GRIN THERAPEUTICS

A Neurvati Neurosciences Company

Developing Radiprodil for GRIN-related Disorders

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

GRIN THERAPEUTICS
A Neurvati Neurosciences Company

Presentation Outline

- About GRIN Therapeutics
- How a compound becomes a medicine
- The NMDA receptor and GRIN-related Disorders
- The status of our clinical trial currently enrolling in Europe

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

GRIN Therapeutics: Who We Are

- NYC-based Biotech company
  - Neurvati Neurosciences oversees the company with full funding through approval from a single investor
- Developing radiprodil for GRIN-related Disorders with Gain-of-Function (GOF) variants
- First clinical trial is currently enrolling in Europe and recently dosed our first patient
- Company formation was inspired by the 2019 GRIN conference at Emory University
  - Partnership with Neurvati and formation of patient focused leadership team in 2021
- Working closely with entire GRIN community (academic and advocacy) to ensure need of the community closely aligned with study objectives

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

How a Compound Becomes a Medicine

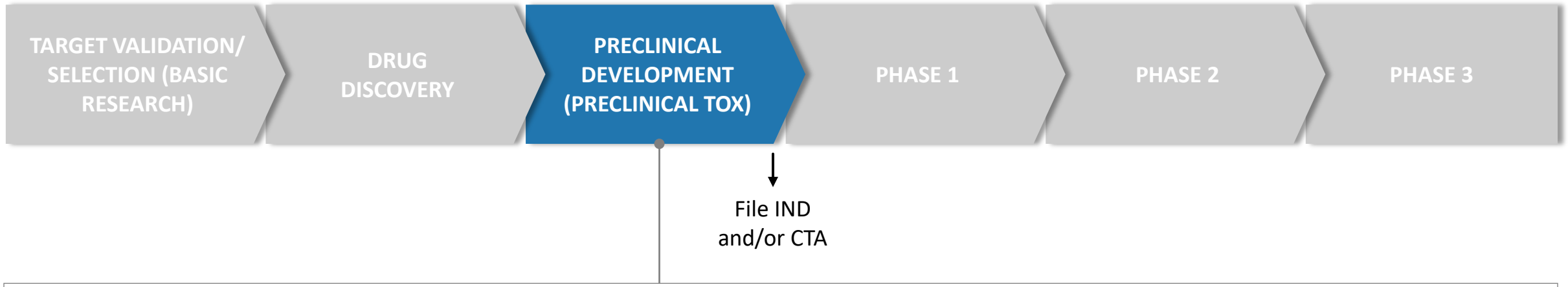
- What are the traditional steps in the development of a medicine?
- Regulatory review process

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

The Traditional Drug Development Pathway

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

The Traditional Drug Development Pathway



- Pharmacology characterization
  - Preclinical PK/PD characterization (how the drug acts in animals)
  - Determination of dose levels that are likely to be active in humans
- Toxicity studies
  - Single and repeat dose studies looking broadly at possible risks
  - Determination of highest dose possible before adverse effects are observed in animals
  - Mimics human dosing as much as possible

- An IND is a US document. Outside of the US, applications to conduct clinical trials are called Clinical Trial Applications (CTAs)

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

The Traditional Drug Development Pathway

- First-in-human testing to confirm expected biological effects
- Phase 1: Safety and Pharmacokinetics
  - Safety
    - Effect of the drug on the body
  - Pharmacokinetics
    - Effect of the body on the drug (how it moves through the body)

- Phase 1a: Single Ascending Doses
- Phase 1b: Multiple Ascending Doses

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

The Traditional Drug Development Pathway

File IND
or New CTA

- Human testing studies to determine potential effect in disease of interest
- Phase 2: Proof-of-Concept
  - Repeat dosing usually for a longer period of time (e.g. ~6 months)
  - Larger patient numbers to assess safety and efficacy
  - May test 2-3 different doses determined based upon Phase 1 studies
  - Designed to determine whether efficacy and safety support larger confirmatory Phase 3 studies

- Phase 2a: Dosing finding
- Phase 2b: Proof of Concept
- Phase 3: Efficacy and Safety

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

Other Potential Scenarios

- Phase 1/2
  - Combines safety and efficacy goals
- Phase 1b/2a
  - Multiple dose, dose-range finding study in patients
- Phase 2/3
  - Study looking for proof of concept and clinical efficacy

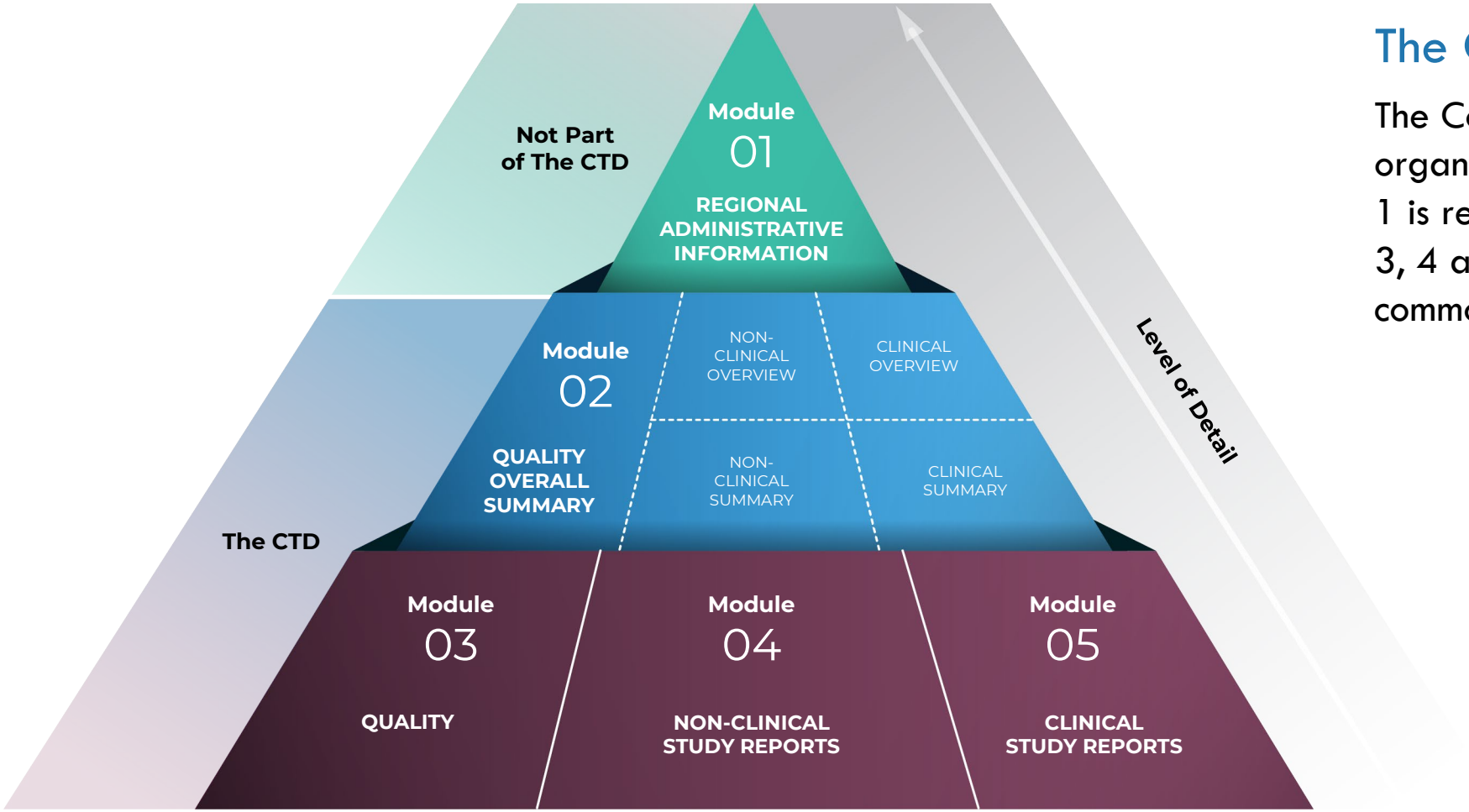
©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

The Traditional Drug Development Pathway

- Submit application to Commercialize an Investigational Drug
  - US: New Drug Application (NDA)
    - Standard review = 12 months
    - Priority review = 8 months
  - EU: Market Authorization Application (MAA)
    - Approval takes ~ 12-14 months

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

ICH: Common Technical Document



The CTD Triangle

The Common Technical Document is organized into five modules. Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

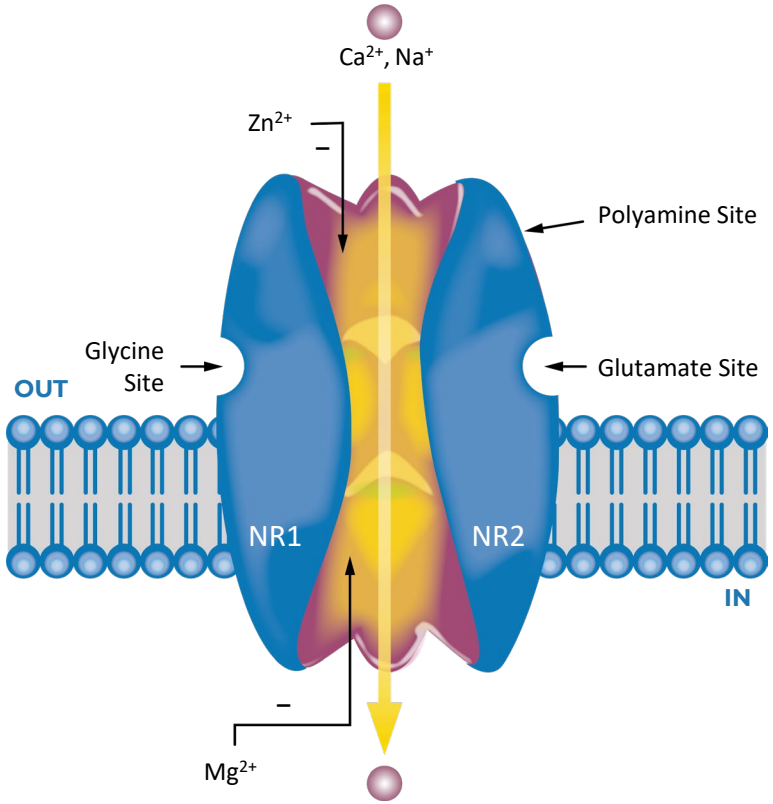
GRIN THERAPEUTICS
A Neurvati Neurosciences Company

What is an NMDA Receptor and Why Test Radiprodil in GRIN-related Disorders?

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

NMDA Receptor Encoded by the GRIN Genes

Glutamate NMDA Receptor with the NR2B subunit

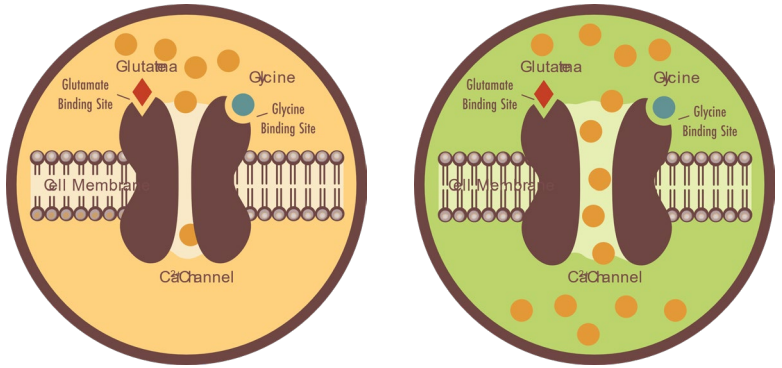


©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

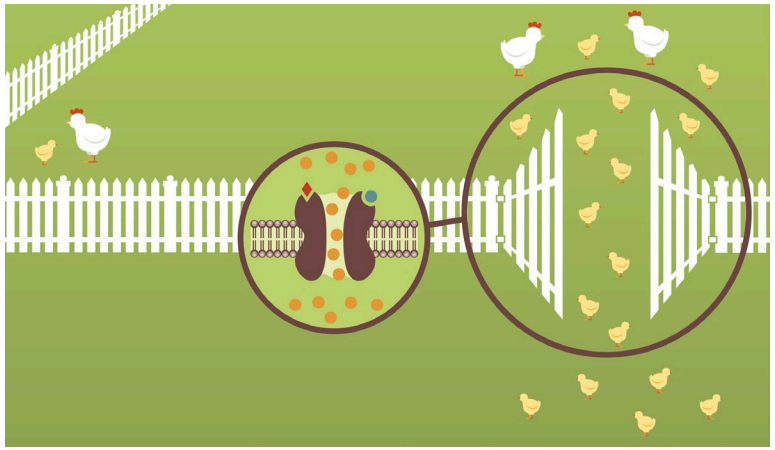
Gain-of-function and Loss-of-function Explained

Everything depends upon whether the gate is open or closed

Imagine the NMDA receptor on the cell membrane like a gate in a fence



LOSS-OF-FUNCTION VS **GAIN-OF-FUNCTION**



LOSS-OF-FUNCTION

is like a locked gate that will not open inhibiting the flow of calcium.

GAIN-OF-FUNCTION

is like a broken latch allowing more to go through the gate than you want.

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

NMDA Receptors Can Be "Overactive" (i.e., with Gain-of-function) in GRIN-Related Disorders

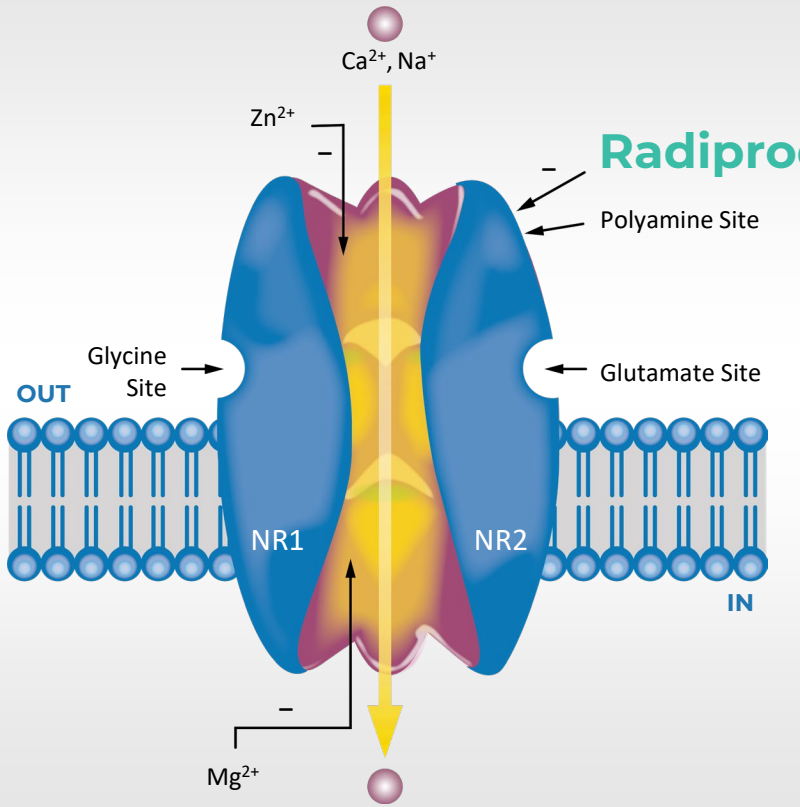
- When the NMDA receptor is overactive, the cells in the brain have trouble communicating and developing normally
- GRIN-related disorders present with developmental and epileptic encephalopathy
  - Most patients have severe profound disabilities requiring continuous supervision.[1]
  - 30-50% of GRIN2B patients (initial target) experience seizures; ~50% of those are resistant to treatment with standard anti-seizure medicines
  - Behavioral symptoms include self-injurious behavior, inappropriate behaviors, elopement, tantrums[2]
- There are therapies specifically targeted for GRIN-related disorders
  - Symptoms are typically resistant to standard treatments
  - Targeted treatments are needed to manage the broader disorder

[1] Benke et al 2021 Neuropharmacology 199. [2] Parent testimony letters submitted to MEB.

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

NMDA Receptor Encoded by the GRIN Genes

Radiprodil NR2B-NMDA Negative Allosteric Modulator



- Radiprodil targets the NR2B part of the NMDA receptor
- It is a “negative allosteric modulator”, meaning it is meant to bind to the receptor to reduce overactivity
- Hypothesis: By binding to NR2B, overactivity may be reduced with the potential for fewer seizures and improved development

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

Radiprodil Phase 1B Currently Enrolling in Europe

Primary Objectives

- Evaluate safety and tolerability of Radiprodil
- Identify the optimal dose range for future studies

Secondary Objectives

- Measure the impact of radiprodil on:
  - Seizure burden
  - EEG
  - Behavioral symptoms
  - Sleep
  - Motor function
  - Caregiver burden
  - Global impression of effect

Inclusion/Exclusion Criteria

- Confirmed Gain-of-Function (GoF) variant
- Age between 6 months and 12 years of age
- For seizure cohort:
  - At least 1 observable seizure per week
  - Seizures did not improve after two medications
- For behavioral cohort:
  - Significant behavioral symptoms

For more information on this trial (NCT05818943) visit: ClinicalTrials.gov

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL

Next Steps: How to Get Involved

- Read more about our trial (NCT05818943) and other enrolling clinical trials at ClinicalTrials.gov
- Stay connected with the advocacy organizations, they can help make you aware of opportunities such as updates on trials
- Participate in efforts to better understand GRIN-related Disorders
- Contact us at: PatientAdvocacy@grintherapeutics.com

[1] *J Med Genet*. 2017 Jul;54(7):460-470; [2] *Eur J Med Genetics* 60(6): 317-320; [3] *Eur J Paediatr Neurol*. 2017 May 21.

©2023 NEURVATI NEUROSCIENCES | ALL RIGHTS RESERVED | CONFIDENTIAL