A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC)

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This study will evaluate the antitumor activity of RAD001 versus placebo in patients with subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC).

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON37063

Source
ToetsingOnline

Brief title
N/A

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: placebo-controlled, RAD001, subependymal giant cell astrocytomas, Tuberous Sclerosis Complex

Outcome measures

Primary outcome

Primary Objective:

To compare the SEGA response rate in patients with TSC-associated SEGA on

RAD001 versus placebo.

Secondary outcome

Secondary Objectives:

To compare RAD001 versus placebo with respect to:

1. Change from baseline in frequency of epileptiform events.

2. Time to SEGA progression.

3. Skin lesion response rate.

4. Change from baseline in plasma angiogenic molecules, e.g. VEGF, basic FGF,

PLGF, soluble VEGF receptor1, and soluble VEGF receptor2.

5. Renal function assessed using calculated creatinine clearance.

6. Safety as assessed by the NCI Common Toxicity Criteria, version 3.0.

In RAD001 treatment arm to :

7. Characterize the pharmacokinetics of RAD001 in this patient population, specifically in terms of exposure.

8. Describe the duration of SEGA response, the time to SEGA response and the duration of skin lesion response.

Exploratory Objectives:

1. Assess changes in additional TSC-associated lesions that are documented at baseline, namely tubers, subependymal nodules (SENs) and angiomyolipomata. Angiomyolipoma response will be evaluated
in the subgroup of patients who have at least one angiomyolipoma lesion with longest diameter * 1.0 cm at baseline.

2. Assess changes from baseline in neuropsychological assessments and cognitive function using an age-appropriate battery of neuropsychological tests.

3. For SEGA lesions, the correlation between volume and longest diameter will be assessed.

4. Assess changes from baseline in severity of seizures using the Seizure Severity Questionnaire (SSQ).

5. Mutation analysis of TSC1 and TSC2 genes will be correlated with SEGA response rate and time to SEGA progression.

6. Assess the relationship between RAD001 concentration and safety/efficacy endpoints.

7. Assess the occurrence of SEGA-related surgery and the time to SEGA-related surgery in both treatment groups

8. Assess changes in anti-convulsant therapy in both treatment groups

Study description

Background summary

TSC is an autosomal dominant genetic disorder caused by inactivating mutations in the TSC1 or TSC2 genes, and characterized by benign, highly vascular, hamartoma growth. Lesions occur in the brain, kidneys, heart, liver, lungs and skin, leading to renal complications, pulmonary failure, autism, mental retardation, seizures and epilepsy.

Measures of childhood prevalence range from 1 in 6,800 to 1 in 17,300 but full ascertainment is difficult to achieve. Brain lesions are the primary cause of morbidity and mortality in this disorder in childhood. The incidence of subependymal giant cell astrocytoma in TSC varies from 5 to 15%. These are slow growing lesions that are typically unapparent clinically until they reach sufficient size to produce ventricular obstruction and hydrocephalus. By the time symptoms are noted they are often irreversible even by emergent surgical intervention. They arise deep within the brain in the region of the foramen of Monro, which hampers their surgical resection, as the approach to the lesion entails removal of substantial amounts of viable cerebral tissue. Surgery, even when successful, often results in significant morbidity. The TSC1/TSC2 protein complex is a negative regulator of the mTOR pathway. Hence, mutation or loss of either of these gene products in preclinical models is associated with increased mTOR pathway activation and heightened sensitivity to mTOR inhibitors mTOR pathway upregulation has also been observed in lesions derived from TSC patients and TSC1
or TSC2 defective experimental animal models exist which recapitulate the pathology, behavioral and neurological aspects of the tuberous sclerosis disease and are sensitive to mTOR inhibition In this respect, experiments are in progress aimed at analyzing the effects of RAD001 in animal models of TSC. Preliminary data indicate that gross kidney lesion scores can be significantly reduced by RAD001 treatment in both TSC1+/- and TSC2+/- mouse models ($p = 0.02$ compared to untreated controls, unpaired ttest). mTOR inhibition is associated with a dramatic inhibition of the phosphorylation of the ribosomal S6 protein in treated kidney lesions (S6 phosphorylation is an established pharmacodynamic marker of mTOR pathway activation status). Furthermore, a dramatic improvement in survival has been observed in a mouse brain model of TSC (genotype : Tsc1cc syn-cre+), with a highly statistically significant improvement in survival ($p < 0.0001$) associated with RAD001 treatment The investigator also noted an improvement in behavior, weight gain and neurological phenotype. Assessment of brain pathology is currently ongoing. Finally, both estrogen and vascular endothelial growth factor (VEGF)

signaling have been implicated in the pathogenesis and vascularization of TSC lesions In this respect, RAD001 has been shown to inhibit both estrogen and VEGF-dependent signaling events Taking all these data into account, there is a strong rationale for using RAD001 for the treatment of patients.
with tuberous sclerosis.

Study objective

This study will evaluate the antitumor activity of RAD001 versus placebo in patients with subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC).

Study design

This is a prospective, double-blind, randomized, parallel group, placebo-controlled, multi-center phase III study evaluating treatment with RAD001 versus placebo in 99 patients with TSC-associated SEGA.

Screening/Baseline Phase:
Screening/baseline evaluations will be performed within 28 days prior to treatment day 1. An MRI of the brain should be performed for the baseline tumor assessment.

Blinded Treatment Phase/Duration of Treatment:
Patients will be randomized to receive either RAD001 or matching placebo. Patients will be treated with blinded
study treatment until SEGA progression, unacceptable toxicity or discontinuation for any other reason.

Open Label Treatment Phase:
If SEGA progression is documented by central radiology review during the blinded treatment phase, then the treating physician may proceed to unblind the patient.

Follow-Up (for patients who discontinue study treatment):
Patients who have not had SEGA progression at the time of study treatment discontinuation will be followed up with MRIs of the brain (and MRIs of the kidney if angiomyolipomata with longest diameter * 1.0 cm were present at baseline) annually until eventual SEGA progression, or until the start of any non-study systemic anti-TSC therapy, whichever occurs soonest.

Extension phase:
The data cutoff date for the final analysis will be 6 months after the last patient is randomized. Once the final trial results are known, and if these results favor RAD001, then an extension phase will be launched. All patients still receiving study treatment at this time, as well as those being followed

for posttreatment evaluation, will be given the option of starting open-label RAD001, which will be provided.

Intervention

During treatment phase patients will receive 4.5 mg/m2/day RAD001 or placebo. Dose adjustments will be permitted based on safety findings and blood trough measurements.

Study burden and risks

Additional side effects of RAD001 occurring in more than 5% of treated patients include fatigue, weaknes nausea and vomiting, dry mouth, skin or nail changes (including acne, rash, redness, itching, dryness or irritation), diarrhea, loss of appetite (anorexia) resulting in weight loss, abdominal pain, swelling of the extremities- usually lower limbs, fever abnormal or loss of taste, inflammation of the throat, bleeding of the nose, inflammation of the lining of the digestive system, inflammation of the throat, feeling tired, pain in arms and legs, shortness of breath, dry skin and headache. In some cases RAD001 could change sleep patterns.

There could be a lowering of the number of blood cells, which help fight infection. This could lead to an infection (which could be potentially life threatening). In addition, there could be a lowering of the blood cells that help the blood to clot and the lowering of the protein (hemoglobin) that helps carry oxygen in the blood. This is not expected to be severe enough to have an impact on the patients health.
Drugs given to patients like chemotherapy and the study drug, everolimus, can cause the patient*s immune system to not work as well. A patient with hepatitis B or hepatitis C could have the virus become more active.

Rarely (less than 1% of patients) RAD001 is associated with a blood clot trapped in a blood vessel (embolism).

The tests done at each visit are standard medical tests. The most unpleasant is often having blood samples taken. The risks of taking blood may include fainting, pain and/or bruising. Rarely, there may be a small blood clot or infection at the site of the needle puncture. The blood pressure cuff may also cause discomfort or bruising to the upper arm.
The sticky patches applied to the chest during an ECG can occasionally cause a rash or redness of the skin when removed.

The risk from a CT scan, for any patients that need to have one if clinically indicated, is small.
*There is a slight risk of developing an allergic reaction to the contrast material. The reaction can be mild (itching, rash) or severe (difficulty

breathing or sudden shock). Death resulting from an allergic reaction is rare. Most reactions can be controlled using medication.
* The contrast material used during CT scanning can cause water loss or damage to the kidneys that may lead to kidney failure.
* If contrast material is used, patients may be at risk for kidney problems if they have diabetes, especially if tjey take metformin (Glucophage).
* There is always a slight risk of damage from being exposed to any radiation, including the low levels of X-rays used for a CT scan. However, the risk of damage from the X-rays is usually very low compared with the potential benefits of the test.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. All Ages;2. Definite diagnosis of Tuberous Sclerosis;3. At least one Subependymal Giant Cell Astrocytoma of at least 1 cm in diameter ;4. Evidence of SEGA progression as compared to prior MRI scans ;5. Females of child bearing potential must use birth control

Exclusion criteria

1. Recent heart attack, cardiac related chest pain or stroke ;2. Severely impaired lung function ;3. Severe liver dysfunction;4. Severe kindney dysfuntion ;5. Pregnancy or breast feeding ;6. Current infection ;7. History of organ transplant;8. Surgery within two month prior to study enrollement ;9. Uncontrolled diabetes ;10.HIV ;11.Patients with metal implants thus prohibiting MRI evaluations

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):	12-08-2010
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Everolimus
Generic name:	Certican
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-05-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-03-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-06-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-07-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-07-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-08-2011

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-09-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-07-2015

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
EudraCT	EUCTR2007-006997-27-NL
Other	N/A
CCMO	NL27377.041.09