anavex® LIFE SCIENCES Corp.

Developing targeted therapies for neurodevelopmental and neurodegenerative diseases

Clinical Pharmacokinetics and Pharmacodynamics Characterization of ANAVEX®2-73 for Designing a Phase 2/3 Study in Mild-to-Moderate Alzheimer's Disease

CTAD November 2017

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Nasdaq: AVXL

Safe Harbor

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Disclosures

- The studies were funded by Anavex Life Sciences
- EF, CM are employees and shareholders of Anavex
- MA, FP are employees and shareholders of Ariana Pharma
- EE is employee and shareholder of Anoixis

Overview

- ANAVEX®2-73 focuses on a new target relevant to Alzheimer's disease and other neurological diseases
- Phase 1 (ANAVEX®2-73-001) with 22 subjects
- Phase 2a (ANAVEX®2-73-002) 57 week study with 32 mild-to-moderate Alzheimer's patients
- ANAVEX®2-73-003: 104 week long-term extension of patients from ANAVEX®2-73-002 study
- Clinical data from a total of 54 subjects were analyzed with formal concept analysis (FCA), non-linear mixed effect (NLME) modeling and non-compartmental analysis methods
- Primary endpoints of both ANAVEX®2-73-002 and ANAVEX®2-73-003: safety and tolerability
- Exploratory secondary endpoints of both ANAVEX®2-73-002 and ANAVEX®2-73-003: cognition (MMSE)[1] and function (ADCS-ADL)[2]

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

Target and Mechanism of Action

The Sigma-1 Receptor (S1R): From Gene to Therapeutic Target

Sigma-1 Receptor is an integral membrane protein involved in cellular homeostasis which targets restoration of neuroplasticity and cellular stress response[2,3]

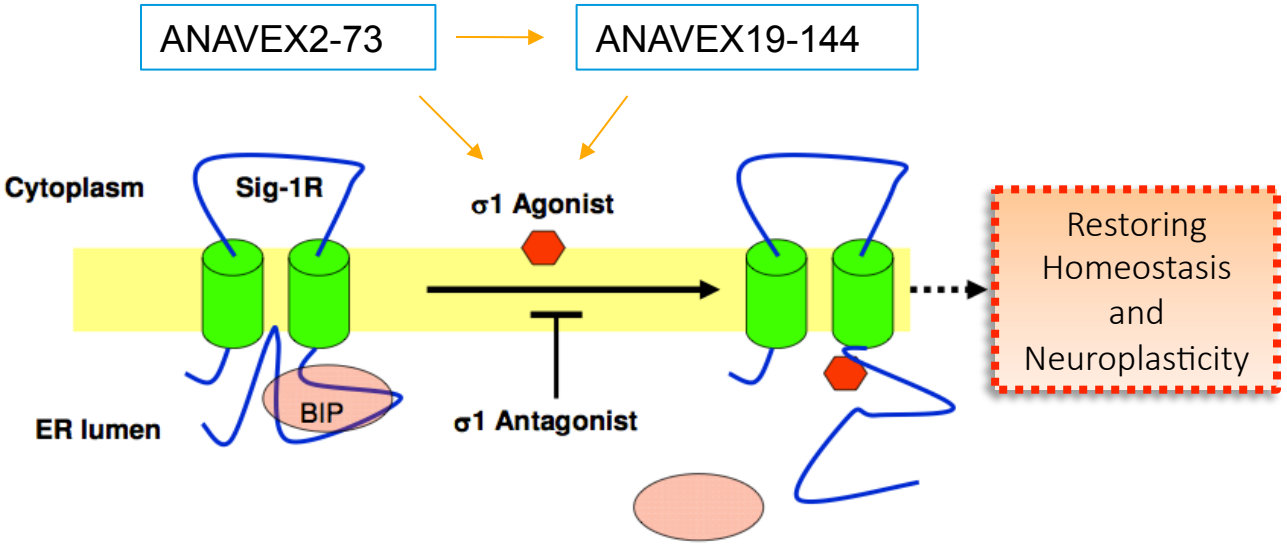
Endogenous S1R agonists activate the Sigma-1 Receptor under conditions with cellular stress[4,5,6]

ANAVEX2-73 is a S1R agonist and activates the Sigma-1 Receptor

Enhancing Activation of endogenous S1R with ANAVEX2-73 improves disease symptoms and underlying pathophysiology

1) Mavlyutov TA et al. Neuroscience. 2013 Jun 14;240:129-34. 2) Su TP et al. Trends Pharmacol Sci. 2016 Apr;37(4):262-78.
3) Ruscher K et al. J Pharmacol Sci. 2015 Jan;127(1):30-5. 4) Dhir A et al. J Psychopharmacol. 2008 Aug;22(6):691-6.
5) Yabuki Y et al. Brain Res. 2015 Oct 5;1622:102-13. 6) Urani A et al. Brain Res. 1998 Jul 13;799(1):64-77.

Sigma-1 Receptor Activation of ANAVEX®2-73 Prolonged with Active Metabolite



- ANAVEX2-73 is metabolized into the pharmacologically active metabolite, ANAVEX19-144
- Metabolite also acts as sigma-1 receptor agonist with neuroprotective action like ANAVEX2-73, restoring homeostasis and neuroplasticity
- The apparent elimination half-life of the metabolite is approximately twice that of ANAVEX2-73
- Hence the active metabolite results in prolonged activation of the sigma-1 receptor

Clinical Trial Strategy

Overview ANAVEX®2-73 Clinical Trials

ANAVEX®2-73-001 Study:
- Randomized, double-blind, placebo-controlled Phase 1 (oral)
- Single ascending dose (SAD)
- 22 healthy subjects

ANAVEX®2-73-002 Study#:
- Randomized, Phase 2a (iv/oral)
- 32 mild-to-moderate AD patients
- MMSE baseline 16-28 (mean 21)
- Adaptive trial with Population PK
- Bioavailability, dose finding (PART A), and exploratory efficacy with 52 week open-label extension (PART B)

ANAVEX®2-73-003 Study##:
- 104-week extension study after PART B

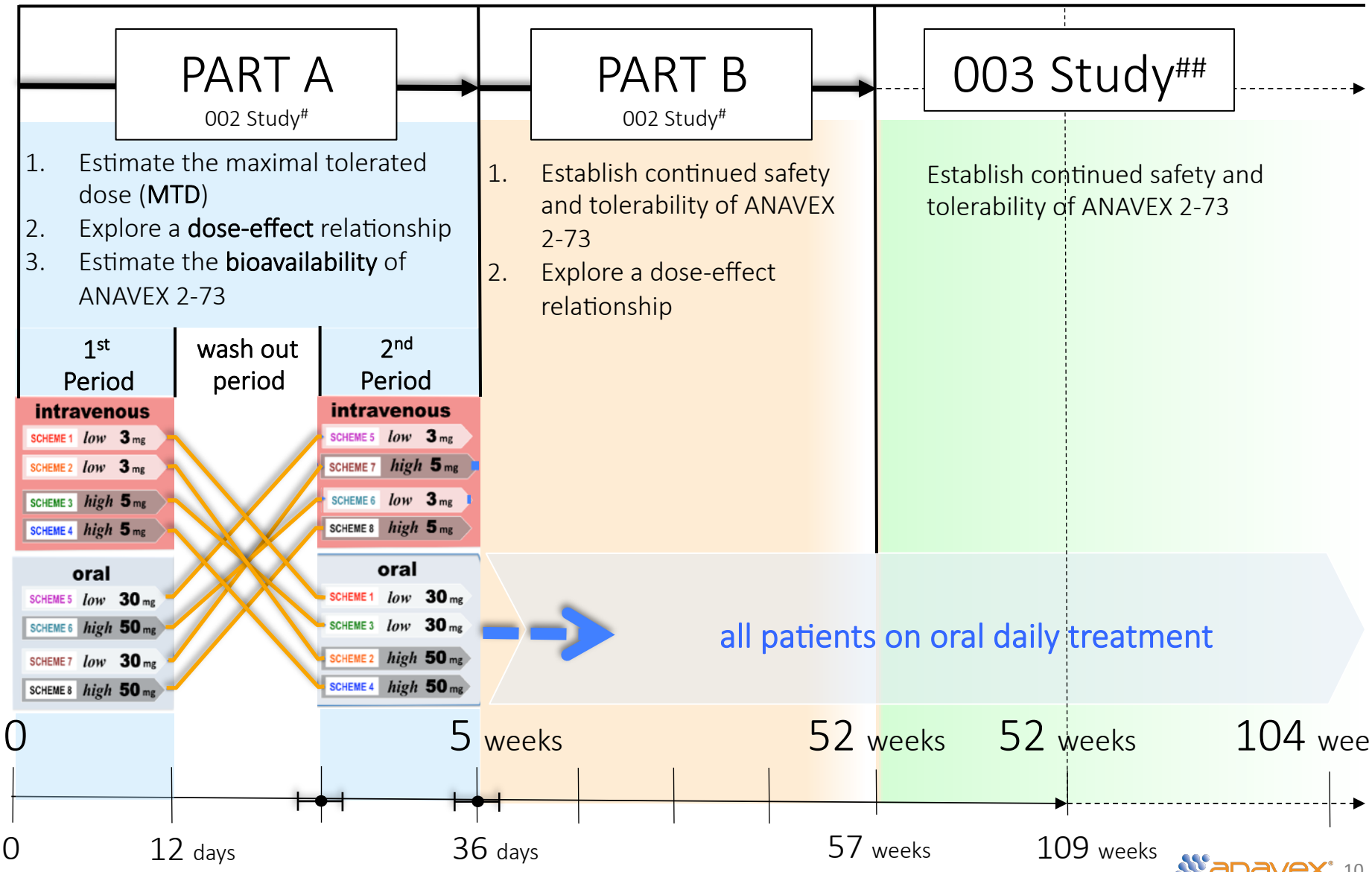
Initiation of subsequent randomized, double-blind, placebo-controlled ANAVEX®2-73 studies:
- Rett syndrome
- Parkinson's disease
- Alzheimer's disease

Population PK, i.e. non-linear mixed effect (NLME) modeling, non-compartmental analysis and formal concept analysis (FCA)

Preparation underway

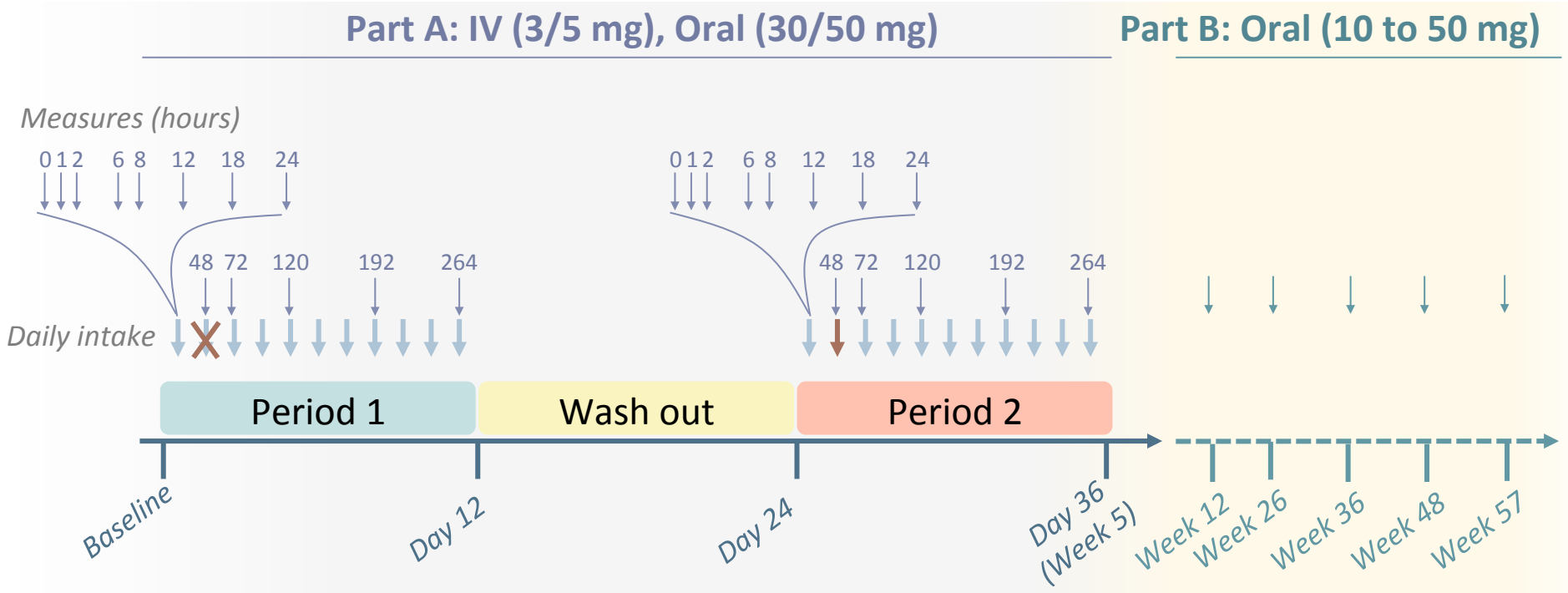
ClinicalTrials.gov Identifier: #NCT02244541; ##NCT02756858

Timelines of ANAVEX®2-73-002 and ANAVEX®2-73-003 Studies



ClinicalTrials.gov Identifier: #NCT02244541; ##NCT02756858

Comprehensive Pre-Specified PK Sampling Protocol during Phase 2a Study



Part B: All patients on ANAVEX®2-73 oral daily doses of 10mg, 20mg, 30mg, 50mg according to pre-specified adaptive trial design implemented during Part A

Analysis of All Relevant Time Periods

Part A1 [0-24h]	Part A2 [24-264h]	Part B [52 weeks]

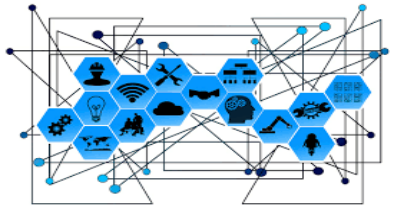
Immediate response

Short-term response

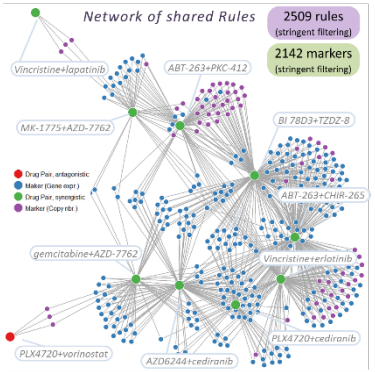
Long-term response

Ariana's KEM® Platform

Advanced Artificial Intelligence Platform Supporting Clinical Trial Design



- KEM®: a Formal Concept Analysis (FCA) Artificial Intelligence framework



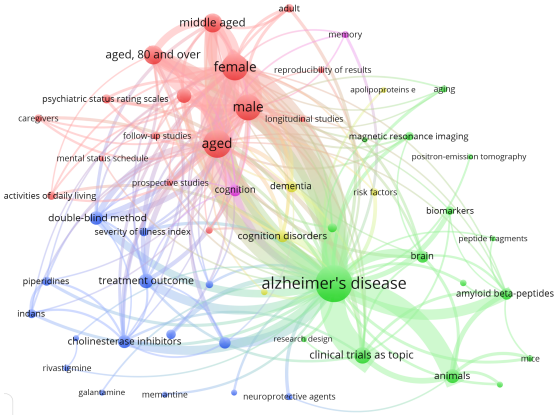
- Comprehensively analyzes complex datasets by measuring all logical relations within a dataset, exploring all combinations of parameters and endpoints

- Identifies most relevant and powerful causal relations, revealing hidden relationships and deriving new hypothesis

- Utilized for oncology and other disease areas from Sanofi, Ipsen, Pierre Fabre, Chemo, ValiRx, Harvard Medical School and the FDA

Precision Medicine Paradigm from Oncology to Alzheimer's Disease

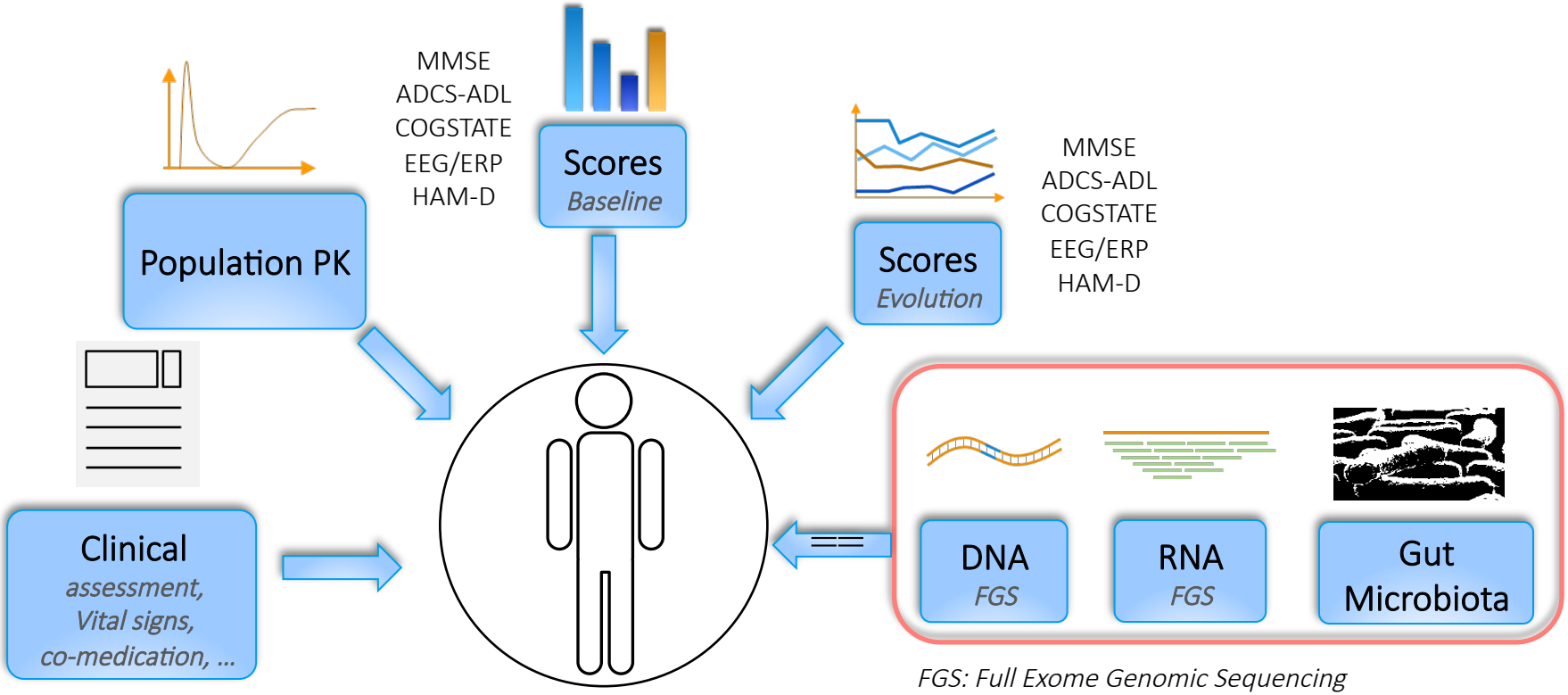
Large number of biomarkers characterize patient tumors, dominated by genomic data from Next Generation Sequencing (NGS)



- Cancer seen as a collection of heterogeneous diseases, characterized by molecular features of the tumor
- Molecular test performed prior to treatment decision: ~40% of new drugs have a companion marker

- Complexity of Alzheimer's disease pathology
- Deconstructing Alzheimer's disease into multiple biological and genetic subsets within this heterogeneous target population
- Precision Medicine strategy treating individual patients with agents likely to work effectively based on the individual's biological make-up

Comprehensive Phase 2a Patient Characterization to Identify Actionable Phase 2/3 Clinical Trial Parameters



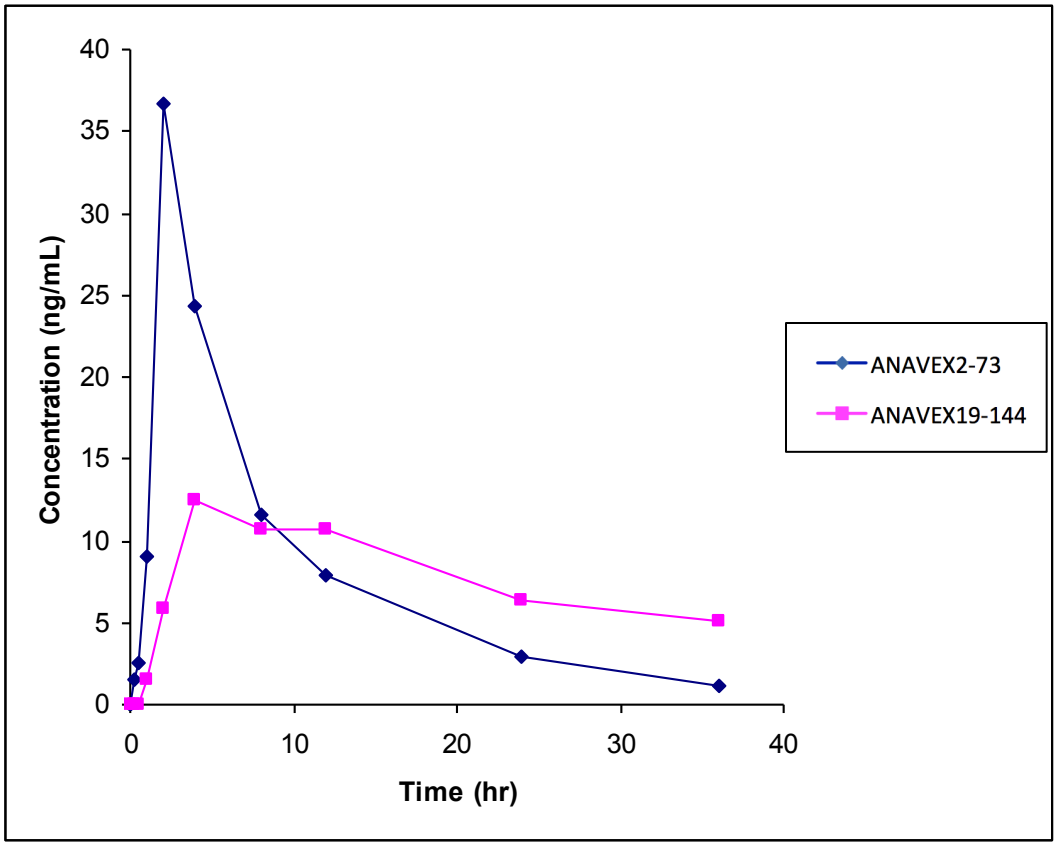
FGS: Full Exome Genomic Sequencing

Ariana's KEM® data analytics:

- Systematic integrated analysis of all combined parameters
- Identification of actionable parameters
- Design of an optimized Phase 2/3 clinical trial

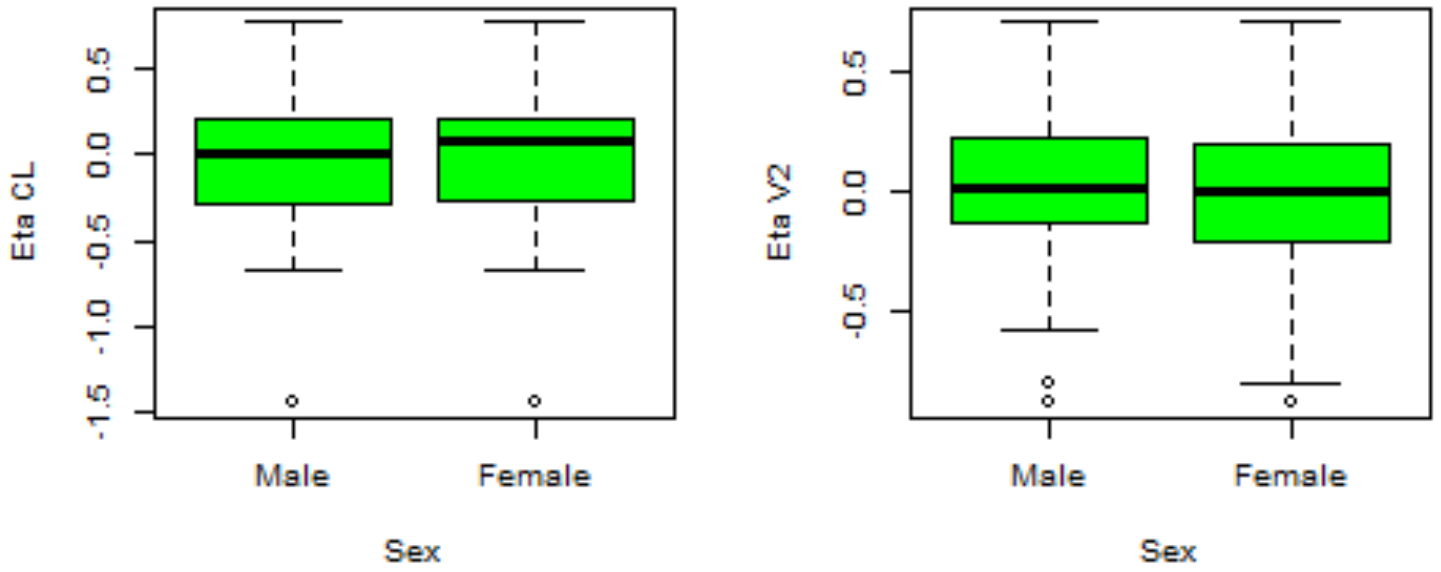
Clinical Trial Data

Metabolite of ANAVEX2-73 Prolongs Activation of Sigma-1 Receptor Activity



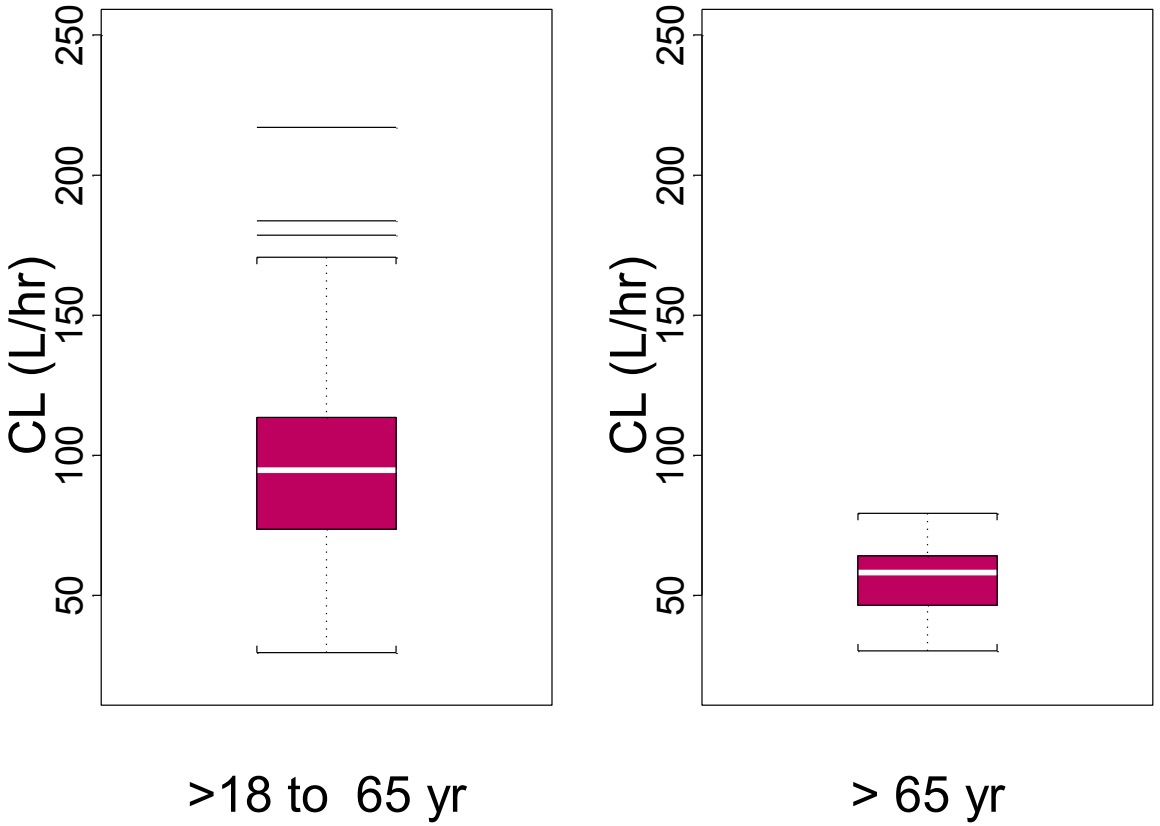
- A typical concentration-time for ANAVEX2-73 and metabolite for a subject administered orally 60 mg ANAVEX2-73
- ANAVEX2-73 is rapidly absorbed with an absorption half-life of 30 min and an apparent elimination half-life of 10.71 hr
- The active metabolite is slowly eliminated with an apparent elimination half-life that is approx. twice that of the parent (21.45 hr)

Population PK Analysis ANAVEX®2-73 Clearance and Volume of Distribution Same for both Male and Female



- No sex difference in the pharmacokinetics of ANAVEX2-73 observed given the inter-patient variability for clearance (CL) and volume of distribution (V2) of the central compartment

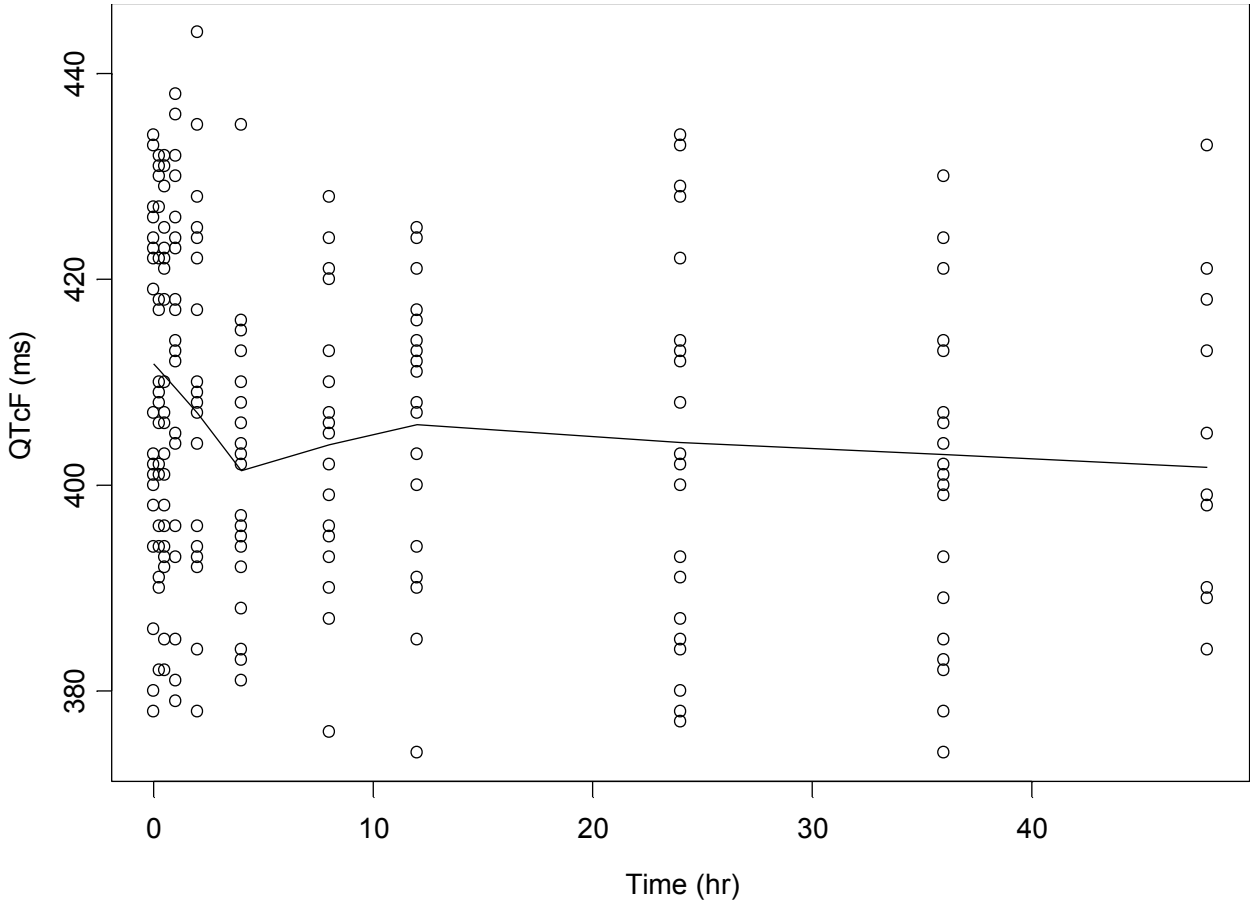
Population PK Analysis ANAVEX®2-73 Clearance faster in Younger Subjects



- The clearance of the drug is not a function of renal function
- Younger subjects (>18 to <65 yr) clear the drug twice as fast as elderly Alzheimer's disease subjects (>65 yr)

ANAVEX®2-73 Shortening the QT Interval by about 10 ms

QTcF over time from ANAVEX2-73 Administration#



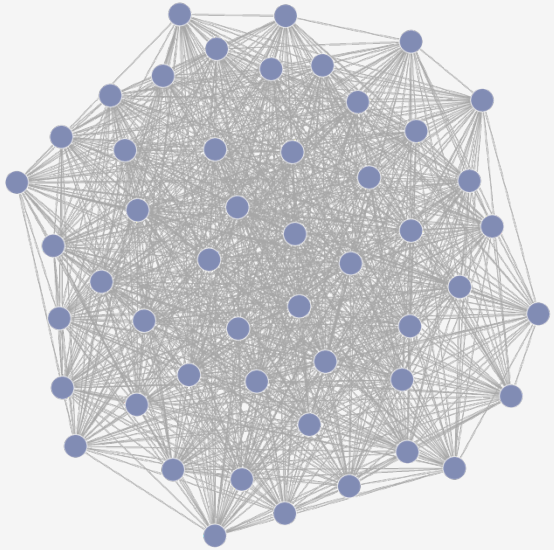
- Overall, QTc interval tended to decrease with time and leveled off over the observation period after ANAVEX2-73 administration
- ANAVEX19-144 was found to be anti-arrhythmic
- A categorical analysis by time point indicated that across sampling times Fridericia corrected QTc (i.e., QTcF) values were consistently <450 ms, including the baseline for ANAVEX2-73 doses from 10 to 60 mg
- No subject had dQTcF >30 ms at any time point

#QT/QTc data was analyzed according to ICH E14 guidelines

KEM® Systematic Analysis

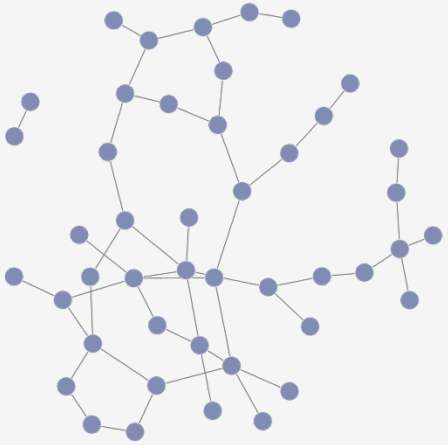
Ariana's KEM® platform enables a systematic and exhaustive search of all possible relations across variables, endpoints, PK parameters and time

71,172 relations



Exploration & pruning

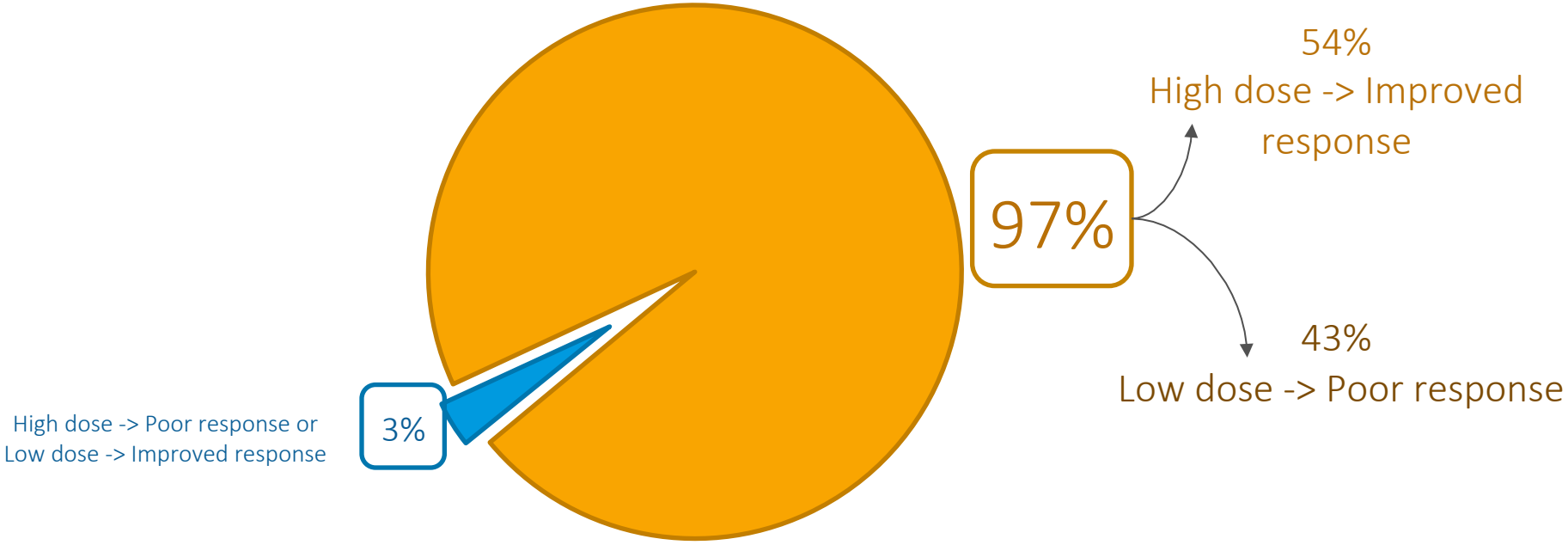
83 rules



3 Periods (A1, A2, B)
12 Endpoints and 3 molecules' PK
4 Transformations
80 Baseline variables
2 or 3 Categories per variables

Robust Dose (Concentration) / Response Effect of ANAVEX®2-73

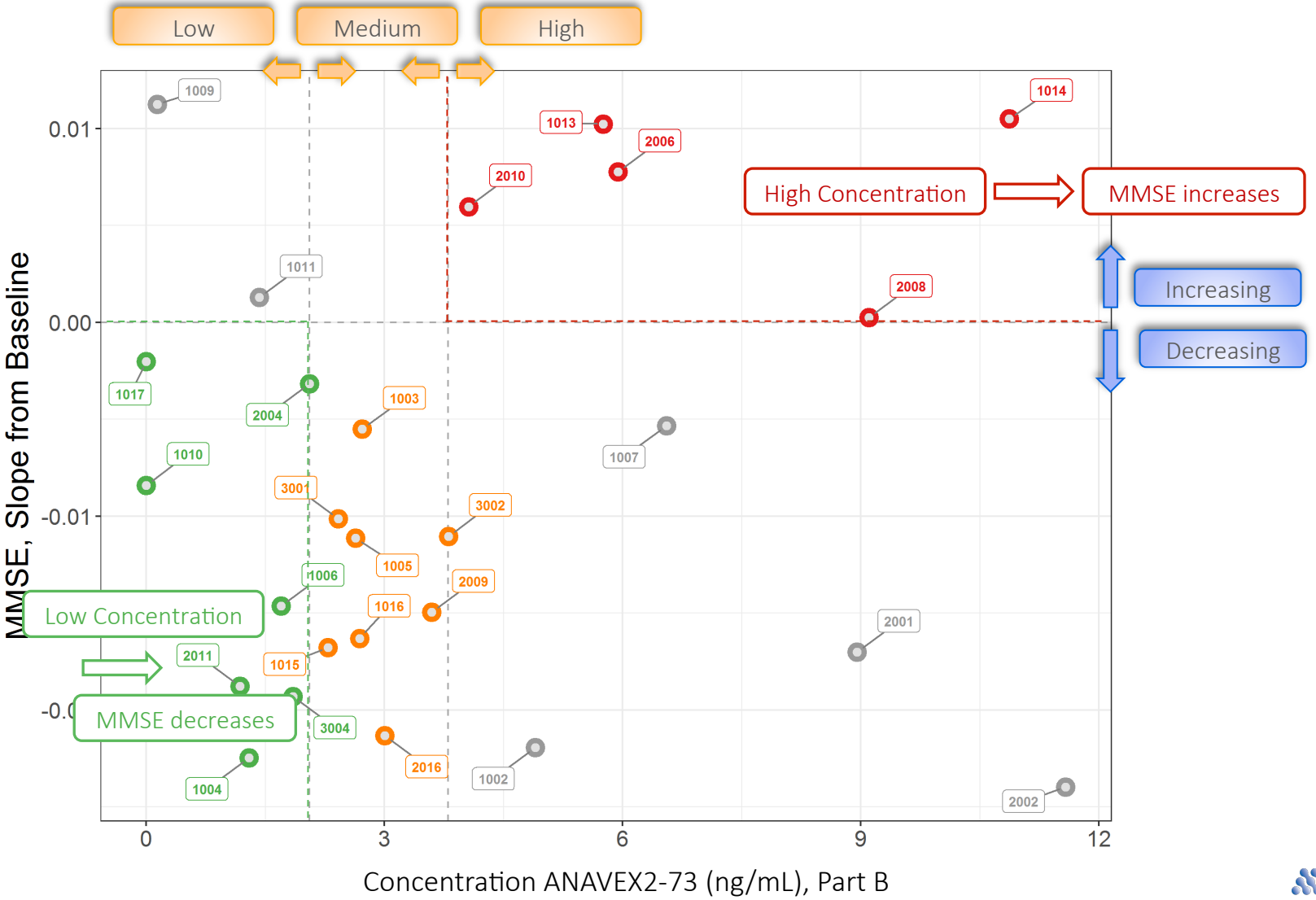
Systematic exploration of the full data matrix using KEM® demonstrates consistent concentration-response relationship for 6 main exploratory endpoints: cognition, function and biomarker (MMSE, ADCS-ADL, EEG/ERPs)



97% Consistency: MMSE, ADCS-ADL and EEG/ERPs: Identified relations show that high dose (concentration) is linked to improved response and low dose (concentration) to poor response

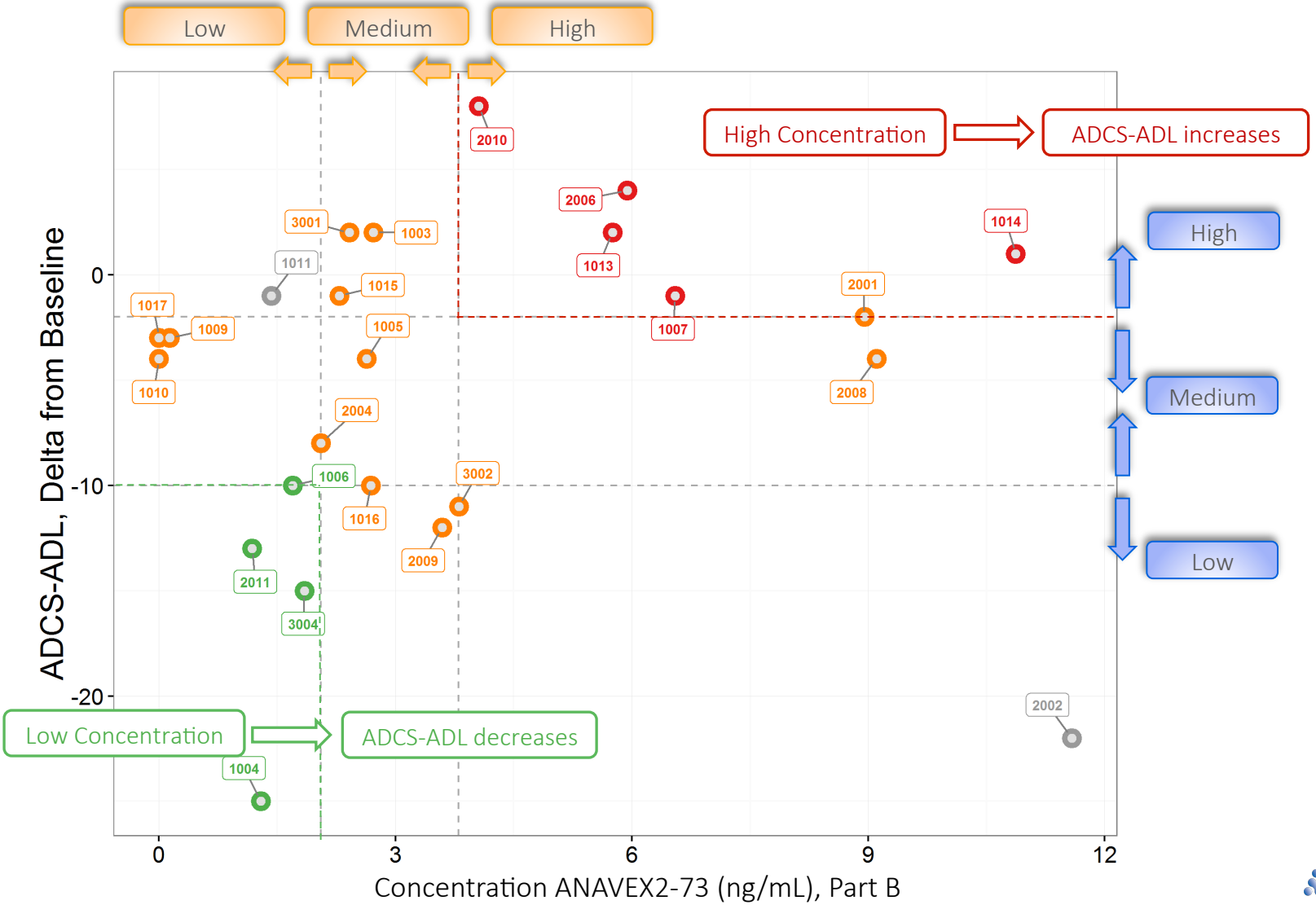
Relation between ANAVEX®2-73 Concentration and MMSE

Apparent broad therapeutic window



Relation between ANAVEX®2-73 Concentration and ADCS-ADL

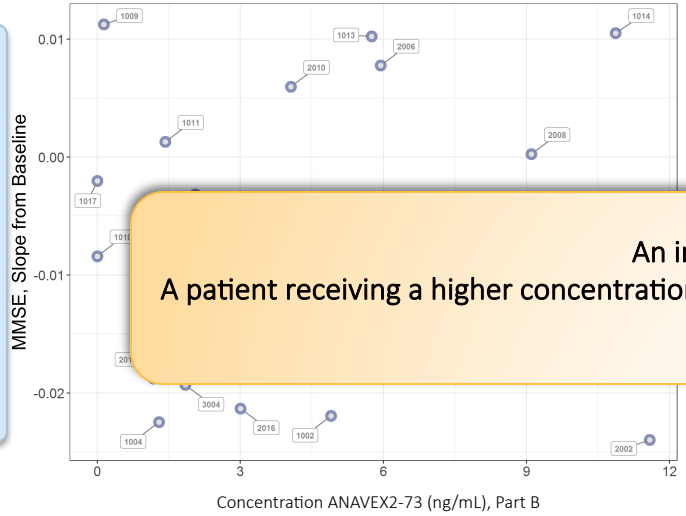
Apparent broad therapeutic window



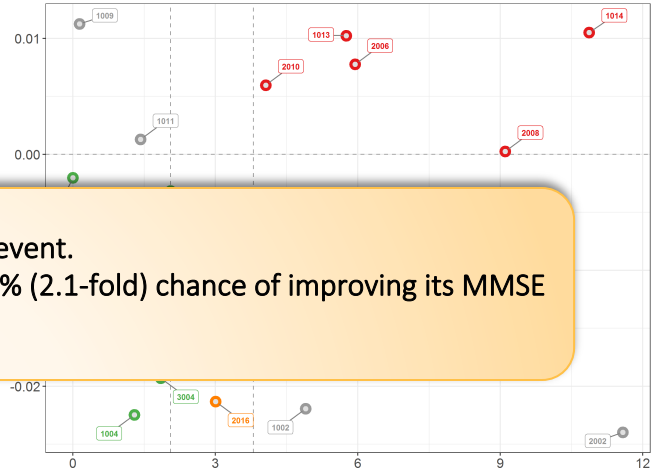
KEM® Identifies Strong non linear Relations Linking Concentration with Response for both MMSE and ADCS-ADL

MMSE

Dose	Response	SupportRatio	Confidence	Lift
Concentration ANAVEX2-73_partB__High	MMSE.SlopeFromBL__Increasing	18,50%	0,556	2,143



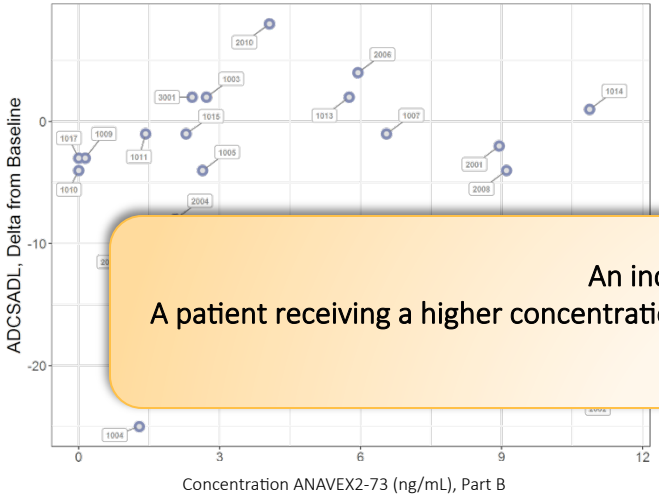
KEM®



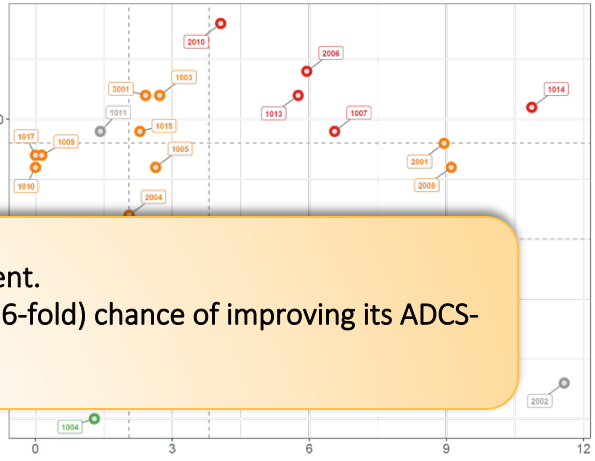
An increase of MMSE is a rare event.
A patient receiving a higher concentration of ANAVEX2-73 has +110% (2.1-fold) chance of improving its MMSE during 57 weeks

ADCS-ADL

Dose	Response	SupportRatio	Confidence	Lift
Concentration ANAVEX2-73_partB__High	ADCS-ADL.DeltaFromBL__High	18,50%	0,625	1,667



KEM®

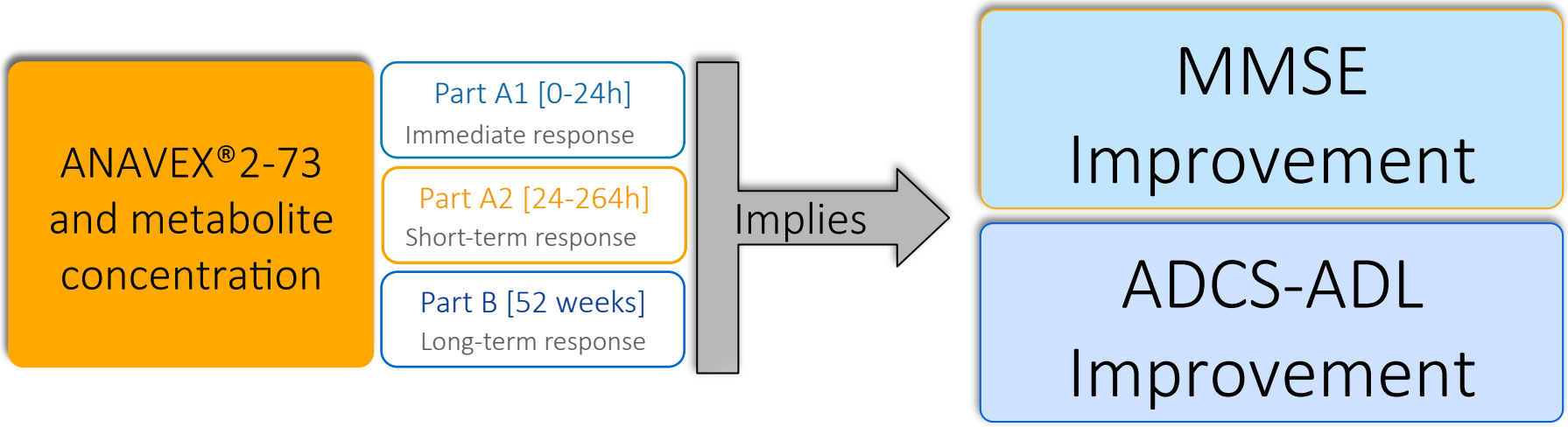


An increase of ADCS-ADL is a rare event.
A patient receiving a higher concentration of ANAVEX2-73 has +67% (1.6-fold) chance of improving its ADCS-ADL during 57 weeks

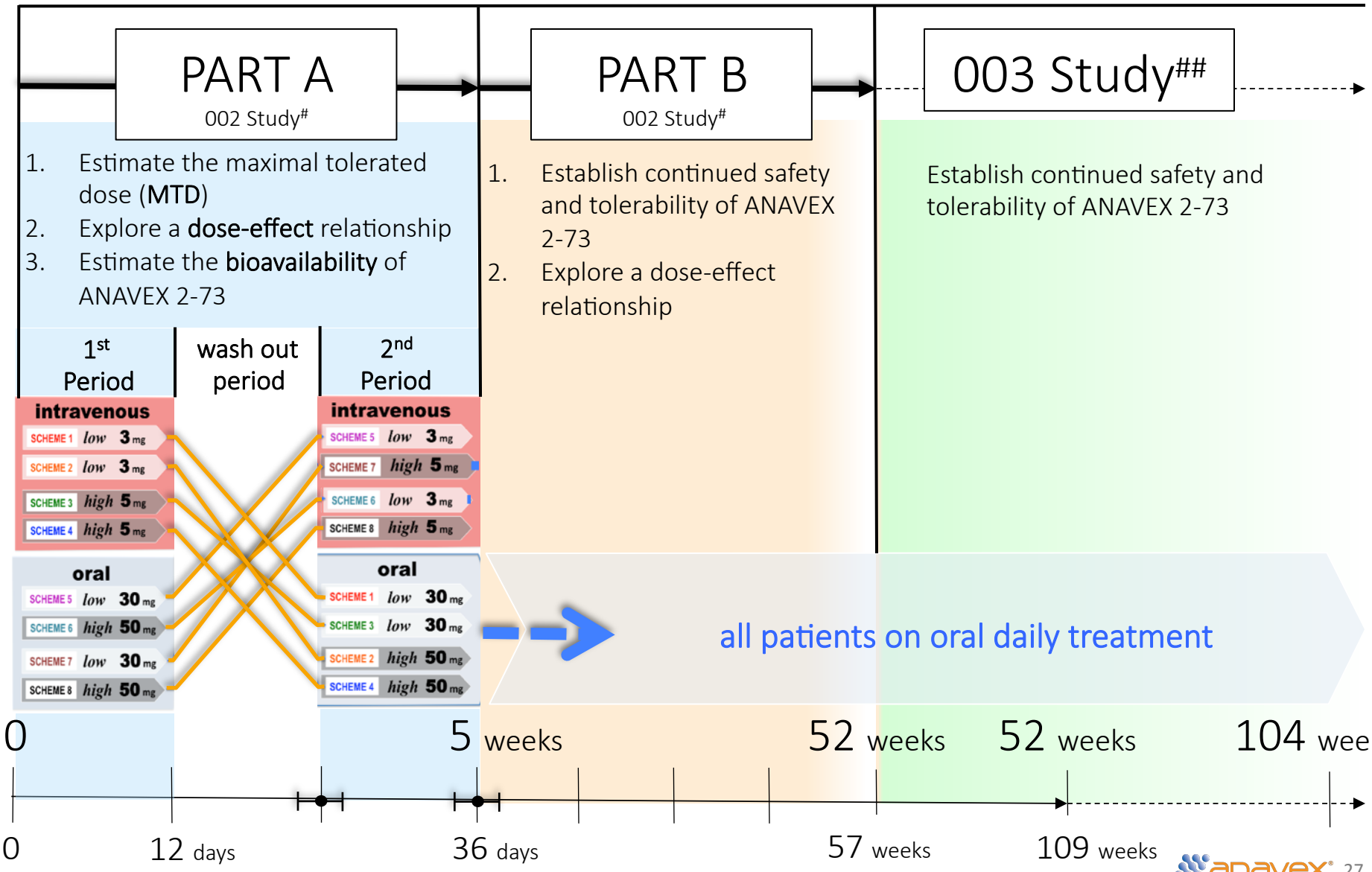
High ANAVEX®2-73 Concentration linked to Improved Response Consistently Across All Analytes and Periods

Both ANAVEX®2-73 and metabolite show a consistent response across the 3 different times frames:

Part A1 [0-24h]	Part A2 [24-264h]	Part B [52 weeks]
Immediate response	Short-term response	Long-term response

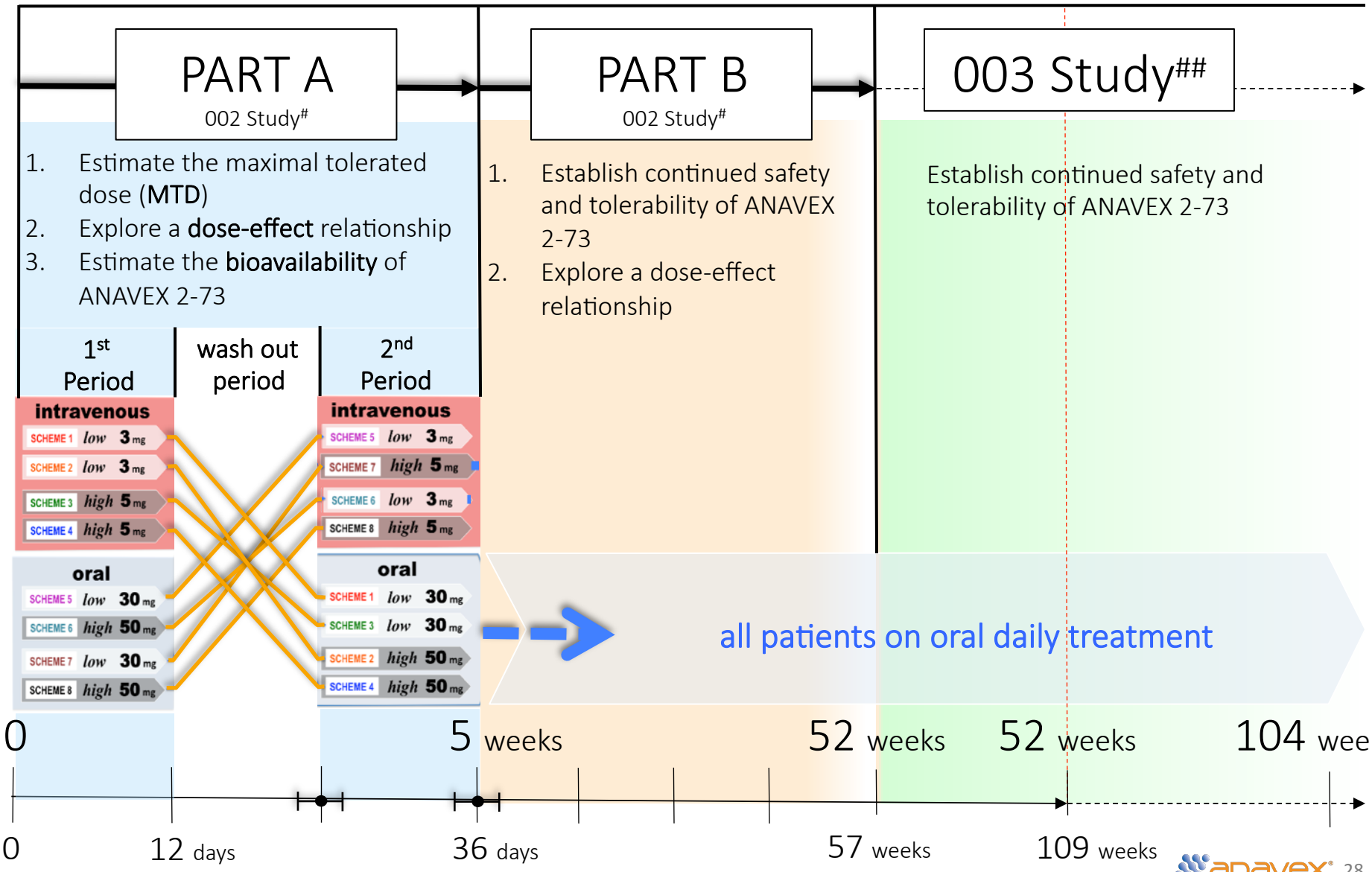


109 Week Update Including First Anniversary of ANAVEX®2-73-003 Study



ClinicalTrials.gov Identifier: #NCT02244541; ##NCT02756858

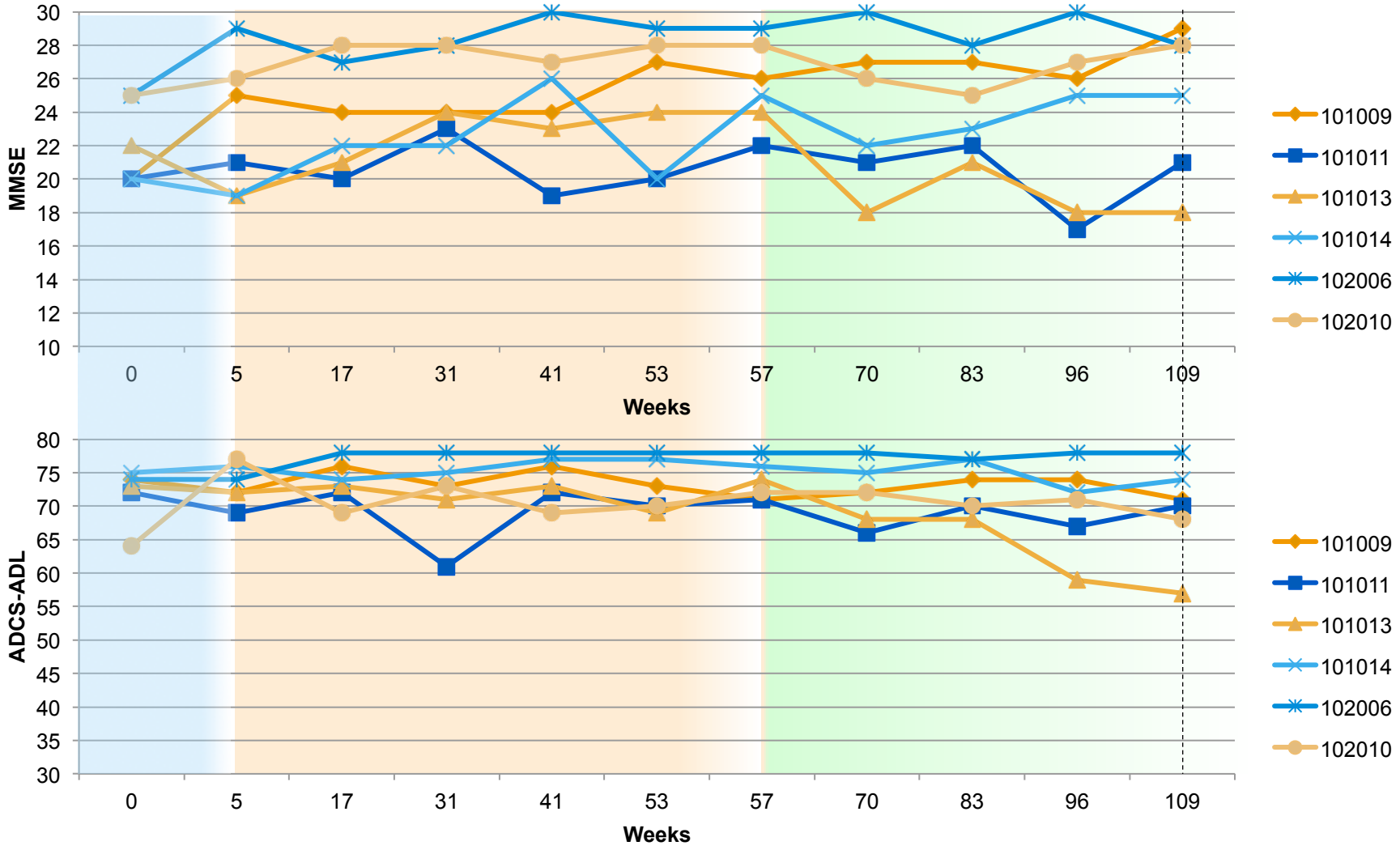
109 Week Update Including First Anniversary of ANAVEX®2-73-003 Study



ClinicalTrials.gov Identifier: #NCT02244541; ##NCT02756858

Patient Cohort with Cognitive and Functional Improvements at 57 Weeks: Retained Response at 109 Weeks

MMSE and ADCS-ADL remained steady over 27 months (109 weeks)



- Patients with milder disease stage (baseline MMSE >20) tended to respond better to ANAVEX®2-73 than patients with more advanced disease stage (baseline MMSE <20)
- Cohort displayed highest concentrations of ANAVEX®2-73
- Continued favorable safety and tolerability through 109 weeks

Summary

- Data analysis demonstrates
  - Patients with highest ANAVEX®2-73 concentrations had improved cognition and function during 57 weeks and retained response at 109 weeks in the first anniversary of the long-term extension cohort Phase 2a study (ANAVEX®2-73-003)
  - Continued favorable safety and tolerability through 109 weeks. ANAVEX2-73 administration does not prolong QTc interval
  - Alzheimer's patients with milder disease stage (baseline MMSE >20) tended to respond better to ANAVEX®2-73 than patients with more advanced disease stage (baseline MMSE <20)
  - No sex difference in the pharmacokinetics of ANAVEX®2-73 was observed
  - Strong drug concentration / response relationship with apparent broad therapeutic window revealed for key Alzheimer's disease trial endpoints cognition and function
  - Data provides support to evaluate ANAVEX®2-73 in a focused Phase 2/3 study using the precision medicine paradigm, including DNA whole exome, RNA expression and gut microbiome characterization
  - Therapeutic benefit potential of sigma-1 receptor activation with ANAVEX®2-73. Further clinical studies in Rett syndrome and Parkinson's disease under development utilizing the translational potential of precision medicine approach of ANAVEX®2-73

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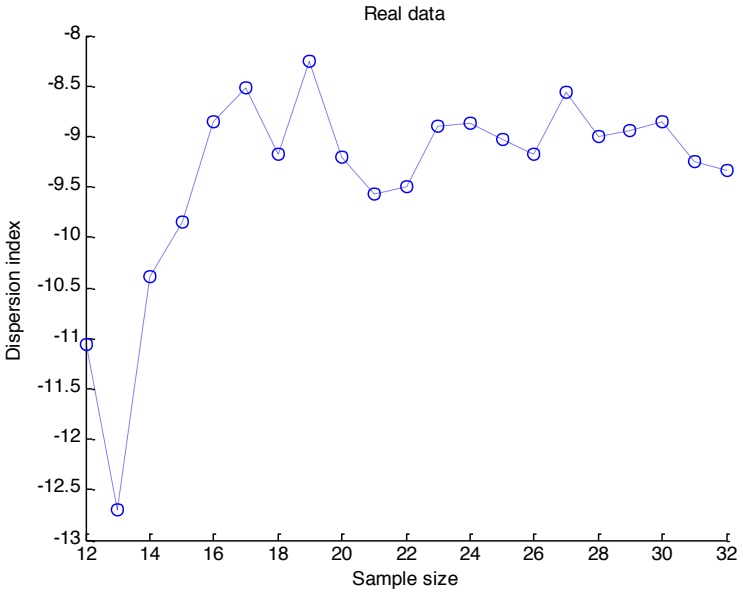
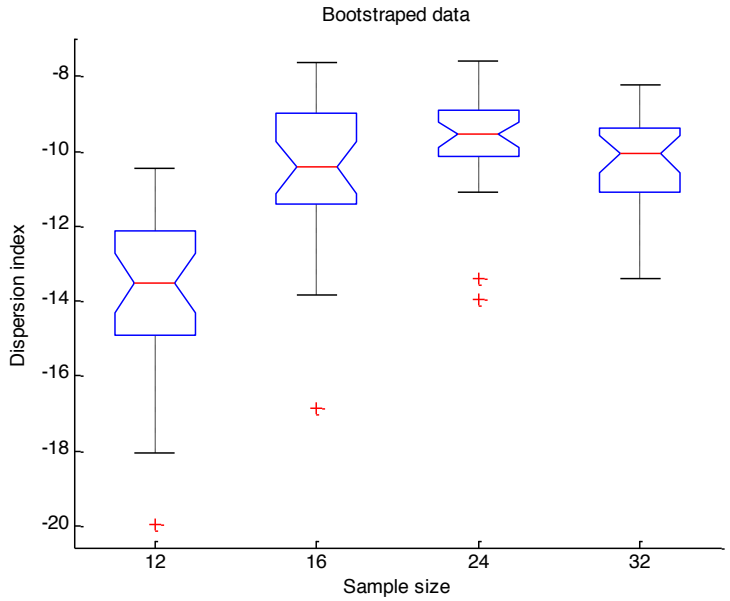
Backup Slides

Confirmed Reliable Inter-Individual Variability (Dispersion) for the ANAVEX2-73 Phase 2a Study with 32 Patient Cohort

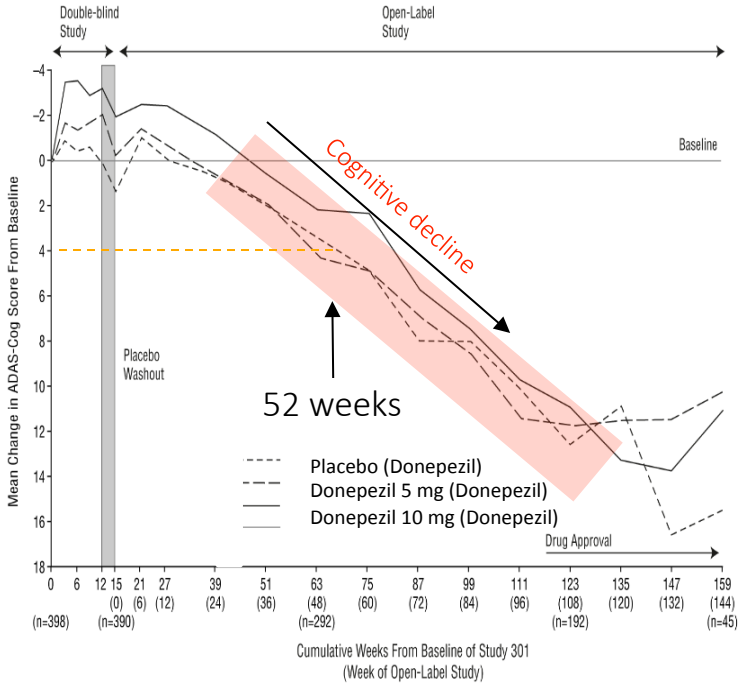


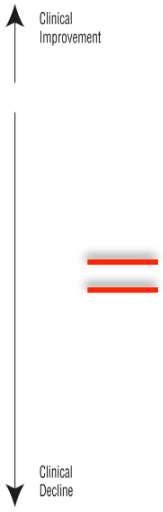


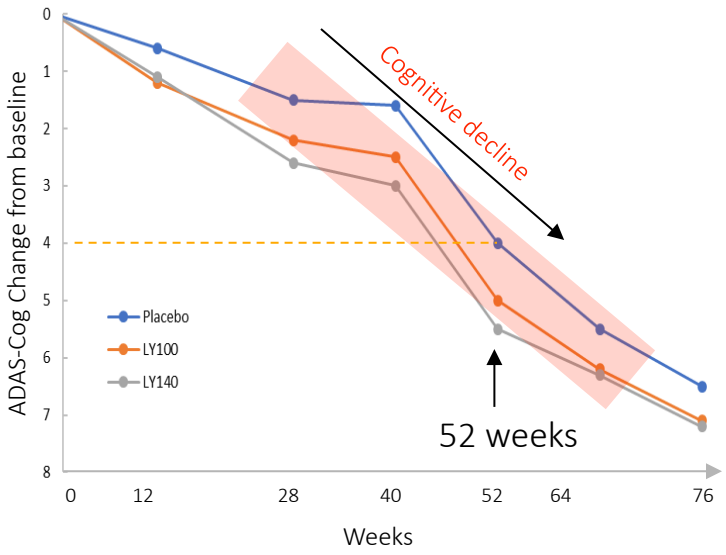
- Evaluation of the dispersion index of all the 32 patient of the Phase 2a reveals that above any random sample of 16 patients, the dispersion index is maintained at a fixed level with the narrowest confidence intervals
- That is confirmation that the sample of 32 patients of the Phase 2a provides reliable information regarding dispersion and as such allows for meaningful predictions for larger populations

Alzheimer's Disease Progression:

Comparable cognitive decline in open-label studies as in placebo-controlled studies







Progressive decline in cognition: Open-label study with standard of care (SoC)#

Progressive decline in cognition: Double-blind placebo-controlled study with standard of care (SoC)##

 # Doody RS et al (2001) Arch Neurol. 58(3):427-433 (SoC = donepezil)

Figure adapted from Doody RS et al (2013) N Engl J Med; 369:341-350 (SoC = Ach inhibitors and/or memantine)

Clearance of ANAVEX®2-73 Independent of given Dose

Total average drug exposure over time

$AUC_{(0 \text{ to infinity})}$

Area Under the Curve, 0-24h