LONGITUDINAL 148-WEEK EXTENSION STUDY OF ANAVEX®2-73 FOR THE TREATMENT OF ALZHEIMER’S DISEASE DEMONSTRATES MAINTAINED ACTIVITIES OF DAILY LIVING SCORE (ADCS-ADL) AND REDUCED COGNITIVE DECLINE (MMSE) FOR PATIENT COHORT ON HIGHER DRUG CONCENTRATION AND CONFIRMS ROLE OF PRECISION MEDICINE PATIENT SELECTION BIOMARKERS
SAFE HARBOR

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Anavex at a Glance

**APPROACH**
Applying precision medicine to CNS disorders
Patient selection based on genomic screening and biomarkers

**MECHANISM**
SIGMAR1 restoring cellular homeostasis

**FOCUS**
Finding effective treatments for neurodevelopmental and neurodegenerative diseases

**LARGE MARKETS**
Addressing unmet needs such as global dementia, other neurodegenerative diseases as well as catastrophic orphan genetically caused diseases
Sigma-1 receptor agonists have been shown to restore neuronal functions in neurodegenerative processes.

ANAVEX®-2-73 alleviates Tau pathology in neurodegenerative disease models.

Sigma-1 receptor agonists have a neuroprotective effect in neurodegenerative disease models.
ANAVERX®2-73 observed to be safe and well tolerated
Efficacy (MMSE & ADCS-ADL) has been evaluated long-term

**002 study**

- Week 0
- Week 5

**Part A**
- 5 weeks
- Period 1
- IV (3mg or 5mg)
- Oral (30mg or 50mg)

**Part B**
- 52 weeks
- Daily Oral Dose: 10mg, 20mg, 30mg, or 50mg
- Period 1
- Period 2

**003 study**

- Week 57
- Week 148
- Week 265

**Extension**
- 208 weeks
- Daily Oral Dose: 10mg, 20mg, 30mg, or 50mg

- N=32
- N=24
- N=30
- N=21**

*ClinicalTrials.gov Identifier: ANAVEX®2-73-AD-002/3 STUDY (NCT02244541/NCT02756858)

** 1 patient is outside inclusion criteria. This patient was excluded from calculations
ANAVEX®2-73 Concentration & MMSE/ ADCS-ADL Trajectories
Significant Relationship between ANAVEX®2-73 Concentration and Patients Response

Activities of Daily Living (ADCS-ADL)*

- High Concentration of ANAVEX®2-73 => High Delta ADCS-ADL (improved response)
- # Plasma concentration of ANAVEX®2-73 is correlated with the administered dose
  - All n=24 patients in study at week 57
  - p = p-value of Mann–Whitney U test

Source: H Hampel et al., AAIC 2018; *Alzheimer's Disease Cooperative Study Activities of Daily Living 23-item scale (ADCS-ADL)
Patients Treated with Higher ANAVEX®2-73 Concentration Maintain ADCS-ADL* Performance vs Lower Concentration Cohort

**High Concentration cohort shows 88 % difference to low concentration cohort**

- High plasma concentration of ANAVEX®2-73 [≥4.0 ng/ml] is correlated with the clinically administered dose.

- In addition to concentration, the significant covariates identified in MMRM-LME model are:
  - **SIGMAR1** (p<0.0080),
  - **COMT** (p<0.0014)

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.

Source: M Afshar et al., CTAD 2018  * Alzheimer’s Disease Cooperative Study Group - Activities of Daily Living Inventory (ADCS-ADL)
Patients Treated with Higher ANAVEX®2-73 Concentration Show Higher MMSE* Performance Compared to Lower Concentration

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

- High plasma concentration of ANAVEX®2-73 (≥4.0 ng/ml) is correlated with the clinically administered dose

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.

Source: M Afshar et al., CTAD 2018

*p Mini Mental State Examination (MMSE)
Precision Medicine (Genomic Biomarkers) & MMSE/ADCS-ADL Trajectories
Identification of Gene “Signature” from ANAVEX®2-73-Treated Patients

- Genomic signature (WT SIGMAR1 gene) strongest responders to ANAVEX®2-73
- This genomic “biomarker” is drug specific, not indication specific, so it applies to all indications treated with ANAVEX®2-73
Majority of the population (~80%) carries SIGMAR1 WT

Majority of patients (~80%) are expected to benefit from SIGMAR1 activation with ANAVEX®2-73

rs1800866 variant found in the remaining (~20%) of the population can cause structural change, leading to impaired protein trafficking

SIGMAR1 WT Gene Associated with Improved Response ...

Delta MMSE (Week 57 from Baseline)

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

p = 0.048

Delta ADCS-ADL (Week 57 from Baseline)

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

p = 0.023

Source: H Hampel et al., AAIC 2018

p = p-value of Mann–Whitney U test
All n=20 patients in study at week 57 with available genomic data

... and validated at 148 weeks
Patients Improvement Correlates with ANAVEX®2-73 and SIGMAR1 RNA Expression

Activities of Daily Living (ADCS-ADL)* Slope pattern from Baseline to Week 57

ANAVEX®2-73 positive response in functional (ADCS-ADL) outcomes in Alzheimer’s disease patients correlate with SIGMAR1 mRNA levels

SIGMAR1 RNA expression (TPM)

- Decrease (Negative)
- Increase (Positive)

p = 0.015

Source: H Hampel et al., AAIC 2018; *Alzheimer's Disease Cooperative Study Activities of Daily Living 23-item scale (ADCS-ADL)

Gut Microbiota in AD

p = p-value of Mann–Whitney U test
All n=20 patients in study at week 57 with available genomic data
Clinical Studies:
• Parkinson’s Disease Dementia (PDD)
• Alzheimer’s Disease (AD)
• Rett Syndrome (RTT)
Overview ANAVEX®2-73 Ongoing Precision Medicine Clinical Trials

**PHASE 2 PARKINSON’S DISEASE DEMENTIA**
- ANAVEX®2-73-PDD-001 STUDY (NCT03774459)*
- 14 WEEK STUDY
- 120

**PHASE 2b/3 ALZHEIMER’S DISEASE**
- ANAVEX®2-73-AD-004 STUDY (NCT03790709)*
- 48 WEEK STUDY
- 450

**PHASE 2 RETT SYNDROME**
- ANAVEX®2-73-RS-001 STUDY (NCT03758924)*
- 7 WEEK STUDY
- 15

**PHASE 2a ALZHEIMER’S DISEASE**
- ANAVEX®2-73-AD-002/3 STUDY (NCT02244541/NCT02756858)*
- 208 WEEK STUDY
- 32

- Sufficient cash including non-dilutive grant and governmental third party support to fund objectives for the next 2 years

*ClinicalTrials.gov Identifier; **FDA granted ANAVEX®2-73 Orphan Drug Designation (ODD) for Rett syndrome
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