Supernus Pharmaceuticals

R&D Day

October 18, 2023

Supernus® Pharmaceuticals

Introduction and Agenda

Jack Khattar

President and Chief Executive Officer

Supernus® Pharmaceuticals

Safe Harbor Statement

This presentation and other matters discussed today or answers that may be given to questions asked include forward-looking statements within the meaning of the federal securities laws. These statements, among other things, relate to Supernus' business strategy, goals and expectations concerning its product candidates, future operations, prospects, plans and objectives of management. The words "anticipate", "believe", "could", "estimate", "expect", "intend", "may", "plan", "predict", "project", "will", and similar terms and phrases are used to identify forward-looking statements in this presentation. Supernus' operations involve risks and uncertainties, many of which are outside its control, and any one of which, or a combination of which, could materially affect its results of operations and whether the forward-looking statements ultimately prove to be correct. Supernus assumes no obligation to update any forward-looking statements except as required by applicable law.

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AGENDA

Introduction

Corporate Overview

Product Candidates

- SPN-820 – Depression
- SPN-817 – Epilepsy
- SPN-443 – ADHD/CNS
- SPN-446 – Narcolepsy

General Q&A and Closing Comments

Participants

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Jack Khattar, MBA
President and Chief Executive Officer

Jonathan Rubin, M.D., MBA
SVP, Research and Development, Chief Medical Officer

Bryan Roecklein, Ph.D.
SVP, Corporate Development

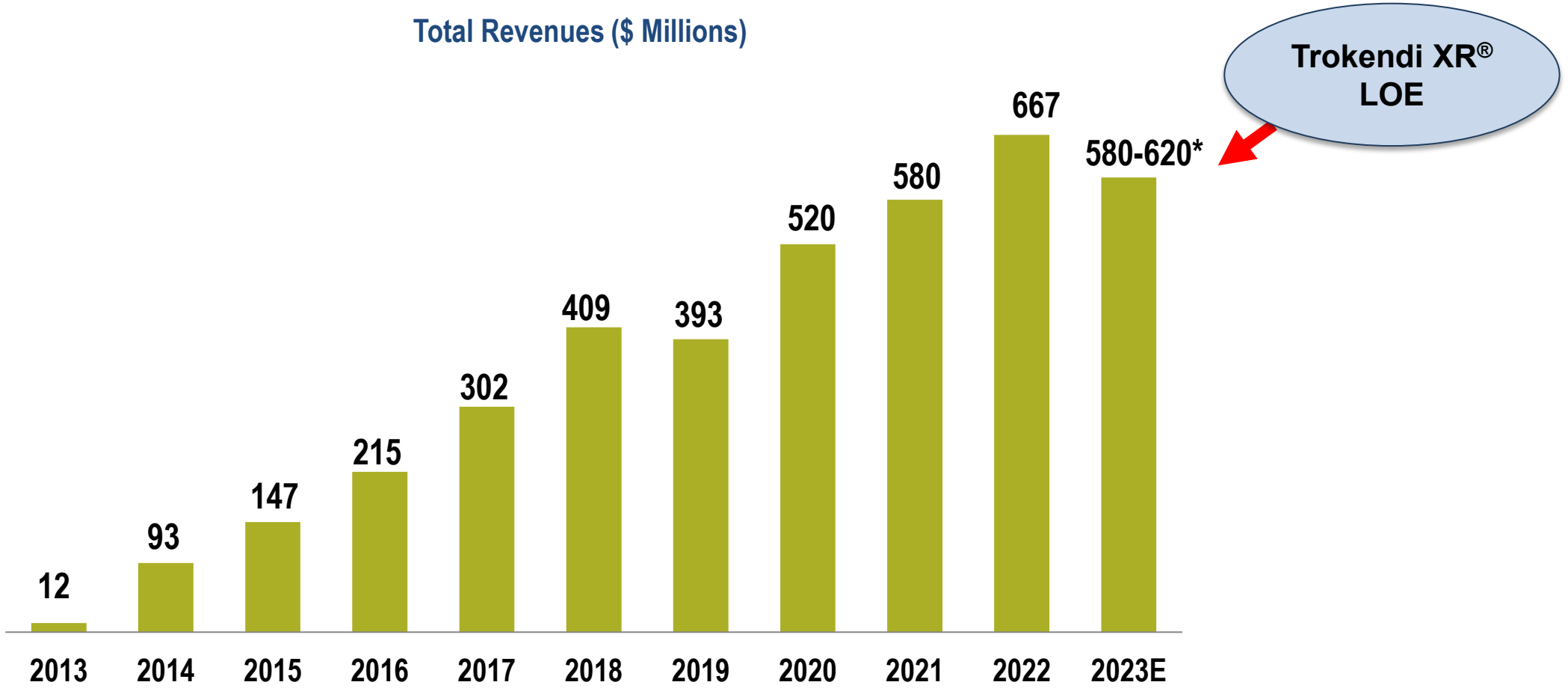
Tim Dec
SVP, Chief Financial Officer

Advisor

Vladimir Maletic, M.D., M.S.
Clinical Professor, Neuropsychiatry and Behavioral Science
University of South Carolina, School of Medicine

Proven Commercial Execution & Growth Strategy

Total Portfolio Revenue Growth



Year-end 2018 inventory build by distribution channel increased 2018 net sales by approximately $10 million and negatively impacted 2019 net sales.
* Guidance updated on August 3, 2023

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Robust CNS Pipeline to Drive Long-Term Growth

Program	Indications	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	NDA	Market
SPN-830	PD							
SPN-820	Depression							
SPN-817	Epilepsy							
SPN-443	ADHD/CNS							
SPN-446	Narcolepsy							
SPN-448	CNS							

PD = Parkinson's Disease

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Strategic Overview

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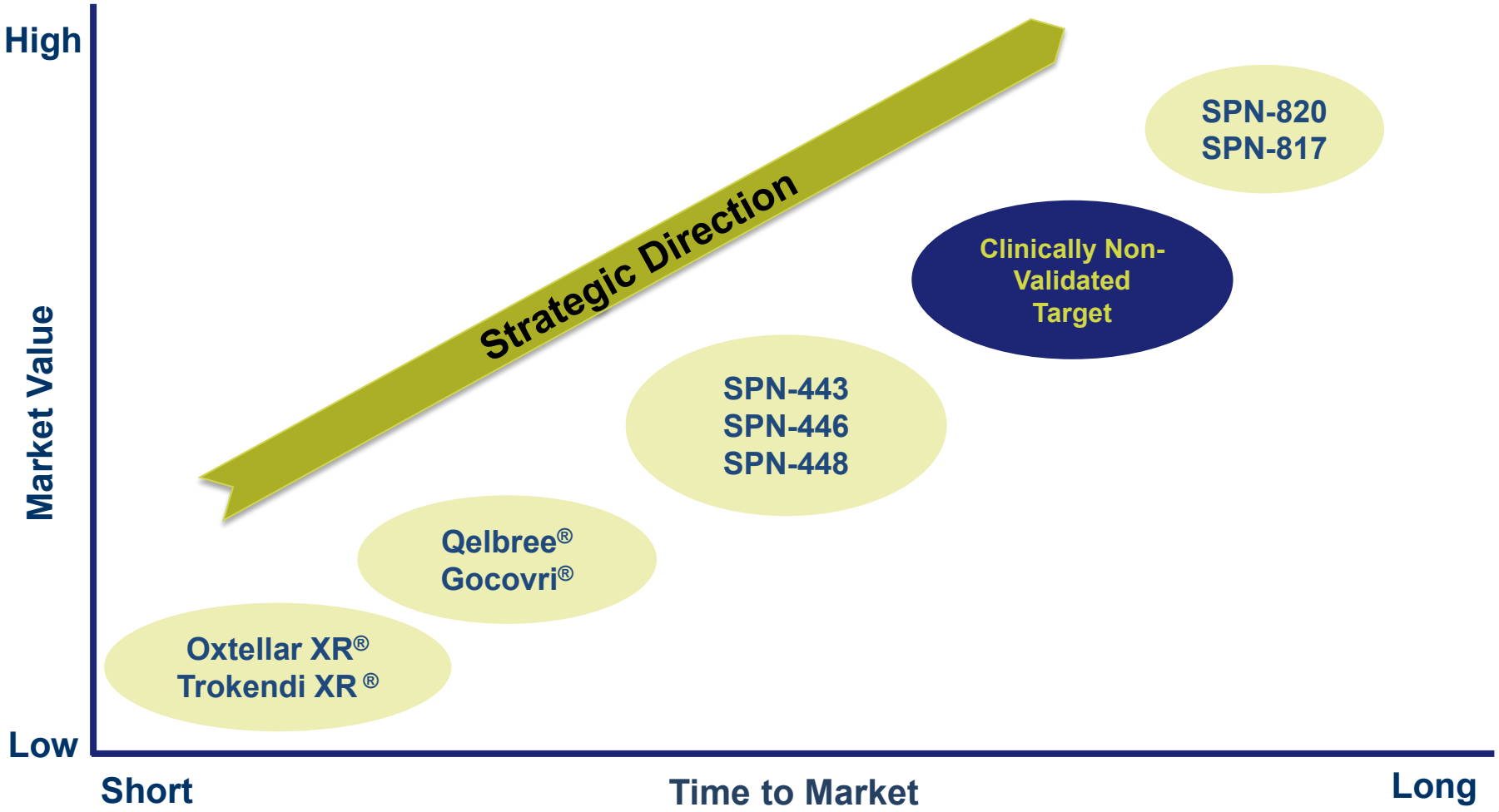
Strategic Overview



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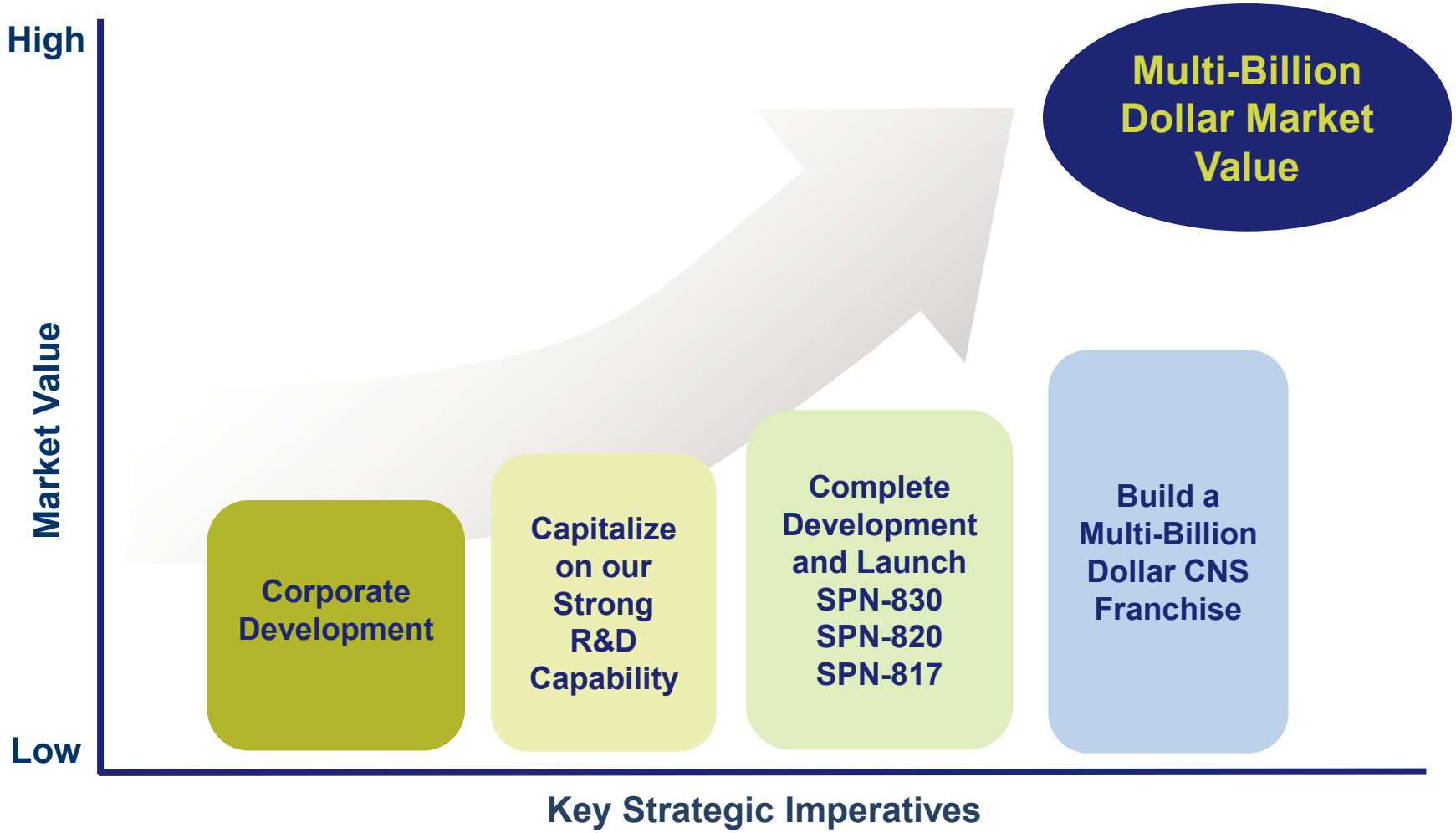
Strategic Overview



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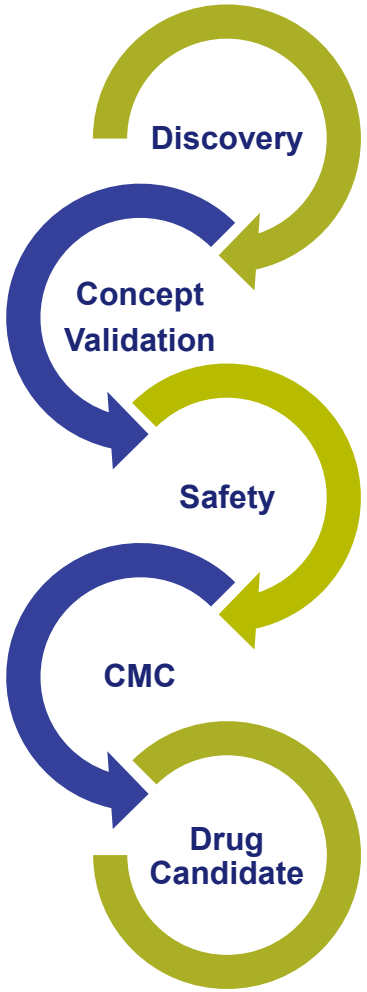
Significant Experience & Capabilities in Drug Development

Discovery Platform
Design and synthesis of new compounds based on structure, function and disease pathways

Toxicology

Validated drug candidates



In vitro, PK, preclinical proof of concept, and stability studies

In-house CMC/drug delivery expertise & GMP manufacturing

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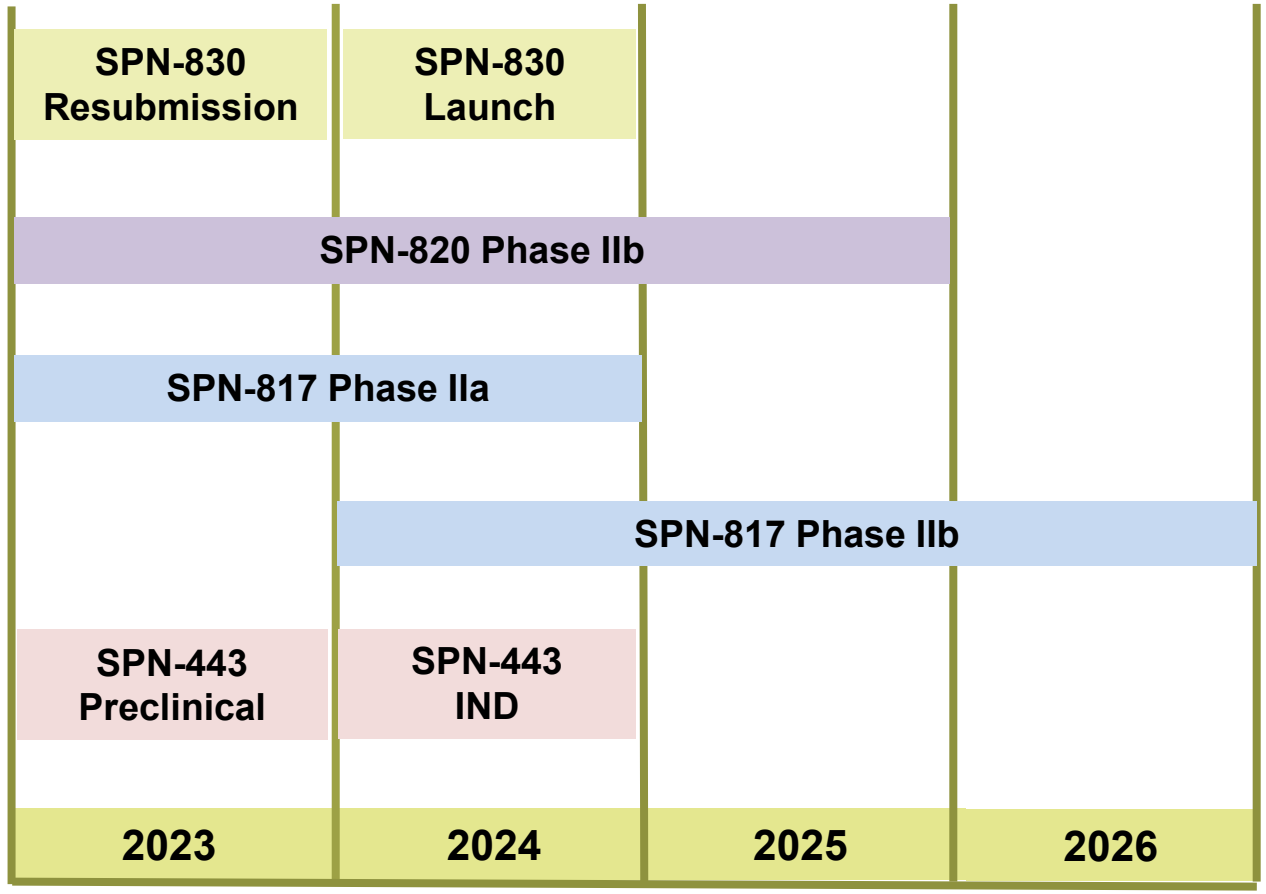
Supernus Near-Term Milestones



Above timelines represent management's estimates that are subject to several factors that are beyond our control and actual results may be significantly different from our estimates

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Positioned For Continued Strong Growth

Multi-Billion Dollar Market Value

Growth Potential of Existing Products

Qelbree® and GOCOVRI®

Innovative R&D Portfolio

SPN-830	Novel Infusion Device for PD
SPN-820	First in Class Novel MOA for Depression
SPN-817	First in Class Novel MOA for Epilepsy
SPN-443	Novel ADHD Stimulant with CIV Scheduling

Corporate Development

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Supernus Pipeline

Jonathan Rubin

SVP, Research and Development, Chief Medical Officer

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Qelbree®

Novel Non-Stimulant ADHD Product

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Co-administration of Qelbree with a Stimulant Provides Incremental Efficacy

Phase IV, Open-Label, Flexible-Dose study in Children and Adolescents with ADHD

- Primary Objective: Safety and tolerability when administered with stimulants (methylphenidate or amphetamine) in children and adolescents with ADHD
- Significant improvement from baseline ADHD-RS-5 & CGI-S scores

	ADHD-RS-5	CGI-S
Baseline (BL); N=56	37.2	4.4
Week 4 change from BL; N=54	-13.5	-0.9
Week 8 change from BL; N=48	-18.2	-1.4

- Well tolerated
  - Adverse events (AEs) included headache (17.9%), decreased appetite (12.5%), and upper respiratory tract infection (10.7%)
  - 3.6% of patients discontinued due to an AE.

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Efficacy of Qelbree in Adults with ADHD and Mood Symptoms

60% of adults with ADHD have comorbid depression and 57% have comorbid anxiety

Viloxazine IR was approved in the EU for the treatment of depression

Phase IV, Open-label, decentralized clinical trial

- Treatment period: 14 weeks. Qelbree 200-600mg/day. N= 750; 500 completers
- Primary efficacy: Change from baseline in AISRS in adults with ADHD and comorbid mood symptoms
- Secondary:
  - Change from baseline in depressive symptoms (SIGMA and PHQ-8), anxiety symptoms (SIGH-A and GAD-7); work/home functioning (SDS), executive function (BRIEF-A), and sleep (PSQI)
  - Safety and tolerability
- Expected to start 4Q 2023

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SPN-830

Treatment of Hypomobility in Parkinson's Disease

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SPN-830: Infusion Device Submission

- Continuous treatment of motor fluctuations (OFF episodes) in Parkinson's disease (PD) patients that are not adequately controlled with oral levodopa and one or more adjunct PD medications.
  - If approved, will give PD patients the option of a continuous daily infusion, instead of "as needed" injections, with a goal of improvement in the amount of ON time for patients
- NDA resubmitted Oct 2023
  - Submission responds to FDA's questions from Oct 2022 Complete Response Letter

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SPN-820

First in Class, Unique Intracellular Mechanism to Treat Depression

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Depression Market Update

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Depression – One of the Largest Therapeutic Areas with ~195M Prescriptions in the U.S. per Year

Prevalence of Major Depressive Episodes in the United States[1]

- ~21.0 million adults (~8.3%) had at least one episode
- Pandemic triggered a 25% increase in prevalence
- Gallup poll in May 2023 indicated that 29% of all adults will be diagnosed with depression in their lifetime
  - 36.7% , women; 20.4%, men

Slow Onset and Side Effects are Prevalent Leading to Switching or Discontinuation

- ADTs can take up to 6 – 8 weeks to reach efficacy[2]
- ~38% of patients experience one or more side effects from SSRIs (sexual and digestive)[2]

Significant Number of Patients do not Respond to Therapy[1]

- 39% refractory to first line therapy
- 27% refractory to second line therapy
- 32% refractory to third line therapy

1. NIMH Health Statistics 2. NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D Study)
2. Trials & Triumphs of Neuropsychiatry: TD Cowen Landscape Analysis and Key Themes

ADT = Antidepressant Treatment

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Major Depressive Disorder (MDD) vs. Treatment Resistant Depression (TRD)

Major Depressive Disorder

DSM-5 classification with specific clinical criteria

Five or more symptoms during the same 2-week period, at least one of the symptoms is (1) depressed mood or (2) loss of interest or pleasure.

- Depressed mood
- Diminished interest or pleasure in activities
- Significant weight loss
- A slowing down of thought and a reduction of physical movement
- Feelings of worthlessness
- Recurrent thoughts of death or recurrent suicidal ideation (including plans or attempts)

Treatment Resistant Depression

Definition is evolving and disparate between regulatory authorities and practitioners

- FDA currently defines TRD as a failure of 2 or more antidepressants
- HCPs consider TRD after the first failure
- Regardless, payers require patients to step through the older generic options first

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Multiple MOAs for Treating Depression

Abbrev.	Treatment Class/MOA/Description	Depression TRx*	% of Total	Most Commonly Prescribed Drug
SSRI	Selective Serotonin Reuptake Inhibitor	60.4M	31.0%	Sertraline (Zoloft®)
SARI	Serotonin Antagonist and Reuptake Inhibitor	39.1M	20.0%	Trazodone (Desyrel®)
NDRI	Norepinephrine and Dopamine Reuptake Inhibitor	27.6M	14.1%	Bupropion (Wellbutrin®)
SGA	Second-Generation Antipsychotic (Atypical)	24.8M	12.7%	Quetiapine (Seroquel®)
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor	20.7M	10.6%	Duloxetine (Cymbalta®)
T_3/T_4	Tricyclic or Tetracyclic Antidepressant	18.5M	9.5%	Mirtazapine (Remeron®)
5-HT/SSRI	5-HT1a Agonist and Serotonin Reuptake Inhibitor	3.9M	2.0%	Vortioxetine (Trintellix®)
NMDA	NMDA Antagonist	0.2M	0.1%	Esketamine (Spravato®)
MAOI	Monoamine Oxidase Inhibitor	65K	0.0%	Tranylcypromine (Parnate®)
FGA	First-Generation Antipsychotic (Typical)	4K	0.0%	Haloperidol (Haldol®)

- "Depression Only" TRx, Integrated IQVIA NPA & NMTA
- All trademarks are owned by their respective owners

Total TRx: 195M

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The Future: Faster Relief, Greater Tolerability, and Improvement of Neuroplasticity for Long-Term Benefits

- Leading brand Trintellix® differentiates with efficacy, impact on DSST/Executive Function and lower sexual dysfunction side effects
- Newer products differentiate with faster onset:
  - Spravato® – onset within 24 hours, however, restricted use due to NMDA receptor activity
  - Auvelity® – separation from placebo within 1 week
- Monoamine products are limited. Moving towards molecules that can impact neuroplasticity
  - Development of psychedelics is prevalent; however, they have significant AEs and intensive therapy will be required for use
  - Could differentiate by “remodeling” neurological synapses to facilitate lasting benefits
  - Anticipated to be a $5B market[1]

[1] GlobalData Forecast 2029, Projected Combined Psychedelic Brands
DSST: Digit Symbol Substitution Test

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Market Needs: Ideal Product Profile

- High effect size with good responder frequency
- Fast onset – one week or less
- No cognitive impairment
- No impact on sexual dysfunction
- Positive impact on neuroplasticity for prolonged effects
- Low to no dissociative side effects
- At home use, as opposed to restricted use and need for intense psychotherapy

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SPN-820

Vladimir Maletic, M.D., M.S.

Clinical Professor
Neuropsychiatry and Behavioral Science
University of South Carolina, School of Medicine

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SPN-820

A Rapid Acting Antidepressant with Novel MOA

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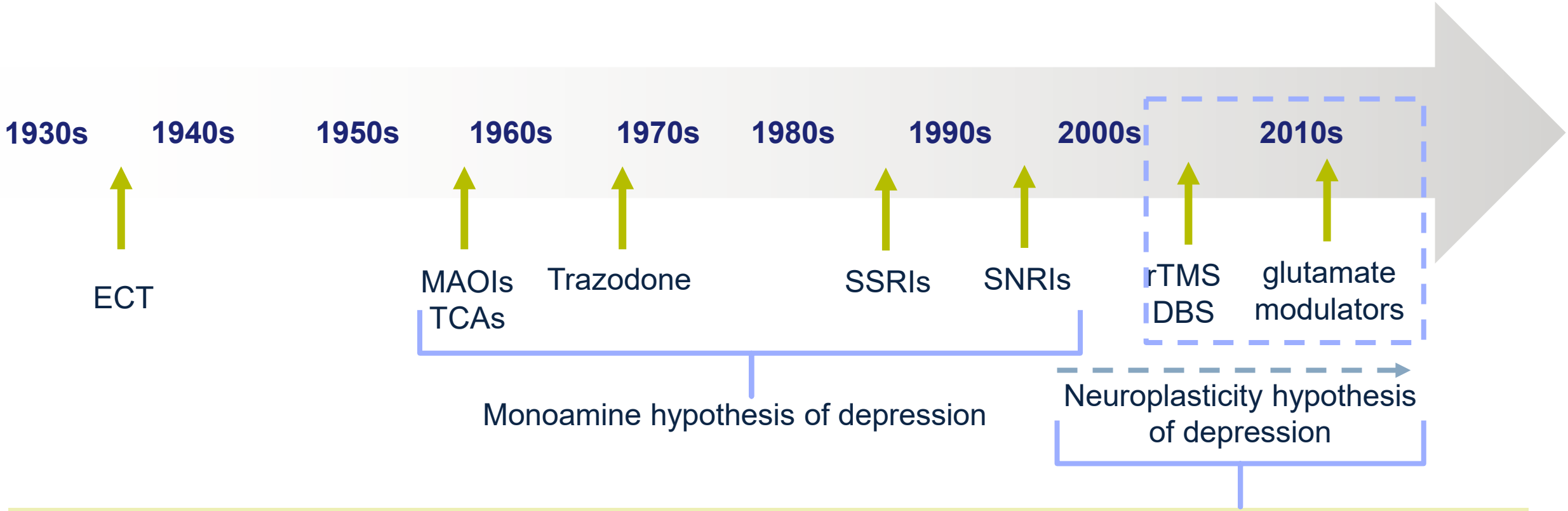
Evolution of Depression Treatment



Recently-developed treatments for TRD ***restore*** neuroplasticity and do so ***rapidly***

ECT=electroconvulsive therapy; MAOIs=monoamine oxidase inhibitors; TCAs=tricyclic antidepressants; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin-norepinephrine reuptake inhibitors; rTMS=repeated transcranial magnetic stimulation; DBS=deep brain stimulation

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Neuroplasticity Hypothesis of Depression

- Dysfunctional neuroplasticity underlies depression manifestation
  - Inability of neuronal connections to undergo activity- and experience-dependent changes in strength; ***brain region and circuit specificity***
    - Imbalance in GABA (inhibitory) and glutamate (excitatory) synapses
    - Reduced number and function of excitatory synapses; reduced neurotrophic factors, e.g., BDNF
  - Reflected as altered communication between and within key brain regions

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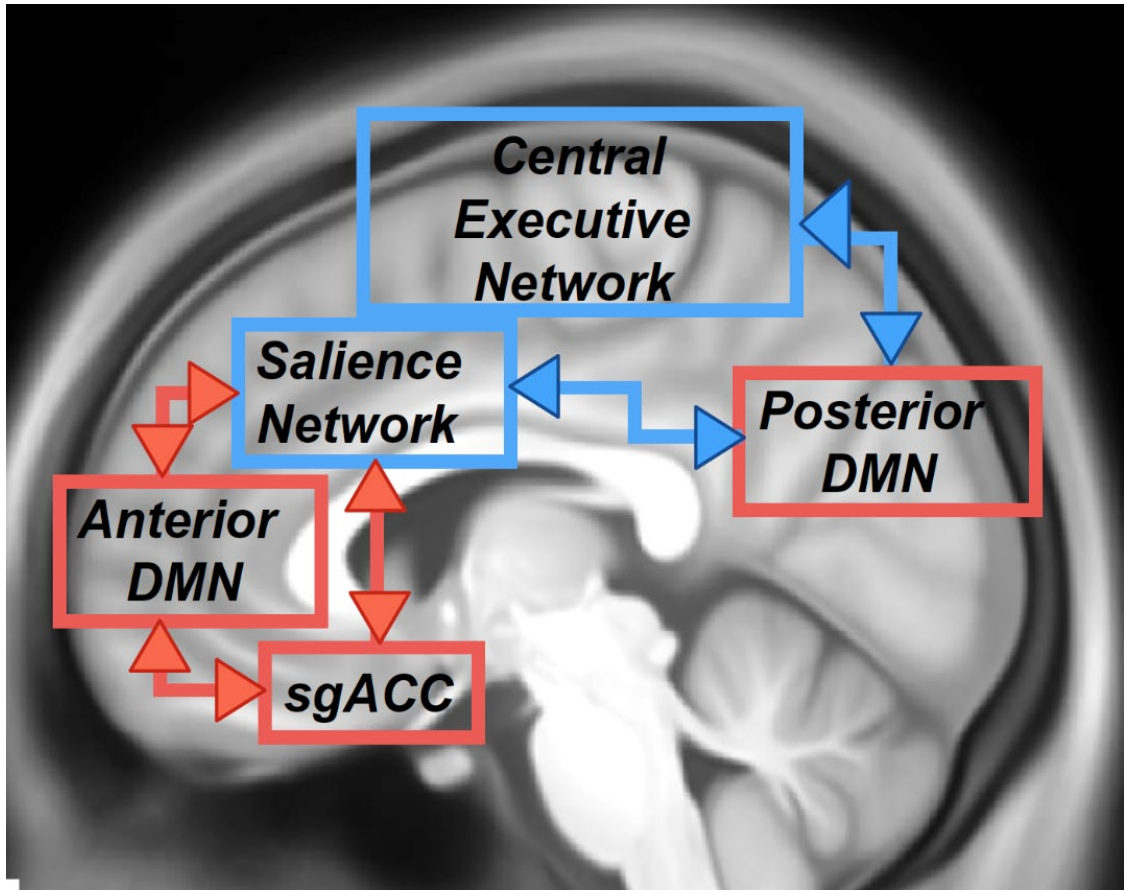
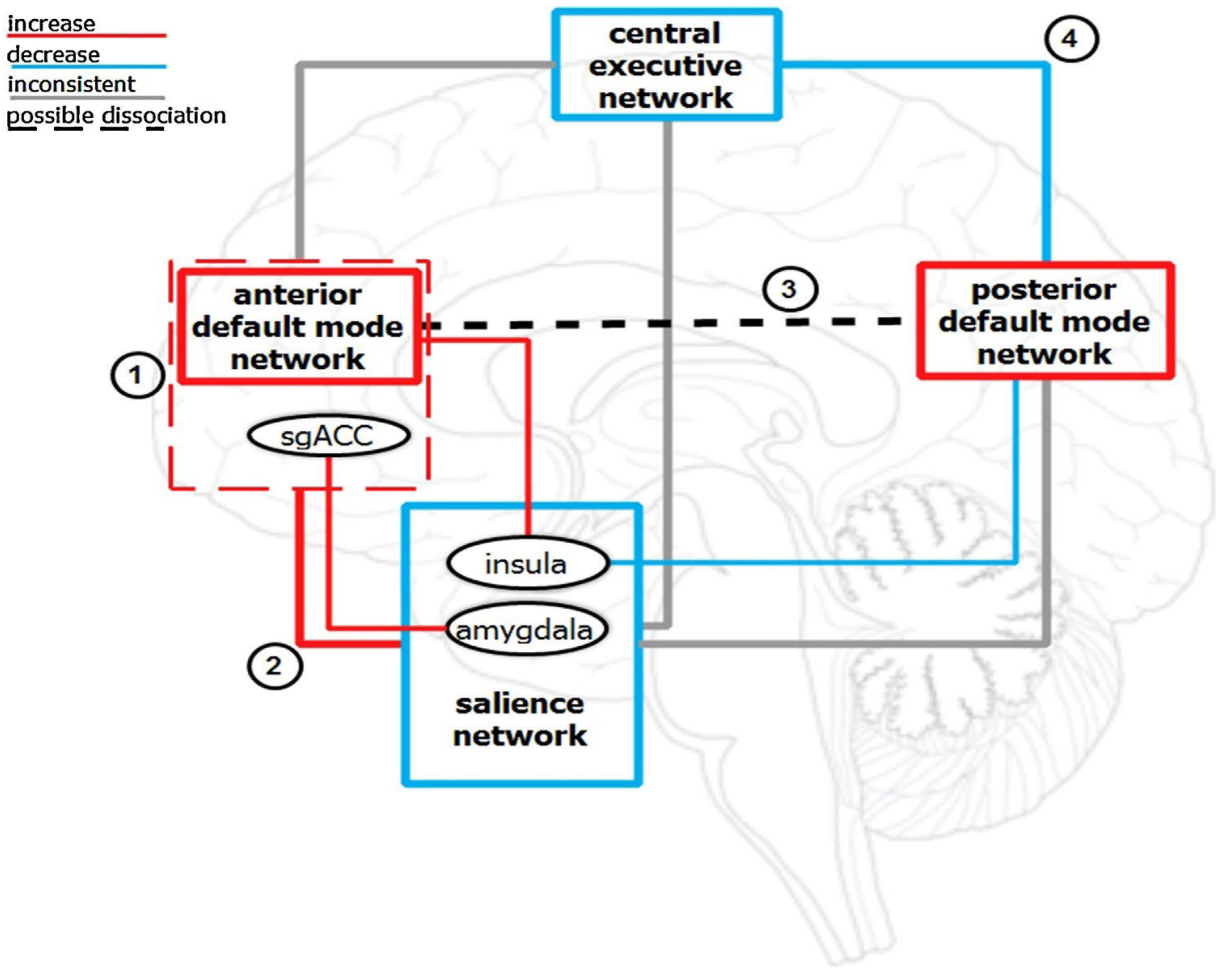
Symptoms of Depression Reflect Disrupted Network Connectivity in MDD



Increased Connectivity Decreased Connectivity



MDD = major depressive disorder; DMN = default mode network; sgACC = subgenual anterior cingulate cortex.
Dunlop et al. *Curr Psychiatry Rep*. 2019;21:87. Mulders PC, et al. *Neurosci Biobehav Rev*. 2015;56:330-344.

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Dysfunctional Network Connectivity and Related Symptoms in TRD

Network	Connectivity increase or decrease in TRD	Associated symptom	References
Default mode network	1. ↑ Connectivity within default mode network	1. Rumination	Sheline et al., 2010; Hamilton et al., 2015; Williams, 2016
Central executive network	1. ↓ DLPFC-parietal cortex 2. ↓ ACC-DLPFC	1. Inattention, false alarm errors 2. Cognitive dysfunction, latency	Qiu et al., 2011; Sylvester et al., 2012; Forster et al., 2015; Williams, 2016
Salience network	1. ↑ Insula-amygdala 2. ↓ Insula-ACC 3. ↓ Amygdala-subcallosal and ventral ACC 4. Striatal hypoactivation 5. ACC hyperactivation	6. Anxious avoidance 7. Negative Bias 8. Threat dysregulation 9. Anhedonia 10. Context insensitivity	Matthews et al., 2008; Stuhrmann et al., 2011; Treadway and Zald, 2011; Klumpp et al., 2013; Zhang et al., 2013; Mulders et al., 2015; Williams et al., 2016

TRD, treatment resistant depression; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

Idlett-Ali SL, et al. *Front Hum Neurosci*. 2023;17:1125074.

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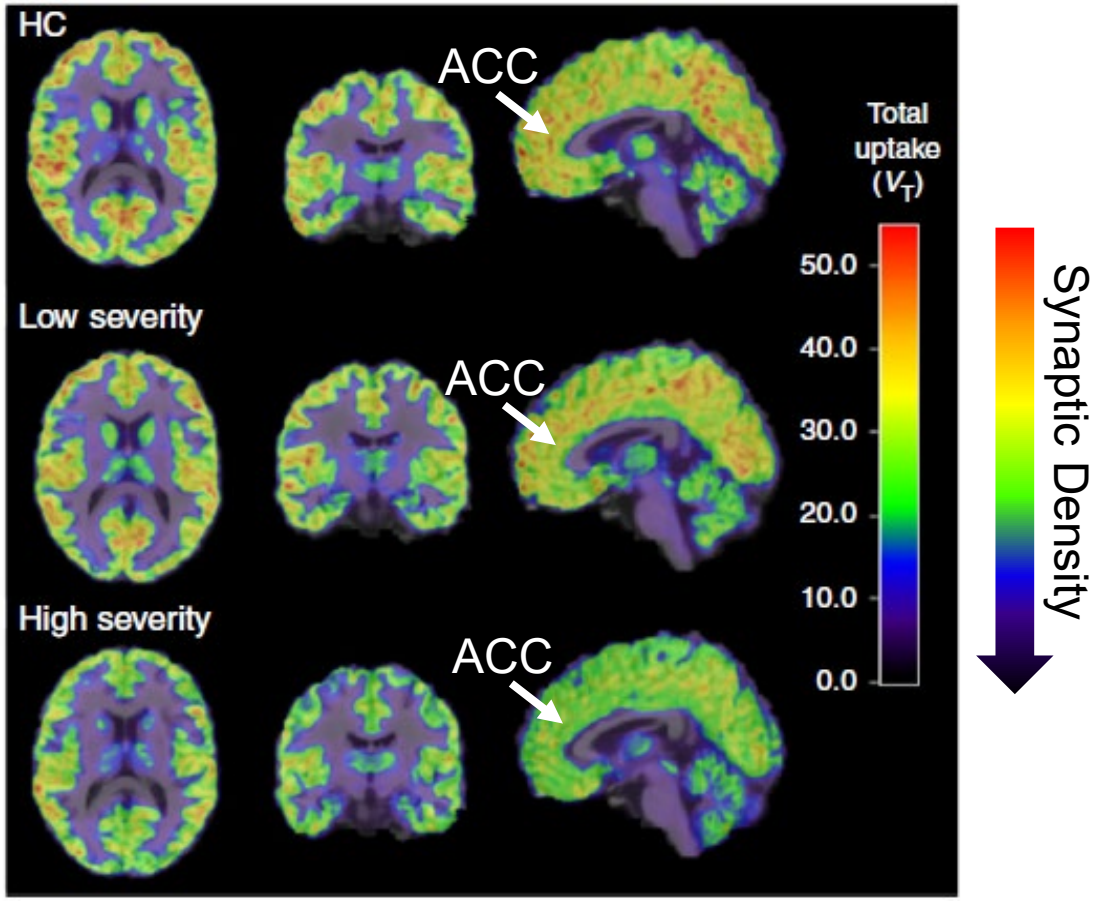
Severely Depressed Subjects Have Decreased Synaptic Density

Healthy Control

Low Severity of Depression symptoms

High Severity of Depression symptoms



- PET study measures synaptic density by uptake of a radiolabeled ligand
  - Radioligand binds to SV2A, a synaptic marker.
- Red is high synaptic density, green to blue is lower synaptic density

Synaptic density in critical areas of the brain decreases with severity of depression

V_T=volume of distribution; ACC=anterior cingulate cortex; HC=healthy control; PET=positron emission tomography; SV2A=synaptic vesicle glycoprotein 2A

Holmes SE, et al. *Nat Comm.* 2019; 10:1529

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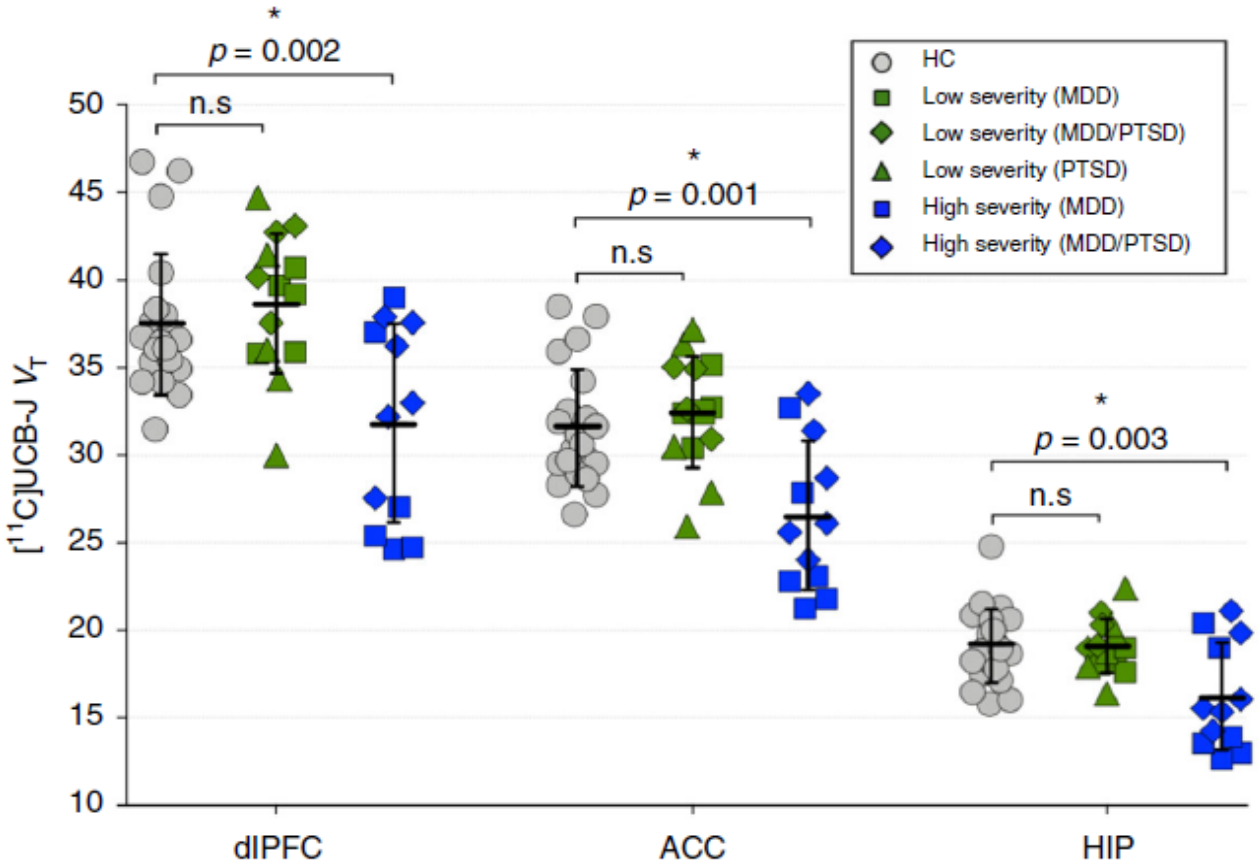
Decreased Synaptic Density Between Healthy Controls and those with Severe Depression is Statistically Significant



PTSD=post-traumatic stress disorder; MDD=major depressive disorder; [^{11}C]UCB-J =SV2A PET ligand; V_T=volume of distribution; dlPFC=dorsolateral prefrontal cortex; ACC=anterior cingulate cortex; HIP=Hippocampus; HC=healthy control; n.s.=not significant

Holmes SE, et al. *Nat Comm.* 2019; 10:1529

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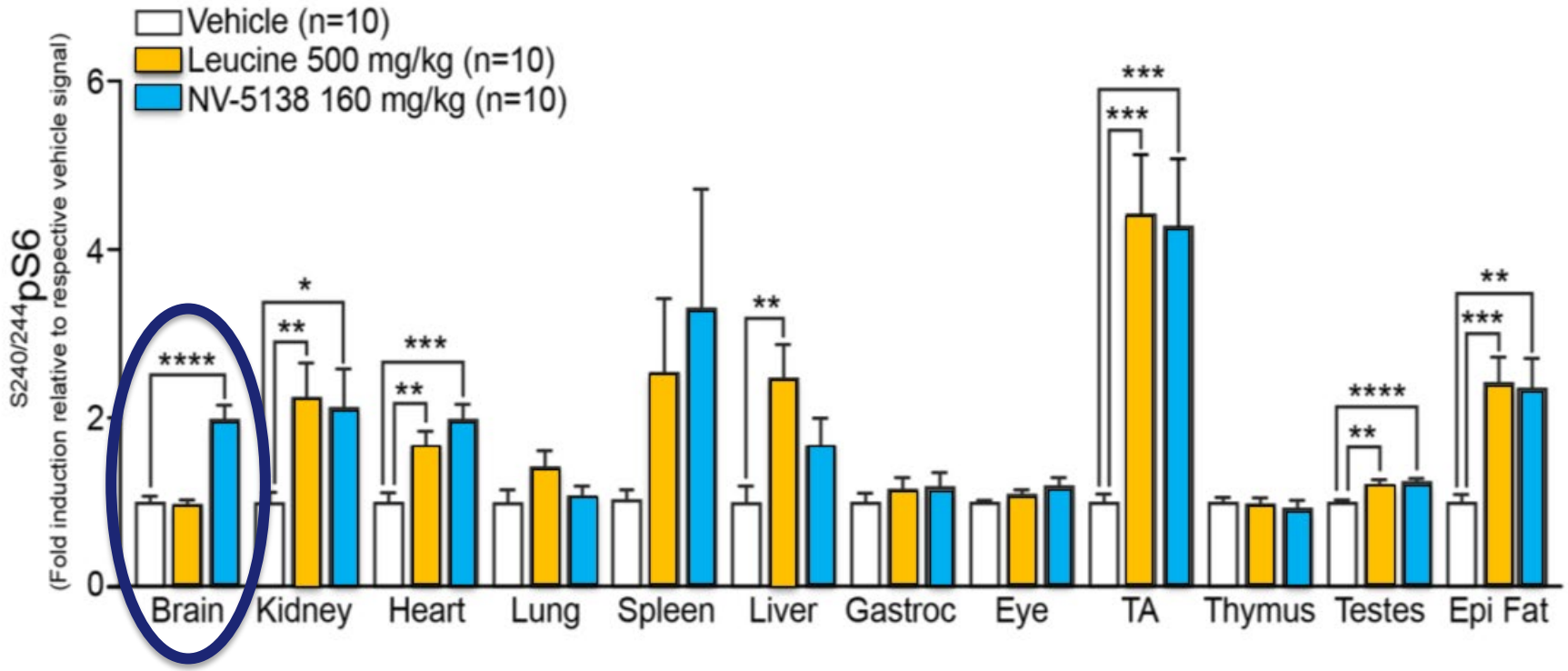
SPN-820 MOA Video

Click Here to Watch SPN-820 MOA Video

mTORC1 Activation in a Physiological Manner



- Generally, equivalent increase in mTORC1 activation between NV-5138 and leucine in peripheral organs suggests low likelihood of peripheral side effects related to increased mTORC1 activation
- mTORC1 activation in the brain is increased only by NV-5138, not leucine

Gastroc=gastrocnemius muscle; TA=tibialis anterior muscle; Epi=epididymal; $^{S240/244}$pS6=phosphorylated pS6 ribosomal protein

Sengupta SS, et al. *Sci Rep.* 2019; 9:4107

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NV-5138 Shows Antidepressant Efficacy in Multiple Preclinical Models

Model	Outcome
Forced swim test	Efficacious in standard antidepressant screening (behavioral despair)
Novelty suppressed feeding test	Anti-anxiety effects
Female urine sniffing test	Increased reward-seeking behavior
Sucrose preference test	Normalization of hedonic behavior after chronic stress
Human threat test	Potential anti-anxiety effects in non-human primates

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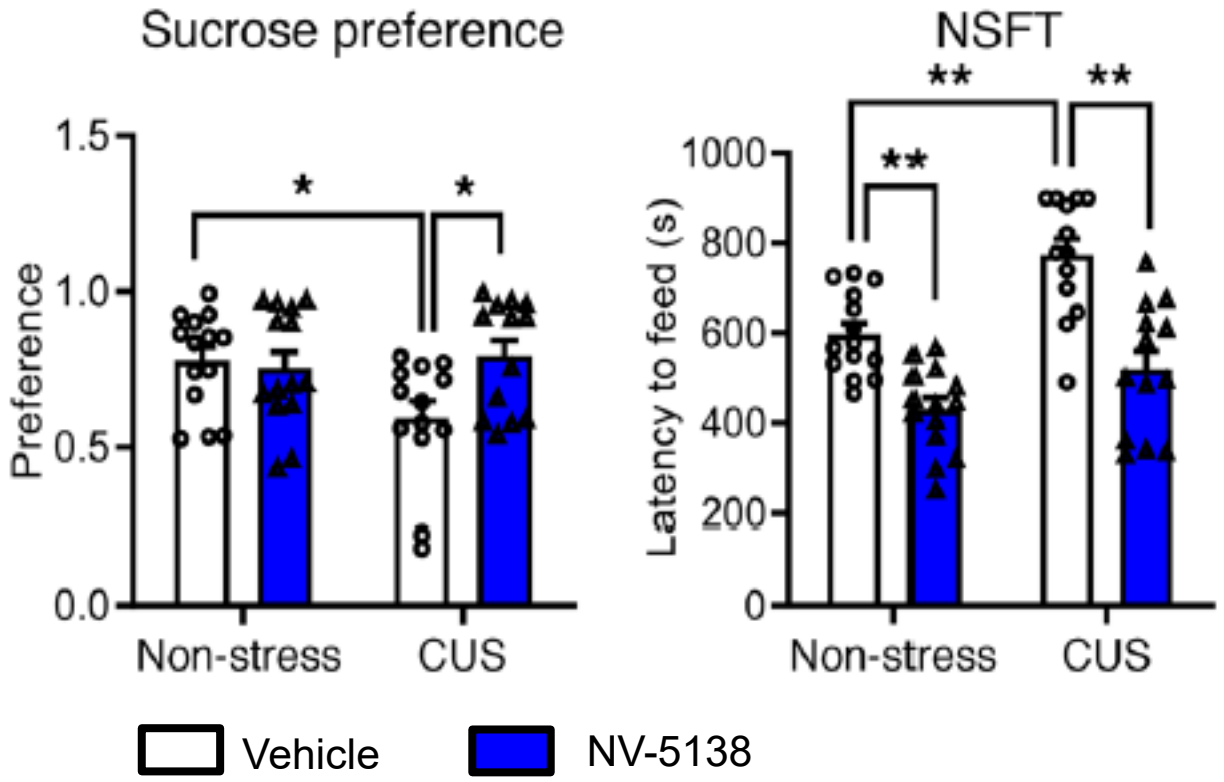
NV-5138 Normalizes Chronic Stress-Induced Behavioral Changes Relevant to Depression



- NV-5138 prevents chronic stress-induced decrease in sucrose preference (reverses anhedonia)
- NV-5138 prevents chronic stress-induced increase in latency to feed in novelty suppressed feeding test (decreases stress-induced anxiety-like behavior)

CUS=chronic unpredictable stress; NSFT=novelty suppressed feeding test; s=seconds

Kato T, et al. *J Clin Inv.* 2019; 129(6):2542-2554

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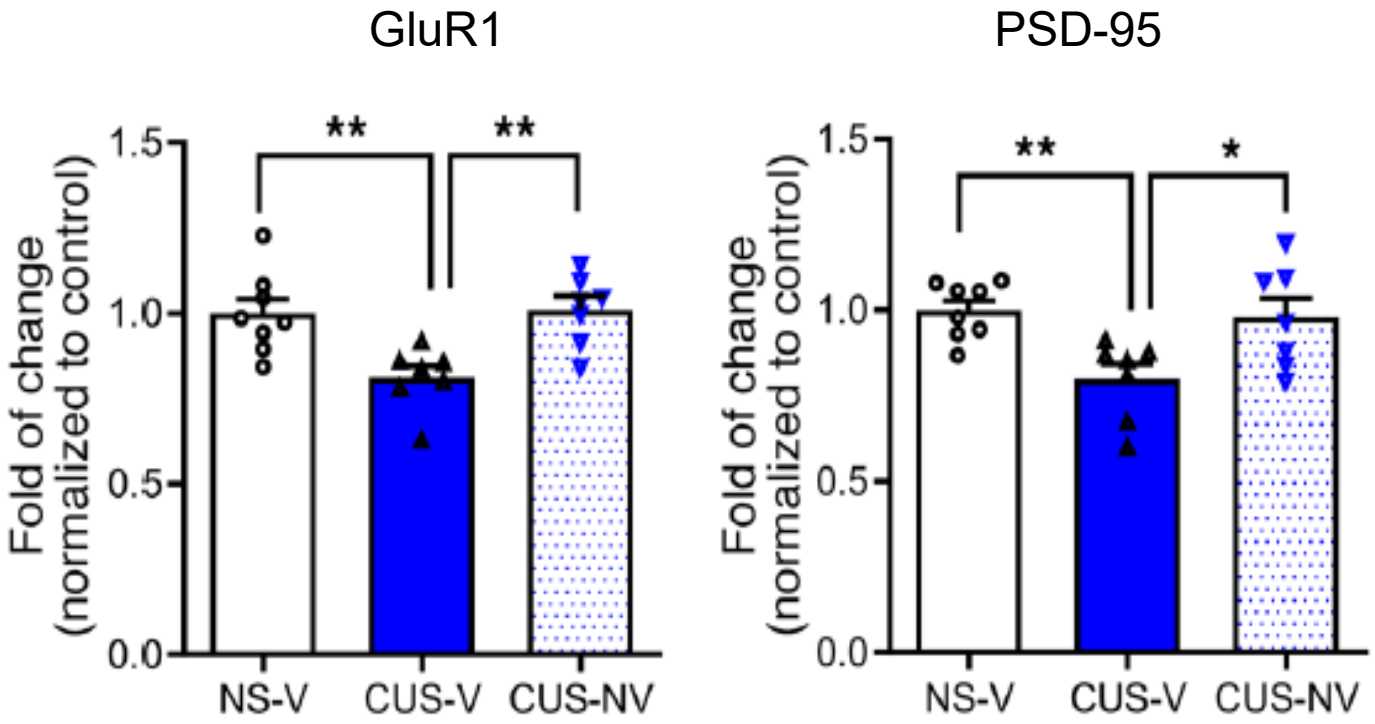
NV-5138 Normalizes Chronic Stress-Induced Decreases in Synaptic Plasticity-Related Proteins in PFC



- NV-5138 reverses chronic stress-induced decreases in GluR1 (left) and PSD-95 (right) protein expression in PFC
- GluR1: AMPA glutamate receptor subunit
- PSD-95: Stabilizes AMPA receptors at post-synaptic membrane

CUS=chronic unpredictable stress; NS=non-stress; NV=NV-5138, V=vehicle; PSD-95=post-synaptic density protein 95; PFC=prefrontal cortex

Kato T, et al. *J Clin Inv.* 2019; 129(6):2542-2554

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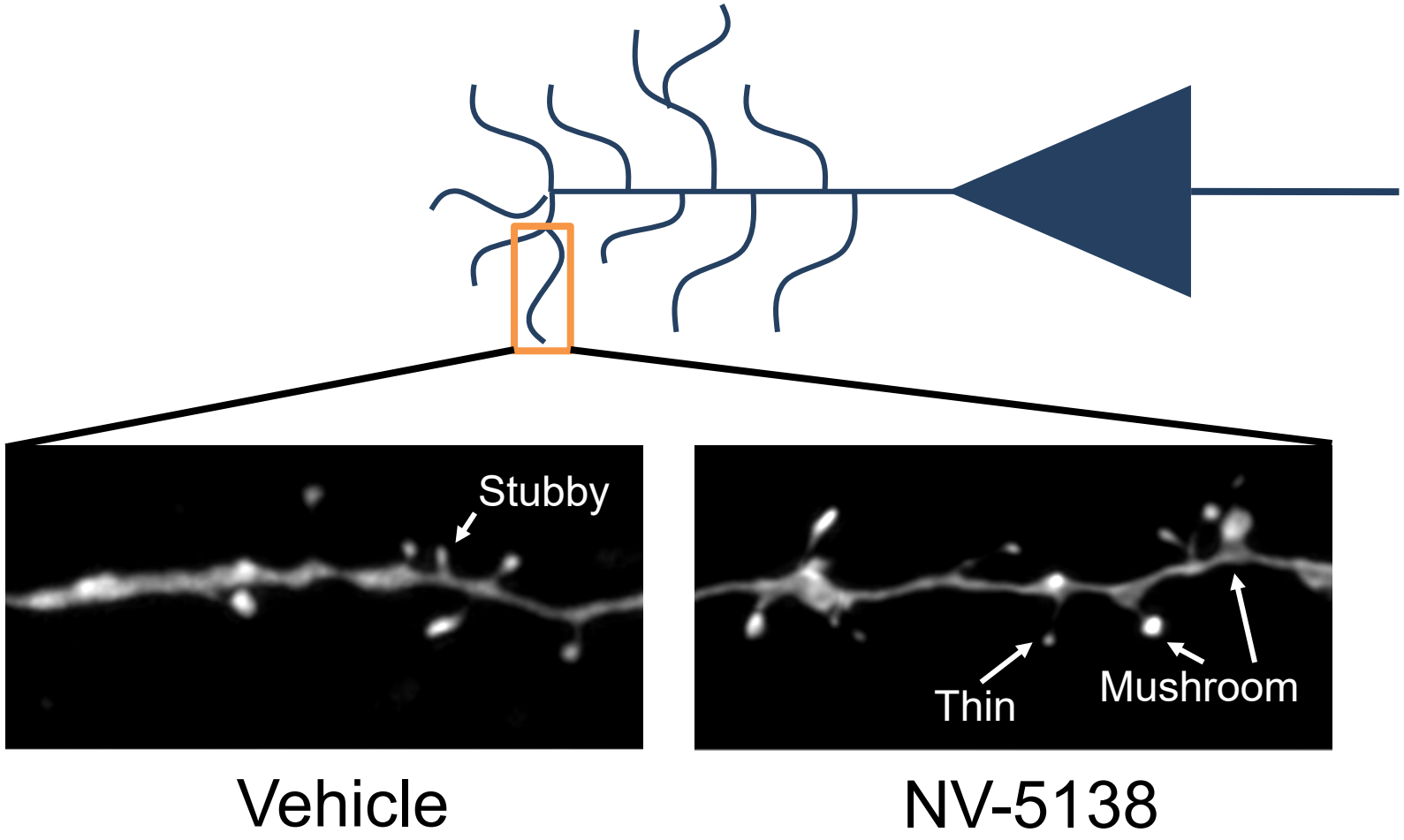
NV-5138 Induces Growth of New Dendritic Spines



Kato T, et al. *J Clin Inv.* 2019; 129(6):2542-2554

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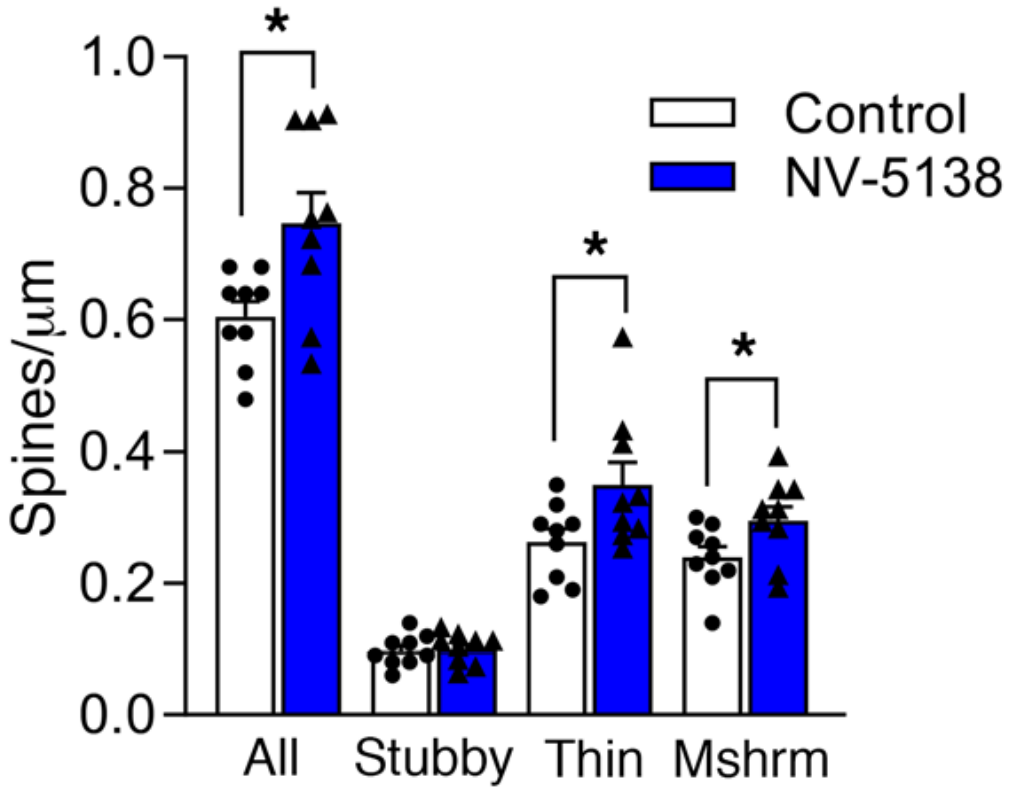
NV-5138 Increases Dendritic Spine Density in PFC



µm=micron; mshrm=mushroom type spine; PFC=prefrontal cortex

Kato T, et al. *J Clin Inv.* 2019; 129(6):2542-2554

- NV-5138 specifically increases thin and mushroom type spines 24 hours after oral administration in Rats
- **Mushroom spines**: Mature, functional synapses known to be enriched in postsynaptic glutamate receptors
- **Thin spines:** Malleable synapses that can become mature mushroom spines with increased synaptic input
- Increased mushroom and thin spines suggest **increased synaptic plasticity** and growth of new synapses

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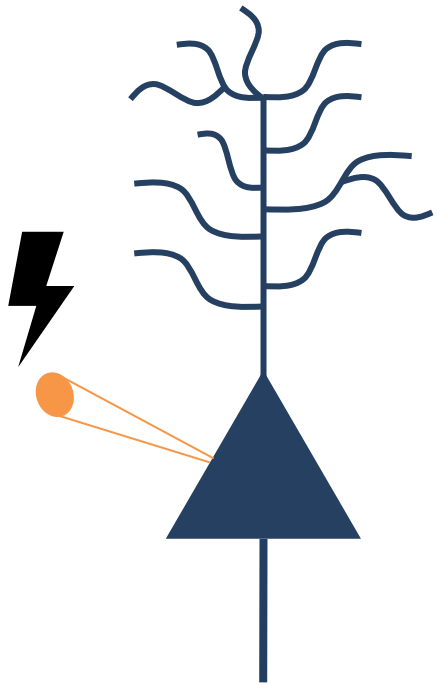
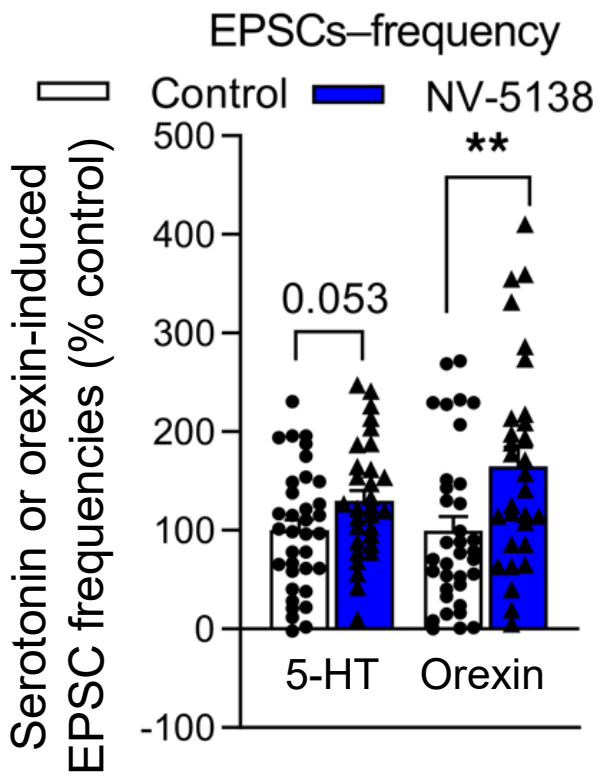
NV-5138 Increases Excitatory Responses in PFC Neurons 24 hours After Oral Administration in Rats

Slice electrophysiology (ex vivo)

+ serotonin or orexin





- NV-5138 increases evoked excitatory responses following application of neuromodulators in PFC neurons 24 hours after oral administration
- Effects were significant for orexin and trending for 5-HT (serotonin)
- Together with increased growth of spines, this result indicates **increased functional synapses**

5-HT=serotonin; EPSC=excitatory post-synaptic current; PFC=prefrontal cortex; ** $p<0.01$ Student's t-test

Kato T, et al. *J Clin Inv.* 2019; 129(6):2542-2554

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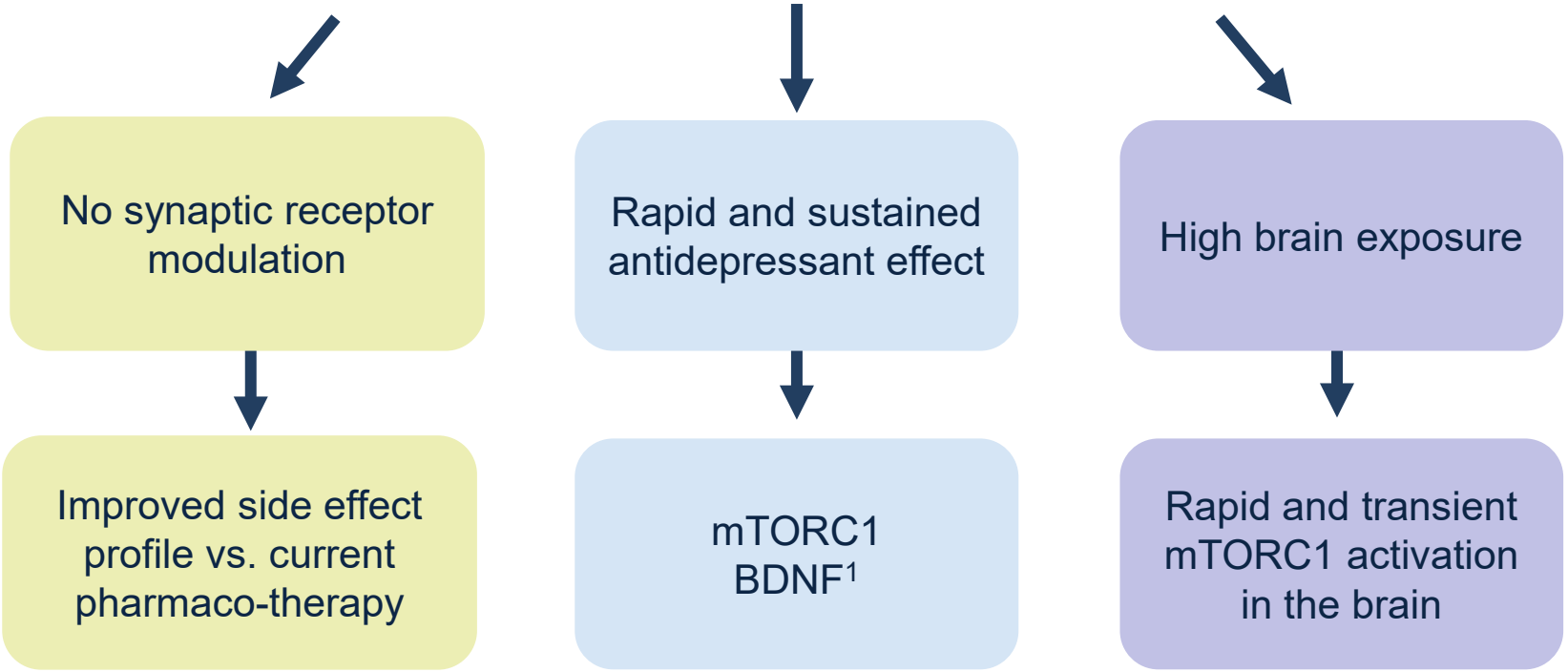
A First in Class Antidepressant

SPN-820

A first in class, small molecule that increases mTORC1 mediated synaptic function *intracellularly*



[1]BDNF=Brain Derived Neurotrophic Factor

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SPN-820

Pharmacology

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PK: Good Development Properties

- **Rapid absorption** in animals across species
  - Rapid uptake in the brain (PFC)
  - No plasma protein binding
- One major **metabolite** identified, not active in mTORC1 activation assay
- **Urine** is primary route of excretion in rodent
  - 93% of administered dose is excreted in urine by 24 hours post dose
- **No** significant *in-vitro* **binding or modulation** to major classes of CYP enzymes, kinases and receptors

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Novel Intracellular Mechanism

- Does not bind to or modulate any cell surface receptors
  - Unlikely to have abuse potential given lack of binding to targets implicated in drug abuse
- Unlike leucine, NV-5138 is not incorporated into proteins during protein synthesis
  - More available at the target site in the brain than leucine
- Antidepressant effect is mTORC1 dependent
  - Rapamycin pretreatment, which inhibits mTORC1, prevents NV-5138's antidepressant effect in rodents

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SPN-820

Phase 1 Studies

SPN-820 PK: Rapid Absorption & Once a Day

- **Half-life:** 10.7 hours in plasma and 11.7 in cerebrospinal fluid (CSF)
- Exposure in CSF is **10 times lower** than plasma
- Confirmed **rapid absorption**: Tmax: 0.5-1.25 hours (Plasma), 4 hours (CSF) and **renal** excretion
- Plasma Cmax is **13.5% lower** with food and peaked 2.5 hours later

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SPN-820 Phase 1 Studies: Rapid Acting Antidepressant

Rapid and sustained effect

- Improvement of core symptoms of depression with a single dose of 2400 mg/day at 4 and12 hours post-dose, with sustained effect to 72 hours, the last timepoint assessed

Rapid absorption

- Rapid brain exposure and pathway activation confirmed by CSF drug levels
- Plasma and CSF exposures suggest 800 to 1600 mg/day dose range for efficacy signal

CSF levels in adults

- Consistent with the fully effective dose in animals

Rapid neuronal activation

- Statistically significant signals on EEG bands associated with increased arousal or alertness (i.e., positive mood states), consistent with rapid change in synaptic function

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SPN-820 Phase 1 Studies: Favorable Safety Profile

- Total of 205 subjects in Phase 1 studies
  - Single oral doses and two sequential oral doses of SPN-820 up to 3000mg/day were safe and well tolerated
  - Maximal tolerated dose not achieved
  - Most common AEs (mild-moderate): nausea, dizziness and headache
  - No psychiatric symptoms or dissociative effects reported
  - No suicidal effects reported

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SPN-820: Proof of Concept in TRD Subjects

- Randomized, two-part, double-blind, placebo-controlled study of single ascending oral solution dose
- Primary endpoint: Changes from baseline to **24, 48, and 72 hours,** post-dose in the **MADRS** rating
- Additional efficacy endpoints: **HAM-D6**, Inventory of Depressive Symptomatology (30-item) and **CGI-S** ratings

Part A	Part B
Healthy Subjects	TRD Subjects
150-2400 mg	2400 mg/Placebo
N= 36 oral solution, N=12 placebo	N=16 oral solution, N=15 placebo
	Randomized 1:1

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SPN-820 POC Study: Rapid Acting & Sustained Efficacy

- Efficacy with HAM-D6 shows early, large effect size, sustained to 72 hours after single dose.
- MADRS did not show efficacy with single dose but showed small effect on acute symptoms.

✓Early Response ✓Core Depression Symptoms ✓**More Severely Depressed at Baseline**

Scale	2h	4h	8h	12h	24h	36h	48h	72h
PRESPECIFIED ANALYSES (N=31)								
MADRS Total Score (prelim. primary @24h)					0.1		0.2	-0.1
HAM-D6	0.6	0.8	0.7	0.8	0.4	0.5	0.5	0.5
IDS-SR 30 Total Score					0.2		0.3	0.2
CGI-S Change from baseline					-0.1		0.1	0.2

Effect sizes: ≥ 0.2 in yellow (early improvement); ≥ 0.4 in green (clinical response).

MADRS= Montgomery Asberg Depression Rating Scale; HAM-D6= Hamilton Depression Rating Scale, 6 items, IDS-SR=Inventory of Depressive Symptomatology (Self-Report); CGI-S= Clinical Global Impression - Severity

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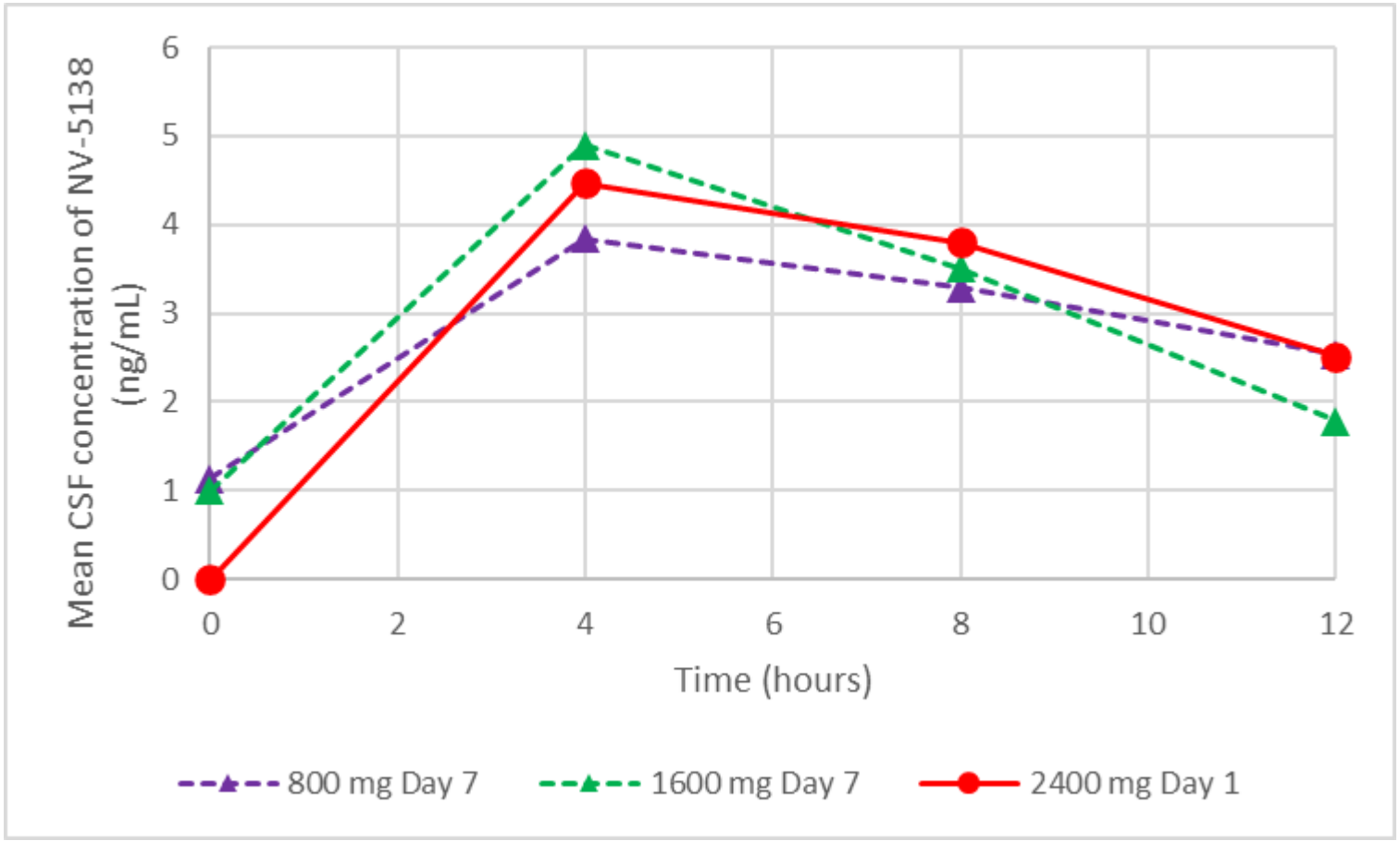
SPN-820: Phase 2 Dose Selection Based on PK

NV-5138 CSF concentration: Day 7 after multiple doses of 800 mg and 1600 mg once daily for 7 days (at steady state) versus single dose of 2400 mg on Day 1



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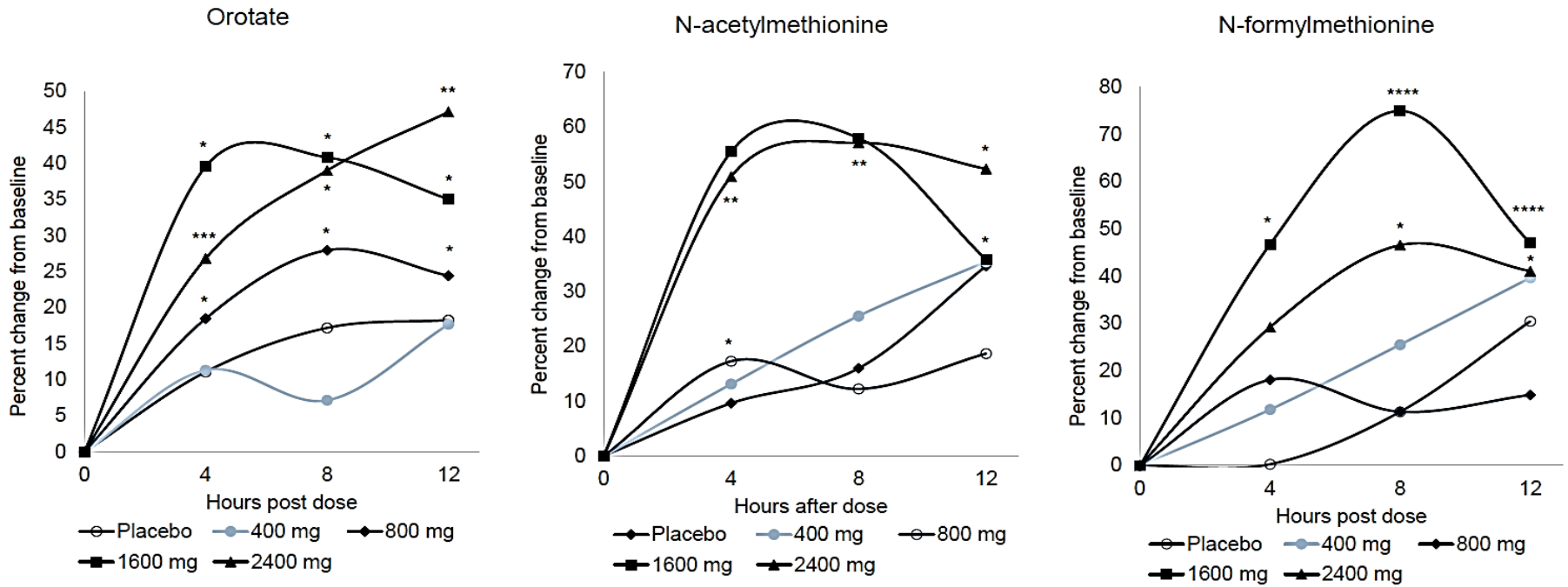
SPN-820: Phase 2 Dose Selection Based on Biomarkers

Biomarkers downstream of mTORC1 activation are increased in CSF at 800 and 1600 mg doses of NV-5138

Nucleotide synthesis

Protein synthesis / turnover



*p,0.05; **p<0.01, ***p<0.005 for Day 1 levels vs Day 1 pre-dose (graphs include all subjects)

SPN-820: Phase 2b Study

Relieve

Study Design

- Multicenter, randomized, double-blind, placebo-controlled, parallel design of **adjunctive therapy**
- Flexible dose: Treatment starts at **1600 mg/day** and tapered down to **800 mg/day**
- Approximately 268 subjects to be randomized, up to 50 sites
- Duration:
  - Screening period: up to 6 weeks
  - Treatment: 5 weeks

Objectives

- Primary efficacy: MADRS
- Key secondary: CGI-S
- HAM-D6
- Onset of effect
- Depression symptoms response and remission
- Individual disability
- Anxiety
- Rate of improvement
- Safety and tolerability

Supernus® Pharmaceuticals

SPN-820: Phase 2b Study Enrollment Status

Relieve

Number of Subjects	Overall
Randomized	62
In-Screening[1]	37
In-Treatment[1]	6
Completed	44
Discontinued (%)	13 (21%)
Discontinued due to AEs	2 (3%)

[1] Data updated as of 11 October 2023

Supernus® Pharmaceuticals

SPN-820: Planned New Phase 2 Study in MDD

- Optimize dosing and assess rapid onset
  - Pulsatile dosing
  - Efficacy in MDD
  - Rapid onset
- Open–label study
  - 40 subjects with MDD
  - Rapid and sustained efficacy (2, 4, 8 and 72 hours after a single administration of 2400 mg SPN-820, dosed every **3 days**)
  - Evaluate rapid onset of efficacy with HAM-D6
  - Evaluate efficacy with MADRS

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SPN-820: Summary of Attributes

- Increases mTORC1-mediated synaptic function through a first in class, unique intracellular mechanism. Adjunctive therapy for patients with TRD
- An average effect size of 0.6 has been measured with a single dose (2400mg) over an initial 72-hour period using HAM-D6
- Rapid onset of effect, beginning within hours of first dose using HAM-D6
- Sustained effect of a single dose persists up to 72 hours in depression core symptoms
- Well-tolerated in clinical trials with no reports of dissociation or hallucinations
- Unlikely to be a controlled substance
- Phase 2b topline results 2025

Supernus® Pharmaceuticals

SPN-820 Q & A

SPN-817

Jonathan Rubin

SVP, Research and Development, Chief Medical Officer

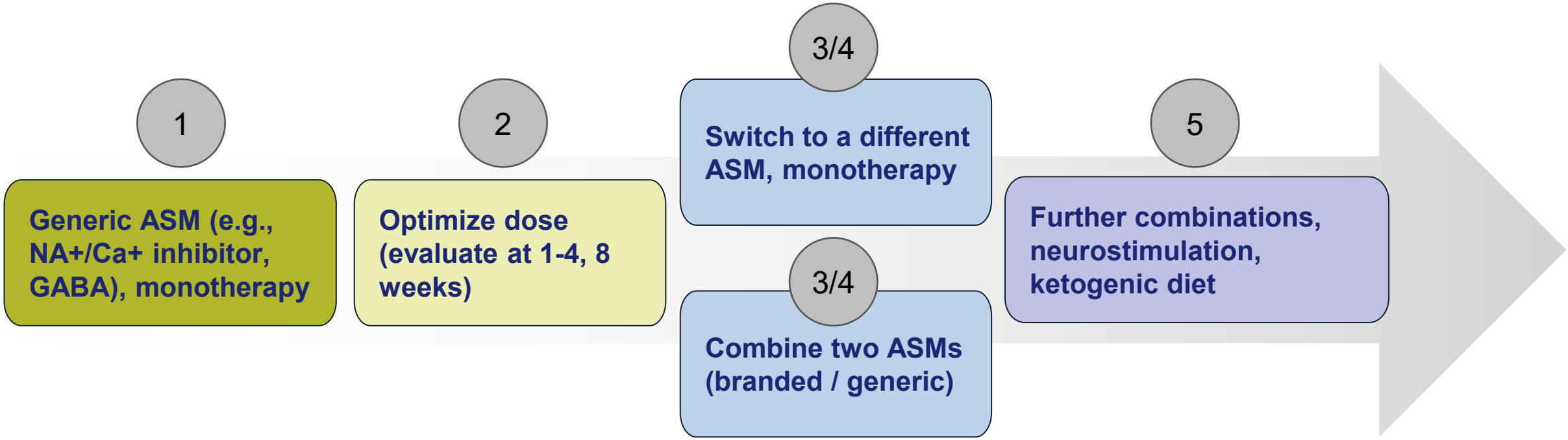
Supernus® Pharmaceuticals

SPN-817

Novel, First in Class, Highly Selective Acetylcholinesterase (AChE) Inhibitor for Focal Epilepsy

Supernus® Pharmaceuticals

Refractory Epilepsy Results in Switching & Polypharmacy



1. American Academy of Neurology Treatment Guidelines
ASM = Anti-Seizure Medication

Supernus® Pharmaceuticals

Epilepsy: Debilitating Disease with Significant Unmet Need

- 1.2% of people in the U.S. have epilepsy (~3.4M people)[1]
- Focal seizures affect up to 61% of people with epilepsy[1]
- 40% of patients with epilepsy are drug resistant[1]
- 28.5M annual prescriptions[2]
- Can be a life-long chronic disease

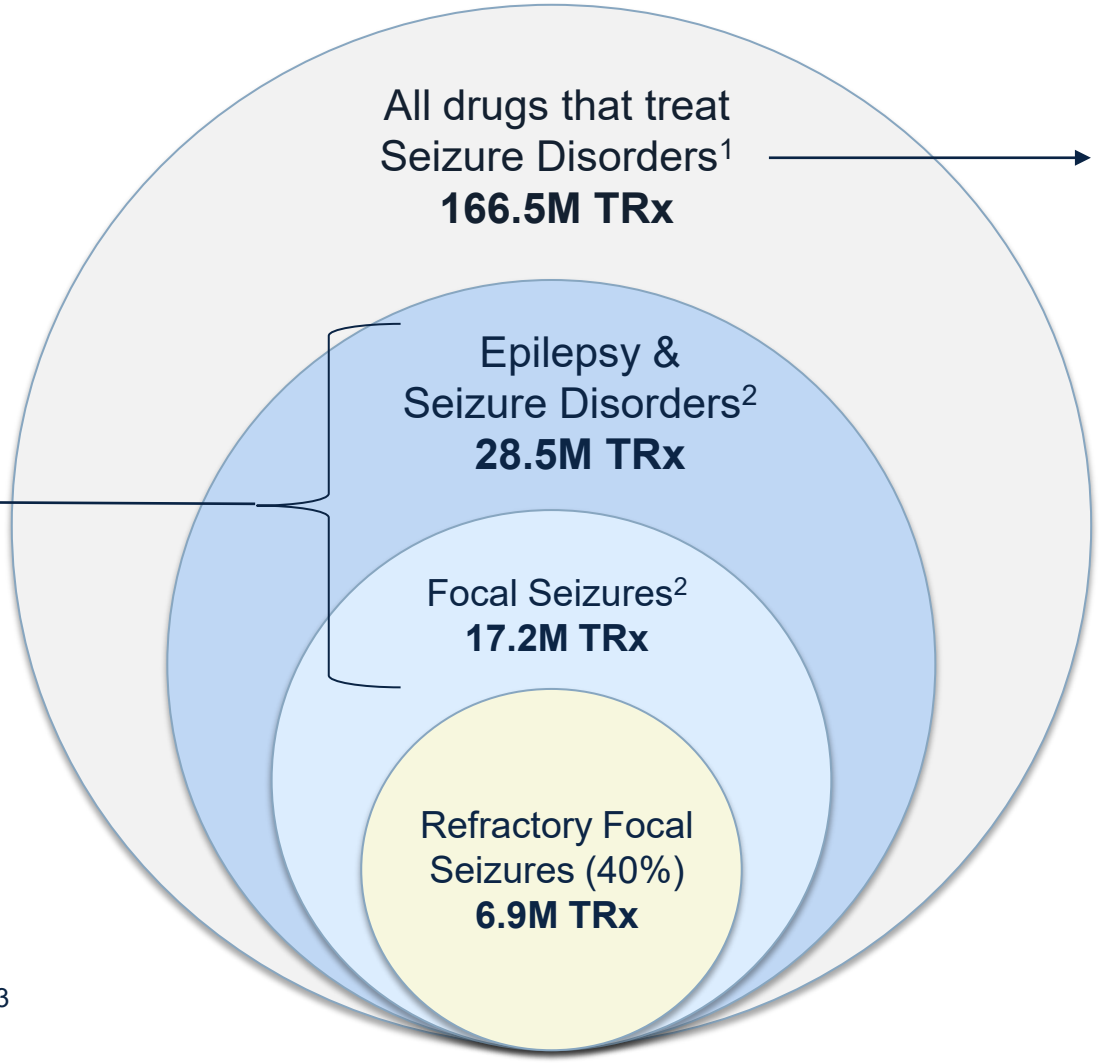
- Probability of achieving seizure freedom decreases substantially with each additional ASM regimen attempted[1]
  - 2nd 11.6%
  - 3rd 4.4%
  - 4th 1.2%
- Higher seizure frequency, AEs, and employment concerns reduce patient and caregiver QoL[3]

Patients are looking for treatments resulting in better seizure control, improved quality of life, and better tolerability

1. Ioannou P, et al. *Brain Behavior* 2022; 12(9): e2589
2. IQVIA, NPA + NMTA, May 2023
3. Data on file – Epilepsy Market Research 2023

Supernus® Pharmaceuticals

SPN-817: Market Opportunity



Includes drugs that treat non-seizure disorders as well (e.g., gabapentin/neuropathic pain, lamotrigine/bipolar, etc.)

Focal seizures represent 60% of all epilepsy/seizure disorder TRx

US Market- $2.7B
GlobalData Net Revenue Sept 2023

1. IQVIA NPA, MAT April 2023 (includes non-seizure disorder indications as well)
2. IQVIA Integrated NPA + NMTA, MAT April 2023

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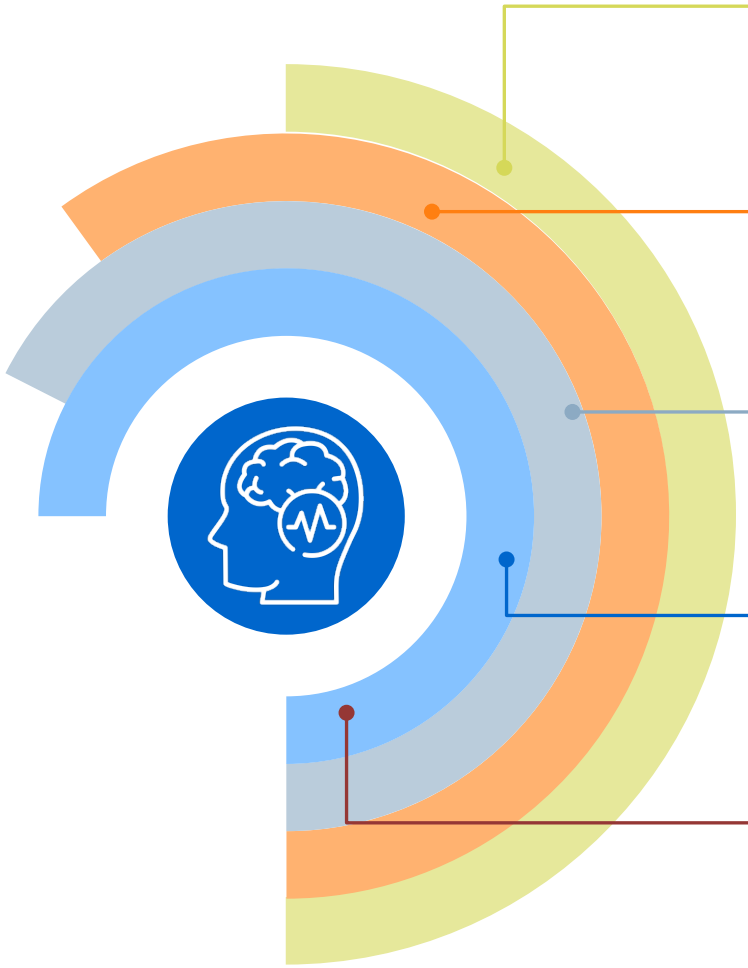
Despite a Competitive Market, There is a Need for Effective Pharmacological Treatments[1]



HCPs are aligned on treatment goals

Reducing seizure frequency, improving QoL, achieving seizure freedom, and reducing severity of seizures are key.

Treatment satisfaction is low

Though there are many treatments available, there are few with which HCPs are truly satisfied.

Efficacy is most important

Efficacy is the single-most important motivator in driving treatment choice, followed by safety / drug interactions.

Adoption is driven by adult treaters

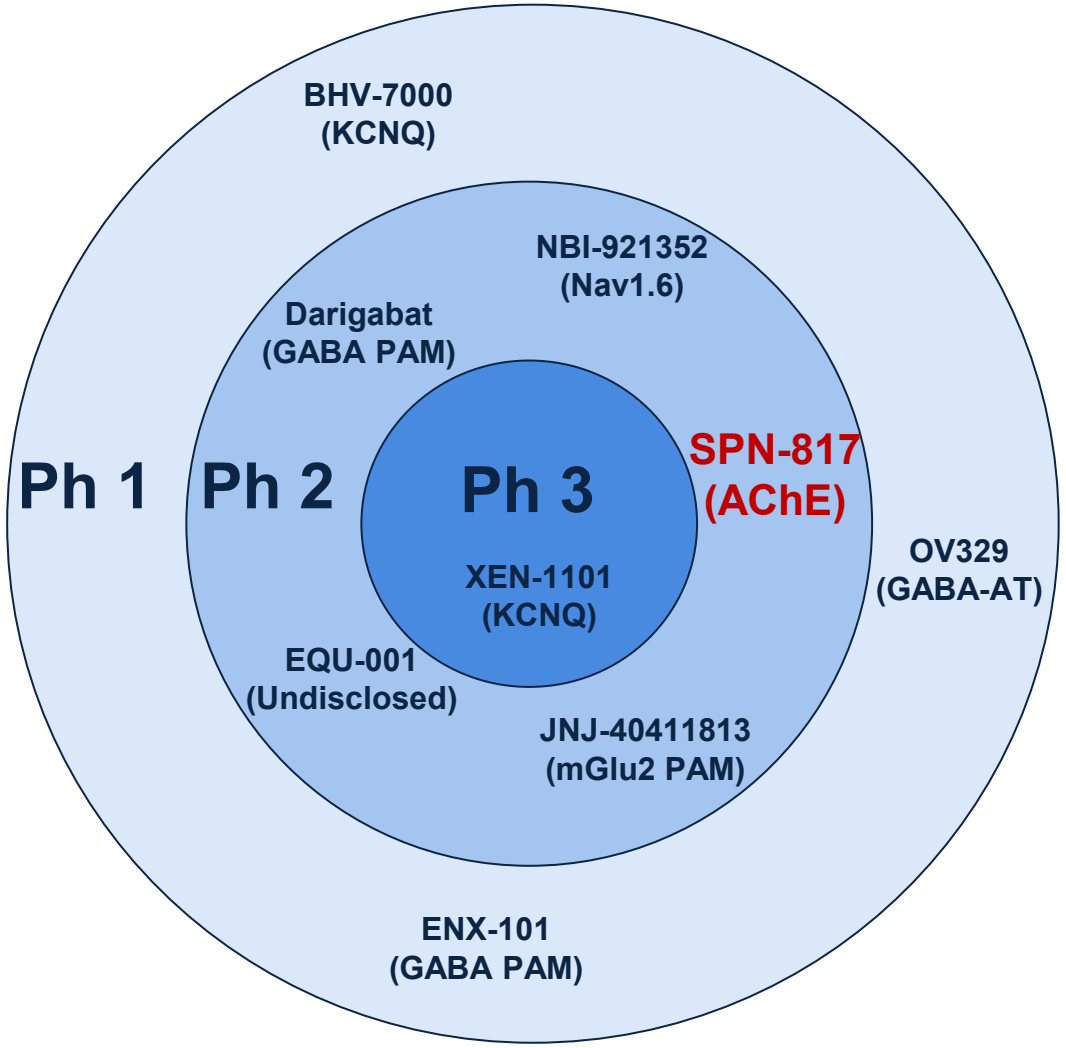
Pediatric treaters are more cautious and slower to adopt.

Adult and pediatric treaters see value in pro-cognitive and neuroprotection benefits

1 – Supernus Conjoint Market Research Study (June 2023)

Supernus® Pharmaceuticals

SPN-817: Only AChE inhibitor in Development for Focal Seizures



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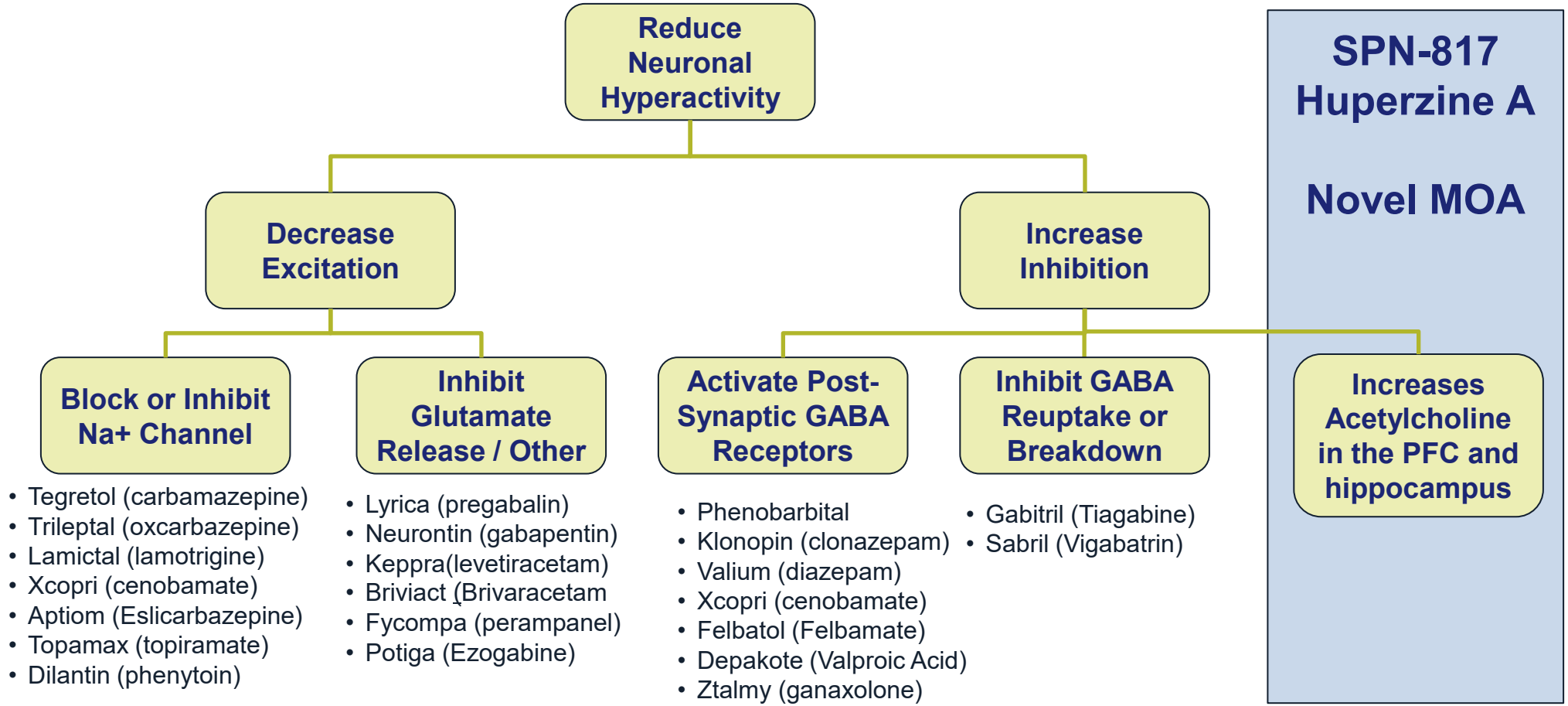
A New Class of Therapy



SPN-817

Pharmacology

Supernus® Pharmaceuticals

SPN-817: Novel MOA for the Treatment of Focal Seizures

- Huperzine A is a potent, selective and reversible acetylcholinesterase (AChE) inhibitor, an enzyme that metabolizes acetylcholine (ACh) after synaptic release[1,2]
- Inhibition of AChE increases extracellular levels of ACh
- Broad and potent anti-seizure effect in different seizure and genetic models of epilepsy[1-4]

[1] Supernus data on file
[2] Damar et al. (2016). *Expert Rev Neurother, 16*(6), 671-680
[3] Wong et al (2016). *Front Pharmacol, 7*, 357
[4] Wong et al (2021). *Neuropsychopharmacology, 46*(11), 2011-2020

Supernus® Pharmaceuticals

SPN-817 Preclinical Data: Refractory Seizures

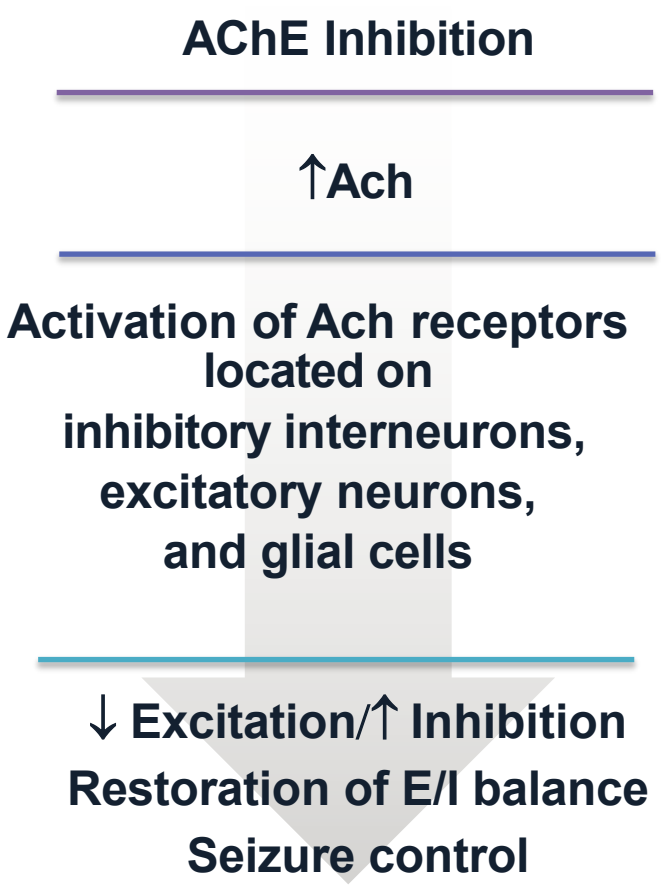
(ED_{50} in mg/kg)	22mA	32mA	44mA
Phenytoin	9.4	>60	>60
Lamotrigine	4.4	>60	>60
Ethosuximide	86.9	167	>600
Valproic Acid	41.5	126	310
Levetiracetam (Keppra)	4.6	19.4	1,089
SPN-817	0.28	0.34	0.58-0.78

- The 6Hz animal seizure model screens compounds as potential therapies for drug-resistant partial seizures.
  - SPN-817 57x more potent than Keppra® at commonly used 32mA stimulation
  - SPN-817 was the only compound tested that produced significant seizure protection at highest seizure inducing state-44mA

Sources: NIH Anticonvulsant Screening Program Data
Data on file. All trademarks are owned by their respective owners.

Supernus® Pharmaceuticals

SPN-817: Current MoA Hypothesis for Seizure Control: Cholinergic Modulation of Neuronal Excitation



- Seizures are the result of the imbalance of the Excitation/Inhibition (E/I) ratio in susceptible regions of the brain
- Acetylcholine augmentation activates cholinergic pathways in different cellular types in the brain to restore E/I balance

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SPN-817: More Selective than Other Cholinesterase Inhibitors

- More selective towards AChE than BuChE [1,2]
- Requires lower doses to block central AChE
  - Displays higher AChE inhibitory activity in various brain regions at lower doses (improved therapeutic index)[3]
  - Donepezil exhibits similar AChE activity to SPN-817 at doses well exceeding maximum prescribed/tolerated doses[1]

[1]Tang, X., Han, YF. (1999). *CNS Drug Reviews, 5(3)*, 281-300
[2]Wang, R., Yan, H., & Tang, X. C. (2006). *Acta Pharmacol Sin, 27*(1), 1-26
[3]Zhao, Q., & Tang, X. C. (2002).Eur J Pharmacol, 455(2-3), 101-107

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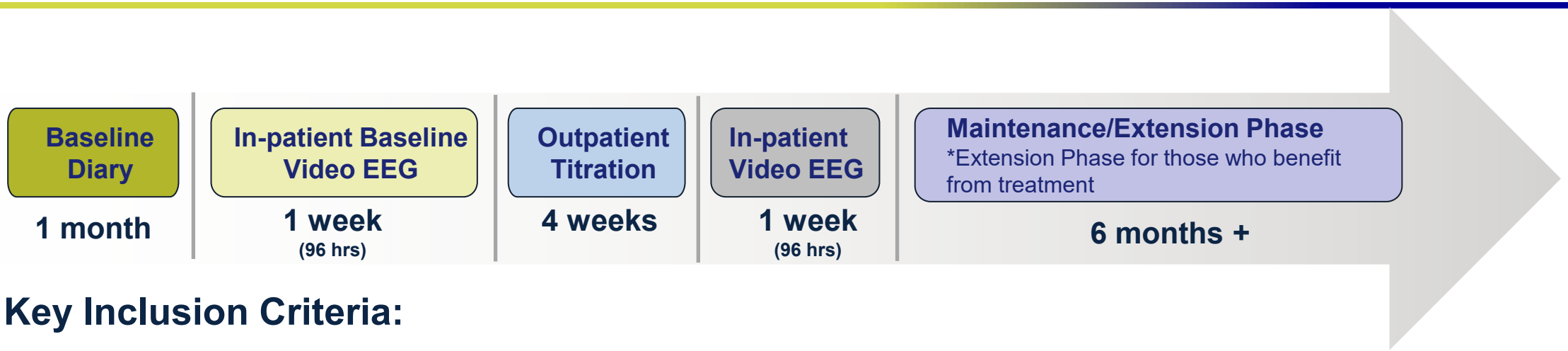
SPN-817: Phase 2a Focal Onset Impaired Awareness Seizure (FIAS) Study



Key Inclusion Criteria:

- Diagnosis of FIAS type epilepsy
- Current minimum average of 5 countable seizures / week to enroll in study
- At least 5 focal impaired awareness seizures during baseline
- Receiving stable doses (for at least 4 weeks) of 1 to 4 currently marketed ASMs

Key Exclusion Criteria:

- Seizures that are difficult to count
- History of status epilepticus in the 6 months prior to enrollment

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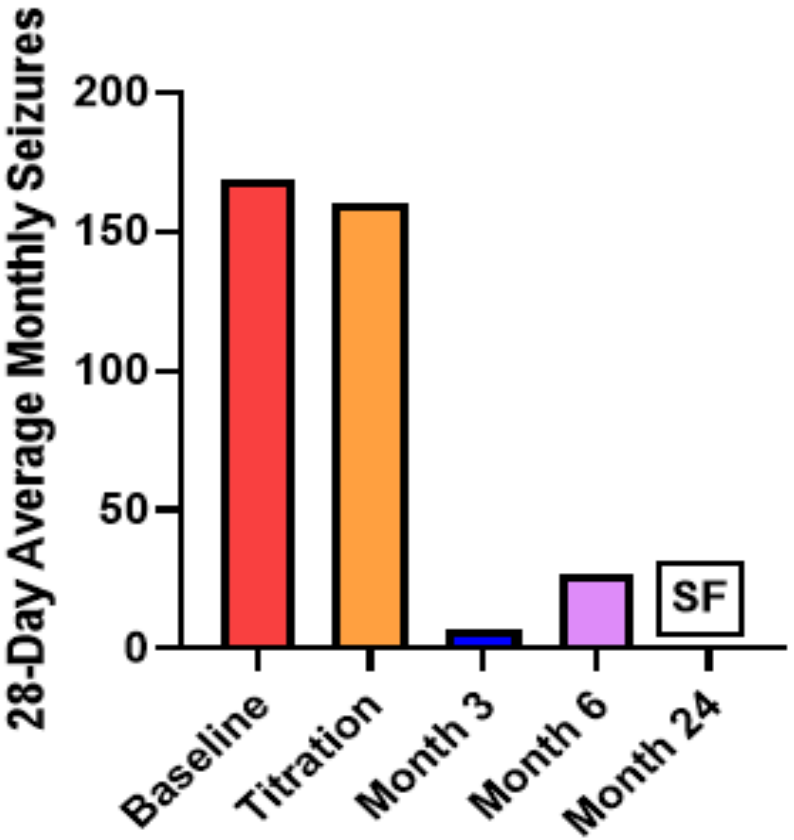
SPN-817: Showed Significant Seizure Reduction in Small POC Study

- Patients had focal impaired-awareness seizures (FIAS) type epilepsy, treated with a maximum dose of 4 mg BID
- Mean reduction in 28-day seizure rate from baseline was:
  - 71.2% until month14 (n=3)
  - 89.8% until month 40 (n=2)
  - 98% until month 51 (n=1)
- One subject has been seizure-free for >3.5 years and regained his driver's license and returned to work
- Most TEAEs were transient, mild or moderate in intensity:
  - Insomnia and nausea followed by nasopharyngitis, pyrexia, and dizziness.



SF = seizure free, graph represents data from 1 subject

SPN-817: Phase 2a Synopsis

- Open-label study
- Number of study sites: up to 8 sites in Australia
- Number of participants: approximately 35 subjects with treatment resistant seizures
- Indication: focal seizures in adults (18-65 years of age)

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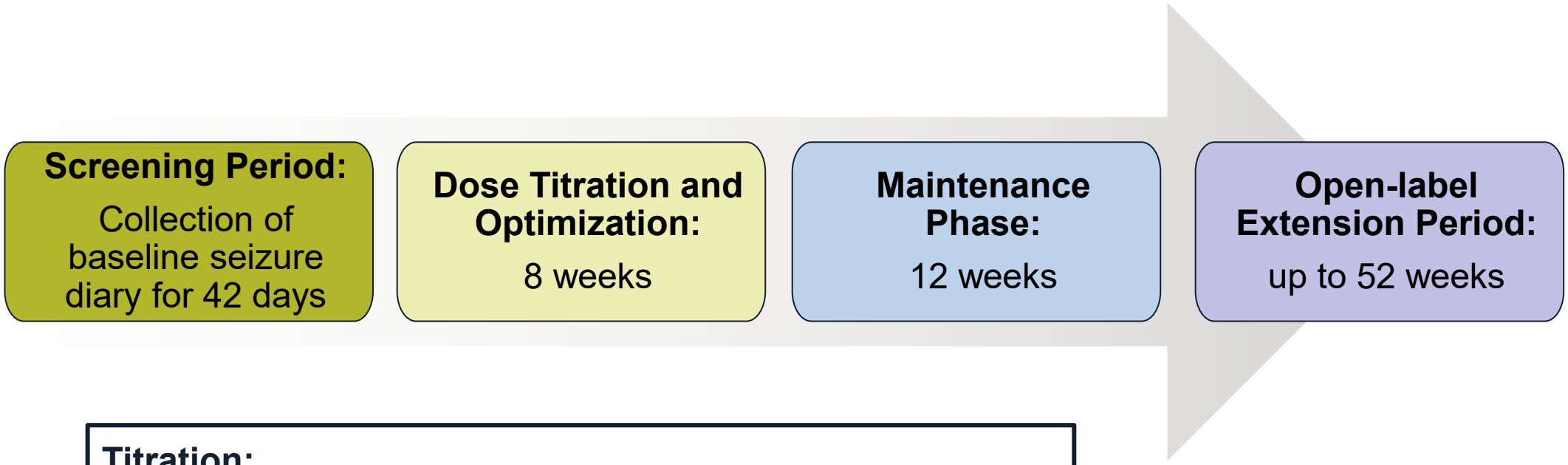
SPN-817: Phase 2a Study Design



Titration:

- All patients initiated on 0.25mg bid
- All will follow a personalized titration schedule
- Dose escalation by increments of 0.25mg or 0.5mg every 3-8 days, depending on tolerability, up to 4.0mg bid

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SPN-817: Phase 2a Endpoints

- Primary:
  - Safety and tolerability as an adjunctive therapy in adult patients with treatment resistant seizures
- Secondary:
  - Percent change from baseline in motor seizure frequency per 28 days
  - Improvement in seizure symptoms (CGI-I)
  - Change in seizure symptom severity (CGI-S)
  - Change in Quality of life in epilepsy (QOLIE-31-P)
  - Change in level of disability (seizure-related disability assessment scale scores, SERDAS)
  - Characterize the PK profile of huperzine A
- Exploratory: Change from baseline:
  - In select inflammatory biomarkers in plasma (interleukin-1 receptor antagonist [IL-1RA], IL-6, IL-10, and C-reactive protein)
  - In cognitive profile as assessed by EpiTrack® and the Controlled Oral Word Association Test (COWAT)
  - In seizures + interictal spikes and sleeping patterns (EEG)

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SPN-817 Phase 2a Study: Interim Data

- 7 patients completed titration at doses ranging from 1.0 mg bid to 4.0 mg bid
  - Most common TEAEs were diarrhea, nausea, headache, insomnia, and affect lability
  - All TEAEs were mild/moderate in severity
- 6 patients completed titration with available seizure diary data
  - 63.5% mean reduction in seizures per 28 days during maintenance period (n=2)
- 2 patients achieved seizure freedom (100% reduction) during titration after 8 weeks and 9 weeks of treatment, respectively
- 1 patient completed the study and moved into OLE with 68.3% reduction in seizures over the entire treatment period

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SPN-817: Planned Phase 2b Treatment Resistant Focal Seizures

Study Schema:

Design: Randomized, double-blind, placebo-controlled, study up to 35 weeks

Study population: Adults who failed to achieve seizure freedom after ≥2 ASMs and taking at least 1 ASM

Subjects: Approximately 436

Randomization: 4 arms, randomized 1:1:1:1 to SPN-817 2.0 mg bid, SPN-817 3.0 mg bid, SPN-817 4.0 mg bid or placebo bid (109 subjects per arm), to achieve 76 subjects per arm in the Full Analysis Set

Number of sites: Up to 102 sites in the United States, Europe, Australia and Asia

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SPN-817: Phase 2b Endpoints

- Primary:
  - Change from baseline in focal seizure frequency per 28 days
- Secondary:
  - Safety and tolerability
  - Pharmacokinetics (PK) of huperzine A
- Exploratory: Change from baseline:
  - In inflammatory biomarkers in plasma
  - In cognitive performance
  - In electroencephalography (EEG)

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SPN-817 Summary:
Novel First in Class Selective AChE Inhibitor for Focal Seizures

- Phase 2 long-term maintenance:
  - mean reduction in 28-day seizure rate from baseline (excluding titration) was 70% (n = 3)
- Well-tolerated according to reported adverse events
- Broad and potent anti-seizure effect in different seizure and genetic models of epilepsy
- Unique AChE inhibitor with high selectivity, low activity on BuChE
- Potential for pro-cognitive, neuroprotective, and anti-inflammatory effects
- Entering Phase 2b in 2024

Supernus® Pharmaceuticals

SPN-817 Q & A

Break

SPN-443

Novel MOA with Potential Stimulant-like Efficacy and Reduced Abuse Liability

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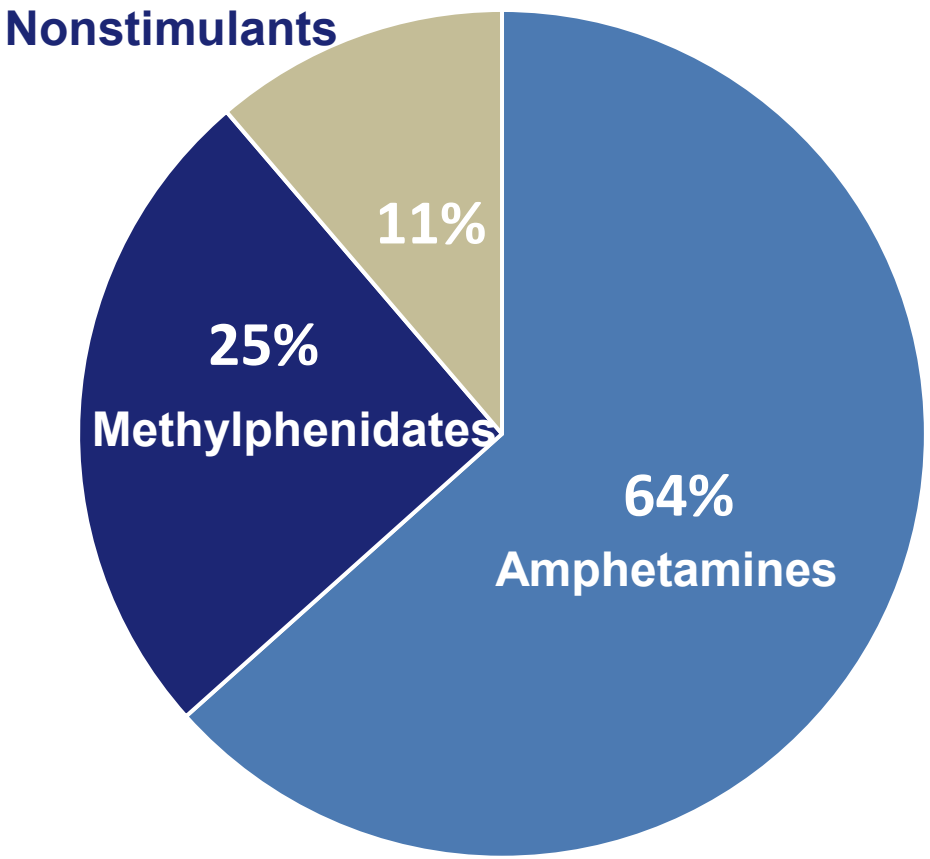
ADHD Annual Prescriptions of 92.1M - 89% are for Stimulants



The market rewards fast onset, predictable response, and good treatment effect.

Source: IQVIA MAT Aug 2023

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Stimulants are Effective, But have Significant Drawbacks

Advantages

- Significant treatment effect
- Rapid onset
- Allows for as needed dosing with some patients
- Many generics available

Drawbacks

- DEA CII controlled substance requirements – HCPs need to meet with patients every 30 days prior to writing a new prescription
- Significant diversion related to appetite suppression, stimulant effect for late night studying, etc.
- Tolerability issues: anxiety, insomnia, mood swings, weight loss, etc.

Supernus® Pharmaceuticals

SPN-443: Leverages Qelbree's Commercial Investment

- Sales force of 245 representatives
  - Established relationships with HCPs and staff
  - Leverage a well-trained and educated sales team
- Well-established relationships with KOLs
- Leadership position among ADHD societies
- Significant resident knowledge of the market

Leveraging our ADHD commercial infrastructure would provide scale efficiencies and faster commercial ramp

Supernus® Pharmaceuticals

SPN-443: NCE with Triple Reuptake Activity & Low Risk for DDI or Abuse

- Active parent and major metabolites based on preclinical models
  - All are triple monoamine transporter (NET, DAT, SERT) inhibitors
- High blood brain barrier permeability
- Low risk for drug-drug Interactions (DDI)

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Parent and Major Metabolites have NET, DAT & SERT Activity

Affinity (human isoforms)

In vitro Binding Assay (Ki in nM)			
	SPN-443	Metabolite 1	Metabolite 2
NET	25	0.71	270
DAT	120	6	10
SERT	670	40	110
MOP	280	160	>10000

Functional Activity (human isoforms)

Functional Assay Transporters (IC_{50} in nM)			
	SPN-443	Metabolite 1	Metabolite 2
NET	12	0.52	53
DAT	110	12	63
SERT	1200	680	1200

- SPN-443 and its metabolites all bind to and inhibit NET, DAT, and SERT but with varying potencies
- Metabolites could provide longer duration of effect

Supernus® Pharmaceuticals

In-vivo Pharmacology: Increase in Monoamines in a Rat Model

- Microdialysis study: SPN-443 (0.3 mg/kg intraperitoneal dosing) significantly increased monoamines in the PFC, but not the nucleus accumbens:
  - Dopamine (300%)
  - Norepinephrine (391%)
  - Serotonin (141%)
  - Lack of activity in nucleus accumbens suggests low abuse potential

Reference: Data on File

Supernus® Pharmaceuticals

SPN-443: Results from Nonclinical Safety Studies Support Advancing into the Clinic

- No evidence of genotoxicity
- No adverse CV or CNS functional effects in safety pharmacology studies
  - Large safety margins in hERG assay
- No dose-limiting toxicity up to 38x human equivalent dose in 14-day repeat dose toxicity studies

Reference: Data on File

Supernus® Pharmaceuticals

SPN-443: Planned FIH Study in 2024

- Study design – Phase 1 single dose to evaluate PK in healthy adults
- Number of subjects: Approximately 24 enrolled and 18 completers
- Objectives:
  - Estimate PK of SPN-443 and its metabolites
  - Calculate relative bioavailability between two oral formulations

STUDY DESIGN

Study Days				
-28 to -2	-1	1 to 7	8 to 14	15
		Period 1	Period 2	
Screening	Entry	Treatment A SD PK	Treatment B SD PK	EOS

FIH= First in Human; SD = single dose; Entry = entry and labs to confirm eligibility; EOS = End of Study; PK = pharmacokinetic sampling 0 to 144 hours after the dose.

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SPN-443: Summary of Potential Attributes

- Effect size within range of leading stimulants (1.0+)
- DEA scheduling of IV or better
- Well tolerated
- Long duration of activity

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SPN-446

Narcolepsy

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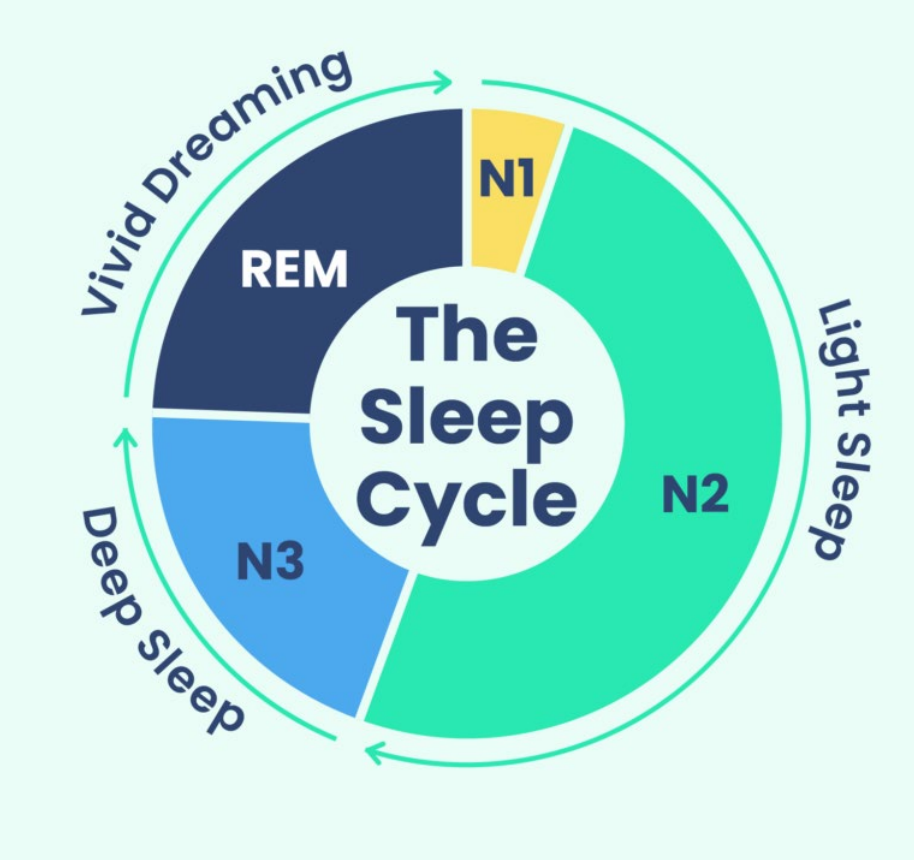
Sleep Cycles



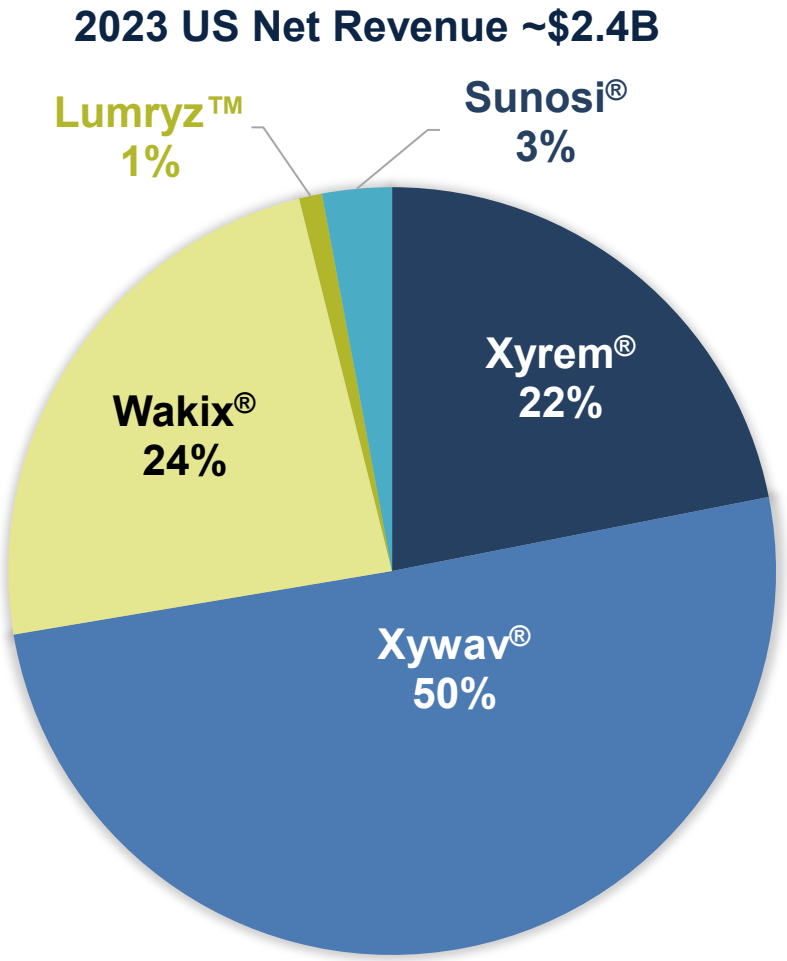
- A single sleep cycle normally includes non-REM (i.e., stages 1-3) and REM (rapid eye movement, stage 4) sleep.
- Alterations in neurocircuitry and neurochemistry can alter this cycle, resulting in different types of sleep disorders or parasomnias.

Roth T, et al. *Journal of Clinical Sleep Medicine* 2013; 9(9): 955-965

Supernus® Pharmaceuticals

Narcolepsy Type 1 (NT1)

- Characterized by excessive daytime sleepiness (falling asleep without warning) along with daytime cataplexy (sudden loss of muscle tone)
- 60% of total narcolepsy population
- Orphan indication
- Typically associated with a loss of orexin signaling
- Diagnosed narcolepsy patients US: 1 per 2,000 people (~165,000)



2. Global Data 2023 forecast- net revenue

1. Szabo ST, et al. *Sleep Medicine Reviews* 2019; 43: 23-36

Supernus® Pharmaceuticals

Need for New Therapies in NT1

- More than 74% of patients still report issues with daily activities[1]
- 84% percent described impaired work or school performance and judged their condition as moderate or severe[1]
- 70% reporting excessive daytime sleepiness every day[1]
- 31% suffering cataplexy daily[1]
- Significant safety/tolerability concerns with sodium oxybate[2]
  - Black box warning
  - REMS[3] program, abuse, etc.

1. Nat Sci Sleep. 2015; 7:51 -61. Unmet needs of patients with narcolepsy: perspectives on emerging treatment options – PMC (nih.gov)
2. Safety Overview of Post marketing and Clinical Experience of Sodium Oxybate (Xyrem): Abuse, Misuse, Dependence, and Diversion - PMC (nih.gov)
3. Unmet needs of patients with narcolepsy: perspectives on emerging treatment options - PMC (nih.gov)

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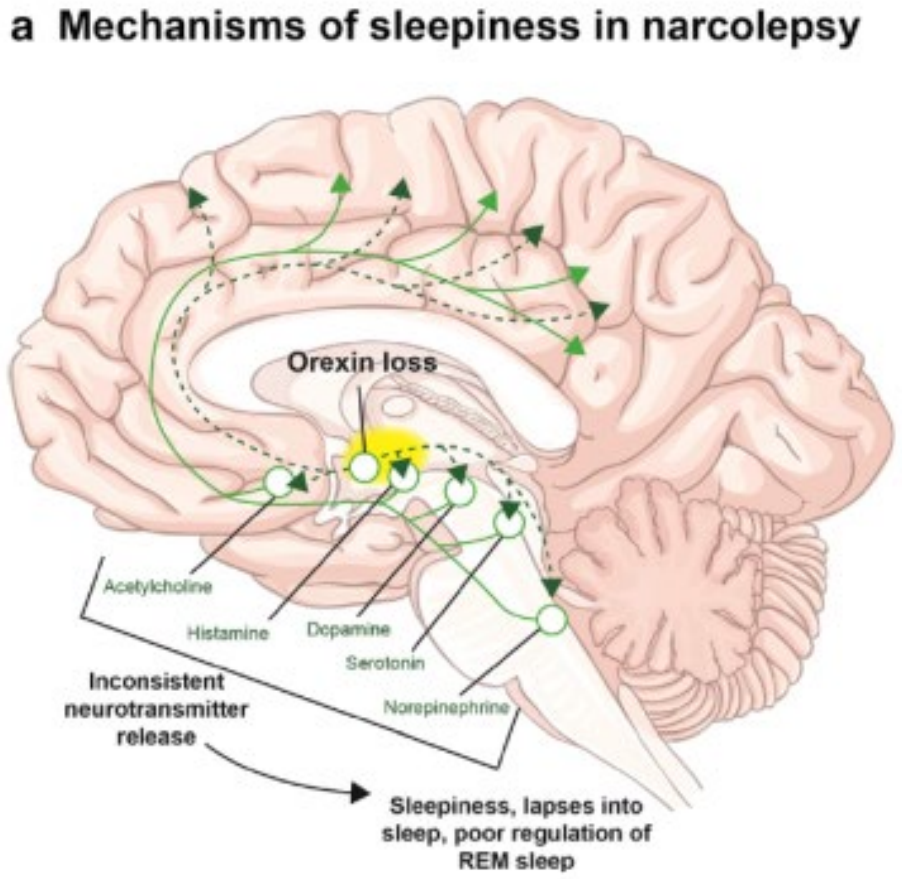
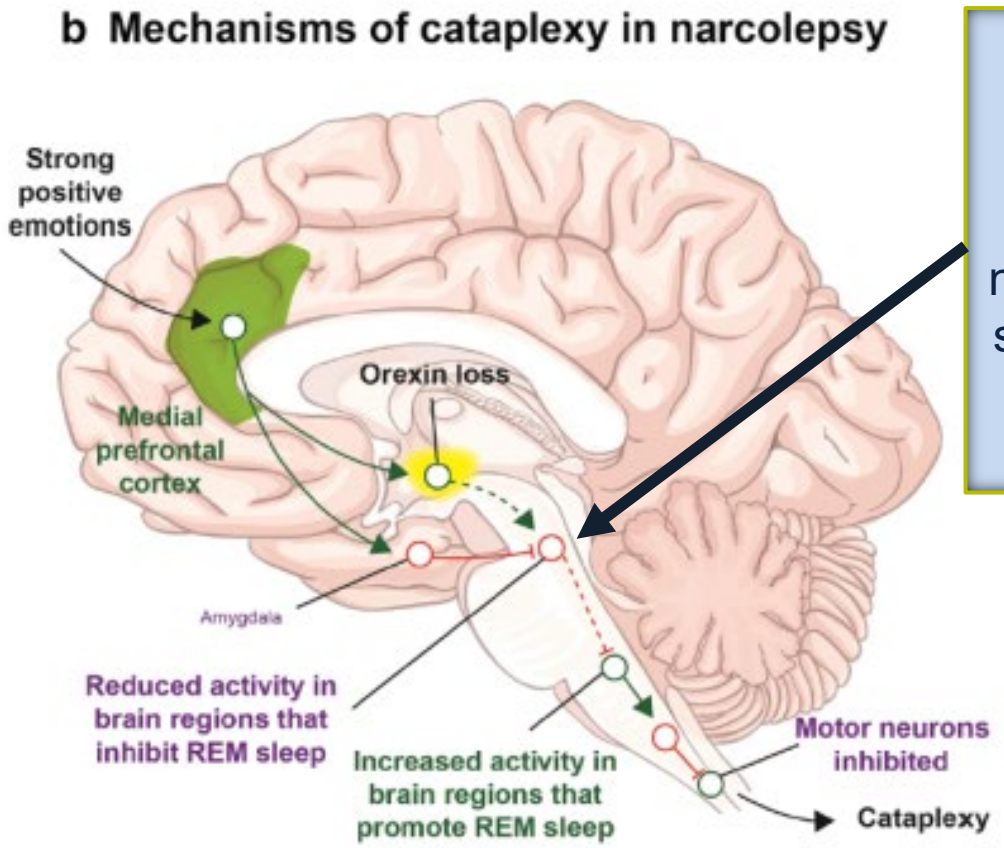
Neurocircuitry of NT1: Role of Norepinephrine (NE)



a) Orexin pathways that promote and maintain wakefulness



b) Orexin pathways that suppress REM sleep and maintain muscle tone during wakeful periods

Reduced activation of NE neurons (due to loss of orexin neurons) leads to sudden induction of REM sleep and cataplexy.

Krahn et al (2022) Adv Ther 39:221–243

Supernus® Pharmaceuticals

SPN-446: Shows Norepinephrine Transporter Inhibition & Activity on Several Serotonin Receptors

- SPN-446 is a NET inhibitor with activity towards different serotonin receptors[1]

Receptor	Binding	Agonism	Antagonism
NET	Ki= 0.11 µM		IC50 = 0.085 uM
5-HT2C	Ki=0.51 µM	EC50=0.5-2.5 µM; Emax=56-74%	
5-HT2B	Ki=0.97 µM		IC50=1.6 µM–34 µM
5-HT7	Ki=0.81 µM		IC50=27 µM

- The role of NE in the transitions between awake-sleep have supported the evaluation of NRI's as potential treatments for narcolepsy (Type I and II)[2]
- NET inhibitors have a potential therapeutic effect in Narcolepsy Type 1 animal models

[1] Data on file
[2] Mitchel and Weinshenker (2010). Biochem Pharmacol 79(6):801-809

Supernus® Pharmaceuticals

SPN-446: Decreases Cataplexy and REM Sleep in Preclinical Models

- Microdialysis
  - Dose dependent increase in dopamine, norepinephrine, and serotonin in rat prefrontal cortex.
- Novel Object Recognition (NOR) test
  - Improved episodic memory
- Orexin neuron ablation (mouse model of narcolepsy type 1)
  - Decrease in cataplexy and REM sleep up to 12 hours post dosing

Data on file

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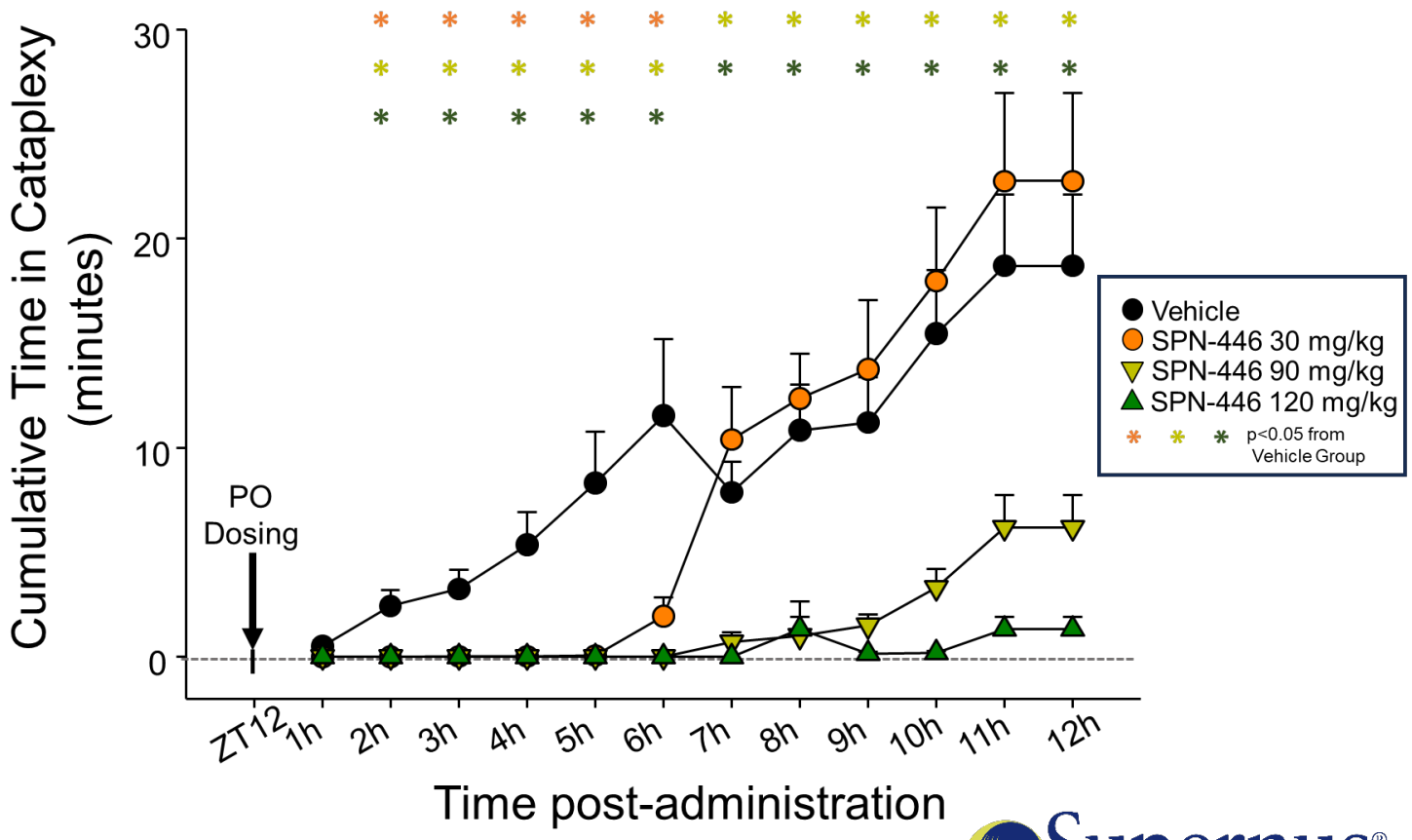
SPN-446: Shows Dose Dependent Decrease in REM Sleep and Cataplexy

NT1 Animal Model (Conditioned orexin neuron ablation or DTA mice):

- Reduces cataplexy and REM sleep up to 12 hours after dosing at the beginning of active time (ZT12 to ZT24).

Effects on cataplexy up to 12 hours after SPN-446 administration during active time



Data on File

Supernus® Pharmaceuticals

Full Q & A

Supernus® Pharmaceuticals

Closing Remarks

Jack Khattar

President and Chief Executive Officer

Strong Foundation for Future Growth

- Successfully transitioned from a drug delivery company to a profitable biopharma with strong R&D capabilities
- Diversified commercial portfolio that continues to deliver good cashflows while losing exclusivity on flagship product
- A “first in class” pipeline of several NCEs with clear differentiation from the market and future pipeline products
- Near term catalysts with SPN-830 approval and launch, and data readouts on SPN-820 and SPN-817

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