Overview

- ANAVEX2-73 focuses on a new target relevant to Alzheimer’s disease and other neurological disorders.
- 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 (AANIC 2018).
- Anaxev Life Sciences identified genomic biomarkers for increasing success rate in Alzheimer’s disease clinical studies.
- Full genomic analysis of ANAVEX2-73 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.

ANAVEX2-73 AD Phase 2a: Timeline and Description of the Cohort

- ANAVEX2-73 was designed to be a Phase 2a study to identify patient selection markers.
- Study results were analyzed by Anaxev Life Sciences using their proprietary AI KEM® platform.
- The results of this analysis showed strong patient identification markers for clinical studies.

Material and Methods: DNA and RNA Sequencing

- DNA and RNA sample extraction
- Library Preparation
- Sequencing
- GENOMICA KEM® version 3.6.2

Data Integration

- Using AI platform KEM® version 3.6.2
- Association rules provide unique, unbiased results and generate new hypotheses
- KEM® (Knowledge Extraction Management) helps to overcome the challenges of analysis of biomarker data in small clinical studies

Data Analysis

- Systematic Generation of all Association Rules
- KEM® generates association rules Xay ≤ d, a ≤ b, in an exhaustive manner. These rules are characterized by a set of data that keep them valid.
- KEM® (Knowledge Extraction Management) helps to overcome the challenges of analysis of biomarker data in small clinical studies

Material and Methods: Focused Data Analysis

- Focused Study Knowledge Base
- KEM® Full Genomic Analysis
- ANAVEX®2-73 Genomic Knowledge Base
- ANAVEX®2-73 Target Gene

Results: COMT Gene Variant Associated with Differentiated Response

- Patients with a wild-type COMT gene were found to have an improved benefit from ANAVEX2-73.
- A higher Cohen’s d implies less patients are needed to show a significant difference between placebo arm and ANAVEX2-73 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 ANAVEX2-73. Patients with a variant of the SIGMAR1 gene (rs1800866) were found to have a limited benefit from ANAVEX2-73.
- Including patients with milder disease stage baseline MMSE (≤ 20) and the exclusion of AD patients carrying SIGMAR1 variants results in a score improvement of +1.7 MMSE and +4.9 ADCS-ADL, respectively at week 57. The additional exclusion of the COMT variant results in a score improvement of +2 MMSE and +4.9 ADCS-ADL, respectively for the same period. Both effects would be clinically meaningful.
- The minority of the population (about 20%) has the wild variant SIGMAR1 gene, hence the majority of patients (about 80%) is expected to benefit from ANAVEX2-73.
- Gene expression analysis suggests more difficult to determine as a patient gene selection markers, but can confirm the information from gene variants as patient selection markers.
- RNA expression analyses are more difficult to determine as a patient gene selection markers, but can confirm the information from gene variants as patient selection markers.
- All AD patients in study with wild-type gene sequence (n=15) showed a score improvement of +2 MMSE and +4.9 ADCS-ADL.

Results: SIGMAR1 Gene Variant Associated with Differentiated Response

- Gene Variant Markers Improve Effect Size (Cohen’s d) with ANAVEX2-73.