NOVARTIS

Clinical Development

Afinitor® (everolimus)

Oncology Clinical Protocol CRAD001M2401 / NCT03525834

Phase IV, single arm study of safety and efficacy of everolimus in Chinese adults with Tuberous Sclerosis Complex who have renal angiomyolipoma not requiring immediate surgery

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List of abbreviations

AE	Adverse Event
ACE	Angiotensin converting enzyme
ADL	Activities of daily living
ADR	Adverse drug reaction
AESI	Adverse events of special interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AACR	American Association for Cancer Research
AML	Angiomyolipoma
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under curve
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin (Vaccine)
b.i.d.	*bis in diem*/twice a day
BOR	Best overall response
BUN	Blood urea nitrogen
CBR	Clinical benefit rate
CFDA	Chinese Food and Drug Administration
CPK	Creatine phosphokinase
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed Tomography
CYP3A4	Cytochrom P450 3A4
DDI	Drug Drug Interaction
DDS	Dose Determining Set
DNA	Deoxyribonucleic acid
DOR	Duration of response
DLCO	Diffusing capacity factor of the lung for carbon monoxide
DLT	Dose limiting toxicity
DM	Diabetes Mellitus
EC	European Commission
ECG	Electrocardiogram
EOT	End of treatment
ESRD	End-stage renal disease
FAS	Full Analysis Set
FDA	Food and drug administration
FEV1	Forced expiratory volume per second
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HBcAb	Hepatitis B virus core antibody

[redacted]

HBcAg	Hepatitis B virus core antigen
HBsAb	Hepatitis B virus surface antibody
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2-	human epidermal growth factor receptor 2 negative
HIF-1	Hypoxy induced factor
HIV	Human Immunodeficiency Virus
HR+	Hormone receptor-positive
HRCT	High resolution computed tomography
HUVECS	Human umbilical vein endothelial cells
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
LAM	Lymphangioleiomyomatosis
NCI	National Cancer Institute
NDA	New drug application
NMPA	National Medical Products Administration
MRI	Magnetic Resonance Imaging
mTOR	Mammalian target of rapamycin
o.d.	*omnia die*/once a day
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression free survival
PFT	Pulmonary function test
PgP	P-glycoprotein
PI3K/AKT	Phosphoinositide 3-kinase/protein kinase
PJP	Pneumocystis jirovecii pneumonia
PNET	Pancreatic neuroendocrine tumor
p.o.	Per os/by mouth/orally
PPS	Per-Protocol Set
PR	Partial response
PTEN	Phosphatase and tensin homolog
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Stable Disease
SEGA	Subependymal Giant Cell Astrocytoma
SOP	Standard Operating Procedure
TSC	Tuberous Sclerosis Complex
TTR	Time to response
ULN	Upper limit of normal (range)

[redacted]

VEGF-D	Vascular endothelial growth factor-D
WBC	White blood cell count
WHO	World Health Organisation

[redacted]

Protocol summary:

Title	Phase IV, single arm study of safety and efficacy of everolimus in Chinese adults with Tuberous Sclerosis Complex who have renal angiomyolipoma not requiring immediate surgery
Brief title	Study of safety and efficacy of everolimus in adult Chinese Tuberous Sclerosis patients who have renal angiomyolipoma not requiring immediate surgery
Sponsor and Clinical Phase	Novartis Pharma AG, Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the safety and efficacy of Afinitor® in Chinese patients with renal angiomyolipoma associated with TSC. The study will evaluate the safety and anti-tumor activity of Afinitor® given at a dose of 10 mg per day.
Primary Objective	To evaluate the safety of Afinitor® in Chinese adults with TSC-renal AML not requiring immediate surgery by determining the incidence of adverse events and laboratory abnormalities within 48 weeks of treatment.
Secondary Objective	To evaluate the efficacy of Afinitor® in Chinese adults with TSC-renal AML not requiring immediate surgery as assessed by AML response and progression rates and renal function change from baseline in 12 weeks intervals up to 48 weeks.
Study design	Open label, single arm, multi-center phase IV post approval commitment study (PAC) of treatment with one daily oral dose of 10 mg everolimus (Afinitor®) for 48 weeks.
Population	The study patient population consists of 40 male or female adult patients (18 years of age or older) who have been diagnosed with renal AML associated with TSC not requiring immediate surgery.
Inclusion criteria	● Eligible for treatment with everolimus as per the locally approved label. ● Presence of at least one AML ≥ 3 cm in its longest diameter using CT or MRI.
Exclusion criteria	● AML related bleeding or embolization during the 6 months prior to enrollment. ● History of myocardial infarction, angina or stroke related to atherosclerosis. ● Impaired lung function ● Significant hematological or hepatic abnormality (e.g. hemoglobin ≤9g/dL, platelets < 100×10^9/L, or absolute neutrophil count (ANC) < 1.5×10^9/L without supportive treatment of hematopoietic growth factor, transaminase levels > 2.5× the upper limit of normal (ULN), serum bilirubin > 2 × ULN). ● Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus). ● Fasting serum cholesterol > 300 mg/dL (or > 7.75 mmol/L) AND fasting triglycerides > 2.5 × ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication. ● Inadequate renal function: Serum creatinine > 1.5 × ULN. ● Any severe and/or uncontrolled medical conditions
Investigational and reference therapy	10 mg RAD001 (everolimus) once daily Patients with impaired liver function ● Child-Pugh grade A: 7.5 mg RAD001 (everolimus) once daily ● Child-Pugh grade B: 5.0 mg RAD001 (everolimus) once daily
Efficacy assessments	● Renal angiomyolipoma lesion volume as assessed by kidney CT/MRI scans at Screening, 12, 24, 48 weeks, and End of Treatment. ● Blood chemistry and urinalysis clinical laboratory assessments at Screening, 4, 12, 24, 48 weeks, and End of Treatment.

Safety assessments	● Incidence of adverse events during treatment until 30 days after End of Treatment. ● Hematology, blood chemistry, and urinalysis clinical laboratory assessments at Screening, 4, 12, 24, 48 weeks, and End of Treatment.
Other assessments	● WHO performance status at Screening, 4, 12, 24, 48 weeks, and End of Treatment. ● If indicated, photographic skin lesion assessment at Screening, 12, 24, 48 weeks, and End of Treatment. ● If indicated chest CT scans at Screening, 12, 24, 48 weeks, and End of Treatment. ● If indicated brain MRI/CT scans at 12, 24, 48 weeks, and End of Treatment. ● If indicated coagulation test at 4, 12, 24, 48 weeks, and End of Treatment. ● For patients with LAM: pulmonary function test and blood gas analysis at 12, 24, 48 weeks, and End of Treatment. ● For female patients of child bearing potential urine pregnancy tests from treatment Day 1 every 4 weeks until End of Treatment.
Data analysis	**Analysis population** The Full Analysis Set (FAS) comprises all patients who received at least one dose of study treatment. The Safety Set comprises all patients who received at least one dose of study treatment. The Safety set and FAS are identical in this study, and will be used for all analysis. **Safety analysis (primary objective)** Safety data including adverse events, laboratory abnormalities, and vital signs will be summarized and listed. The incidence of treatment-emergent adverse events (new or worsening from screening) will be summarized by MedDRA system organ class and/or preferred term, severity (based on CTCAE grades), seriousness, and relation to study treatment. All deaths (on-treatment and post-treatment) will be summarized. Laboratory values will be graded by CTCAE v4.03. Shift tables to compare screening to the worst on-treatment value will be presented. **Efficacy analysis (secondary objective)** AML response and progression rates, and renal function change from baseline (using the calculated creatinine clearance and NCI CTCAE grade 3/4 serum creatinine) will be summarized and listed. **Rationale for Sample Size** Approximately 40 patients will be enrolled to meet the NMPA post approval requirements. The sample size is based on feasibility; there is no hypothesis testing and statistical power consideration.
Key words	Tuberous Sclerosis Complex, TSC, angiomyolipoma, AML, Afinitor®, everolimus

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Amendment 2 (06-Dec-2019)

Amendment rationale

At the time of this amendment study enrollment was completed with 40 patients enrolled and treated. Currently all 40 patients are on treatment.

The reason for this protocol amendment is to eliminate the interim analysis.

The intent of the interim analysis was to use the limited available data from CRAD001M2401 for the Chinese Afinitor® license renewal package which was planned at the end of 2020. However, due to swift enrollment (12m actual vs 24m planned) the final analysis will be delivered in time to support the Afinitor® license renewal for the TSC associated renal AML indication thus eliminating the need for the interim analysis.

The protocol also describes a cut-off date for the interim analysis and a submission date for the Afinitor® license renewal, which under new circumstances are not being pursued. Therefore this information will be removed from the protocol.

In addition, some clarifications will be made in the visit evaluation schedule (VES) table and the patient re-screening section.

Major change

1. Elimination of the interim analysis

Minor changes

1. New subject number will be assigned to patients that are re-screened
2. HIV history is sourced documented. Table 7-1 is updated with appropriate category "S"
3. TSC diagnosis has been added to Table 7-1
4. Unscheduled ECGs have been added to Table 7-1
5. The appropriate category "D", is now assigned to all imaging assessments
6. Protocol reference hyperlinks will be added to the VES Table 7-1 so the reader can link to specific assessments described in Table 7-1
7. Within several sections. Chinese Food and Drug Administration (CFDA) has been replaced with NMPA (National Medical Products Administration), which is the new name for the Chinese Health Authority

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 4.2 Timing of Interim Analysis: entire section removed describing an interim analysis
- Section 6.4.1 Statement added, "If a patient fails screening and is re-screened a new 7 digit subject number will be assigned".
- Table 7-1 changes to the VES table include; protocol reference hyperlinks added to each assessment, unscheduled ECGs added, TSC diagnosis added, HIV history data source

[redacted]

updated to source, visit numbers added to efficacy follow up visits, imaging assessments data source updated to documented in database "D".

- Section 7.1.2 sub section "Rescreening" paragraph 2 updated to state "In this case the Subject Number assigned to the patient will not be used and the patient will be assigned a new 7 digit subject number. If the patient has been enrolled and treated, re-screening of the patient is not allowed."
- Section 10 entire section updated to state the following: One safety and efficacy analysis (Final Analysis) will be conducted on all patients after they complete their treatment and efficacy follow-up (after 48 weeks of treatment or earlier).
- Section 10.7 Interim analysis: This section now updated to state the following:
- Final Analysis
    - The final analysis will be performed after all patients have completed Week 48 (or discontinued earlier but were followed up for efficacy up to Week 48) and their safety follow-up visit.

IRBs/IECs

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.

The changes herein do not affect the Informed Consent. The informed Consent will not be updated.

[redacted]

Amendment 1 (24-Apr-2018)

Amendment rationale

No patients have yet been enrolled and no patients are planned to be enrolled until after this amendment is approved and in place. The changes identified in this protocol amendment address the omission of an important laboratory parameter and include clarifications of instructions and corrections of typographical errors. Furthermore the language concerning withdrawal of consent was aligned with Novartis' latest guidelines.

Protocol amendment 1 to this study has been prepared for the following reasons:

Minor changes

1. To add fasting serum cholesterol to the parameters to be tested in all laboratory biochemistry assessments of the study. The serum cholesterol value is required to confirm exclusion criteria #10. Furthermore, elevated serum cholesterol (hypercholesterolemia) is a very common adverse drug reaction to everolimus treatment and should be monitored throughout the study.
2. To reflect the patient's legal rights regarding their data and samples collected during the study when they discontinue or withdraw consent.
3. To add clarification which radiological imaging modalities for brain, chest, abdomen, and pelvis are preferred and accepted.
4. To add clarification that for coagulation tests either prothrombin time (PT) or international normalized ratio (INR) should be determined. Both tests are not required.
5. To add clarification that a serum pregnancy test is not required on study Day 1 if it was completed within 28 days prior to Day 1. In this case a urine pregnancy test is sufficient on Day 1.
6. To add clarification that the safety follow-up visit has to be done 30 days after last dose of everolimus with an allowed window of +7 days. The visit should not be done sooner.
7. To add clarification that results of serum pregnancy tests will be recorded in the database of the assigned central lab vendor.
8. To add clarification that reasons why a patient is not eligible for enrollment into the study are to be recorded on the disposition CRF and not the screening CRF.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Minor changes

- Changes due to the addition of the serum cholesterol test to all lab biochemistry evaluations:
  - Table 7-5
- Changes to reflect the patient's legal rights regarding their data and samples collected during the study when they discontinue or withdraw consent:
  - Section 7.1.5

[redacted]

- Changes due to clarification of preferred and allowed radiological imaging modalities:
  - Section 4.1, Section 7.2.1, Table 7-1, Table 7-3
- Changes due to clarification of requirements of coagulation test:
  - Section 7.2.2.5.4
- Changes due to clarification of requirements of serum pregnancy test on study Day 1:
  - Sections 4.1, 7.2.2.5
- Changes due to clarification of timing of the safety follow-up visit:
  - Section 4.1, Table 7-1
- Changes due to clarification of recording of serum pregnancy test results:
  - Sections 7.1.2.3, 7.2.2.5.5
- Changes due to clarification of CRF for recording of screening failure reasons:
  - Section 6.4.1

IRBs/IECs

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

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

1 Background

1.1 Overview of Tuberous Sclerosis Complex (TSC) and renal Angiomyolipoma (AML)

Tuberous Sclerosis Complex (TSC) is an autosomal dominant genetic disorder caused by inactivating mutations in the tuberous sclerosis complex tumor suppressor genes, *TSC1* or *TSC2*, affecting tuberin and hamartin respectively. The results of second somatic mutation in the heterozygous background include benign, highly vascular, hamartomatous growths. Lesions occur in the brain, kidneys, heart, liver, lungs and skin, and phenotypically can manifest with renal and/or pulmonary complications, autism, mental retardation and epilepsy (Gomez 1999, Astrinidis 2005, Inoki 2005, Kwiatkowski 2005).

Angiomyolipomata are the most common renal manifestation of TSC (Gomez et al 1999) developing during later childhood and adolescence. As the name implies, they are composed of blood vessels, smooth muscle and adipose tissue. The majority of adults affected by the disease have multiple bilateral lesions which are usually asymptomatic but can cause life-threatening hemorrhage or impaired renal function. Angiomyolipomata can occur in the liver but these are rarely of clinical significance (Yates 2006). Renal cysts are also a common finding (Gomez et al 1999). They are usually asymptomatic except in the rare case of patients with both TSC and polycystic kidney disease owing to contiguous deletions of the *TSC2* and *PKD1* genes who usually present with severe early onset renal cystic disease and progress to end-stage renal failure by early adult life (Sampson et al 1997). Patients with TSC appear to be at increased risk of renal cell carcinoma, estimated at 1-3% (Nelson and Sanda 2002).

There are two morbidities associated with renal angiomyolipomata. The first and more dramatic is Wunderlich syndrome (Chesa Ponce et al 1995), a retro-peritoneal hemorrhage originating in the angiomyolipoma. As they enlarge, angiomyolipomata frequently develop both micro- and macro-aneurysms which can rupture (Adler 1984, Bissler 2002). Patients with this sudden, painful, and often life-threatening event are most often first seen in the emergency department (Bissler and Kingswood 2004). It was estimated that up to 20% of patients with such hemorrhages present in shock (Pode et al 1985). With such a presentation, the treatment may be a total nephrectomy, and this approach complicates the patient's long-term care. Angiomyolipomata associated with TSC are usually bilateral and a nephrectomy would result in a significant loss of functional renal tissue, thus hastening the need for renal replacement therapy (Bissler and Kingswood 2004). A population study suggests that the cumulative risk of a hemorrhage is 18% for females and 8% for males (Webb et al 1994). However, among a clinic population of approximately 310 adult and pediatric TSC patients in Cincinnati, only nine cases of hemorrhage (3%) were observed (Bissler and Kingswood 2004). This difference may be, at least in part, due to an aggressive embolization program, population age differences or length of follow-up. Angiomyolipomata appear to grow over time, and there is an association between lesion size and hemorrhage (Steiner 1993, Dickinson 1998).

The second morbidity of renal angiomyolipomata is the insidious encroachment of the angiomyolipoma on normal renal tissue, which may lead to renal failure (Schillinger 1996,

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Clarke 1999). The precise incidence of end-stage renal disease (ESRD) in the tuberous sclerosis population has not been well defined. However, European surveys suggest that approximately 1% of the TSC patient population with normal intellect is receiving dialytic renal replacement therapy (Schillinger 1996, Clarke 1999), leading to an estimate that over 30,000 TSC patients are on dialysis worldwide. Shepherd et al examined death certificates of patients in their TSC clinic and found that of 355 patients, 40 died as a result of their TSC, most commonly due to renal failure (Shepherd et al 1991). The percentage of TSC patients developing ESRD because of polycystic kidney disease, multiple interventions for hemorrhage, or replacement of renal tissue by angiomyolipomata is unclear (Bissler and Kingswood 2004).

Approximately 35% of patients with TSC will have renal cysts (Cook et al 1996). Although these lesions may be large, they usually are not numerous and rarely cause problems (Bissler and Kingswood 2004).

The primary reason to intervene in patients with renal angiomyolipomata has been to alleviate symptoms such as pain or hemorrhage. The recent urological literature has embraced a renal sparing approach for angiomyolipomata (Nelson and Sanda 2002). Key to the long-term outcome of patients with multiple renal angiomyolipomata is the preservation of renal function. Indications for a total nephrectomy are limited and include a non-functioning kidney resulting in uncontrolled hypertension, local tissue invasion, tumor in the renal vein, or very strong evidence of malignancy (Bissler and Kingswood 2004). Partial or nephron-sparing nephrectomies run the risk of significant hemorrhage, and therefore should be undertaken only if unequivocally indicated (Bissler and Kingswood 2004). Embolization is currently regarded as a suitable alternative to such invasive procedures. The procedure obliterates the blood supply to the angiomyolipoma and thus reduces the risk of hemorrhage. Nevertheless, embolization also has significant side effects. In a review of published series, it was estimated that 85% of patients develop post-embolization syndrome, including significant fever and pain (Bissler and Kingswood 2004). In addition, although embolization and surgical therapies can successfully treat solitary lesions, the much more vexing clinical problem of coalescent renal angiomyolipomata that replace renal parenchyma has remained largely unaddressed. When bleeding occurs in this circumstance, it can be impossible to identify which lesion is the source.

A compelling argument can be made for treatment with pharmacological mTOR inhibitors. Loss of TSC1and TSC2 leads to increased mTOR activity and downstream activation of S6-kinase-dependent gene expression, including the lymphangiogenic factor VEGF-D.. Study CRAD001M2302 (also referred as M2302) is the pivotal Phase III study that investigated the use of everolimus in treating renal angiomyolipoma associated with TSC. In this international multi-center study, 118 patients were 2:1 randomized to everolimus or placebo. The primary endpoint, angiomyolipoma response rate, was defined as the proportion of patients with a reduction in angiomyolipoma volume of at least 50% relative to baseline. At the primary analysis data cut-off date (30-Jun-2011) with a median follow up duration of 8.8 months, the angiomyolipoma response rate was statistically significantly higher in the everolimus arm compared to the placebo arm (33/79 patients, 41.8% vs 0/39 patients, 0.0%; $p<0.0001$). 33 patients in the placebo arm transferred to everolimus treatment after study unblinding or disease progression. At the time of the final analysis data cut-off date (04-Feb-2015), all 112

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patients with at least one dose of everolimus had discontinued treatment as per protocol. The median (range) duration of study follow-up was 47.2 months (0.9 to 65.3). Cumulative response rate was 58% (65/112; 95% CI: 48.3, 67.3). The study data also showed that everolimus was associated with a clinically relevant SEGA response rate of 48.0% (n=24/50, 95% CI: 33.7, 62.6). The overall skin lesion response rate was 68.2% (73/107 patients) with one patient reporting a confirmed complete clinical skin lesion response and no patients experiencing progressive disease as their best response.

Results from a one year non-interventional follow-up phase indicated that clinically significant treatment effects were attenuated in the evaluable patients following everolimus discontinuation, as shown by an increase in the volume of angiomyolipoma lesions previously reduced in size as a result of everolimus treatment. While in some cases post-discontinuation growth plateaued following discontinuation of everolimus and while lesion volumes did not return to pre-treatment values, profound reduction in volumes were no longer detectable in the majority of patients within approximately one year of everolimus discontinuation. These findings suggest that persistence of clinically significant angiomyolipoma volume reduction requires ongoing treatment in most patients.

Choice of a minimum angiomyolipoma size

Angiomyolipomata appear to grow over time, and there is an association between lesion size and hemorrhage (Steiner 1993, Van Baal 1994, Oesterling 1986, Dickinson 1998).

Conservative clinical practice varies between a watchful waiting policy to an aggressive embolization program. Patients eligible for the current study should have at least one angiomyolipoma 3 cm or more in the largest dimension. The choice of 3 cm is aligned with the criteria that were used in the pivotal study CRAD001M2302 and reflects the vague limits between a justified wait and watch policy and the more proactive surgical intervention approaches.

Volumetric assessment of tumor response

Assessment of tumor response to therapy is a critical component for drug development and for the clinical management of patients. Current approaches for classifying tumor response are based on anatomical measurements in either one dimension (Response Evaluation Criteria in Solid Tumors [RECIST] (Therasse et al 2000)) or two dimensions (World Health Organization [WHO] (Miller et al 1981)). However, response rates as determined from these criteria may not always be sufficiently accurate.

As tumors grow in three dimensions, shrinkage can thus be accurately defined as a decrease in tumor volume. RECIST and WHO measurements are essentially surrogates for volume. With developing state-of-the-art imaging techniques providing a 3-D information set and computer algorithm development, it is now possible to obtain accurate and true tumor measurements using volume (Twombly 2006), rather than only one or two dimensional measurements. Also, for the changes in uni- and bi-dimensional measurements to be a good surrogate for changes in volume, one should assume that target lesions are spherical in shape, which may not be true for all tumor types. As shown in a study by Mayr et al 2006 three-dimensional volumetry, which can optimally measure irregular volumes, may provide better response assessment during treatment than diameter-based measurement.

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Finally, in a public workshop on brain tumor clinical trial endpoints organized by the FDA, AACR and ASCO on January 20, 2006, it was recognized that measuring tumor diameter is probably an outdated methodology, as small percentage changes in diameter can reflect much larger changes in tumor volume. It was also mentioned that both manual and automated segmentation techniques provide more accurate measurements of tumor volume than diameter measurement. In addition, the regional distribution of the lesion was considered an important issue; a 1 mm^3 reduction in tumor volume in a certain part of the brain might have a dramatic clinical effect whereas a larger volume reduction elsewhere in the brain might be clinically meaningless.

1.2 Introduction to investigational treatment

1.2.1 Overview of everolimus

Organ transplantation

Everolimus was initially developed for the prophylaxis of organ transplant rejection. It was originally approved in Europe on 18-Jul-2003 under the trade name Certican® for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk, receiving an allogenic renal or cardiac transplant, in combination with cyclosporine for microemulsion and corticosteroids, and has since been granted approval in 107 countries worldwide. In the United States (US), everolimus was approved by the Food and Drug Administration (FDA) on 20-Apr-2010 under the trade name Zortress® (NDA 21-560) for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. Certican®/Zortress® is also approved for the prophylaxis of organ rejection in adult patients receiving a liver transplant in 83 countries worldwide (approval in Europe received 17-October-2012 and FDA approval on 15-February-2013). Additional registrations for use of Certican® in organ transplantation are pending in Africa, South America, Middle East, and Asia-Pacific region.

Oncology

Everolimus first entered clinical development for one of numerous oncology indications in 2002.

It was approved by the FDA on 30-Mar-2009 under the trade name Afinitor® for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. The European Commission (EC) approved it 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. Since then, everolimus has received approvals in more than 120 countries worldwide for the treatment of patients with advanced RCC.

On 05-May-2011, FDA approved Afinitor® for the treatment of progressive neuroendocrine tumors of pancreatic origin (pNET) in patients with unresectable, locally advanced or metastatic disease. The EC approved it 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.

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Furthermore, on 26-Feb-2016, FDA approved Afinitor® for advanced non-functional NET of gastrointestinal (GI) or lung origin followed by the EC on 26-May-2016 for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional NET of GI or lung origin in adults with progressive disease. Overall, Afinitor® has been approved in more than 110 countries worldwide for the treatment of patients with pNET/neuroendocrine tumors.

On 20-Jul-2012, FDA approved Afinitor® for the treatment of postmenopausal women with advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. The EC granted approval on 23-Jul-2012 for the treatment of HR+, HER2- advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. To-date, everolimus has been approved in more than 110 countries worldwide for the treatment of patients with advanced HR+, HER2- breast cancer.

In China, everolimus was first approved by the NMPA on 22-Jan-2013 under the trade name Afinitor® for the treatment of adult patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

On 13-Feb-2014, NMPA also approved Afinitor® for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic (pNET) origin that are unresectable, locally advanced or metastatic, well differentiated (moderately differentiated or highly differentiated).

On 17-Oct-2018, NMPA also approved Afinitor® for adult patients with progressive, well differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic.

Tuberous Sclerosis

To-date, everolimus has been developed and received regulatory approvals for three manifestations of TSC: subependymal giant cell astrocytoma associated with TSC, renal angiomyolipoma associated with TSC, and refractory seizures associated with TSC.

On 29-Oct-2010, everolimus received accelerated approval from FDA on the basis of data from the Phase II study CRAD001C2485 (also abbreviated C2485) for the "treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated." Subsequently on 29-Aug-2012, the indication was revised by the FDA based on the results of the Phase III study CRAD001M2301 (also abbreviated M2301) to the "treatment of pediatric and adult patients with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The effectiveness is based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC have not been demonstrated".

In Europe the EC conditionally approved everolimus on 02-Sep-2011 based on the data of study C2485 under the trade name Votubia® for the "treatment of patients aged 3 years and

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older with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated". On 15-Nov-2013, based on the results of study M2301, the indication was revised with the removal of the age restriction to "Votubia is indicated for the treatment of patients with SEGA associate with TSC who require therapeutic intervention but are not amendable to surgery. The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated".

The follow-up data from studies C2485 and M2301 demonstrated sustained efficacy and safety of everolimus in this patient population. In 2015/2016, these data allowed the conversion of the conditional marketing authorization to full approval in the EU (on 16-Nov-2015) and fulfillment of the Subpart H requirement and the Post Marketing Requirements in the US (on 29-Jan-2016). The limitation statement was also removed from the indication in the US.

Overall, everolimus has been approved in more than 100 countries worldwide for the treatment of patients with TSC who have SEGA.

On the basis of the results of the Phase III study M2302, everolimus received accelerated approval from the FDA on 26-Apr-2012 for the "treatment of adult patients with renal angiomyolipoma and TSC, not requiring immediate surgery. The effectiveness of Afinitor® in the treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months".

On 31-Oct-2012, the EC granted approval to Votubia® for the "treatment of adult patients with renal angiomyolipoma associated with TSC who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery".

On 18-Feb-2016, the FDA considered the Subpart H requirement and the Post Marketing Requirement related to Study M2302 as fulfilled based on the final study results and the limitation statement was removed from the indication.

Overall, everolimus has been approved in more than 90 countries for the treatment of renal angiomyolipoma associated with TSC.

Finally, on 27-Jan-2017, the EC granted a decision for Votubia for the "adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC". This approval was based on the results of the Phase III Study CRAD001M2304. So far, everolimus has been approved in 31 countries for the treatment of TSC-associated refractory seizures.

In China, NMPA approved Afinitor® on 13-Feb-2014 for pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. This approval was based on the results of global studies C2485 and M2301. The effectiveness is based on the demonstration of durable objective response, as evidenced by reduction in SEGA tumor

[redacted]

volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC has not been demonstrated.

On 29-Nov-2016, NMPA also approved Afinitor® for adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC-AML) not requiring immediate surgery. This approval was based on the results of the global study M2302 and the local investigator initiated study MCN30T.

Approximately 136,053 patients have been enrolled in studies with everolimus as of 31-Mar-2019 (this number excludes patients who received marketed Afinitor®/Votubia®/Afinitor DISPERZ, those on planned and roll over studies as well as those on investigator-sponsored studies):

- 133,748 patients in Novartis-sponsored clinical trials
- 2,305 patients in the individual patient program

Approximately 49,988 patients were enrolled globally in all investigator-sponsored studies as of 31-Mar-2019.

The following is a brief summary of the main characteristics of everolimus (Afinitor®). More complete information can be obtained from the Chinese product information for Afinitor®.

Mechanism of action

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor (Table 1-1, Figure 1-1). Everolimus selectively inhibits mammalian target of rapamycin (mTOR), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers (Boulay and Lane 2007).

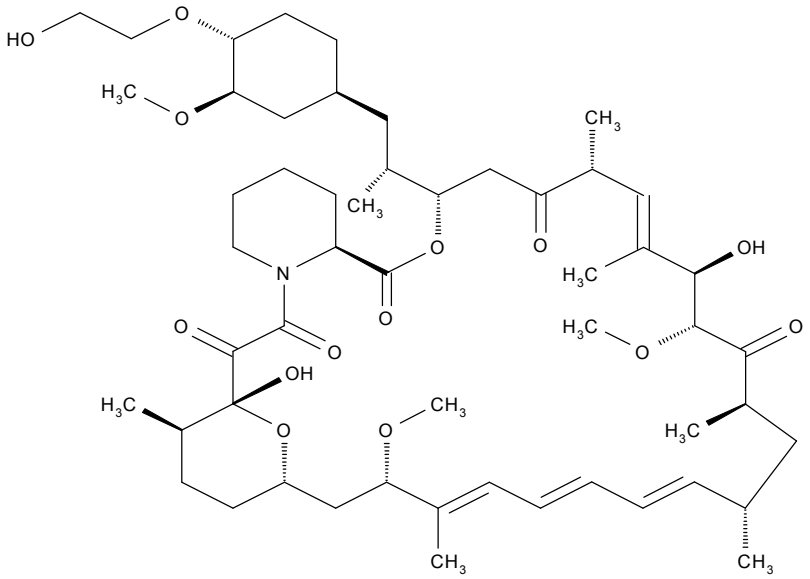
Everolimus is being investigated as an anticancer agent based on its potential to act

- 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 VEGF 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[30.3.1.04,9]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1-1 Chemical structure of Everolimus



mTOR pathway and cancer

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 PI3K pathway through AKT/PKB and TSC1/2. Mutations in these components or in phosphatase and tensin homolog (PTEN), a negative regulator of PI3K, 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;
- PI3K mutations have been reported in the primary tumor in 10-20% of human colorectal cancers (Frattini 2005, Velho 2005);
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers (Goel et al 2004);
- 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.

[redacted]

1.2.2 Non-clinical experience of everolimus

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

[redacted]

recovery period with the exception of the changes in male reproductive organs, most notably testes.

1.2.3 Clinical experience of everolimus

Clinical Safety, Tolerability and Efficacy

Phase III study CRAD001M2302 in renal angiomyolipoma associated with TSC (EXIST-2)

A total of 118 patients with renal angiomyolipoma associated with TSC were enrolled to this study between 2009 and 2014 (01-Apr-2014 cut-off). 79 were initially treated with everolimus and 39 with placebo. Upon disease progression or study unblinding, patients were allowed to crossover from placebo to everolimus. A total of 112 patients were treated with at least 1 dose of everolimus. The data described below represent the cumulative experience of 112 patients treated with everolimus at the time of the final treatment cut-off date, 04-Feb-2015.

Efficacy

At the primary analysis cut-off date (30-Jun-2011), the angiomyolipoma response rate was statistically significantly higher in the everolimus arm compared to the placebo arm (33/79 patients, 41,8% vs 0/39 patients, 0.0%; p<0.0001). Cumulative experiencefor angiomyolipoma response at the final cut-off date (04-Feb-2015) demonstrated that the tumors in 65/112 patients had responded to treatment (response rate = 58.0%; 95% CI: 48.3, 67.3). The percentage of patients achieving ≥30% reduction in angiomyolipoma volume was sustained while the degree of reduction (≥50% volume reduction and median percentage reduction) improved over the course of the study:

- 78/104 patients (75%) experienced reductions of ≥ 30% at Week 12, 79/98 patients (80.6%) at Week 96, and 52/61 patients (85.2%) at Week 192;
- 46/104 patients (44.2%) experienced reductions of ≥ 50% at Week 12, 62/98 patients (63.3%) at Week 96, and 42/61 patients (68.9%) at Week 192;
- The median percentage reduction in angiomyolipoma volume at Week 12, 96 and 192 was 46.4%, 58.9% and 61.9%, respectively.

The efficacy results confirmed that everolimus treatment effects in patients with TSC-associated angiomyolipoma were sustained over a period of time.

Everolimus was associated with a clinically relevant SEGA response rate of 48.0% (n=24/50, 95% CI: 33.7, 62.6).

The overall skin lesion response rate was 68.2% (73/107 patients) with one patient reporting a confirmed complete clinical skin lesion response and no patients experiencing progressive disease as their best response. Of 73 patients who had a response of the skin lesions, the median time to skin lesion response was 8.41 months (95% CI: 5.59, 11.53).

Results from the non-interventional follow-up phase indicate that clinically significant treatment effects were attenuated in the evaluable patients following everolimus discontinuation, as shown by an increase in the volume of angiomyolipoma lesions previously reduced in size as a result of everolimus treatment. While in some cases post-discontinuation growth plateaued following discontinuation of everolimus and while lesion volumes did not

[redacted]

return to pre-treatment values, profound reduction in volumes were no longer detectable in the majority of patients within approximately one year of everolimus discontinuation.

Safety

The most common AEs (≥ 30% of patients) regardless of study drug relationship were nasopharyngitis (44.6%), stomatitis (42.9%), hypercholesterolemia (35.7%), headache (33.0%), acne (32.1%), and urinary tract infection (31.3%). Stomatitis, which is a known identified risk of everolimus treatment, was the most frequently reported individual AE suspected by the Investigator to be study-drug related in everolimus-treated patients (42.0%).

Other frequently reported AEs (⩾20% of patients) with suspected relationship to study drug included hypercholesterolemia (30.4%), acne (25.9%), aphthous stomatitis (21.4%), and nasopharyngitis (21.4%). Amenorrhea (n=18/71, 25.4%) was frequently reported in the female population at risk (10-55 years of age).

Ten patients (8.9%) discontinued study drug due to the AEs.

Phase II study RAD001MCN30T in renal angiomyolipoma associated with TSC

18 Chinese adult patients with TSC-AML were enrolled in this single site investigator initiated study. A preliminary analysis was done with cut-off date 10-Oct 2015 when 15 patients were enrolled and 13 patients had received 10 mg everolimus per day for 3 months. Out of the 13 patients with at least 3 months treatment, 4 patients met the primary endpoint, which was defined as 50% or more reduction of renal AML volume relative to baseline in the absence of new renal AML >1cm and no renal AML-related bleeding of grade ≥2. The mean volume decrease at 3 months and 6 months was 30.78% and 50.22%, respectively.

Mouth ulceration, nasopharyngitis, hypercholesterolemia and irregular menstruation in females were the most common adverse events of which only 2 events had a CTCAE grade of 3 in the first 3 months.

Clinical Pharmacodynamics

Results of a linear mixed model analysis in study M2302 indicated a 10.37% (95% CI= -15.96, -4.40) reduction in AML volume from baseline for a 2-fold Cmin increase, which was statistically significant at 5% level. No apparent relationship was observed between absolute or percent change from baseline in SEGA volume and time-normalized Cmin. This was attributed to interpatient variability in the exposure-response relationship and the relatively narrow concentration range reported within individual patients as a result of the fixed daily dosing regimen. Box plot analysis of time-normalized Cmin in patients with skin lesion responses of partial response (PR) and stable disease (SD) indicated that the median time-normalized Cmin was higher in patients with PR than in patients with SD response at Week 12, while the median Cmin was comparable in patients with PR and SD at week 24. Higher Cmin or C2h was not indicative of a higher probability/risk for stomatitis and infections events of all grades within the Cmin and C2h ranges observed in the study.

Clinical Pharmacokinetics

After administration of Afinitor® Tablets in patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to

[redacted]

70 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional with daily dosing between 5 and 10 mg. AUC shows dose-proportionality over the 5 to 70 mg dose range.

After administration of Afinitor® Tablets in patients with advanced solid tumors, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg with a daily dosing regimen. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg daily. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on a daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

Pharmacokinetics in the TSC patient population is comparable to what was observed in the approved oncology indications (e.g. RCC, pNET).

In healthy subjects, high fat meals reduced systemic exposure to 10 mg Afinitor Tablets (as measured by AUC) by 22% and the peak blood concentration C_{max} by 54%. Low-fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile 24 h post-dose of either dosage form.

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, it is the main circulating component in human blood. Elimination of everolimus is mainly through faeces.

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to assess the safety and efficacy of Afinitor® in Chinese patients with renal angiomyolipoma associated with TSC. The study will evaluate the safety and anti-tumor activity of Afinitor® given at a dose of 10 mg per day. Study CRAD001M2302 has shown that the volume of TSC-AML lesions was reduced in a significant portion of TSC renal AML patients that received treatment with Afinitor®. CRAD001M2302 was conducted at 24 sites in 11 countries but China was not a participating country and no Chinese patients were enrolled. The overall angiomyolipoma response rate was 41.8% (95% CI: 30.8, 53.4) for the everolimus arm and 0% (95% CI: 0.0, 9.0) for the placebo arm ($p < 0.0001$) in the FAS.

Study CRAD001MCN30T enrolled 18 Chinese adult patients with TSC-AML. At the preliminary analysis 4 out of 13 patients with at least 3 months Afinitor® treatment (10 mg per day) had an angiomyolipoma response.

Based on these results NMPA approved Afinitor® on 29-November 2016 for the treatment of TSC-renal AML patients not requiring immediate surgery.

This study is conducted to fulfill a post approval commitment (PAC) to assess the safety and efficacy of Afinitor® in adult Chinese patients with TSC associated renal AML lesions based on Chinese current clinical practice. The patient population in this study represents the population of the approved indication which is at significant risk for renal morbidities and is therefore well-suited for testing the effect of everolimus on tumor burden.

TSC is an autosomal dominant genetic disorder that is caused by inactivating mutations in the TSC1 or TSC2 genes, and characterized by benign, highly vascular, hamartoma growth. The

TSC1/TSC2 protein complex is a negative regulator of the mTOR pathway and mutations in one of the two genes causes loss of function and leads to increased mTOR pathway activation. Everolimus is an inhibitor of the mTOR pathway and has a similar effect as the TSC1/TSC2 protein complex. The rationale of using everolimus in TSC patients is that it compensates the missing inhibitory effect of TSC1/TSC2 on mTOR.

2.2 Rationale for the study design

This single arm, open label, phase IV PAC study will evaluate the safety and efficacy of Afinitor® (10 mg/day) in 40 Chinese adult patients with renal angiomyolipoma associated with TSC. The study design is based on the positive outcome of the pivotal study CRAD001M2302.

Patients eligible for the study should have a confirmed diagnosis of TSC and at least one renal angiomyolipoma lesion of 3 cm or more in the largest dimension.

2.3 Rationale for dose and regimen selection

The dose in this phase IV study will follow the recommended dose approved as per the Chinese product information of Afinitor®. The starting dose will be 10mg/day. For patient with abnormal liver function, starting dose will be 7.5mg/day, or 5mg /day if Child-Pugh grade is A or B，respectively.

2.4 Risks and benefits

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.2.3 and Table 6-3. The risk to subjects in this study may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring. There may be unforeseen risks with Afinitor® which could be serious. Please refer also to the Chinese product information for Afinitor®.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the safety of Afinitor® in Chinese adults with TSC-AML not requiring immediate surgery.	● Incidence of adverse events, laboratory abnormalities.	
Secondary		Refer to Section 10.5.1
To evaluate the efficacy of Afinitor® in Chinese adults with TSC-renal AML not requiring immediate surgery.	● AML response	
Other Secondary		Refer to Section 10.5.2 and 10.5.3
To further evaluate the efficacy of Afinitor® in Chinese adults with TSC-renal AML not requiring immediate surgery.	● AML progression ● Renal function change from screening	
Exploratory		
None		

[redacted]

4 Study design

4.1 Description of study design

This is an open label, single arm, multi-center phase IV study of treatment with one daily oral dose of 10 mg everolimus (Afinitor®) in 40 patients with renal angiomyolipoma associated with TSC.

There are three separate phases in this study: a "Screening phase", an "Open-label treatment phase", and a "Treatment discontinuation follow-up phase" for patients who discontinue study drug for other reasons than disease progression.

Screening phase

At screening, the investigator or his/her designee will assign a unique number (refer to Section 6.4.1) to patients being considered for the study. **Patients are required to sign an Informed Consent Form prior to any study screening evaluations. Once the patient provides a signed informed consent form and eligibility is confirmed (all inclusion/exclusion criteria have been verified), the investigator can enroll the patient and start treatment with Afinitor®.**

During the 28-day screening period, all patients will have a CT/MRI of the kidneys and MRI/CT of the brain performed for identification of angiomyolipoma and SEGA lesions; the kidney CT/MRI will be used to assess patient eligibility. Although the study will use an Independent Central Radiology Review to measure tumor volume, the decision to enroll the patient will be made based on the judgment of the investigator and local radiologist. Once the patient is enrolled, the baseline kidney CT/MRI and brain MRI/CT should be sent within 2 business days by the study site to the Independent Central Radiology Reviewer to assess the tumor volume.

Prior to start of study drug, all patients should be tested for hepatitis B viral load and serologic markers: HBV-DNA, HBsAg, HBsAb, and HBcAb. All patients should also be tested for hepatitis C using quantitative RNA-PCR. Patients with quantifiable HBV DNA and/or positive HbsAg or quantifiable HCV-RNA are excluded from the study.

Other screening tests include blood sampling, urinalysis, WHO performance status, and ECG. If safety laboratory collections are collected more than 14 days prior to Treatment Day 1 (i.e. day of first dose of study drug) they will need to be repeated prior to the patient's first dose of study drug. The central laboratory collections that must be repeated are: hematology, biochemistry and lipid profile, coagulation and urinalysis.

Patients with LAM will have a lung function test (FEV1, DLCO) and blood gas analysis performed during screening.

Patients with skin lesions at screening will have digital photos of these lesions taken during screening.

Screening evaluations will also include demography, inclusion/exclusion criteria, relevant medical history/current medical conditions, a physical examination, and vital signs. All

[redacted]

screening evaluations should be completed in the 28 days prior to Treatment Day 1 and after signing the informed consent. A complete list of screening evaluations is provided in the visit evaluation schedule (Table 7-1). All of the above assessments/procedures must be conducted prior to enrollment.

Open label treatment phase

Patients who meet the study eligibility criteria will start treatment with Afinitor®. The treatment duration will be 48 weeks. Patients will have their first daily dose of Afinitor® at Day 1 and will continue on treatment until angiomyolipoma progression (as defined in Section 7.2.1.1, an unacceptable toxicity, occurrence of serious protocol deviations, withdrawal of consent or investigator decision to discontinue the patient from study treatment.

Patients with normal liver function will start with a dose of 10 mg/day. Patients with hepatic impairment will start with a dose of 7.5 mg/day (Child-Pugh grade A) or 5 mg/day (Child-Pugh grade B). Dose adjustments (reduction, interruption) will occur based on safety findings. All doses taken by the patient and all dose changes during the study must be recorded on the study treatment CRF.

Safety evaluations are routinely performed at each visit according to the visit schedule (Table 7-1). Patients must be in a fasting state (at least 12 hours) at the time of blood sampling for all laboratory evaluations including the lipid profile. Hematology, biochemistry and urinalysis evaluations will be performed according to the visit schedule (Table 7-1). Note that hematology, biochemistry and urinalysis assessments are performed at screening and do not need to be repeated on Day 1 if Day 1 occurs within 14 days of the screening visit. Otherwise, the patient will need to repeat the screening visit blood and urine collections. All blood samples obtained at each visit will be sent to a Central Laboratory for analysis. Urinalysis will be performed locally. If laboratory results are requested on an urgent basis, the attending physician will use the local laboratory results for treatment decisions. Complete details regarding all study required safety assessments are provided in Section 7.

All patients will have a CT/MRI of the kidney performed at 12, 24 and 48 weeks in the open-label treatment phase, after the start of study treatment, until angiomyolipoma progression. A CT/MRI of the kidneys should be repeated at the End of Treatment (EOT) visit if the patient has discontinued for any reason other than angiomyolipoma progression, and if it has been more than 8 weeks since their most recent kidney CT/MRI.

In addition to the CT/MRI of the kidney, patients with a SEGA lesion having a longest diameter ≥ 1.0 cm documented at screening will also have a MRI/CT of the brain at 12, 24 and 48 weeks in the open-label treatment phase. For each patient, the same imaging modality should be used throughout the study. All kidney CT/MRIs and brain MRI/CTs will be sent to the central radiologist for an independent centralized radiology review. The central radiologist will determine the angiomyolipoma volume and verify whether the radiological criteria for angiomyolipoma response have been met (Section 7.2.1.1). Since not all study centers will have the technical capability to measure angiomyolipoma volume, there is no plan to collect data from the local radiologist at each site. MRI and CT scans must be digitized and sent to Central Radiology within 2 business days of the scan date. The central review of the CT/MRIs will be conducted at the agreed upon frequency between Novartis and the assigned Imaging

[redacted]

Vendor after its receipt by the central radiology vendor. Once the data is available, the results will be sent immediately to the study site and to Novartis. Clinical suspicion of angiomyolipoma progression at any time requires a physical examination and expedited radiological confirmation by the Independent Central Radiology Reviewer.

Other tests that will be conducted routinely include laboratory tests for safety, physical examinations, vital signs, and WHO performance status. In addition, for LAM patients, pulmonary function tests will be carried out at 12, 24, 48 weeks, in the open-label treatment phase. Patients with skin lesions will have digital photos of their skin lesions taken at 12, 24, and 48 weeks, in the open-label treatment phase. A complete list of evaluations can be found in Table 7-1. If unforeseen circumstances (i.e., unexpected personal reasons) prevent the patient from complying with the established visit schedule, the site can re-schedule the visit within the prescribed visit window as noted in Table 7-1. The reason(s) for any visit or treatment delays will be documented for the appropriate visit.

All female patients of child bearing potential should perform urine pregnancy tests at home every 4 weeks ±7 days from Day 1 to end of treatment (EOT), and enter the result in the pregnancy diary.

Every patient will have end of treatment (EOT) visit within 28 days after last dose. Laboratory tests and imaging will be done at the EOT visit as described in Table 7-1. Laboratory tests that were done within 1 week and imaging that was done within 8 weeks don't have to be repeated at EOT.

All patients will have a safety follow-up visit 30 days after last dose to capture AEs and SAEs that may have occurred after EOT.

Treatment Discontinuation Follow-up phase

Patients without angiomyolipoma progression at the time of early discontinuation of study treatment will enter the Treatment Discontinuation follow-up phase and will be followed with CT/MRI tumor assessments 12, 24 and 48 weeks after Day1, until eventual angiomyolipoma progression, the start of any non-study systemic anti-angiomyolipoma therapy, or withdrawal of consent, whichever occurs first. Patients with SEGA lesions should be followed for routine follow-up with brain MRI/CT scans 12, 24 and 48 weeks after Day1. During this follow up period, the site will continue to send CT/MRIs for central review, and use of non-study systemic anti-angiomyolipoma therapies will be recorded in CRF. Patients with skin lesions will also be followed with digital photography during Treatment Discontinuation follow-up phase.

4.2 Definition of end of study

The study will end when 40 patients will have completed all scheduled visits as per protocol.

At the end of the study, patients who in the opinion of the Investigator still derive clinical benefit can transfer to prescribed commercial medication. Afinitor® is commercially available in China for the studied indication. It is listed on the national reimbursement plan. Patients will need to obtain the medication with a prescription and pay for it per related reimbursement policy after the study ends.

[redacted]

4.3 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or 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 study patient population consists of 40 male or female adult patients (18 years of age or older) who have been diagnosed with renal AML associated with TSC that do not require immediate surgery.

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. Patients enrolled in this study are not permitted to participate in additional parallel investigational drug studies.

5.2 Inclusion criteria

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

1. Eligible for treatment with everolimus as per the locally approved label.
2. Presence of at least one AML ≥ 3 cm in its longest diameter using CT or MRI.
3. If female of child bearing potential, documentation of negative pregnancy test at time of Screening. Females of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during dosing and for 8 weeks after stopping medication. 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 partner sterilization (at least 6 months prior to screening). 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.

[redacted]

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

4. Sexually active males must use a condom during intercourse while taking the drug during treatment, and for 8 weeks after stopping treatment. They should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.
5. Written informed consent according to local guidelines must be obtained prior to any screening procedures.

5.3 Exclusion criteria

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

1. AML related bleeding or embolization during the 6 months prior to enrollment.
2. History of myocardial infarction, angina or stroke related to atherosclerosis.
3. Impaired lung function, defined as any of the following:

   For patients without LAM

   - Known impaired lung function (e.g. FEV1 or DLCO ≤ 70% of predicted)
     Note: pulmonary function testing at screening is not required for patients without LAM

   For patients with LAM

   - DLCO ≤35%, or
   - O2 saturations below 90% at rest, or
   - O2 saturation ≤88% on 6 minute walking test with up to 6 liter O2/minute nasal Oxygen
4. Chylous ascites sufficient to affect diaphragmatic function or pulmonary function testing.
5. Significant hematological or hepatic abnormality (e.g. hemoglobin ≤9g/dL, platelets < 100×10^9/L, or absolute neutrophil count (ANC) < 1.5×10^9/L without supportive treatment of hematopoietic growth factor, transaminase levels > 2.5× the upper limit of normal (ULN), serum bilirubin > 2 × ULN).
6. Pregnancy or breast feeding.
7. Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus).
8. Patients who cannot discontinue CYP3A4 strong inhibitors or inducers 2 weeks before study treatment.
9. Use of an investigational drug within the 30 days prior to enrollment.
10. Fasting serum cholesterol > 300 mg/dL (or > 7.75 mmol/L) AND fasting triglycerides > 2.5 × ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.
11. Uncontrolled diabetes mellitus as defined by fasting serum glucose > 1.5 × ULN despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary.
12. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus.

[redacted]

13. Known history of HIV seropositivity.
14. Inadequate renal function: Serum creatinine > 1.5 × ULN.
15. Patients who have a history of another primary malignancy, with the exceptions of non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for ≥3 years.
16. Any severe and/or uncontrolled medical conditions such as:
    a. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to enrollment, serious uncontrolled cardiac arrhythmia,
    b. active or uncontrolled severe infection,
    c. liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA),
    d. known severely impaired lung function (DLCO ≤70% for patients without LAM or ≤35% for patients with LAM),
    e. active, bleeding diathesis

6 Treatment

6.1 Study treatment

The investigational drug used in the course of this study will be relabeled local commercial Afinitor® (everolimus).

Definition of terms: Study treatment / Study drug = RAD001 = Afinitor® = everolimus

6.1.1 Dosing regimen

This is a single arm study. All patients except those with impaired liver function will be administered a dose of 10 mg Afinitor® orally once daily (Table 6-1) at the same time every day, either consistently with or without food.

Medication labels for study drug will comply with the legal requirements in China and be printed in local language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

Table 6-1 Dose and treatment schedule

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Afinitor®	Tablet for oral use	10 mg for patients without hepatic impairment; 7.5 mg for patients with mild hepatic impairment (Child-Pugh grade A) 5 mg for patients with moderate hepatic impairment (Child-Pugh grade B)	Daily

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

Tablets

[redacted]

Everolimus will be supplied as 2.5 mg and 5-mg Afinitor® tablets. The tablets are packaged in blisters. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed.

For patients with TSC who have SEGA and are unable to swallow tablets whole, the tablet(s) can be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring until the tablet(s) are fully disintegrated (approximately 7 minutes), 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.

6.1.2 Treatment duration

The planned duration of treatment is 48 weeks. Patients may be discontinued from treatment with the study drug earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the patient.

6.1.3 Guidelines for continuation of treatment

Not applicable.

6.2 Dose modifications

6.2.1 Starting dose rationale

The starting dose for Afinitor®, for patients enrolled in this study, is set at 10 mg /day p.o. administered continuously once daily. This starting dose was selected to be in accordance with the starting dose used in the pivotal study CRAD001M2302 and recommended starting dose in the approved Chinese product information of Afinitor®. Patients with mild hepatic impairment (Child-Pugh grade A) will start with 7.5 mg per day and patients with moderate hepatic impairment (Child-Pugh grade B) will start with 5 mg per day.

6.2.2 Dosing modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Details of study treatment schedule adjustments and dose levels are provided in Table 6-2.

Table 6-2 Study treatment schedule adjustments and dose levels

	Afinitor® Starting dose level - 0	Dose level - 1	Dose level - 2
Patients without hepatic impairment	10 mg daily	5 mg daily	5 mg every other day
Patients with mild hepatic impairment (Child-Pugh grade A)	7.5 mg daily	5 mg daily	5 mg every other day
Patients with moderate hepatic impairment (Child-Pugh grade B)	5 mg daily	5 mg every other day	Not permitted

Notes:
- Dose reduction should be based on the worst toxicity demonstrated after the most recent dose received.
- Dose reduction below 5 mg every other day is not allowed. Treatment must be discontinued.

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption (with or without dose reduction) or discontinuation of Afinitor® therapy. If

[redacted]

dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered.

The lowest permitted Afinitor® dose in this study is 5 mg every other day. Patients who don't tolerate 5 mg Afinitor® every other day must be discontinued permanently.

Table 6-3 and Table 6-4 summarize the recommendations for dose interruption, reduction, or discontinuation of Afinitor® in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 6-3 Dosing guidelines for study drug-related non-hematologic toxicities

Adverse drug reaction	Severity[1]	Afinitor® dose adjustment[2] and management recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, clinical or diagnostic observations only; intervention not indicated	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated; limiting instrumental ADL[3]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤ 1. Re-initiate Afinitor® at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Severe symptoms; limiting self-care ADL[3] O_2 indicated	Interrupt Afinitor® until symptoms resolve to Grade ≤ 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating Afinitor® at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)	Discontinue Afinitor®, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Asymptomatic or mild symptoms; intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day.
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor® at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate Afinitor® at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4]

[redacted]

Adverse drug reaction	Severity[1]	Afinitor® dose adjustment[2] and management recommendations
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor® at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4]
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue Afinitor® and treat with appropriate medical therapy.
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor® at the same dose. If toxicity recurs at Grade 2, interrupt Afinitor® until recovery to Grade ≤1. Re-initiate Afinitor® at a lower dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating Afinitor® at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue Afinitor® and treat with appropriate medical therapy.
Metabolic events (e.g. hyper-glycemia, dys-lipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate Afinitor® at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue Afinitor® and treat with appropriate medical therapy.

[1] Severity Grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

[2] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

[3] Activities of daily living (ADL)

[4] Avoid using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Table 6-4 Dosing guidelines for study drug-related hematologic toxicities

Adverse event	Severity[1]	Afinitor® Dose Adjustment
Thrombocytopenia (Platelet count	Grade 1 (<LLN-75.0x10^9/L)	No dose adjustment required.

[redacted]

Adverse event	Severity[1]	Afinitor® Dose Adjustment
decreased)	Grade 2 (<75.0-50.0x10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor® at the same dose.
	Grade 3 (<50.0-25.0x10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor® at a lower dose.
	Grade 4 (<25.0x10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor® at a lower dose.
Neutropenia (Neutrophil count decreased)	Grade 1 (<LLN-1.5x10^9/L)	No dose adjustment required.
	Grade 2 (<1.5-1.0x10^9/L)	No dose adjustment required.
	Grade 3 (<1.0-0.5x10^9/L)	Temporary dose interruption until recovery to Grade ≤2 (ANC≥1.0x10^9/l). Re-initiate Afinitor® at the same dose.
	Grade 4 (<0.5x10^9/L)	Temporary dose interruption until recovery to Grade ≤2 (ANC≥1.0x10^9/l). Re-initiate Afinitor® at a lower dose.
Febrile neutropenia	Grade 3 (ANC<1.0x10^9/L with single temperature >38.3°C (101°F) or sustained temperature ≥38°C (100.4°F) for >1h)	Temporary dose interruption until recovery to Grade ≤2 (ANC≥1.25x10^9/l) and no fever. Re-initiate Afinitor® at a lower dose.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue Afinitor®.
Any hematologic toxicity requiring study drug interruption for >28 days		Discontinue Afinitor®.

[1] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03

All dose changes must be recorded on the Dosage Administration Record CRF.

6.2.3 Management of specific toxicities

6.2.3.1 Management of infections

Everolimus has immunosuppressive properties and may predispose patients 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, candidiasis or pneumocystis jirovecii pneumonia (PJP) 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 sepsis, including septic shock, respiratory or hepatic failure) and occasionally have had a fatal outcome.

[redacted]

Physicians and patients 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.

Cases of PJP, some with fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents is required.

6.2.3.2 Management of stomatitis / oral mucositis / mouth ulcers

Patients with a clinical history of stomatitis/oral 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. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to study drug should be treated using local supportive care. Please note that investigators in earlier studies have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If the clinical examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please refer to Table 6-3 for management of stomatitis/oral mucositis/mouth ulcers.

In addition agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is recommended to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, therefore leading to higher everolimus exposure. Therefore, topical antifungal agents are preferred if a fungal infection is diagnosed.

6.2.3.3 Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) should 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 should

[redacted]

be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Hyperglycemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of study drug and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia.

6.2.3.4 Management of renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with everolimus. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, and serum creatinine, is recommended prior to the start of study drug and periodically thereafter.

6.2.3.5 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 should be considered in patients 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. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt everolimus until resolution to less than or equal to grade 1. Everolimus may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of everolimus. For cases of grade 4 noninfectious pneumonitis, everolimus therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP may be considered.

Individuals participating in this study will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. Moreover, potential lung radiological changes can be detected by the chest CT/MRI scans that are performed on all

[redacted]

patients with LAM for tumor assessment according to the schedule of events (Table 7-1). In addition, pulmonary function tests (PFTs), including spirometry, D_LCO, and room air O_2 saturation at rest should be performed. Bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL), should be conducted, if clinically indicated, to monitor for pneumonitis. If non-infectious pneumonitis develops, the guidelines in Table 6-3 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

6.3 Concomitant medications

Concomitant medications and therapies for adverse events or supportive treatments are permitted. Some medications may however have drug-drug interactions with everolimus and the guidelines below should be followed.

In clinical studies and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of angiotensin-converting-enzyme (ACE) inhibitors. The risk of angioedema events may be increased with concomitant administration of ACE inhibitors.

Cytochrome P450 and P-glycoprotein (PgP) inhibitors/inducers/substrates

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/PgP should be avoided and may cause increased everolimus concentrations.
- Co-administration with moderate CYP3A4/PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4/PgP inhibitors, reduce the dose of study drug to half the currently used dose. Additional dose reductions may be required to manage toxicities. If the inhibitor is discontinued, consider a washout period of at least 2-3 days (average for the most commonly used moderate inhibitors), before the study drug dose is returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.
- Co-administration with strong inducers of CYP3A4 should be avoided.
- If a patient requires co-administration of strong CYP3A4 inducer, an increase in the dose of study drug up to twice the currently used daily dose should be considered, using 5 mg increments or less. This dose adjustment of study drug is predicted 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, consider a washout period of at least 3-5 days (reasonable time for significant enzyme de-induction), before the study drug dose is returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to Table 6-5 listing relevant inducers and inhibitors of CYP3A and to Table 6-6 for a list of relevant substrates, inducers, and inhibitors of PgP.

[redacted]

Table 6-5 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A4

Inducers
Strong inducers:
avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort (HYPERICUM PERFORATUM), rifabutin, phenobarbital, mitotane, enzalutamide
Moderate inducers:
bosentan, efavirenz, etravirine, modafinil, nafcillin, genistein, ritonavir, thioridazine, tipranavir, semagacestat, talviraline, lopinavir, lersivirine,
Weak inducers:
amprenavir, aprepitant, armodafinil bexarotene, clobazam, danshen5, dexamethasone, echinacea, gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, pleconaril, primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, troglitazone, vinblastine, eslicarbazepine, ginseng, vemurafenib, boceprevir, sulfinpyrazone, ticagleror, vicriviroc/ritonavir, ritonavir, ticlopidine, brivacetam, stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), quercetin. honey,yin zhi huang
Inhibitors
Strong inhibitors:
VIEKIRA PAK, indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat (GS-9350) ,indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole,mibefradil, LCL161, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, saquinavir, idelalisib, boceprevir, darunavir/ritonavir
Moderate inhibitors:
Erythromycin, fluconazole, darunavir, diltiazem, dronedarone, crizotinib, atazanavir, aprepitant, casopitant, amprenavir, faldaprevir, imatinib, verapamil, netupitant, nilotinib, tofisopam, cyclosporine, ACT-178882, ciprofloxacin, schisandra, sphenanthera, isavuconazole, cimetidine, FK1706Ferula asafetida resin (Ferula assa-foetida)
Weak inhibitors:
Tabimorelin, ranolazine, amlodipine,lomitapide, fosaprepitant (IV), Seville orange juice, amiodarone, chlorzoxazone, M100240, fluvoxamine8, ranitidine, fostamatinib, goldenseal, clotrimazole, tacrolimus, palbociclib, cilostazol, ticagrelor, peppermint oil, ivacaftor, GSK2248761, Guan Mai Ning, AZD2327, resveratrol, roxithromycin, suvorexant, propiverine, isoniazid, berberine, oral contraceptives, delavirdine, daclatasvir, simeprevir, atorvastatin, tolvaptan, almorexant, GSK1292263, evacetrapid, linagliptin, lacidipine, cranberry juice, pazopanib, everolimus, blueberry juice, AMD070, alprazolam, Tong Xin Luo, bicalutamide, sitaxentan, azithromycin, ginkgo, teriflunomide, Garden Cress seeds (Lepidium sativum)
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated May2016 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.

Table 6-6 PgP substrates, inducers, inhibitors

Category
NTI substrates of P-gp[1]:
digoxin, quinidine, paclitaxel, cyclosporine, sirolimus, tacrolimus, fentanyl, phenytoin
Substrates of Pgp (≥2X AUC change)[2]
aliskiren, ambrisentan, atorvastatin, atorvastatin acid, azithromycin, cerivastatin, colchicine, CP-481,715, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, fentanyl, fexofenadine, lapatinib, linezolid, loperamide, maraviroc, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, topotecan, voclosporin
Substrates of Pgp mentioned in US label[3]

[redacted]

afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
P-gp Inhibitors
alogliptin, amiodarone[4], azithromycin, canaglifozin, captopril, carvedilol, clarithromycin, clopidrogel, conivaptan, cremophor RH0, curcumin, diltiazem, dronedarone, elacridar, eliglustat, erythromycin, felodipine, fluvoxamine, fostamatinib, ginko, indinavir, isavuconazole, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir, mibefradil, milk thistle (silymarin, silibinin), mirabegron, nelfinavir, nifedipine, nitredipine,ombitasvir, paritaprevir, paroxetine, propafenone, quercetin, quinidine, quinine, ranolazine, rifampin, ritonavir, sequinavir, schisandra chinesis extract, simepravir, St. John's wort extract (HYPERICUM PERFORATUM), survorexant, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, vandetanib, verapamil, voclosporin, vorapaxar.
P-gp Inducers
avasimibe, carbamazepine, danshen (Salvia miltiorhiza), efavirenz, genistein[2], phenytoin, quercetin[2], rifampin, St. Johns wort extract. garlic extract
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated May2016 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.
1 These drugs have both a narrow therapeutic index and an in vivo DDI outcome ascribed at least in part ascribed to Pgp (inhibition or induction) that exceeds a 20% change in AUC. 2 These drugs have in vivo DDI outcomes (inhibition) which are ≥2x increase in AUC and are at least in part ascribed to Pgp. 3 The US labels for these drugs have specific language on in vivo Pgp substrate status. 4 Dual P-gp and CYP3A4 inhibitor

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.

Other prohibited concomitant therapy

Patients may not take any other mTOR inhibitors or other investigational treatments while on study treatment.

6.4 Patient numbering and treatment assignment

6.4.1 Patient numbering

Each patient is identified in the study by a 7 digit subject number, that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The subject number consists of the 4-digit center number (as assigned by Novartis to the investigative site) with a 3-digit sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient will be assigned the next

[redacted]

available sequential patient number by the investigator or designee. Once assigned to a patient, a patient number will not be reused. If a patient fails screening and is re-screened a new 7 digit subject number will be assigned. If after signing the informed consent, it is determined that the patient does not qualify for the study, reason(s) will be entered on the disposition CRF and Novartis notified.

6.4.2 Treatment assignment

All patients who fulfill all inclusion/exclusion criteria will start receiving study treatment with Afinitor®. The investigator will assign patients to the 10 mg, 7.5 mg, or 5 mg O.D. Afinitor® dose depending on their hepatic function (no liver impairment, Child-Pugh grade A, Child-Pugh grade B).

6.4.3 Treatment blinding

Not applicable.

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Study Treatment CRF.

Table 6-7 Preparation and dispensing

Study treatment	Dispensing	Preparation
RAD001 (everolimus)	Afinitor® tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

6.5.1 Study treatment packaging and labeling

Study treatment, Afinitor®, will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and re-labeled as study drug. Study treatment labels will comply with the legal requirements in China and will include storage conditions, a unique medication number (corresponding to strength).

Table 6-8 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
RAD001 (everolimus)	Tablets in blister	Labeled as 'Afinitor®/RAD001/everolimus' Study treatment packaging has a 2-part label. A unique medication number is printed on each part of this label.

6.5.2 Drug supply and storage

Study treatments 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, the study treatment should be stored according to the instructions specified on the drug label.

[redacted]

6.5.3 Study drug compliance and accountability

6.5.3.1 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. The Afinitor® dose that each patient is taking will be recorded on the Study Treatment CRF. This information must also be captured in the source document at each patient visit.

The investigator and/or assigned study personnel will also collect any information about concomitant medications and non-drug therapies at each patient visit and enter it on the 'Concomitant Medication / Non-drug Therapies' CRF page.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, 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.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. If study medication is to be destroyed by a third party or at the investigational site this must be approved by the sponsor and destruction certificates must be provided.

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.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column). No CRF will be used as a source document.

Allowed visit windows are specified as follows:

- Screening assessments as listed in Table 7-1 should occur within 28 days prior to Day 1.
- The 4, 12, 24, and 48 weeks visits should be performed within a ± 7 day window.

[redacted]

- The 12, 24, and 48 weeks efficacy follow-up visits, where applicable, should be performed within a ± 7 day window.
- Urine pregnancy tests (when applicable) should be performed every 4 weeks during the treatment phase within a ± 7 day window.
- The End of Treatment (EOT) visit should be performed within 28 days of last dose.
- All patients should be followed for at least 30 days for AEs and SAEs after last dose.

Every effort should be made to follow the schedule outlined in Table 7-1.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening	Open Label Treatment								Treatment Discontinuation Follow-up
Visit Name			Screening	Day 1	Week 4	Week 12	Week 24	Week 48	Every 4 weeks after Week 4 until EOT	End of study treatment (EOT)	Safety follow-up (Last dose +30days)	Efficacy follow-up (Week 12, 24, 48)
Visit number			1	100	110	120	130	140		1999		1010,1020 ,1030
Visit window			-28 to -1 days		±7days	±7days	±7days	±7days	±7days	Within 28 days from last dose	+7 days	±7days
Obtain Informed Consent	D	11.3	X									
Demography	D	7.1.2.3	X									
Inclusion/exclusion criteria	D	5.2 5.3	X	X								
TSC diagnosis	D	7.1.2	X									
Relevant medical history	D	7.1.2.3	X									
HIV history	S	7.1.2.3	X									
Prior/concomitant medications	D	7.1.2.3	X	X	X	X	X	X		X	X	
Physical examination	S	7.2.2.1	X	X	X	X	X	X		X		
WHO Performance status	D	7.2.2.4	X	X	X	X	X	X		X		
Height	D	7.2.2.3	X									
Weight	D	7.2.2.3	X	X	X	X	X	X		X		

[redacted]

	Category	Protocol Section	Screening	Open Label Treatment								Treatment Discontinuation Follow-up
Visit Name			Screening	Day 1	Week 4	Week 12	Week 24	Week 48	Every 4 weeks after Week 4 until EOT	End of study treatment (EOT)	Safety follow-up (Last dose +30days)	Efficacy follow-up (Week 12, 24, 48)
Visit number			1	100	110	120	130	140		1999		1010,1020 ,1030
Visit window			-28 to -1 days		±7days	±7days	±7days	±7days	±7days	Within 28 days from last dose	+7 days	±7days
Vital signs	D	7.2.2.2	X	X	X	X	X	X		X		
Hematology	D	7.2.2.5	X	X	X	X	X	X		X		
Biochemistry	D	7.2.2.5	X	X	X	X	X	X		X		
Coagulation	D	7.2.2.5	X	If clinically indicated						If clinically indicated		
Pulmonary function tests (FEV1, DLCO) for LAM patients only	D	7.2.2.6	X			X	X	X		X		
Blood gas analysis (O_2 saturation) for LAM patients only	D	7.2.2.6	X			X	X	X		X		
HCV-RNA, HBV-DNA, HBsAg, HBs-Ab, HBc-Ab	D	7.1.2	X									
Urinalysis	D	7.2.2.5	X	X	X	X	X	X		X		
ECG	D	7.1.2	X	If clinically indicated								
Serum pregnancy test	D	7.1.2.3	X							X		

[redacted]

	Category	Protocol Section	Screening	Open Label Treatment								Treatment Discontinuation Follow-up
Visit Name			Screening	Day 1	Week 4	Week 12	Week 24	Week 48	Every 4 weeks after Week 4 until EOT	End of study treatment (EOT)	Safety follow-up (Last dose +30days)	Efficacy follow-up (Week 12, 24, 48)
Visit number			1	100	110	120	130	140		1999		1010,1020 ,1030
Visit window			-28 to -1 days		±7days	±7days	±7days	±7days	±7days	Within 28 days from last dose	+7 days	±7days
Urine pregnancy test	S	7.2.2.5.5		X	X	X	X	X	X			
Abdomen and pelvis CT/MRI	D	7.2.1	X			X	X	X		X		X
Brain MRI/CT	D	7.2.1	X			If clinically indicated				If clinically indicated		If clinically indicated
Chest CT	D	7.2.1	If clinically indicated			If clinically indicated				If clinically indicated		If clinically indicated
Digital photography of skin lesions	D	7.2.1	If present			If identified at screening				If identified at screening		If identified at screening
Adverse events	D	8.1	X	X	X	X	X	X		X	X	
Serious adverse events	D	8.2	X	X	X	X	X	X		X	X	
Study Drug administration	D	6.1.1		X	X	X	X	X		X		
End of phase Disposition	D									X		X

[redacted]

	Category	Protocol Section	Screening	Open Label Treatment								Treatment Discontinuation Follow-up
Visit Name			Screening	Day 1	Week 4	Week 12	Week 24	Week 48	Every 4 weeks after Week 4 until EOT	End of study treatment (EOT)	Safety follow-up (Last dose +30days)	Efficacy follow-up (Week 12, 24, 48)
Visit number			1	100	110	120	130	140		1999		1010,1020 ,1030
Visit window			-28 to -1 days		±7days	±7days	±7days	±7days	±7days	Within 28 days from last dose	+7 days	±7days
Antineoplastic therapies since discontinuation of study treatment	D									X	X	X

[redacted]

7.1.1 Molecular pre-screening

Molecular pre-screening is not required to fulfill the inclusion criteria. If patients have undergone genetic testing for TSC in the course of their routine care this information can be used to confirm the TSC diagnosis (refer to Table 7-2).

7.1.2 Screening

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to Day 1 (see Table 7-1 for list of assessments to be performed). All inclusion and exclusion criteria will be evaluated and the investigator verifies that all patients have a clinically definite diagnosis of TSC according to the criteria described below.

Clinically definite diagnosis of TSC

All patients should have a clinically definite diagnosis of TSC according to the updated diagnostic criteria for TSC 2012 (Holpe Northrup, Darcy A. Krueger on behalf of the international TSC consensus (Hyman 2013) to be eligible. Clinically definite diagnosis of tuberous sclerosis according to the updated criteria is defined as either of the following:

- Two major features or one major feature with ≥2 minor features from Table 7-2.
- Genetic diagnostic criteria: The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins, prevents protein synthesis, or is a missense mutation whose effect on protein function has been established by functional assessment. Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC.

Note: In this study TSC genetic testing is not mandated. Patients who don't meet criteria in Table 7-2 can be regarded as fulfilling TSC diagnosis criteria if previous TSC1 or TSC2 pathogenic mutation is documented in medical history.

Table 7-2 Diagnostic criteria for Tuberous Sclerosis Complex

Major Features
1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias[a]
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)[b]
11. Angiomyolipomas (≥2)[b]

[redacted]

Minor Features
1. “Confetti” skin lesions 2. Dental enamel pits (>3) 3. Intraoral fibromas (_2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas
[a] Includes tubers and cerebral white matter radial migration lines. [b] A combination of the two major clinical features (LAM and angiomyolipoma) without other features does not meet criteria for a definite diagnosis.

Screening for hepatitis B and C

At screening all patients have to be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab. Additionally, all patients have to be tested for hepatitis C using quantitative RNA-PCR.

Please note that patients who test negative for HBV-DNA, HBsAg, and HBcAb but positive for HBs Ab, due to prior history of vaccination against Hepatitis B will be eligible. The fact that the patient had been vaccinated should be entered into the patient’s Medical History CRF.

Patients with serological markers indicative of chronic hepatitis B infection or measurable hepatitis C RNA will be excluded from the study.

Electrocardiogram (ECG)

A standard 12-lead ECG is to be performed at screening. Tracings must be dated and signed by the investigator (or his/her designee) and filed with the subject’s source documentation. Results from 12-lead ECG should be captured on the ECG Evaluation CRF. Significant findings must be recorded as Relevant Medical History.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. ECG assessments may also be performed at any time during the study at the discretion of the investigator.

Paper ECGs should be labeled with the study number, patient initials (where regulations permit), patient number, date and time and be kept in the source documents at the study site.

Rescreening

Reassessment of any screening criteria is permitted once for previously screen failed patients.

In this case the Subject Number assigned to the patient will not be used and the patient will be assigned a new 7 digit subject number. If the patient has been enrolled and treated, re-screening of the patient is **not** allowed.

In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria. A new informed consent form must be signed only if there is an interruption in the patient’s eligibility evaluation and the investigator chooses to re-screen the patient following screen failure; the 28 day screen period does not apply to the informed consent process. If a new informed consent form is signed, AEs and medical history will be assessed relative to the new

[redacted]

informed consent date. Patients who did not have the required AML lesion size would need to wait at least 3 months before re-screening. For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the patient. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. For details of assessments see Table 7-1.

7.1.2.1 Eligibility screening

The investigator is responsible to ensure only subjects who meet all inclusion and do not meet any exclusion criteria are included in the study.

7.1.2.2 Information to be collected on screening failures

Subjects who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered screen failures. Subjects who are found not eligible after signing the study consent will also be considered as screening failures. The screening failure will be entered on the Disposition Page.

The subject ID, visit date, subject status-screening, demographic information, informed consent, Inclusion/Exclusion and Disposition pages must also be completed for Screen Failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If a screen failure patient experiences an AE which does not meet the SAE criteria, details about the AE will be recorded only in the investigator's source documents. In case of an SAE after signing of main study informed consent, data must be recorded on both the AE and SAE forms.

7.1.2.3 Patient demographics and other baseline characteristics

During the Screening visit data will be collected on patient characteristics including demographic information (age, sex, race) and other background or relevant medical history (TSC diagnosis, prior anti-angiomyolipoma and TSC therapies), hepatitis and HIV history and any other assessments that are done for the purpose of determining eligibility for inclusion in the study (i.e. complete physical examination, height, weight, vital signs, WHO performance status, hematology, blood chemistries including coagulation and a serum lipid profile, urinalysis, CT/MRI of abdomen and pelvis, MRI/CT of brain, CT of chest (for patients with lymphangioleiomyomatosis), and ECG).

A serum pregnancy test must be completed for all female patients of child bearing potential within 28 days of Day 1 and a urine pregnancy test follow-up on Day 1 (prior to first dosing) to confirm eligibility.

The results of urine pregnancy tests will only be recorded in the patient source documents (pregnancy diary, patient records) whereas serum pregnancy test results will be recorded in the database of the assigned central lab vendor.

Prior and current concomitant medication use will also be collected and recorded.

[redacted]

For further details on eligibility assessments, please see Table 7-1.

Baseline assessments of kidney AML

A CT/MRI assessment of the kidneys will be performed for all patients at baseline to confirm presence of at least one angiomyolipoma lesion with longest diameter ≥ 3.0 cm. The CT/MRI images will be sent to the independent radiology service for measuring of kidney tumor volume at each time point. For information regarding the scan acquisition protocol, please refer to the Independent Radiology Review Charter provided by the assigned Imaging Vendor. The presence or absence of polycystic kidney disease will also be documented by the central reviewer.

A MRI/CT of the brain will be performed at baseline to identify any SEGA lesions. These images will be centrally collected and held with no independent assessment.

7.1.3 Treatment period

Patients will receive the first dose of study drug on Day 1 and continue to be treated per protocol until documentation of angiomyolipoma progression, unacceptable toxicity, pregnancy, withdrawal of consent or investigator decision to stop the study. However, study treatment may prematurely be discontinued for other reasons as well; please refer to Section 7.1.4. The maximum treatment duration is 48 weeks. Patients will visit the investigator site 4, 12, 24, and 48 weeks from Day 1 (±7days) and be followed as per the schedule of assessments. At these visits sufficient study drug will be dispensed to the patients to last until the next scheduled visit and unused drug will be returned to the site. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient or caregiver. This information should be captured in the source document at each visit.

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, 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 in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue study treatment for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

In addition to mandatory discontinuation reasons for study treatment listed in Section 6.2, study treatment **must** also be discontinued under the following circumstances:

- Pregnancy
- Death
- Subject/Guardian decision
- Adjustments to study treatment due to toxicity that result in treatment discontinuation (see Section 6.2)
- Any other protocol deviation that results in a significant risk to the patient's safety.

[redacted]

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, kidney lesion assessments must continue to be performed as per the schedule of assessments until documented disease progression (per independent radiology review), death, lost to follow-up, or withdrawal of consent.

7.1.4.1 Replacement policy

Not applicable.

7.1.5 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.6 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment. Safety information can be collected during a visit to the site or per telephone.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

[redacted]

7.1.7 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

Each center must have a designated radiologist or other physician who is responsible for the interpretation of CT scan or multiphase MRI. The same radiologist/physician should perform the evaluation for the entire duration of the study. All radiology evaluations will be performed initially by the local radiologist, but designation of AML response and progression will be based only on the evaluations made by the Independent Central Radiology Review. The results of the central evaluations will be used for analysis purposes.

CT/MRIs of the kidneys and brain must be digitized and sent to central radiology within 2 business days of the scan date. Following receipt of each scan, the Independent Central Radiology Review will be completed and the results of the kidney lesion assessments will be communicated back to the participating center and to Novartis. Details of the central review process will be described in the independent review charter developed between Novartis and the assigned imaging vendor.

Although the study will use an Independent Central Radiology Review to measure tumor volume, the decision to enroll the patient will be made based on the judgment of the investigator and local radiologist. The vendor will not decide whether patients should be removed from study treatment. This decision remains solely with the investigator.

Screening imaging assessments

Imaging assessments will be performed at screening within 28 days of start of treatment (Day -28 to Day -1 prior to Day 1).

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after treatment start cannot be considered baseline images. The same imaging modality that was performed at screening should be used for all assessments throughout the course of the study.

The following assessments are required at screening (see imaging collection plan, Table 7-3):

- Kidney (abdomen and pelvis)
  Preferred modalities: CT or MRI with contrast medium.
  If intravenous injection of either CT or MRI contrast medium is not tolerated by the patient the respective other modality with contrast medium should be performed. In case of intolerance to both CT and MRI contrast media it is accepted to perform MRI without

[redacted]

contrast. CT without contrast medium is not a recommended modality but accepted if none of the other modalities can be performed.
For instructions regarding screening assessments of angiomyolipoma lesions, please refer to Section 7.1.2.3.

- Brain
  A brain scan should be completed at screening to identify if any SEGA lesions are present.
  Preferred modality: MRI with contrast medium.
  If MRI contrast medium is not tolerated a contrast enhanced CT or MRI/CT without contrast are acceptable.
- Lung (thorax)
  A thorax scan at screening is only required if clinically indicated for patients with LAM.
  Preferred modality: CT with contrast medium.
  If a patient is known to have a contraindication to intravenous CT contrast media or develops a contraindication during the trial, a non-contrast CT can be performed. MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead.
- Skin lesions
  If skin lesions are present at screening, digital color photographs should be taken using a high resolution digital camera (≥3 megapixels) in clear focus, including a caliper, scale or ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

Imaging assessments during treatment and treatment discontinuation follow-up phase

Imaging assessments as described in Table 7-3 should be performed using the same imaging modality used at screening, irrespective of study treatment interruption or actual dosing (see Table 7-1). Imaging assessments for response evaluation will be performed 12, 24, and 48 weeks after start of treatment and at End of Treatment. The End of Treatment assessments can be omitted if the most recent assessment was done less than 8 weeks ago. Imaging assessments should be scheduled using the treatment start date as the reference date, and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

Table 7-3 Imaging collection plan

Procedure (see below for the preferred imaging modalities, requirements to use contrast medium)	**Screening**	**"Open-Label treatment" phase and "Treatment Discontinuation Follow-up" phase where applicable**
Abdomen and pelvis CT or MRI (pelvis only if required due to kidney size)	Mandated	Mandated at 12, 24, 48 weeks and at EOT
Brain MRI or CT	Mandated	Mandated at 12, 24, 48 weeks and EOT if SEGA lesion with longest diameter ≥1cm present at screening
Chest CT	If clinically indicated	At 12, 24, 48 weeks and EOT if clinically indicated
Digital photography of skin lesions	If skin lesions present	Mandated at 12, 24, 48 weeks and EOT if skin lesions present at screening

[redacted]

The preferred and allowed radiological imaging modalities are the same as at screening.

- Kidney (abdomen and pelvis)
  Preferred modalities: CT or MRI with contrast medium.
  If intravenous injection of either CT or MRI contrast medium is not tolerated by the patient the respective other modality with contrast medium should be performed. In case of intolerance to both CT and MRI contrast media it is accepted to perform MRI without contrast. CT without contrast medium is not a recommended modality but accepted if none of the other modalities can be performed.
- Brain
  Preferred modality: MRI with contrast medium.
  If MRI contrast medium is not tolerated a contrast enhanced CT or MRI/CT without contrast are acceptable.
- Lung (thorax), only performed if clinically indicated for LAM patients
  Preferred modality: CT with contrast medium.
  If a patient is intolerant to intravenous CT contrast media or develops a contraindication during the trial, a non-contrast CT can be performed. MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

All study kidney imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control and volumetric measurement of AML lesions. Brain MRI/CT images, chest CT scans and digital photographs of skin lesions (including any off-schedule imaging studies) should be sent to the designated imaging CRO for quality control and archiving. Any chest CT scans, brain imaging and photographs of skin lesions should be evaluated by the local radiologist/physician as per standard care.

All patients being discontinued from the study for angiomyolipoma progression must have their progression documented using the criteria specified in Section 7.2.1.1. In particular, a discontinuation reason of "angiomyolipoma progression" will not be sufficient to establish that angiomyolipoma progression actually occurred.

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed as per imaging collection plan (Table 7-3) until documented disease progression (per central radiology), end of study (week 48), death, lost to follow-up, or withdrawal of consent.

7.2.1.1 Angiomyolipoma response evaluation

Angiomyolipoma response and progression evaluation will be performed according to the criteria outlined below.

[redacted]

Screening requirement:

At baseline, all measurable angiomyolipomata with longest diameter ≥ 1.0 cm should be identified from each kidney. Only patients with at least one angiomyolipoma ≥ 3.0 cm in longest diameter will be eligible to be randomized into the trial. All baseline evaluations should be performed as close as possible to the beginning of treatment and never more than 28 days before the beginning of treatment. The same imaging modality must be used throughout the trial.

Target lesions:

Up to five of the largest measurable lesions on each kidney seen at screening should be identified as target angiomyolipoma, where measurable means at least 1.0 cm in longest diameter. The volume of these lesions will be measured at each kidney CT/MRI assessment during the trial. The same imaging modality must be used throughout the trial. Angiomyolipoma volume is defined as the sum of the volumes of the individual target angiomyolipoma, and it is angiomyolipoma volume that is used directly in the definition of angiomyolipoma response and angiomyolipoma progression.

Kidney volume:

All other angiomyolipoma (i.e., lesions other than the target angiomyolipoma as defined above) present at screening are non-target angiomyolipoma. In some cases there may be many non-target angiomyolipoma (e.g., >20), including non-measurable lesions (i.e., with longest diameter <1.0 cm). Instead of attempting to individually assess each non-target angiomyolipoma during the trial, the volume of each kidney will be measured. Increases in the volume of either kidney will then be taken as evidence of worsening angiomyolipoma. This is expected to be particularly useful when target angiomyolipoma are relatively stable, but non-target angiomyolipoma are clearly progressing.

Angiomyolipoma response assessment:

Angiomyolipoma response will be defined as:

- a reduction in angiomyolipoma volume of at least 50% relative to screening, where angiomyolipoma volume is the sum of the volumes of all target angiomyolipoma identified at screening.

In addition, angiomyolipoma response requires satisfying all of the following criteria:

- no new angiomyolipoma ≥ 1.0 cm in longest diameter are identified
- neither kidney increases in volume by more than 20% from nadir (where nadir is the lowest kidney volume obtained for the patient, separately for each kidney, previously in the trial including screening)
- the patient does not have any angiomyolipoma-related bleeding of grade ≥2 (as defined by NCI CTCAE, version 4.03).

Angiomyolipoma progression will be defined as one or more of the following:

- an increase from nadir of 25% or more in angiomyolipoma volume to a value greater than screening (where angiomyolipoma volume is the sum of the volumes of all target

angiomyolipoma identified at screening and where nadir is the lowest angiomyolipoma volume achieved by the patient previously in the trial (including screening))

- the appearance of a new angiomyolipoma ≥ 1.0 cm in longest diameter
- an increase from nadir of 20% or more in the volume of either kidney to a value greater than screening, where nadir is the lowest kidney volume obtained for the patient, separately for each kidney, previously in the trial (including screening)
- angiomyolipoma-related bleeding grade ≥2 as defined by NCI CTCAE, version 4.03.

Note: In some instances, disease that is measurable as a target lesion at screening and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the image review system allows the central reviewer to identify the separate sub-lesions as unique and non-overlapping so that the volume of each sub-lesion can be determined. The combined volumes of the sub-lesions will be reported as the volume of the lesion that has split. The individual split lesions will not be considered as new lesions, and will not automatically trigger an angiomyolipoma progression.

Conversely, it is also possible that two or more lesions which were distinctly separate at screening become confluent at subsequent visits. The central reviewer will be required to separate the confluent mass into regions relating to the original several distinct lesions. These regions will continue to be measured as separate lesions. Although this raises the possibility of increased variability in the measurements of the individual lesions due to the lack of distinct borders within the confluent mass, the primary endpoint (sum of lesion volumes) will still be accurately measured so long as the confluent mass itself has distinguishable borders.

7.2.1.2 SEGA evaluation

SEGA lesions should be assessed as per local standard practice by the site radiologist/physician at the scheduled time points (week 12, 24, 48, EOT).

In the unlikely event that a patient has SEGA lesion progression and does not meet the criteria for angiomyolipoma progression, it will be up to the investigator to determine if the patient should remain on study or be discontinued.

SEGA response assessment

The SEGA response assessment is not part of the efficacy assessments in this study and is not required. However, since clinical decisions may have to be made on SEGA response，these lesions need to be followed during the study by the local investigator.

7.2.1.3 Evaluation of skin lesions

Skin lesions resulting from TSC include hypomelanotic macules, the shagreen patch, periungual or subungual fibromas, facial angiofibromas and/or forehead plaques. Descriptions of each are given below.

Hypomelanotic macules are flat areas of skin that appear lighter than the surrounding skin. They can be any size or shape or may be the classic “ash-leaf” shape. Skin cells in this areacontain less pigment, so the area appears lighter than the surrounding skin.

[redacted]

The shagreen patch is a patch of skin that is similar in color to surrounding skin, but may be tough and dimpled like an orange peel. The shagreen patch is usually found on the lower back and nape of the neck, but they may also be seen on other parts of the body.

Periungual or subungual fibromas are small fibrous growths that appear around the fingernails or toenails and are usually not seen until adult life.

Facial angiofibromas are benign tumors of the face that often appear across the cheeks and nose and on the chin. They are initially small reddish spots or bumps that may increase in size with age.

Lastly, a forehead plaque is similar to the angiofibroma but is found on the forehead and scalp. These flesh-colored plaques are soft or compressible of doughy to hard lesions.

Digital photographs of all skin lesions will be taken at screening and then at 12, 24, 48 weeks and EOT. The investigator should document the presence of all relevant skin lesions in the patient records. There will not be any efficacy analysis concerning skin lesions but the photographic scans should be sent to the assigned Imaging Vendor.

7.2.1.4 Evaluation of renal function

Renal function will be assessed by the central lab using creatinine clearance calculated from the formula of Cockcroft and Gault (1976) at screening and at subsequent time points as specified in Table 7-1. For further details see Section 7.2.2.5.2.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examinations, vital signs, laboratory assessments including hematology, chemistry, coagulation, urine analysis as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

The physical examination must be performed by the Investigator as scheduled in Table 7-1.

The complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs include blood pressure, pulse measurement, and body temperature.

[redacted]

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.4 Performance status

WHO Performance status scale will be used as described in the Table 7-1 and Table 7-4.

Table 7-4 Performance Status WHO grade:

Grade 0:	Fully active, able to carry out all normal activity without restriction.
Grade 1:	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Grade 2:	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
Grade 3:	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
Grade 4:	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Grade 5:	Dead

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry, coagulation, hepatitis markers, serum pregnancy) are to be performed centrally according to the schedule of assessments and collection plan outlined in Table 7-1 and Table 7-5. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Central Laboratory Manual/Flowchart. The urinalysis will only be performed by the local laboratory using dipstick analysis.

If at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used (except in case of re-sampling and the results from the central laboratory are not yet available or are partial at Day 1, then eligibility may be based on the results from the local laboratory. In such case the results of the local laboratory will need to be recorded in the eCRF unplanned pages and a copy of the local lab normal ranges must be provided). Screening safety laboratory tests (hematology, biochemistry, lipid profile, urinalysis, and coagulation) will need to be repeated at Treatment Day 1 if they were collected more than 14 days prior to Treatment Day 1.

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel

[redacted]

with local analysis. The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an AE not reported by the central lab, or
- Local lab results document an AE where the severity is worse than the one reported by the central lab, or
- Eligibility had to be based on the local lab results due to pending / missing central lab results.

At any time during the study up to 30 days safety follow-up, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE CRF page. The severity of laboratory data will be graded using the Common Terminology Criteria for Adverse events (CTCAE) version 4.03. Additional analyses are left to the discretion of the investigator.

Table 7-5 Central clinical laboratory parameters collection plan

Test category	Test name
Hematology	Hemoglobin, platelets, total white blood cell count (WBC), absolute & differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils
Chemistry	Total LDH, fasting glucose, sodium, magnesium, phosphate, potassium, creatinine, BUN, albumin, SGOT (AST), SGPT (ALT), total bilirubin, direct bilirubin, triglycerides, cholesterol, alkaline phosphatase, uric acid, calcium
Urinalysis (Local Lab)	Standard urinalysis dipstick assessment must include: pH, protein, glucose, blood, ketones, and leukocytes.
Coagulation (mandated at screening, then only if indicated)	Prothrombin time (PT) or International normalized ratio [INR])
Hepatitis markers	HCV-RNA, HBV-DNA, HBsAg, HBs-Ab, HBc-Ab
Pregnancy test	Serum pregnancy test

7.2.2.5.1 Hematology

Hematology tests are to be performed centrally according to the schedule of assessments and collection plan outlined in Table 7-1. Detailed hematology panel is described on Table 7-5.

7.2.2.5.2 Chemistry

Chemistry tests are to be performed centrally according to the schedule of assessments and collection plan outlined in Table 7-1. Detailed chemistry panel is described in Table 7-5.

The creatinine clearance should be calculated from the formula of Cockcroft and Gault.

[redacted]

7.2.2.5.3 Urinalysis

Macroscopic urinalysis dipstick analysis (pH, protein, glucose, blood, ketones, and leukocytes) will be performed locally according to the schedule of assessments and collection plan outlined in Table 7-1. Detailed urinalysis panel is described in Table 7-5.

7.2.2.5.4 Coagulation

Prothrombin time (PT) or International normalized ratio (INR) will be assessed centrally according to the schedule of assessments and collection plan outlined in Table 7-1.

7.2.2.5.5 Pregnancy

Female patients of child bearing potential will perform urine pregnancy tests as outlined in Table 7-1 every 4 weeks (±7days) while receiving study drug until study drug discontinuation. The urine tests will be performed at the patient's home or at clinical site when a visit is scheduled. Patients should be instructed to inform site of a positive urine pregnancy result. A serum hCG pregnancy test should be performed by the central lab at screening and at end of treatment.

The results of urine pregnancy tests will be recorded in the patient source documents (pregnancy diary, patient records) whereas serum pregnancy test results will be recorded in the database of the assigned central lab vendor.

7.2.2.6 Pulmonary function test

Individuals participating in this trial will be questioned at each visit as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. If an investigator suspects a patient may be developing pneumonitis, investigations such as pulmonary function tests, CT chest and referral to a pulmonologist should be considered.

Pulmonary function tests (spirometry [FEV_1, FVC], DL_{CO} and room air O_2 saturation at rest or O_2 saturation on 6 minute walking test with up to 6 liters O_2/minute nasal oxygen) will be performed at screening on all patients with LAM. For these patients, PFTs will be performed at week 12, 24 and 48. In addition, PFTs should be performed as medically necessary in any patient with evidence of non-infectious pneumonitis.

A bronchoscopy with biopsy and/or a bronchoalveolar lavage (BAL) will be performed only when medically necessary for ensuring patient care (details are provided in Section 6.2.3.5 and Table 6-3).

Other assessments

No additional tests will be performed on patients entered into this study.

7.2.3 Resource utilization

Not applicable.

7.2.4 Patient reported outcomes

Not applicable.

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event 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 adverse events 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).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (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 Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

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

1. The severity grade (CTCAE Grade 1-5)
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, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met

[redacted]

7. Outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequalae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the concomitant medication CRF.

Once an adverse event 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, and the outcome.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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), should be recorded on the Adverse Events CRF. 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 Adverse Events 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 adverse event, 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 adverse event, should not be reported as adverse events. 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 adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data.

[redacted]

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 serious adverse events:
    - 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 serious adverse event

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 additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An 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.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event 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 study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

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

[redacted]

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 Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) 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 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 oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should 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.

8.4 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 product label. Additional safety information will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Data Monitoring Committee

Not applicable.

8.6 Steering Committee

Not applicable.

[redacted]

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 CRO) will review the protocol and CRFs 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 CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment 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 CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. 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

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (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 is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Safety labs will be collected centrally and data transferred to the study database at regular intervals.

The radiological imaging scans performed for this trial will be submitted by the sites to the CRO (designated by Novartis) to undergo central radiological review. The results of the radiological kidney assessments will be transferred from the CRO to the study database at regular intervals (as agreed upon between Novartis and the designated CRO).

Results from at home pregnancy tests will be recorded in patient diaries for source documentation only.

9.4 Database management and quality control

Novartis personnel 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.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Lab samples (hematology, chemistry, coagulation, serum pregnancy tests) and/or imaging data (kidney CT/MRI scans) will be processed centrally and the results will be sent electronically to Novartis. Digital photographs, brain and chest MRI/CT scans will only be quality checked and archived by the assigned imaging vendor. No central review will take place for the digital photographs, brain, and chest scans.

At the conclusion of the study, 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. 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.

After database lock, the investigator will receive a CD-ROM of the patient data for archiving at the investigational site

[redacted]

10 Statistical methods and data analysis

One safety and efficacy analysis (Final analysis) will be conducted on all patients after they complete their treatment and efficacy follow-up (after 48 weeks of treatment or earlier).

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of study treatment.

10.1.2 Safety set

The Safety Set comprises all patients who received at least one dose of study treatment. The Safety set and FAS are identical in this study, and will be used for all analysis.

10.1.3 Other analysis sets

Not applicable

10.2 Patient demographics/other characteristics

Demographic and other screening data including disease characteristics will be listed and summarized descriptively using the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, 25^{th} and 75^{th} percentiles median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at screening will be summarized by system organ class and preferred term for all patients.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to everolimus as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics.

The number of patients with dose adjustments (reduction, interruption, possible dose re-escalation to starting dose, or permanent discontinuation) and the reasons will be summarized for all patients and all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for all patients.

[redacted]

10.4 Primary objective

The primary objective in this study is to evaluate the safety of Afinitor® in Chinese adults with TSC-renal AML not requiring immediate surgery.

10.4.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented for all patients together.

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 30+1 after last dose of study medication.

10.4.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the Open-label Treatment phase, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from screening) will be summarized by system organ class and/or preferred term, severity (based on CTCAE version 4.03), type of adverse event, relation to study treatment

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from Screening phase and 30 days safety follow-up visit) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

10.4.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v4.03

[redacted]

- Worst post- screening CTCAE grade (regardless of the screening status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare screening to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03,

- Shift tables using the low/normal/high/ (low and high) classification to compare screening to the worst on-treatment value.

10.4.4 Other safety data

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

10.4.4.1 Supportive analyses for primary objective

Not applicable

10.4.4.2 Tolerability

Not applicable

10.5 Secondary objectives

The secondary objectives in this study are to evaluate the efficacy of Afinitor® in Chinese adults with TSC-renal AML not requiring immediate surgery with respect to angiomyolipoma response rate, angiomyolipoma progression, and renal function change from screening.

10.5.1 Angiomyolipoma response rate

Angiomyolipoma response rate, is defined as the proportion of patients with an angiomyolipoma response, as defined in Section 7.2.1.1, using data from the Independent Central Radiology Review of CT/MRIs and the Adverse Events CRF page (to identify angiomyolipoma-related bleeding of grade 2 or worse as defined by NCI CTCAE version 4.03).

Angiomyolipoma response rate will be calculated based on the FAS and presented together with its 95% confidence interval for all patients.

10.5.2 Angiomyolipoma progression

Patients with angiomyolipoma progression, as defined in Section 7.2.1.1, will be listed and described in narratives.

10.5.3 Renal function change from screening

Renal function will be assessed using the calculated creatinine clearance (CrCl) from the Cockcroft-Gault formula (Cockcroft et al 1976). The proportions of patients with severe renal impairment (defined as calculated CrCl < 30 mL/min), and in addition the proportion of patients with NCI CTCAE grade 3/4 serum creatinine will be determined.

[redacted]

10.5.4 Pharmacokinetics

Not applicable

10.5.5 Biomarkers

Not applicable

10.5.6 Resource utilization

Not applicable

10.5.7 Patient-reported outcomes

Not applicable

10.6 Exploratory objectives

Not applicable

10.7 Final analysis

The final analysis will be performed after all patients have completed Week 48 (or discontinued earlier but were followed up for efficacy up to Week 48) and their safety follow-up visit.

10.8 Sample size calculation

Approximately 40 patients will be enrolled to meet the CFDA post approval requirements. The sample size is based on feasibility, there is no hypothesis testing.

10.9 Power for analysis of key secondary variables

Not applicable

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 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 informed consent form 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 informed consent form (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.

Additional consent form

Not applicable.

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 Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

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Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

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 call 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 Principal Investigator. The study case report form (CRF) 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 CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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.

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Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) 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 informed consent forms 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 CSR.

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 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.

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