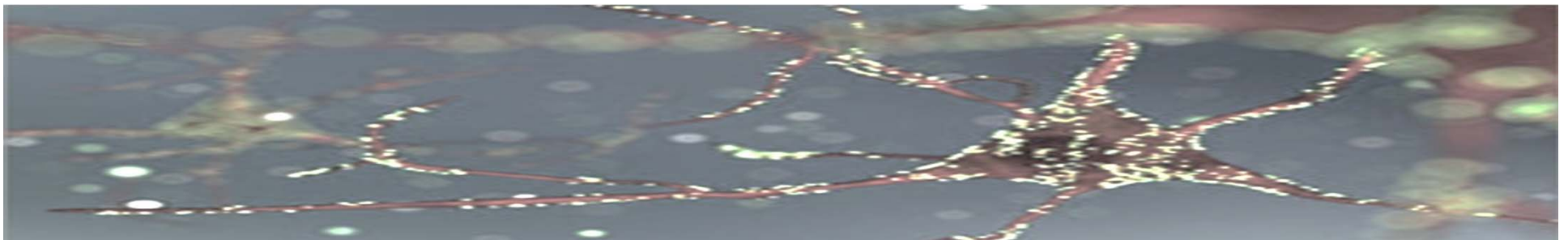


# NEURALSTEM INC.

June 2016 Corporate Presentation



# NEURALSTEM, INC.

## *Safe Harbor Statement*

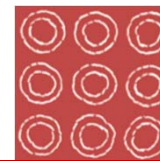
Safe Harbor statements under the Private Securities Litigation Reform Act of 1995: This presentation contains forward-looking statements as defined in Section 27A of the Securities Act of 1933 as amended, and section 21E of the Securities Exchange Act of 1934, as amended. Such forward-looking statements are based upon Neuralstem, Inc.'s management's current expectations, estimates, beliefs, assumptions, and projections about Neuralstem's business and industry. Words such as "anticipates," "expects," "intends," "plans," "predicts," "believes," "seeks," "estimates," "may," "will," "should," "would," "potential," "continue," and variations of these words (or negatives of these words) or similar expressions, are intended to identify forward-looking statements. In addition, any statements that refer to expectations, projections, or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. These forward-looking statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict. Therefore, our actual results could differ materially and adversely from those expressed in any forward-looking statements as a result of various risk factors. These risks and uncertainties include the risks associated with the effect of changing economic conditions, trends in the products markets, variations in Neuralstem's cash flow, market acceptance risks, technical development risks and other risk factors detailed in Neuralstem's Securities and Exchange Commission filings.

Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this presentation as a result of, among other factors, the factors referenced in the "Risk Factors" section of our Annual Report on Form 10-K for the year ended December 31, 2015 filed with the Securities and Exchange Commission on March 14, 2016. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this presentation, they may not be predictive of results or developments in future periods. Any forward-looking statements that we make in this presentation speak only as of the date of such statement, and we undertake no obligation to update such statements to reflect events or circumstances after the date of this presentation, except as required by law.

You should read carefully our Special Note Regarding Forward-Looking Statements and the factors described in the "Risk Factors" section of our Annual Report on Form 10-K for the year ended December 31, 2015 filed with the Securities and Exchange Commission on March 14, 2016, to better understand the risks and uncertainties inherent in our business.

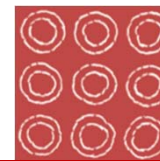
# Key Highlights

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- **Refocused Business Strategy:**
  - New, experienced management team
  - Focus on lead program: NSI-189
  - Internal reorganization
  - Partner NSI-566 programs
- **May 2016 \$9mn Financing**
- **NSI-189: Novel Neurogenic Small Molecule targeting MDD**
  - Compelling early clinical data
  - Intellectual property portfolio, protection expiring from 2016-2034
  - Near term milestones: Phase II MDD Data expected 2H17
  - Renowned scientific advisory team
- **NSI-566**
  - Partner for continuing development

# Management



Richard Daly, CEO	<ul style="list-style-type: none"><li>• President, AstraZeneca Diabetes, US; President, BMS Diabetes, US; Co-Founder &amp; Partner, SagePath Partners; EVP, Takeda Pharmaceuticals (North and South America); VP, Commercial Strategy, TAP Pharmaceuticals</li><li>• Boards: Catalyst Pharmaceuticals; Synergy Pharmaceuticals</li><li>• Education: MBA, Kellogg Graduate School of Management; BS, Microbiology, University of Notre Dame</li></ul>
Dr. Karl Johe, CSO	<ul style="list-style-type: none"><li>• Co-founder, Chairman of the Board of Neuralstem; NIH/NINDS Staff Scientist</li><li>• Education: Post-doctoral fellow, UCSF; Ph.D, Biochemistry, Albert Einstein College of Medicine; MA/BA, Biochemistry, University of Kansas</li></ul>
Jonathan Lloyd Jones, CFO	<ul style="list-style-type: none"><li>• Sr. Director, Corporate Development, Genzyme Corporation; V.P Finance, TransMolecular; CFO and V.P Corporate Development, TetraLogic; CFO, Columbia Laboratories, Inc.</li><li>• Professional Qualification: Chartered Accountant, Institute of Chartered Accountants in England &amp; Wales.</li><li>• Education: MBA, University of Pennsylvania Wharton School of Business; BSc. Business Studies, University of Bradford</li></ul>

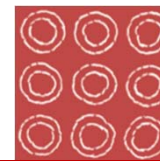
# NSI-189 Scientific Advisory Board



## World Class Psychiatric, Clinical and Regulatory Experts

Dr. Maurizio Fava	Harvard, MGH, Executive Vice Chair, Dept. of Psychiatry Principal Investigator: NSI-189 Phase 2 MDD clinical trial
Dr. Michael Thase	Univ. of Pennsylvania, Chief, Division of Mood and Anxiety Disorders Treatment and Research Program
Dr. Mark Frye	Mayo Clinic, Chair, Psychiatry and Psychology
Dr. John Greden	Univ. of Michigan, Founder and Executive Director, Healthy System Depression Center
Dr. Richard Keefe	Duke Institute for Brain Sciences, Director Schizophrenia Research Group
Dr. Thomas Laughren	Harvard, MGH, Director, Regulatory Affairs, Former Director of Psychiatric Division, CDER, FDA

# Pipeline



Compound / Indication	Preclinical	Phase I	Phase II	Phase III	Status*
<b>Small Molecule: Lead Asset</b>					
NSI-189 US Major Depression Disorder					Results 2H17 <sup>(1)</sup>
NSI-189 Pipeline Expansion					Update 2Q16 <sup>(2)</sup>
NSI-189 & undisclosed Multiple POP studies					Publications <sup>(3)</sup> 2016
<b>Cell Therapy (outsourced funding)</b>					
NSI-566 ALS, cSCI, Stroke					BD initiatives <sup>(4)</sup>

Status\*

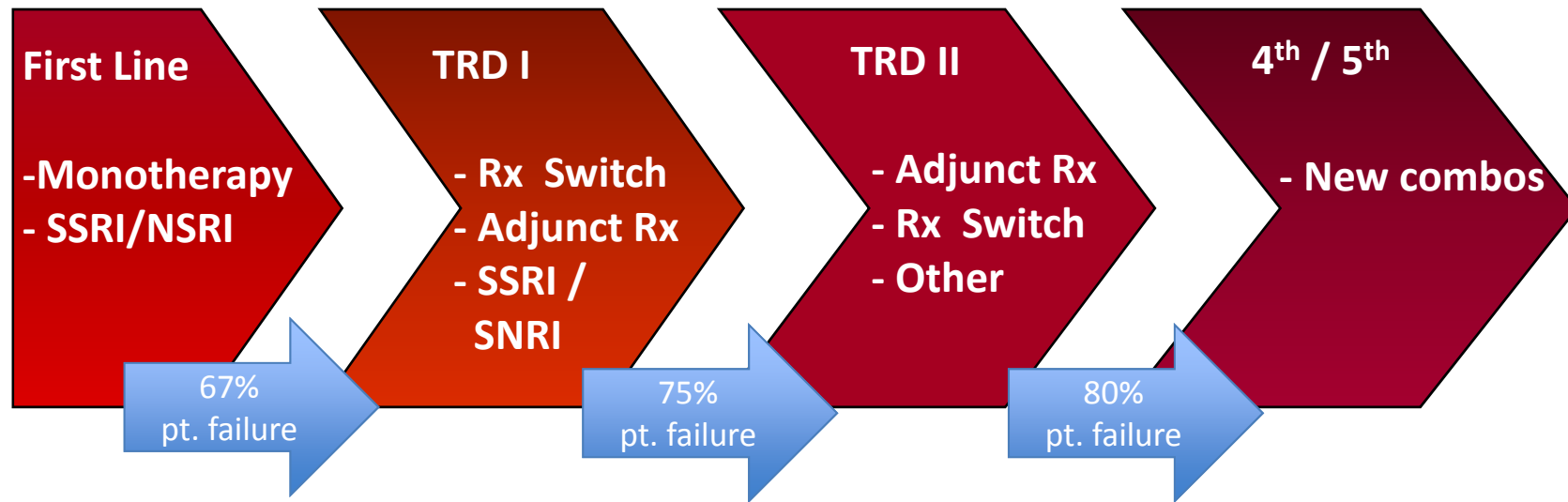
(1) Phase II MDD clinical trial results to be provided 2H17

(2) Second Indication to be determined in 2Q16

(3) Ongoing preclinical studies in NSI-189 and other undisclosed compounds. Multiple NSI-189 POP publications to be submitted in 2016

(4) NSI-566: Active efforts to pursue partnerships

# MDD Market Opportunity



US Market: Estimated 14.8 mn patients\*

Patients	First Line	TRD I	TRD II	4th line +
% patients in given line of therapy	33%	17%	10%	40%
% patients that fail given line of therapy	67%	75%	80%	N/A

Information regarding patient failure derived from: Rush AJ, Fava M, et al; *Am J Psychiatry* 163:11, November 2006

\* Anxiety and Depression Association of America (ADAA), website: <http://www.adaa.org/about-adaa/press-room/facts-statistics> retrieved March

# NSI-189 Overview



- Unique New Chemical Entity (NCE)
  - Novel neurogenic MOA
  - Highly stable and well characterized
- MDD Market Opportunity
  - Unsatisfied patient population\*
  - High patient turnover rate in MDD\*
  - Strong IP position through 2024 (2029 with patent term extension)
- Efficacy:
  - Compelling Phase Ib MDD randomized, double-blind data
  - Large effect size
  - Cognitive benefit profile
  - Potential disease modifying, durability profile
  - Excellent safety profile
- Upcoming Data
  - Additional human data
  - Preclinical data in 4 indications

• Gaynes BN, et al; A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR\*D clinical trial. Gen Hosp Psychiatry. 2005 Mar-Apr;27(2):87-96 and Rush AJ, Fava M, et al; STAR\*D Investigators Group. Sequenced treatment alternatives to relieve depression (STAR\*D): rationale and design. Control Clin Trials. 2004 Feb;25(1):119-42.



# Building the Case for MOA



Extensive screening showed novel MOA  
vs. currently marketed therapies

## Screening:

- **52 neurotransmitter related receptors/ion channels/enzymes**

Novoscreen: Adenosine, GABA, Glutamate, Histamine, Muscarinic, Nicotinic, norepinephrine, opioid, or and serotonin receptors, Ca<sup>++</sup>, Cl<sup>-</sup>, K<sup>+</sup> channels, PKA, PKC, CRF, MAO-A/B, or CREB and ERK pathways (related to BDNF release)

- **900 other kinases**

## NSI-189 Binding Activities $\geq 50\%$ at 10 $\mu$ M

Target	IC50 ( $\mu$ M)
Dopamine Transporter (h)	14.2
Norepinephrine Transporter (h)	1.1
5-HT Transporter (h)	>30
5-HT3 Receptor	2.1
5-HT7 Receptor (h)	11.1
Opioid mu Receptor (h)	15.7
Opioid delta 1 Receptor	12.7

# Clinical Results from NSI-189 MDD Phase Ib



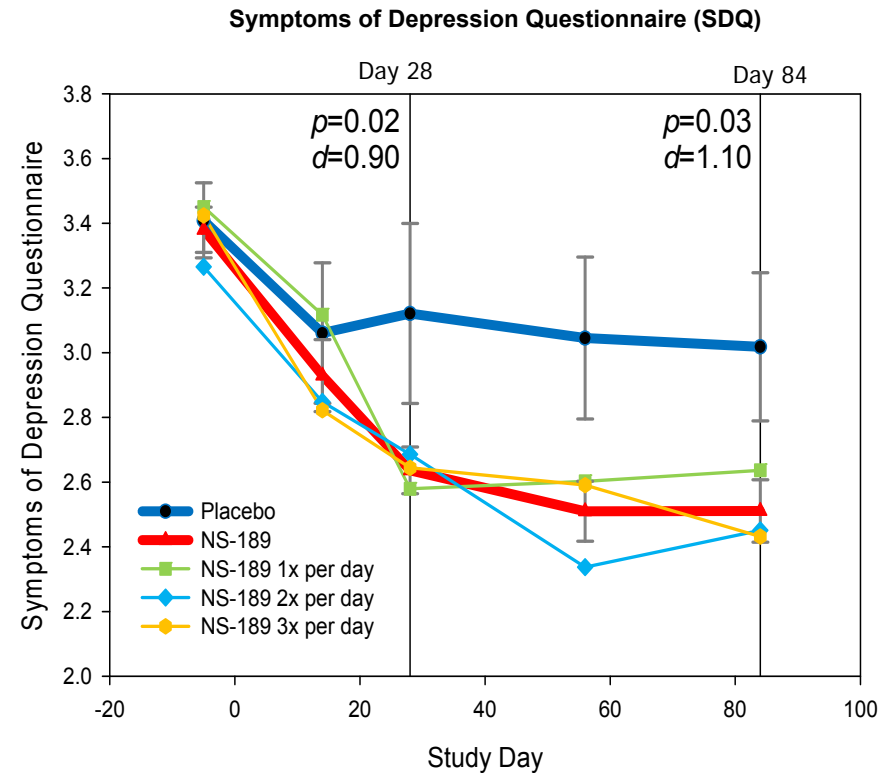
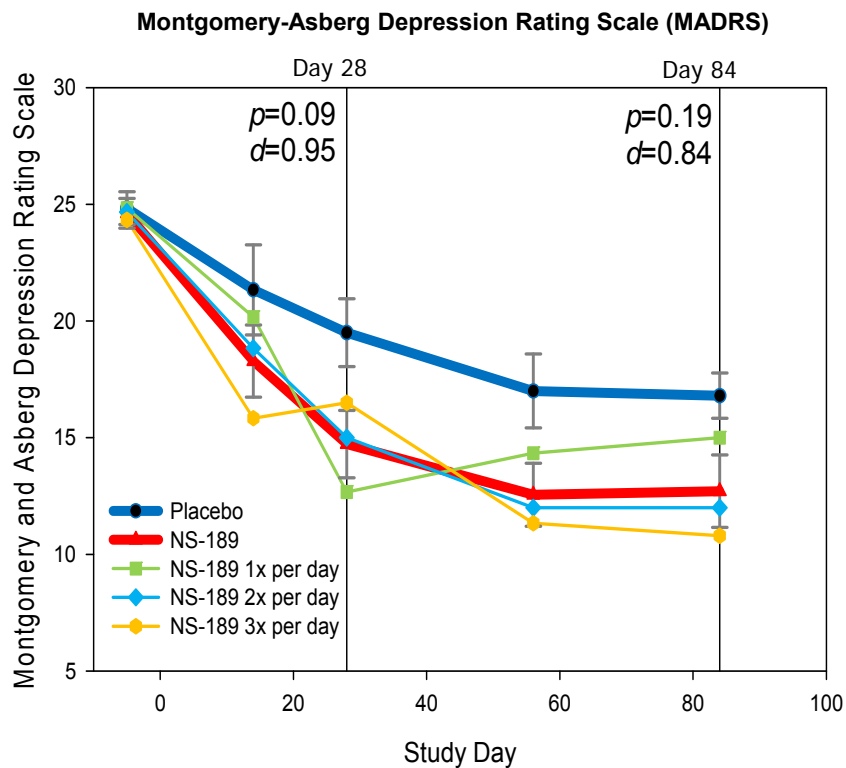
***NSI-189 Phase Ib double-blind, randomized, placebo-controlled, dose-escalating study assessing safety and tolerability***

<b>Cohort 1</b>	N=8 (6 drug, 2 placebo)	40 mg QD
<b>Cohort 2</b>	N=8 (6 drug, 2 placebo)	40 mg BID
<b>Cohort 3</b>	N=8 (6 drug, 2 placebo)	40 mg TID

<b>Acute treatment: 28 days</b>	<b>Follow up: Days 35, 42, 49, 56, 70, 84 (End-of-study)</b>
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- Early indication of efficacy in MDD and Cognition
- Large effect size

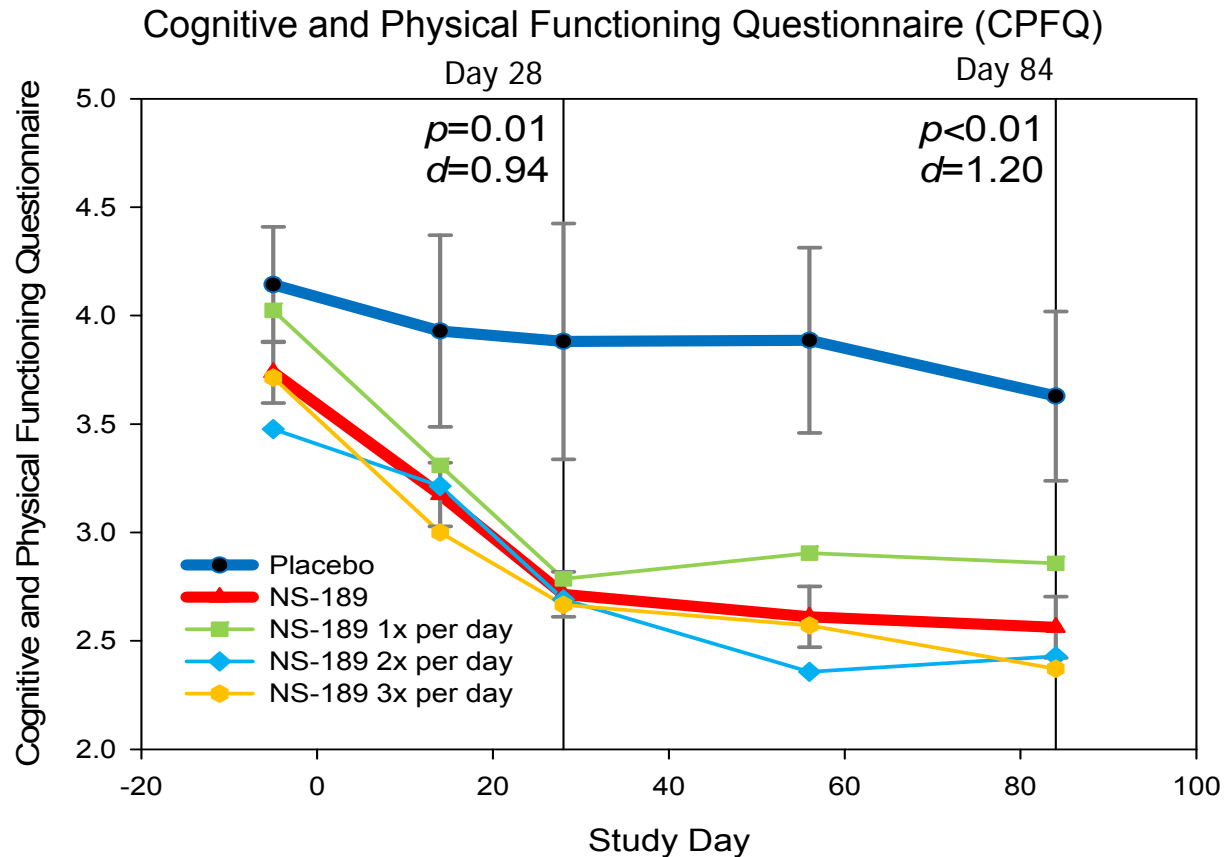
# Clinical Results from NSI-189 MDD Phase Ib



- Large effect size ( $d = 0.95$ ) MADRS
- Responder ( $\geq 50\%$  reduction in MADRS): 10/18 or 56%;
- Remission ( $\leq 10$  score in MADRS): 9/18 or 50%
- Encouraging durable effect

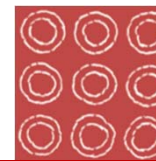
All: A Phase 1B, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Escalation Study Evaluating the Effects of NSI-189 Phosphate, a Neurogenic Compound, in Patients with Major Depressive Disorder (MDD), presented June 2014, by Maurizio Fava, M.D., Karl Johe, Ph.D., Lev G. Gertsik, MD, Larry Ereshefsky, PharmD, Bettina Hoepfner, Ph.D., Martina Flynn, David Mischoulon, M.D., Ph.D., Gustavo Kinrys, M.D., and Marlene Freeman, M.D.

# Clinical Results from NSI-189 MDD Phase Ib



- Large effect size ( $d=0.94$ ) in cognitive function improvement
- Persistent improvement over the drug-free 8 weeks in CPFQ

# Biomarker Results from NSI-189 MDD Phase Ib



## Blood biomarker panel:

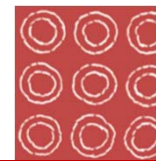
- Blood panel analysis correlates to MADRS response rate
- MDD panel was developed based on SSRIs activity profile
- Rapid and persistent efficacy

Response Rate	Partial Responder (<14) + Responders (≥ 50%)	Responder (≥ 50%)	Remission (≤ 10)
By MADRS	13/18 (72%)	10/18 (56%)	9/18 (50%)
By Blood Panel	13/18 (72%)		

## 10 Biomarkers:

- A1AT
- ApoC3
- BDNF
- Cortisol
- EGF
- MPO
- Prolactin
- Resistin
- TNFR2
- TSH

# Biomarker Results from NSI-189 MDD Phase Ib

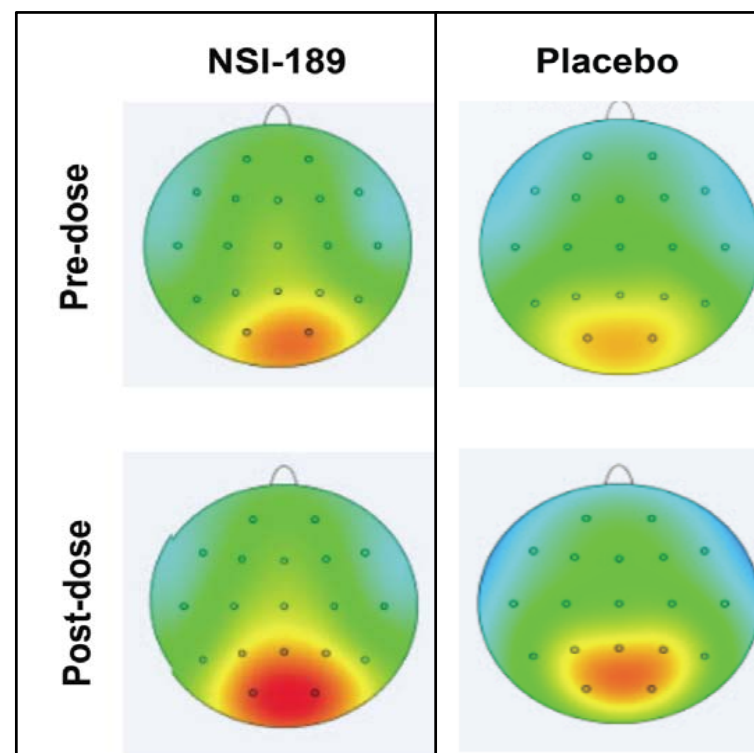


## qEEG

### Quantitative EEG (qEEG) biomarker:

- Increases coherence activity between prefrontal cortex and hippocampus
- Two coordinating brain centers utilized for depression and cognition

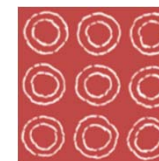
Topographs of High Frequency alpha (10-12 Hz): Day 28 from Baseline



Left posterior temporal (T5) ( $t=2.45$ ,  $p=0.02$ )

Left parietal regions (P3) ( $t=3.31$ ,  $p=0.004$ )

# NSI-189 MDD Phase Ib: Adverse Events



<b>Side effect</b>	<b>Pooled placebo</b>	<b>40mg q.d.</b>	<b>40mg b.i.d.</b>	<b>40mg t.i.d.</b>	<b>Pooled active</b>	<b>Pooled placebo</b>
	<b>(n=6) N (%)</b>	<b>(n=6) N (%)</b>	<b>(n=6) N (%)</b>	<b>(n=6) N (%)</b>	<b>(n=18) N (%)</b>	<b>(n=6) N (%)</b>
<i>Autonomic</i>						
Dry mouth	0 (0%)	0 (0%)	2 (33.3%)	0 (0%)	2 (11.1%)	-
Palpitation	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (5.6%)	-
<i>CNS/psychiatric</i>						
Headache	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	9 (50%)	3 (50%)
Dizziness	1 (16.7%)	0 (0%)	1 (16.7%)	4 (66.7%)	5 (27.8%)	1 (16.7%)
Somnolence	1 (16.7%)	3 (50.0%)	1 (16.7%)	1 (16.7%)	5 (27.8%)	1 (16.7%)
Fatigue	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (5.6%)	-
Restlessness	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)	-
Poor quality of sleep	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (5.6%)	-
Nightmare/vivid dream	0 (0%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (16.7%)	-
Paresthesia	0 (0%)	1 (16.7%)	0 (0%)	1 (16.7%)	2 (11.1%)	-
Insomnia	0 (0%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (16.7%)	-
Irritability	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (5.6%)	-
Difficulty concentrating	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	-	1 (16.7%)
Hyperthymia	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	-	1 (16.7%)
<i>Gastrointestinal</i>						
Dyspepsia	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	-	1 (16.7%)
Abdominal pain	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	-	1 (16.7%)
Nausea	0 (0%)	0 (0%)	0 (0%)	2 (33.3%)	2 (11.1%)	-
<i>Skin and subcutaneous tissue disorders</i>						
Skin pain	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (5.6%)	-
Rash	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)	-

# NSI-189 Phase II MDD Trial



***Randomized, Double-Blind, Placebo-Controlled, 2-Dose Study***

## **Milestones:**

- First Patient enrolled May 2016
- Phase 2 Results expected 2H17

## **Study Objectives**

- Primary: Montgomery-Asberg Depression Rating Scale (MADRS)
- Secondary: SDQ, HAMD17, CGI-S, CPFQ, SFI, Cogscreen Battery, Cogstate Brief Battery

**Principal Investigator:** Maurizio Fava, M.D. Slater Family Professor of Psychiatry at Harvard Medical School, Massachusetts General Hospital



# NSI-189 Phase II MDD Trial



## *Placebo-reducing, Study Design*

### Innovative Trial Design

- Experienced MDD trial sites (n=12)
- Dual patient screening requirement
  - Secondary confirmatory screen: independent, remote MADRS diagnosis by MGH
- Placebo-reducing prescreen process, re-randomization

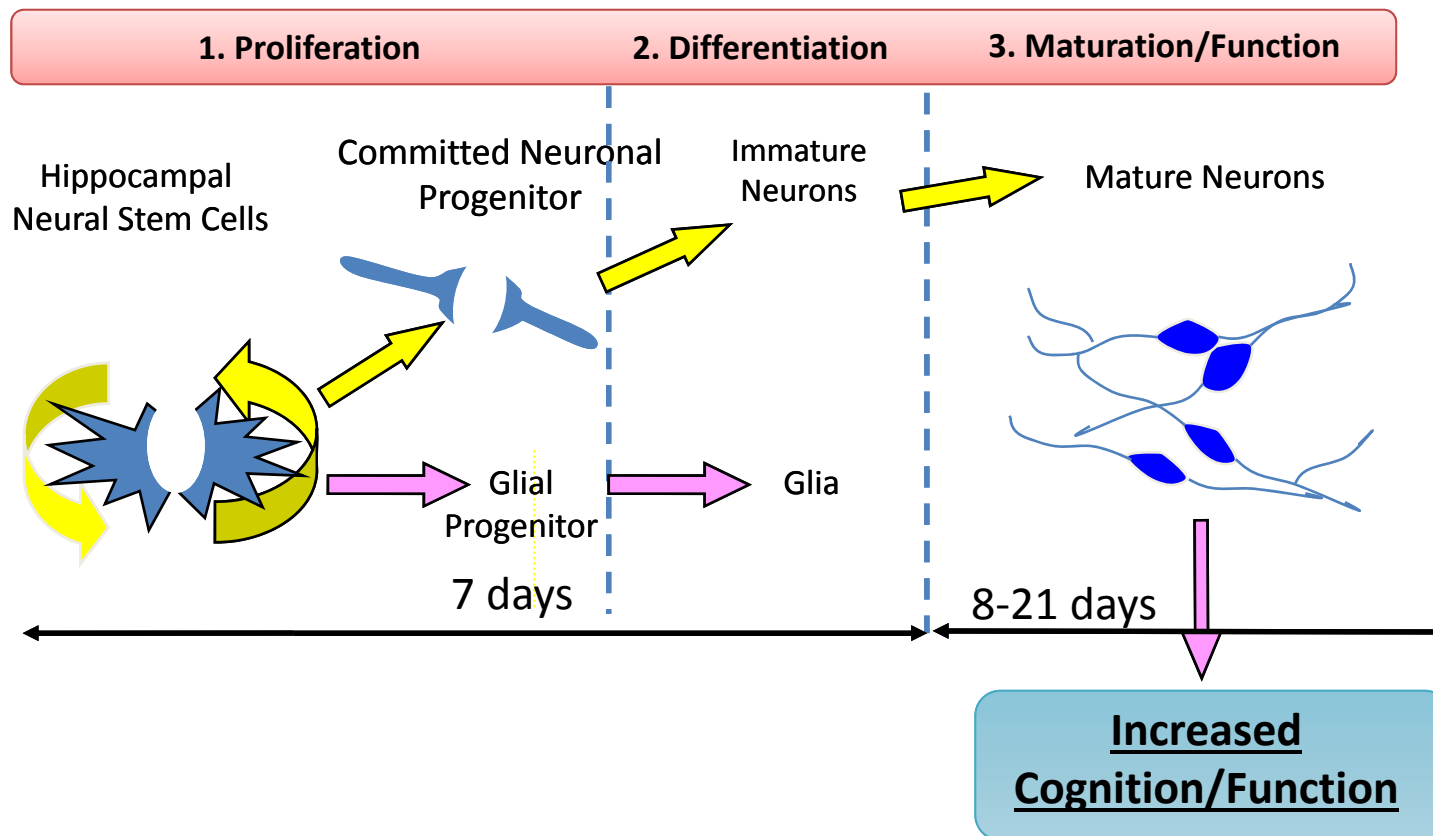
### Study Design

- Three arm: 40mg BID, 40mg QD, & placebo (n=220 randomized)
- Power: >80%, 2-sided  $p \leq 0.05$ ;  $d=0.5$ 
  - Potential registration study
- 12 week study; 6 month follow-up study

# Pipeline Expansion

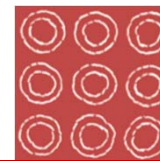


- Based on human neural stem cell differentiation in vitro
- Through the use of our proprietary drug screening platform
- Captures large window of neurodevelopment: neurogenesis to synaptogenesis
- Multiple potential sites of action during stages of neurogenesis
- Anticipated to identify additional indications



# Key Highlights

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- Experienced Management Team
- Recent \$9mn Capital Raise
- Implementation of Reorganization
- Lead Candidate: NSI-189 novel neurogenic small molecule
- Protected IP: 2024 (2029 with patent term extension) – New Chemical Entity
- Near term milestones:
  - Phase II MDD trial; results expected 2H17
  - Preclinical POP publications; expected 2016
  - Additional human data
  - Pipeline expansion opportunities
- Compelling randomize, double blind, Phase Ib MDD data, large effect size
  - Supporting biomarker data
  - Potential disease modifying
- Phase II MDD innovative trial design
- Cell therapy business development opportunities

# Intellectual Property



## Small Molecule

### 11 US & 65 World Issued and Pending Patents

- 16 Neurogenic compounds (including 189), composition of matter, US (7,560,553) to 2024, Patent Extension to 2029.
- Assay method for screening neurogenic compounds, US (8,293,488) and Europe to 2023
- Synthesis method for NSI-189, World-wide to 2030
- Treatment of MDD, World-wide, pending (filing date 6/2015)

## Neural Stem Cells

### 13 US & 63 World Issued and Pending Patents\*

- Adherent neural stem cells, composition of matter (US 5,753,506) to 2016
- Stable neural stem cells, composition of matter (US 7,544,511) to 2016
- Method of culturing human neural stem cells (US 7,691,629) to 2025
- Method of expanding human neural stem cells (US 8,236,299) to 2025

\* The Company also licenses 3 U.S. and 6 foreign patents related medical devices used in connection with the Company's stem cell therapies.