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Novel Molecular Targets in Mood Disorders and Psychosis

The Road Ahead for Emerging Drug Targets

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Outline

- mTORC1 pathway:
  - Background
  - Targeting mTORC1 for treatment of mood disorders

- NV-5138 as an mTORC1 activator through Sestrin2:
  - Discovery, biochemical characterization, pharmacokinetics and and *in vivo* pharmacology
  - Clinical data

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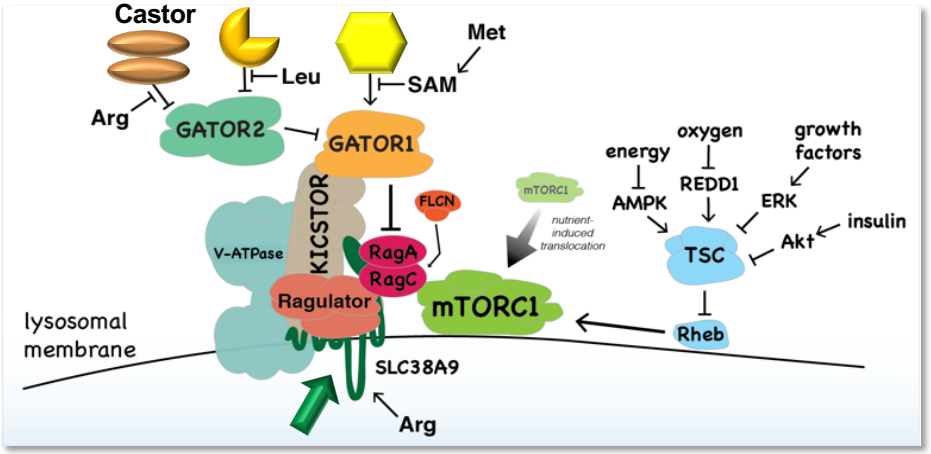
Navitor is Focused on a New Generation of Therapeutics Targeting mTORC1, a Key Pathway Involved in Multiple Diseases of Aging

- mTORC1 is a hub of cellular signaling controlling the response to nutrients and growth factors availability
- Pathway targeted historically for inhibition:
  - Rapamycin, everolimus, active site kinase inhibitors…
- New and expanding understanding of mTORC1 pathway led by David Sabatini:
  - Amino acid sensor proteins required for the activation of mTORC1 recently discovered:
    - Sesterin2: leucine sensor
    - CASTOR: arginine sensor
    - SAM: S-adenosylmethionine sensor
  - Ability to achieve greater specificity and therapeutic control of mTORC1 pathway modulation, reflective of the natural mechanism of mTORC1 regulation by nutrients
  - Opportunity for tissue specificity based on differential exposure and responses to nutrients
  - Opportunity to develop small molecule modulators that can inhibit or activate mTORC1 opening a completely new area of therapeutic drug discovery targeting mTOR



Sabatini, D.M. *Proc. Natl. Acad. Sci. USA 114:11818-11825* (2017)
Wolfson, R.L., et. al. *Science* **351**:43-47 (2016)
Wang, S., et. al. *Science* **347**:188-194 (2015)
Chantranupong, L., et. al. *Cell* **165**:153-164 (2016)
Wyant, G.A.., et. al. *Cell* **171**:642-654 (2017)
Gu, X., et. al. *Science* **358**: 813-818 (2017)

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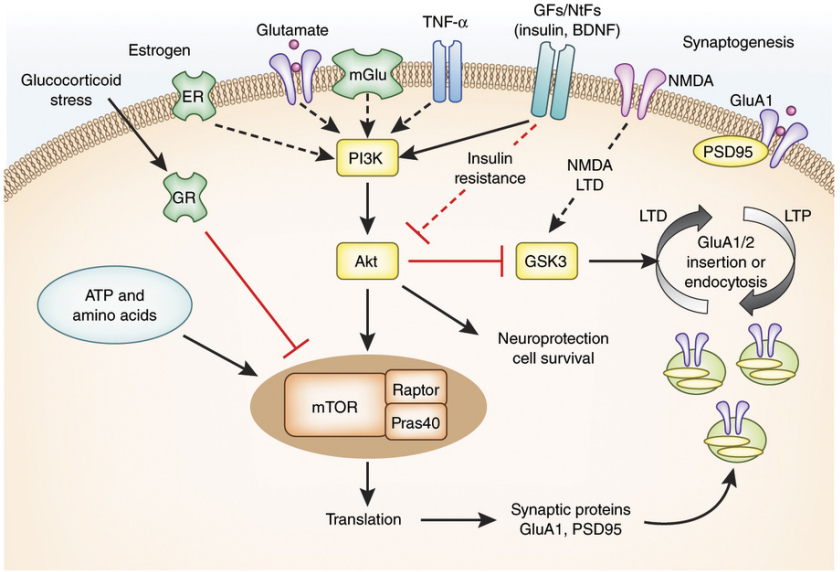
Role of mTORC1 in Brain and Mood Disorders

- mTORC1 regulates synaptogenesis via protein synthesis, spine enlargement, axon elongation and dendritic arborization
- Several studies showed that the mTOR pathway is suppressed in major depressive disorder in the brain
  - Human data from depressed patients who committed suicide
  - Data from chronically stressed animals
- Ketamine efficacy was shown to require the activation of the mTORC1 signaling pathway:
  - *In vivo* activation of p4E-BP1, pS6K, pmTOR in animal models following treatment with ketamine
  - Increase synaptic proteins (GluR1 and Synapsin) and spine number in the medial prefrontal cortex of rats for pharmacological efficacy is blocked by the direct mTORC1 inhibitor rapamycin
- The opportunity: an effective oral agent with therapeutic efficacy similar to ketamine in the absence of abuse liability, psychotomimetic or other adverse effects



Marina Corral Spence/Nature Publishing Group

Ota, K.T., et al *Nature Medicine,* **20**:531-535 (2014)
Jernigan, C.S. *Prog Neuropsychopharmacology,* **35**:1774-1779 (2011)
Duman, R.S., et. al. *Nat Med* **22**:238-249 (2016)
Liu, R-J., et. al., Neuropsychopharmacology doi:10.1038/npp.2016.202
Lener, M.S., et. al., *Drugs* **77**:381-401 (2017)
Garay, R.P., et al *Expert Review of Neurotherapeutics* (online) (2017
Burgdorf, J.B., et al *Neuropsychopharmacology* **38**:729-742 (2013)

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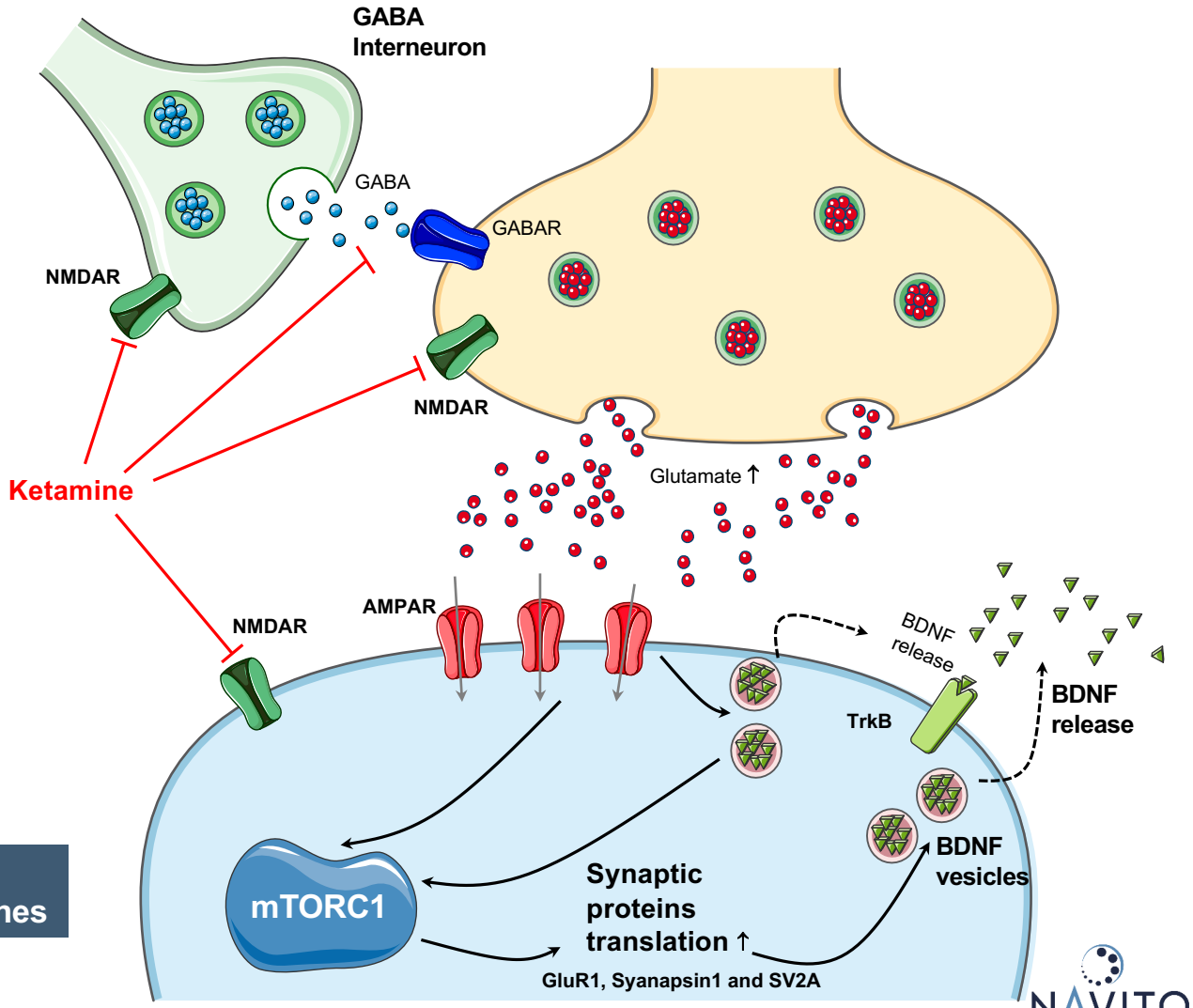
Working Model for the Role of mTORC1 in Antidepressants Response



mTORC1 activation increases synaptic protein synthesis and restores lost spines

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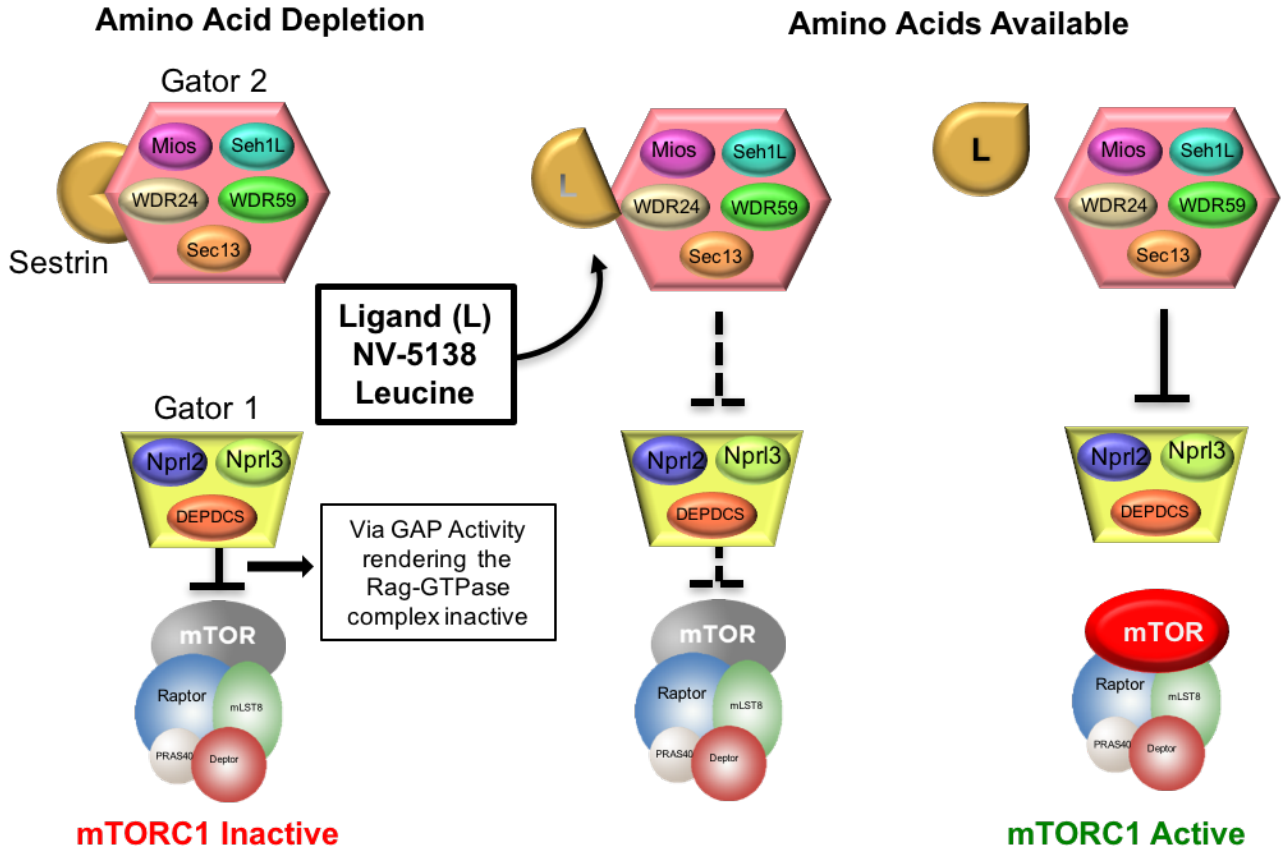
Targeting the Sestrin Leucine Sensor to Yield Novel Small Molecule Activators of mTORC1



Wolfson, R.L., et. al. *Science* 2016;**351**:43-47
Wolfson R.L. and Sabatini D.M. *Cell Metabol.* **2017** ;26:301-309

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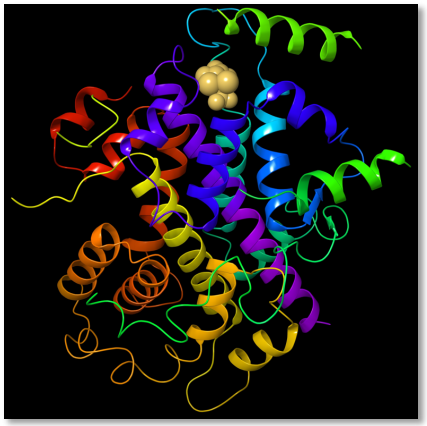
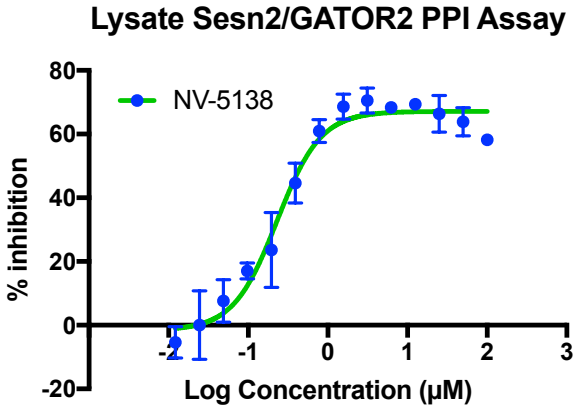
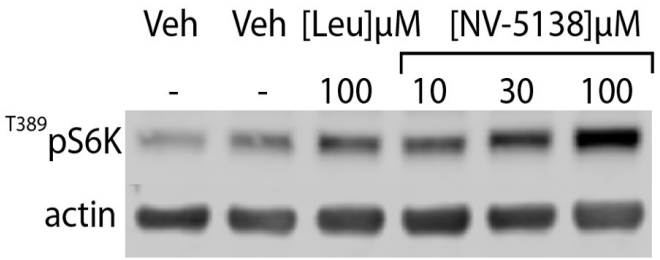
NV-5138: A Novel Small Molecule mTORC1 Activator That Binds to Sestrin2



NV-5138 bound to sestrin2



NV-5138 disrupts the interaction between Sestrin2 and GATOR2



NV-5138 activates mTORC1 in multiple cell lines.
Data shown in neuronal derived SH-SY5Y cells

- NV-5138 has favorable PK in all tested species (mouse, rat, dog and cyno)
  - High exposure
  - Terminal half life between 3 and 12 hours depending on the species
  - 100% oral bioavailability

Sengupta, S. Scientific Reports, **2019**, volume 9, 4107

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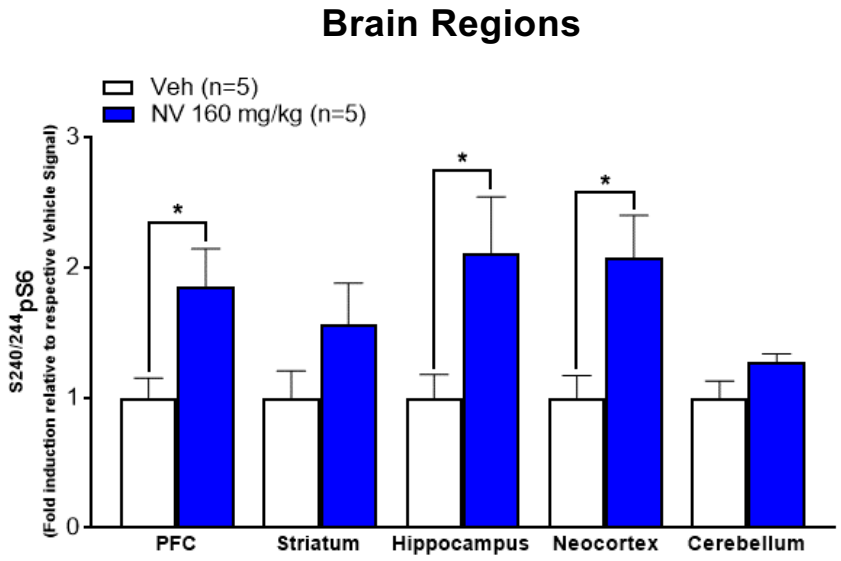
NV-5138 Mediated mTORC1 Transient Activation in Various Brain Regions and Selected Peripheral Tissues



Bar graph show fold-change of $^{S240/244}$pS6 compared to Veh which was normalized to 1 in various regions of the rat brain 1 hr. following oral administration. All data are mean ± SEM. *p<0.05 indicates a significant difference by an unpaired two-tailed students t-test.

Sengupta, S. Scientific Reports, **2019**, volume 9, 4107

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NV-5138: Summary of *in Vivo* Pharmacology and Efficacy in Various Pre-Clinical Models

- NV-5138 activates mTORC1 and induces key synaptic proteins in the Medial Prefrontal Cortex (mPFC) of SD Rats (GluR1, Syanapsin1 and SV2A)
- NV-5138 was tested head-to-head with Ketamine and showed comparable efficacy in the following models:
  - Forced Swim Test (FST)
  - Female Urine Sniffing Test (FUST)
  - Novelty Suppressed Feeding Test (NSFT)
  - Chronic Unpredictable Stress (CUS)
    - Efficacy after a single dose
    - Persistent efficacy up to 7 days
  - The efficacy of NV-5138 was shown to be dependent on mTORC1: treatment with rapamycin blocks the effect of NV-5138
  - NV-5138 effects are dependent on BDNF signaling:
    - Behavioral actions of NV-5138 are blocked by mPFC infusion of a BDNF antibody that binds and neutralizes BDNF released into the interstitial space
    - Effects of NV-5138 are completely blocked in mice with a knockin of the BDNF Met allele
  - NV-5138 induces mature apical dendrites in type 1 mPFC Layer V pyramidal neurons

Karo, T. et al. J Clin Invest. **2019** :2542-2554

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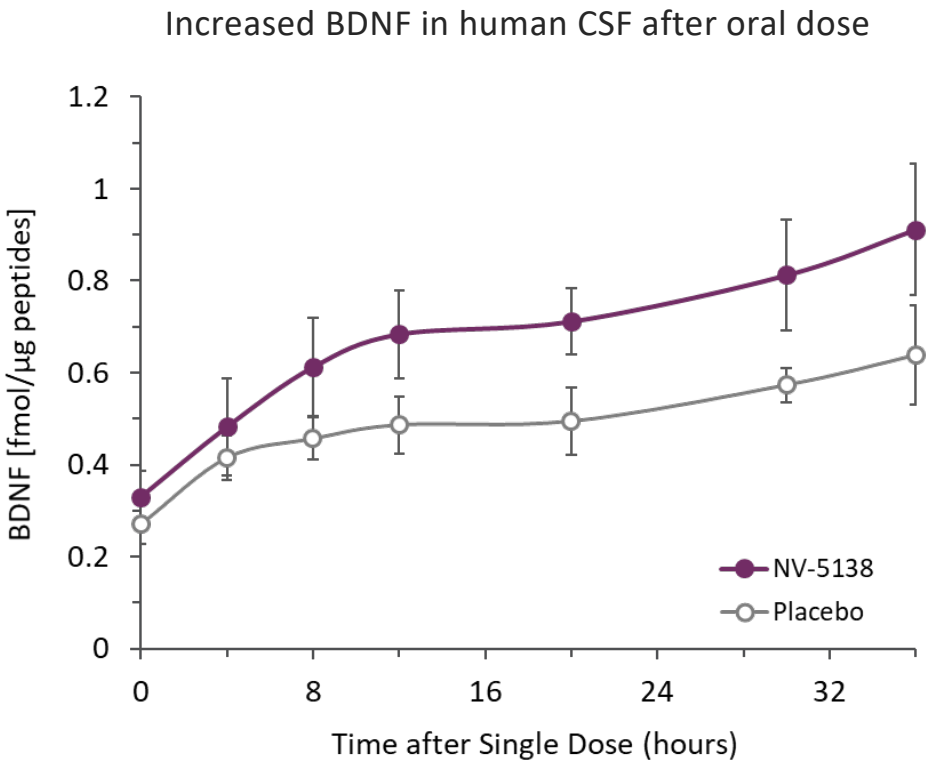
NV-5138 Phase 1 Data Consistent with Preclinical Data

- **Pharmacokinetics**
  - Rapidly absorbed and transported into the brain
- **Safety**
  - AEs mild to moderate
  - No serious or severe adverse events or early discontinuations due to AE
- **Biomarkers**
  - Rapid effects on BDNF, neurotransmitters and qEEG within hours of dosing



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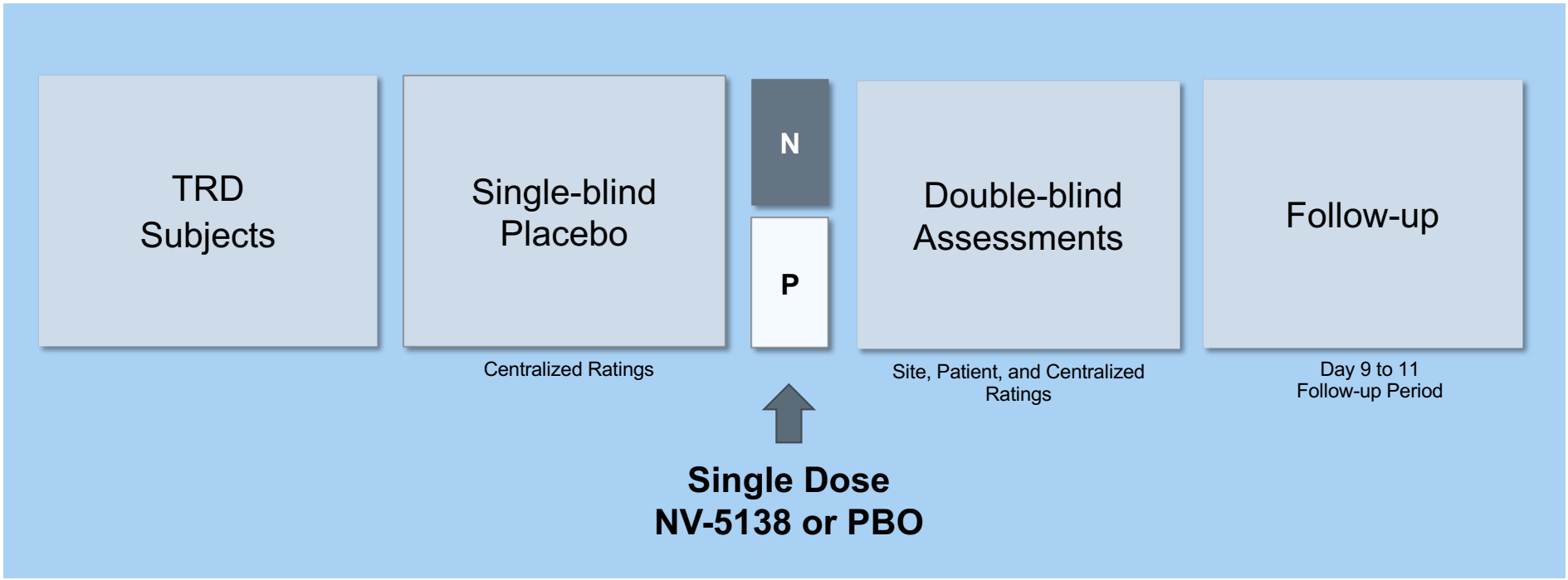
Study 001B

Exploratory Safety and Efficacy in Treatment Resistant Depression



ClinicalTrials.gov Identifier: NCT03606395

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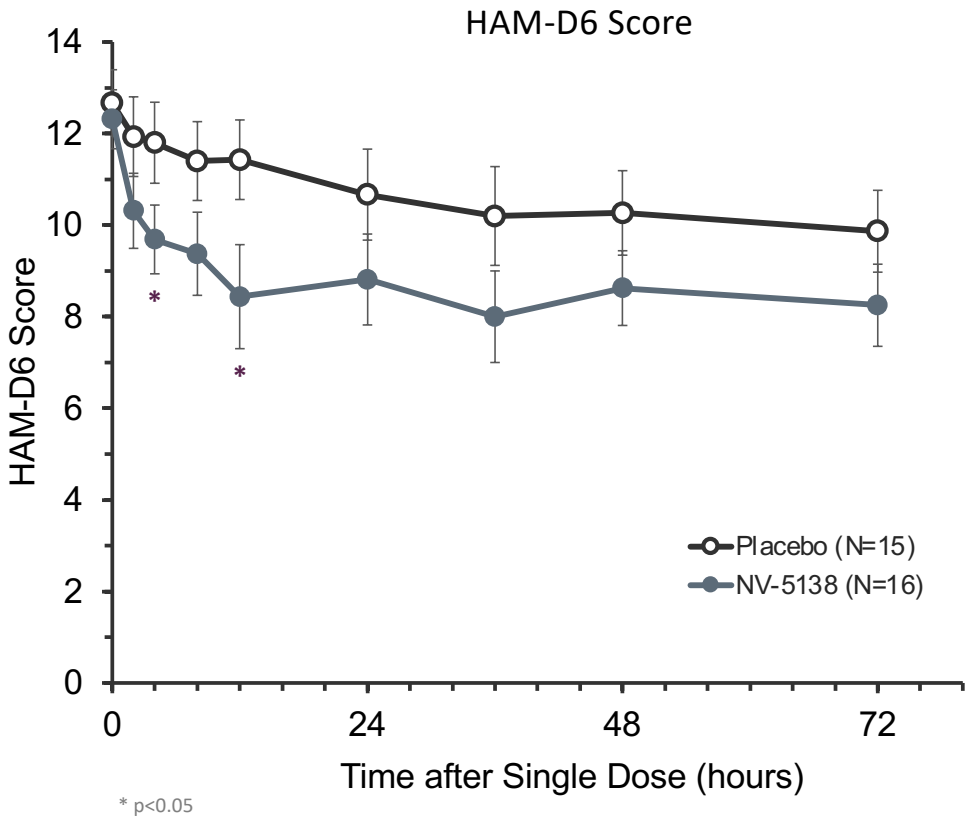
Study 001B

Rapid and Sustained Efficacy Signals with Single Dose NV-5138



* p<0.05

HAM-D6 Score	NV-5138	PBO	Delta	P-Value	Effect Size
2 hours	-2.0	-0.7	-1.3	0.066	0.6
4 hours	-2.6	-0.9	-1.8	0.017	0.8
8 hours	-2.9	-1.3	-1.7	0.051	0.7
12 hours	-3.9	-1.1	-2.7	0.020	0.8
24 hours	-3.5	-2.0	-1.5	0.172	0.5
36 hours	-4.3	-2.5	-1.8	0.145	0.5
48 hours	-3.7	-2.4	-1.3	0.135	0.5
72 hours	-4.1	-2.8	-1.3	0.214	0.4

Baseline Scores (Mean±SD): NV-5138: 12.3 ± 2.6, Placebo: 12.7 ± 2.8

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NV-5138 is First-in-Class Direct mTORC1 Activator

Rapid Absorption and Brain Penetration

Rapid and Persistent Pathway Engagement
Metabolites, Neurotransmitters, Synaptic proteins, and EEG Spectra

Rapid Signals of Efficacy
Core Symptoms of Depression

Encouraging Safety and Tolerability

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