PLEASE NOTE: *This study has been imported from ClinicalTrials.gov without additional data checks.*

Trial Description

Title

Open Label Phase II Study of Everolimus (RAD001) in Patients With Segmental Overgrowth Syndrome

Trial Acronym

EPASOS

URL of the trial

[---]*

Brief Summary in Lay Language

This is an open-label, multicenter, single-arm, phase II clinical trial of Everolimus (RAD001) in patients with segmental overgrowth syndrome.

Brief Summary in Scientific Language

Segmental overgrowth syndromes are very rare diseases with an extremely relevant genetic background. In some of them, only about 200 cases are known worldwide, such as for example the Proteus syndrome which presents with asymmetric and fast growth of extremities. Further overgrowth diseases are the SOLAMEN and the CLOVE syndrome with lipomatosis, vascular malformations and epidermal nevus as well as the Cowden syndrome with multiple hamartomas and the Bannayan-Riley-Ruvalcaba syndrome with lipomatosis and macrocephalus. The patients with overgrowth syndromes all show close clinical overlap. For several years, clinical criteria (phenotype) for diagnosis and discrimination of these syndromes have been defined.

Results of genetic research can today help to diagnose most of the segmental overgrowth syndromes which means they can clearly be named. Genes of the PI3K/AKT/PTEN/mTOR signalling pathway have been identified to be causative for some of these syndromes. PTEN germline mutations have been known to be present in SOLAMEN, Cowden and Ruvalcaba syndrome patients

all showing tissue overgrowth and close clinical overlap. However, very rarely, somatic PTEN mutations could be detected in surgical specimen of lipomas or hamartomas of other segmental overgrowth patients. Only recently, recurrent somatic activating mutations of AKT1 have been identified in overgrowth tissue of Proteus syndrome patients. Because AKT1 is also activated by loss-of-function mutations in PTEN, patients with syndromes harbouring germline PTEN mutations (SOLAMEN, Cowden and Ruvalcaba) and Proteus syndrome patients with activating mutations of AKT1 show close overlap in clinical manifestations. Furthermore, somatic PI3KCA mutations have been described to be responsible for the CLOVE syndrome, again a phenotypically closely related variant of the other overgrowth syndromes. These genetic results confirmed that patients with overgrowth all share a common feature involving the PI3K/AKT/PTEN/mTOR signal pathway.

Next to surgical approaches in functional handicapped patients, a standard medical therapy is not available. Therefore, in most cases, a watch-and-wait strategy is followed. Taking into account the genetic background of segmental overgrowth patients, mTOR is a promising target for a possible medical treatment. For example, because the direct molecular consequence of PTEN loss-of-function is an aberrant activation of the mTOR pathway, targeting mTOR holds the promise of a causative treatment in PTEN-positive segmental overgrowth patients.

Until today, three case reports have described the successful use of the mTOR inhibitor Rapamycin for the therapy of patients with segmental overgrowth and PTEN germline mutation.
The Investigator recently started with "off label" use of Rapamycin in these patients. First results with successfully treated patients have been presented at The Annual meeting of the German Society of Human Genetics in 2011 and the meeting of the International Society on the Studies of Vascular Anomalies in 2012. In one patient with segmental overgrowth syndrome and response to Rapamycin, the investigators could identify a PI3KCA mutation in one lesion.
This case is currently prepared for publication. Interestingly, response on mTOR inhibition could be demonstrated in some patients although lack of mutation in the published genes responsible for overgrowth syndromes.

A clinical trial sponsored by the National Cancer Institute tested the ability of Rapamycin to decrease the activity of proteins that are regulated by mTOR in both benign and cancerous tumour tissue in Cowden syndrome patients (NCT00971789). Only patients over the age of 18 years were included and multiple biopsies were performed before starting treatment and during therapy with Rapamycin.

Organizational Data

- DRKS-ID: **DRKS00009508**
- Date of Registration in DRKS: **2015/10/09**
- Date of Registration in Partner Registry or other Primary Registry: **2015/03/18**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **[---]***
- (leading) Ethics Committee Nr.: **[---]***

Secondary IDs

- EudraCT-No. (for studies acc. to Drug Law): **2014-004019-35**
- Primary Registry-ID: **NCT02569125 (ClinicalTrials.gov)**
- Sponsor-ID: **CRAD001CDE40T (Jochen Roessler)**
- Other Secondary-ID: **2014-004019-35**

Health condition or Problem studied

- Free text: **Segmental Overgrowth Syndrome**

Interventions/Observational Groups

- Arm 1: **Drug: Everolimus**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***

Study Type: **Interventional**

Study Type Non-Interventional: **[---]***

- Allocation: **Single arm study**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Uncontrolled/Single arm**
- Purpose: **Treatment**
- Assignment: **Single (group)**
- Phase: **II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

- Number of patients with partial or complete response measured by MRI.; time frame: until 12 months

Secondary Outcome

[---]*

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- **Vivantes Klinikum Neukölln, Berlin**
- **Universitätsklinikum Bonn, Bonn**
- **Universitätsklinikum Freiburg, Freiburg**
- **Universitätsklinikum Leipzig, Leipzig**

Recruitment

- Planned/Actual: **[---]***
- (Anticipated or Actual) Date of First Enrollment: **2016/01/31**
- Target Sample Size: **18**

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Target Sample Size: **18**

- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **1 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

1. Male or female patients aged ≥ 1 years.

2. Signed written informed consent (patient older than 18 years or person(s) having the care and custody of the patient younger than 18 years).

3. Segmental overgrowth syndrome patients independently of genetic background (that means with/ without PTEN germline mutations or with/without AKT/PI3K somatic mutations in an overgrowth lesion).

4. Patients who meet clinical criteria for segmental overgrowth syndromes, including a soft tissue lesion composed of one or several tissue components such as fat, vessels, muscle, muscle or connective tissue.

5. Identification of a target lesion by MRI > 5 cm3. The target lesion must be externally visible (photos) and composed by soft tissue.

6. Normal organ and bone marrow function (i.e. transaminase levels > 2.5 x ULN or serum bilirubin > 1.5 x ULN, hemoglobin > 9 g/dL).

7. Negative urine pregnancy test in females with a childbearing potential.

8. If female and of child-bearing potential, documentation of negative pregnancy test prior to enrollment. Sexually active female patients (and female partners of male patients) must use adequate contraceptive measures while on study and for up to 8 weeks after ending treatment.

Exclusion criteria

1. Any concurrent therapy with chemotherapy agents or biologic agents or radiation therapy.

2. Patients who have received live vaccines in the past 30 days prior to informed consent.

3. Patients on medication with CYP3A4 inhibitors / inducers which are not replaced by other equivalent medications for the study period.

4. Patients who have known immunodeficiency or HIV seropositivity.

5. Patients with known interstitial lung disease, pneumonitis or with bleeding diathesis.

6. Patients with prior use of Everolimus or other mTOR inhibitors such as f.e. Rapamycin or any analogue within the last 6 months; regardless of therapeutic effect, but with risk assessment due to former side effects.

7. Any planned surgery within study period.

8. Pre-existing chronic wounds.

9. Triglycerides > 400 mg/dL (> 4.5 mmol/L) or total cholesterol > 300 mg/dL (> 7.8 mmol/L).

10. Creatinine clearance ≤ 60 mL/min (Cockcroft and Gault formula).

11. Proteinuria ≥ 30 mg/dL on dipstick and 24 hours proteinuria > 0.8 g/24 hours.

12. Intake of St John's Wort and/or grapefruit and grapefruit juice.

13. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks:

- **Uncontrolled hypercholesterolemia/hypertriglyceridemia.**
- **Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome).**

14. Patients with a known hypersensitivity to Everolimus or other mTOR inhibitors such as f.e. Rapamycin or any analogs or to its excipients.

15. Patients unwilling to or unable to comply with the planned therapeutic intervention or to comply with the study treatment visits including blood sample collection within the protocol.

16. Female patients who are pregnant or breast feeding, or patients of reproductive potential who are not using effective birth control methods. If barrier contraceptives are used, they must be continued throughout the study by both sexes.

Addresses

- **Primary Sponsor**

  Jochen Roessler

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

- **Contact for Scientific Queries**

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  URL: **[---]***

- **Collaborator, Other Address**

  Clinical Trials Unit Freiburg

  Telephone: **[---]***

Collaborator, Other Address

Clinical Trials Unit Freiburg

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Sources of Monetary or Material Support

- **[---]***

Bitte wenden Sie sich an den Sponsor / Please refer to primary sponsor

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Status

- Recruitment Status: **Recruiting withdrawn before recruiting started**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

The parameters in ClinicalTrials.gov and DRKS are not identical. Therefore the data import from ClinicalTrials.gov required adjustments. For full details please see the DRKS FAQs.
- Translation on version: 5
- Last processed date by ClinicalTrials.gov: 2016/02/24

** This entry means the parameter is not applicable or has not been set.*

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