Developing targeted therapies for neurodevelopmental and neurodegenerative diseases

Corporate Presentation
Christopher U Missling, PhD
President & CEO
September 2017

Nasdaq: AVXL
Safe Harbor

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Anavex Investment Highlights

FDA granted Orphan status to ANAVEX™ 2-73 for Rett syndrome; Clinical trial Q4 2017
- Orally available novel sigma-1 receptor (S1R) agonist with strong IP (COM to 2033)
- S1R linked to cellular homeostasis and plasticity relevant to CNS disorders

Safety with signals of efficacy established in Phase 2a Alzheimer’s Disease trial
- 54 subjects treated with ANAVEX 2-73 (Phase 1 and Phase 2a)

Preclinical validation in other orphan and larger CNS diseases
- Portfolio of clinical and preclinical compounds varying in S1R and muscarinic binding kinetics

Partnerships with RettSyndrome.org, Michael J. Fox Foundation, FRAXA, and FAST
- Clinical studies focused on pursuing fastest path to market

Near term clinical advancements
- 4Q 2017 Phase 2a Alzheimer’s disease – PK/PD data
- 4Q 2017 Phase 2 clinical trial in Rett syndrome
- 4Q 2017 Phase 2 clinical trial in Parkinson’s disease
- 4Q 2017 Phase 2/3 clinical trial in Alzheimer’s disease

Cash to fund operations over the next 2 years
# Neurodegenerative and Neurodevelopmental Pipeline Overview

<table>
<thead>
<tr>
<th>CANDIDATE</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANAVEX™ 2-73</td>
<td>* RETT SYNDROME [Repsyndrome.org]</td>
<td>ALZHEIMER’S DISEASE</td>
<td>PARKINSON’S DISEASE</td>
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<td>INFANTILE SPASMS</td>
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<td>FRAGILE X [FRAXA]</td>
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<td>ANGELMAN’S [FAST]</td>
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<td>ANAVEX™ 3-71 (AF710B)</td>
<td>* FRONT. DEMENTIA (FTD)</td>
<td>ALZHEIMER’S DISEASE</td>
<td>PARKINSON’S DISEASE</td>
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<td>ANAVEX™ 1-41</td>
<td>DEPRESSION</td>
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<td>STROKE</td>
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<td>PARKINSON’S DISEASE</td>
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<td>ALZHEIMER’S DISEASE</td>
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<td>ANAVEX™ 1066</td>
<td>VISCERAL PAIN</td>
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<td>ACUTE &amp; NEUROPATHIC PAIN</td>
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<td>CANCER (PANCREAS)</td>
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</table>

* = Orphan Drug Designation by FDA
The Sigma-1 Receptor (S1R): From Gene to Therapeutic Target

Lack of S1R exacerbates disease progression\(^1\)

Sigma-1 Receptor is an integral membrane protein involved in cell homeostasis and cellular stress response\(^2\)

Endogenous S1R agonists activate the Sigma-1 Receptor under cell stressed conditions\(^3,4,5\)

**ANAVEX 2-73** is a S1R agonist and activates the Sigma-1 Receptor

Enhancing activation of endogenous S1R with ANAVEX 2-73 improves disease symptoms and underlying pathophysiology

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Sigma-1R Agonists MoA: Restoring Homeostasis

ANAVEX 2-73 

Sigma-1R helping / stimulating own body to regain functionality


Adapted from Miki et al, Dec 9. doi: 10.1111/neup.12080 Neuropathology 2013; Glembotski et al., Circulation Research. 2007;101:975-984
Unmet Medical Need in Rett Syndrome (RTT)

There are no current treatments for RTT
Affects approximately 16,000 females in U.S.
  1:10-15K females worldwide
RTT is primarily caused by a MECP2 mutation in X chromosome
  Males die before birth or early in infancy
For females who survive infancy, Rett syndrome leads to a deficiency in motor learning, cognitive impairment and seizures

Maria Chahrour, Huda Zoghbi., The Story of Rett Syndrome: From Clinic to Neurobiology, Science Direct (2007); D.Valenti et al., Neuroscience and Biobehavioral Reviews 46 (2014) 202–217
De Novo MECP2 Mutation Identified as Main Genetic Cause in Rett Syndrome

MECP2 modulates expression of BDNF (brain-derived neurotrophic factor)

Mutation in MECP2 occurs in 95% of classic Rett

Dysregulation of BDNF in Rett syndrome stalls neuronal development, synaptogenesis and plasticity

Administration of ANAVEX 2-73 significantly restores BDNF expression in the hippocampus to the same levels observed in vehicle-treated wild-type mice in the Fmr1 KO mouse model (p<0.05, KO vehicle vs. KO ANAVEX 2-73)

2) D.Valenti et al., Neuroscience and Biobehavioral Reviews 46 (2014) 202–217
ANAVEX 2-73 in MECP2 Rett Syndrome Mouse Model

Clasping at 8 weeks

Clasping at 12 weeks

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.</th>
<th>Het vehicle v.</th>
<th>Het vehicle v.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Het vehicle</td>
<td>Het AV2-73, 10 mg/kg</td>
<td>Het AV2-73, 30 mg/kg</td>
</tr>
<tr>
<td>Overall</td>
<td>90, p=0</td>
<td>53, p&gt; 0.69</td>
<td>62, p&gt; 0.24</td>
</tr>
<tr>
<td>GAIT</td>
<td>78, p&lt; 0.01</td>
<td>63, p&gt; 0.09</td>
<td>69, p&lt; 0.05</td>
</tr>
<tr>
<td>Paw Features</td>
<td>91, p&lt; 0.001</td>
<td>52, p&gt; 0.78</td>
<td>55, p&gt; 0.56</td>
</tr>
<tr>
<td>Correlation</td>
<td>53, p&gt; 0.66</td>
<td>56, p&gt; 0.40</td>
<td>76, p&lt; 0.005</td>
</tr>
<tr>
<td>Body Motion</td>
<td>71, p&lt; 0.02</td>
<td>60, p&gt; 0.20</td>
<td>81, p&lt; 0.003</td>
</tr>
<tr>
<td>Paw Positioning</td>
<td>84, p&lt; 0.0001</td>
<td>53, p&gt; 0.57</td>
<td>57, p&gt; 0.36</td>
</tr>
</tbody>
</table>

Presented at 2016 Epilepsy Pipeline Conference, 2016 Rett Syndrome Symposium
ANAVEX 2-73: Dose-Dependent Anti-Seizure Effects

Significant Seizure Reduction with ANAVEX2-73 in Angelman Seizure Model ANAVEX 2-73 (10 mg/kg ip dosed daily for 14 days)

Significant Seizure Reduction with ANAVEX2-73 in both MES and PTZ-Induced Seizure Models p<0.001

Vehicle 10 mg/kg (p.o.) 30 mg/kg (p.o.) 100 mg/kg (p.o.)

MES-induced convulsions#

PTZ-induced convulsions

Significant Reduction Number of Spasms with Pre-treated ANAVEX2-73 in Infant Rat Model (30mg/kg ip)

Presented at AES Meeting 2015, # results have been confirmed by the ETSP screening program; Presented at AEDD 2017
ANAVEX 2-73 Phase 2 Rett Syndrome Study Design

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

4 weeks Baseline Observation Period

N<90

Randomization to 1 of 3 arms

AV 2-73: Low dose

AV 2-73: High dose

Placebo

8 weeks Full Dose Treatment Period

AV 2-73: Low dose

AV 2-73: High dose

Placebo

12 Weeks Voluntary Open Label

Baseline Observation Period

Titration Treatment Period

Full Treatment Period

Initial screen
- ANAVEX 2-73 was evaluated in the 6-OHDA Parkinson’s disease model
- ANAVEX 2-73 significantly improves motor behaviors compared 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 significantly decreased the expression of CD68 (marker of activated microglia) in the substantia nigra.

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
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 during 57 weeks.

- Primary endpoints met with favorable safety and tolerability.
- Secondary endpoints met with supportive exploratory biomarker, cognition and functional measures correlating.
  - Low-High dose was statistically significant to affect MMSE-Δ and EEG/ERP-Δ scores with $\text{MMSE-Δ (} p=0.0285 \text{)}$ and $\text{EEG/ERP-Δ (} p=0.0168 \text{)}$, respectively.

Macfarlane, presented at CTAD 2016
ANAVEX 2-73 Phase 2a Alzheimer’s Disease

Randomized, Crossover Assignment, Open Label Study of ANAVEX 2-73 (ANAEX™2-73-002 Study#)

Baseline

N = 32
- Mild-to-moderate AD patients
- Baseline MMSE: 16-28

Randomized to 1 of 2 arms

36 Days (5 Weeks)
Two-period, cross-over treatment
✓ Safety, MTD
✓ Bioavailability of ANAVEX 2-73
✓ Dose-effect relationship
✓ PK/PD modeling

Oral → IV
IV → Oral

52 Weeks
Voluntary open label extension
✓ Safety
✓ Multiple doses of ANAVEX 2-73
✓ Dose-effect relationship
✓ PK/PD modeling

Oral

PK/PD Data Expected 4Q 2017

# ClinicalTrials.gov Identifier: NCT02244541
57 Week Safety Profile of ANAVEX™ 2-73 Phase 2a (MTD Study)

- The most common AEs at highest doses were mild dizziness followed by mild headache
  - Consistent with Blood Brain Barrier (BBB) penetration
  - 98% of all AEs were mild or moderate and reversible with 76% being Grade 1
  - 2% were 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
57 Week Longitudinal Cognition MMSE and Function ADCS-ADL

- Unblinded, uncontrolled, and small N, but encouraging observations
- 57 week longitudinal MMSE and ADCS-ADL without dose optimization
- Cognition MMSE and Quality of life score ADCS-ADL (Activities of Daily Living) maintained close to baseline through week 57

Macfarlane, presented at CTAD 2016
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#
Patient Characterization to Identify Phase 2/3 Parameters

**Hypothesis**

**Advanced Data Analytics using KEM®**

**Population PK**

**Scores**
- **Baseline**
- **Evolution**

**Clinical assessment, Vital signs, co-medication, ...**

**New**

**FGS**: Full Genomic Sequencing

**DNA FGS**

**RNA FGS**

**Actionable optimized Phase 2/3 clinical trial parameters**

**Population**
- PK
- MMSE
- ADCS-ADL
- COGSTATE
- EEG/ERP
- HAM-D

**Scores**
- MMSE
- ADCS-ADL
- COGSTATE
- EEG/ERP
- HAM-D

**Scores Evolution**

**Clinical assessment, Vital signs, co-medication, ...**
Stepwise Strategy to Address Major Unmet CNS Indications

✓ Valuable feature of sigma-1R agonists are their favorable safety profiles, particularly in humans due to the modulatory action of sigma-1R

✓ Selectively only under pathological conditions while sparing normal physiological activity, thus limiting adverse side effects#

✓ Rational clinical strategy targeting first shorter-term endpoints. Goal: Reduction of clinical development risk

✓ Later expansion of indication scope with disease modification or prevention trial – ANAVEX 2-73 has already demonstrated preclinically to prevent symptoms of Alzheimer’s##

Financial Position and Near Term Catalysts

- Cash (as of June 30, 2017): $24.8M; No debt
- The company is well capitalized to achieve clinical readouts

<table>
<thead>
<tr>
<th>up to 2017</th>
<th>Granted Orphan Drug Designations for the following indications: Rett syndrome, Infantile spasms and Frontotemporal dementia</th>
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<tbody>
<tr>
<td></td>
<td>Phase 2a – Reported 57 week data at CTAD scientific meeting</td>
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<td>4Q 2017 Phase 2a Alzheimer’s disease – PK/PD data</td>
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<td>4Q 2017 Phase 2 clinical trial in Rett syndrome</td>
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<th>2018</th>
<th>2018 Potential for several clinical read-out in 2018</th>
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<td>Ongoing in-licensing/out-licensing review to optimize value of pipeline</td>
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## Expertise in Drug Development, Neurodegenerative Diseases

### Management Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Company/Institution</th>
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<tbody>
<tr>
<td>Christopher U. Missling, PhD</td>
<td>President &amp; CEO</td>
<td>CURIS, Immunogen Inc.</td>
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<tr>
<td>Emmanuel O Fadiran, RPh, PhD</td>
<td>SVP of Regulatory Affairs</td>
<td>FDA, University of Strathclyde Glasgow</td>
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<tr>
<td>Tasos Zografidis, IMS, PhD</td>
<td>VP of Clinical Operations</td>
<td>Pfizer</td>
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<tr>
<td>Ulrich Eben, PhD</td>
<td>VP of Preclinical Operations</td>
<td>Wyeth</td>
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<tr>
<td>Daniel Klamer, PhD</td>
<td>VP of Business Development &amp; Scientific Strategy</td>
<td>Vertex, Aventis, URI SEARCH, RetrPhin, NeuroSearch</td>
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AFDA Commissioner’s award of Excellence

### Scientific Advisory Board Members

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<thead>
<tr>
<th>Name</th>
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<th>Institution/University</th>
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<tr>
<td>Jeffrey Cummings, MD</td>
<td></td>
<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>University of Pittsburgh (UPMC)</td>
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<tr>
<td>Norman Relkin, MD, PhD</td>
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<td>Weill Cornell Medicine</td>
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<td>Abraham Fisher, PhD</td>
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<td>Weizmann Institute of Science</td>
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<tr>
<td>Jacqueline French, MD</td>
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<td>NYU</td>
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<tr>
<td>Andrew Cole, MD</td>
<td></td>
<td>Harvard Medical School</td>
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<tr>
<td>Tanya Simuni, MD</td>
<td></td>
<td>Northwestern University Feinberg School of Medicine</td>
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<tr>
<td>Daniel Weintraub, MD</td>
<td></td>
<td>Perelman School of Medicine University of Pennsylvania</td>
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<tr>
<td>Kalpana Merchant, PhD</td>
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<td>Northwestern University Feinberg School of Medicine</td>
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Contact Us

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NASDAQ: AVXL

ANAVEX is a trademark of Anavex Life Sciences Corp.
BDNF Val66met Polymorphism implicated in Neurodevelopmental and Neurodegenerative Disorders

BDNF Val66met polymorphism correlates with:

- Higher seizure frequency and severity of Rett syndrome³
- Cognitive decline and increased Aβ accumulation in Alzheimer’s disease¹,²

3) Zeev BB et al. Neurology. 2009 Apr 7;72(14):1242-7
Supportive Exploratory Biomarker, Cognition and Function Measures: PART A and PART B Data of All Patients

- Exploratory Physiologic Biomarker measures:
  - EEG/ERP (P300) measures cortical network performance

- Exploratory Cognitive measures:
  - Cogstate battery
  - MMSE

- Exploratory Behavioral and Functional measures:
  - HAM-D
  - ADCS-ADL

The following data represents all evaluable patients.
P300 Decline Halted with ANAVEX 2-73 – Expected to Decline in Alzheimer’s Disease

- P300 amplitude recovers to healthy levels over 53 weeks
- Temporary improvement in P300 amplitude seen with donepezil therapy persists with ANAVEX 2-73

# Theoretical comparisons to historical models of disease progression are for illustrative purposes
Comparable AD Study: Standard of Care (SoC) vs ANAVEX 2-73 Study

Data from *Australian Imaging Biomarkers and Lifestyle* (AIBL-ROCS-AD) study evaluating mild-to-moderate Alzheimer’s disease patients on SoC (Standard of Care) acetylcholinesterase medications and/or memantine with Cogstate battery #

<table>
<thead>
<tr>
<th>Baseline data:</th>
<th>SoC (AIBL-ROCS-AD)</th>
<th>ANAVEX 2-73</th>
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<tbody>
<tr>
<td>Participants (n)</td>
<td>35</td>
<td>32</td>
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<tr>
<td>Age (mean)</td>
<td>78.6</td>
<td>71.0</td>
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<tr>
<td>% Female</td>
<td>48.8</td>
<td>40.6</td>
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<tr>
<td>ApoE4 carrier</td>
<td>68%</td>
<td>53%</td>
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<tr>
<td>MMSE (mean)</td>
<td>21.2</td>
<td>21.0</td>
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Computerized Cogstate Test Battery: No Rater Bias

Cogstate’s test battery for Alzheimer’s disease measures the following core cognitive domains:

- Processing speed ➔ Detection Test
- Attention ➔ Identification Test
- Working memory ➔ One Back Test
- Visual learning ➔ One Card Learning Test
- Verbal learning ➔ International Shopping List Test (ISLT)
- Verbal memory ➔ Delayed International Shopping List Test (ISLT-delay)

Cogstate’s computerized battery includes tests that have been utilized previously in clinical trials and have demonstrated repeated testing reliability#
Side-by-Side Standard of Care (SoC) vs ANAVEX 2-73

- Significant larger magnitude of Effect Size (ES) change from baseline (Cohn’s d) with ANAVEX 2-73

# Standard of Care (SoC) acetylcholinesterase medications and/or memantine
Examples of Continued Improvements and Reported Events ‘Therapeutic Response’ during 57 Weeks

### Examples of MMSE "Strong" Patient Responders

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>EVENTS: THERAPEUTIC RESPONSE UNEXPECTED</th>
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<tbody>
<tr>
<td>101001</td>
<td>MORE ALERT REGARDING SURROUNDINGS</td>
</tr>
<tr>
<td>101002</td>
<td>FEELS MUCH HAPPIER MAKING JOKES</td>
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<tr>
<td>101003</td>
<td>MUCH HAPPIER WHEN ATTENDING CLINIC APPTS AND ENJOYS MAKING JOKES AND ENGAGES WELL IN CONVERSATION</td>
</tr>
<tr>
<td>101004</td>
<td>BETTER HAND COORDINATION. CALMER AND MORE COMMUNICATIVE</td>
</tr>
<tr>
<td>101006</td>
<td>IMPROVING MOODS. READING MORE BOOKS</td>
</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>
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<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>

**HAM-D Mean ± SEM**

- **Baseline**: 3.0
- **31 week**: 1.5

*p<0.05*
ANAVEX 2-73: Robust Correlation of Cognition, Function and Behavior Response

ANAVEX 2-73 Response cluster in a homogeneous 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
ANAVEX 2-73 TARGETED INDICATIONS

PRECLINICAL VALIDATION
- Parkinson's disease*
- Rett Syndrome**
- Fragile X***
- Angelman syndrome****
- Multiple sclerosis*****
- Depression
- Anxiety
- Epilepsy seizures
- Infantile spasms

CLINICAL VALIDATION PHASE 2a
- Population PK

CLINICAL CONFIRMATION PHASE 2
- Placebo-controlled

CLINICAL CONFIRMATION PHASE 2/3
- Placebo-controlled

Alzheimer's disease
- Rett syndrome
- Parkinson's disease

Clinical funding:

* MJFF
** RettSyndrome.org
*** FRAXA
**** CUREAngelman.org
***** Wayne State/Biogen
Phase 2a Study Design

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

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

- **1st Period**: Intravenous and oral treatment
- **Wash Out Period**: 36 days
- **2nd Period**: Intravenous and oral treatment
- **52 weeks**: All patients on oral daily treatment
Alzheimer’s 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™ 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

Reversed cognitive impairments in Morris water maze

Reduced Abeta pathology
{Abeta40, Abeta42 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
Pathological GSK-3β Activation can be Inhibited with 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.

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

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
Common in both Neurodegenerative & Neurodevelopmental Diseases: ER-Mitochondria Axis Disruption...sigma-1R Restores Association ...

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

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.
- 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.

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

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

An estimated 46 Million people worldwide live with dementia