A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in female children with protocadherin 19 (PCDH19)-related epilepsy followed by long-term open-label treatment

Published: 05-06-2019
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Primary: To assess the efficacy of GNX compared with PBO, as adjunctive therapy for the treatment of primary seizure types in children with genetically-confirmed PCDH19-related epilepsy during the 17-week double-blind (DB) phase. Secondary: • To...

Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON55218

Source
ToetsingOnline

Brief title
4407/0002 Marinus 1042-PCDH19-3002

Condition

- Neurological disorders congenital

Synonym
PCDH19-related epilepsy; PCDH19 female epilepsy

Research involving

Human

Sponsors and support

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

Intervention

Keyword: epilepsy, ganaxolone, pediatrics, protocadherin 19

Outcome measures

Primary outcome

Criteria for Evaluation: Seizures: All seizure types and frequency will be recorded daily in an eDiary. Days in which no seizures occur will also be noted. Subsets of seizure types will be defined below. Primary Endpoint (seizure control) The primary efficacy endpoint is the percent change in 28-day primary seizure frequency during the 17-week DB phase relative to the baseline. The primary seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types for the primary efficacy endpoint. The analyses of the primary endpoint will be performed on the sum of the individual countable seizures and each series of continuous uncountable seizures (each contributes 1 to the sum). Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data in the phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline

phase divided by the number of days with seizure data in the phase, multiplied by 28.The difference between the GNX and placebo groups in the percent changes will be tested using the Wilcoxon Rank-Sum statistic. The primary analysis will be conducted in the TT poulation. If nominal statistical significance is achieved in the ITT population, the primary analysis will be conducted in the biomarker-positive stratum of the ITT population as a secondary endpoint.

Secondary outcome

Secondary endpoints (seizure control): • The percent change in 28-day primary seizure frequency during the 17-week DB Phase relative to baseline in biomarker-positive subjects • Percentage of subjects experiencing a >= 50% reduction in 28-day primary seizure frequency compared to the baseline Secondary endpoints (behavioral/neuropsychiatric): • Behavior Rating Inventory of Executive Function (BRIEF, preschool version BRIEF-P) • Aberrant Behavior Check - Community (ABC-C) • Children*s Sleep Habit Questionnaire (CHSQ) Exploratory Endpoints: Except for the exploratory endpoints of seizure frequency within the titration and maintenance phases of the DB phase, derived seizure exploratory endpoints will be based on data through the end of the 17-week DB phase relative to the prospective baseline period. • Percent change in 28-day primary seizure frequency during the DB Phase relative to the baseline in biomarker-negative subjects and comparision to biomarker-positive subjects. • Arithmetic change in percentage of seizure-free days, based on all countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. • Percentage of subjects experiencing a 28-day seizure reduction

from baseline >= 25%, and 75% (titration + maintenance and maintenance only). Analysis will be conducted for primary and all seizure types. • Percent change in 28-day seizure frequency through the end of the 4-week titration phase of the DB period relative to the prospective baseline period (all countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component). • Percent change in 28-day seizure frequency during just the maintenance phase of the DB period (ie, from the end of the 4-week titration phase to the end of the 17 week DB phase) relative to the prospective baseline period (all countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component). • Percent change in 28-day seizure frequency, based on all seizure types. • Percent change per seizure subtype. • Percentage of subjects taking rescue medication at least once during the maintenance phase of the 17-week DB phase. • Number of doses of rescue medication. • Exposure response analysisElectroencephalogram (EEG) findings Arithmetic changes in quality of life scales: -• Quality of Life Inventory - Disability (QI-Disability) -• Pediatric Quality of Life Inventory - Family Impact Module (PedsQL-FIM) • Caregiver Global Impression of Change (CGI-C) - Target Behavior Clinical Global Impression - Improvement (CGI-I, Parent/caregiver and clinician)

Study description

Background summary

Protocadherin19 (PCDH19)-related epilepsy is a serious epileptic condition characterized by early-onset cluster seizures, cognitive and sensory impairment of varying degrees, and psychiatric and behavioral disturbances affecting primarily females (Camacho 2012). The condition is caused by an inherited mutation of the PCDH19 gene located on the X chromosome. This gene encodes for a calcium-dependent cell-cell adhesion molecule that is expressed in the central nervous system (CNS; eg, hippocampus, cerebral cortex, thalamus, amygdala) and which appears to be related to synaptic transmission and formation of synaptic connections during brain development (Depienne 2009).
The mean age of seizure onset in this condition is approximately 10 months (range of 3-38 months) (Scheffer 2008, Specchio 2011, Dipienne 2011, Cappelletti 2015, van Harssel 2013). The mean age of offset of epileptic seizures is approximately 12.5 years (1-35 years). PCDH19-related epilepsy has been described as a *semiprogressive* condition, meaning that seizure frequency increases during the first few years of life (Specchio 2011). However, over time the seizure frequency lessens, and seizures become less frequent with increased age.
There is also evidence supporting an allopregnanolone deficiency as a proposed contributor to the onset of seizures in individuals with PCDH19-related epilepsy (Tan 2015). It was found that individuals with this genetic mutation demonstrated a downregulation of steroid hormone-metabolizing enzymes resulting in reduced allopregnanolone levels compared to non-affected, age-match controls. Since these neurosteroids are known to have strong anti-convulsant properties, it is hypothesized that treatment with neurosteroids with similar action, or analogs such as GNX, may have therapeutic benefit to seizure control.
Ganaxolone is the 3β-methylated synthetic analog of allopregnanolone, an endogenous allosteric modulator of CNS γ-Aminobutyric acid type A (GABAA) receptors. Ganaxolone has potency and efficacy comparable to allopregnanolone (Carter 1997) in activating synaptic and extrasynaptic GABAA receptors at a site distinct from benzodiazepines and barbiturates. Ganaxolone has protective activity in diverse rodent seizure models (Reddy 2012, Bialer 2010). Clinical studies have demonstrated that GNX has anticonvulsant activity with an acceptable safety and tolerability profile in the dose range of 900 to 1800 mg in adults and children (Sperling 2017, Laxer 2000, Kerrigan 2000, Pieribone 2007). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an OL study, pediatric subjects aged 2 to 60 months with refractory seizures and a history of IS were treated with GNX doses up to 36 mg/kg for up to 3 months (Kerrigan 2000). Sixteen of the 20 subjects completed treatment, 15 of whom had a history of IS. Five of the 15 subjects had a decrease from baseline in the number of spasms of >= 50%, 5 had a decrease of 25 to 50%, and 5 had a decrease of < 25%. One subject became spasm-free and 1 non-responder (with a decrease of < 25%) was spasm-free from weeks 2 to 7.
An anticonvulsant treatment effect signal of GNX in PCDH19-related epilepsy has emerged from an ongoing OL flexible-dose exploratory study (Study 1042-0900) of GNX in children (age range 2-15 years) with rare genetic epilepsies (including PCDH19) with uncontrolled seizures despite multiple antiepileptic drug (AED) regimens (ClinicalTrials.gov Identifier: NCT02358538). Following the

screening and baseline evaluations, consenting subjects enrolled into a 26-week study during which investigators could dose GNX starting with a titration up to 1,800 mg/day for subjects whose body weight was > 30 kg or up to 63 mg/kg /day for subjects whose body-weight was < 30 kg. The dose could also be reduced for tolerability reasons. The primary efficacy measure was the percent change from baseline in the 28-day seizure frequency count. Safety and tolerability assessments were among the secondary objectives. The median change in 28-day seizure frequency from baseline in the intent-to-treat (ITT) population (primary endpoint) was a decrease of 25% (n = 11).
The median change from baseline in seizure-free days in the ITT population (key secondary endpoint) was an increase of 14% (n = 11). Baseline levels of allopregnanolone sulfate (Allo-S, an endogenous neurosteroid) and 28-day seizure rates were also assessed. A ganaxolone-responder was specified by post-hoc definition, as having at least a 25% reduction in 28-day seizure rate. In the PCDH19 cohort, responders (n = 6) and non-responders (n = 5) had plasma Allo-S concentrations (mean ± SD) of 501 ± 430 pg mL-1 and 9,829 ± 6,638 pg mL-1, respectively. When performing a retrospective separation of the PCDH19 cohort according to their Allo-S level, the 7 subjects with Allo-S levels below 2,500 pg mL-1 (biomarker-positive) had a 50% reduction in seizure rates while the 4 subjects with Allo-S levels above 2,500 pg mL-1 (biomarker-negative) had a 84% increase (performed in the research lab of Dr. Graziano Pinna at the University of Illinois, Chicago, the only laboratory during the conduct of the study that could reliably produce results for sulphated neurosteroids). The Clinical Global Impression Scale rated by Investigators (CGI-I) and Caregivers (CGI-P) has been consistent with seizure control. In the OL study (1042-0900), there were 4 SAEs (3 related to seizures and 1 related to rash) possibly related to the study drug in the PCDH19 subjects.
In addition to anticonvulsant activity, GNX has shown positive effects on anxiety, hyperactivity, and attention in children with fragile X syndrome (Ligsay 2016). Similar behavior problems occur in individuals with PCDH19 mutations (Smith 2018). It is hypothesized that GNX treatment will increase and improve GABAA-mediated signaling by boosting the signaling capacity of existing receptors and improve not only seizure control, but also other behavioral abnormalities in individuals with the PCDH19 mutation.

Study objective

Primary: To assess the efficacy of GNX compared with PBO, as adjunctive therapy for the treatment of primary seizure types in children with genetically-confirmed PCDH19-related epilepsy during the 17-week double-blind (DB) phase. Secondary: • To assess the effect of GNX on primary seizure rate in biomarker-positive subjects. • To assess behavioral/neuropsychiatric changes in subjects receiving GNX compared with subjects receiving PBO as adjunctive therapy during the 17-week DB phase. • To assess the safety and tolerability of GNX compared with PBO as adjunctive therapy during of the 17 week DB phase. • To assess pharmacokinetic (PK) parameters in subjects receiving GNX doses up to

63 mg/kg/day (or 1800 mg/day maximum) throughout the study. • To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the open-label (OL) phase. • To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the open-label phase. Exploratory Efficacy: • To assess the effect of GNX on primary seizure rate in biomarker-negative subjects, and compare biomarker-positive vs. biomarker-negative subjects • To assess changes to quality of life as reported by the parent/caregiver/LAR. • To assess the effect of GNX on background EEG activity and to assess any major alterations as possible biomarkers for change in underlying brain function. To assess changes in other types of seizures (non-primary) in PCDH19-related epilepsy

Study design

Methodology: This is a global, biomarker-stratified, DB, randomized, PBO-controlled trial of adjunctive GNX treatment in children with a confirmed pathogenic or likely pathogenic PCDH19 mutation. The trial consists of a 12-week prospective baseline period to collect seizure data, followed by a 17-week DB phase, which is then followed by a long-term OL phase. An interactive web response system (IWRS) will be used to randomize subjects, dispense drug, track treatment, and maintain the blind throughout the duration of the study. , AA 12-week daily historical seizure calendar will be reviewed at the screening visit to determine eligibility per inclusion/exclusion criteria. Acceptable historical seizure data must include at least 12 consecutive weeks prior to the Screening visit of documenting seizure type and frequency (also noting seizure-free days). Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent from the subject*s parent or legally authorized representative (LAR) and/or subject assent has been appropriately obtained. In the event that parent/caregiver/LAR do not routinely maintain a daily seizure calendar or genetic testing has not been performed per standard of care, written informed consent will be obtained from the parent/LAR and/or subject assent, and the subject will be asked to return to the clinic for the screening visit after they have maintained a 12 week daily historical seizure calendar and/or genetic testing has been completed. During the screening visit, each subject*s biomarker level will be assessed via a blood draw and subsequent analytical quantification. Each subject will then be assigned to 1 of 2 groups: biomarker-positive or biomarker-negative. A subject will be considered biomarker-positive if her baseline Allo-S level is less than or equal to 2500 pg/mL (Pinna Lab method or similar). The biomarker group assignment will remain blinded until database unblinding after the study has completed. Based on the completed 11-subject 1042-0900 Phase 2a study, it is estimated that approximately 65% of all subjects will be biomarker-positive. Subject rescreening is allowed as agreed by Sponsor and Investigator unless there is a general concern for subject safety or an inability for the subject to become eligible (eg, GNX allergy, sensitivity or exposure, non-PCDH19 and/or other ineligible epilepsy, chronic prohibited medical condition or treatment).

Subsequent screening should take place at least 30 days from the subject*s last visit. The DB phase includes 4 weeks of investigational product titration followed by 13 weeks of dose maintenance. After meeting the eligibility criteria, approximately 25 children aged 1-17 years (inclusive) with PCDH19-related epilepsy will be randomly assigned to receive GNX or PBO (1:1 ratio within each biomarker stratum) for 17 weeks in addition to their standard anti-seizure treatment. Participants will be titrated to 63 mg/kg/day (max 1800 mg/day) over 4 weeks, and then maintained at that dose for another 13 weeks. Subjects who are not able to tolerate 63 mg/kg/day (or 1800 mg/day maximum) may be maintained on a lower dose . A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the DB escalation period, unless a lower dose is agreed to with the sponsor due to tolerability issues such as somnolence. Dose changes including alternative dosing paradigms (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the clinical research organization (CRO)/sponsor medical monitor prior to making the change or within 48 hours of making the change. Of note the sponsor defers the final decision to adjust IP to the treating clinician; dose changes may not exceed the maximum total daily dose defined by the protocol. For any subject who is unable to be maintained at the minimum dose, the investigator should contact the sponsor to discuss continued investigational product dosing. Subjects who discontinue investigational product should undergo a 2-week taper period, unless otherwise medically indicated such as drug-induced rash. Subjects who discontinue investigational product treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up assessments. After completing the initial 17-week, DB, PBO-controlled treatment phase, all subjects will be treated with GNX in the OL phase of the study. Ganaxolone subjects will continue GNX treatment and PBO subjects will titrate onto GNX. To maintain the blind, subjects initially randomized to GNX will undergo a blinded titration (increasing PBO doses) for 4 weeks, while PBO subjects will titrate up to 63 mg/kg/day GNX (1800 mg/day maximum) during the same time period. Any subject who completes the study or discontinues investigational product treatment should undergo a 2 week drug de-escalation (taper) period and return to the site 2 weeks later for safety follow-up assessments. Taper is not required if the subject is receiving the doe of 18 mg/kg/day or 450 mg/day (or lower). Participants will be required to complete an eDiary to determine GNX*s effect on seizures. A variety of clinician and caregiver administered instruments will be used to assess the efficacy of GNX in PCDH19-related epilepsy, and include: • Behavior Rating Inventory of Executive Function (BRIEF) • Aberrant Behavior Checklist - Community (ABC-C) • Children*s Sleep Habit Questionnaire (CSHQ) • Pediatric Quality of Life Inventory - Family Impact Module (PedsQL-FIM) • Quality of Life Inventory - Disability (QI-Disability) • Caregiver Global Impression of Change (CGI-C) - Target Behavior, Clinical Global Impression Improvement (caregiver), and Clinical Global Impression-Improvement (clinician)

Intervention

Investigational product, dose, and mode of administration: Ganaxolone is to be administered in increments of 15 mg/kg/day up to 63 mg/kg/day given as an oral suspension with food. Subjects <= 28 kg will be dosed on an mg/kg basis. Subjects > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day. Ganaxolone is to be administered during the 4-week titration period of the DB phase of the study as follows: Dosinga for Subjects Weighing <= 28 kg (62 pounds)b Dose Total mg/kg/day Days 6 mg/kg TID 18 1-7 11 mg/kg TID 33 8-14 16 mg/kg TID 48 15-21 21 mg/kg TID 63 22-28 Dosinga for Subjects Weighing > 28 kg (62 pounds)c Dose mL per Dose Total mg/day Days 150 mg TID 3 450 1-7 300 mg TID 6 900 8-14 450 mg TID 9 1350 15-21 600 mg TID 12 1800 22-28 TID = 3 times daily. a. To be administered in 3 divided doses following a meal or snack. b. Subjects weighing <= 28 kg will be dosed according to the subject*s weight in kilograms. c. Subjects > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day. Any subject not tolerating the next dose level can be maintained at the lower dose for additional days before advancing to the next dose. If the next dose level is still not tolerated, the subject can drop back to the last tolerated dose. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the DB escalation period, unless a lower dose is agreed to with the sponsor due to tolerability issues such as somnolence. Dose changes including alternative dosing paradigm (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the sponsor /CRO medical monitor prior to making the change or within 48 hours of making the change. Of note, the sponsor defers the final decision to adjust IP to the treating study clinician; dose changes may not exceed the maximum total daily dose defined by the protocol. For any subject who is unable to be maintained at the minimum dose, the investigator should contact the sponsor to discuss continued investigational product dosing. Subjects who discontinue investigational product treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up assessments. During the OL phase, all subjects will be treated with GNX. Those subjects who received GNX oral suspension in the 17-week DB phase will receive the same GNX dose in the OL phase of the study. However, to maintain the study blind, GNX subjects will enter into a 4-week blinded titration phase by increasing PBO doses in addition to maintaining GNX. Subjects who received PBO oral suspension in the 17-week DB phase will enter a 4-week, GNX titration period in the OL phase of the study.

Study burden and risks

Please refer to patient information sheet section 7

Contacts

Public
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Scientific
Marinus Pharmaceuticals, Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Molecular confirmation of a pathogenic or likely pathogenic PCDH19 variant.Genetic mutations will be confirmed by the sponsor*s chosen central laboratory.
2. Female subjects aged 1 through 17 years, inclusive.
3. Subject/parent or LAR willing to give written informed consent/assent, after being properly informed of the nature and risks of the study and prior to engaging in any study related procedures.
4. Failure to control seizures despite appropriate trial of 2 or more anti-seizure mediations at therapeutic doses.
5. Have at least 12 countable/witnessed primary seizures over an 84 day (12 week) period prior to the screening visit (pre-baseline screening). The primary

seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types.
6. Subject must be approved to participate by sponsor or its designee (eg, Epilepsy Consortium) after review of medical history, genetic testing, seizure classification video (if available), and historical seizure calendars.
7. Ketogenic diets and modified Atkins diets should be unchanged for 3 months prior to screening and must remain stable throughout baseline and the DB phase.
8. Subjects with surgically implanted VNS will be allowed to enter the study provided that all of the following conditions are met:
• The VNS has been in place for >= 1 year prior to the screening visit.
• The settings must have remained constant for 3 months prior to the screening visit and remain constant throughout baseline and the DB phase.
• The battery is expected to last for the duration of baseline and the DB phase.
9. Parent/caregiver is able and willing to maintain an accurate and complete daily seizure diary for the duration of the study.
10. Able and willing to take investigational product (suspension) with food 3 times daily. Ganaxolone must be administered with food.
11. Sexually active female of childbearing potential must be using a medically acceptable method of birth control and have a negative quantitative serum β-human chorionic growth hormone (β-HCG) test collected at the initial screening visit. Childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes intrauterine devices in place for at least 3 months prior to the screening visit, surgical sterilization, or adequate barrier methods (eg, diaphragm or condom and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. Use of oral contraceptives in combination with another method (eg, a spermicidal cream) is acceptable. In subjects who are not sexually active, abstinence is an acceptable form.

Exclusion criteria

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. Subjects with >8 consecutive weeks (56 consecutive days) of primary seizure freedom during the 12-week pre-baseline screening period.
4. Subjects with <= 3 primary seizures during the 12-week baseline period.
5. Concurrent use of strong inducers or inhibitors of CYP3A4/5/7 is not permitted. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Baseline/Randomization Visit. This does not include approved AEDs.
6. Subjects with a positive result on tetrahydrocannabinol (THC) or non-approved cannabidiol (CBD) test (via plasma drug screen). Tetrahydrocannabinol and/or non-approved CBD will be allowed in the OL phase.

7. Chronic use of oral steroid medications, ketoconazole (except for topical formulations), St. John*s Wort, or other investigational products is not permitted. Intermittent (<5 consecutive days/month or 10cumulative days per month) use of corticosteroids as a rescue medication for breakthrough seizures may be allowed after sponsor approval.
8. Changes in any chronic AED medications (i.e., changes in dose or starting a new chronic AED) within the last month prior to the screening visit (Visit 1) and during the 12 week baseline period (i.e., between Visit 1 and Visit 2). Changes in rescue AED medications to treat acute breakthrough seizures may be permitted with sponsor*s approval. Changes in other (i.e., non-AED) chronic medications may be permitted with sponsor *s approval.
9. Have an active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain imaging (magnetic resonance imaging [MRI]).
10. Have any disease or condition (medical or surgical; other than PCDH19-related epilepsy) at the screening visit that might compromise the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, or hepatic systems; or other conditions that might interfere with the absorption, distribution, metabolism, or excretion of the investigational product, or would place the subject at increased risk.
11. An aspartate aminotransferase (AST/serum glutamic oxaloacetic transaminase [SGOT]) or alanine aminotransferase (ALT/serum glutamic pyruvic transaminase [SGPT]) > 3 × the upper limit of normal (ULN) at screening and if applicable, confirmed by a repeat test. If the subject has another reason to be excluded, repeated liver enzymes are not required.
12. Total bilirubin levels > 1.5 × ULN at screening and if applicable confirmed by a repeat test. In cases of documented, stable medical condition (ie, Gilbert*s Syndrome) resulting in levels of total bilirubin > ULN, the medical monitor can determine if a protocol exception can be made.
13. Subjects with significant renal insufficiency, estimated glomerular filtration rate (eGFR) < 30 mL/min (calculated using the Cockcroft-Gault formula or Pediatric GFR calculator or Bedside Schwartz), will be excluded from study entry or will be discontinued if the criterion is met post baseline.
14. Have been exposed to any other investigational drug within 30 days or fewer than 5 half lives prior to the screening visit.
15. Unwillingness to withhold grapefruit, Seville oranges star fruit, or grapefruit containing products from diet 14 days prior to 1st dose and for the duration of the study 16. Unwillingness to withhold alcohol throughout the entire clinical trial.
17. Have active suicidal plan/intent or have had active suicidal thoughts in the past 6 months or a suicide attempt in the past 3 years.
18. Known sensitivity or allergy to any component in the investigational product(s), progesterone or other related steroid compounds.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-05-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ganaxolone
Generic name:	Ganaxolone

Ethics review

Approved WMO Date:	05-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	05-06-2019
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO Date:	23-09-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-09-2019
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	30-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-10-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO	

Date:	06-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	29-10-2020

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
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Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	11-04-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	21-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-04-2022
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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
EudraCT	EUCTR2018-004496-12-NL
ClinicalTrials.gov	NCT03865732
CCMO	NL69850.075.19

Study results

Date completed: 20-07-2022

Summary results
Trial ended prematurely