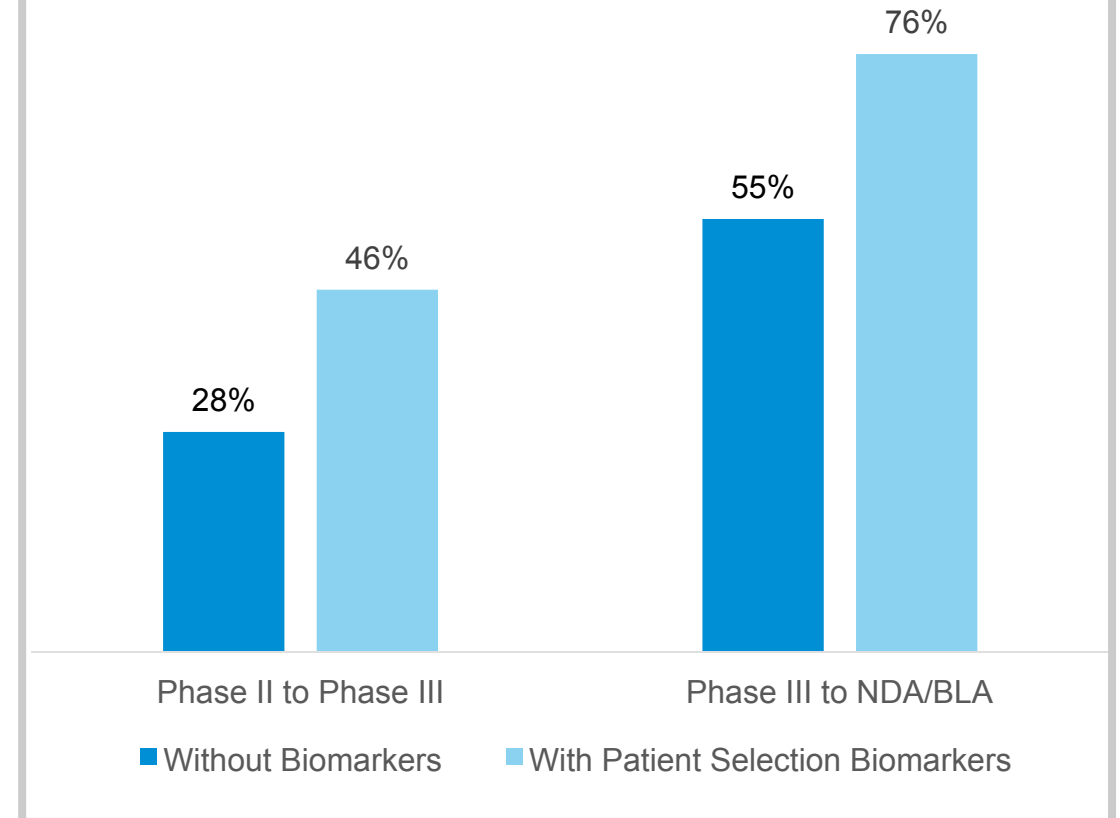
PHARMACOLOGY + GENOMIC = PHARMACOGENOMICS

The ideal pharmacogenomics test will be able to determine:



- Potential for a medication to be effective – for this person
- The best dose of a medication – for this person
- Avoid risk of serious side effects – for this person

Patient Selection with Biomarker Increases Probability of Success

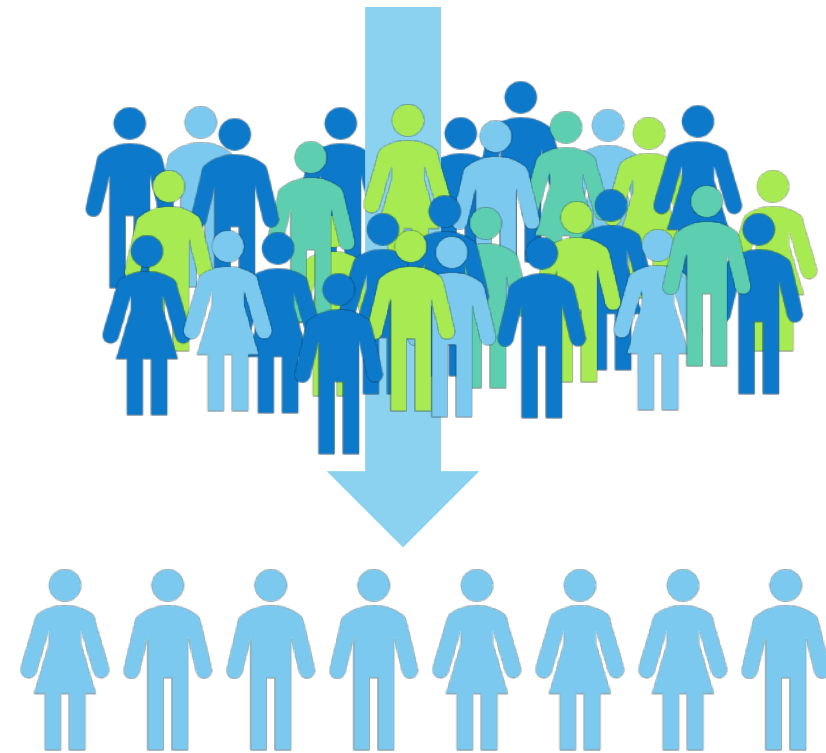


Thomas DW et al. Clinical Development Success Rates 2006-2015. BIO Industry Analysis

Identification of Gene “Signature” from ANAVEX[®]2-73-Treated Patients

- Genomic signature (WT SIGMAR1 gene) strongest responders to ANAVEX[®]2-73
- This genomic “biomarker” is **drug specific**, not indication specific, so it applies to all indications treated with ANAVEX[®]2-73

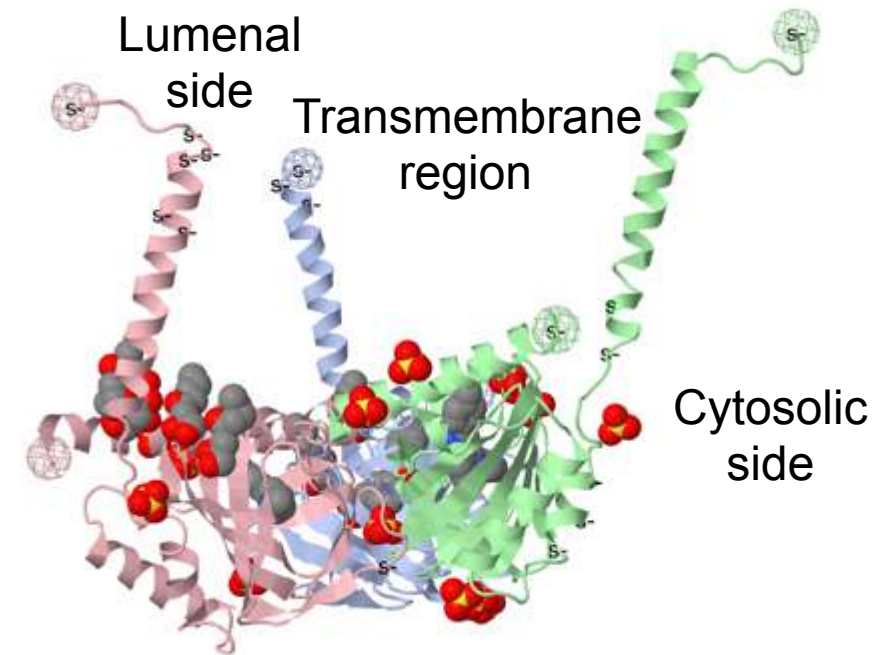
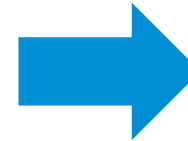
PRECISION MEDICINE



SIGMAR1 Gene Plays a Role in Protein Trafficking

SIGMAR1 WT
structure

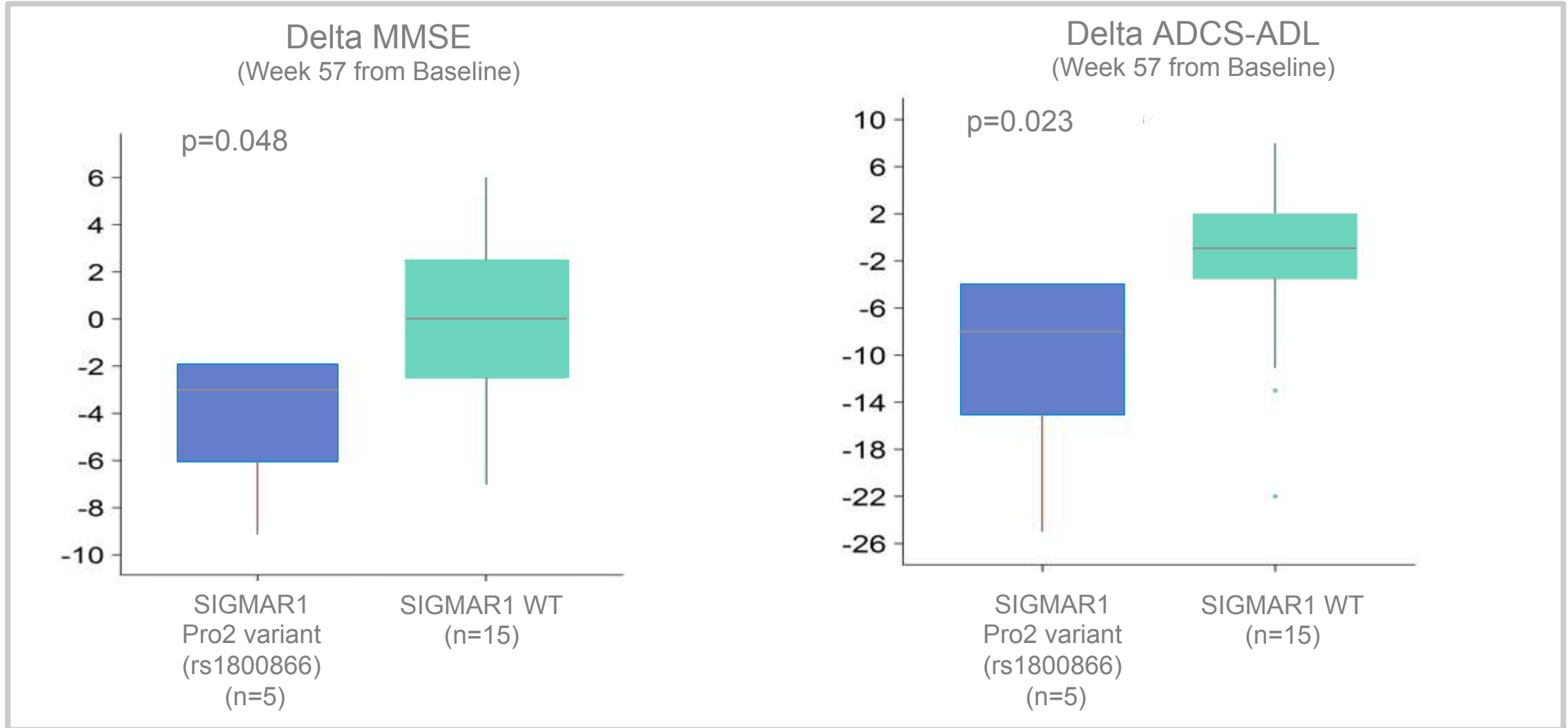
rs1800866 variant
impairs protein trafficking



- Majority of the population (~80%) carries SIGMAR1 WT
- Majority of patients (~80%) are expected to benefit from SIGMAR1 activation with ANAVEX[®]2-73
- rs1800866 variant found in the remaining (~20%) of the population can cause structural change, leading to impaired protein trafficking

SIGMAR1 WT Gene Associated with Improved Response ...

... and validated at **148** weeks



Source: H Hampel et al., AAIC 2018

p = p-value of Mann-Whitney U test
All n=20 patients in study at week 57 with available genomic data

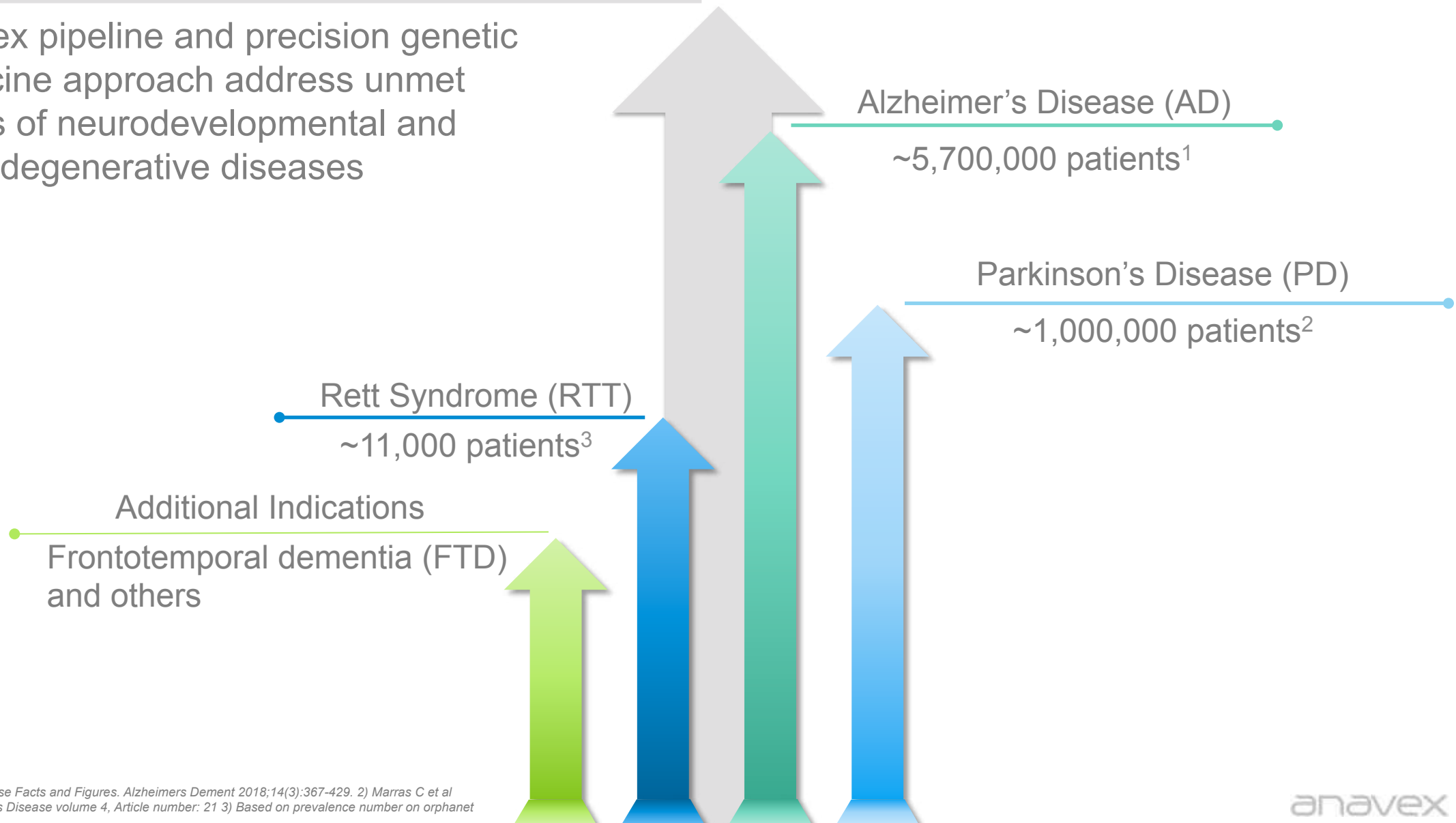


Clinical Studies:

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

Pipeline Addresses both Rare and Large Indications

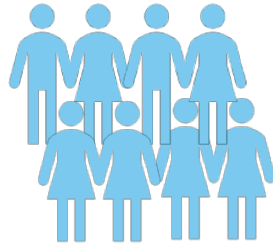
Anavex pipeline and precision genetic medicine approach address unmet needs of neurodevelopmental and neurodegenerative diseases



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 orphanet

ANAVEX[®]2-73 Phase 2 Parkinson's Disease Dementia Study

N=120



14 WEEK STUDY

PDD patient population

- Diagnosis of probable Parkinson's disease dementia (PDD)
- Diagnosis of idiopathic Parkinson's disease
- Patients aged ≥ 50 years
- MoCA score 13-23
- DNA and RNA sequencing

Randomization
1:1:1

ANAVEX[®]2-73
High dose[#]

ANAVEX[®]2-73
Medium dose[#]

Placebo

Primary Endpoints

- CDR Continuity of Attention
- Safety and tolerability of ANAVEX[®]2-73

Key Secondary Endpoints

- MDS-UPDRS
- Sleep function
- Actigraphy
- MoCA
- Other CDR battery measures

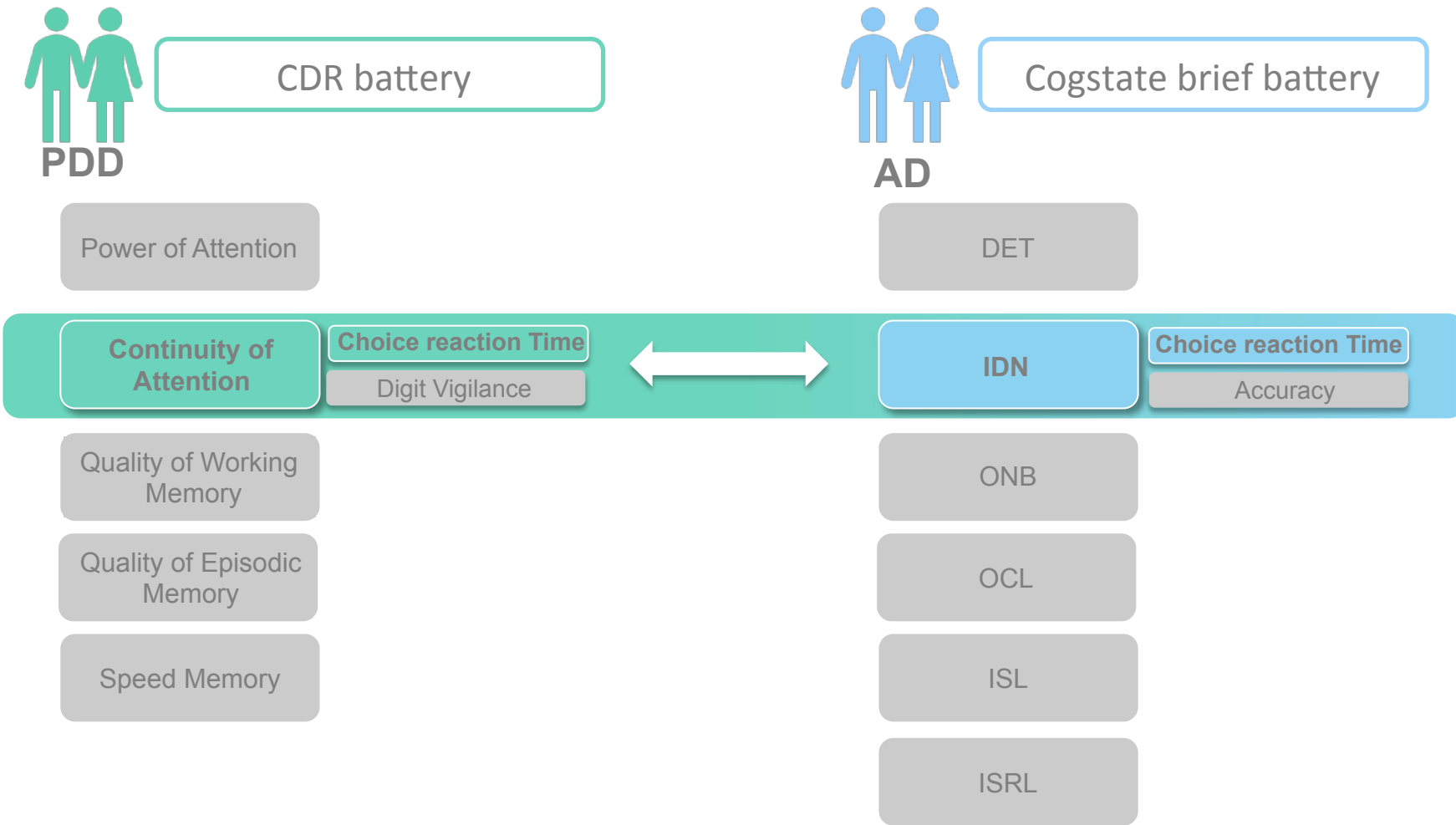
Pre-specified Endpoints

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

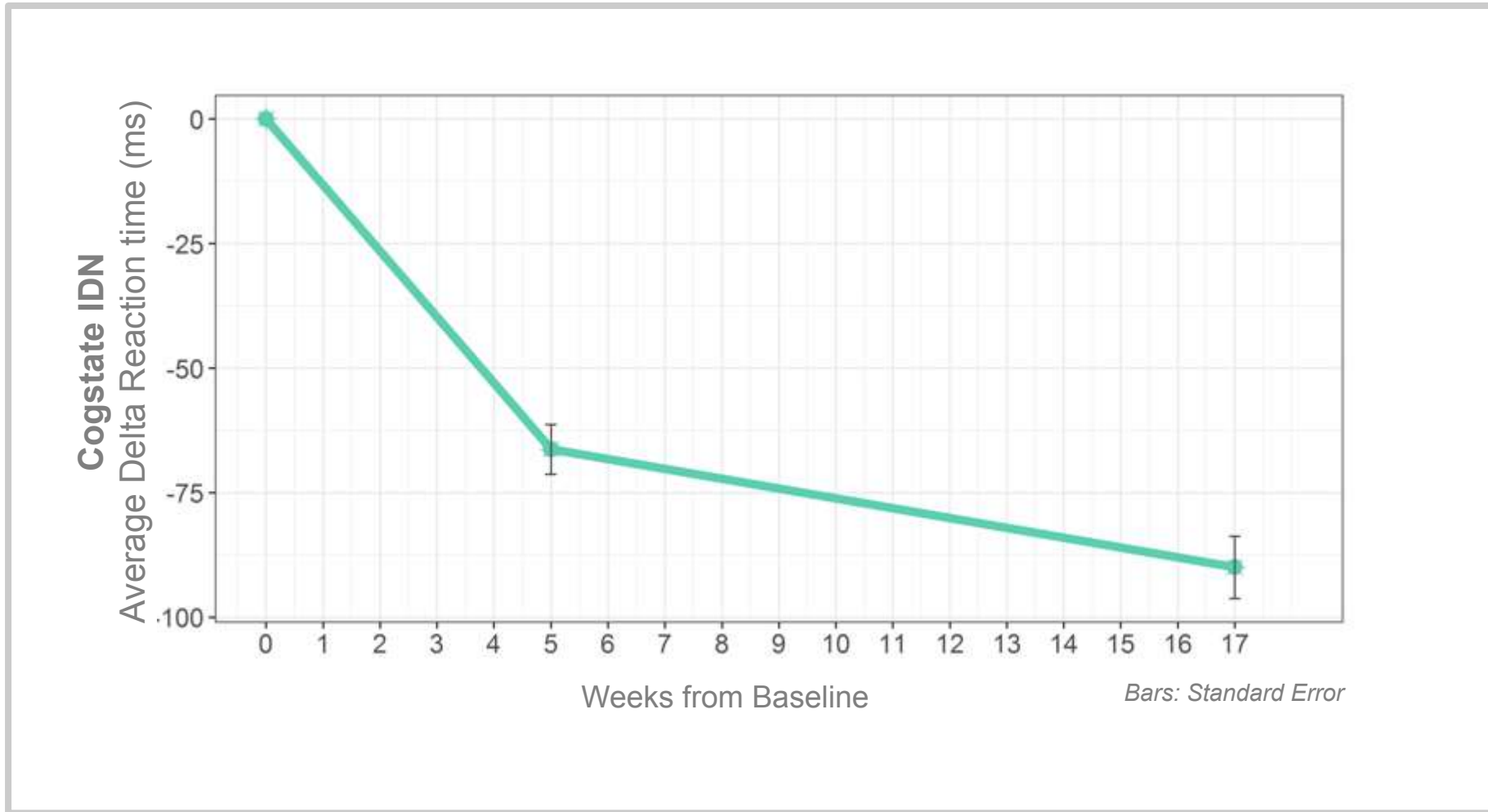
[#] Restricted to maintain complete blinding

Primary Endpoint 'CDR Continuity of Attention' of PDD ANAVEX[®]2-73 Ph2 Study: Confirmed Beneficial Effect in Previous Ph2a AD Study

Identification (IDN) in Cogstate battery assessed in ANAVEX[®]2-73 Ph2a AD Study *comparable to CDR Continuity of Attention (choice reaction time paradigm)*



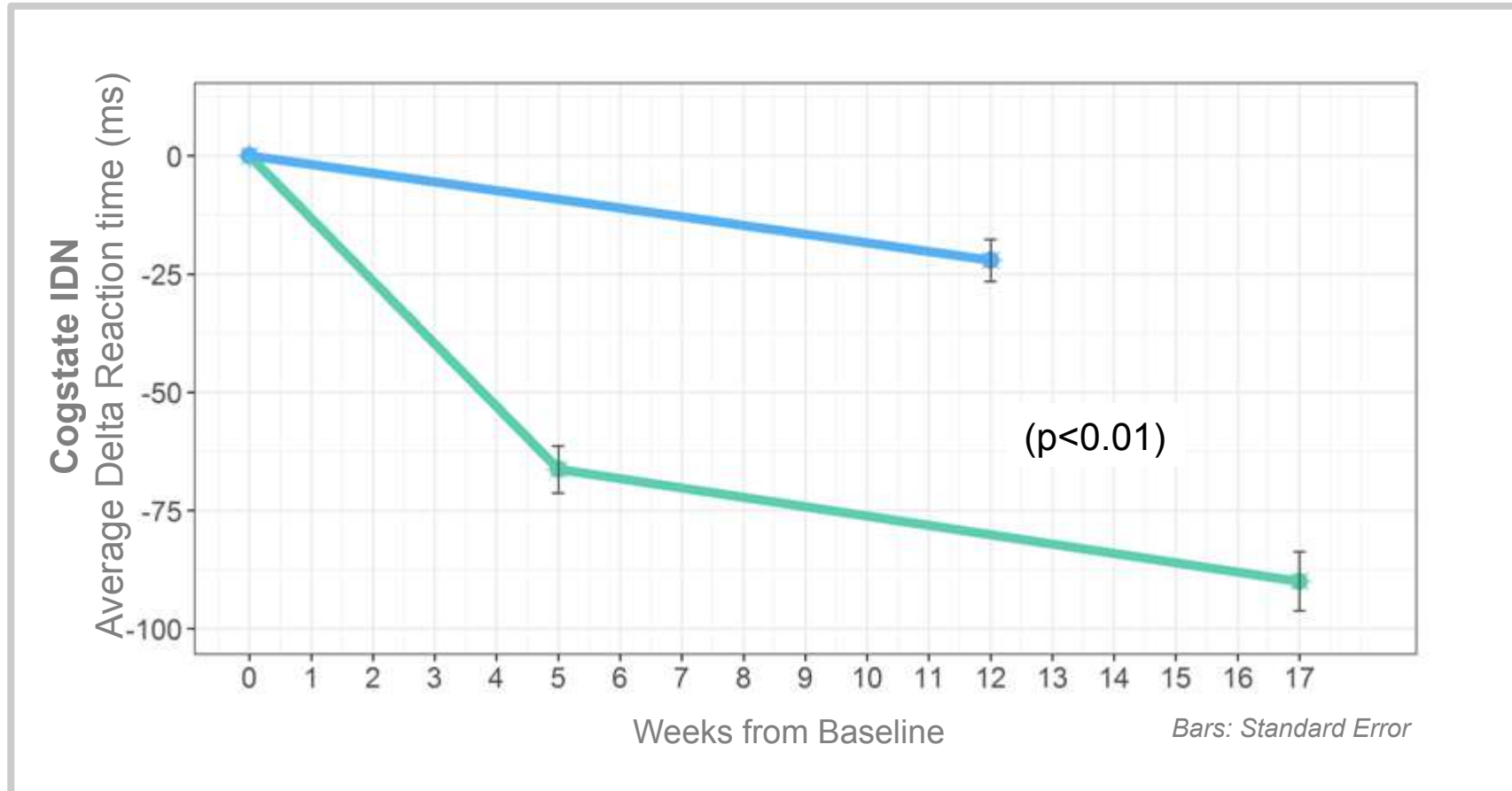
Cogstate IDN from Baseline



ANAVEX[®]2-73

Cogstate IDN: ANAVEX[®]2-73 Ph2a AD Patients Improve within Weeks vs Standard of Care AD Patients

AIBL-ROCS-AD* cohort as standard of care comparator



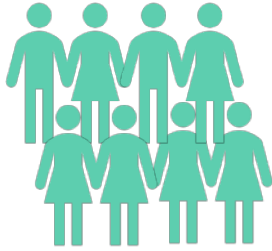
| Baseline data: | SoC (AIBL-ROCS-AD) | ANAVEX [®] 2-73 |
|------------------|--------------------|--------------------------|
| Participants (n) | 35 | 32 |
| MMSE (mean) | 21.2 | 21.0 |

- ANAVEX[®]2-73
- AIBL-ROCS-AD

* Australian Imaging Biomarkers and Lifestyle (AIBL-ROCS-AD) study evaluating mild-to-moderate Alzheimer's disease patients on SoC (Standard of Care) acetylcholinesterase medications and/or memantine with Cogstate battery; Lim YY et al (2013) Arch Clin Neuropsychol. Jun;28(4):320-30 and Cogstate unpublished data

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

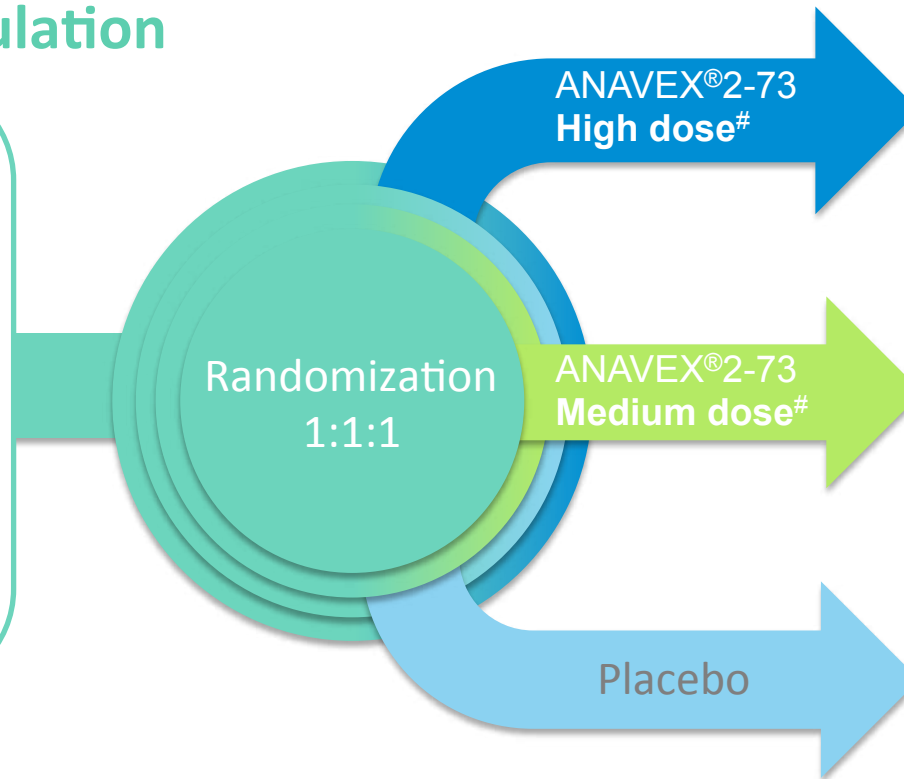
N=450



48 WEEK STUDY

Early AD patient population

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



Primary Endpoints

- ADAS-Cog
- ADCS-ADL
- Safety and tolerability of ANAVEX[®]2-73

Key Secondary Endpoints

- CDR-SB
- Structural and functional MRI
- Biomarkers: Abeta₄₀/Abeta₄₂, T-tau, P-tau, NFL, YKL-40, neurogranin, BACE1

Pre-specified Endpoints

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

ANAVEX[®]2-73 Phase 2 Rett Syndrome Study

N=15



7 WEEK STUDY

RTT patient population

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

Randomization
3:2

ANAVEX[®]2-73
Active dose*

Placebo

Primary and Secondary Endpoints

- Safety and tolerability of ANAVEX[®]2-73
- Behavioral symptoms
- Sleep function
- Seizure activity

Pre-specified Endpoints

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

Investment Highlights

- **Pursuing Large Markets By Applying Precision Medicine to Develop Treatments For Neurodegenerative and Neurodevelopmental Diseases With High Unmet Needs** – Novel genomic biomarker-driven programs to treat small patient populations such as Rett syndrome* as well as major public health burdens such as Parkinson's and Alzheimer's disease.
- **Strong IP Position Around Novel Mechanism of Action** – Lead product candidate, ANAVEX[®]2-73, is an orally available Sigma-1 receptor agonist that has been shown to restore homeostasis. (Composition of matter patent protection to 2033).
- **Compelling Human Data** – ANAVEX[®]2-73 has undergone a Phase 2a trial in Alzheimer's disease with favorable safety and exploratory efficacy results through 148 weeks.
- **Precision Medicine Improves Chance of Clinical Success** – Testing for genomic biomarkers has demonstrated improved clinical response to ANAVEX[®]2-73 in Alzheimer's patients carrying wild-type (WT) SIGMAR1 and COMT genes.
- **Value-Creating Catalysts** – Clinical updates from Phase 2 Parkinson's disease dementia study, Phase 2b/3 Alzheimer's disease and Phase 2 Rett syndrome studies anticipated in 2019. Clinical data publications and additional indications to be announced in 2019.
- **Sufficient Cash to Achieve Key Milestones** – Cash on hand and non-dilutive cash from Australian government for Alzheimer's study, and from Rettsyndrome.org for Rett syndrome study.

*FDA granted ANAVEX[®]2-73 Orphan Drug Designation (ODD) for Rett syndrome

Anavex Life Sciences Expertise

Management Team

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Walter E Kaufmann, MD - Chief Medical Officer

Stephan Toutain, MS, MBA - SVP of Operations

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

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



Scientific Advisory Board Members

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Harald Hampel, MD, PhD



Norman Relkin, MD, PhD



Ottavio Arancio, MD, PhD



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Dag Aarsland, MD, PhD



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