Full Genomic Analysis of ANAVEX®2-73 Phase 2a Alzheimer's Disease Study Identifies Biomarkers Enabling Targeted Therapy and a Precision Medicine Approach

P4-206

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Overview

- ANAVEX®2-73 focuses on a new target relevant to Alzheimer's disease and other neurological diseases
- Sigma-1 receptor (SIGMAR1) serves as an intracellular chaperone and functional modulator of calcium homeostasis and synaptic plasticity. It is involved in several pathways related to Alzheimer's disease, i.e. *reduction* of beta amyloid, hyperphosphorylated tau, oxidative stress, and neuroinflammation
- The direct occupancy of ANAVEX®2-73 at the SIGMAR1 has been established using quantitative PET scan (AAIC 2018)
- Anavex Life Sciences identified genomic biomarkers for increasing success rate in Alzheimer's disease clinical studies
- Full genomic analysis of ANAVEX®2-73 Phase 2a Alzheimer's disease study identifies biomarkers enabling targeted therapy and a Precision Medicine approach
- Targeted therapy benefit is expected for about 80% of patient population

What is a Patient Selection Marker for Precision Medicine in Alzheimer's?

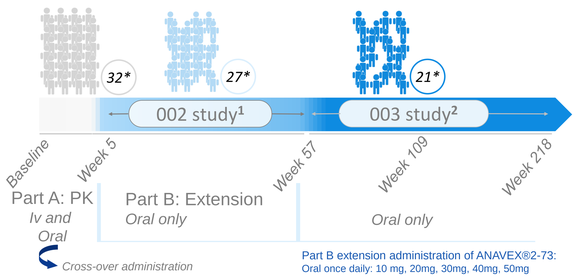
Objective criteria for selecting patients into a clinical study who are likely to benefit from the therapy

- Minimum baseline thresholds for cognitive or functional evaluations
- Genomic biomarkers: variants in DNA which identify who will – or will not – benefit from the therapy

Anavex did a preliminary Phase 2a study with ANAVEX®2-73 to identify patient selection markers

- Study results were analyzed by Ariana Pharma using their proprietary AI KEM® platform
- The results of this analysis showed strong patient identification markers for clinical studies

ANAVEX®2-73 AD Phase 2a: Timeline and Description of the Cohort

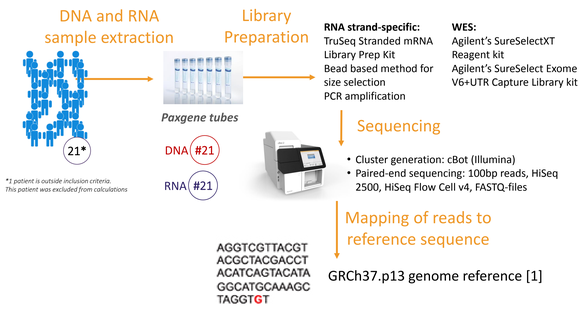


Cohort characteristics:
Alzheimer's disease patients
Age range: 55 to 85
Diagnosed with MRI and/or PET scans

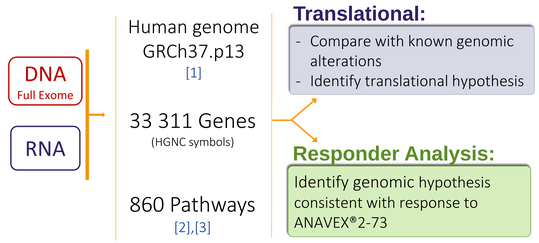
*1 patient is outside inclusion criteria. This patient was excluded from calculations
[1], [2]: ClinicalTrials.gov Identifier: [1]NCT02244541; [2]NCT02756858

References
[1] Genome Reference Consortium Human Build 38 patch release 10 (GRCh38.p10). https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.25/#/st
[2] Kanehisa M, Goto S. (2000) KEGG: Kyoto encyclopedia of genes and genomes. Nucleic Acids Res. 2000;28(1):27–30. doi: 10.1093/nar/28.1.27.
[3] Fabregat A, et al. The Reactome pathway Knowledgebase. (2016) Nucleic Acids Res. 2016;44:D481–D487. doi: 10.1093/nar/gkv1351.
[4] Afshar M, Lanoue A, and Sallantin J. (2007) Multiobjective/Multicriteria Optimization and Decision Support in Drug Discovery. Comprehensive Medicinal Chemistry II. Volume 4, edn. 2007: 767-774.

Material and Methods: DNA and RNA Sequencing

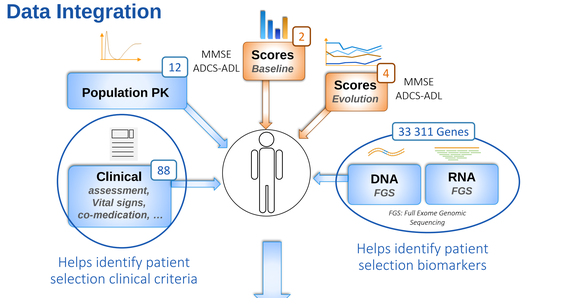


ANAVEX®2-73 Genomic Knowledge Base :

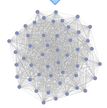


Material and Methods: Data Integration and Analysis

Data Integration



Data Analysis



Using AI platform KEM® version 3.6.2

Systematic Generation of all Association Rules
>20 Million relations extracted and characterized from study data

- Association rules provide unique, unbiased results and generate new hypotheses
- KEM® (Knowledge Extraction Management) helps overcome the challenges of analysis of biomarker data in small clinical studies [4]

Rule example

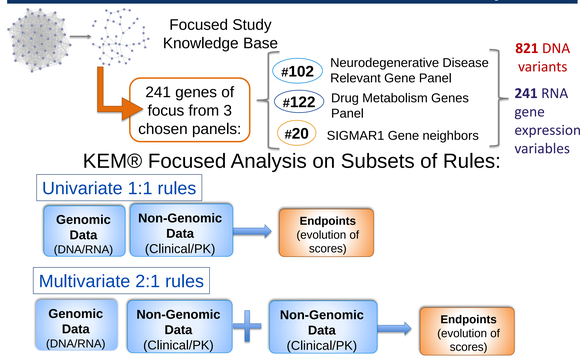
Var 1 = High → Ept 3 = High

KEM® generates association rules $Var_i \rightarrow Ept_i$ in an exhaustive manner. These rules are characterized by 4 metrics that help ranking them.

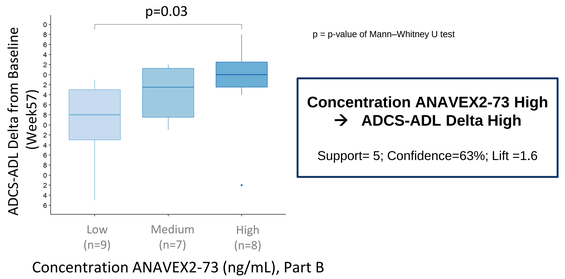
Metrics

- **Support** number of times that the rule is checked in the dataset
- **Confidence** proportion of cases verifying Var1 = low and Var3 = True.
- **Lift** ratio of the observed support to that expected if Var1 = low and Var3 = True were independent.
- **P-value** Fisher's exact test

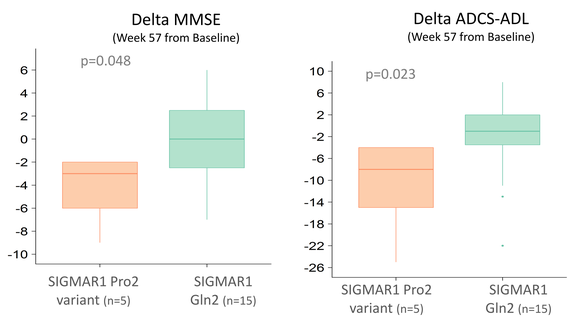
Material and Methods: Focused Data Analysis



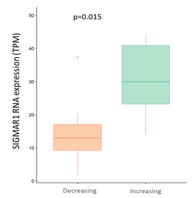
Results: Significant Relation between ANAVEX®2-73 Concentration and Response (ADCS-ADL)



Results: SIGMAR1 Gene Variant Associated with Differentiated Response



- RNA expression analyses are more difficult to determine as patient gene selection markers, but can confirm the information from gene variants as patient selection markers

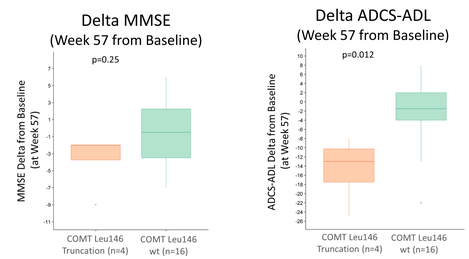


All N=20 patients in study at week 57 with genomic data

p = p-value of Mann–Whitney U test

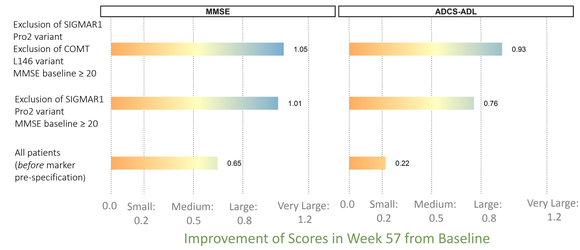
Results: COMT Gene Variant Associated with Differentiated Response

Patients with a wild-type COMT gene were found to have an improved benefit from ANAVEX®2-73.



Gene Variant Markers 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.



Summary

- Systematic analysis using KEM® identifies actionable parameters enabling a precision medicine approach to include best responders in follow-up Phase 2b/3 study
- Patients with a wild-type SIGMAR1 gene were found to have an improved benefit from ANAVEX®2-73. Patients with a variant of the SIGMAR1 gene were found to have a limited benefit from ANAVEX®2-73
- The minority of the population, about 20% has the variant SIGMAR1 gene, hence the majority of patients (about 80%) is expected to benefit from ANAVEX®2-73
- Gut microbiota has been collected and will be incorporated in future analysis
- The data provides support to further clinical development of ANAVEX®2-73 and further clinical studies in other indications are planned or underway
- Anavex is pioneering the use of precision medicine in CNS disorders, including Alzheimer's disease