Novel Therapeutics to Treat Neurodevelopmental and Neurodegenerative Diseases
Investment Highlights

Developing Next Generation Therapy for the Treatment of High Value Neurodevelopmental and Neurodegenerative Diseases

- Lead program: **EM-036**, a novel nitro-aminoadamantane N-methyl-d-aspartate receptor (NMDAR) antagonist in preclinical development (IND-enablement) for the treatment of several CNS diseases

- Data demonstrate S-nitrosylation of NMDAR resulting in dramatic and significant efficacy improvement over memantine (Namenda®) in Alzheimer’s disease (AD) and Autism Spectrum Disorder (ASD) models

- Driving execution of development plan with:
  - IND filing by end of 2020
  - Phase I complete 1H’21
  - Phase 2 initiated 2H’21
### Potential Indications

**Initial Target Indications Represent Multi-Billion Dollar Market Opportunity Alone**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Incidence</th>
<th>Prevalence (US/EU)</th>
<th>Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism Spectrum Disorder (ASD)(^1)</td>
<td>1/59 (live births)</td>
<td>1.5M/2M</td>
<td>Birth</td>
</tr>
<tr>
<td>Rett Syndrome</td>
<td>1/10,000 (fem)</td>
<td>16K/25K</td>
<td>Birth</td>
</tr>
<tr>
<td>Mef2c Haploinsufficiency</td>
<td>Est. 30x that of Rett</td>
<td>150K/200K</td>
<td>Birth</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>1/6,000</td>
<td>60K/90K</td>
<td>Birth</td>
</tr>
<tr>
<td>Alzheimer’s disease(^1,2)</td>
<td>1/50</td>
<td>5.5M/8.8M</td>
<td>65+</td>
</tr>
</tbody>
</table>

1: Multibillion $$ market; 2: †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 - affect millions
• High cost of care & growing - $400 billion currently
• Limited therapeutic options
  • AD -- only 4 drugs approved (3 AChE Inhibitors, memantine/Namenda®)
  • Other neurodeg. -- anti-psychotics
  • ASD – anti-psychotics, SSRI, stimulants
Excessive glutamate release leads to aberrant extrasynaptic (e)NMDAR activity in Alzheimer’s disease (AD) and Autism Spectrum Disorder (ASD), with consequent synaptic damage. Synaptic damage contributes to E/I imbalance (mechanism for this shown in later slides).
Our Approach

- Excessive extrasynaptic (e)NMDAR activity leads to excitatory/Inhibitory (E/I) imbalance of neurotransmission, which is implicated in the pathogenesis of a variety of neurological diseases including Autism Spectrum Disorder (ASD) and Alzheimer’s disease (AD).

- EuMentis has developed EM-036, a proprietary nitro-aminoadamantane. EM-036 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. This prevents excessive activation of eNMDARs to protect synapses and correct E/I synaptic imbalance in a disease-modifying fashion.

- Preclinical data demonstrate dramatic improvement in efficacy of EM-036 over Namenda® in AD and ASD models.

- Scientific Founders developed/patented NMDAR antagonist memantine (Namenda®), most recent drug approved to treat AD ($3B peak annual sales).

- Received $2M in NIH SBIR awards to support IND-enabling work on EM-036.
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, non-psychotic NMDAR antagonist with dual-allosteric mechanism of uncompetitive fast-off rate OCB plus NO donor selectively affecting redox site
- Preferentially acts on overactive eNMDARs and sparing 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
**Dual Allosteric Mechanism of Action of EM-036**

- **EM-036** binds at NMDAR Mg\(^{2+}\) site in the channel, facilitating targeted S-nitrosylation of critical cysteine residues on NMDAR to inhibit activity. Crystal structure published\(^1\)
- EM-036 preferentially inhibits *excessively active* eNMDARs
- *Excessively active* eNMDARs contributes to pathological synaptic damage

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Patch-Clamp Recordings Demonstrate Improved Inhibitory Activity via Channel Block and Targeted S-Nitrosylation of NMDAR

**IC$_{50}$ = 1.7 µM**

**Brain levels [3-4 µM] at therapeutic doses**

Rapid-onset channel block of NMDARs

**EM-036 (µM)**

**EM-036**

10 µM

**NMDA 50 µM**

**Plus prolonged redox-mediated inhibition via S-nitrosylation**

**Biotin-switch Assay Demonstrating S-nitrosylation of principal subunit of NMDAR**

**WT**

**ASD het mouse model**

**Vehicle**

**Mem**

**EM-036**

**SNO-GluN1**

**GluN1**

**Brain levels [3-4 µM] at therapeutic doses**

**250 pA**

**100 s**
Model diseases with hiPSCs that form “Mini Brains” in vitro

MEF2C haploinsufficient hiPSCs and CRISPR/Cas9 isogenic controls generated
Normal Electrical Activity by Calcium Imaging of WT hiPSC-Derived Neurons
Excessive Electrical Activity of MEF2C Haploinsufficient hiPSC-Derived Neurons
NitroSynapsin (EM-036) Treatment of Excessive Electrical Activity of MEF2C Haploinsufficient hiPSC-Derived Neurons
Autism Spectrum Disorder Background

• ASD is a developmental disability that affects the way people communicate, behave, and interact with others socially.

• ASD occurs in 1 in every 59 live births in the USA according to the latest CDC statistics.

• Transcription factor MEF2C drives other major hub genes involved in ASD:
  • Mutations in Mef2c leads to profound ASD and intellectual disability.
  • Mutations in MeCP2 leads to Rett Syndrome.
  • Mutation in TSC leads to Tuberous Sclerosis Complex.

• Thus, therapies aimed at treating MEF2C-associated ASD phenotypes may potentially treat many forms of ASD.
Mef2c-heterozygous Mouse Model of Human MEF2C Haploinsufficiency Syndrome ASD

Comparison

Wild-type (WT): two healthy copies

Mef2c-het: one mutated or deleted copy

Mef2c-het mice show (like hiPSCs in vitro) hyper-excitation resulting in aberrant histology and behaviors
• Het 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 Far Superior to Memantine in Sociability Test

EM-036 (N) 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.
Summary of EM-036 Results in Autism Spectrum Disease Models

- Mef2C heterozygous mice (Mef2c +/-) exhibit symptoms of autism spectrum disorder and intellectual disability such as impaired learning/memory and social aversion

- Treatment with EM-036 improves memory of Mef2c +/- mice in Morris Water Maze Model

- Treatment with EM-036 improves social engagement of Mef2c +/- mice in Sociability Test with stranger mice

- EM-036 is far superior to memantine (Namenda®) in multiple ASD models, including Mef2c Haploinsufficiency, Rett Syndrome, and Tuberous Sclerosis Complex
## Memantine Trials for ASD

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Duration of Treatment</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label- Chez (2.5-30mg/day)</td>
<td>$n=151$ 2-26 yo</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>$n=40$ 4-11 yo</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>$n=18$ 18-47 yo</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, $-28 \pm 25$; $P &lt; 0.001$</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 + ABA (Applied behavior analysis)</td>
<td>$n=60$ &lt;14 yo</td>
<td>12 weeks</td>
<td>Gilliam autism rating scale</td>
<td>Improvement of communication, social interaction, &amp; stereotypic behavior with memantine + ABA vs ABA alone</td>
</tr>
<tr>
<td>RPCT Memantine vs placebo (5-15mg/d) MEM-MD-57A</td>
<td>$n=121$ 6-17yr</td>
<td>12 weeks</td>
<td>SRS, CATS-I, CAASTS-I, CCC-2, CGI-S, CGI-I, and ABC-C</td>
<td>No significant change in primary or secondary endpoints vs placebo in 12-week trial. Trend in improvement in 48wk open-label phase</td>
</tr>
</tbody>
</table>
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
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
Synaptic NMDARs, triggered by normal neurotransmission, promote survival pathways, e.g., the CREB-PGC1α cascade and BDNF expression.

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.

Okamoto... Lipton, Nature Med, 2009; Hardingham and Bading Nat Rev, Neurosci 2010; Talantova... Lipton, PNAS, 2013
EM-036 Blocks Extrasynaptic NMDAR Responses while Sparing Synaptic Responses

**Extrasynaptic NMDAR Responses**

**Synaptic NMDAR Responses**

Greater effect of EM-036 than memantine on eNMDARs

Lesser effect of EM-036 than memantine on synaptic NMDARs
EM-036 Protects Synapses in Alzheimer’s Disease Mice

AD mice = 3xTg
EM-036 Blocks Synaptic Loss and Improves Behavior in AD Mice

Oligomerized Aβ₁₋₄₂

+ Memantine

Oligomerized Aβ₁₋₄₂
+ EM-036

Number of contacts

Old Location
New Location

EM-036
Memantine
Veh

Spine density (No. of spines/μm)

No - + -
+ - +
- + +

Oligomerized Aβ₁₋₄₂
Memantine
EM-036
Summary of EM-036 Results in Alzheimer’s Disease Models

- Transgenic mice with 3 gene mutations (APP Swedish, MAPT-P301L, and PSEN1 M146V) are a model of familial Alzheimer's disease. These 3xTg mice display progressive plaque and tangle pathology and learning and memory deficits.

- Treatment with EM-036 improves neuronal survival as detected by synaptic marker-synaptophysin.

- Treatment with EM-036 protects synaptic connections in response to synaptotoxicity caused by oligomerized Ab\textsubscript{1-42} exposure.

- Treatment with EM-036 improves in Location Novelty Recognition Test in AD model mice.

- EM-036 also effective in a second AD model, hAPP-J20 mice.

- EM-036 is far superior to memantine (Namenda\textsuperscript{®}) in these AD models.
EM-036 Clinical Development Plan

• **Route:** Oral

• **Phase 1a:** SAD in normal healthy volunteers (age >18 yrs)
  • Doses: placebo, 2, 5, 10, 20, 40, 80, and 100 mg po, (6:2 A:P/cohort; n=56)
  • Primary Endpoints: Safety, Tolerability, PK, PD (EEG- ERPs & EROs)

• **Phase 1b:** MAD in MEF2C or Rett Syndrome patients (age >18 yrs)
  • Doses: P, L, M, H Phase 1a dose which gave peak PD markers; (8/cohort; n=32)
  • Treatment: 7 days, QD or BID
  • Primary Endpoints: safety, PK, PD (EEG gamma oscillations or SV2A PET neuroimaging)
  • Secondary endpoints: PD (biomarkers), Irritability & agitation

• **Phase 2:** Multiple Phase 2a Studies in Rett Syndrome, MEF2C Haploinsufficiency and Alzheimer’s Disease

• **TPP:** Daily treatment to improve or stabilize cognitive function, and reduce irritability and agitation
Potential PoC Clinical Endpoints

• 36 patients Stage 1-2 ASD confirmed MECP2 or MEF2C mutation; 6 mos treatment

• Primary Endpoint
  • Rett Syndrome Clinical Severity Score (physician outcome measure). Similar measures for MEF2C since in same genetic pathway as MECP2.
  • Changes from baseline through last study visit in safety assessments.

• Secondary Endpoints
  • Rett Syndrome Natural History Motor Behavior Assessment (RSBA), Aberrant Behavior Checklist (ABC), Vineland Adaptive Behavior Scale (VABS), Clinical Global Impression of Severity (CGI-S), Hand Apraxia Scale
  • Social Responsiveness Scale (SRS) and Resident Behavior Rating Scale (RBRS)
  • EEG activity (absolute change in number of spikes per hour during the awake state, gamma oscillations (decreased in ASD; increased by aminoadamantane drugs)
  • Autonomic function, i.e. respiratory rhythm, hyperventilation, apneas, oxygen desaturation, heart rate variation and cardiorespiratory coupling and body temperature
  • Growth (height, weight, head circumference)
Management Team

Mark Tepper, Ph.D.

**President & Chief Executive Officer**

- Ph.D. Columbia Univ, 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
- Key member of project teams which developed the following marketed drugs: Taxol® (Ovarian Cancer, 2000 peak sales of $1.6B), Orencia® (RA, 2018 sales of $3B), Rebif® (MS, 2013 sales of $2.59B), Gonal-F® (Fertility, 2013 sales of $815MM), lenabasum (2020 Phase 3 readout)

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.
- Co-inventor on memantine patent (Namenda®)
Scientific Advisory Board

Stuart Lipton, M.D., Ph.D.
**Scripps Research Institute, La Jolla**
- Harvard-trained board-certified neurologist- KOL
- Scientific Founder of EuMentis Therapeutics
- Developer/Patent Holder for memantine (Namenda®, NamendaXR®, Namzaric®); FDA-approved for Alzheimer’s disease
- Preclinical studies of EM-036 in MEF2C haploinsufficiency, Rett syndrome, Tuberous Sclerosis, Alzheimer’s disease
- Has run advanced human clinical trials for dementia & presented to FDA regulators

Jeffrey L. Neul, M.D., Ph.D.
**Vanderbilt School of Medicine**
- Expert in neurodevelopmental disorders/ASD including Rett Syndrome
- Lead PI on Rett syndrome clinical trials (Ketamine P3 & ours)
   • 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
## Competitive Landscape

### Rett Syndrome

<table>
<thead>
<tr>
<th>Product</th>
<th>Class/Target</th>
<th>MoA</th>
<th>Company</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM-036</td>
<td>Nitro-aminoadamantane</td>
<td>eNMDAR antagonist</td>
<td>EuMentis</td>
<td>IND</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>S1P receptors</td>
<td>S1PR antagonist</td>
<td>Novartis</td>
<td>Phase 1</td>
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<tr>
<td>BHV-5000</td>
<td>Lanicemine prodrug</td>
<td>NMDAR antagonist</td>
<td>BioHaven</td>
<td>Phase 1</td>
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<tr>
<td>EPI-743</td>
<td>15-Lipoxygenase</td>
<td>Anti-inflammatory</td>
<td>BioElectron</td>
<td>Phase 2</td>
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<tr>
<td>Trofinetide/NNZ-2566</td>
<td>IGF-1 Tripeptide mimetic</td>
<td>Augments IGF-1 signaling</td>
<td>Neuren/Acadia Pharma</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Sarizotan</td>
<td>5HT-1A receptor agonist</td>
<td>Serotonin modulator</td>
<td>Newron</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Dissociative</td>
<td>NMDAR antagonist</td>
<td>RS-RT</td>
<td>Phase 2</td>
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</table>

### Mef2C Haploinsufficiency

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<td>None</td>
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</table>
Summary

• Strong scientific rationale for EM-036
  • Unique non-psychotic, eNMDAR antagonist
  • Protects synapses
  • Corrects underlying E/I imbalance in ASD and AD
  • Improved activity with differentiation from memantine
  • Safe, well-tolerated in animals

• Compelling business case:
  • Streamlined regulatory path: Fast Track, Breakthrough, Priority Review Voucher eligibility
  • Memantine success de-risks path in AD
  • Earliest patent expiry of 2038
  • Experienced scientific founders and operational team
  • Potential for platform targeting other eNMDAR-mediated indications
Thank you!

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