Novel Therapeutics to Treat Neurodevelopmental and Neurodegenerative Diseases
Developing Next Generation Therapies for High Value Neurodevelopmental and Neurodegenerative Diseases

Lead program: EM-036, a novel nitro-aminoadamantane NMDA receptor antagonist for major CNS diseases
Dual allosteric mechanism (ion channel block plus targeted S-nitrosylation of NMDAR) produces dramatically superior efficacy over memantine in Autism Spectrum Disorder (ASD) and Alzheimer’s disease (AD) models

Potential first approved therapy for ASD core symptoms
Biomarker-driven development plan de-risked by recent unpublished memantine trial.

Potential first new therapy for Alzheimer’s disease in nearly 20 years
Unlike the many failed AD trials, EM-036 is based on a clinically-validated target (NMDAR antagonism). Desperate unmet medical need will drive utilization of a novel approved therapy in AD.

Potential first approved therapy for Cognitive Impairment Associated with Schizophrenia (CIAS)
Development plan de-risked by positive memantine trials from academia.

Potential efficacy in rare neurological diseases characterized by excitation/inhibition (E/I) imbalance
First approved therapy possible for MEF2C haploinsufficiency syndrome, Rett syndrome, Tuberous sclerosis complex.

Aggressively seeking BD opportunities in clinical stage neurology and psychiatry assets
Potential acquisitions identified for novel target NCE with phase 1 data, and with IND-ready dossier.

Highly experienced team with successful track record will drive execution of development plan
IND filing by end of Q1 2021 / Phase I SAD, MAD complete Q4 2021 / Phase 2 initiated 1H 2022.
Novel clinical asset to be acquired by mid-2020 with Phase 2 trial started by late 2020
Management Team/Founders

Mark Tepper, Ph.D.
**President & Chief Executive Officer**
- Ph.D., Columbia P&S, Biochemistry/Biophysics
- Previously held positions as: President & CSO, Corbus Pharmaceuticals, CEO, Multiple Life Science startups, VP USA Research & Operations, EMD Serono; Sr. Investigator, Bristol-Myers Squibb

James Larrick, M.D., Ph.D.
**Chief Scientific Officer**
- M.D., Ph.D. Duke, Post-doc Stanford; Board-certified Internal Medicine.
- Founder >12 biotech companies which led to 5 IPOs and multiple acquisitions: TargetQuest (acquired by Dyax, IPO 2000), Arana (IPO 2005, acquired by Teva), KaloBios (IPO 2013), InterMune (IPO 2000), PanGenetics (acquired by Tanox, IPO 2000, then Genentech), Adamas (IPO 2014), Planet Biotech, Igenex (sold 2015), and others.

Randall Marshall, M.D.
**Chief Medical Officer**
- M.D., Johns Hopkins, Residency Columbia P&S,
- Board-certified neuropsychiatrist
- Past CMO ArTara (founder), Scientific Advisor to multiple start-ups; leadership Retrophin, Alkermes, Neurovance, Sepracor
- 15 years academic medicine as PI on > $10M in NIH grants
- Author of > 100 peer reviewed publications, 25+ book chapters in neuropsychiatry
- Clinical science expertise across neurological and psychiatric disorders, phases 1-4
Scientific Advisors

Stuart Lipton, M.D., Ph.D. (Scientific Founder)
Professor, Scripps Research Institute and UC San Diego, La Jolla
- Harvard-trained board-certified neurologist, on Harvard faculty for 25 yrs - KOL
- Scientific Founder of EuMentis Therapeutics & Adamas
- Developer/Patent Holder of memantine (Namenda®, NamendaXR®, Namzaric®)
- Preclinical studies of EM-036 in MEF2C haploinsufficiency, Rett syndrome, Tuberous sclerosis complex, Alzheimer’s disease
- Has run advanced human clinical trials for dementia & presented to FDA regulators

Jeffrey L. Neul, M.D., Ph.D.
Professor, Vanderbilt School of Medicine, Nashville, TN
- Expert in neurodevelopmental disorders/ASD including Rett Syndrome
- Lead PI on Rett syndrome clinical trials (Ketamine P3 & our planned trial

Xiaoming Zhang, Ph.D.
Sr. VP, Nonclinical & CMC, Menlo Therapeutics, Sunnyvale, CA
- Co-founder of EuMentis Therapeutics
- Expert in medicinal chemistry, CMC, drug development
Initial Target Indications Represent Multi-Billion Dollar Market Opportunities

<table>
<thead>
<tr>
<th>Indication</th>
<th>Incidence</th>
<th>Prevalence (US/EU)</th>
<th>Age of Onset</th>
<th>Market Size (Approved Drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism Spectrum Disorder (ASD)</td>
<td>1/59 (live births)</td>
<td>1.5M/2M</td>
<td>Birth</td>
<td>$4.6-6 Billion (None)</td>
</tr>
<tr>
<td>Cognitive Impairment Associated with Schizophrenia (CIAS)</td>
<td>1/150</td>
<td>2.6M/4M</td>
<td>Teens-20s</td>
<td>$1.7-6 Billion (None)</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>1/50</td>
<td>5.5M/8.8M</td>
<td>65+</td>
<td>$15-20 Billion (AChEi, memantine³)</td>
</tr>
</tbody>
</table>

De-risked by positive memantine clinical data

1: Also, efficacy shown in Vascular dementia models, subarachnoid hemorrhage (SAH), epilepsy, traumatic brain injury (TBI)/posttraumatic stress disorder (PTSD)/chronic traumatic encephalopathy (CTE), and Lewy body dementia (LBD)/Parkinson’s disease (PD) models of dementia
The Problem

Neurodegenerative and Neurodevelopmental Diseases Are Overwhelming the Healthcare System

High prevalence - affects millions
High cost of care & growing - $400 billion currently

No approved drugs for:
ASD (core symptoms), CIAS, Rett syndrome
MEF2C Haploinsufficiency, Tuberous sclerosis complex

Only 2 types of drugs approved for AD:
(3 AChE Inhibitors and memantine/Namenda®)
Synaptic (GluN2A/NR2A) receptors mediate phasic signaling.

**Synaptic NMDARs**, triggered by normal neurotransmission, promote survival pathways, e.g., the CREB-PGC1a cascade and BDNF expression.

**Extrasynaptic** (GluN2B/NR2B) receptors mediate tonic signaling.

**Extrasynaptic NMDARs** are activated by excessive glutamate released by astrocytes in response to Aβ. This promotes toxicity pathways & protein misfolding, inhibits BDNF expression, and results in synapse loss.

Hardingham and Bading Nat Rev, Neurosci (2010) 11:682
Talantova, Lipton, PNAS, (2013) 110:E2518
Excitatory-Inhibitory Imbalance Contributes to Neurological Disease

Excessive glutamate release leads to aberrant extrasynaptic (e)NMDAR activity with consequent synaptic damage in many neurological diseases.
Dual Allosteric Mechanism of Action of EM-036

- Excessively active eNMDARs contribute to pathological synaptic damage
- **EM-036** binds at or near the NMDAR Mg\(^{2+}\) site in the open channel, facilitating targeted S-nitrosylation of critical cysteine residues on the extracellular surface of the NMDAR to inhibit activity.
- EM-036 preferentially inhibits *excessively active* eNMDARs

1: crystal structure published. Takahashi et al. Neuron, 2007
EM-036 Blocks Extrasynaptic NMDAR Responses while Sparing Synaptic Responses

### Extrasynaptic NMDAR Responses (Ca+2 influx)

- Greater effect of EM-036 than memantine on eNMDARs

### Synaptic NMDAR Responses (patch-clamp)

- Lesser effect of EM-036 than memantine on synaptic NMDARs

**Legend:**
- AP5 - NMDAR antagonist which completely blocks ion channel
- EM-036 Blocks Extrasynaptic NMDAR Responses while Sparing Synaptic Responses

**Graph:**
- Bar graph showing normalized Fura-2/Ca^2+ fluorescence (a.u.)
- Monomeric Aβ_{1-42} +
- Oligomeric Aβ_{1-42} +
- Memantine +
- EM-036 +

**Notes:**
- Greater effect of EM-036 than memantine on eNMDARs
Autism Spectrum Disorder (ASD)
Our Lead Indication
Autism Spectrum Disorder is a De-Risked Target for EM-036

ASD is a developmental disability affecting communication, behavior, and social interaction, affecting ~1.5M children and adults in the USA alone.

EM-036 is effective in genetic models of rare ASD subgroups capturing final common pathways linked to I/E imbalance:
- Mutations in Mef2c (associated with ASD and severe intellectual disability)
- Mutations in MeCP2 (Rett syndrome)
- Mutation in TSC (Tuberous Sclerosis Complex)

In most patients the genetic etiology of ASD is unknown, but biomarkers of excessive glutamate activity are agnostic across genetic defects:
- SPECT Imaging studies suggest elevated glutamate in the anterior cingulate cortex
- Biomarker of EEG gamma power is decreased in ASD and increased with aminoadamantane drugs like memantine and EM-036

A recent unpublished clinical trial demonstrates memantine is highly effective in a biomarker-identified subgroup.

Thus, EM-036 is likely to benefit ASD patients with elevated glutamate levels at baseline, enabling a biomarker-driven clinical trial program.
Memantine vs Placebo in ASD Children 8-17 Years as a Function of High Glutamate (SPECT) in the Anterior Cingulate Nucleus

Clinical Trial Methods

Children ages 8-17 with ASD, IQ>70, and social impairment

12-week randomized placebo-controlled trial of memantine (10mg bid) vs placebo

SPECT of glutamate levels in anterior cingulate nucleus at baseline, week 12

Analysis of high glutamate patients’ response to memantine

EuMentis can share unpublished clinical data under CDA

Findings support a precision medicine, biomarker driven ASD program to develop EM-036 as a first approved therapy for ASD

These findings will have a major impact on the field of ASD research, and EuMentis is a leader in this approach
Creating Disease Models with hiPSCs that form “Mini Brains” in vitro

MEF2C haploinsufficient hiPSCs and CRISPR/Cas9 isogenic controls generated
Normal Electrical Activity by Calcium Imaging of Wild-Type hiPSC-Derived Neurons
Excessive Electrical Activity of MEF2C Haploinsufficient hiPSC-Derived Neurons
EM-036 Treatment of Excessive Electrical Activity of MEF2C Haploinsufficient hiPSC-Derived Neurons
Cognitive Impairment Associated with Schizophrenia (CIAS)
Cognitive Impairment Associated with Schizophrenia (CIAS) is an FDA-Validated Indication with No Approved Therapies

Schizophrenia is a severe neurodevelopmental disorder affecting ~2.4M patients in the US.

Severe cognitive impairment in patients with schizophrenia is independent of psychotic symptoms and highly predictive of functional impairment.

Over the last 10+ years, NIMH, industry, FDA, and leading KOLs collaborated to validate clinical trial measures for CIAS (the MATRICS and CINTRICS initiatives).

Despite multiple programs, there is no approved therapy for this blockbuster indication.

However, 4 independent memantine clinical trials from academia support the development of EM-036 as a superior therapy.

1 Buchanan et al Schiz Bull 2005; 31(1) 5-19
2 Buchanan, Keefe et al Schiz Bull 2011; Nov 37(6):1209-17
Memantine Improves Cognition and Negative Symptoms in Clozapine-Refractory Schizophrenia

12-week crossover trial of memantine (10mg bid) in N=52 adults on clozapine with inadequate response

- Mean Age 42 years
- Duration of illness 22 years
- Refractory patients on multiple meds

Effect Sizes: Cognitive Measures and Negative Symptoms in Patients with Schizophrenia

An Effect size >0.2 is clinically significant for this indication


Effect Size drug vs placebo*

*Effect Size=drug (mean) - placebo (mean) / SD (standard deviation)
Alzheimer’s Disease
Alzheimer’s Disease affects 5.5 Million US Patients Alone

The most common form of dementia, with a relentlessly progressive course of illness
• Begins with memory loss, progresses to complete inability to function or engage with others
• Risk increases with age, but also affects >200,000 patients under 65 years in the US alone

The hallmark histopathology of plaques and tangles, amyloid and tau deposition, is well documented
• However, treatments that successfully reduce amyloid burden in the brain have repeatedly failed in clinical trials (e.g., solenuzamab, aducanumab, gantenerumab, LY3002813)

Despite billions of dollars invested, the only clinically validated therapies are memantine (developed by the Founders of EuMentis), and the cholinesterase inhibitors
EM-036 Protects Synapses in Alzheimer’s Disease Transgenic Mice

The best pathological correlate with clinical dementia is the loss of synapses, NOT plaques or tangles.
EM-036 shows Neuroprotection in Alzheimer’s Disease Models

EM-036 abrogates dendritic spine loss mediated by oligomerized Aβ in hippocampal slices better than memantine.

EM-036 treated AD transgenic mice display significantly improved function in the location-novelty recognition test.

In vitro AD Model
- Oligomerized Aβ1-42
- Oligomerized Aβ1-42 + Memantine
- Oligomerized Aβ1-42 + EM-036

Re-growth of postsynaptic dendritic spines

In vivo AD Model (3X Tg)

Number of contacts

<table>
<thead>
<tr>
<th></th>
<th>Old Location</th>
<th>New Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM-036</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Memantine</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Veh</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Spine density (No. of spines/μm)

- + Oligomerized Aβ1-42
- - Memantine
- - EM-036

* Indicates significant difference.
**Summary of EM-036 Results in Preclinical CNS Models**

**EM-036 is far superior to memantine in nonclinical ASD models**
- EM-036 improves memory of ASD mice in Morris Water Maze Model.
- EM-036 improves social engagement of ASD mice in Sociability Test.
- EM-036 is effective in Rett syndrome and TSC mouse models
- Memantine is far superior to placebo in ASD patients (8-17 years) with elevated glutamate at baseline by SPECT imaging
- US target population is large (525-700k)

**EM-036 is far superior to memantine in AD models**
- EM-036 reverses synaptic loss as detected by the presynaptic marker-synaptophysin
- EM-036 also protects postsynaptic spines caused by oligomerized Ab1-42
- EM-036 improves performance in the Novel Location Recognition Test in AD model mice
- EM-036 is effective in two AD animal models: 3xTg Mice (APP Swedish, MAPT-P301L, and PSEN1 M146V) & J20 hAPP mice

**Memantine clinical trials support the development of EM-036 as a superior therapy for ASD, CIAS and AD**
   - Claims method of use of EM-036 for treating neurological conditions including ASD, Rett Syndrome, Tuberous Sclerosis, MEF2 Haploinsufficiency and epilepsy
   - PCT patent filed 7-31-2018

2. PCT US18/61981
   - Claims composition of matter and use of new 3rd generation aminoadamantane nitrate compounds
   - Patent filed 11-20-2018

3. Patent 7,326,730
   - Composition of matter and use of aminoadamantane nitrates. Work ongoing to extend IP (salt screen, polymorph, co-crystals, formulations, etc.)
   - Patent expires 2023

4. Provisional Patents- multiple filed in 2020
Series A Nonclinical Plan to Value Inflection

Series A: $15 million

- **IND-enabling CMC**
  - Scale Up & Manufacture 2Kg GMP drug substance
  - Capsule Formulation Development GMP manufacturing of drug product & Stability for Phase I & 2

- **Non-clinical**
  - ADME- TK, Metabolite ID in tox species and human
  - Animal POC studies for expanded indications- Rett syndrome (J Neul), Fragile X syndrome, Down’s syndrome
  - Safety/Toxicology- GLP safety studies (dog), 28-day tox (rat & dog), Genotox studies

- **Regulatory**
  - Pre-IND Meeting (Oct 2020)
  - IND Filing (Q1 2021)
  - Phase I Protocol

- **Series A: $15 million**
  - **IND-enabling CMC**
    - $1.3M
  - **Non-clinical**
    - $2.5M
  - **Regulatory**
    - $0.2M
Series A Clinical Plan to Value Inflection

**Phase 1**
- **Single Ascending Dose in healthy normal volunteers** (6 drug/2 placebo per cohort) N=56
  - Estimated Doses: 2mg, 5mg, 10mg, 20mg, 40mg, 80mg, 100mg
- **Multiple Ascending Dose in healthy normal volunteers** (6/2) N=32
  - Estimated doses: 10mg, 20mg, 40mg (BID)
  - Biomarkers: EEG (gamma oscillations),

**Phase 2 Autism Spectrum Disorder (ASD)**
- **12-week randomized placebo-controlled trial in ASD adults and adolescents with IQ>70, social impairment, and elevated glutamate in anterior cingulate cortex (aCC) by SPECT at baseline**
  - N=90, 2 doses vs placebo, N=30 per group
  - 2-stage enrollment: N=15 adults, followed by safety review, and then enrollment of adolescents
  - Endpoints: Social Responsiveness Scale, CGI-I, CGI-S, consider EEG (enhanced gamma band)
  - Sample size: power=0.8, alpha=0.5, 1-tailed T test, ES=0.65 (medium) for this sample size.

**Second clinical stage asset in a large neurological indication (ongoing BD discussions)**
- **4-week Phase 2 dose-ranging RCT in Parkinson’s Disease** (3 doses vs placebo, N=100)
  - Some additional CMC work needed
The Opportunity

Novel approach to target the pathophysiology of multiple neurological diseases

- Excessive extrasynaptic (e)NMDAR activity causes excitatory/Inhibitory (E/I) imbalance, implicated as pathogenic in ASD, CIAS, Alzheimer’s disease (AD), Rett Syndrome, MEF2C Haploinsufficiency, and other rare neurological diseases

Novel mechanism of EM-036

- **EM-036**, a proprietary nitro-aminoadamantane, is a dual-allosteric drug that blocks excessively open eNMDAR-channels while selectively targeting the nitro group to S-nitrosylate and thus further inhibit NMDARs
- **EM-036** blocks excessive activation of eNMDARs to protect synapses and correct E/I imbalance in a disease-modifying fashion

Efficacy data in nonclinical (EM-036) and clinical (memantine) support development.

- Preclinical data demonstrate dramatic improvement in efficacy of **EM-036** over memantine in ASD and AD models
- Clinical data with memantine de-risk ASD, CIAS, and AD therapeutic indications

Highly experienced & successful drug development team.

- Building a pipeline of neurology products with EM-036 & acquisition of other clinical phase neurology assets
  - Late stage BD discussions ongoing
Thank you!

Contact:

Mark A. Tepper, PhD
Boston, MA USA
617-413-3020
Mtepper@eumentistx.com
Appendix (Additional Information)
EM-036 Lead Generation

EM-036
2nd generation NCE of memantine (Namenda®) with vastly improved efficacy

Acts as open-channel blocker (OCB) plus redox-mediated inhibitor of NMDAR
- Best-in-class NMDAR antagonist with dual-allosteric mechanism of uncompetitive fast off-rate OCB plus nitrous oxide (NO donor) selectively affecting redox site

Preferentially acts on overactive eNMDARs and spares normal and necessary synaptic activity far better than memantine

Restores synaptic number & function and thus E/I balance

**Dramatically improved efficacy** in AD & ASD vs. memantine (preclinical data)
- Equal or better safety to memantine, no ketamine-like safety issues due to fast off-rate
Synapse Communication between Neurons

Synapses mediate memory, language, and emotion—the very essence of being human.

BUT Synapses between neurons are lost in Alzheimer’s disease.

Thus Synapse protection is necessary for disease modification.
Patch-Clamp Recordings Demonstrate Improved Inhibitory Activity via Channel Block and Targeted S-Nitrosylation of NMDAR

- Brain levels (~3-10 μM at the channel mouth) at therapeutic doses
- IC₅₀ = 1.7 μM
- Rapid-onset open-channel block of NMDARs

Biotin-switch assay demonstrating S-nitrosylation (SNO) of principal Subunit of NMDAR (GluN1)

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>ASD het mouse model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM-036</td>
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</tr>
</tbody>
</table>

- SNO-GluN1
- Total GluN1

Plus prolonged redox-mediated inhibition via S-nitrosylation

EM-036 (μM)
MEF2C-heterozygous (Het) Mouse Model of Human MEF2C Haploinsufficiency Syndrome (ASD)

MEF2C-het (MEF2C^{+/-}) mice

- Show hyperexcitation (similar to hiPSCs in vitro) resulting in aberrant histology and behaviors.
- Exhibit symptoms of Autism Spectrum Disorder and Intellectual Disability such as social aversion and impaired learning/memory.
EM-036 Far Superior to Memantine in Morris Water Maze Test

EM-036 Rescues Impaired Performance (Memory) of MEF2C\(^+/-\) Mice

- MEF2X\(^+/-\) mice have trouble learning and remembering location of the swim platform
- EM-036 >> memantine administered at equimolar doses BID for 3 months starting at age 2.5 weeks (equiv. to juvenile humans) improved maze memory in MEF2C het mice
EM-036 (N) Far Superior to Memantine (M) in Sociability Test

EM-036 Rescues Altered Performance of MEF2C+/- Mice

EM-036 or memantine was administered at equimolar doses BID parenterally for 3 months starting at age 2.5 weeks
## Published Memantine Trials for ASD

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Duration</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label- Chez (2.5-30mg/day)</td>
<td>n= 151</td>
<td>21 months</td>
<td>CGI- language, behavior, and self-stimulatory behaviors,</td>
<td>~80% Improvements in language function, social behavior, and ~20% improvement in self-stimulatory behaviors.</td>
</tr>
<tr>
<td>RPCT(Risp +/- Mem) -Ghaleiha (3-20mg/day)</td>
<td>n= 40</td>
<td>10 weeks</td>
<td>Aberrant Behavior Checklist–Community (ABC-C)</td>
<td>Memantine group showed statistically significant reduction in irritability, stereotypic behavior, hyperactivity &amp; inappropriate speech</td>
</tr>
<tr>
<td>Open label- Joshi (5-20mg BID)</td>
<td>n= 18</td>
<td>12 week</td>
<td>SRS-A, CGI, Behavior Rating of Executive Functioning, Nonverbal Accuracy Scale, and Cambridge Neuropsychological Test</td>
<td>Significant improvement in all endpoints SRS-A, −28 ± 25; P &lt;0.001)</td>
</tr>
<tr>
<td>Open Label- MEM-MD-91 (3-20mg/day)</td>
<td>n=906</td>
<td>50 weeks</td>
<td>SRS, CGI-S, CGI-I, and ABC-C</td>
<td>~60% responders for all groups (ASD, Asperger’s, PPD-NOS). 95-100 days for max response</td>
</tr>
<tr>
<td>RSBT-Karahmadi Memantine + behavior Tx</td>
<td>n=60</td>
<td>12 weeks</td>
<td>Gilliam autism rating scale</td>
<td>Improved communication, social interaction,&amp; stereotypic behavior: memantine + ABA vs ABA alone</td>
</tr>
<tr>
<td>RPCT Memantine vs placebo (5-15mg/d) MEM-MD-57A</td>
<td>n=121</td>
<td>12 weeks</td>
<td>SRS, CATS-I, CAASST-I, CCC-2, CGI-S, CGI-I, and ABC-C</td>
<td>Failed trial. Under-dosed and poorly executed.</td>
</tr>
<tr>
<td>RPCT memantine vs placebo</td>
<td>N =43</td>
<td>12 weeks</td>
<td>SRS, CGI-I. SPECT of ant. Cingulate cortex</td>
<td>Biomarker-driven positive findings vs placebo</td>
</tr>
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Target Product Profile: EM-036 for Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Target</th>
<th>Compared to Standard of Care (SOC)</th>
<th>Clinical and Preclinical Rationale</th>
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</thead>
<tbody>
<tr>
<td><strong>Indications and Use</strong></td>
<td>For the treatment of Autism Spectrum Disorder in Patients with Glutamate Elevation</td>
<td>First approved therapy for core symptoms of ASD</td>
<td>1. Memantine effective for social impairment in ASD patients &gt; 12 years of age</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>2. Treatment in children ages 4-12 years will meet high unmet medical need, potentially reverse neurodevelopmental damage from elevated glutamate</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>Patients with ASD &gt; 4 years of age</td>
<td>First approved therapy for core symptoms of ASD</td>
<td>1. Memantine effective in ASD patients &gt; 12 years of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Treatment in children ages 4-12 years will meet high unmet medical need, potentially reverse neurodevelopmental damage from elevated glutamate</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Oral, once or twice daily dosing</td>
<td>Similar to memantine</td>
<td>animal models suggest similar potency and duration of efficacy to memantine</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>NMDA receptor antagonism</td>
<td>Addresses core symptoms vs associated symptoms (risperidone for irritability)</td>
<td>dual-action mechanism is known and is superior to memantine in multiple models</td>
</tr>
<tr>
<td><strong>Onset of Action</strong></td>
<td>4-8 weeks</td>
<td>Superior to memantine</td>
<td>Similar to memantine in Joshi et al trial</td>
</tr>
<tr>
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<tr>
<td><strong>Duration of effect</strong></td>
<td>28+ weeks</td>
<td>Similar or superior to memantine</td>
<td>Effect is durable in Joshi et al trial</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Possibly other NMDA antagonists</td>
<td>Similar to memantine</td>
<td>rational analysis</td>
</tr>
<tr>
<td><strong>Specific Populations</strong></td>
<td>No dose adjustment needed for hepatic or renal impairment</td>
<td>Similar to memantine</td>
<td>consistent with metabolism data to date</td>
</tr>
</tbody>
</table>
FDA-NIMH-MATRICS Guidelines for Outcomes in CIAS Trials

MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia)

- A 10+ year collaboration across FDA, NIMH, academia and industry developed guidelines and a validated set of outcome measures for CIAS studies \(^1\)\(^-\)\(^2\)
- Guidelines have been implemented in many phase 2 and 3 industry studies with FDA oversight

MCCB (MATRICS Consensus Cognitive Battery), fully computerized batteries available (CogState, CANTAB)

- 7 cognition domains assessed: attention/vigilance, reasoning and problem solving, speed of processing, social cognition, verbal learning and memory, visual learning and memory, and working memory

Functional outcomes co-primary measure required, FDA is flexible on specific measure

- UPSA UCSD Performance-based Skills Assessment \(^3\)
- VRFCAT Virtual reality Functional Capacity Assessment Tool \(^4\)
- SCoRS Schizophrenia Cognition Rating Scale \(^5\)

Outcome measures validated by successful cognitive remediation trials but no drug therapy to date

1 Buchanan et al Schiz Bull 2005; 31(1) 5-19
2 Buchanan, Keefe et al Schiz Bull 2011; Nov 37(6):1209-17
3 Green et al Am J Ps 2011; 168:400-407
4 Keefe et al Schiz Res 2016; 175:90-96
5 Harvey et al Schiz Res 2019; (210) 30-38
Alzheimer’s Disease (AD)

Misfolded Proteins Contribute to AD

Healthy Brain  Advanced Alzheimer’s  Tau protein forms tangles  Amyloid-β protein forms plaques

But the best pathological correlate with clinical dementia is the loss of synapses, NOT plaques or tangles
Competitive Landscape

Autism Spectrum Disorder

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td>Marketed- None</td>
<td></td>
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<tr>
<td>Phase III</td>
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<tr>
<td>Balovaptan</td>
<td>Roche</td>
<td>Vasopressin 1a receptor antagonist</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Servier</td>
<td>Diuretic</td>
</tr>
<tr>
<td>CM-AT</td>
<td>Curemark</td>
<td>Protease regulator</td>
</tr>
<tr>
<td>Serelsa</td>
<td>Autism Therapeutics</td>
<td>Selective 5-HT reuptake inhibitor</td>
</tr>
<tr>
<td>ASD-002</td>
<td>Asdera</td>
<td>NSAID</td>
</tr>
</tbody>
</table>

Source: EvaluatePharma 2020

Alzheimer’s Disease

![Alzheimer's Drug Development Pipeline](chart.png)

Fig. 1. Agents in clinical trials for treatment of Alzheimer’s disease in 2018 (from clinicaltrials.gov accessed January 30, 2018).