SAFE HARBOR

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Anavex utilizes **genomic biomarkers** in **precision medicine** to treat severe and devastating neurological disorders.

Anavex is focusing on **rare diseases** with no available therapy (Rett syndrome) and **high risk CNS** patient populations (Alzheimer’s disease, Parkinson’s disease).
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
Overview ANAVEX® 2-73 Ongoing Precision Medicine Clinical Trials

1. **Phase 2 Parkinson’s Disease Dementia**
   - 14 WEEK STUDY
   - 120 participants
   - ANAVEX®2-73-PDD-001 STUDY (NCT03774459)*

2. **Phase 2b/3 Alzheimer’s Disease**
   - 48 WEEK STUDY
   - 450 participants
   - ANAVEX®2-73-AD-004 STUDY (NCT03790709)*

3. **Phase 2a Alzheimer’s Disease**
   - 208 WEEK STUDY
   - 32 participants
   - ANAVEX®2-73-AD-002/3 STUDY (NCT02244541/NCT02756858)*

4. **Phase 2 Rett Syndrome**
   - 7 WEEK STUDY
   - 15 participants
   - ANAVEX®2-73-RS-001 STUDY (NCT03758924)*

- 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
Catalysts to Drive Value

The company is well positioned to achieve key clinical readouts

- ✔ Phase 2a – Reported 148-week data at CTAD 2018 scientific meeting
- ✔ Phase 2b/3 clinical trial in Alzheimer’s disease – ongoing
- ✔ Phase 2 clinical trial in Parkinson’s disease dementia (PDD) – ongoing
- ✔️ Initiate Phase 2 clinical trial in Rett syndrome (RTT)
- ✔️ Topline data Phase 2 Parkinson’s disease dementia (PDD)
- ✔️ Topline data Phase 2 Rett syndrome (RTT)
- ✔️ Clinical data publications in 2019
- ✔️ New indications and licensing opportunities
SIGMAR1 Activation has been Shown to Modulate Multiple Aspects of Neurodegenerative Processes

Sigma-1 receptor agonists have been shown to restore neuronal functions in neurodegenerative processes

ANAVERX®-2-73 alleviates Tau pathology in neurodegenerative disease models

Sigma-1 receptor agonists have a neuroprotective effect in neurodegenerative disease models
Sigma-1 receptor activation by ANAVEX2-73 enhances autophagy in *C. elegans*

Sigma-1 Receptor Activation Induces Autophagy and Increases Proteostasis Capacity In Vitro and In Vivo

Maximilian G. Christ, Heike Huesmann, Heike Nagel, Andreas Kern and Christian Behl *

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Received: 29 January 2019; Accepted: 27 February 2019; Published: 2 March 2019

**Sigma-1 receptor activation by ANAVEX2-73 enhances autophagy in *C. elegans***

*p ≤ 0.001*
The SIGMAR1 receptor is an integral membrane protein involved in cellular homeostasis which targets restoration of neuroplasticity and cellular stress response.

Impaired SIGMAR1 function leads dysfunction in ER-mitochondria crosstalk, calcium homeostasis impairment, ER stress activation.

- SIGMAR1 null mice display muscle weakness, axonal degeneration and motor neuron loss
- Mutations in SIGMAR1 have been identified in
  - frontotemporal lobar degeneration co-occurring with ALS (FTLD-ALS)
  - juvenile ALS
  - the rare neuromuscular disorder distal hereditary motor neuropathy (dHMN)
  - In Alzheimer's disease, variants of the SIGMAR1 have been shown to be a risk factor

Genetic SIGMAR1 Variations Linked to Neurological Disorders

Patients Improvement Correlates with ANAVEX®2-73 and SIGMAR1 RNA Expression

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

Patients Improvement Correlates with ANAVEX®2-73 and SIGMAR1 RNA Expression

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

All \( n = 20 \) patients in study at week 57 with available genomic data

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

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

* Mini Mental State Examination (MMSE)
The ideal pharmacogenomics test will be able to determine:

- Potential for a medication to be effective – for this person
- The best dose of a medication – for this person
- Avoid risk of serious side effects – for this person

**PHARMACOLOGY + GENOMIC = PHARMACOGENOMICS**

Patient Selection with Biomarker Increases Probability of Success

- Phase II to Phase III
  - Without Biomarkers: 28%
  - With Patient Selection Biomarkers: 46%

- Phase III to NDA/BLA
  - Without Biomarkers: 55%
  - With Patient Selection Biomarkers: 76%

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
SIGMAR1 Gene Plays a Role in Protein Trafficking

- 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)

p=0.048

SIGMAR1 Pro2 variant (rs1800866) (n=5)

SIGMAR1 WT (n=15)

Delta ADCS-ADL
(Week 57 from Baseline)

p=0.023

SIGMAR1 Pro2 variant (rs1800866) (n=5)

SIGMAR1 WT (n=15)

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
Clinical Studies:
• Parkinson’s Disease Dementia (PDD)
• Alzheimer’s Disease (AD)
• Rett Syndrome (RTT)
Anavex pipeline and precision genetic medicine approach address unmet needs of neurodevelopmental and neurodegenerative diseases.

**Pipeline Addresses both Rare and Large Indications**

- **Alzheimer’s Disease (AD)**
  - ~5,700,000 patients\(^1\)

- **Parkinson’s Disease (PD)**
  - ~1,000,000 patients\(^2\)

- **Rett Syndrome (RTT)**
  - ~11,000 patients\(^3\)

- **Additional Indications**
  - Frontotemporal dementia (FTD)
  - and others

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2) Marras C et al 2018. npj Parkinson’s Disease volume 4, Article number: 21  
3) Based on prevalence number on orphanet
ANAVEX®2-73 Phase 2 Parkinson’s Disease Dementia Study

**N=120**

**PDD patient population**
- Diagnosis of probable Parkinson’s disease dementia (PDD)
- Diagnosis of idiopathic Parkinson’s disease
- Patients aged ≥ 50 years
- MoCA score 13-23
- DNA and RNA sequencing

**Randomization 1:1:1**
- ANAVEX®2-73 High dose#
- ANAVEX®2-73 Medium dose#
- Placebo

**14 WEEK STUDY**

**Primary Endpoints**
- CDR Continuity of Attention
- Safety and tolerability of ANAVEX®2-73

**Key Secondary Endpoints**
- MDS-UPDRS
- Sleep function
- Actigraphy
- MoCA
- Other CDR battery measures

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

*Restricted to maintain complete blinding*
Identification (IDN) in Cogstate battery assessed in ANAVEX®2-73 Ph2a AD Study comparable to CDR Continuity of Attention (choice reaction time paradigm)

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<tr>
<th>PDD</th>
<th>CDR battery</th>
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<tr>
<td>AD</td>
<td>Cogstate brief battery</td>
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<th>Power of Attention</th>
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<td>Continuity of Attention</td>
<td>Choice reaction Time</td>
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Cogstate IDN from Baseline

ANAVEX®2-73 Ph2 AD Study - Cogstate IDN Improves within Weeks

Average Delta Reaction time (ms) from Baseline

Weeks from Baseline

Bars: Standard Error
Cogstate IDN: ANAVEX®2-73 Ph2a AD Patients Improve within Weeks vs Standard of Care AD Patients

AIBL-ROCS-AD* cohort as standard of care comparator

ANAVEX®2-73 Phase 2b/3 Alzheimer's Disease Study

**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

**Primary Endpoints**
- ADAS-Cog
- ADCS-ADL
- Safety and tolerability of ANAVEX®2-73

**Key Secondary Endpoints**
- CDR-SB
- Structural and functional MRI
- Biomarkers: Abeta40/Abeta42, 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
ANAVEX®2-73 Phase 2 Rett Syndrome Study

**Primary and Secondary Endpoints**
- Safety and tolerability of ANAVEX®2-73
- Behavioral symptoms
- Sleep function
- Seizure activity

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

**RTT patient population**
- Diagnosis of confirmed RTT
- Patients age >18
- DNA and RNA sequencing

**Randomization 3:2**
- ANAVEX®2-73 Active dose*
- Placebo

**N=15**

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*Restricted to maintain complete blinding*
Investment Highlights

- **Pursuing Large Markets By Applying Precision Medicine to Develop Treatments For Neurodegenerative and Neurodevelopmental Diseases With High Unmet Needs** – Novel genomic biomarker-driven programs to treat small patient populations such as Rett syndrome* as well as major public health burdens such as Parkinson’s and Alzheimer’s disease.

- **Strong IP Position Around Novel Mechanism of Action** – Lead product candidate, ANAVEX®2-73, is an orally available Sigma-1 receptor agonist that has been shown to restore homeostasis. (Composition of matter patent protection to 2033).

- **Compelling Human Data** – ANAVEX®2-73 has undergone a Phase 2a trial in Alzheimer’s disease with favorable safety and exploratory efficacy results through 148 weeks.

- **Precision Medicine Improves Chance of Clinical Success** – Testing for genomic biomarkers has demonstrated improved clinical response to ANAVEX®2-73 in Alzheimer’s patients carrying wild-type (WT) SIGMAR1 and COMT genes.

- **Value-Creating Catalysts** – Clinical updates from Phase 2 Parkinson’s disease dementia study, Phase 2b/3 Alzheimer’s disease and Phase 2 Rett syndrome studies anticipated in 2019. Clinical data publications and additional indications to be announced in 2019.

- **Sufficient Cash to Achieve Key Milestones** – Cash on hand and non-dilutive cash from Australian government for Alzheimer’s study, and from Rettsyndrome.org for Rett syndrome study.

*FDA granted ANAVEX®2-73 Orphan Drug Designation (ODD) for Rett syndrome*
Anavex Life Sciences Expertise

### Management Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
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<td>Chief Medical Officer</td>
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<td>Stephan Toutain, MS, MBA</td>
<td>SVP of Operations</td>
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<td>Emmanuel O Fadiran, RPh, PhD</td>
<td>SVP of Regulatory Affairs</td>
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<tr>
<td>Daniel Klamer, PhD</td>
<td>VP of Business Development &amp; Scientific Strategy</td>
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### Scientific Advisory Board Members

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<tr>
<th>Name</th>
<th>Institution</th>
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<td>UPMC</td>
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<td>Ottavio Arancio, MD, PhD</td>
<td>Columbia University Medical Center</td>
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<td>Dag Aarsland, MD, PhD</td>
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<td>Tanguí Maurice, PhD</td>
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