Safe Harbor

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Anavex utilizes precision genetic 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).
### Summary

<table>
<thead>
<tr>
<th>Focus</th>
<th>Finding effective treatments for neurodevelopmental and neurodegenerative diseases, areas of high unmet need</th>
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<tr>
<td>Mechanism</td>
<td>Sigma-1 Receptor (S1R) targeting cellular homeostasis</td>
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<tr>
<td>Approach</td>
<td>Applying precision medicine to CNS</td>
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ANAVEX®2-73, orally available S1R agonist with strong IP (COM 2033) and has completed a successful Phase 2a clinical trial for Alzheimer’s disease

Utilizing patient genomic analysis as well as clinical PK/PD data to effectively incorporate into three clinical trials initiating in 2018:

- Phase 2 clinical trial in **Rett syndrome** – IND filed
- Phase 2 clinical trial in **Parkinson’s disease dementia**
- Phase 2/3 clinical trial in **Alzheimer’s disease**

*FDA granted ANAVEX®2-73 Orphan Drug Designation (ODD) for Rett syndrome*
Identification of Gene “Signature” from ANAVEX®2-73 Patients

ANAVEX®2-73 Phase 2a clinical trial

Corresponding approach to oncology precision medicine

NOW:

ANAVEX®2-73 treatment

Genetic signatures of the strongest responders to ANAVEX®2-73
Portfolio of Compounds Varying in Sigma-1 Receptor Binding Activities

<table>
<thead>
<tr>
<th>CANDIDATE</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
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<td>ANAVEX®2-73</td>
<td>*RETT SYNDROME</td>
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<td>ANAVEX®3-71 (AF710B)</td>
<td>*FRONT. DEMENTIA (FTD)</td>
<td>ALZHEIMER’S DISEASE</td>
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<td>ANAVEX®1-41</td>
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<td>VISCERAL PAIN</td>
<td>ACUTE &amp; NEUROPATHIC PAIN</td>
<td>ACUTE &amp; NEUROPATHIC PAIN</td>
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<td>CANCER (PANCREAS)</td>
<td>CANCER (PANCREAS)</td>
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* = Orphan Drug Designation by FDA
ANAVEX®2-73 is a S1R Agonist and Activates the Sigma-1 Receptor

S1R is an integral membrane protein involved in cellular homeostasis which targets restoration of neuroplasticity and cellular stress response\(^2,3\)

Endogenous S1R agonists activate the Sigma-1 Receptor in situation of cellular stress

Enhancing activation of endogenous S1R agonist with ANAVEX®2-73 remedies disease symptoms and underlying pathophysiology

S1R deficiency accelerates disease progression\(^1\)

Sigma-1R Agonists MoA: Restoring Homeostasis

Glembotski et al., Circulation Research. 2007;101:975-984
Endoplasmic Reticulum (ER) - Mitochondrial Axis Membrane (MAM) is Key Area Involved in Neurodegenerative Diseases

Common Cellular Processes in Neurodegenerative Diseases

Sigma-1 Receptor Restores MAM Association

- Normally quiescent, S1Rs become activated during periods of cellular stress
- ANAVEX®2-73 is well-positioned to enhance this response

*Miller et al. Trends Neurosci., 2016; Lahmy et al. Neuropsychopharmacol., 2013*
Sigma-1R Translocates to Play a Role in Gene Transcription: Functional Connection Between Cell Body and DNA

The Sigma-1R is mainly expressed in the cell body at the MAM.

Upon Activation, the S1R is relocated to the nuclear envelope (NE), where it is involved in controlling gene transcription.

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Overview ANAVEX®2-73 Clinical Trials

ANAVEX®2-73-001 Study:
- Randomized, double-blind, placebo-controlled Phase 1 (oral)
- Single ascending dose (SAD)
- 22 healthy subjects

ANAVEX®2-73-002 Study#:
- Randomized, Phase 2a (iv/oral)
- 32 mild-to-moderate AD patients
- MMSE baseline 16-28 (mean 21)
- Adaptive trial with Population PK
- Bioavailability, dose finding (PART A), and exploratory efficacy with 52 week open-label extension (PART B)

ANAVEX®2-73-003 Study##:
- 208-week extension study after PART B

Initiation of subsequent randomized, double-blind, placebo-controlled ANAVEX®2-73 studies:
- Rett syndrome
- Parkinson’s disease dementia
- Alzheimer’s disease

Population PK, i.e. non-linear mixed effect (NLME) modeling, non-compartmental analysis and formal concept analysis (FCA) and both RNA and whole exome DNA genome sequencing using Illumina HiSeq 2500 Next Generation Sequencing (NGS) technology

Preparation underway

ClinicalTrials.gov Identifier: #NCT02244541; ##NCT02756858
Using Precision Medicine to Increase Clinical Trial Success Rate

- All Patients
- Biomarker that Defines Patient Population
- Pre-specified Patients
- Treatment

Increased Probability of Success

Patient Selection with Biomarker Increases Probability of Success:

- +64%
- +38%

Increased Probability with Patient Selection Biomarkers

- Without Biomarkers
- With Patient Selection Biomarkers

Rett Syndrome (RTT): A Devastating Monogenic Disorder

Rett syndrome (RTT) is caused by spontaneous (de novo) mutation in the MECP2 gene located on the X chromosome.

For males the gene mutation is lethal since males have only one X chromosome (females have two X chromosomes).

Affects approximately 16,000 females in U.S., 1:10-15K females worldwide.

For females who survive infancy, RTT leads to a deficiency in motor function, cognitive impairment and seizures.

There are no approved treatments for RTT.

FDA granted ANAVEX® 2-73 Orphan Drug Designation for Rett syndrome.
MECP2 is Mutated in Rett Syndrome Leading to Loss of Neuronal Function and Loss of BDNF

- MECP2 is a calcium dependent gene, affects dendritic spine development and necessary for other gene expressions, including BDNF
- Loss of MECP2 function alters excitatory/inhibitory synaptic balance
- MECP2 function required for neuronal survival, synaptic development and plasticity
- BDNF is an important neuronal plasticity-related gene affected by loss of MECP2

Healthy Individual

Rett Syndrome Individual

Beneficial effect of ANAVEX®2-73: Restores calcium homeostasis

ANAVEX® 2-73 fully restores BDNF expression levels in the hippocampus in the Fmr1 KO mouse model (p<0.05, KO vehicle vs. KO ANAVEX® 2-73)
ANAVEX® 2-73 Significantly Reduces Impairment in Mutated MECP2 Rett Syndrome Mouse Model

Mice treated with ANAVEX 2-73 (30 mg/kg) clasped less than vehicle-treated mutant mice (p<0.05 at 8 and 12 weeks)

*Presented at 2016 Epilepsy Pipeline Conference, 2016 Rett Syndrome Symposium*
Significant Improvement in Multiple Movement Impairments

**Rotarod**

- **Motor Coordination** and exercise capacity are assessed: ANAVEX®2-73 treated mice took significantly more time to fall off rod & fell at higher speeds compared to vehicle-treated mutant mice.

**Neurocube**

- Platform that employs computer vision to detect changes in gait geometry and gait dynamics: Gait, Correlation, Body Motion demonstrate significant improvement.

**Startle**

- Wild type (WT) mice have a higher startle response compared to impaired mice: ANAVEX®2-73 treated mice showed a significant increase in startle response compared to vehicle-treated mutant mice.

<table>
<thead>
<tr>
<th></th>
<th>WT vehicle v. Het vehicle</th>
<th>Het vehicle v. Het AV2-73, 10 mg/kg</th>
<th>Het vehicle v. Het AV2-73, 30 mg/kg</th>
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<td>Overall</td>
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<td>90, p=0</td>
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<td>GAIT</td>
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<td>63, p &gt; 0.09</td>
<td>69, p &lt; 0.05</td>
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<td>Paw Features</td>
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<td>91, p &lt; 0.001</td>
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<td>52, p &gt; 0.78</td>
<td>55, p &gt; 0.56</td>
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<td>Correlation</td>
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<td>53, p &gt; 0.66</td>
<td>76, p &lt; 0.005</td>
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<td>56, p &gt; 0.40</td>
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<tr>
<td>Body Motion</td>
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<td>71, p &lt; 0.02</td>
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<td>60, p &gt; 0.20</td>
<td>81, p &lt; 0.003</td>
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<td>Paw Positioning</td>
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<td>84, p &lt; 0.0001</td>
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<td>53, p &gt; 0.57</td>
<td>57, p &gt; 0.36</td>
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Presented at 2016 Epilepsy Pipeline Conference, 2016 Rett Syndrome Symposium
ANAVEX®2-73 Phase 2 Rett Syndrome Study Design

Randomized, Double-Blind, Placebo-Controlled Study of ANAVEX®2-73

- **Baseline Observation Period**: N<90
- **Randomization to 1 of 3 arms**
- **Titration Treatment Period**: AV 2-73: High dose, Placebo
- **Full Treatment Period**: AV 2-73: Low dose, AV 2-73: High dose, Placebo

12 Weeks Voluntary Open Label
Parkinson’s Disease Dementia (PDD): A Devastating Dementia Disorder

- Parkinson's disease is a fairly common neurological disorder in older adults, estimated to affect nearly 2 percent of those older than age 65.
- About 1 million Americans have Parkinson's disease.
- It is estimated that 50 to 80 percent of those with Parkinson's disease eventually experience Parkinson's disease dementia.
- The brain changes caused by Parkinson's disease begin in a region that plays a key role in movement.
- As Parkinson's brain changes gradually spread, they often begin to affect mental functions, including memory and the ability to pay attention, make sound judgments and plan the steps needed to complete a task.

www.alz.org/dementia/parkinsons-disease-symptoms
ANAVEX®2-73 Targets MAM to Reduce Cellular Damage: How it May Work in Parkinson’s Pathogenesis

- A specific type of phosphorylated α-syn aggregate leads to neurotoxicity in PD
- These aggregates co-localize with MAM
- They induce mitochondrial toxicity, oxidative and energetic stress, mitochondrial fragmentation and mitophagy

Grassi et al., PNAS March 13, 2018. 115 (11) E2634-E2643
Parkinson’s Disease Model: ANAVEX®2-73 Significantly Improves Motor Behaviors

- ANAVEX®2-73 was evaluated in the 6-OHDA Parkinson’s disease model
- ANAVEX®2-73 significantly improves motor behaviors compare to a double-blind control group (saline)
  - (A) Spontaneous rotation activity
  - (B) Cylinder test of forelimb use asymmetry
  - (C) Stepping test of forelimb use asymmetry
ANAVEX®2-73 Normalizes Pathophysiological Biomarkers

ANAVEX®2-73 reduces microglia over-activation
ANAVEX®2-73 significantly decreased the expression of CD68 (marker of activated microglia) in the substantia nigra

ANAVEX®2-73 restores dopaminergic neurons
ANAVEX®2-73 significantly increases tyrosine-hydroxylase fibers (marker of dopaminergic neurons) in the striatum

These results support the hypothesis that pharmacological stimulation of the sigma-1 receptor may have both disease-modifying and symptomatic effects in Parkinson’s disease

Cenci et al., presented at World Parkinson Congress 2016
ANAVEX®2-73-003 Alzheimer’s Disease Study: Continued Favorable Safety and Tolerability through 109 weeks

**PART A**
002 Study

1. Estimate the maximal tolerated dose (MTD)
2. Explore a dose-effect relationship
3. Estimate the bioavailability of ANAVEX 2-73

**PART B**
002 Study

1. Establish continued safety and tolerability of ANAVEX 2-73
2. Explore a dose-effect relationship

**003 Study**

Establish continued safety and tolerability of ANAVEX 2-73

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ClinicalTrials.gov Identifier: #NCT02244541; ##NCT02756858
ANAVEX®2-73 Primary and Secondary Endpoints Met in Phase 2a Clinical Trial of Mild-to-Moderate Alzheimer’s Patients

- Phase 2a results demonstrate a favorable safety, bioavailability, dose-response curve and tolerability/risk profile at doses between 10mg and 50mg of oral daily ANAVEX®2-73
- Primary endpoints met with favorable safety and tolerability
- Secondary endpoints met with supportive exploratory biomarker, cognition and function measures correlating
  - Dose-response relationship was statistically significant to affect MMSE-Δ and EEG/ERP-Δ scores with MMSE-Δ ($p=0.0285$) and EEG/ERP-Δ ($p=0.0168$), respectively

Macfarlane, presented at CTAD 2016
The most common adverse event (AE): mild dizziness
- When patients were first dosed with highest dose
- Was transient and reversible
- Consistent with Blood Brain Barrier (BBB) penetration
- 98% of all AEs were mild or moderate and reversible with 76% being Grade 1
- 2% were not drug-related Grade 3
- There were no Grade 4 and 5 events

AE profile similar to that of healthy volunteer Phase 1 data
- No differences in blood pressure or resting heart rate
- Clinical laboratory parameters, vital signs, and 12-lead ECG did not show any clinically relevant or dose-dependent changes

Voges et al., presented at CNS Summit 2014; Macfarlane, presented at CTAD 2016
Secondary Endpoints: High ANAVEX® 2-73 Concentration linked to Consistent Improved Response Across All Analytes and Periods

ANAVEX® 2-73 shows a consistent response across the 3 different times frames:

- **Part A1 [0-24h]**: Immediate response
- **Part A2 [24-264h]**: Short-term response
- **Part B [52 weeks]**: Long-term response

ANAVEX® 2-73 concentration

- **Part A1 [0-24h]**: Immediate response
- **Part A2 [24-264h]**: Short-term response
- **Part B [52 weeks]**: Long-term response

Implies

- MMSE Improvement
- ADCS-ADL Improvement

Afshar et al., presented at CTAD 2017
Systematic exploration of the full data matrix using KEM® demonstrates consistent concentration-response relationship for 6 main exploratory endpoints: cognition, function and biomarker (MMSE, ADCS-ADL, EEG/ERPs).

97% Consistency: MMSE, ADCS-ADL and EEG/ERPs: Identified relations show that high dose (concentration) is linked to improved response and low dose (concentration) to poor response.

Afshar et al., presented at CTAD 2017
Relation between ANAVEX® 2-73 Concentration and MMSE

An increase of MMSE during 57 weeks is a rare event. A patient receiving a higher concentration of ANAVEX2-73 has a 2.1-fold chance of improving its MMSE.
An increase of ADCS-ADL during 57 weeks is a rare event. A patient receiving a higher concentration of ANAVEX2-73 has a 1.6-fold chance of improving its ADCS-ADL concentration.
Patient Cohort with Cognitive and Functional Improvements at 57 Weeks:

- MMSE and ADCS-ADL remained steady over 27 months (109 weeks)

- Patients with milder disease stage (baseline MMSE >20) tended to respond better to ANAVEX®2-73 than patients with more advanced disease stage (baseline MMSE <20)

- Cohort displayed highest concentrations of ANAVEX®2-73
Comparison to historical control subjects with mild-to-moderate AD with comparable MMSE baseline, assigned to the placebo arm from pooled cohort study conducted by the Alzheimer Disease Cooperative Study Group, age adjusted.

1.8 MMSE points improvement to historical control (SoC)\# at week 57 (p=0.0164)

4 ADCS-ADL points improvement to historical control (SoC)\# at week 57 (p=0.0186)
ANALEX®2-73 appears to have a favorable safety profile and to be generally well tolerated

ANALEX®2-73 has demonstrated efficacy in the clinic as well as in multiple preclinical disease models validating the Sigma-1R mechanism of action

Genetic Signatures for those who respond best to ANAVEX®2-73 have been determined

These signatures can be applied to neurological indications beyond Alzheimer’s disease, such as Rett syndrome and Parkinson’s disease dementia

Three clinical trials will be initiated in 2018 for Rett syndrome, Alzheimer’s disease and Parkinson’s disease dementia

Anavex has enough cash for 2 years
Financial Position and Near Term Catalysts

- Cash (as of March 31, 2018): $25.7M; No debt
- The company is well capitalized to achieve clinical readouts

- Orphan Drug Designations granted for the following indications: Rett syndrome, Infantile spasms and Frontotemporal dementia
- Phase 2a – Reported 109 week data at CTAD scientific meeting
- Phase 2a – PK/PD data CTAD scientific meeting
  - Phase 2 clinical trial in Rett syndrome – IND filed
  - Phase 2 clinical trial in Parkinson’s disease dementia (PDD)
  - Phase 2/3 clinical trial in Alzheimer’s disease

*Ongoing in-licensing/out-licensing review to optimize value of pipeline*
# Anavex Life Sciences Expertise

## Management Team

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<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Affiliation</th>
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<tr>
<td>Christopher U. Missling, PhD</td>
<td>President &amp; CEO</td>
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<tr>
<td>Emmanuel O. Fadiran, RPh, PhD</td>
<td>SVP of Regulatory Affairs</td>
<td>FDA, University of Strathclyde, Aventis</td>
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<tr>
<td>Stephan Toutain, MS, MBA</td>
<td>SVP of Operations</td>
<td>NOVARTIS, TESARO, Alexion</td>
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<tr>
<td>Paul Vancutsem, DVM, PhD</td>
<td>VP of Preclinical Development</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>
<td>Jeffrey Cummings, MD</td>
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<td>Cleveland Clinic</td>
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<tr>
<td>Paul Aisen, MD</td>
<td></td>
<td>USC University of Southern California</td>
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<tr>
<td>Harald Hampel, MD, PhD</td>
<td></td>
<td>UPMC, Weill Cornell Medicine</td>
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<tr>
<td>Norman Relkin, MD, PhD</td>
<td></td>
<td>NWU, Perelman School of Medicine, University of Pennsylvania</td>
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<td>Abraham Fisher, PhD</td>
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<tr>
<td>Jacqueline French, MD</td>
<td></td>
<td>NYU, Harvard Medical School</td>
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<td>Andrew Cole, MD</td>
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<td>Tanya Simuni, MD</td>
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<td>Daniel Weintraub, MD</td>
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<td>Tangui Maurice, MD</td>
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NASDAQ: AVXL
Comprehensive Phase 2a Patient Characterization to Identify Actionable Phase 2/3 Clinical Trial Parameters

Ariana’s KEM® data analytics:
- Systematic integrated analysis of all combined parameters
- Identification of actionable parameters
- Design of an optimized Phase 2/3 clinical trial

FGS: Full Exome Genomic Sequencing
Example of a Gene “Signature”: BDNF Polymorphism *Val66met*

BDNF Val66met Polymorphism implicated in Neurodevelopmental and Neurodegenerative Disorders

- **Higher seizure frequency and severity of Rett syndrome symptoms**
  
- **1/3 of all patients have this mutation**

- **Accelerated cognitive decline and increased Aβ accumulation in Alzheimer’s disease**

Sources: 1) Zeev BB et al Neurology. 2009 Apr 7;72(14):1242-7  
Example of a Targeted Genomic-Driven Clinical Trial Approach in Alzheimer’s Disease

Sporadic Alzheimer’s disease
based on evidence that genomic
dysfunction is a conserved Alzheimer’s
disease-causing mechanism

Other genetic drivers
of genetic dysfunction in
Alzheimer’s disease
(incl. Tau and Amyloid beta)

E.g. BDNF mutation
in Alzheimer’s disease

6 million patients

2 million patients

Low

High

U.S. Patient Prevalence

DIRECT  
Scientific Rationale for Genomic Pre-specification

INDIRECT

Boots EA et al., Neurology. 2017 May;88(22):2098-210
Brookmeyera R et al., Alzheimer’s & Dementia. 2017 in press
Patient Genomic Analysis - Number of Associated Genetic Mutations Linked to Alzheimer’s Disease have Increased

Identification of disease-relevant variants
- CR1: copy number variation
- CLU: rare variants in β chain
- BIN1: indel variant
- CD33: splicing variant
- ABCA7: loss-of-function mutations
- SORL1: rare pathogenetic variants

Identification of genes in risk loci
- For example: Transcriptomics, Methytopomics, Epigenomics, Proteomics, Drosophila screenings

Risk profiling
- Clinical subdivision of patients with Alzheimer’s disease

In-vivo and in-vitro screening assays
- For example: Pluripotent induced cell lines, Drosophila screenings, Transcriptomics

Contribution of gene variants to the development of Alzheimer's disease has clinical implications, including enhancing diagnostic accuracy and providing targets for pre-specified drug development
Rare Disease Drug Discovery Approach: Higher Success Rate of Clinical Trials Expected

Genomic insight from Alzheimer’s patients treated with ANAVEX®2-73

Alzheimer’s is a mix of pathologies

‘Rare disease’ drug discovery approach

Focus first on ‘prespecified’ patient population

Smaller clinical trial

Lower trial costs

Higher clinical trial success expected

Learning from progress against cancer

- Driven by genomic insight
- Today two-thirds of those diagnosed with cancer can expect to live at least another five years
Shift to Use Precision Medicine to Break the Notion That Alzheimer’s is a Single Disease

- Researchers are starting to combine genetics with lessons learned from the failed β amyloid-based clinical trials, not only to find new targets but also to stratify patients.
- The view now is that the disease is more like cancer, a heterogeneous condition that can be kicked off by a variety of cellular mechanisms.
- The key is to identify those mechanisms and match them to the right patients.

Alzheimer’s disease research has moved away from β amyloid, tau, and cholinergic targets and shifted toward other targets.

Examples of Continued Improvements and Reported Events ‘Therapeutic Response’ during 57 Weeks

<table>
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<tr>
<th>PATIENT</th>
<th>EVENTS: THERAPEUTIC RESPONSE UNEXPECTED</th>
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<tr>
<td>101001</td>
<td>MORE ALERT REGARDING SURROUNDINGS</td>
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<td>101002</td>
<td>FEELS MUCH HAPPIER MAKING JOKES</td>
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<td>101003</td>
<td>MUCH HAPPIER WHEN ATTENDING CLINIC APPTS AND ENJOYS MAKING JOKES AND ENGAGES WELL IN CONVERSATION</td>
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<td>101004</td>
<td>BETTER HAND COORDINATION. CALMER AND MORE COMMUNICATIVE</td>
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<td>101006</td>
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</tr>
<tr>
<td>101007</td>
<td>ABILITY TO PLAY THE PIANO AND READ MUSIC NOTES AT ABOUT 9 MONTHS INTO TRIAL. SHE USED TO PLAY THE PIANO AT AGE 5 AND LOST HER ABILITY PRE-ALZHEIMER TRIAL</td>
</tr>
<tr>
<td>101010</td>
<td>ABLE TO FOLLOW PLOT WHEN WATCHING MOVIES WHEREAS PREVIOUSLY COULD NOT</td>
</tr>
<tr>
<td>101010</td>
<td>MORE COMPASSION FOR CHILDREN</td>
</tr>
<tr>
<td>101011</td>
<td>WIFE THINKS PATIENT IS A BIT MORE CHEERFUL</td>
</tr>
<tr>
<td>101013</td>
<td>ABLE TO DO MUCH MORE HOUSEWORK THAN BEFORE</td>
</tr>
<tr>
<td>101013</td>
<td>MORE DRIVEN AND UPBEAT LESS ANXIOUS ACCORDING TO CARER</td>
</tr>
<tr>
<td>101014</td>
<td>AN INTERNATIONAL ARTIST WHO RESUMED HER PAINTING ABILITIES AND NOW HAVING AN EXHIBITION IN NOV 2016. WRITTEN A 3 PAGE LETTER TO LONG LOST BROTHER</td>
</tr>
<tr>
<td>101015</td>
<td>PLAYING MORE GOLF NOW BY HIMSELF. MORE CONFIDENT AT GOING OUT BY HIMSELF</td>
</tr>
<tr>
<td>101017</td>
<td>ENJOYED HER TRIP TO BELGIUM - TALKS ABOUT SOME BITS OF HER TRIP</td>
</tr>
<tr>
<td>102001</td>
<td>IMPROVED ENGAGEMENT WITH FAMILY/FRIENDS/OUTSIDE WORLD</td>
</tr>
<tr>
<td>102008</td>
<td>IMPROVEMENT IN MOOD</td>
</tr>
<tr>
<td>102010</td>
<td>FEELING GREAT - IMPROVEMENT IN COGNITION AND MOOD, BALANCE AND GAIT HAS IMPROVED</td>
</tr>
<tr>
<td>103001</td>
<td>PATIENT REMEMBERING SOMETHING HE WOULDN'T HAVE PREVIOUSLY</td>
</tr>
</tbody>
</table>
## HAM-D: Reduction of Insomnia, Anxiety and other Symptoms

<table>
<thead>
<tr>
<th>Improved Items of HAM-D</th>
<th>Scored Improvement Count</th>
<th>in [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>8</td>
<td>29%</td>
</tr>
<tr>
<td>Work and activities</td>
<td>6</td>
<td>21%</td>
</tr>
<tr>
<td>Anxiety (psychic and somatic)</td>
<td>5</td>
<td>18%</td>
</tr>
<tr>
<td>Agitation</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td>Depressed</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td>Insight</td>
<td>3</td>
<td>11%</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>Loss of libido or other genital symptoms</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>Guilt</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Hypochondriasis, Loss of libido or other genital symptoms presented as mean ± SEM.

*p<0.05

![Graph showing HAM-D Mean ± SEM](image)
ANA VEX® 2-73: Robust Correlation of Cognition, Function and Behavior Response

**ANA VEX® 2-73 Response cluster in a homogenous manner: Consistent response across multiple domains**

- Principal component analysis of the Δ sub-scores between week 31 and baseline for MMSE (MM), ADCS-ADL (AD), and HAM-D (HA)
  - Good = increasing MM & AD, decreasing HA
  - Bad = decreasing (MM & AD), increasing HA
1. ERP peak measures (P300): fundamental measures of synaptic network performance
2. ERP target detection task measures: direct measures of attention, speed of brain processing, and simple behavioral performance
4. Psychometric measures (MMSE): cognitive measures
5. Behavioral measures (ADCS-ADL): behavioral measures

Each of these metrics measures a higher level of brain function
Comprehensive Pre-Specified PK Sampling Protocol during Phase 2a Study

Part A: IV (3/5 mg), Oral (30/50 mg)

Part B: Oral (10 to 50 mg)

**Measures (hours):**
- 0, 1, 2, 6, 8, 12, 18, 24, 48, 72, 120, 192, 264

**Daily intake:**
- Baseline
- Day 12
- Day 24
- Day 36 (Week 5)
- Week 12
- Week 26
- Week 36
- Week 48
- Week 57

**Period 1:**
- Wash out
- Period 2

Part B: All patients on ANAVEX®2-73 oral daily doses of 10mg, 20mg, 30mg, 50mg according to pre-specified adaptive trial design implemented during Part A
Clearance of ANAVEX® 2-73 Independent of given Dose

Total average drug exposure over time

$\text{AUC}_{(0 \text{ to } \infty)}$

Area Under the Curve, 0-24h

ANAVEX2-73 Treatment

A: 3 mg, iv
B: 5 mg, iv
C: 30 mg, oral
D: 50 mg, oral

\[
\begin{align*}
\text{A:} & \quad \frac{44.55}{66.58} = 0.67 \\
\text{B:} & \quad \frac{127.34}{185.75} = 0.68 \\
\end{align*}
\]
Confirmed Reliable Inter-Individual Variability (Dispersion) for the ANAVEX2-73 Phase 2a Study with 32 Patient Cohort

- Evaluation of the dispersion index of all the 32 patient of the Phase 2a reveals that above any random sample of 16 patients, the dispersion index is maintained at a fixed level with the narrowest confidence intervals.

- That is confirmation that the sample of 32 patients of the Phase 2a provides reliable information regarding dispersion and as such allows for meaningful predictions for larger populations.
Alzheimer Disease Progression: Comparable cognitive decline in open-label studies as in placebo-controlled studies

Progressive decline in cognition:
Open-label study with SoC#

Progressive decline in cognition:
Double-blind placebo-controlled study with SoC##

- Open-label and double-blind controlled studies equivalent for long-term cognition changes

## Figure adapted from Doody RS et al (2013) N Engl J Med; 369:341-350 (SoC = Ach inhibitors and/or memantine)
ANAVEX®2-73: Dose-Dependent Anti-Seizure Effects

Significant Seizure Reduction with ANAVEX®2-73 in Angelman Seizure Model ANAVEX 2-73 (10 mg/kg ip dosed daily for 14 days)

**Significant Seizure Reduction with ANAVEX®2-73 in both MES and PTZ-Induced Seizure Models**

<table>
<thead>
<tr>
<th>Dose (mg/kg, p.o.)</th>
<th>% of Seizure Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0%</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>20% (p.o.)</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>80% (p.o.)</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>100% (p.o.)</td>
</tr>
</tbody>
</table>

MES-induced convulsions

PTZ-induced convulsions

Significant Reduction Number of Spasms with Pre-treated ANAVEX®2-73 in Infant Rat Model (30mg/kg ip)

- **p<0.001**
- **p=0.0065**

Presented at AES Meeting 2015, *results have been confirmed by the ETSP screening program; Presented at AEDD 2017*
Positive Preclinical Data in Parkinson’s Disease

✓ At all doses tested ANAVEX®2-73 reduced novelty/stress-induced activity while basal activity levels were not significantly affected

✓ Mouse behavioral and motor patterns were completely normal; no signs of dystonia or stereotypic behaviors were observed

✓ Chronic treatment with ANAVEX®2-73 (0.3 & 1.0 mg/kg) to 6-OH-DA-lesioned mice yielded a general motor recovery, accompanied by improved dopamine neuronal survival, and reduced microglia activation in the substantia nigra

These results support the hypothesis that pharmacological stimulation of the S1R may have disease-modifying effects in parkinsonian disorders, and identify ANAVEX®2-73 as a suitable investigational drug for these indications
Critical review

Role of sigma-1 receptors in neurodegenerative diseases

Linda Nguyen a, b, c, Brandon P. Lucke-Wold d, Shona A. Mookerjee e, John Z. Cavendish d, Matthew J. Robson f, Anna L. Scandinaro a, b, c, Rae R. Matsumoto a, b, c, e, f

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Review Article

Roles of sigma-1 receptors in Alzheimer’s disease

Jia-Li Jin*, Min Fang*, Yan-Xin Zhao, Xue-Yuan Liu

Department of Neurology, Shanghai Tenth People’s Hospital, Tongji University, School of Medicine, China. *Equal contributors.

Received February 4, 2015; Accepted April 3, 2015; Epub April 15, 2015; Published April 30, 2015
The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems

Tsung-Ping Su,¹,* Tzu-Chieh Su,¹ Yoki Nakamura,¹ and Shang-Yi Tsai¹

The sigma-1 receptor (Sig-1R) is an endoplasmic reticulum (ER) protein that resides specifically in the mitochondria-associated endoplasmic reticulum (ER) membrane (MAM), an interface between ER and mitochondria. In addition to being able to translocate to the plasma membrane (PM) to interact with ion channels and other receptors, Sig-1R also occurs at the nuclear envelope, where it recruits chromatin-remodeling factors to affect the transcription of genes. Sig-1Rs have also been reported to interact with other membranous or soluble proteins at other loci, including the cytosol, and to be involved in several central nervous system (CNS) diseases. Here, we propose that Sig-1R is a pluripotent modulator with resultant multiple functional manifestations in living systems.
Confirmed Effects of Sigma-1 Receptor Activation ...

✓ Synaptogenesis
✓ Restores Ca\(^{2+}\) imbalance
✓ Reduces Inflammation
✓ Reduces Oxidative stress
✓ Reduces Tau hyper-phosphorylation
✓ Restores Mitochondrial dysfunction
✓ Reduces Protein Misfolding

... effects relevant in both neurodevelopmental as well as neurodegenerative diseases
ANAVEX®3-71 Significantly Decreases Hallmark Pathologies in 3xTg-Alzheimer’s Disease Model

- 10 month-old 3xTg-AD and WT mice
- administered i.p. with tap water or ANAVEX®3-71 (10 mcg/kg/day) for 2 months

**P < 0.01 versus nTg (vehicle); *P < 0.05 versus 3xTg-AD (vehicle)**

Reduced cognitive impairments in Morris water maze

Reduced Abeta pathology {Abeta1-40, Abeta1-42 and Abeta plaques}

Reduced neuroinflammation {activated astrocytes (GFAP) and microglia (Iba-1)}

Reduced tau pathology

Source: Fisher et al., Neurodegenerative Diseases 2015 DOI: 10.1159/000440864
Sigma-1 Receptor’s Role in Regulating Gene Transcription

Sigma-1 receptor agonist such as ANAVEX 2-73

S1R can translocate to the nuclear envelope where it binds emerin that in turn recruits barrier-to-autointegration factor (BAF) and histone deacetylase (HDAC) to form a complex with specific protein 3 (Sp3) which can then suppress the gene transcription of monoamine oxidase B (MAOB)

Adapted from Su, Tsai et al., Proc Natl Acad Sci USA 2015 Nov 24; 112(47):E6562-E65570
Pathological GSK-3β Activation can be Inhibited with ANAVEX®2-73

Injection of Aβ_{25-35} yields a hyper-inflammatory state that is accompanied by increases in GSK-3β phosphorylation in the hippocampus --> An Effect reduced by ANAVEX 2-73

Active GSK-3β has been found in AD brains with neurofibrillary changes and an increase in tau hyperphosphorylation, neurodegeneration and spatial learning deficits. Activated GSK-3β also stimulates the amyloidogenic processing of amyloid precursor protein (APP) by β- and γ-secretases

Possible means to impact underlying pathology of various neurodegenerative and neurodevelopmental disorders

Source: Inestrosa et al. Journal of Molecular Cell Biology (2014), 6, 64–74
RARE DISEASES: MORE COMMON THAN YOU THINK?

Rare diseases are defined as those affecting a small percentage of a population – fewer than 200,000 in the U.S. and fewer than 1 in 2,000 in Europe.

7,000 diseases are classified as rare.

Children account for 50% of rare disease patients.

More than 80% of rare diseases are caused by faulty genes.

More than 300 million people worldwide have a rare disease.

95% of rare diseases have no FDA-approved drug treatment.

In the last 5 years, 1/3 of all new drug approvals were for rare diseases.

On average, it takes most rare disease patients 8 years to receive an accurate diagnosis.

Sources: GlobalGenes.org, PhRMA, NIBR
NEURODEGENERATIVE DISEASES

The global cost of dementia is estimated to be US$ 818 billion

More than 10 Million people are believed to have Parkinson's disease

Economic burden of Alzheimer's disease (AD) care is estimated to reach $1.5 trillion by 2050

An estimated 46 Million people worldwide live with dementia

FDA has approved 4 drugs for AD that only temporarily slow worsening of symptoms for 6-12 months in ~50% of patients