Everolimus Investigator-initiated Protocol

RAD001 (Everolimus)

Everolimus for treatment of disfiguring cutaneous lesions in Neurofibromatosis-1

CRAD001CUS232T

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List of abbreviations

4E-BP1	4E-binding protein
AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
CDS	Core data sheet
CoA	Coenzyme A
CPK	Creatine phosphokinase
CRF	Case Report Form
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DLCO	Diffusing capacity of the Lung for Carbon Monoxide
DNA	Deoxyribonucleic acid
DS&E	Drug Safety and Epidimology
EOT	End of treatment
EU	European Union
FDA	Food and drug administration
GERD	Gastroesophageal reflux disease
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HMG	3-hydroxy-3-methyl-glutaryl
IB	Investigator brochure
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
$\log_{10}$	Decadic logarithm (common logarithm)
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NF-1	Neurofibromatosis-1
NCI	National Cancer Institute
PCR	Polymerase chain reaction

PgP	P-glycoprotein
PFT	Pulmonary function tests
PI3K	Phosphoinositide 3-kinase
PIP2	Phosphatidylinositol 4,5-biphosphate
PIP3	Phosphatidylinositol 3,4,5-triphosphate
PNET	Pancreatic neuroendocrine tumor
RCC	Renal cell carcinoma
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SEGA	Subependymal giant cell astrocytoma
TS	Tuberous sclerosis
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WOCBP	Women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	For efficacy evaluations, the baseline assessment will be the last available assessment before or on the date of randomization. For safety evaluations (i.e. laboratory assessments and vital signs), the baseline assessment will be the last available assessment before or on the start date of study treatment. The value obtained at baseline assessments, referred to as "baseline value" will be used as reference for the subject.
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dose level	The dose of drug given to the subject (total daily or weekly etc.)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the subject as part of the required study procedures that was not included in the investigational treatment
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the subject will be followed for progression and/or survival

Stop study participation	Point/time at which the subject came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the subject (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason; may or may not also be the point/time of premature subject withdrawal
Subject ID	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Neurofibromas are benign tumors found in patients with NF-1. A loss of heterozygosity of the NF-1 gene in peripheral Schwann cells results in proliferation of the Schwann cells and the formation of visible fibromas within and beneath the skin (Figure 1-1). These tumors can develop at any point along a nerve and are composed of Schwann cells, fibroblasts, mast cells, and vascular components.

Neurofibromas are typed by depth. Surface lesions involve only the superficial skin and subcutaneous tissues. Deep lesions involve nerve roots including deep peripheral nerves. Three subtypes of cutaneous neurofibromas are clearly defined: pure cutaneous (dermal), subcutaneous, and plexiform. Dermal and subcutaneous lesions are circumscribed and appear brown, pink, or skin colored. They may be soft or firm to the touch and are associated with cutaneous sensory nerves and/or a single peripheral nerve. Dermal neurofibromas continue to increase in number and size throughout life. These lesions disfigure by remodeling the surface tissues including flat bones of the skull and face. Plexiform neurofibromas are highly vascular, noncircumscribed, thick, and irregular. Plexiform neurofibromas cause disfigurement by infiltrating important supportive structures. They are more difficult to define and are associated with multiple nerve bundles.

Although they rarely undergo malignant transformation, neurofibromas are present in most NF-1 patients and can become large, resulting in disfigurement and discomfort (stinging, itching, pain) (Figure 1-2A). Neurofibromas can also become so numerous and widespread that they appear confluent and are impossible to isolate for cosmetic surgical removal (Figure 1-2B). Although multiple therapies have been tried, there currently is no effective medical management for reduction of these lesions.

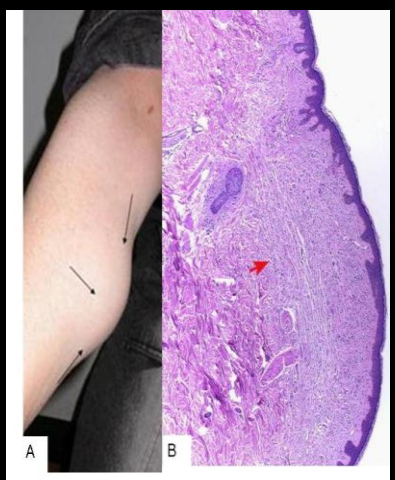


Figure 1-1. A. Peripheral neurofibroma on the right arm. B. Pathology of a neurofibroma showing the poorly circumscribed dermal proliferation.

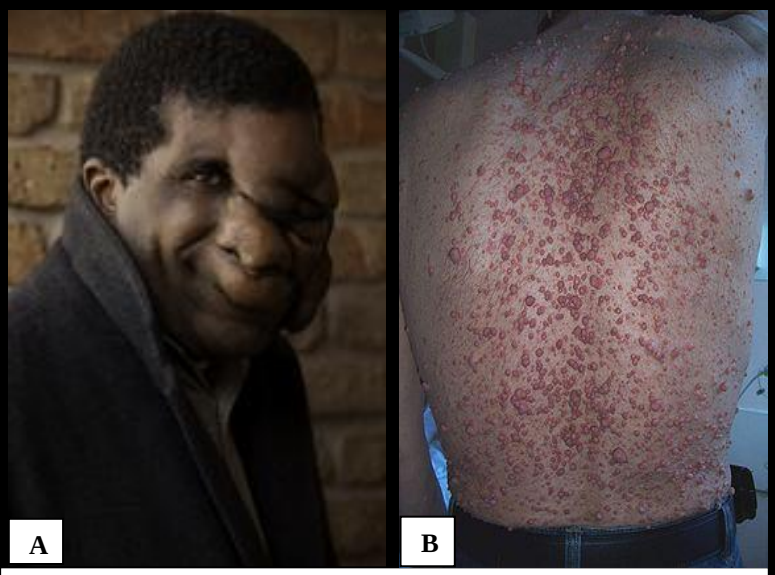


Figure 1-2. A. Photo of a young man with disfiguring facial cutaneous NF-1 lesions with skull remodeling. **B.** Photo of a young man with confluence of mixed type neurofibromas resulting in disfigurement.

1.2 Introduction to investigational treatment

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Everolimus was developed in oncology as Afinitor® and was approved for advanced renal cell carcinoma (RCC) in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TS. Afinitor® was approved for "progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone

receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of adult patients with TS who have renal angiomyolipoma not requiring immediate surgery.

Approximately 18,730 cancer patients have been treated with everolimus as of 30-Sep-2011:

- 9,528 patients in Novartis-sponsored clinical trials
- 2,559 patients in the individual patient supply program
- 6,638 in investigator-sponsored studies.

1.2.1 Overview of Everolimus

The following is a brief summary of the main characteristics of everolimus. More complete information can be obtained from the Everolimus Investigator's Brochure (IB).

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor (Table 1-1, Figure 1-3). Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers.

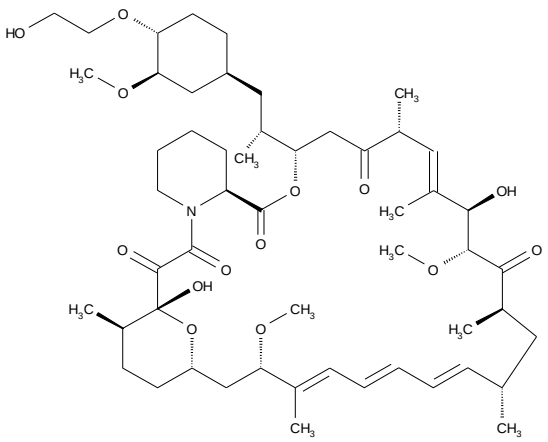
Everolimus is being investigated in this setting based on its potential to act:

- directly on tumor cells by inhibiting tumor cell growth and proliferation;
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

Table 1-1 Everolimus - Drug substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1-3 Chemical structure of Everolimus



1.2.1.1 mTOR pathway and cancer

At the cellular and molecular level, everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). The main known functions of mTOR include:

- sensor of mitogens, growth factors and energy and nutrient levels;
- facilitation of cell-cycle progression from G1-S phase in appropriate growth conditions;
- production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation;
- regulation of protein translation, including the HIF-1 proteins through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1)

Mutations in this pathway or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development:

- The PI3K/mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors;
- PI3-kinase mutations have been reported in the primary tumor in 10-20% of human colorectal cancers;
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers;

1.2.1.2 Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to µM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with everolimus showed a significant reduction in blood vessel density when compared to controls.

The potential of everolimus as an anti-cancer agent was shown in rodent models. Everolimus is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to everolimus *in vitro*.

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and "relatively resistant" *in vitro*. In general, everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e.,

doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

It is not clear which molecular determinants predict responsiveness of tumor cells to everolimus. Molecular analysis has revealed that relative sensitivity to everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma) there is also a correlation with PTEN status.

In vivo studies investigating the anti-tumor activity of everolimus in experimental animal tumor models showed that everolimus monotherapy typically reduced tumor cell growth rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day.

In preclinical models, the administration of everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

All significant adverse events observed in toxicology studies with everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

Further details can be found in the Everolimus Investigator's Brochure.

2 Rationale

Clinical manifestations of NF-1 arise from mutations in the NF-1 gene. The NF-1 gene product, neurofibromin, is intricately involved in the regulation of cell growth and division exhibiting sequence similarity to the Ras family of proteins.

During steady states, neurofibromin suppresses Ras and through its signaling pathway, effectively inhibiting mTOR. When the NF-1 gene is defective, Ras function is unable to be suppressed, resulting in a cascade of events that leads to a continuous state of uninhibited mTOR activity. Constitutively active mTOR leads to a state of cell overgrowth and tumor formation. Everolimus binds with high specificity to mTOR; binding results in inhibition of the activity of mTOR, effectively compensating for the dysfunctional Ras pathway in NF-1.

3 Objectives and endpoints

3.1 Primary

Objective: Determine if orally administered everolimus reduces the surface volume of dermal cutaneous and subcutaneous neurofibromas in subjects with NF-1.

Endpoint: Reduction in lesion surface volume by 50% as determined using the 3D LIFEVIZ Micro system (QuantifiCare, Sophia Antiopolis, France).

3.2 Secondary

Objective: Determine if orally administered everolimus is safe in subjects with NF-1.

Endpoint: Lack of Grade 3-4 adverse events during trial period.

3.3 Tertiary

Objective: Determine how orally administered everolimus modifies protein expression in cutaneous neurofibromas.

Endpoint: Quantification via immunohistochemical staining of PTEN, pS6, p4EBP-1, TSC2, mTOR, NF-1, pAKT, VEGF-A, and IGF-1R expression in biopsied neurofibroma tissue samples.

4 Study design

20 adult subjects will be identified through the clinical practices of the principle investigators. All subjects will take everolimus with a target trough level of 5-15 ng/ml for 6 months. Target lesions will consist of disfiguring dermal cutaneous and subcutaneous neurofibromas that are amenable to photodocumentation. The target lesions will be identified by the principle investigators at the baseline study visit. Each subject will also have a separate neurocutaneous lesion identified by the principle investigators for baseline biopsy. Photographs of target lesions will be obtained at baseline, at 3 months, and at 6 months using the 3 D LIFEVIZ Micro photography system.

Photodocumentation will be performed with a 3D LIFEVIZ Micro photography system (QuantifiCare, Sophia Antiopolis, France). This system uses a split lens with polarized flash illumination capturing two images with different viewing angles of the same surface at the same time. A stereovision algorithm is then applied to reconstruct and quantitatively analyze the skin surface in 3D allowing for accurate measures of surface volume (see attached LIFEVIZ Micro Validation for detailed information).

Everolimus PK serum levels will be measured 2 weeks after trial initiation and dose will be titrated at 2 week intervals until the target level of 5-15 ng/ml is reached. Once the target level is achieved, PK serum levels will be assessed again at the 3 month visit and at study termination (6 months) to verify compliance. Complete blood counts, bilirubin level, ALT, AST, INR, beta-hCG (where appropriate), total cholesterol level, fasting triglycerides, fasting glucose, serum creatinine, VEGF-A, VEGF-D, sVEGFR-1, sVEGFR-2, PIGF, c-Kit, and collagen type IV will also be measured pre-treatment, at 3 months, and at study termination (6 months).

5 Population

Any adult patient with NF-1 and disfiguring cutaneous lesions that are amenable to photodocumention will be screened for participation.

5.1 Inclusion and Exclusion criteria

Subjects will have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been

satisfied, will be reviewed by the Principal Investigator or his/her designee prior to enrollment of that subject. In addition, the subject will be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent will be obtained from the subject prior to enrollment. The following criteria apply to all subjects enrolled onto the study unless otherwise specified.

5.1.1 Inclusion criteria:

1. Subject is at least 18 years of age at the time of enrollment;
2. Subject is informed and given ample opportunity to think about his/her participation and has given his/her written consent/assent;
3. Subject is willing and able to comply with all trial requirements, including cooperation with blood draws and photographs;
4. Subject has a diagnosis of NF-1 and has cutaneous neurofibromas that are located in a region amenable to photography;
5. Female subjects of child-bearing potential (those who are not surgically sterile or 2 years post-menopausal) must not be pregnant as confirmed by a negative pregnancy test (blood beta-hCG level) prior to study enrollment. Female subjects of child-bearing potential must also agree to use appropriate contraceptive methods for the duration of the trial;
6. Subject must have adequate bone marrow function as shown by:
   a. ANC $\geq 1.5 \times 10^9$/L
   b. Platelets $\geq 100 \times 10^9$/L
   c. Hb >9 g/dL;
7. Subject must have adequate liver function as shown by:
   a. Total serum bilirubin ≤2.0 mg/dL,
   b. ALT and AST ≤2.5x ULN,
   c. INR ≤2;
8. Subject must have adequate renal function:
   a. Serum creatinine ≤1.5x ULN;
9. Subject must have adequate lipid profile:
   a. Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L
   b. Fasting triglycerides ≤2.5x ULN.

5.1.2 Exclusion criteria:

1. Subjects currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of the start of everolimus (including chemotherapy, radiation therapy, antibody based therapy, etc.);
2. Known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus);

3. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus;
4. Uncontrolled diabetes mellitus despite adequate therapy;
5. Subjects who have any severe and/or uncontrolled medical conditions such as:
   a. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to start of everolimus, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease,
   b. Symptomatic congestive heart failure of New York heart Association Class III or IV,
   c. Known active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, or chronic hepatitis,
   d. Known severely impaired lung function (spirometry and DLCO 50% or less of normal and O_2 saturation 88% or less at rest on room air),
   e. Active, bleeding diathesis;
6. Chronic treatment with corticosteroids or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed;
7. Known history of HIV seropositivity;
8. Subjects who have received live attenuated vaccines within 1 week of start of everolimus. Subject should avoid close contact with others who have received live attenuated vaccines during the study;
9. Subjects who have a history of primary malignancy, with the exceptions of: non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the subject has been disease free for ≥3 years;
10. Subjects 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;
11. Subjects who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing;
12. Pregnant or nursing (lactating) women;
13. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment. Highly effective contraception methods include:

    A combination of any two of the following (a+b or a+c or b+c):

    a. Use of oral, injected or implanted hormonal methods of contraception;
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;

    OR

    d. Total abstinence;

    OR

    e. Male/female sterilization.

Women are considered not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (post-menopausal) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

14. Male subjects whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment.

6 Treatment

Everolimus will be administered orally in the morning consistently either with or without food. Starting dose will be 10 mg Daily and will be adjusted either up or down by 2.5 mg at 2 week intervals to attain a trough concentration of 5-15 ng/ml.

All dosages prescribed and dispensed to the subject and all dose changes during the study will be recorded.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the subject. The storage conditions for everolimus will be described on the medication label.

Everolimus is supplied by Novartis. Everolimus is formulated as tablets for oral administration of 1mg, 2.5mg, 5mg, 10mg strength. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

6.1 Study Treatment

6.1.1 Treatment assignment

As this is an open-label single-arm trial, all subjects will be assigned to the same treatment group.

6.1.2 Dosing regimen

The investigator will promote compliance by instructing the subject to take the study drug exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject will be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

6.1.3 Medication Administration Instructions

Everolimus should be administered orally once daily at the same time every day, either consistently with or consistently without food.

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For subjects unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

If vomiting occurs, no attempt should be made to replace the vomited dose. Subjects will be instructed that if they miss a dose on one day, they must not take any extra dose, but instead should immediately contact the study center as soon as possible to ask for advice.

6.2 Dose modifications

6.2.1 Dosing modifications

For subjects who develop intolerable AEs, dose reductions will be made to allow the subject to continue the study treatment as long as the everolimus trough concentration remains within the 5-15 ng/ml level. Dose reductions will occur at 2.5 mg intervals with a minimum dose of 2.5 mg daily allowable for continuation in the study. The CTCAE Version 4.0 will be used for the severity grading of adverse events. Tables 6-1 and 6-2 list the dosing modificaitons that will occur for everolimus-related non-hematologic and hematologic toxicities.

Table 6-1 Dosing guidelines for everolimus-related non-hematologic toxicities

Toxicity	Action
Non-Infectious Pneumonitis	Please refer to Table 6-3.
Diagnosis of HBV or HCV	Discontinue everolimus. Withdraw from study.
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower, if available.
AST or ALT elevation Grade 4 (> 20 x ULN)	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at one dose level lower. If resolution takes > 7 days, discontinue everolimus.
Recurrence of grade 4 after dose reduction or toxicity requiring everolimus interruption for > 28 days	Discontinue everolimus.
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 6.2.2.5)	Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower, if available. Subjects will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days.
Any other non-hematologic grade 4 AE	Hold everolimus until recovery to grade ≤ 1 or baseline value Reintroduce everolimus at one dose level lower, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue everolimus.
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 2.5 mg daily. Below this level, everolimus must be discontinued.
Recurrence of grade 4 after dose reduction	Discontinue everolimus.
Any non-hematologic toxicity requiring everolimus interruption for > 28 days	Discontinue everolimus.

Table 6-2 Dosing guidelines for everolimus-related hematologic toxicities

Toxicity	Action
Grade 2 thrombocytopenia (platelets <75, ≥ 50x10^9/L)	No action.
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets < 25 x10^9/L)	Interrupt everolimus until recovery to grade ≤ 1. Then reintroduce everolimus at one dose level lower, if available.
Grade 3 neutropenia (neutrophil <1, ≥0.5 x10^9/L) or anemia (hemoglobin <8.0 g/dL)	Interrupt everolimus until resolution to grade ≤1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce everolimus at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 neutropenia or anemia	Interrupt everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce everolimus at one dose level lower, if available.*
Febrile neutropenia	Interrupt everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower, if available.*
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 2.5 mg daily. Below this level, everolimus must be discontinued.
*Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction	Discontinue everolimus.
*Any hematologic toxicity requiring everolimus interruption for > 28 days	Discontinue everolimus.

6.2.2 Management of specific toxicities

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.

Adverse events most frequently observed with everolimus are rash, stomatitis /oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

6.2.2.1 Management of infections

Everolimus has immunosuppressive properties and may predispose subjects to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and subjects should be aware of the increased risk of infection with everolimus. Treat pre-existing infections prior to starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

6.2.2.2 Management of skin toxicity

For subjects with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Subjects with grade 2 or higher toxicity may be treated with the following supportive measures at the discretion of the investigators: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

6.2.2.3 Management of stomatitis / oral mucositis / mouth ulcers

Subjects with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Subjects will be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to everolimus will be treated using local supportive care. (Investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis.)

The following paradigm will be applied for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day will be used until resolution.
2. For more severe toxicity (grade 2 in which case subjects have pain but are able to maintain adequate oral alimentation, or grade 3 in which case subjects cannot maintain adequate oral alimentation), topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®) will be prescribed.
3. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers and will be avoided.
4. Antifungal agents will be avoided unless a fungal infection is diagnosed. Topical antifungal agents are preferred if an infection is diagnosed.

6.2.2.4 Management of diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity will be treated with supportive care such as loperamide, initiated at the earliest onset (4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

6.2.2.5 Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia will take into account the pre-treatment status and dietary habits of the subject. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) will be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity

manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy will be determined for individual subjects based on their risk of cardiovascular complications of hyperlipidemia.

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose will be performed prior to the start of everolimus and optimal glycemic control will be achieved before starting a subject on everolimus. Mild (grade 1) fasting hyperglycemia (serum glucose < 160 mg/dL) may not need treatment. Subjects in this range will be instructed to modify their diet and lifestyle to lower glucose levels via recommendations of the American Diabetes Association. Subjects who are refractory to diet and lifestyle modifications and/or injectable medications depending on their concomitant health and/or medical status. Those with grades 3-4 fasting hyperglycemia (>250 mg/dL) will be hospitalized for treatment. Everolimus will be discontinued until the subject reaches a fasting glucose level < 160 mg/dL and the dose will be adjusted per section 6.2.1.

6.2.2.6 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- A diagnosis of non-infectious pneumonitis will be considered in subjects presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Subjects will be advised to report promptly any new or worsening respiratory symptoms.
- Subjects who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration at the discretion of the principle investigators.

Individuals participating in this trial will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. If non-infectious pneumonitis develops, the guidelines in Table 6-3 will be followed and the subject will be referred to a pulmonologist. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 6-3 Management of non-infectious pneumonitis

Worst grade pneumonitis	Required investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required.	No dose adjustment required. Initiate appropriate monitoring.
Grade 2	CT scan with lung windows. Consider pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of everolimus until symptoms improve to Grade ≤ 1. Re-initiate everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, including: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue everolimus.

6.3 Concomitant medications

Subjects will be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator will instruct the subject to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit will be reported on the CRF.

6.3.1 Permitted concomitant therapy

Any medication that is not know to affect the P450 and P-glycoprotein systems will be allowed.

6.3.1.1 Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall.

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor will be avoided.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors will be used with caution. If a subject requires co-administration of a moderate CYP3A4 inhibitor or PgP inhibitor, the dose of everolimus will be reduced. Additional dose reductions may be required to manage toxicities. If the inhibitor is discontinued, the everolimus dose will be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.
- Grapefruit and citrus juices affect P450 and PgP activity. Concomitant use will be avoided.
- Co-administration with strong inducers of CYP3A4 will be avoided. If a subject requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of everolimus up to twice the currently used daily dose will be considered. Enzyme induction usually occurs within 7-10 days; therefore everolimus dose will be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose may be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer. If the strong inducer is discontinued the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.
- Refer to Table 6-4 for a list of relevant inducers and inhibitors of CYP3A and Table 6-5 for a list of relevant substrates, inducers, and inhibitors of PgP.

Table 6-4 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone, efavirenz, nevirapine, topiramate, avasimibe, bosentan, etravirine, nafcillin, ritonavir, talviraline (not available in US market), tipranavir, amprenavir, aprepitant, armodafinil (R-modafinil), dexamethasone, nevirapine, prednisone, pleconaril (not available in US market), rufinamide
Inhibitors
Strong inhibitors: clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, tipranavir, elvitegravir, Posaconazole **Moderate inhibitors:** aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, grapefruit juice (citrus paradisi fruit juice), imatinib, tofisopam, verapamil, amprenavir, fosamprenavir, dronedarone

Table 6-5 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel
Inducers
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
amiodarone, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, ginkgo (ginkgo biloba), indinavir, itraconazole, , lopinavir, mibefradil, milk thistle (silybum marianum), nifedipine, nitrendipine, quercetin, quinidine, ranolazine, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, telmisartan, tipranavir, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

6.3.2 Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

6.3.3 Prohibited concomitant therapy

Anti-neoplastic therapies

Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents).

7 Visit schedule and assessments

Study flow and visit schedule

Table 7-1 Visit evaluation schedule

	*Screening**	*Baseline**	*2 Weeks****	*Monthly*	*Mid-Point*	*Termination*
Month	*0*	*0*	*0*	*1,2,4,5*	*3*	*6*
Examination	*X*					
Informed consent	*X*					
Medical History	*X*					
Inclusion/exclusion criteria	*X*					
Vital signs		*X*	*X*	*X*	*X*	*X*
Physical examination		*X*	*X*	*X*	*X*	*X*
3-D Photography		*X*			*X*	*X*
Everolimus level			*X*		*X*	*X*
*Laboratory tests***		*X*			*X*	*X*
Punch biopsy of cutaneous lesion		*X*			*X*	*X*

*Screening & Baseline visits may occur at the same time.

**Laboratory Tests = CBC, bilirubin, ALT, AST, INR, fasting triglycerides, fasting cholesterol level, creatinine, beta-hCG (when appropriate), VEGF-A, VEGF-D, s-VEGFR-1, sVEGFR-2, PIGF, c-Kit, collagen type IV

***Everolimus level to be performed at 2 weeks after initiation, 2 weeks after any dose change, and at the 3 & 6 month visits

7.1 Assessment types

7.1.1 Pregnancy and assessments of fertility

Serum pregnancy testing is required for all women of child-bearing potential (WOCBP) at screening, 3 months, and termination visits.

WOCBP, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:

- Total abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Sterilization: subject has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected, implanted or other hormonal methods of contraception. In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Sexually active males must use a condom during intercourse while taking the study drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Female partners of male subjects must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal

methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

7.1.2 Laboratory evaluations

Everolimus PK levels will be measured every 2 weeks after trial initiation until the target level of 5-15 ng/ml is reached. Once the target level is achieved, levels will be assessed again at the 3 month visit and at study termination (6 months) to verify compliance.

Complete blood counts, bilirubin level, ALT, AST, INR, beta-hCG (where appropriate), total cholesterol level, fasting triglycerides, fasting glucose, serum creatinine, VEGF-A, VEGF-D, sVEGFR-1, sVEGFR-2, PIGF, c-Kit, and collagen type IV will also be measured pre-treatment, at 3 months, and at study termination (6 months).

8 Safety monitoring and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

8.1 Adverse events

8.1.1 Definitions and reporting

Adverse events that begin or worsen after informed consent will be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the subject's CRF. Adverse event monitoring will be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) will be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom will be reported as a separate Adverse Event.

The occurrence of adverse events will be sought by non-directive questioning of the subject at each visit during the study. Adverse events also will be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event will be evaluated to determine:

1. The severity grade (CTCAE Version 4 Grade 1-4)
2. The duration (start and end dates or if continuing at the safety follow-up visit)
3. Its relationship to the study treatment (reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it will be followed until its resolution, and assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure. This information will be included in the subject informed consent and will be discussed with the subject during the study as needed.

Adverse event monitoring will be continued for at least 30 days following the last dose of study treatment.

8.1.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse Event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), will be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom will be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events will be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, the lab/test result will not be separately recorded as an additional event.

Laboratory abnormalities, that do not meet the definition of an Adverse Event, will not be reported as Adverse Events. A Grade 3 or 4 Adverse Event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

8.2 Serious Adverse Events

8.2.1 Definition

A serious adverse event is an undesirable sign, symptom or medical condition that:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition

- is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

8.2.2 Reporting

The principal investigator will report all Serious Adverse Events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

All events reported to the FDA by the investigator will be filed utilizing the Form FDA 3500A (MedWatch Form).

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until at least 30 days after the subject has stopped study treatment/participation, will be reported to Novartis within 24 hours of learning of its occurrence **(fax: 877-778-9739)**. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy will be reported within 5 working days.

Any SAEs experienced after this 30 days period will be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one will be reported separately as a new event. The end date of the first event will be provided.

The original copy of the SAE Report and the fax confirmation sheet will be kept by the investigators at the study site.

Follow-up information will be sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event will be reported as a follow-up to that event regardless of when it occurs. The follow-up information will describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Everolimus Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancy

Preclinical data regarding reproductive toxicity is described in the Investigator Brochure. The potential reproductive risk for humans is unknown. Women of childbearing potential will be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped.

To ensure subject safety, each pregnancy occurring while the subject is on study treatment will be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed for at least 12 months.

Pregnancy will be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up will be recorded on the same form and will include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on the SAE Report Form.

9 Statistical methods

Studies with everolimus in TSC associated SEGAs have shown a reduction of 50% of the volume of the target lesion in approximately 33% of subjects following 6 months of treatment. Response will therefore be defined as a reduction of at least 50% in the volume of the target lesion during the 6 month treatment period.

The natural history of NF-1 indicates a significantly low probability of spontaneous regression of lesions during the 6 month treatment period. The null hypothesis states 'The proportion of subjects who respond will be 0%', ie, no subjects with NF-1 will have spontaneous regression of at least 50% of the tumor surface volume of their cutaneous target lesion during the 6 month treatment period. The alternative hypothesis states 'the proportion of subjects who respond is greater than 0%' with response defined as a 50% reduction in the targeted cutaneous lesion's surface volume.

If 33% of subjects have a reduction of 50% of their targeted tumor surface volume at the 6 month endpoint, there is an 80% chance of finding that impact with 20 study subjects. Alternatively there is a 5% chance of finding a Type I error, ie, rate is set at 0.05.

10 Protocol amendments, or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at the study center. A copy of the written approval of the IRB will be provided to Novartis. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

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