NOVARTIS

Clinical Development

RAD001, everolimus

Clinical Trial Protocol CRAD001C1X01B / NCT02017860

An open-label, multi-center everolimus roll-over protocol for patients who have completed a previous Novartis-sponsored everolimus study and are judged by the investigator to benefit from continued everolimus treatment

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List of abbreviations

AE	Adverse event
AUC	Area under the drug plasma (serum/blood) concentration-time curve
BSC	Best supportive care
Cmax	Maximal drug blood concentration
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Event
DDI	Drug-drug interaction
DS&E	Drug Safety and Epidemiology
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IIT	Investigator initiated trial
IN	Investigator notification
IRB	Institutional review board
mTOR	mammalian target of rapamycin
NET	Neuroendocrine tumors
PgP	P-glycoprotein
PHI	Protected health information
PI	Principal investigator
pNET	Pancreatic neuroendocrine tumors
RAD001	Everolimus
REB	Research ethics board
RECIST	Response evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SEGA	Subependymal giant cell astrocytoma
Tmax	Time to reach the maximum drug blood concentration following drug administration
TSC	Tuberous sclerosis complex
VEGF	Vascular endothelial growth factor

Glossary of terms

Assessment	A procedure used to generate data required by the study
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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: every 28 days)
Dose level	The dose of drug given to the patient (total daily dose)
Enrollment	Point/time of patient 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 treatment	Drug whose properties are being tested in the study. 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
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Roll-over study	A roll-over study allows patients from multiple parent studies spanning multiple indications to continue to be treated within one study after the completion of the parent study(ies)
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (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.

Amendment 01 (30-Aug-2016)

Amendment rationale

The amendment provides latest guideline of follow up toxicities such as evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases. In addition, this amendment has been implemented to provide updated information as well as clarification of sections of the protocol where additional guidance was required.

Changes to the protocol

Section 1.2.1.2: Clinical experience language updated

Section 5.3: Updated contraception languagebased on new guidelines on pregnancy prevention.

Section 6.1: Definition of study treatment clarified. Relevant sections were also updated.

Section 6.3.2.1: New section added for drug-induced liver toxicity language.

Section 6.4: Added reference to IB for use concomitant medications.

Table 6-2: Updated inducers, and inhibitors of isoenzyme CYP3A based on IB update.

Table 6-3: Updated substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors based on IB update.

Section 6.4.2: Updated vaccination language based on IB update.

Section 7.1.4.1: Section name updated in addition to adding new language.

Section 7.1.5: Section name updated.

Section 7.1.6: Added Lost to follow up language.

Section 7.2.2: Updated pregnancy testing language.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Protocol summary:

Protocol number	CRAD001C1X01B
Title	An open label, multi-center everolimus roll-over protocol for patients who have completed a previous Novartis-sponsored everolimus study and are judged by the investigator to benefit from continued everolimus treatment.
Brief title	Study to collect and assess long-term safety of everolimus in patients who are on everolimus treatment in a Novartis-sponsored study and are benefiting from the treatment as judged by the investigator.
Sponsor and Clinical Phase	Novartis, II
Study type	Interventional
Purpose and rationale	The purpose of this study is to collect and assess long-term safety of everolimus in patients who are on everolimus treatment in a Novartis-sponsored study and are benefiting from the treatment as judged by the investigator.
Primary Objective(s) and Key Secondary Objective	To collect and assess long-term safety of everolimus of patients receiving everolimus in a Novartis-sponsored study which has reached its objectives and who are benefiting from treatment with everolimus.
Secondary Objectives	Not applicable
Study design	This is a multi-center, open label study to collect and assess long-term safety of everolimus in patients being treated in current Novartis-sponsored studies and who are benefiting from treatment with everolimus judged by the investigator. There will be no screening period for this study. Eligible patients are to be consented and can start their treatment with everolimus as soon as they enter the study. At least, patients must return to the study center on a yearly basis (± 3 months), but for resupply of study medication, the frequency of the receipt and dispensing must follow local practice (e.g., every 2 to 3 months). At this time the dose of everolimus is based on the investigator's judgment. Adverse events (AEs) will be collected continuously throughout the study. For the safe and effective use of everolimus, patient may return to the clinic at any given time following local practice. When AEs are observed, additional visits will be arranged by investigator's discretion. Patients will continue to be treated until they are no longer benefiting from everolimus as defined in the parent protocol (disease progression), develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue everolimus therapy or the patient dies, whichever comes first. A patient will reach the end of study when everolimus treatment is permanently discontinued and the end of treatment visit has been performed. All patients must be followed for AEs for 30 days after the last dose of everolimus. The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with everolimus, whichever comes first.
Population	Male and female patients, who are currently enrolled in a Novartis-sponsored everolimus study, are benefiting from treatment with everolimus and have fulfilled all their requirements in the parent study.
Inclusion criteria	Patient is currently enrolled in a Novartis- sponsored everolimus study, receiving everolimus and has fulfilled all their requirements in the parent study. Patient is currently benefiting from the treatment with everolimus, as determined by the guidelines of the parent protocol. Patient has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.
Exclusion criteria	Patient has been permanently discontinued from everolimus study treatment in the parent study due any reason.
Investigational and reference therapy	Everolimus, 2.5 – 10 mg/day.
Efficacy assessments	Not applicable

Safety assessments	Reported AEs will be collected continuously throughout the study. For the safe and effective use of everolimus, medical monitoring should be performed as clinically indicated at the physician's discretion.
Other assessments	Not applicable
Data analysis	Statistical analysis will be performed when all patients discontinued the trial or the 30-day safety follow-up was completed, whichever comes earlier. Those analyses results will be used to document the summary of the safety. Data will be used only for descriptive summary of patients remaining on drug.
Key words	Everolimus, roll-over study

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

The purpose of this study is to allow continued use of everolimus in patients who are currently receiving everolimus treatment in a Novartis-sponsored study that has reached its study objectives, are not progressing on the current study treatment as defined by the parent protocol and are unable to access everolimus treatment outside of a clinical study. The roll-over study is designed to accept patients with varied disease origins. Please refer to the parent protocol for the disease background information and rationale for use of everolimus in their individual indications. See also Section 1.2.1.2.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of everolimus (RAD001)

Everolimus is a proliferation signal inhibitor in the mammalian target of rapamycin (mTOR) drug class. The mTOR pathway activity is modulated by the PI3K/AKT pathway, a pathway known to be dysregulated in numerous human cancers.

Everolimus is being investigated as an anticancer agent based on its potential to act

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

At the cellular and molecular level, everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR, 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 (TSC). Mutations in these components or in phosphatase and tensin homolog, 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 (Cohen et al 2005).

The main known functions of mTOR include the following (Bjornsti and Houghton 2004):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels;
- Facilitating cell-cycle progression from G1-S phase in appropriate growth conditions;
- The PI3K/mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors;
- The mTOR pathway is involved in the production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation;
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including

the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

1.2.1.1 Non-clinical experience

For latest information on the pre-clinical pharmacology and toxicology of everolimus, please refer to the current Investigator's Brochure (IB).

1.2.1.2 Clinical experience

In oncology, everolimus has been in clinical development since 2002 for patients with various hematologic and non-hematologic malignancies; as a single agent or in combination with antitumor agents. Malignancies that are currently being evaluated in Novartis sponsored studies include the following: metastatic renal cell carcinoma, breast cancer, pancreatic neuroendocrine tumors (pNET/NET), diffuse large B cell lymphoma, and hepatocellular cancer. In addition, treatment of patients with TSC associated subependymal giant cell astrocytoma (SEGA), renal angiomyolipoma, and epilepsy are also being evaluated.

Phase I dose escalating studies, exploratory Phase I/II/III studies with everolimus as single agent or in combination with other anti-cancer agents, Phase II/III studies of everolimus in different indications, Phase III double-blind studies and Phase IV studies are contributing to the extensive clinical database.

Approximately 27,399 patients, (excluding those patients who received marketed Afinitor®/Votubia®, those on roll over studies as well as excluding investigator-sponsored studies) have been enrolled in studies with everolimus as of 31-Mar-2015.

Oncology

Everolimus was approved by FDA on 30-Mar-2009 under the trade name Afinitor® for the treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib. The European Commission (EC) approved Afinitor® on 03-Aug-2009 for the treatment of patients with advanced RCC, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy. As of 31-Mar-2015, Afinitor® has been approved in 121 countries worldwide including Japan for the treatment of patients with advanced RCC.

On 05-May-2011, FDA approved Afinitor® for the "treatment of progressive pNET in patients with unresectable, locally advanced or metastatic disease. Afinitor is not indicated for the treatment of patients with functional carcinoid tumors". The EC approved Afinitor® on 24-Aug-2011 for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors of pancreatic origin in adults with progressive disease. As of 31-Mar-2015, Afinitor® has been approved in >115 countries worldwide for the treatment of patients with pNET/neuroendocrine tumors. In Japan, Afinitor was approved in pNET in 2011 and approved in NET in 2016 based on the additional results from the study for patients with GI or lung NET.

On 20-Jul-2012, FDA approved Afinitor® for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. The EC approved Afinitor®

on 23-Jul-2012 for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. As of 31-Mar-2015, Afinitor® has been approved in >115 countries including Japan for the treatment of patients with advanced hormone receptor-positive, HER2-negative breast cancer.

Tuberous sclerosis complex

Afinitor® received accelerated approval from FDA on 29-Oct-2010 for the "treatment of patients with SEGA associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The EC granted conditional approval on 02-Sep-2011 for everolimus under the trade name Votubia® for the "treatment of patients aged 3 years and older with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. Afinitor® received accelerated approval from FDA on 26-Apr-2012 for the "treatment of adult patients with renal angiomyolipoma and TSC, not requiring immediate surgery

In Japan, Afinitor® was approved for adult patients with SEGA associated with TSC as well as AML associated with TSC.

For further details please refer to the current everolimus IB.

Pharmacokinetics

Everolimus is rapidly absorbed after oral administration, with a time to reach the maximum drug blood concentration (t_{max}) of 1-2 hours postdose. The extent of absorption is estimated at above 11%. The area under the blood concentration-time curve (AUC) is dose-proportional over the dose range of 5 to 70 mg tested while maximum drug blood concentration (C_{max}) appears to plateau at dose levels higher than 20 mg. The terminal half-life in cancer patients averaged 30 hours, which is similar to that in healthy subjects. A high-fat meal altered the absorption of everolimus with 1.3 hour delay in t_{max}, a 60% reduction in C_{max} and a 16% reduction in AUC. In whole blood, approximately 80% of everolimus is contained in red blood cells. Of the fraction of drug contained in plasma, 74% is protein-bound. The apparent distribution volume (Vz/F) after a single dose was 4.7 L/kg. Everolimus is eliminated by metabolism, mainly by hydroxylation, then excreted into the feces >80%.

Everolimus is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Everolimus is also a substrate of P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of systematically absorbed everolimus may be influenced by medicinal products that interact with CYP3A4 and/or P-glycoprotein. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6 substrates, potentially increasing the concentrations of medicinal products eliminated by these enzymes. In two phase III clinical trials in patients following kidney transplantation, strong inhibitors of CYP3A4 (azoles, antifungals, cyclosporine, erythromycin) have been shown to reduce the clearance of everolimus therapy thereby increasing everolimus blood levels. Similarly, Rifampin, a strong inducer of CYP3A4, increases the clearance of everolimus thereby reducing everolimus blood levels. Another drug-drug interaction study of everolimus administered with a sensitive CYP3A4 substrate midazolam showed that while everolimus did not influence the hepatic

metabolism of midazolam, it led to minor increases in bioavailability of midazolam likely due to influences of pre-systemic metabolism. Caution should be exercised when co-administering everolimus with CYP3A4 inhibitors, inducers, or substrates with a narrow therapeutic index.

Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition in a peripheral biomarker (S6 kinase inhibition in peripheral blood mononuclear cells) suggests that 5 to 10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition. Furthermore, molecular pharmacodynamic (MPD) studies using IHC in biopsied tumor tissue assessed the degree of inhibition and its duration (for p-S6, p-4E-BP1 and p-Akt expression) with the daily and weekly dosing. The pathologist was blinded for the biopsy sequence. There was almost complete inhibition of p-S6 at all doses and schedules studied (p=0.001). Preliminary results suggest a dose-related decrease in p-4E-BP1 and increase in p-Akt expression with maximal effect at 10 mg daily and ≥50 mg weekly.

For further details please refer to the current everolimus IB.

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to collect and assess long-term safety of everolimus in patients who are currently receiving everolimus treatment in a Novartis-sponsored study that has reached its study objectives, are not progressing on the current study treatment as defined by the parent protocol and are unable to access everolimus treatment outside of a clinical study. Parent studies eligible to participate in the roll-over study will be decided by Novartis. Investigator initiated trials (IITs) will not be included. The primary objective of the parent study must have been reached and the parent study must be in the process of being completed and reported.

Patients will continue to receive everolimus until one of the following occurs: no treatment benefit (disease progression) as defined in the parent protocol, unacceptable toxicity develops, consent withdrawal, protocol non-compliance, the investigator feels it is no longer in the patient's best interest to continue therapy, or the patient's death.

2.2 Rationale for the study design

This is a multi-center, open-label, phase II study to collect and assess long-term safety of everolimus for patients being treated in a current Novartis-sponsored study and who are benefiting from treatment with everolimus.

The study will not include a screening phase as patients will transfer directly from the parent studies and will commence treatment with everolimus as soon as they are consented and meet the inclusion criteria of this roll-over study protocol.

2.3 Rationale for dose and regimen selection

The selected doses and regimen will be based on the dose ranges and regimen available in the parent studies. Everolimus will be provided as 2.5 or 5 mg tablets to be administered using every day. See more details in Section 6.1.1.

2.4 Rationale for choice of combination drugs

Patients may be allowed to continue combination with everolimus in combination with other therapies if they are currently receiving the therapies on the parent protocol and are driving benefit judged by the investigator.

2.5 Rationale for choice of comparators drugs

Not applicable.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To collect and assess long term safety of everolimus	Frequency and nature of AEs	

4 Study design

4.1 Description of study design

This is a multi-center, open label study to collect and assess long-term safety of everolimus in patients currently being treated in a Novartis-sponsored Oncology CD & MA study, who are not progressing on the current study treatment as defined by the parent protocol and are unable to access everolimus treatment outside of a clinical study. Parent studies eligible to participate in the roll-over study will be decided by Novartis. Investigator initiated trials (IITs) will not be included.

There will be no screening period for this study. Eligible patients can start their treatment with everolimus as soon as they enter the study. All patients must report to the study site for their first visit and commence study participation. Patients must return to the study center at least on a yearly basis (± 3 months) for resupply of study medication. Limited drug dispensing information will be collected. The patient may return to the clinic at any given time as per standard of care or be treated by physician's recommendation, however at least one study visit every year will be scheduled and AEs reported at general medical care will be collected continuously throughout the study. When AEs are observed, additional visits will be arranged by investigator's discretion (see Section 6.3.2).

Patients entering the roll-over protocol should be followed at the investigator's discretion for known or clinically notable AEs that occur on everolimus treatment as described in the current version of the everolimus IB.

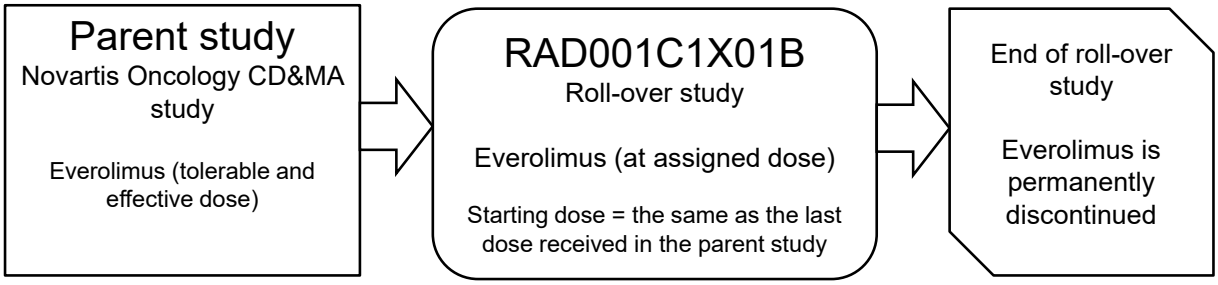
Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from their everolimus treatment as defined in the parent protocol (disease progression), they develop unacceptable toxicities, they withdraw consent, they are non-compliant to the protocol,

the investigator feels it is no longer in the patient's best interest to continue everolimus therapy or the patient dies, whichever comes first.

A patient will reach the end of study when everolimus treatment is permanently discontinued.

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with everolimus, whichever comes first.

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

Not applicable.

4.3 Definition of end of the study

The end of the study is defined as when the patient permanently discontinues treatment with everolimus and the end of treatment visit has been performed for each patient.

4.4 Early study termination

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with everolimus, whichever comes first.

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be informed as soon as possible and should stop taking study labeled drug. Assessments should be performed as described in Section 7.1.4 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient is currently enrolled in a Novartis-sponsored study, receiving everolimus and has fulfilled all their requirements in the parent study.
2. Patient is currently benefiting from the treatment with everolimus, as determined by the guidelines of the parent protocol.
3. Patient has demonstrated compliance, as assessed by the investigator, with the parent study protocol requirements.
4. Willingness and ability to comply with scheduled visits and treatment plans.
5. Written informed consent obtained prior to enrolling into the roll-over study.
    - If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has been permanently discontinued from everolimus study treatment in the parent study.
2. Sexually active males, unless they use a condom during intercourse while taking drug and for 8 weeks after stopping study medication. Males also should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
3. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 8 weeks after everolimus last dose. Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) 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
   Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have 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 sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

If a study patient or partner becomes pregnant or suspects being pregnant during the study or within 30 days after the last dose of everolimus, the investigator needs to be informed immediately and ongoing study treatment with everolimus has to be stopped immediately.

6 Treatment

6.1 Study treatment

For study treatment refer to everolimus plus combination drugs used in the parent study and for investigational treatment refer to everolimus.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Investigational treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
RAD001/everolimus	Tablet for oral use	2.5 – 10 mg/day	Daily

Everolimus will be provided as 2.5 mg or 5 mg tablets. The investigational treatment is to be stored in a secure locked area while under the responsibility of the investigator. The investigator should assess compliance of study drug at each patient visit (see Section 6.6.3.1). Receipt and dispensing of investigational drug must be recorded by an authorized person at the investigator's site (see Section 6.6.3.2).

At the time of transition to the roll-over study, the starting dose of everolimus should be the same as the last dose that was given in the parent study. Dose modification thereafter may be done at the discretion of the investigator based upon what is in the patient's best interest.

Patients will be instructed to take everolimus orally with a glass of water, once daily at the same time each day, either consistently with food or consistently without food. Dietary habits at the time of enrolling in the study from the parent study should be kept as consistent as possible throughout the study. The tablet should be swallowed as a whole and should not be chewed or crushed.

Please refer to the current everolimus IB and Section 6.3 for further important information on potential dosing precautions regarding concomitant medication interaction with cytochrome p450, p-glycoprotein, and CYP3A4 and the recommended dosing guidance.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

Please refer to the Section 6.3.1.

6.1.5 Treatment duration

Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from their everolimus treatment as defined in the parent protocol (disease progression), they develop unacceptable toxicities, they withdraw consent, they are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue everolimus therapy or the patient dies, whichever comes first. A patient will reach the end of the roll-over study when everolimus treatment is permanently discontinued.

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with everolimus, whichever comes first.

6.1.6 Other study treatment

Please refer to the parent protocol and Package Insert for treatment, management of toxicities and dose modifications.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modifications and dose delay

Patients will begin the roll-over study at the same dose as the last dose administered in the parent protocol. Dose adjustments are permitted to allow the patient to continue the study treatment at the investigator's discretion. The same dose modifications as followed in the parent protocol may apply at the investigator's discretion, but the dose of everolimus will not be over 10 mg/day.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, should be followed up at least once a week (or more frequently if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary. Patients must be followed serious AEs for 30 days after the last dose of everolimus.

6.3.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.3.3 Anticipated risks and safety concerns of everolimus

It is anticipated that the patients entering the roll-over protocol have tolerated everolimus treatment and are anticipated to benefit from continued treatment.

Guidelines and recommendations for the management of specific everolimus study drug induced toxicities (hyperglycemia, hyperlipidemia, stomatitis, infectious pneumonitis, reactivation of Hepatitis B and C) are provided in the parent protocol and the current everolimus IB.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

In general, concomitant medications/therapies deemed necessary for the supportive care of the patient is permitted.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of study drug to half the currently used dose. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the study drug dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.
- Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.
- Co-administration with strong inducers of CYP3A4 should be avoided. If a patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of study drug up to twice the currently used daily dose should be considered, 5mg increments. Enzyme induction usually occurs within 7-10 days; therefore study drug dose should 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 can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer.
- This dose adjustment of study drug is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the study drug dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to Table 6-2 listing relevant inducers and inhibitors of CYP3A and to Table 6-3 for a list of relevant substrates, inducers, and inhibitors of PgP. Please refer to the most recent Investigator's Brochure for a complete list.

Table 6-2 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
Strong inducers: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum) **Moderate inducers:** bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir **Weak inducers:** amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone] , vinblastine
Inhibitors
Strong inhibitors: **boceprevir**, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole (Krishna et al 2009), ritonavir, saquinavir, **telaprevir**, telithromycin, tipranavir, troleandamycin, voriconazole **Moderate inhibitors:** Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib, schisandra sphenanthera, tofisopam, verapamil

Table 6-3 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel, talinolol, everolimus
Inducers
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated 29-Oct-2012 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.

Vaccinations

The use of live vaccines and close contact with those who have received 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.

For further details please refer to the current everolimus IB.

6.4.3 Prohibited concomitant therapy

Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents) other than everolimus is not permitted until disease progression is documented and everolimus is permanently discontinued.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled in the roll-over study and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. .

Additionally an electronic Case Report Form (eCRF) will be completed that identifies the patient by gender and date of birth and previous study, site/center and subject number.

6.5.2 Treatment assignment or randomization

All consented patients who meet all inclusion criteria and none of the exclusion criteria are eligible to receive everolimus.

6.5.3 Treatment blinding

Not applicable.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All everolimus dosages prescribed to the patient and all dose changes during the study must be recorded on the Everolimus Dosage Administration Record eCRF.

Table 6-4 Preparation and dispensing

Investigational treatments	Dispensing	Preparation
Everolimus	Blister packed tablets (2.5 – 5 mg) including instructions for administration will be dispensed by study personnel on an outpatient basis. Patients will be provided with an adequate supply of everolimus for self-administration at home until at least their next scheduled study visit. Dispensing of investigational drug must be managed regularly according to local practice (e.g., every 2 to 3 months).	Not applicable

6.6.1 Study drug packaging and labeling

Everolimus printed description on patient kit box will be in Japanese and comply with the legal requirements of Japan. They will include storage conditions for the drug but no information about the patient.

Everolimus for the roll-over study can be provided where appropriate as investigational medical products, packed under the responsibility of Novartis Drug Supply Management in Japan.

The remained study drugs of the parent study which satisfies the legal requirements and no change in the description on patient kit box can be used for this roll-over study. More details can be found in the study drug manual of CRAD001C1X01B.

Table 6-5 Packaging and labeling

Investigational treatment	Packaging	Labeling (the printed description on patient kit's box)
Everolimus	Tablets in blisters	As per local requirements

6.6.2 Drug supply and storage

Everolimus must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, everolimus should be stored according to the instructions specified on the drug labels and in the current everolimus IB.

Table 6-6 Supply and storage of Investigational treatments

Investigational treatments	Supply	Storage
Everolimus	Local clinical study supply (open label) supplied by Novartis	Refer to everolimus printed description on patient kit box

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of everolimus in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused everolimus, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused everolimus, packaging, the patient kit's box, and a copy of the completed drug accountability log to the Novartis monitor.

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. Patients must return to the study center at least yearly (± 3 months) for resupply of study medication.

The table indicates which assessments produce data to be entered into the clinical database (D) or documented at the site level in the source documents (S) ("Category" column).

Table 7-1 Visit evaluation schedule

	Category	Protocol Reference Section 7.2	Enrollment	Annual Visits during treatment phase (± 3 months visits during treatment phase)				End of study treatment (EoT)	30 day safety follow-up post last dose of study drug
Visit Number			**1**	**2**	**3**	**4**	**5**	**777**	
Demographic: Patients' previous study, site, subject number, race, gender, date of birth,	D	7.1.1.3	x						
Informed consent	D	7.1.1	x						
Inclusion/exclusion criteria	D	5.2 / 5.3	x						
Serum pregnancy testing	S	7.2.2	x					x	
Urine pregnancy testing	S	7.2.2		monthly					
AEs	D	8.1	x	Continuous					
Everolimus dosing administration	D	6.1.1	x	Continuous				x	
End of study treatment	D	7.1.4						x	

7.1.1 Enroll visit

There will be no screening period for this study. At the enrollment visit, the patient will need to complete a written informed consent. Once consented, patients will be evaluated for eligibility via the inclusion and exclusion criteria.

7.1.1.1 Eligibility screening

Not applicable.

7.1.1.2 Information to be collected on screening failures

Not applicable.

7.1.1.3 Patient demographics and other baseline characteristics

For patients who are eligible to participate in this roll over study, an eCRF will be completed that identifies the patients' race, gender, data of birth and previous study, site/center and subject number.

7.1.2 Run-in period

Not applicable.

7.1.3 Treatment period

The starting dose of everolimus on this roll-over protocol should be the same dose as that which the patient was receiving in the parent study at roll over.

At least, patients must return to the study center on a yearly basis (± 3 months), but for resupply of study medication, the frequency of the receipt and dispensing must follow local practice (e.g., every 2 to 3 months). At this time the dose of everolimus is based on the investigator's judgment.

Patient whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, should be followed up at least once a week (or more frequently if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

The study is expected to remain open for 5 years or until such time that enrolled patients no longer need treatment with everolimus, whichever comes first.

7.1.4 End of treatment visit including study completion and premature withdrawal

Patients will continue to be treated until they are no longer benefiting from everolimus treatment, develop unacceptable toxicities, withdraw consent, are non-compliant to the protocol, or the patient dies, whichever comes first.

At the time the patient discontinues study treatment, a visit should be scheduled as soon as possible, at which time the End of Treatment visit will be performed. End of Treatment information will be completed in the eCRF giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for the required safety evaluation during the 30 days after the last dose of everolimus.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the appropriate eCRF page.

A patient will reach the end of study when everolimus treatment is permanently discontinued and there will be **no** further follow-up study visits. Thirty-day safety follow-up could be done via a phone contact.

7.1.4.1 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Everolimus must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

Patients may be withdrawn from the study if any of the following occur:

- Death
- Lost to follow-up
- Staying in the study would be harmful
- Patient/guardian decision
- Physician decision
- Non-compliance to protocol requirements
- Protocol deviation
- Pregnancy
- Study terminated by sponsor
- Unsatisfactory therapeutic effect

7.1.4.2 Replacement policy

Not applicable.

7.1.5 Follow up for safety evaluations

All patients must be followed up for safety evaluations for 30 days after the last dose of everolimus. At the end of this period, the investigator should contact the patient to inquire about any AE observed during this period. This could be done via a phone contact. Following this there are **no** further follow-up study visits.

7.1.6 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Not applicable.

7.2.2 Safety and tolerability assessments

Safety will be monitored by collecting AEs throughout the study on a continuous basis. See Section 8.

Women of child-bearing potential must complete the following pregnancy tests:

- Baseline/Enrollment - serum pregnancy test done locally
- Every 4 weeks during treatment - urine pregnancy test can be performed at patient's home.
- End of Treatment visit - serum pregnancy test done locally

Women of child-bearing potential who administer urine pregnancy testing at home should complete a simple diary with the dates and the outcome of the urine pregnancy test while on study treatment. In case of a positive pregnancy test, the instructions in Section 8.4 should be followed.

7.2.3 Pharmacokinetics

Not applicable.

7.2.4 Biomarkers

Not applicable.

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

AEs that begin or worsen after informed consent should be recorded in the AEs eCRF. AE monitoring should be continued for at least 30 days after the last dose of everolimus. AEs (including lab abnormalities that constitute AEs) should 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 should be reported as a separate AE.

AEs will be assessed according to the Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected in the End of Treatment eCRF page.

The occurrence of AEs should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. AEs also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates or Ongoing at End of Study)
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, concomitant medication taken, non-drug therapy given, hospitalizaion)
5. Whether it is serious, where a SAE is defined as in Section 8.2.1

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the AE eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method [for example, as per Response evaluation Criteria in Solid Tumors (RECIST) criteria for solid tumors or as per Cheson's guidelines for hematological malignancies], should not be reported as a SAE.

AEs separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AEs eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should 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 AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an AE, should not be reported as AEs. A Grade 3 or 4 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 in which case the lab abnormality would still, by definition, be an AE and must be reported as such.

8.1.3 AEs of special interest

The treating doctor should be aware of the important potential risks of everolimus as reported in the current IB. In addition, the treating doctor should report any events noted below as AEs which are being closely monitored by safety to rule out causality:

Refer to preclinical toxicity and or clinical data found in the current everolimus IB.

In addition to all serious AEs reported on a continuous basis throughout the study, the investigator should use the SAE form to report the following medically significant potential risks:

- Postnatal development toxicity
- Pregnant or breast-feeding women
- Intestinal obstruction /ileus
- Male infertility

- Pancreatitis
- Cholelithiasis
- Muscle-wasting/Muscle-loss

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Note that hospitalizations for the following reasons should not be reported as SAEs:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a SAE

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must 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 should be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in Japanese, and send the completed, signed form by fax within 24 hours to the Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form 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 should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the current IB or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, a Novartis DS&E department 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 Emergency unblinding of treatment assignment

Not applicable.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should 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.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Novartis DS&E. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Preclinical data regarding reproductive toxicity is described in the most recent IB. The potential reproductive risk for humans is unknown. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IB. Additional safety information collected between IB updates will be communicated in the form of IN. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel [or designated contract research organization (CRO)] will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that everolimus is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (ICF) (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of AEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator (PI) is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Statistical analysis will be performed when all patients discontinued the trial or the 30-day safety follow-up was completed, whichever comes earlier. Those analyses results will be used to document the summary of the safety.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose (partial or complete) of everolimus. The FAS will be used for all listings of raw data.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose (partial or complete) of everolimus, and have at least one valid post-baseline safety assessment. The statement that a patient had no AEs (on the AEs CRF) constitutes a valid safety assessment.

10.2 Patient demographics/other baseline characteristics

Patient demographics and baseline characteristics will be listed by patient.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Everolimus dose administration will be listed by patient.

10.4 Primary objective

Primary objective of this trial is to collect and assess the long-term safety everolimus in patients who are currently receiving treatment in the parent study and who are benefiting from treatment with everolimus.

10.4.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used.

The overall observation period will be divided into two mutually exclusive segments:

1. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
2. post-treatment period: starting at day 30 after last dose of study medication.

10.4.2 Adverse events (AEs)

Summary tables for AEs have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the post-treatment periods) will be listed and those collected during the post-treatment period are to be flagged.

The incidence of AEs (new or worsening from baseline) will be summarized by system organ class and preferred term, severity (based on CTCAE grades), type of AE and relation to study treatment.

Deaths reportable as SAEs and non-fatal serious AEs will be listed by patient.

Specific safety event categories will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s).

10.5 Sample size calculation

No formal sample size calculation is required for this trial since only patients who are still on treatment in the parent study will be enrolled in this trial.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the

duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in the clinical study agreement.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For eCRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed ICFs and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13 References (available upon request)

Bjornsti MA, Houghton PJ (2004) The TOR Pathway: A target for Cancer therapy. Nat Rev Cancer; 4(5):335-48.

Boulay A, Lane HA (2007) The mammalian target of rapamycin kinase and tumor growth inhibition. Recent Results Cancer Res. 2007;172:99-124.

Cohen HT, McGovern FJ (2005) Renal Cell Carcinoma. N Engl J Med; 353(23):2477-90.

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