Longitudinal 148-Week Update of ANAVEX®2-73 Phase 2a Alzheimer's Disease Extension Study

CTAD October 2018

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Disclosures

- The studies were funded by Anavex Life Sciences
- HH serves as Senior Associate Editor for the Journal Alzheimer's & Dementia; he is the speaker of the Alzheimer Precision Medicine Initiative (APMI), he received lecture fees from Biogen and Roche, research grants from Pfizer, Avid, and MSD Avenir (paid to the institution), travel funding from Functional Neuromodulation, Axovant, Eli Lilly and company, and Oryzon Genomics, consultancy fees from Axovant, Anavex, Oryzon Genomics, Functional Neuromodulation, and participated in scientific advisory boards of Functional Neuromodulation, Axovant, Eli Lilly and company, Oryzon Genomics, Roche Diagnostics
- MA, FP, CW and AD are employees and shareholders of Ariana Pharma
- FG is employee and shareholder of Regulatory Pathfinders
- CM is an employee and shareholder of Anavex

Agenda

- Introduction
- Background
- ANAVEX®2-73-003 Extension Study Update
- Precision Medicine Paradigm from Oncology to Alzheimer's Disease
- KEM® platform to Select Relevant Biomarkers
- Mixed-Effect Models for Repeated Measures with a Linear Time Component

Introduction

- **ANAVEX®2-73** is a **novel compound** relevant to AD and neurodegenerative, neurological diseases

- **Targeting the Sigma-1 receptor (SIGMAR1)**

- **Selective under pathological conditions while sparing normal physiological activity, thus limiting adverse side effects[#]**

- **ANAVEX®2-73 is an orally available small molecule** that activates SIGMAR1 which serves as an intracellular chaperone and functional modulator of **calcium homeostasis** and **synaptic plasticity** through targeting protein-misfolding, oxidative stress, mitochondrial dysfunction, inflammation, cellular stress

[#]Nguyen et al. J Pharmacol Sciences 127 (2015) 17-29

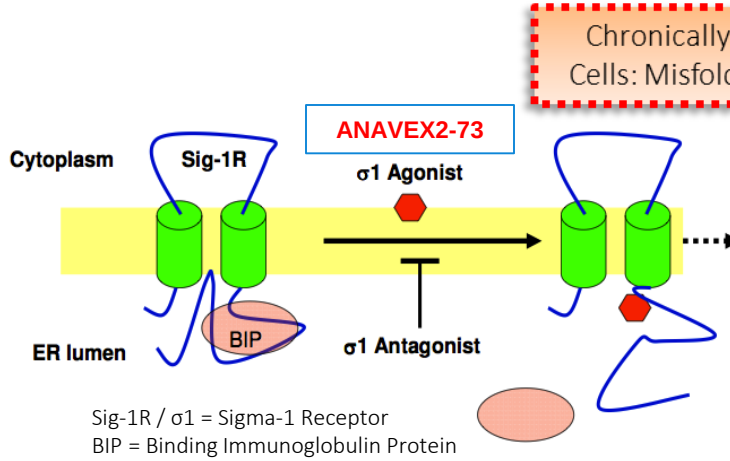
Background

- ANAVEX®2-73 is **a new targeted therapy in Alzheimer and other neurological diseases**
- **57-week Phase 2a study:** ANAVEX®2-73 was tested in a 57-week Phase 2a study (AV2-73-002[1]) with 32 mild-to-moderate Alzheimer's disease dementia patients. This study showed:
  - **Concentration-dependent response** in this population for exploratory functional (ADCS-ADL[2]) and cognitive (MMSE[3]) endpoints
  - **New AD patient selection genomic biomarker variants** of
    - **SIGMAR1 (rs1800866)**
    - **COMT (rs113895332/ rs61143203)**
  - These new patient selection biomarkers enable a **targeted therapy for patients which are likely to benefit from ANAVEX®2-73**
- 57-week Phase 2a study was **extended by 208 weeks** (AV2-73-003[4]) in 21 patients
- **Update at 148-week** of Phase 2a extension: The impact of these SIGMAR1 and COMT biomarkers on ANAVEX®2-73 response has been assessed at 148-week extension

[2]Mini Mental State Examination (MMSE)
[3]Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory (ADCS-ADL)

[1,4] ClinicalTrials.gov Identifier:
[1]NCT02244541; [4]NCT02756858

ANAVEX®2-73 activates Sigma-1 Receptor Restoring Cellular Homeostasis

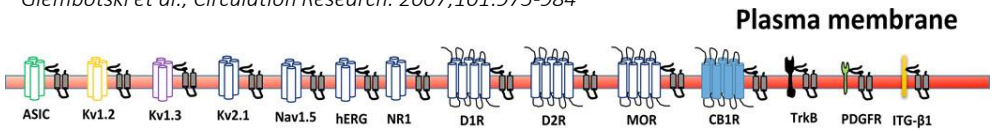


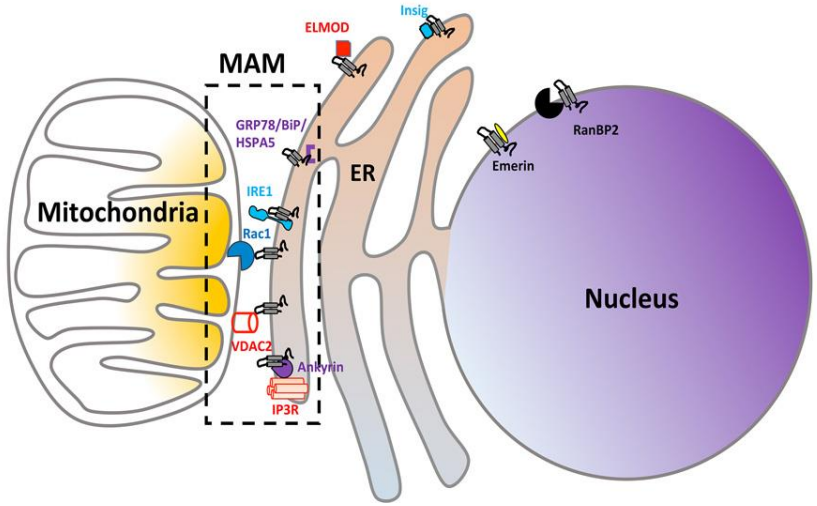
Sig-1R / σ1 = Sigma-1 Receptor
BIP = Binding Immunoglobulin Protein

Restoring Homeostasis and Neuroplasticity

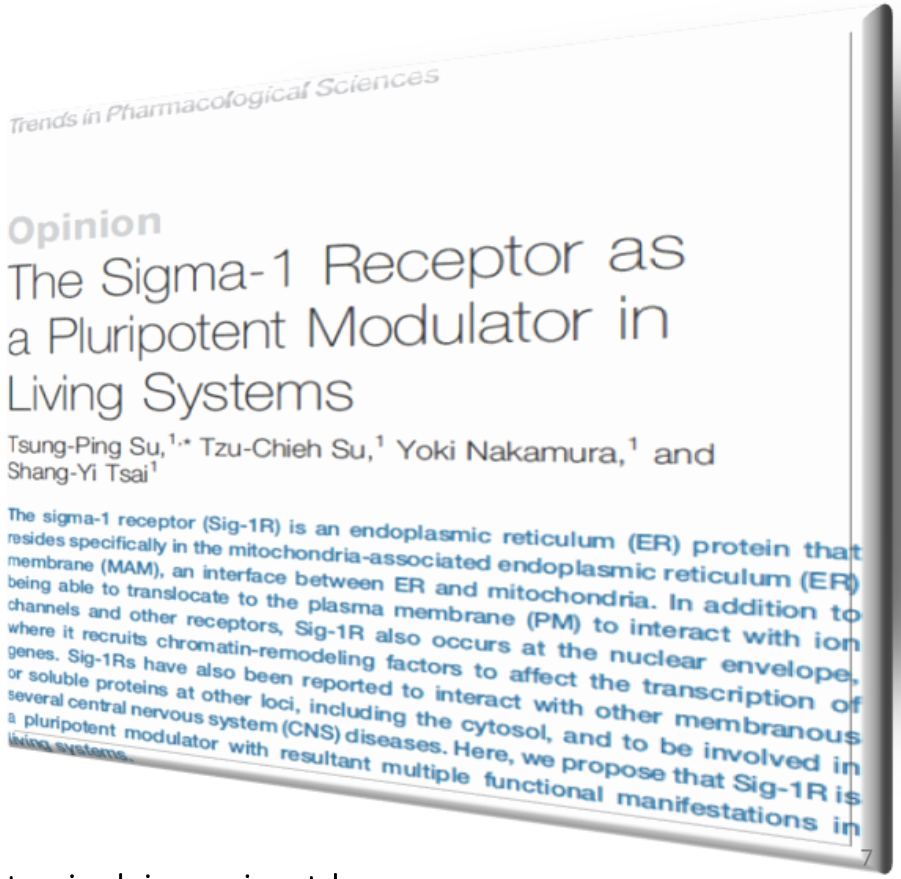
stimulating cells to regain functionality & plasticity

Source: Schematic approximation adapted from Miki et al, Dec 9. doi: 10.1111/neup.12080 Neuropathology 2013
Glembotski et al., Circulation Research. 2007;101:975-984





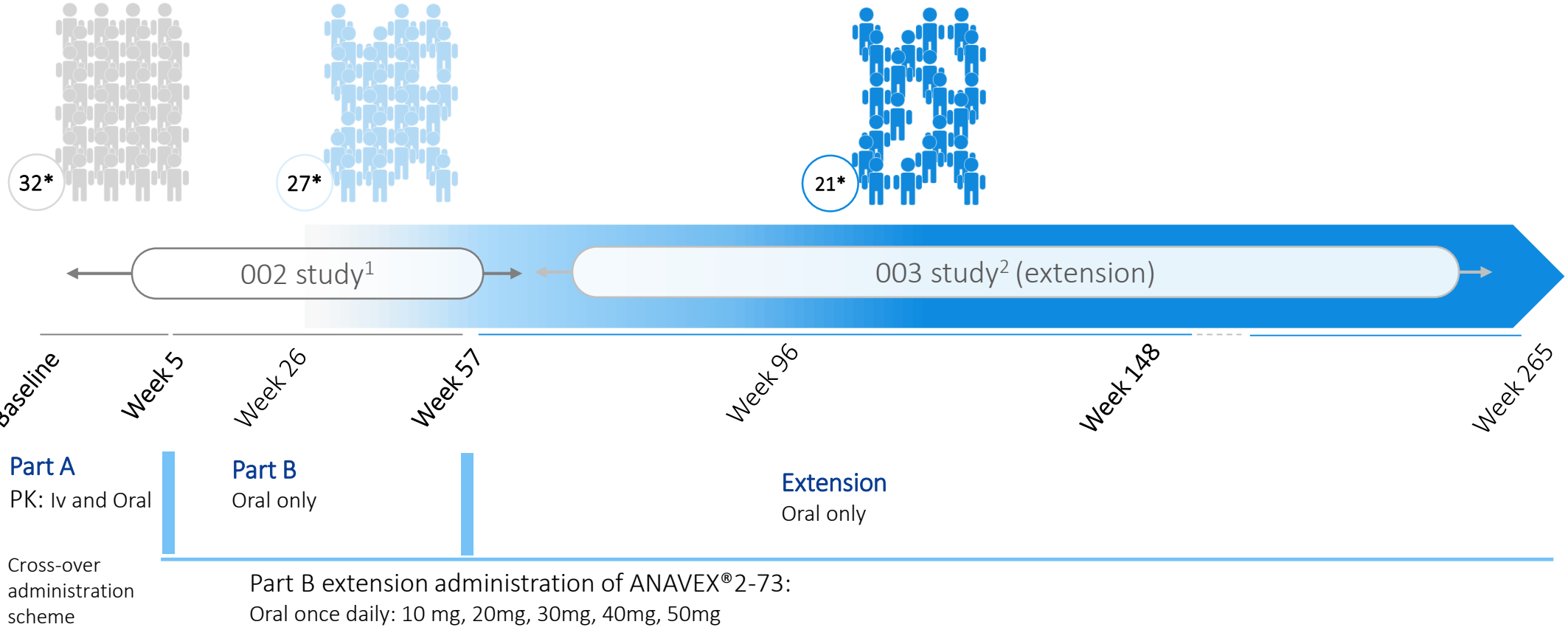
Su et al., Trends Pharmacol Sci. 2016



Two-trans-membrane SIGMAR1 is an ER protein that resides in the mitochondrial assoc. ER membrane (MAM)
Tanslocates to the cytosol/plasma membrane and interacts with numerous receptors, ion channels and proteins as determined via experimental means

Overview ANAVEX®2-73 Phase 2a Clinical Study

Patient inclusion characteristics:
- Mild-moderate AD patients
- Age range: 55 to 85
- Clinically diagnosed with MRI and/or PET scans



[1, 2] *ClinicalTrials.gov Identifier: [1]NCT02244541; [2]NCT02756858*

*: 1 patient is outside inclusion criteria. This patient was excluded from calculations

ANAVEX®2-73 Phase 2a Alzheimer Extension Study Safety Update

- Safety update through 148 weeks:
  - Continued favorable safety and tolerability
  - No ANAVEX®2-73 related AE or SAE

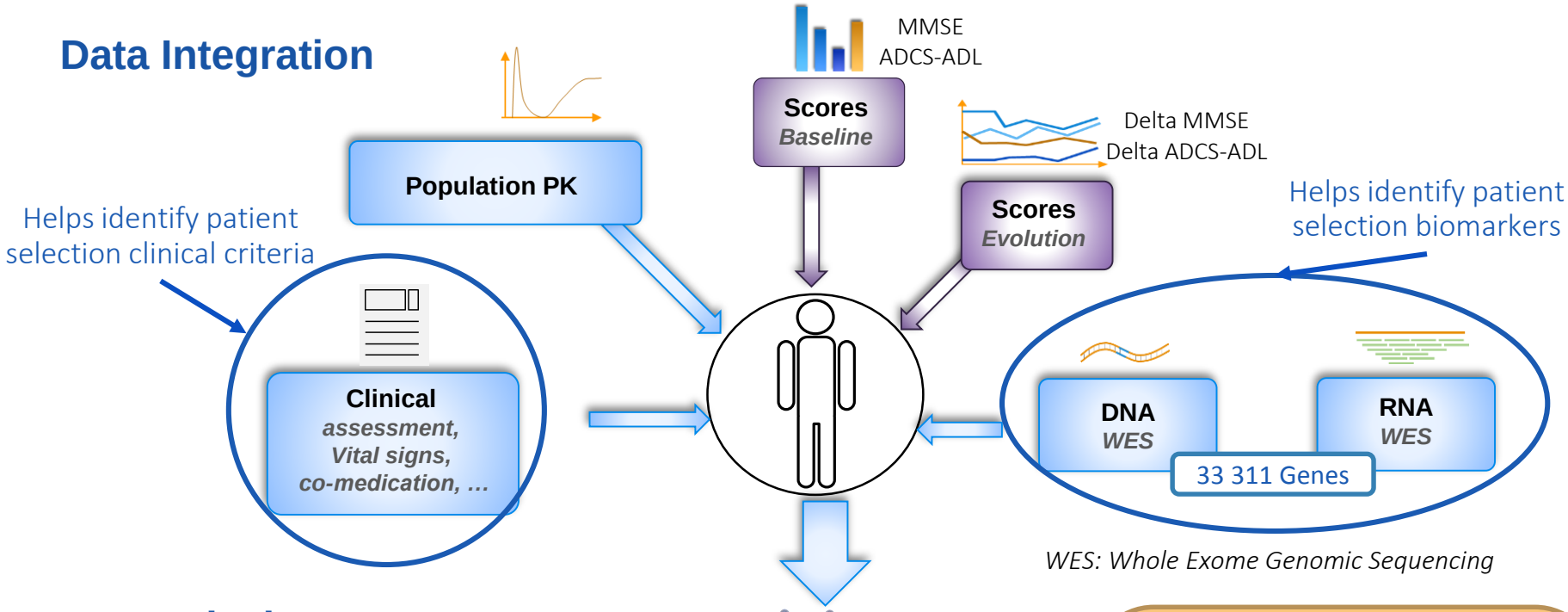
Translation of Precision Medicine Paradigm from Oncology to Alzheimer's Disease

- **Cancer**
  - Broad spectrum of diseases, characterized by molecular markers specific to different tumors
  - Molecular test required for treatment decision
  - ~40% of new drugs have a companion diagnostic

- **Alzheimer's Disease**
  - Broad spectrum of diseases, characterized by molecular markers specific to different patient populations
  - Identify molecular markers to select patients who will benefit from targeted AD therapies

ANAVEX®2-73 Data Integration and Data Analysis with KEM®

Data Integration

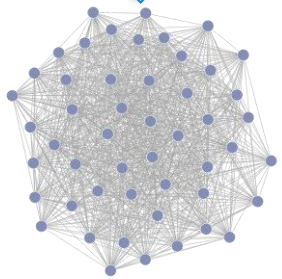


WES: Whole Exome Genomic Sequencing

Data Analysis

Advanced Machine Learning Platform Supporting Clinical Trial Design KEM® using Formal Concept Analysis (FCA) generates all Association Rules:

>20 Million relations extracted and characterized from study data

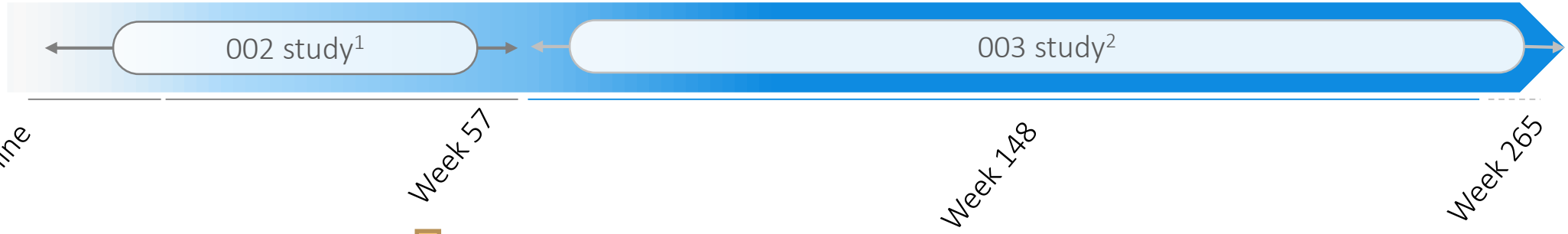


Relation Lattice generated by KEM®

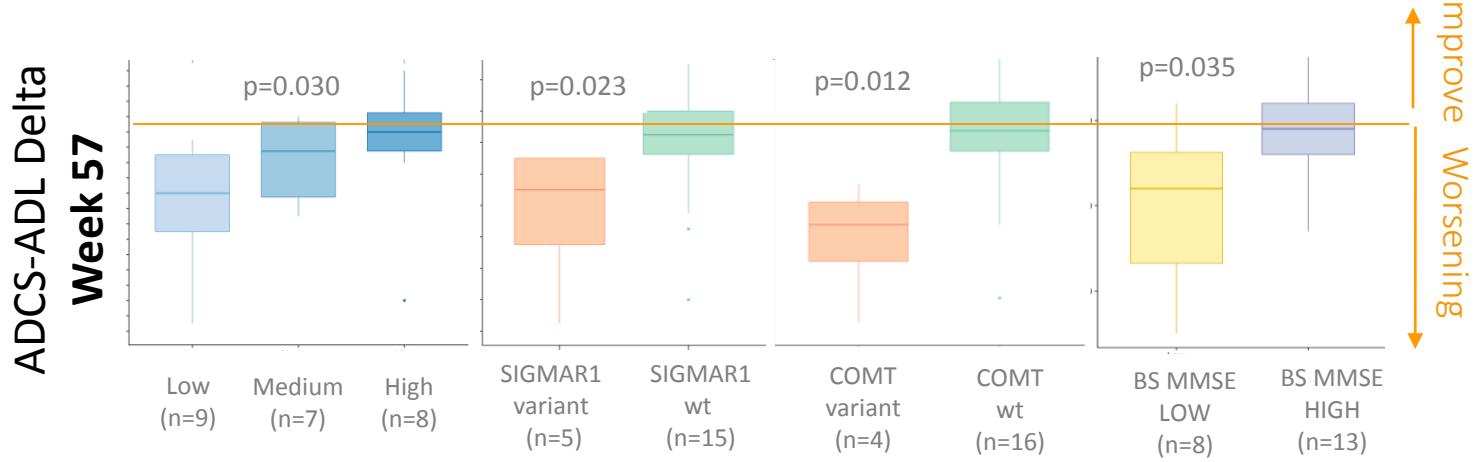
Unbiased systematic analysis identifies key drivers of response at Week 57:

- Concentration ANAVEX®2-73
- SIGMAR1 & COMT variants
- Baseline MMSE

Validating Week 57 Drivers of Clinical Response at Week 148



Four key drivers of response identified at Week 57 with KEM®



1) Mean Concentration AV2-73[#] (ng/mL) Part B

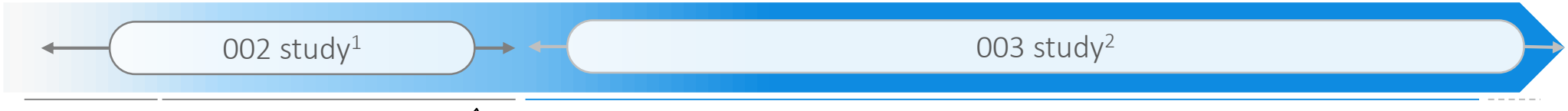
2) SIGMAR1-Q2P variant

3) COMT-Leu146 variant

4) Baseline MMSE

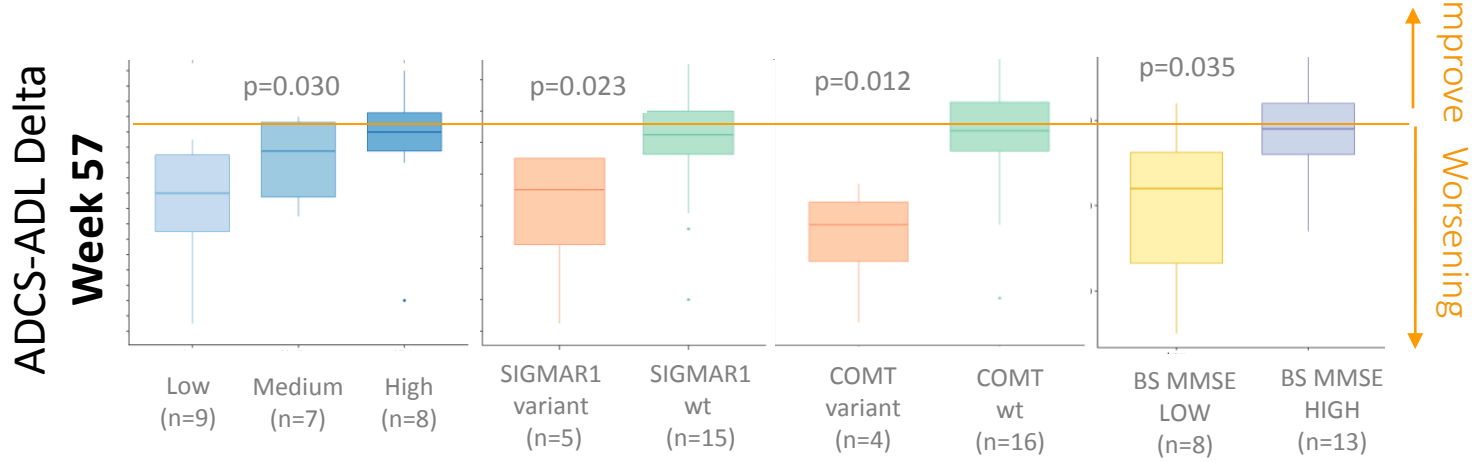
[#] Plasma concentration of ANAVEX®2-73 is correlated with the administered dose

Validating Week 57 Drivers of Clinical Response at Week 148



Four key drivers of response identified at Week 57 with KEM®

Response hypothesis tested at Week 148 using KEM® MMRM-LME analysis



1) Mean Concentration AV2-73[#] (ng/mL) Part B

2) SIGMAR1-Q2P variant

3) COMT-Leu146 variant

4) Baseline MMSE

[#] Plasma concentration of ANAVEX®2-73 is correlated with the administered dose

Mixed Effect Models for Repeated Measures with Linear Time Effect (MMRM-LME) combined with Parameters extracted with KEM®

Mixed Effect Model for Repeated Measures[1] - Linear Mixed Effect[2] :

- Inter-patient variability is modelled over time
- **Time is modelled as a continuous variable**, hence **reducing the number of parameters** used in the adjustments[2] (Mixed Effect Model for Repeated Measures with Linear time effect -MMRM-LME)
- Covariates included and tested in models:
  - KEM® identified variables:

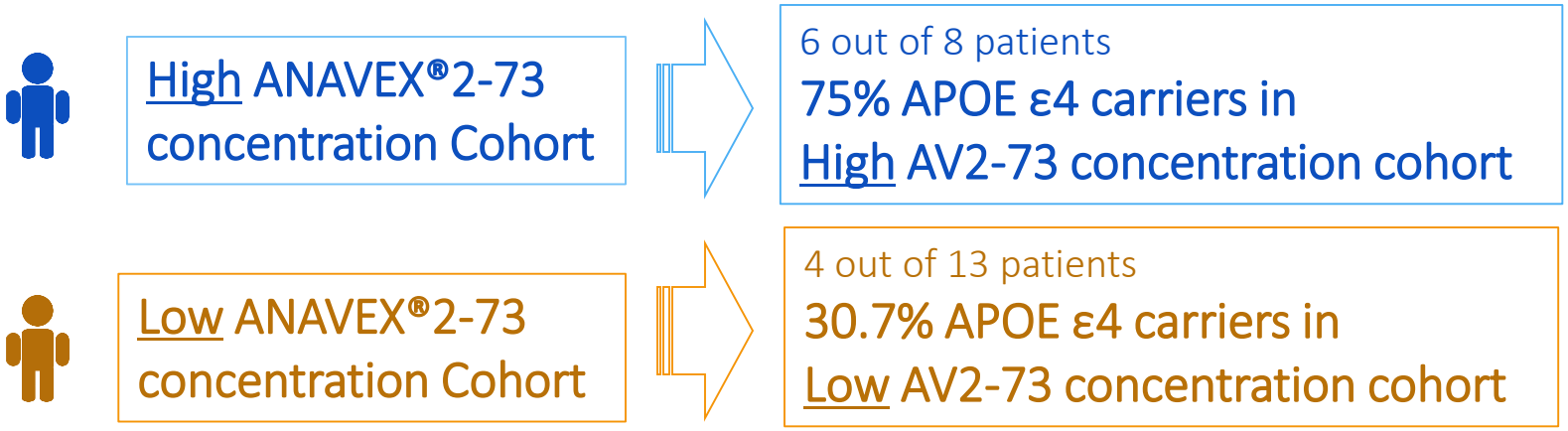
Variable Name	Variable type	Categories
Concentration	categorical	Low/Med (<4ng/ml) ; High (≥4ng/ml)
Baseline MMSE score	categorical	Low (<20) ; High (≥20)
SIGMAR1-Q2P variant	categorical	Absent ; Present
COMT-L146FS variant	categorical	Absent ; Present

  - Other:

APOE ε4 Status	categorical	True; False
Age	categorical	Low; High
Sex	categorical	Female ; Male
Donepezil treatment	categorical	True; False

[1] Lane , P. W. (2008). *Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches*. Pharmaceutical Statistics 7 : 93–106
[2] Verbeke , G. , Molenberghs , G. (2000). *Linear Mixed Models for Longitudinal Data*. New York : Springer

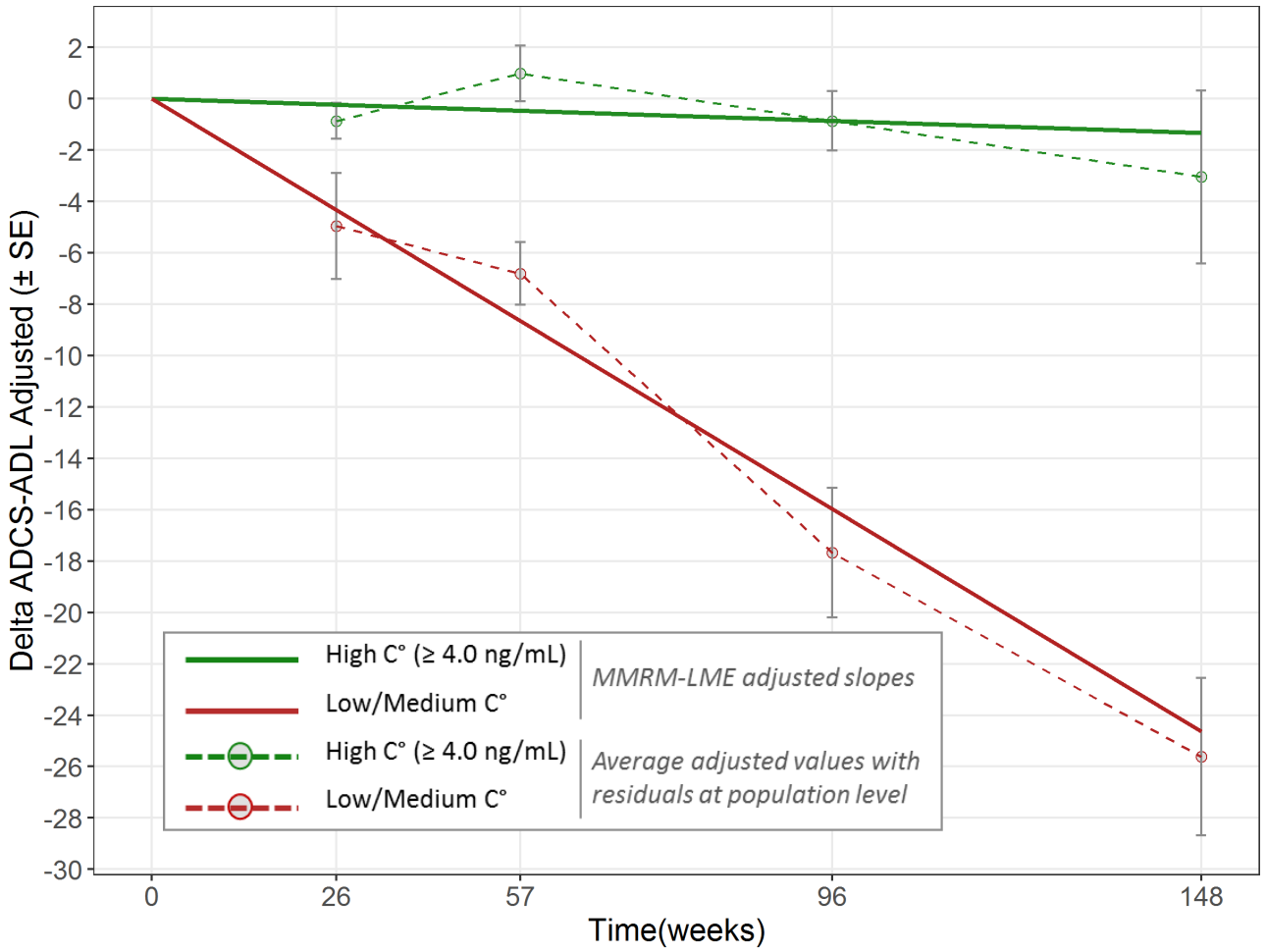
APOE ε4 Allele Distribution in ANAVEX®2-73 Study



→ APOE ε4 carriers are 2.4 times more frequent in the High AV2-73 concentration cohort compared to Low concentration cohort

→ APOE ε3/ε2 carriers are 2.8 times more frequent in the Low AV2-73 concentration cohort compared to High concentration cohort

Patients treated with higher ANAVEX®2-73 Concentration maintain ADCS-ADL[1] Performance over the 148 Week Period, vs lower Concentration cohort (**p-value < 0.0001**)



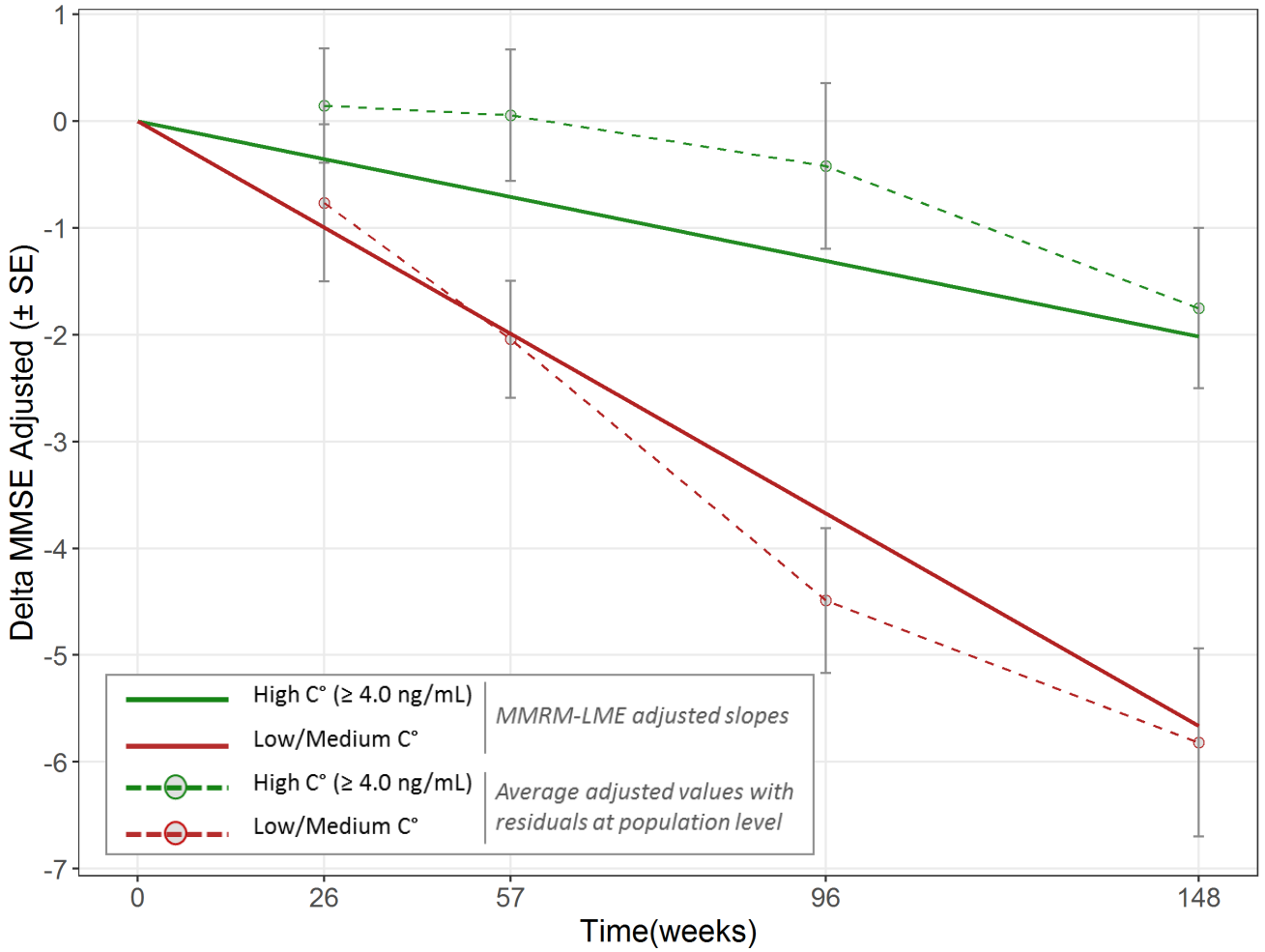
High Concentration cohort shows 88 % difference to low concentration cohort

In addition to Concentration, the significant covariates identified in MMRM-LME model are:
SIGMAR1 (p<0.0080),
COMT (p<0.0014) and
APOE ε4 status (p<0.0001)

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 ε4 status, age (Low, High), baseline MMSE score, ongoing Donepezil treatment, SIGMAR1-Q2P, COMT-L146FS variants, interactions between time and concentration group, time and APOE ε4 status, time and SIGMAR1, time and COMT, concentration group and APOE ε4 status, and concentration group and SIGMAR1 variant.

[1]Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory (ADCS-ADL)

Patients treated with higher ANAVEX®2-73 Concentration show higher cognitive MMSE[1] Performance over 148 Weeks, compared to the lower Concentration (**p-value < 0.0008**)



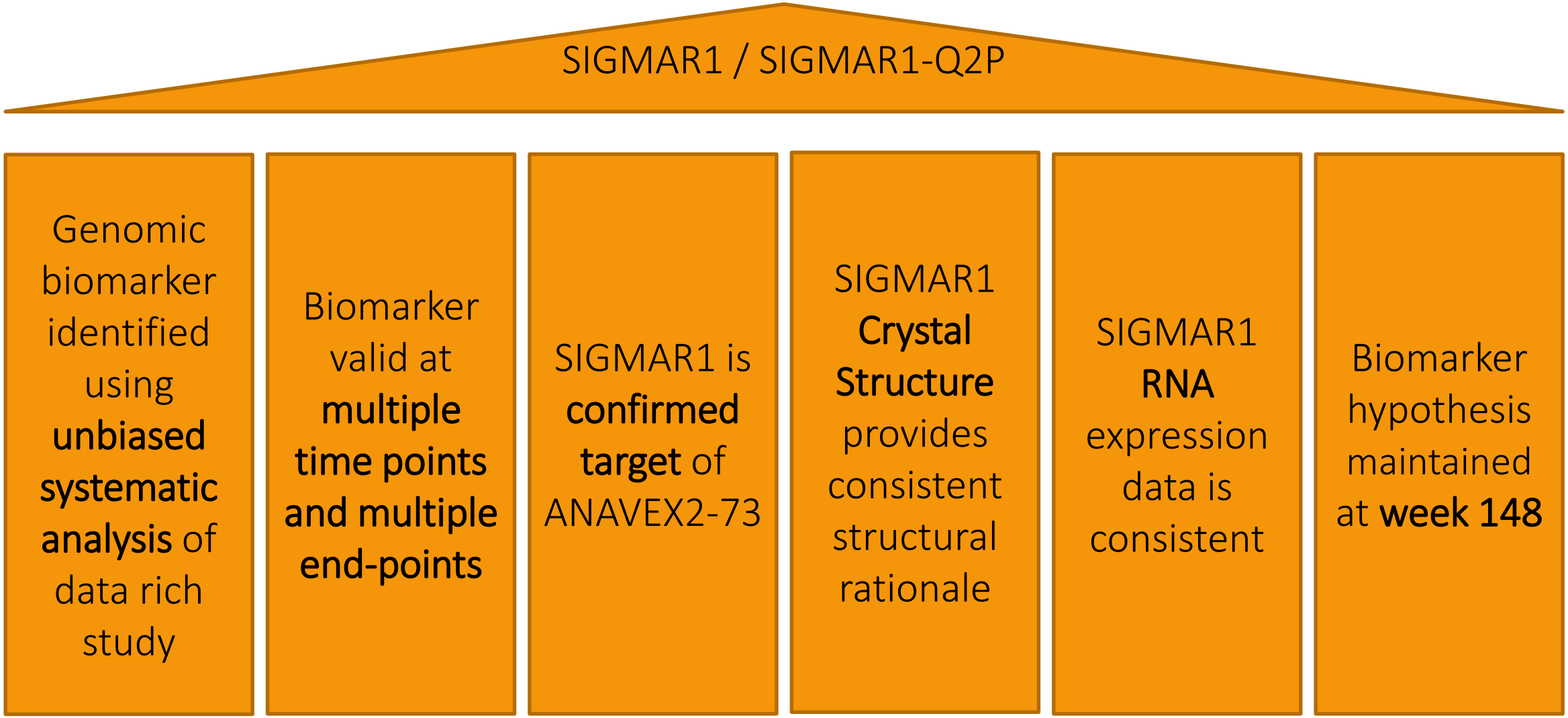
High Concentration cohort shows 64 % less decline than low concentration cohort

Other significant covariates identified in MMRM-LME model are:
APOE ε4 status (p<0.0001)

Covariates included in the MMRM-LME model for MMSE change are: time as continuous, AV2-73 concentration group (High and Low/Med), APOE ε4 status, age (Low, High), baseline MMSE score, SIGMAR1-Q2P variant, interactions between time and concentration group, time and APOE ε4 status, time and SIGMAR1, and concentration group and SIGMAR1 variant.

[1]Mini Mental State Examination (MMSE)

Supporting Precision Medicine Approach and Genomic Biomarker Hypothesis



Remarks regarding the ANAVEX®2-73-002/003 Studies

- **Data rich study (scores, PK, DNA, RNA)** provides a unique opportunity to characterize response
- Combination of data rich study and KEM® ***unbiased*** **systematic analysis enables identification of biomarker hypothesis in a small patient population**
- **Longitudinal study provides confirmation of biomarker effect** identified at week 57 **at week 148**
- Identified biomarker is consistent with a structural rationale for the mechanism of action of ANAVEX®2-73 against its confirmed target SIGMAR1. **The consistency of the DNA and RNA findings, as well as the longitudinal effect provides additional strength to the initial biomarker-based hypothesis**

Conclusions & Perspective

- The **longitudinal 148-week data show that patient cohort with the higher concentration of ANAVEX®2-73 maintains the ADCS-ADL score and better perform at MMSE**, along the trial duration, when compared to the lower concentration cohort
- A **significant impact of SIGMAR1 and COMT biomarkers on the drug response level was confirmed over the 148-week period**, irrespective of the fact that A*POE ε4* carriers were more frequent in the higher concentration cohort
- The hypothesis that **ANAVEX®2-73 induces an improved clinical outcome with adequate effect size** holds
- Results demonstrate robustness by using both DNA- and RNA-based biomarkers, multiple endpoints and time points. Excluding the patients with the two identified biomarker variants (approximately 20% of the population), the **resulting 80% of the enrolled population would lead to further clinically significant improved functional and cognitive scores**
- The combination of KEM® FCA and MMRM-LME data analysis methodologies shows the **innovative ability to identify early biomarkers in clinical trials** with small size-population recruited
- This study supports the study design of the initiated ANAVEX®2-73 studies in several indications underway, including a **Phase 2b/3 study in 450 patients with early Alzheimer's disease**
- This approach may **expand the access to Precision Medicine and Precision Pharmacology** for a wide range of neurodegenerative diseases

Acknowledgments

Thanks to:

- 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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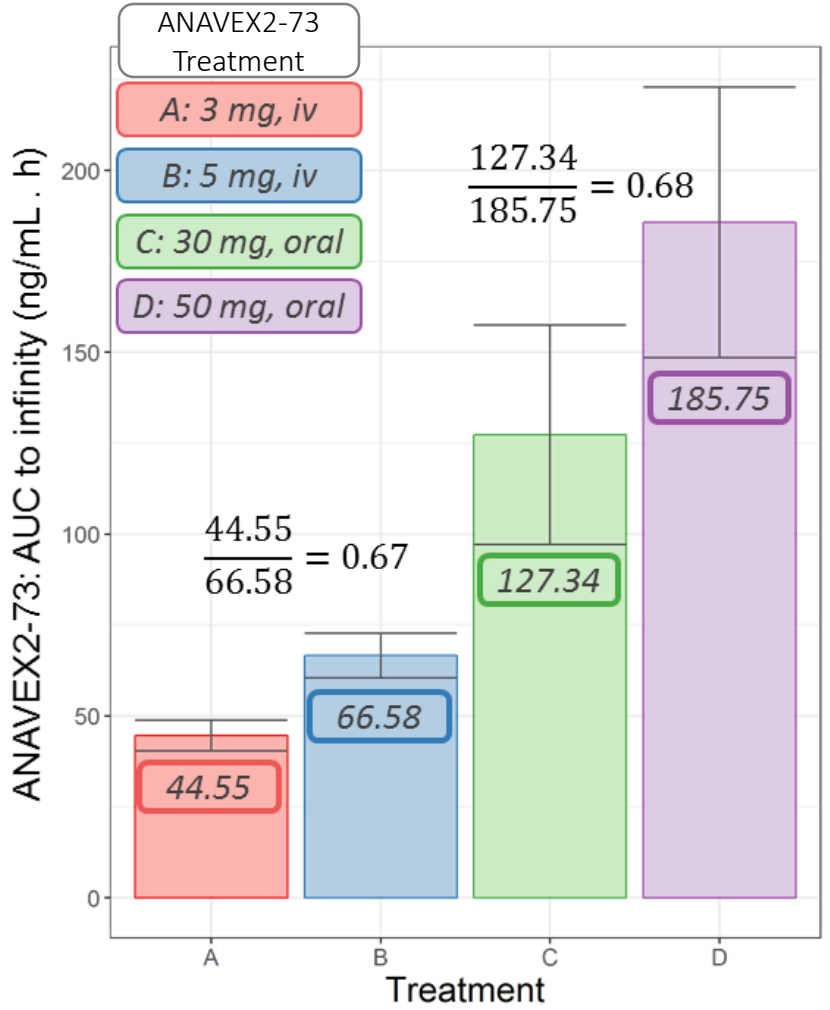
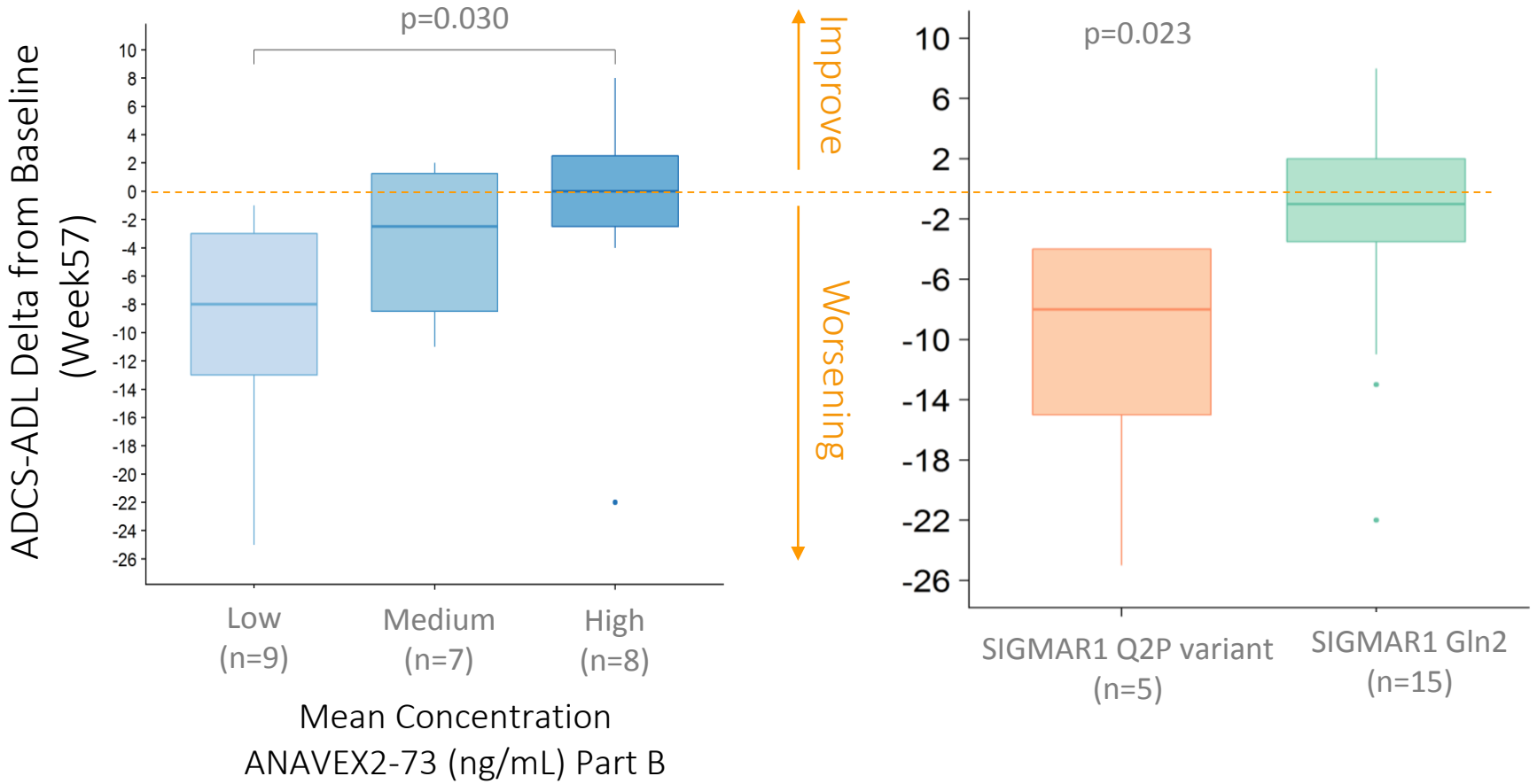
Backup Slides

Plasma Concentration of ANAVEX®2-73 is Correlated with the Administered Dose

Phase 2a Study Part A
Total average drug exposure over time
$AUC_{(0 \text{ to infinity})}$
Area Under the Curve, 0-24h



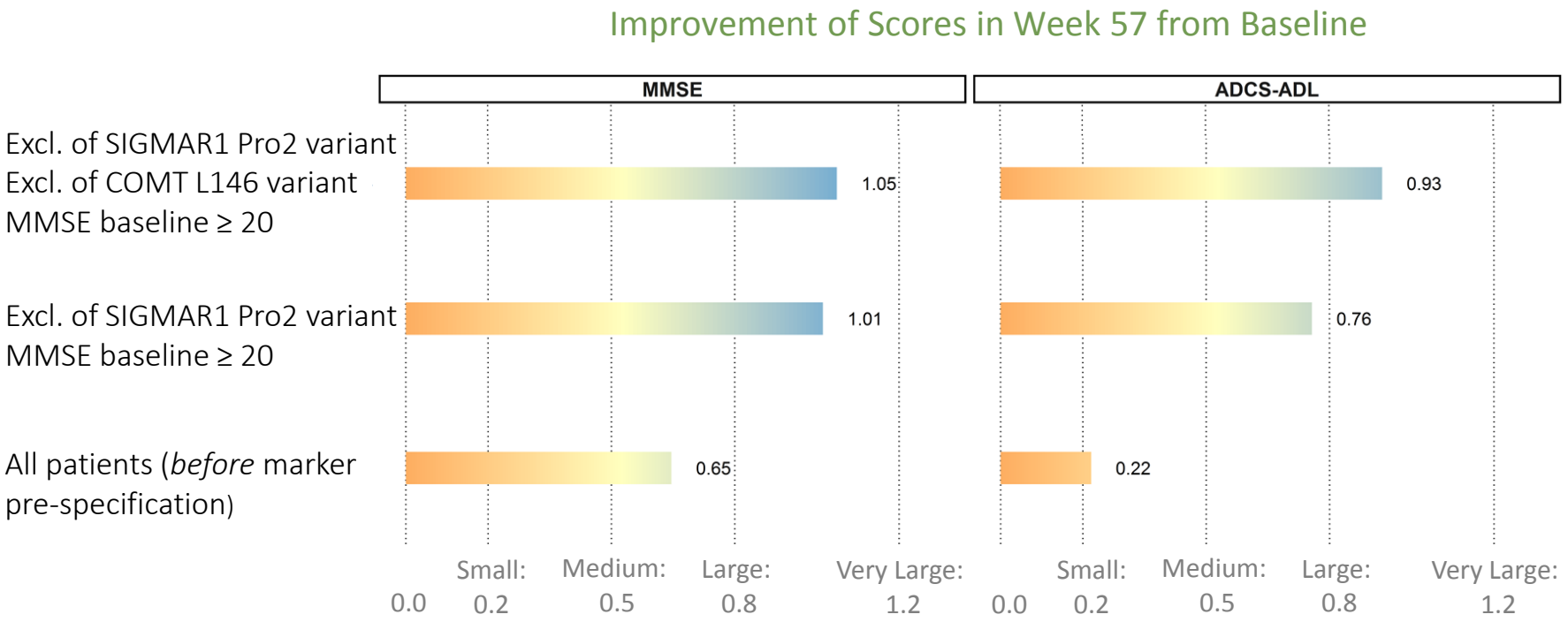
KEM® Analysis: Higher ANAVEX®2-73 Concentration and Exclusion of SIGMAR1-Q2P Variant linked to Improved Response at Week 57



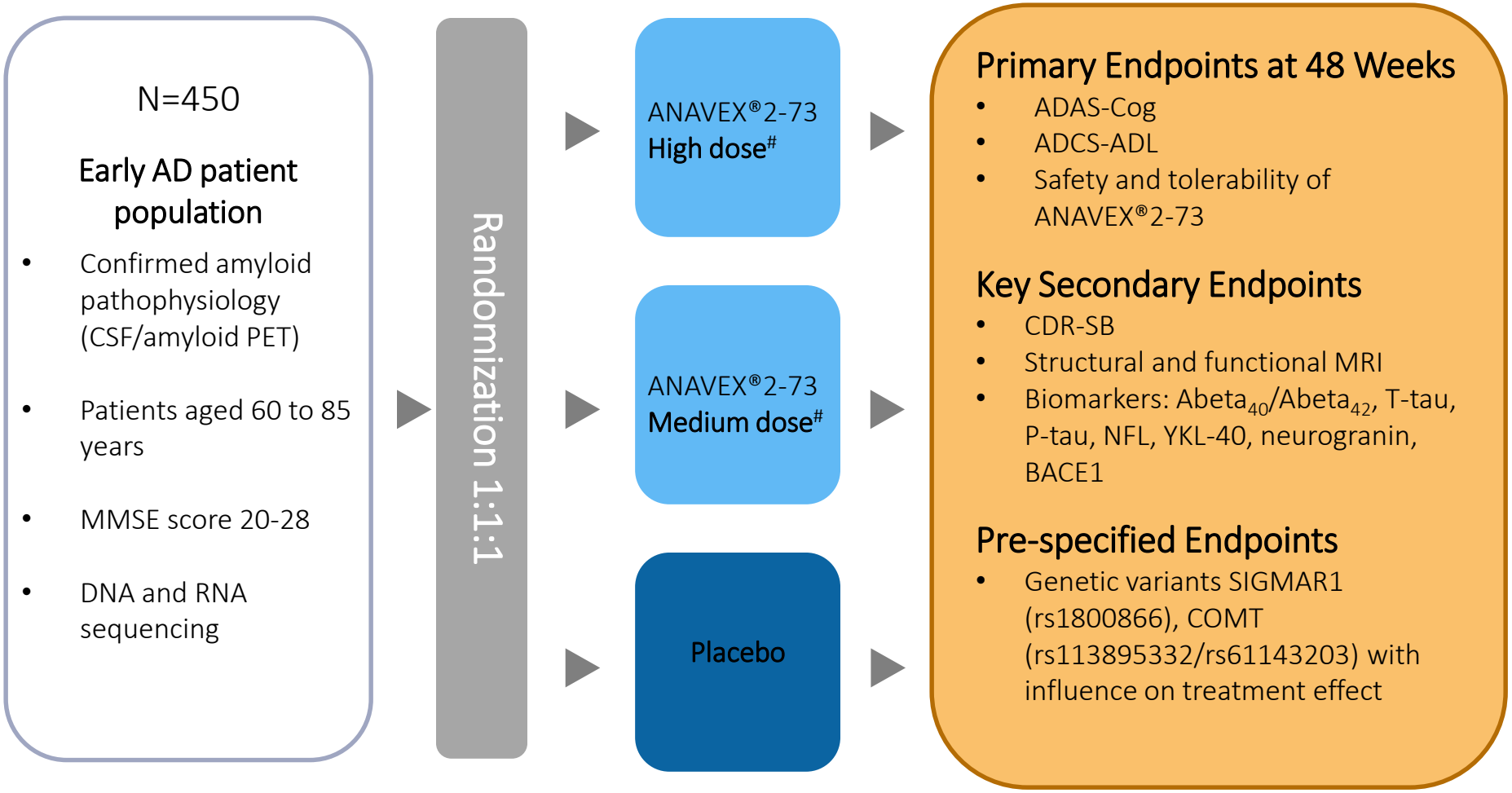
Results for change in ADCS-ADL scores at Week 57. Similar significant relationships were also found for change in MMSE scores.

Gene Markers and Baseline Characteristics improve Effect Size (Cohen's d) with ANAVEX®2-73

A higher Cohen's d implies less patients are needed to show a significant difference between placebo arm and ANAVEX®2-73 arm in a clinical study



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



 # Restricted to maintain complete blinding

Creating a Precision Medicine Franchise