Systematic Processing of Full Genomic Analysis of ANAVEX®2-73 Phase 2a Alzheimer’s Disease Study Identifies Biomarkers Enabling a Precision Medicine Approach

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Nasdaq: AVXL
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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 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

ANAVEX®2-73 activates the Sigma-1 receptor restoring cellular homeostasis

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

Chaperoning Misfolded proteins

Restoring Homeostasis and Neuroplasticity

stimulating cells to regain functionality & plasticity

Glembotski et al., Circulation Research. 2007;101:975-984


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

- **Sigma-1 receptor ligands** have been shown to modulate multiple aspects of neurodegenerative processes, affecting both neurons and glia

  - i.e. resulting in reduction of beta amyloid, hyperphosphorylated tau, oxidative stress, neuroinflammation - leading to synaptic dysfunction and neuronal loss
ANADEX®2-73 phase 2a Alzheimer study

- 57-week proof-of-concept randomized open-label phase 2a study of ANAVEX®2-73 in 32 mild-moderate AD dementia patients (MMSE 16-28)^

- Results showed favorable safety profile

- Dose-dependent target engagement

- Favorable dose-response using cognitive and functional endpoints

^ClinicalTrials.gov Identifier: NCT02244541
Confirmation with quantitative PET Scan:

Dose-dependent ANAVEX®2-73 target engagement with the Sigma-1 receptor

2D [18F]FTC-146-PET imaging of ANAVEX®2-73

Frontal Cortex
Brain Stem

Dose of AV2-73: 0 mg/kg, 1 mg/kg, 10 mg/kg, 30 mg/kg

Sigma-1 receptor target occupancy study with quantitative PET analysis of ANAVEX®2-73
(Presented at AAIC 2018 - P4-262)
Significant relation between mean ANAVEX®2-73 concentration and response Alzheimer's Disease Cooperative Study Activities of Daily Living 23-item scale (ADCS-ADL)

Mean Concentration ANAVEX2-73 High => ADCS-ADL Delta High

All n=24 patients in study at week 57 having available ADCS-ADL scores
ANAVEX®2-73 phase 2a extension Alzheimer study

- +104/+104-week extension study in 21 patients#
- With full NGS exome (DNA) and transcriptome (RNA) sequencing

#ClinicalTrials.gov Identifier: NCT02756858
RNA/DNA sequences/study data analyzed using neuroinformatics platform KEM®

Systematic unbiased generation of all possible causal associations in a multi-parametric dataset

- >20 million relations extracted and characterized from study data
- Identification & ranking of biomarkers relating to outcome derived from a small n of samples, avoiding overfitting

Advanced Machine Learning - Artificial Intelligence Platform Supporting Clinical Trial Design
KEM® using Formal Concept Analysis (FCA)

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
Successfully utilized in oncology and other disease areas
DNA variant analysis shows patient selection gene (variant) biomarkers related to SIGMAR1 gene.

The presence of specific variants results in worse outcomes, and that of others in improved outcomes for MMSE\(^1\) and ADCS-ADL\(^2\).

\(^1\)Mini Mental State Examination (MMSE)  
\(^2\)Alzheimer’s Disease Co-operative Study – Activities of Daily Living Inventory (ADCS-ADL)
Gene variant patient selection biomarkers confirmed through *RNA expression*

RNA expression analyses can confirm the information derived from DNA (gene) variants as patient selection biomarkers.

RNA expression analyses show *concordance with results* for the SIGMAR1 variant markers.
▪ AD patients with **wild-type SIGMAR1 gene** were found to have **improved benefit** from ANAVEX®2-73

▪ AD patients with a **variant of the SIGMAR1 gene (rs1800866)**, were found to have a **limited benefit** from ANAVEX®2-73

▪ Majority of AD population, about **80% has no variant SIGMAR1 gene**, hence the majority of patients is expected to benefit from ANAVEX®2-73
**SIGMAR1 Gene Variant** associated with decreased response

**Delta MMSE**
(Week 57 from Baseline)

- SIGMAR1 Pro2 variant (n=5) (rs1800866)
- SIGMAR1 Gln2 (n=15)

\[ p = 0.048 \]

**Delta ADCS-ADL**
(Week 57 from Baseline)

- SIGMAR1 Pro2 variant (n=5) (rs1800866)
- SIGMAR1 Gln2 (n=15)

\[ p = 0.023 \]

\[ p = p\text{-value of Mann–Whitney U test} \]

*All n=20 patients in study at week 57 with available genomic data*
Confirmation: Significant correlation of ADCS-ADL response and SIGMAR1 RNA expression levels

All $n=20$ patients in study at week 57 with available genomic data

$p = 0.015$

$p$-value of Mann–Whitney U test

ADCS-ADL Slope from Baseline to Week 57
Other associated gene variant identified: COMT Leu146 Truncation

Catechol-O-methyltransferase is one of several enzymes that degrade catecholamines.

All n=20 patients in study at week 57 with available genomic data.

**Delta MMSE** (Week 57 from Baseline)

**Delta ADCS-ADL** (Week 57 from Baseline)

\[ p = \text{p-value of Mann–Whitney U test} \]
Gene markers improve effect size (Cohen’s d) with ANAVEX®2-73

Higher Cohen’s d implies less patients are needed to show a significant difference between placebo arm and ANAVEX®2-73 arm in the Phase2b/3 study.
**Summary**

**ANAVEX®2-73 study**

- Confirmed safety & dose-dependent target engagement with SIGMAR1 using PET
- Exome sequencing showed response-linked gene variants using formal concept analyses (FCA)
- Identified SIGMAR1/COMT variants shown to be linked to limited clinical response
- Targeted therapy benefit on WT variants is expected for about 80% of patient population
- Confirmation through high SIGMAR1 RNA expression levels linked to clinical response
- Results consistent across cognition (MMSE) and activities of daily living (ADCS-ADL)
- Identified actionable genetic variants support enrichment with genetic biomarkers in the clinical development of ANAVEX®2-73

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**Targeted therapy studies approved to initiate:**

- Alzheimer’s Disease - Phase 2b/3
- Parkinson’s Disease Dementia - Phase 2
ANAVEX®2-73 phase 2b/3 early Alzheimer's Disease study design

N=450
Early AD patient population
- Confirmed amyloid pathophysiology (CSF/amyloid PET)
- Patients aged 60 to 85 years
- MMSE score 20-28
- DNA and RNA sequencing

Randomization 1:1:1

Primary Endpoints at 48 Weeks
- ADAS-Cog
- ADCS-ADL
- Safety and tolerability of ANAVEX®2-73

Key Secondary Endpoints
- CDR-SB
- Structural and functional MRI
- Biomarkers: Abeta_{40}/Abeta_{42}, T-tau, P-tau, NFL, YKL-40, neurogranin, BACE1

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

*Restricted to maintain complete blinding
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