

## 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 fillings. For links to SEC documents please visit the company's Web site: neuralstem.com.

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, 2016 filed with the Securities and Exchange Commission on March 14, 2017, Form 10-Q for the period ended September 30, 2017, an in other reports filed with the SEC. 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 bylaw.

## Topics



Highlights



Platform/Pipeline



NSI-189: Major **Depressive Disorder** 

Overview Clinical Results **Preclinical Programs** 





NSI-566: ALS, Stroke, **cSCI** 

Overview Clinical Results



**Execution** 



**Scientific Advisory Board** 



**Financials** 

08

Management

### 1. Key Highlights

### **Lead Program**

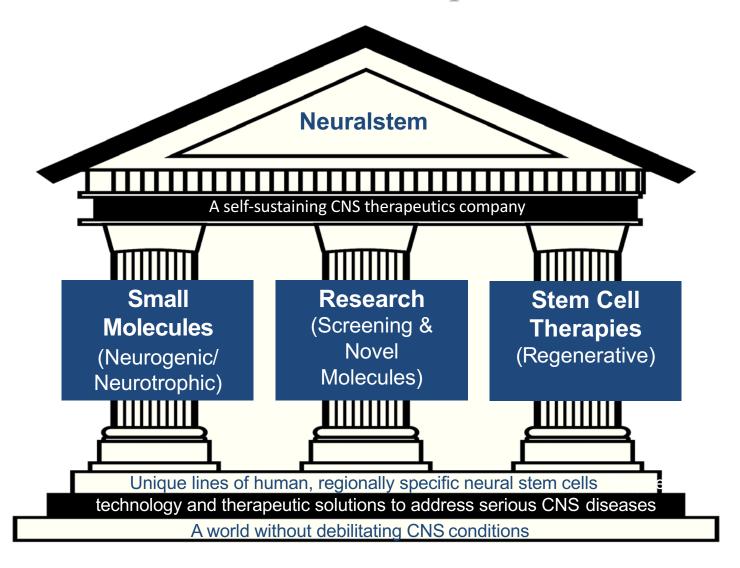
- Novel neurogenic small molecule approach
- NSI-189: Positive, randomized placebo-controlled Phase 1b in MDD
- Phase II Exploratory Study in Major Depressive Disorder (MDD)
  - Key metrics:
    - Montgomery-Asberg Depression Rating Scale (MADRS) primary endpoint
    - Secondary endpoints:
      - Physician reported
      - Patient reported
      - Cognition
  - Long-term durability data anticipated in 1H 2018
  - Strong IP position through 2035

### **Cell Therapy Strategy**

- NSI- 566 biological activity across three indications
- Improving regulatory environment: US, Japan, China
- Partnering efforts underway for continuing development

Cash balance as of 3Q17 expected to last through 2018

## 2. The Neuralstem Platform/Pipeline



## 2. The Neuralstem Platform/Pipeline

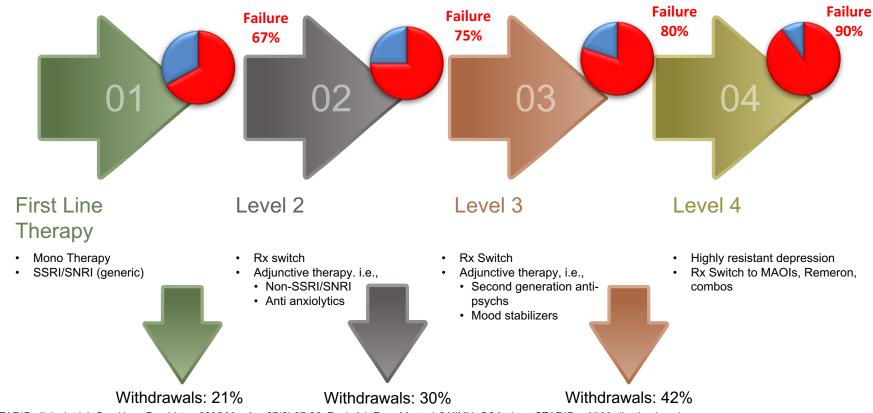
Therapy	Indication	Preclinical	Phasel	Phasell	PhaseIII	Status	
Small Molecule:	Small Molecule: LeadAsset						
	Major Depressive Disorder (MDD)					ToplineResults Reported	
	Long-term Follow- up Study(MDD)					6 Month Observation Ongoing	
	Supplementary Pr	eclinical Program f	or Signal Generation	on			
	Angelman Syndrome						
	IschemicStroke						
NSI-189	Type 1 & 2 Diabetes-related Neuropathy					Ongoing	
	Irradiation-induced Cognitive Deficit						
	LTP Enhancement (cognition)						
Cell Therapy (to be advanced with external funding)							
	Amyotrophic Lateral Sclerosis (ALS)					— BD Initiatives	
NSI-566	ChronicSpinal Cord Injury					Dominians	
1101 000	IschemicStroke						

## 3. NSI-189:

A New Chemical Entity for Major Depressive Disorder and Other Debilitating CNS Conditions

## Major Depressive Disorder: Overview

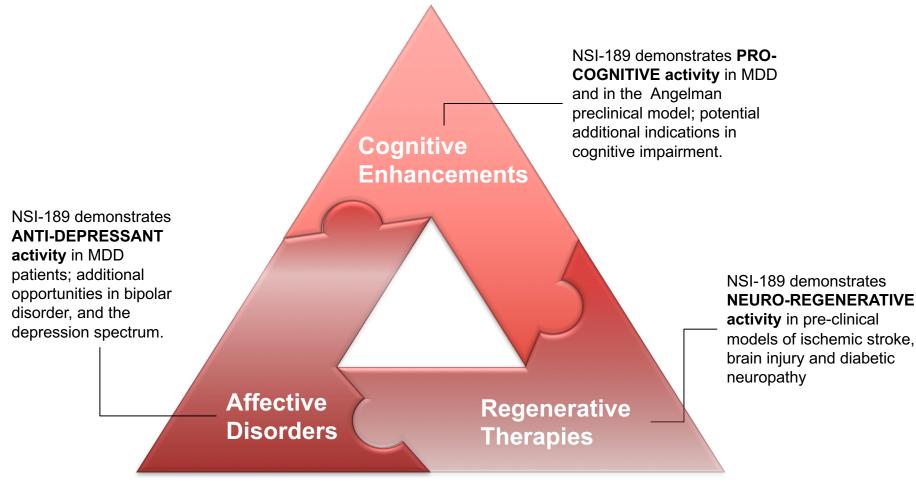
- Large, Unmet Medical Need: 16M US Patients<sup>1</sup>
- Overall, about 50% of patients in therapy fail to receive sufficient benefit<sup>2</sup>
- However, many patients may withdraw from therapy before the full benefits can be realized<sup>3</sup>
- Large patient Rx turnover due to low efficacy results in high market churn
- Highly dissatisfied market: efficacy, poly pharmacy, adverse events



1 NIMH; 2 STAR\*D clinical trial. Gen Hosp Psychiatry. 2005 Mar-Apr;27(2):87-96. Rush AJ, Fava M, et al; 3 NIMH: Q&A about STAR\*D – All Medication Levels



## NSI-189 Clinical Development Approach: A Functionally-Driven Development Strategy



Provides the potential for a broad development paths in CNS

### NSI-189's Activities and Potential Benefits & Indications

- Neurogenesis:
  - -reversal of stress-induced damage
    - treatment-resistant depression
- Rapid, long-lasting, synaptic plasticity:
  - -improvement of working memory, executive functioning
    - •cognitive impairment in schizophrenia, bipolar, age-associated memory loss, mental retardation, epilepsy, ADHD, autism-spectrum disorder
- Synaptogenesis:
  - -repair and remodel post injury
    - •recovery from stroke, TBI, neurodegenerative diseases
- Neurotrophic activity:
  - —nerve growth and regeneration
    - peripheral neuropathy due to diabetes, chemo-toxicity

2

## NSI-189: Phase 2 Exploratory MDD Trial Design

### **Study Objectives**

- Primary: Montgomery-Asberg Depression Rating Scale (MADRS)
- Secondary\*: SDQ, HAM-D17, CGI-S, CPFQ, SFI
- Exploratory: Cogscreen Battery, Cogstate Brief Battery

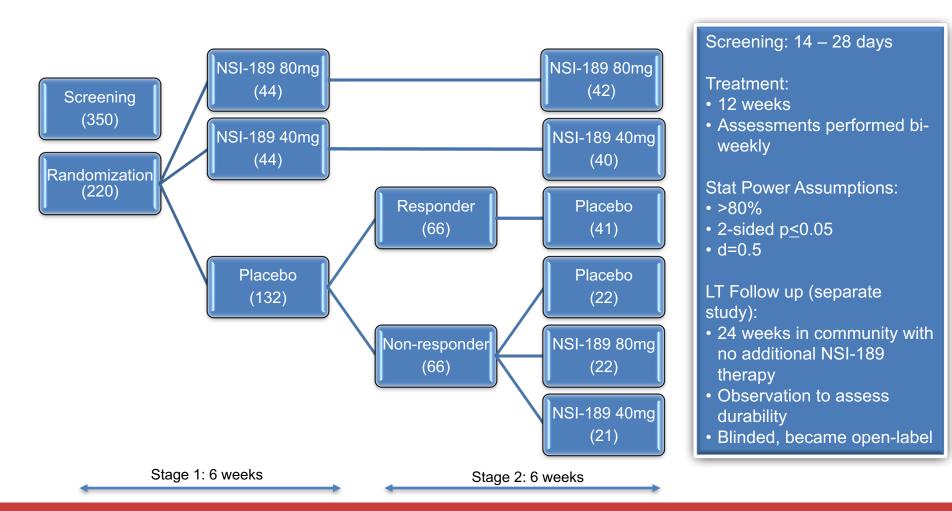
### **Innovative Study Design**

- Randomized, double blind, 3 cohorts (n=220): 40mg QD, 40mg BID & placebo
- 12-week study, additional 6 month follow-up study
- Fewer, quality MDD trial sites (n=12)
- SAFER Interview: confirmatory, independent, remote MADRS diagnosis by MGH
- Prescreen process to manage placebo risk
- Potential registration study if successful in either active arm
  - Power: >80%, 2-sided p≤ 0.05
  - Cohen effect size: d=0.5

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

\*Symptoms of Depression Questionnaire (SDQ) Hamilton Depression Rating Scale 17-items (HAM-D17) Clinical Global Impressions Scale (CGI-S) Cognitive and Physical Functioning Questionnaire (CPFQ) Sexual Functional Index (SFI)

## NSI-189 P2 MDD Exploratory Study Design



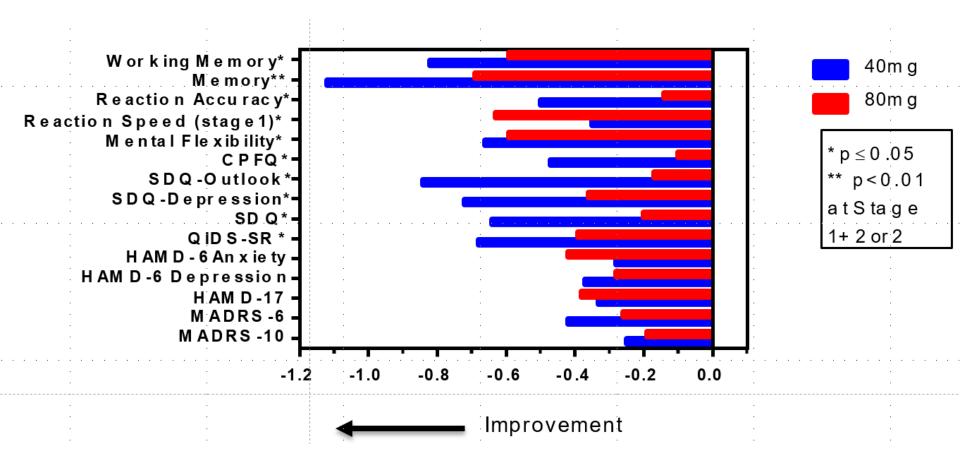
## MDD Phase 2a Study Endpoints/Results

Endpoint	Validated/ FDA Accepted	40mg stat sig (combined)	Cohen's d (stage 2)	80mg statsig (combined)	Cohen's d (stage 2)
MADRS (Primary)	Yes/Yes	No	0.25	No	0.19
HAMD-17	Yes/Yes	No	0.33	No	0.38
QIDS-SR (patient reported)	Yes/No	p=0.040*	0.68	No	0.39
SDQ (patient reported)	Yes/No	p = 0.044	0.64	No	0.20
CPFQ (patient reported)	Yes/No	p=0.035	0.47	No	0.10
Clinical Global Impressions	Yes/Yes (2°)				
CGI-I		Trend p=0.148	0.58	Trend p=0.081	0.46
CGI-S		Trend p=0.132	0.56	Trend p=0.055	0.66
Cogstate Brief Battery	Yes/No	No	0.2-0.3	No	0.2-0.3
CogScreen	Yes/Yes (safety or	nly)			
Executive functioning		p=0.048	0.66	Trend P=0.150	0.59
Attention		P=0.034	0.27	No	0.17
Memory		p=0.002	1.12	p=0.015	0.69
Working memory		p=0.020*	0.81	Trend P=0.125	0.51

<sup>\*</sup>significant in Stage 2 only



## Stage 2 Cohen's d Effect Size



## Summary MDD Phase 2a Study -- Safety

- **Side effects**: Fewer subjects than the placebo with symptoms and signs associated with MDD
- Vital Signs: No clinically meaningful changes in body weight or BMI
- ECG: No clinically significant changes
- Sexual Functioning Inventory: No clinically meaningful changes
- Suicidal Ideation: No clinical meaningful changes
- **Drop-outs** in Stage 1 = 25 (19%) Placebo : 5 (5%) Active Suggests that disease burden is less in active group, a sign of positive drug effect

## Greater number of MDD-related symptoms in Placebo than Active

Another sign of positive drug effect

## NSI-189 Pre-clinical Data

Insight into MOA and Support for Broad Potential in CNS



### Pre-clinical Overview

Preclinical data suggests a <u>new paradigm</u> of reversing damage caused by disease/injury

- Restores LTP of Angelman Syndrome mouse brain
- Enhances short-term and long-term potentiation of normal mouse brain
- Enables faster, better, durable recovery after ischemic stroke in rat, that corresponds with increased neurogenesis - and synaptic remodeling
- Ameliorates cognitive deficit in irradiated rat
- Prevents/Reverses Type 1 and/or 2 diabetic neuropathy

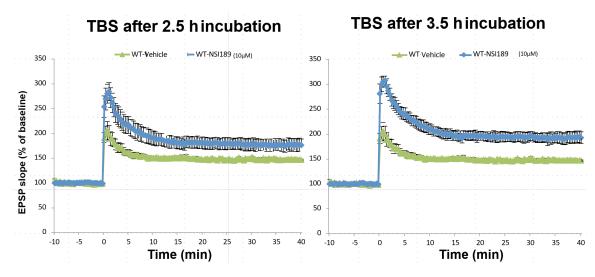
## NSI-189 Enhances LTP Magnitude<sup>1</sup>

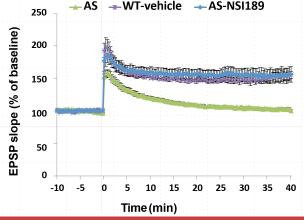
#### For mechanistic studies:

- cognition = memory
- LTP is a cellular biomarker of memory

- Enhances short- and long-term potentiation of normal mouse brain slices (n=8)
- Effect increases with exposure time and concentration.

- Restores LTP of Angelman Syndrome mouse brain slices.
- Confirmatory model of the genetic disease.





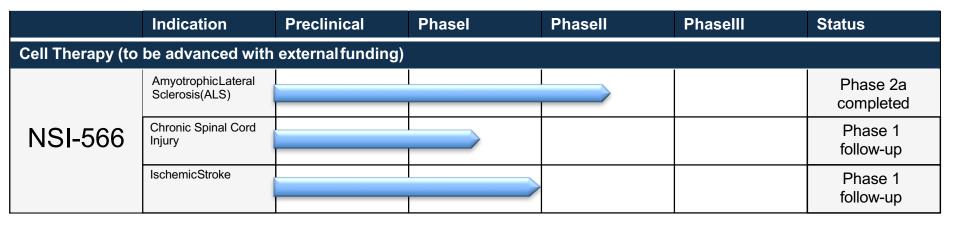
Excitatory postsynaptic potential (EPSP); Theta burst stimulation (TBS)

By courtesy of Yan Liu¹, Xiaoning Bi¹, Michel Baudry¹ Western University of Health Sciences, Pomona, CA91766

### 4. NSI-566

ALS, Stroke & Chronic Spinal Cord Injury

## Cell Therapy: Activity Across Three Indications



- ALS Phase 1 & 2: demonstrates preliminary clinical benefit against historical data
- Phase I stroke completed dosing all 9 patients and currently evaluating safety
- cSCI is currently evaluating 4 Phase 1 thoracic patients; Phase 1 trial recruiting additional (Group B) 4 cervical patients
- Over 300 proprietary neural stem cell lines

### Cell Therapy Program Overviews

#### **ALS**

#### **MARKET CONSIDERATIONS**

- Orphancondition
- NSI-566 granted orphan status by FDA
- Rapid acceleratingdisease/poor prognosis
- Limited treatment options
- Opportunity for RMAT designation (21st Century Cures Act)

#### **PROGRAM OVERVIEW**

- Transplantation into spinal cord of ALS patients
- Phase 1 & Phase 2a dose-escalation, safety studies completed
- 30 subjects with 2-6 years of safety
  Data
- Additional matched pairs analysis with historic data set (PROACT) insightful

#### **KEYTAKEAWAYS**

- Procedure and treatment is welltolerated
- Long-term cell graft survival (2.5 years) proven at autopsy

#### **Ischemic Stroke**

#### **MARKET CONSIDERATIONS**

- 1.8 million with paralysis due to stroke in the US\*
- No treatment to reverse paralysis
- Majority of patients not aware of the stroke until well after the event
- Current therapies require access within hours of event

#### **PROGRAM OVERVIEW**

- Phase 1 open-label, dose-escalation, feasibility & safety study for the treatment of paralysis from chronic motorstroke
- Patient profile: Stable patients 3-24 months post-event with stable hemiparalysis
- N = 9
- Follow up 1 year post-surgery
- Secondary endpoints include improved recovery

#### **KEYTAKEAWAYS**

- Treatmentwell-tolerated
- Innovative transplantation (platform/brain injection cannula) system developed

#### **Chronic Spinal Cord Injury**

#### MARKET CONSIDERATIONS

- 1.5 million with paralysis due to spinal cord injury in the US\*
- 17,000 new injuries peryear
- No treatmentoptions

#### **PROGRAM OVERVIEW**

- USCDfunded
- Phase I cSCI Group A 4 Thoracic AISA-A complete spinal cord injury (dosingcompleted)
- Phase I cSCI Group B 4 Cervical AISA-A complete spinal cord injury (recruiting)

#### **KEYTAKEAWAYS**

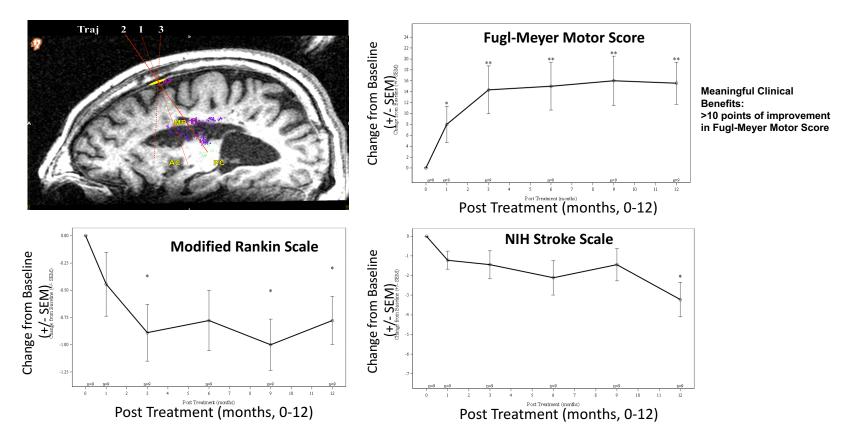
- Stem cell treatment was safe and well-tolerated
- No serious adverseevents
- Self-reported ability to contract some muscles below the level of injury in one of the four subjects treated was confirmed via clinical and electrophysiological follow-up examinations

\*Prevalence and Causes of Paralysis—United States, 2013. Armour, B.S. et al. (2016) Am J Public Health. 106: 1855-1857.

### NSI-566: ALS Phase I and II, 2-Year Follow-Up vs Historical Data

ALSFRS-R						
	Ph1/2		PRO-ACT			
	N	Mean (SD)	N	Mean (SD)	t-test	
Baseline	21	36·5±5·4	1108	38·1±4·7	0.17	
6 months	18	30·6±6·5	974	32·5±7·6	0.25	
12 months	14	30·5±9	655	28·3±9·3	0.37	
18 months	11	31·8±8·1	165	24·6±10·4	0.016	
24 months	11	30·1±8·6	86	24·0±10·2	0.048	
ALS/SURV						
ALS/SURV						
ALS/SURV	Ph1/2		PRO-ACT			
ALS/SURV	Ph1/2 N	Median (IQR)	PRO-ACT N	Median (IQR)	Wilcoxon	
ALS/SURV  Baseline		Median (IQR) 38 (31,40)		Median (IQR) 39 (35,42)	Wilcoxon 0·12	
	N	, ,	N			
Baseline	N 21	38 (31,40)	<b>N</b> 1108	39 (35,42)	0.12	
Baseline 6 months	N 21 20	38 (31,40) 29·5 (23,35·5)	<b>N</b> 1108 1012	39 (35,42) 33 (27,38)	0·12 0·11	

### NSI-566 stroke: Phase I interim data



## Neuralstem's Technical Expertise/Differentiation

### **Chemically defined culture system**

- No serum, no feeder cells, no particulates, no undefined raw material
- Fully tested for potential pathogens; validatedSOPs

### **Efficient expansion**

- Multi-tiered cell banks for maximum efficiency
- Scalable expansion
- Relatively small infrastructure

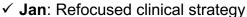
### Stable phenotype

- Normal karyotype of 44 + XY chromosomes
- Reproducible bank release characteristics (identity, purity, potency)
- Predictable in vivo differentiation

### 5. Execution

### 2016

Focus: Strategy, Balance Sheet Strength and Execution



- ✓ Feb: Rich Daly joins as CEO
- ✓ May:
  - ✓ Initiation of P2 MDD study
  - √ \$9M institutional raise
- ✓ Jun: Corporate Reorganization to align with updated strategy
- ✓ Rich Daly appointed Chairman, Board of Directors
- ✓ Dec: Closing of Tianjin Pharmaceuticals Group \$20M strategic investment

### 2018

- √ NSI-189 P2 MDD 6-month durability results expected in 1<sup>st</sup> half
- ✓ FDA meeting re: NSI-189
  MDD data in 1<sup>st</sup> half

### 2017

- √ Jan: 13-1 reverse split, ensuring NASDAQ compliance
- ✓ Feb: LSE P2 MDD study
- ✓ Jul:
  - ✓ P2 NSI-189 MDD topline readout
  - √\$6M capital raise post-data
- ✓ Sep: Cristina Csimma, PharmD, MPH joins the Neuralstem Board
- ✓ Nov: David Recker, MD joins Neuralstem as Chief Medical Officer
- ✓ Dec:
  - ✓ Full P2 NSI-189 MDD results released at ACNP
  - √Xi Chen, PhD Joins the Neuralstem Board
  - ✓NSI-566 Stroke P1 paper submitted for publication

# 6. Scientific Advisory Board Comprised of WorldClass 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

## 7. Financials

#### Unaudited Condensed Consolidated Balance Sheet

#### Selected Line Items

	Se	ptember 30, 2017
ASSETS		
Total current assets	S	14,707,225
Total assets	S	16,188,766
LIABILITIES		
Total current liabilities	\$	1,834,727
Total liabilities	\$	4,623,990
STOCKHOLDERS' EQUITY		
Convertible preferred stock, 7,000,000 shares authorized, \$0.01 par value; 1,000,000 shares		
issued and outstanding	S	10,000
Common stock, \$0.01 par value; 300 million shares authorized, 15,146,027 shares issued and		
outstanding	\$	151,460
Total stockholders' equity	S	11,564,776

## 8. Management

Richard Daly Chief Executive Officer & acting CFO	25+ years of Pharma & biotech leadership experience; start up, scale up and transformations	AstraZeneca Takeda  Bristol-Myers Squibb
Karl Johe, Ph.D. Chief Scientific Officer	Discoverer of neural stem cells and neurogenic molecules, co-founder of Neuralstem, developer of the Company's clinical programs.	NEURALSTEM INC Co-founder  National Institutes of Health
Thomas Hazel, Ph.D. Senior Vice President, Research	25 years of experience in human neural stem cell R&D, scale-up and manufacturing, and assay development	NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE NEURALSTEM INC.
David Recker, M.D Chief Medical Officer	30+ years of clinical development expertise; small molecule and cell therapy: pain, CV/metabolic, GI, RA	VERICEL Takeda SEARLE