SAFE HARBOR

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New Therapeutic Strategy to Treat CNS Disorders

• 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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Disease</th>
<th>Duration</th>
<th>Participants</th>
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<tbody>
<tr>
<td>PHASE 2</td>
<td>PARKINSON’S DISEASE DEMENTIA</td>
<td>14 WEEK STUDY</td>
<td>120</td>
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<tr>
<td>PHASE 2b/3</td>
<td>ALZHEIMER’S DISEASE</td>
<td>48 WEEK STUDY</td>
<td>450</td>
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<td>PHASE 2</td>
<td>RETT SYNDROME**</td>
<td>7 WEEK STUDY</td>
<td>15</td>
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<tr>
<td>PHASE 2a</td>
<td>ALZHEIMER’S DISEASE</td>
<td>208 WEEK STUDY</td>
<td>32</td>
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- 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
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.
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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Sigma-1 receptor activation by ANAVEX2-73 enhances autophagy in *C. elegans*
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

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

Activities of Daily Living (ADCS-ADL)* Slope 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

*p = p-value of Mann–Whitney U test

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

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**

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**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)

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![Graph showing comparison between high and low concentration cohorts](image)

(p < 0.0001)

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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.

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* Alzheimer’s Disease Cooperative Study Group - Activities of Daily Living Inventory (ADCS-ADL)

Source: M Afshar et al., CTAD 2018
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

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.

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

Source: M Afshar et al., CTAD 2018

* Mini Mental State Examination (MMSE)
Precision Medicine
PHARMACOLOGY + GENOMIC = PHARMACOGENOMICS

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

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Patient Selection with Biomarker Increases Probability of Success

<table>
<thead>
<tr>
<th>Phase II to Phase III</th>
<th>Phase III to NDA/BLA</th>
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<tbody>
<tr>
<td>Without Biomarkers</td>
<td>28%</td>
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<tr>
<td>With Patient Selection Biomarkers</td>
<td>46%</td>
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<td>55%</td>
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• 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®
- 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

... and validated at 148 weeks
Clinical Studies:
• Parkinson’s Disease Dementia (PDD)
• Alzheimer’s Disease (AD)
• Rett Syndrome (RTT)
Pipeline Addresses both Rare and Large Indications

Anavex pipeline and precision genetic medicine approach address unmet needs of neurodevelopmental and neurodegenerative diseases

Alzheimer’s Disease (AD)
~5,700,000 patients

Parkinson’s Disease (PD)
~1,000,000 patients

Rett Syndrome (RTT)
~11,000 patients

Additional Indications
Frontotemporal dementia (FTD) and others

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

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
Primary Endpoint ‘CDR Continuity of Attention’ of PDD ANAVEX®2-73 Ph2 Study: Confirmed Beneficial Effect in Previous Ph2a AD Study

Identification (IDN) in Cogstate battery assessed in ANAVEX®2-73 Ph2a AD Study comparable to CDR Continuity of Attention (choice reaction time paradigm)
ANAVEX®2-73 Ph2 AD Study - Cogstate IDN Improves within Weeks

Cogstate IDN from Baseline

Average Delta Reaction time (ms)

Cogstate IDN

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: 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

Randomization 1:1:1

ANAVERX®2-73

High dose

Medium dose

Placebo

48 WEEK STUDY

# Restricted to maintain complete blinding

# Pre-specified endpoints restricted to maintain complete blinding
ANAVEX®2-73 Phase 2 Rett Syndrome Study

N=15

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

Randomization 3:2

ANA®VEX®2-73 Active dose*

Placebo

7 WEEK 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

N=15 RTT patient population

Randomization 3:2

ANA®VEX®2-73 Active dose*

Placebo

7 WEEK 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

* 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>
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<th>Title</th>
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<tbody>
<tr>
<td>Christopher U. Missling PhD</td>
<td>President &amp; CEO</td>
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<tr>
<td>Walter E Kaufmann, MD</td>
<td>Chief Medical Officer</td>
</tr>
<tr>
<td>Stephan Toutain, MS, MBA</td>
<td>SVP of Operations</td>
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<tr>
<td>Emmanuel O Fadiran, RPh, PhD</td>
<td>SVP of Regulatory Affairs</td>
</tr>
<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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<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tr>
<td>Jeffrey Cummings, MD</td>
<td>Cleveland Clinic</td>
</tr>
<tr>
<td>Harald Hampel, MD, PhD</td>
<td>UPMC</td>
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<tr>
<td>Ottavio Arancio, MD, PhD</td>
<td>Columbia University Medical Center</td>
</tr>
<tr>
<td>Andrew Cole, MD</td>
<td>Harvard Medical School</td>
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<tr>
<td>Daniel Weintraub, MD</td>
<td>Perelman School of Medicine</td>
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<td>Paul Aisen, MD</td>
<td>USC University of Southern California</td>
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<td>Norman Relkin, MD, PhD</td>
<td>Weill Cornell Medicine</td>
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<tr>
<td>Jacqueline French, MD</td>
<td>NYU</td>
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<tr>
<td>Dag Aarsland, MD, PhD</td>
<td>King's College London</td>
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<td>Tanguy Maurice, PhD</td>
<td>Université de Montpellier</td>
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