A Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effect on Seizures and Behavioral Symptoms of Multiple Individually Titrated Doses of Radiprodil in Children with GRIN-related Disorder.

Published: 21-07-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2023-509672-42-00 check the CTIS register for the current data. Primary Objective:-To determine the long-term safety and tolerability of multiple individually titrated doses of radiprodil as an addon...

Ethical review	Approved WMO
Status	Pending
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON53530

Source
ToetsingOnline

Brief title
RAD-GRIN-101 study

Condition

- Congenital and hereditary disorders NEC
- Encephalopathies

Synonym

2A-, 2B- of 2D-genes; GRIN-related disorder, GRIN1-

Research involving
Human

Sponsors and support

Primary sponsor: GRIN Therapeutics, Inc.
Source(s) of monetary or material Support: industry

Intervention

Keyword: Children, GRIN, Radiprodil, Titration

Outcome measures

Primary outcome

• Adverse events (AEs), serious adverse events (SAEs), and adverse drug reactions (ADRs) (frequency, type, severity, and duration)

• Changes in vital signs

• Physical examination findings

• 12-lead electrocardiogram (ECG) findings

• Clinically significant changes in laboratory parameters

• Emergence of new seizure types

• Occurrence of suicidal ideation or behavior

• Determination of the maximum tolerated dose of radiprodil based on safety and tolerability data

• Plasma concentrations of radiprodil at predefined timepoints

Secondary outcome

• Change from Baseline to end of treatment in seizure frequency from daily

seizure electronic diary (eDiary)

• Percent change from Baseline to end of treatment in video electroencephalogram (V EEG) seizure burden (e.g., seizure type, severity, and frequency recorded during V EEGs)

• Seizure free days and longest period with no seizures

Change from Baseline to end of treatment in seizure frequency from daily seizure electronic diary (eDiary)

• Percent change from Baseline to end of treatment in video electroencephalogram (V EEG) seizure burden (e.g., seizure type, severity, and frequency recorded during V EEGs)

• Seizure free days and longest period with no seizures

• Change from Baseline to end of treatment in behavioral features as measured by Vineland adaptive behavioral scale (VABS), Bayley scale of infant development (BSID), and the aberrant behavior checklist-community (ABC-C), as well as other disorder features as measured by gross motor function measure (GMFM), sleep disturbance scale for children (SDSC), quality of life (Pediatric Quality of Life Inventory [PedsQL]), Caregiver Burden Inventory (CBI),and global impression (Caregiver Global Impression of Change [CaGI C] evaluating seizures, behavioral symptoms and overall condition),]), and Clinical Global Impression of Change [CGI-C] scales)

• Plasma concentrations of the 2 major metabolites of radiprodil

Study description

Background summary

The first description of GRIN2B mutations causing neurodevelopmental disorders was in 2010 and was followed by reports of patients with drug-resistant infantile spasms (IS) caused by GRIN2B mutations4 This has since been described as GRIN2B-related disorder, a severe developmental disorder with onset during first months of life and characterized by the presence of a variety of neuropsychiatric symptoms that include developmental delay and intellectual disability, epilepsy, hypotonia, and movement disorders. GRIN2B-related disorder is part of a broader category called GRIN related disorders, a group of neurodevelopmental syndromes caused by mutations in the different subunits that assemble to form the NMDA glutamate receptor (i.e., GRIN1, GRIN2A, GRIN2B, and GRIN2D). Since the first description of GRIN2B-related disorder, a few hundred patients have been identified.

The unmet clinical need for patients with GRIN-related disorders, including variants in GRIN1, GRIN2A, GRIN2B, and GRIN2D, is significant. Most of the clinical manifestations and symptoms of GRIN-related disorders are poorly responsive to available therapies, which aim to manage the most severe symptoms, such as seizures and behavioral symptoms. The main therapeutic approach for patients with epilepsy is to control abnormal brain activity, as observed by electroencephalogram (EEG) recordings, or that manifests as seizures.

To date, there are no effective nor approved treatments for GRIN-related disorder. Non-seizure symptoms can be managed through physical, speech, behavioral, or occupational therapies.

Full Background: see Protocol section 5.1.1

Study objective

This study has been transitioned to CTIS with ID 2023-509672-42-00 check the CTIS register for the current data.

Primary Objective:

-To determine the long-term safety and tolerability of multiple individually titrated doses of radiprodil as an addon therapy to standard of care (SOC) in pediatric participants

-To establish a safe and well tolerated dose after 8 weeks of continuous treatment in Part A

-To determine the PK and plasma exposure of radiprodil and its metabolites after administration of different doses in pediatric participants

Secondary Objective:

-To evaluate initial signs of efficacy on frequency and severity of epileptic seizures in those participants with seizures
-To evaluate initial signs of efficacy of radiprodil on additional CNS features including communication, cognition, behavior, motor symptoms, sleep, and quality of life, and the maintenance of the treatment effect
-To determine the PK and the plasma exposure of radiprodil major metabolites obtained at different doses in Part A

Study design

This is an open-label, multicenter phase 1B study to evaluate the safety, tolerability, and PK of multiple individually titrated doses of radiprodil and to assess the treatment effect on seizures and behavioral symptoms in 2 cohorts of pediatric participants: 1 cohort of participants with treatment resistant seizures (with or without behavioral symptoms) and 1 cohort of participants with behavioral symptoms (but no qualifying seizures) caused by GoF variants in the GRIN1- , 2A-, 2B- of 2D- genes.

More information see Protocol Summary 1.1 Synopsis

Intervention

The pediatric radiprodil formulation used in this study is an oral suspension obtained by reconstitution of dispersible granules with a diluent. The oral suspension will be prepared extemporaneously at the clinical site.
The volume of radiprodil will be determined based on the participant*s weight and assigned dose.

Study burden and risks

The following information originate from the ICF:

While it is possible that treatment with radiprodil may improve your child*s symptoms, he/she might not have any benefits from taking part in this study. The purpose of this study is to learn more about radiprodil.

- The child may experience the side effects or adverse effects of radiprodil:
The child may have some unwanted effects and symptoms because of treatment with radiprodil. In healthy adult study participants who were treated with radiprodil, the most frequently reported unwanted effects and symptoms were headache, sleepiness, dizziness, vertigo, disturbance in attention, having trouble falling and/or staying asleep, changes in mood, sore throat, and feeling intense excitement and happiness. In adult study participants with nerve pain related to high blood sugar (diabetes) who were treated with radiprodil, the most frequently reported unwanted effects and symptoms were having trouble falling and/or staying asleep, dizziness, headache, and feeling tired or having low energy.
Because this is a clinical research study, there may be other risks that are not yet known.
- The child may feel some pressure when the blood pressure cuff is inflated.
- The child may feel discomfort when the blood samples or finger or heel-pricks are being taken. It may cause pain, bleeding, or bruising at the spot where the needle is inserted into the skin. The study staff might give your child a numbing medicine to help it hurt less. Sometimes taking blood causes fainting or infection. Swelling of a vein or a blood clot occurs in very rare cases.
- The sticky pads used to perform an ECG may cause skin irritation and itchiness.
- The VEEG procedure (see also Appendix C) will be recorded by video and will take from between 8 to 24 hours. The test is generally safe and painless, but there is a small risk of having a seizure during the test. Some children will find this test unacceptably challenging and may have difficulty completing it.
- Some of the questions in the questionnaires might make the parents and/or child feel embarrassed or upset.
- Completing all the questionnaires will take you 30 to 45 minutes.
- Parents need to take a note of the child*s treatments, seizures, and symptoms (if applicable) every day. This will take 5-10 minutes, depending on the number of seizures per day.
- Attending all the study visits will cost extra time.
- The child will need to stay overnight in the hospital.
- The parents and child must comply with the study agreements

Contacts

Public
GRIN Therapeutics, Inc.

101 Main street Suite 1210
Cambridge Ma 02142
US

Scientific
GRIN Therapeutics, Inc.

101 Main street Suite 1210
Cambridge Ma 02142
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Inclusion criteria:
For Part A and Part B (unless stated otherwise):
1. For Part A, pediatric participants aged >=6 months to <=12 years with GRIN 1, 2A, 2B, or 2D gene variants known to result in GoF of the NMDA receptor. For Part B, pediatric participants aged >=6 months with GRIN 1, 2A, 2B, or 2D gene variants known to result in GoF of the NMDA receptor.
2. Participant to be enrolled in the first cohort experiences the following (Part A only):
a) At least 1 observable motor seizure per week and >=4 observable motor seizures (generalized or focal) during the prospective 4-week Observation Period.
b) Has failed to obtain adequate seizure control with at least 2 ASMs used at appropriate dose and duration with assured medication adherence (if applicable).
3. Participant to be enrolled in the second cohort experiences the following (Part A only):
a) Significant behavioral and/or motor symptoms based on caregiver report with a CGI-S score >=4 at the Screening Visit and Day -1 of Visit T1.
4. For part A, current therapies need to be on a stable dose for at least 4 weeks prior to Screening and should be maintained stable throughout the whole study duration, nonpharmacological treatments such as ketogenic diet should be

kept as stable as possible during screening and participation in the study. Changes in antiseizure medication should be discussed with the sponsor in consultation with the investigator.
For all inclusion criteria see Protocol.
Rescreening criteria for Part B only:
1. Participant has received at least 8 weeks of treatment (combined Titration and Maintenance Period) with radiprodil during Part A.
2. The benefit-risk of continuing radiprodil treatment remains favorable as determined by the investigator*s clinical assessment and is eligible to continue treatment according to the judgement of the investigator.

Exclusion criteria

Exclusion criteria (at initial Screening and following completion of the Maintenance Period of Part A, unless stated otherwise): 1. Participant with any other clinically relevant medical, neurologic, or psychiatric condition and/or behavioral disorder unrelated to GRIN related disorders that would preclude or jeopardize participant*s safe participation or administration of study drug or the conduct of the study according to the judgement of the investigator. 2. Participant with a body weight <10 kg on Day -1 of Visit T1 for whom a gastric tube is the only possibility for radiprodil dosing (during treatment with the first dose in Part A only). 3. Participant with any clinically significant laboratory or ECG abnormalities. 4. Participant has severe hepatic dysfunction (Child-Pugh grade C). 5. Participant has a history of brain surgery for epilepsy or any other reason. For all exclusion criteria see Protocol.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-02-2023

Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	radiprodil
Generic name:	radiprodil

Ethics review

Approved WMO Date:	21-07-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-11-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-08-2023

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-509672-42-00
EudraCT	EUCTR2022-000317-14-NL
CCMO	NL80839.000.22