# Topical rapamycin to treat fibrofolliculomas in Birt-Hogg-Dubé syndrome

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Primary Objective: To determine whether topical application of rapamycin can lead to reduction in size and/or number of fibrofolliculomas in BHD patients and may prevent the growth of new ones. Secondary Objectives: Safety, formula acceptability and...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Chromosomal abnormalities, gene alterations and gene variants |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON35713

**Source**
ToetsingOnline

**Brief title**
Topical rapamycin

### Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Skin appendage conditions

**Synonym**
fibrofolliculomas, hair follicle tumors

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universiteit Maastricht
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** Birt-Hogg-Dubé syndrome, fibrofolliculomas, rapamycin, topical

## Outcome measures

### Primary outcome

Significant regression of lesions (reduction of fibrofolliculoma size and

count) in the treated area. Defined as assessment by at least 2 of 3 observers

with at least 2 points.

The following 7-point scale is used:

-3= strong worsening

-2= moderate worsening

-1= minimal worsening

0= no improvement

1= minimal improvement

2= moderate improvement

3= strong improvement

### Secondary outcome

Secondary parameters/endpoints:

The absence of any effect.

Safety evaluation is assessed by tolerance and adverse event profiles.

Formula acceptance is assessed with a 5-point rating scale en patient

satisfaction with some statements.

# Study description

## Background summary

Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disorder characterized by the occurrence of benign, mostly facial, hair follicle tumors called fibrofolliculoma, multiple lung cysts and spontaneous pneumothorax and an increased renal cancer risk. The fibrofolliculomas can be quite disfiguring and are usually the reason that patients come to medical attention. They usually appear after the age of 25 years and are progressive. Typically presenting around the nose, they can spread onto the ears, neck and trunk. Although they do not grow beyond 3-4mm in size, their numbers increase with age so that patients can eventually have hundreds of tumors. Presently, ablative laser is the preferred treatment. In addition, surgical interventions like excision and shaving and elektrocoagulation are performed. Disadvantages of these treatments are the risk of complications (scarring, hypo-and hyperpigmentation), recurrence (from lasertherapy is known that fibrofolliculomas recur after 2-3 years.) and the fact that these treatments do not prevent the growth of new fibrofolliculomen. A topical treatment that is suitable for chronic use and reduces the number of tumors and/or prevents the growth of new ones would be preferable but is not yet available. New insights from genetic and cell biological studies now suggest a potential topical therapy. BHD syndrome is caused by germline mutations in the BHD gene coding for the protein folliculin. Strongly conserved in evolution, folliculin*s function is mostly unknown. We now know, from research on mouse models and our own human data, that in BHD syndrome there is possibly deregulation of mTOR signalling. mTOR, mammalian target of rapamycin, is a multiprotein-complex that is a central player in cellular growth regulation and energy sensing. Thus, BHD syndrome belongs in a larger family of disorders characterized by mTOR deregulation, such as tuberous sclerosis complex (TSC). In TSC, as in BHD, patients develop facial hair follicle tumors called angiofibroma. These tumors strongly resemble fibrofolliculoma and are increasingly seen as a variant of the latter. Very recent findings indicate that angiofibromas of TSC respond favorably to the mTOR inhibitor rapamycin - they disappear after some months of oral rapamycin. This mode of administration has potential side effects that are not acceptable in the context of BHD syndrome. However, there are several studies showing that topical application is safe and may be a feasible strategy. Rapamycin oral solution 1mg/ml has already been used off-label for a non-related mucosal and skin disorder and was both safe and effective when applied topically. Thus, we have theorized that rapamycin oral solution might be used for the treatment of BHD-associated fibrofolliculomas.

## Study objective

Primary Objective: To determine whether topical application of rapamycin can lead to reduction in size and/or number of fibrofolliculomas in BHD patients and may prevent the growth of new ones.

Secondary Objectives: Safety, formula acceptability and patient satisfaction.

### Study design

Double-blind placebo-controlled randomized intervention study. It's possible to switch to an open labelled study after 3 months.

### Intervention

Application of rapamune 1 mg/ml oral solution to one predefined skin area on one facial half, twice daily. The other facial half will be similarly treated with a placebo.

### Study burden and risks

Participation requires patients to apply rapamycin liquid and placebo liquid twice daily.
Participation in the study will take the patient 5 minutes a day, plus the 4 control visits that will take approximately 30 minutes.
Local irritation due to the excipient, which contains alcohol, is possible but this can be easily controlled. An allergic reaction to one of the ingredients of rapamune is also possible. In this case we will stop treating this specific patient with rapamune. There will be one biopsy for patients who have not yet undergone one. A skin biopsy is taken by means of a 3 mm punch after injection of local anesthetic which is briefly painful. A properly taken biopsy will leave no or minimal scarring.
Previous studies have shown that topical application of rapamycin is safe and does not lead to therapeutic plasma levels. The benefit for the patients is in the potential reduction in facial tumor size and number. For BHD patients in general the benefit will be an easily used topical treatment with which fibrofolliculomas may be treated or prevented.

## 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

Minimum age of 18 years.
At least 10 facial fibrofolliculomas, histologically confirmed.
Entered in a screening program and free of malignancy as determined during screening (already had a baseline MRI or CT-scan).
Being able to understand instructions.
Mutation status must be known.
For females: not pregnant and willing to use both oral and barrier contraceptives during the treatment period.

## Exclusion criteria

Not capable of informed consent.
Age under 18 years.
Pregnancy or failure to comply with contraceptive measures.
Proven or suspected malignancy of skin or other organs.
No histological confirmation.
Skin lesions other than fibrofolliculoma that might worsen under sirolimus such as active infections.
Not able to comprehend instructions.
No proven mutation.
Less than 10 fibrofolliculomas.
Planned facial surgery in the treatment period.
Concomitant disease requiring systemic immunosuppressive treatment during the trial or within 30 days before start of therapy.

Concomitant disease requiring facial topical immunosuppressive treatment or facial topical drugs that interfere with rapamycin during trial period or within 30 days before start of therapy.
Tendency to form keloids or hypertrophic scars.
Drug or alcohol abuse.

# 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): | 06-01-2010 |
| Enrollment: | 20 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Rapamune oral solution 1mg/ml |
| Generic name: | Rapamycin |
| Registration: | Yes - NL outside intended use |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 27-05-2009 |

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|---|---|
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 30-07-2009 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 16-11-2009 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 20-11-2009 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 25-03-2010 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 29-03-2010 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

# 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 | EUCTR2009-012740-17-NL |
| ClinicalTrials.gov | NCT00928798 |
| CCMO | NL28245.068.09 |