A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures

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Primary: To compare the reduction in frequency of partial-onset seizures on each of two trough ranges of everolimus (3-7 ng/mL and 9-15 ng/mL) versus placebo in patients with TSC who are taking one to three AEDs. Key secondary: Ability to completely…

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

Summary

ID

NL-OMON39634

Source
ToetsingOnline

Brief title
CRAD001M2304

Condition

- Congenital and hereditary disorders NEC
- Seizures (incl subtypes)

Synonym

tuberous sclerosis complex; seizures

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma BV
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: epilepsy, everolimus, partial-onset, TSC

Outcome measures

Primary outcome

Reduction from baseline in partial-onset seizure frequency during maintenance period of the core phase.

Secondary outcome

Seizure-free rate during maintenance period of the Core phase, proportion of patients with at least a 25% reduction from baseline in seizure frequency, categorical variable of six levels of reduction from baseline in seizure frequency, frequency of seizure-free days, time from randomization until treatment discontinuation, QOL scores, adverse events. Vineland and Wechsler sub-test scores (change from baseline).

Study description

Background summary

Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic disorder, with a prevalence ranging from 1 in 6000 to 1 in 25,000. Clinical disease spectrum is highly variable, with manifestations ranging from mild skin findings to seizures (which affect up to 90% of patients), learning disabilities (38% to 80%), mental retardation (50% to 70%), autism (20% to

60%), and fatal renal, cardiac, or pulmonary disease. Despite this broad range of clinical findings, a limited number of features are responsible for the decreased life expectancy associated with the disease, including neurologic disorders such as seizures.
TSC represents one of the most common genetic causes of epilepsy, that manifests usually very early during the first year of life. Seizures with partial-onset are observed in most TSC patients. Patients with seizure onset before the age of 4 years, particularly when the seizures are frequent or refractory to treatment, have a substantially increased risk of subsequent mental retardation or autism. Between 20-60% of patients with TSC-associated epilepsy fail to demonstrate improvement in seizure frequency with available therapies.
The primary goal of this study is to assess the efficacy and safety of everolimus as adjunctive therapy in patients with TSC who have partial-onset refractory seizures. Epileptogenesis in these patients has been attributed in part to the overexpression of mTOR. Encouraging nonclinical and preliminary clinical evidence illustrates that two different mTOR targeting drugs (rapamycin and everolimus), can limit the development of new onset seizures and increase survival in models of TSC associated seizures. Rapamycin has been shown to decrease the seizure frequency after the development of seizures in these animals. In the clinical setting, although in a phase study III findings were inconclusive, 2 phase II studies provided proof of concept for the activity of everolimus in seizure control. These findings justify the clinical evaluation of the mTOR inhibitor everolimus for an indication of seizure reduction.

Study objective

Primary: To compare the reduction in frequency of partial-onset seizures on each of two trough ranges of everolimus (3-7 ng/mL and 9-15 ng/mL) versus placebo in patients with TSC who are taking one to three AEDs.
Key secondary: Ability to completely suppress partial-onset seizures, proportion of patients with * 25% reduction from baseline in average weekly frequency of partial-onset seizures, distribution of reduction from baseline in seizure frequency, seizure-free days, treatment duration, quality of life, relationship between everolimus concentration and efficacy / safety endpoints, safety and tolerability. To assess everolimus in relation to neurocognitive, neurobehavioral and neurodevelopmental measures using the Vineland Adaptive Behavior Scales-II and the Wechsler Non-Verbal Scale of Ability

Study design

Randomized, double blind, placebo controlled, phase III study.
Baseline phase (8 weeks), core phase (18 weeks, double-blind), extension phase (everolimus for all patients).
Randomization (1:1:1) to

* Everolimus target trough range 3-7 ng/mL
* Everolimus target trough range 9-15 ng/mL
* Placebo.
Stratification for age.
355 patients.

Intervention

Treatment with everolimus or placebo.

Study burden and risks

Risk: Adverse effects of study medication.
Burden: Visits 1 during screening, 10 during core phase, during follow-up: 3 visits after 1, 1 and 2 weeks and every 4 weeks thereafter. Duration 1-5 h.
Blood draw 12x, 4-28 ml.
ECG 1x.
MRI 1x.
Wechler test (up to 22 years of age) 2x in core phase, every 6 months thereafter .
Questionnaires quality of life 6x.
Seizure diary.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female between the ages of 2 and 65 years (except in Europe where the minimum age will be 1 at the request of the EMA).;2. Clinically definite diagnosis of TSC per modified Gomez criteria ;3. Diagnosis of partial-onset epilepsy according to the classification of the International League Against Epilepsy (1989) and revised in 2009. ;4. Uncontrolled partial-onset seizures; must meet the following: ;a. At least 16 reported quantifiable partial-onset seizures over the Baseline period with no continuous 21-day seizure-free period between Visit 1 (Screening Visit) and Visit 2 (Randomization visit), as per data captured in daily seizure diaries. ;b. Prior history of failure to control partial-onset seizures despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs.;c. Prior or concurrent use of vagal nerve stimulator (VNS) is allowed. If the patient is using VNS, device stimulator parameters must remain constant throughout the study. ;d. Prior epilepsy surgery is allowed if performed at least 12 months before study entry. ;5. Must be receiving one, two, or three AEDs at a stable dose for at least 4 weeks at the start of the 8-week prospective Baseline phase, remain on the same regimen throughout the Baseline phase, and intend to continue the same regimen throughout the 18-week double blind Core phase (rescue medications are permitted). ;6. If female of child bearing potential, documentation of negative pregnancy test at time of informed consent and must use highly effective contraception during the study and for 8 weeks after stopping treatment ;7. Sexually active males must use a condom during intercourse while taking study drug, and for 8 weeks after stopping study treatment ;8. Hepatic, renal and blood laboratory values within the following range at screening:

a. AST and ALT levels < 2.5 x ULN ;b. serum bilirubin <1.5 × ULN (this limit does not apply to patients with an elevated indirect bilirubin, if they have Gilbert*s Syndrome);c. serum creatinine < 1.5 x ULN ;d. hemoglobin * 9 g/dL ;e. platelets * 80,000/mm3 ;f. absolute neutrophil count * 1,000/mm3 ;9. Written informed consent. Subjects or their legal guardians must have the ability to comprehend the informed consent form and be willing to provide informed consent. ;10. Patient or caregiver must be able to reliably record seizures and keep a daily diary and recall adverse events.

Exclusion criteria

1. Patients with seizures secondary to metabolic, toxic, infectious or psychogenic disorder or drug abuse or current seizures related to an acute medical illness ;2. Presence of only non-motor partial seizures (Criteria Not Applicable per Amendment 2);3. Patients with TSC who have SEGA in need of immediate surgical intervention;4. Patients under two years of age with untreated infantile spasms;5. Within 52 weeks prior to study entry, an episode of status epilepticus as defined in the protocol;6. Patients with history of seizure clusters (where individual seizures cannot be accurately counted;according to the judgment of the investigator) occurring within 26 weeks prior to study entry;7. Patients who require rescue medication during the Baseline phase for more than 6 days;8. Patients with non-TSC related progressive encephalopathy;9. Patients who weigh less than 12 kg;10. Patients with coexisting malignancies within the 3 years prior to randomization, except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin. ;11. Patients with any severe and/or uncontrolled medical conditions at randomization such as: ;a. Symptomatic congestive heart failure of New York Heart Association Class III or IV, history of left ventricular ejection fraction (LVEF) <50%, QTc interval >460ms, congenital QT syndrome, unstable angina pectoris, myocardial infarction within 6 months of study entry, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease;b. Significant symptomatic deterioration of lung function ;c. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, malabsorption syndrome or small bowel resection);d. liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis ;e. Uncontrolled diabetes as defined by fasting serum glucose > 1.5 × ULN;f. Active skin, mucosa, ocular or GI disorders of Grade > 1. ;g. Active (acute or chronic) or uncontrolled severe infections;h. A known history of HIV seropositivity or other active viral infections;12. Patients with an active, bleeding diathesis;13. Patient with uncontrolled hyperlipidemia: fasting serum cholesterol > 300 mg/dL OR >7.75 mmol/L AND fasting triglycerides > 2.5 x ULN;14. Patients who have had a major surgery or significant traumatic injury within 4 weeks of study entry. ;15. Patients with a prior history of organ transplant;16. Patients receiving more than 3 antiepileptic drugs at any time in the baseline phase or at randomization or who change the dose of the AEDs during 4 weeks before screening or during the baseline period;17. Patients being treated with felbamate, unless treatment has been continuous for * 1 years ;18. Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of study entry (including chemotherapy, radiation therapy, antibody based therapy, etc.) ;19. Prior treatment with any investigational drug within the preceding 4 weeks prior to study entry.;20. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent at study entry. Topical or inhaled corticosteroids are allowed. ;21. Patients who have received prior treatment with a systemic mTOR inhibitor (sirolimus, temsirolimus, everolimus) within 24 months of study entry. Patients who have received prior treatment with a topical mTOR inhibitor (sirolimus, temsirolimus, everolimus) within 4 weeks of study entry. ;22. Patients with a known hypersensitivity to everolimus or other rapamycinanalogues (sirolimus, temsirolimus) or to its excipients. ;23. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study ;24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the

termination of gestation, confirmed by a positive hCG laboratory test. ;25. Patient with a score of 4 or 5 on the Suicidal Ideation item within 2 years of Screening, or any *yes* on the Suicidal Behavior item of the Columbia-Suicide Severity Rating Scale at Screening or baseline,- who upon follow up with a healthcare professional are found to be severely depressed or suicidal.;26. Maintenance of a diet consisting of <40 g of carbohydrate per day within 3 months of
screening.

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:	Recruitment stopped
Start date (anticipated):	14-11-2013
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Certican/ Afinitor
Generic name:	everolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-02-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-07-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	16-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-09-2015
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Approved WMO Date:	16-10-2015
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	clinivaltrials.gov; registratienummer n.n.b.
EudraCT	EUCTR2011-000860-90-NL
CCMO	NL42664.041.12