NOVARTIS

Clinical Development

RAD001/Everolimus /Afinitor®

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

Statistical Analysis Plan (SAP)

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02-Dec-2019	Prior to DB lock	Protocol amendment	Elimination of interim analysis	Section 1 Section 1.1 Section 2.1 Section 2.14 Section 5.1.1
			Change in threshold for subgroup analyses	Section 2.2.1.1 Section 2.2.1.2
			Elimination of forest plot	Section 2.2.1.2
			Elimination of frequency figure for daily dose	Section 2.4.1
08-Apr-2020	Prior to DB lock	Protocol amendment	Addition of potential supportive analyses due to COVID-19	Section 2.5.4
			Addition of handling of missing values of secondary efficacy objective	Section 2.7.3
			Addition of CTC Grade 5 for AE coding	Section 5.2
			Addition of handling rules for test values below LLOQ and above HLOQ	Section 5.3.1
19-Feb-2021	Post-DBL	Addendum 1	Update the Kaplan-Meier analysis method for time to angiomyolipoma progression (TTAP) calculation	Section 2.7.1

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List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
AML	Angiomyolipoma
ATC	Anatomical therapeutic classification
BMI	Body mass index
BSA	Body surface area
CFDA	China Food and Drug Administration
CRF	Case Report/Record Form
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DI	Dose intensity
DL_{CO}	Diffusing capacity factor of the lung for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FAS	Full Analysis Set
FEV1	Forced expiratory volume per second
FVC	Forced vital capacity
LAM	Lymphangioleiomyomatosis
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OS	Overall survival
PDI	Planned dose intensity
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PT	Preferred erm
RAP	Report and Analysis Process
RDI	Relative dose intensity
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TSC	Tuberous Sclerosis Complex
TTAP	Time to angiomyolipoma progression
WHO	World Health Organisation

1 Introduction

This document provides the detailed statistical analysis plan for study CRAD001M2401, which is referenced in the RAP documentation and/or study report.

This document supports one final analysis for safety and efficacy. Final analysis will be reported in a final CSR to support the license renewal submission and fulfill a post approval commitment (PAC).

The current analysis plan is based on the final protocol (Version 02) and original mock CRF draft ver0.3.

1.1 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.

A 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.

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1.2-1 below.

Table 1.2-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate the safety of Afinitor® in Chinese adults with TSC-AML not requiring immediate surgery.	• Incidence of adverse events, lab abnormalities	Refer to Section 2.8
Secondary		
To evaluate the efficacy of Afinitor® in Chinese adults with TSC-renal AML not requiring immediate surgery.	• AML response	Refer to Section 2.7.1
Other Secondary		
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	Refer to Section 2.7.1
Exploratory		
None		

2 Statistical methods

2.1 Data analysis general information

Novartis will be performing the final analysis.

SAS version 9.4 or higher will be used to conduct the analysis.

Categorical data will be presented as frequencies and percentages. For continuous data, the number of patients with assessable data, mean, standard deviation, median, minimum, maximum, lower quartile, and upper quartile will be presented. For time-to-event analyses, the number of patients at risk, the number and percentage of patients at risk with the event, the number and percentage of patients censored with the reason for censoring, Kaplan-Meier survival estimates with 95% CIs every 3 months, the median survival estimate and the 25^{th} and 75^{th} percentiles survival estimates with their 95% CI will be presented.

2.1.1 General definitions

2.1.1.1 Study drug and study treatment

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

Definition of terms: Study treatment = RAD001 = Afinitor® = everolimus.

2.1.1.2 Date of first administration of study treatment

The date of first administration of RAD001 is defined as the first date when a non-zero dose of RAD001 was administered, as per the Study Treatment CRF. For the sake of simplicity, the date of first administration of study drug will also be referred to as the start of study drug.

2.1.1.3 Date of last administration of study treatment

The date of last administration of RAD001 is defined as the last date when a non-zero dose of RAD001 was administered and recorded on the Study Treatment CRF.

2.1.1.4 Study day

The study day ***for safety assessments*** (e.g., adverse event (AE) onset date, laboratory abnormality occurrence, vital sign measurement, dose interruption) will be calculated using the start date of study treatment as the origin.

Safety assessments that occur on or after the start date of study treatment will have study day calculated as

(date of safety assessment) – (start date of study treatment) + 1.

Safety assessments that occur before the start date of study treatment will have study day calculated as

(date of safety assessment) – (start date of study treatment).

Then study day 1 will be the first day of study treatment and study day -1 will be the day before the first day of study treatment.

The study day ***for all other, i.e., non-safety assessments*** (e.g., Magnetic Resonance Imaging [MRI] assessment, angiomyolipoma progression, angiomyolipoma response, World Health Organization [WHO] performance status) will be calculated as same as safety assessments.

Study day will be displayed in the data listings.

2.1.1.5 Baseline

The baseline will be defined when appropriate as the last available assessment on or before the start date of RAD001.

2.1.1.6 On-treatment assessment/event

Adverse event summaries will present only on-treatment assessments, where on-treatment means that the AE started in the following time interval in the open-label period (including the lower and upper limits):

<date of first administration of open-label RAD001; date of last administration of open-label RAD001 + 30 days>.

Other safety summaries will present baseline and on-treatment assessments, where on-treatment means that the assessment occurred in the following time interval in the open-label period (including the lower and upper limits):

<date of first administration of open-label RAD001 + 1; date of last administration of open-label RAD001 + 30 days>.

2.1.1.7 Time windows

In order to summarize data over time, the following data types will be time slotted using time windows.

CT/MRI assessments for efficacy

CT/MRI assessments for efficacy will be performed at screening/baseline, and at 12, 24 and 48 weeks after the start of study treatment, and at the End of Treatment visit.

- The baseline time window is defined as being any time on or before the start of study treatment.
- The first on-study time window is from study day 2, i.e., the day after the start of study treatment, until study day 126 (i.e., week 18). The upper limit of this time window is midway between the first and second planned post baseline CT/MRI assessments, i.e., at weeks 12 and 24.
- The second on-study time window is from study day 127 until study day 252 (i.e., week 36). The lower limit of this time window is midway between the first and second planned post baseline CT/MRI assessments, i.e., at weeks 12 and 24, and the upper limit is midway between the second and third planned CT/MRI assessments, i.e., at weeks 24 and 48.

- The third on-study time window is from study day 253 until study day 343 (i.e., week 48 + 7 days). The lower limit of this time window is midway between the second and third planned post baseline CT/MRI assessments, i.e., at weeks 24 and 48, and the upper limit is day between the third assessment and its 7 day window, i.e., at weeks 48 and weeks 48 + 7 days.

Table 2.1-1 summarizes the time windows for CT/MRI assessments for efficacy.

Table 2.1-1 Time windows for CT/MRI assessments for efficacy

Time Window	Planned Visit Timing	Time Window Definition
Baseline	On or before Study Day 1	≤ Study Day 1
Week 12	Study Day 84	Study Days 2 – 126 (Baseline to Week 18)
Week 24	Study Day 168	Study Days 127 – 252 (Week 18 to Week 36)
Week 48	Study Day 336	Study Days 253 – 343 (Week 36 to Week 48 + 7 days)

Study Day 1 = Start date of study treatment

If more than one assessment is done within the Baseline time window, the assessment closest to study day 1 (i.e., the start of study treatment) will be used; if two or more assessments are equidistant from study day 1, then the mean value will be used. For all other time windows, the assessment closest to the planned assessment date will be used; if two or more assessments are equidistant from the planned date, then the mean value will be used.

Pulmonary function tests

Pulmonary function tests (PFT) will be performed on sporadic LAM and LAM patients at screening/baseline, and at 12, 24 and 48 weeks after the start of study treatment, and at the End of Treatment visit.

Table 2.1-2 summarizes the time windows for pulmonary function tests.

Table 2.1-2 Time windows for pulmonary function tests

Time Window	Planned Visit Timing	Time Window Definition
Baseline	On or before Study Day 1	≤ Study Day 1
Week 12	Study Day 84	Study Days 2 – 126 (Baseline to Week 18)
Week 24	Study Day 168	Study Days 127 – 252 (Week 18 to Week 36)
Week 48	Study Day 336	Study Days 253 – 343 (Week 36 to Week 48 + 7 days)

Study Day 1 = Start date of study treatment

If more than one assessment is done within the Baseline time window, the assessment closest to study day 1 (i.e., the start of study treatment) will be used; if two or more assessments are equidistant from study day 1, then the mean value will be used. For all other time windows, the assessment closest to the planned assessment date will be used; if two or more assessments are equidistant from the planned date, then the mean value will be used.

WHO performance status

WHO performance status will be collected at screening/baseline, on the start date of study treatment, at 4, 12, 24 and 48 weeks, and at the End of Treatment visit.

Table 2.1-3 summarizes the time windows for WHO performance status.

Table 2.1-3 Time windows for WHO performance status

Time Window	Planned Visit Timing	Time Window Definition
Baseline	On or before Study Day 1	≤ Study Day 1
Week 4	Study Day 28	Study Days 2 – 42 (Baseline to Week 6)
Week 12	Study Day 84	Study Days 43 – 126 (Week 6 to Week 18)
Week 24	Study Day 168	Study Days 127 – 252 (Week 18 to Week 36)
Week 48	Study Day 336	Study Days 253 – 343 (Week 36 to Week 48 + 7 days)

Study Day 1 = Start date of study treatment

If more than one assessment is done within the Baseline time window, the assessment closest to study day 1 (i.e., the start of study treatment) will be used; if two or more assessments are equidistant from study day 1, then the mean value will be used. For all other time windows, the assessment closest to the planned assessment date will be used; if two or more assessments are equidistant from the planned date, then the mean value will be used.

2.2 Analysis sets

This section defines the populations applicable to this study and their use in the statistical analyses.

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of study treatment. The FAS will be the primary population in the assessment of efficacy analysis.

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. The Safety Set will be the population used in the assessments of safety analysis.

2.2.1 Subgroup of interest

2.2.1.1 Safety

The main analyses on adverse events and abnormal laboratory values will be repeated on the Safety Set in the following subgroups:

- Gender
- Age (< 65 years and ≥ 65 years)

The objective of carrying out these subgroup analyses is to identify safety problems that are limited to a subgroup of patients, or that are more commonly observed in a subgroup of patients.

Summary tables will only be performed on the Safety Set and only if at least 10% of patients are present in each class.

2.2.1.2 Efficacy

For the primary efficacy variable of angiomyolipoma response rate, subgroup analyses will also be performed using the following:

- Gender
- Age (< 65 years and ≥ 65 years)

Efficacy analyses in subgroups are intended to explore the uniformity of any treatment effects found overall. Summary tables will present response rates with the exact 95% confidence interval.

The efficacy analyses in subgroups will be performed on the FAS and only if at least 10% of patients are present in each class (some grouping of classes will be considered for race).

2.3 Patient disposition, demographics and other baseline 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, 25th and 75th percentiles, median, minimum, and maximum will be presented.

Basic demographic and background data

All demographic and background data will be listed. The summary table will include age, sex, weight, height, body mass index (BMI), body surface area (BSA), race, ethnicity and WHO performance status.

Qualitative data will be summarized by means of contingency tables, and quantitative data will be summarized by appropriate descriptive statistics (mean, standard deviation, 25th and 75th percentiles, median, minimum, and maximum).

Body surface area in m^2 will be presented and is calculated using the (Dubois and Dubois, 1916) formula:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184,$$

where W is weight in kilograms and H is height in centimeters.

Diagnosis of TSC disease at Baseline

The diagnosis of TSC-related conditions or symptoms will be documented at the time of screening.

Diagnosis of TSC at baseline will be summarized according to the criteria listed in Table 2.3-1 below.

Table 2.3-1 Diagnostic Criteria for Tuberous Sclerosis Complex (TSC)

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 dysplasiasa 7. Subependymal nodules 8. Subependymal giant cell astrocytom[a] 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM) [b] 11. Angiomyolipomas (≥2) [b]
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.

Time since initial diagnosis of TSC-related conditions or symptoms will be summarized in years (defined as 365.25 days), and will be measured until the time of baseline (i.e., start date of everolimus).

Medical history

Medical history, including TSC-related conditions and symptoms, will be summarized and listed.

Summaries will be presented by primary system organ class and preferred term. Medical history/current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

2.3.1 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. Information from the “End of study treatment” will be used to provide a summary showing:

1. Number (%) of patients still on everolimus.
2. Number (%) of patients completed everolimus.
3. Number (%) of patients discontinued everolimus.
4. Primary reason for study treatment discontinuation.
5. Number (%) of patients completed follow-up phase.

6. Primary reason for discontinuation from follow-up phase

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The duration of study treatment (i.e., everolimus) exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized. In addition, the duration of exposure to study treatment will be categorized into time intervals, and frequency counts and percentages will be presented for the number of patients in each interval. The number of exposed patients will be summarized by gender and age. The number of patients with dose reductions or interruptions, and the reasons, will also be summarized.

Listings of all doses of the study treatment along with dose change reasons will be produced.

The Safety Set will be used for all summaries and listings of study treatment.

Duration of study treatment exposure

The following algorithm will be used to calculate the duration of study treatment exposure:

> Duration of exposure (days) = (date of last administration of study treatment) – (date of first administration of study treatment) + 1.

The duration includes periods of temporary interruption of study treatment, for any reason. “Date of last administration of study treatment” and “date of first administration of study treatment” were defined in Sections 2.1.1.3 and 2.1.1.2, respectively.

Cumulative dose

Cumulative dose is defined as the total dose given during study treatment exposure, expressed in units of mg. For patients who did not take any study drug, the cumulative dose is by definition equal to zero.

Dose intensity and relative dose intensity

Dose intensity is defined as follows:

> DI (mg/m^2/day) = Cumulative dose (mg/m^2) / Duration of exposure (days).

For patients who did not take any study drug, the DI is by definition equal to zero.

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as per protocol in the same dose unit and unit of time as that of the DI. The PDI in this study is 10 mg/day.

Relative dose intensity is defined as follows:

> RDI = DI (mg/day) / PDI (mg/day).

Cumulative dose, dose intensity and relative dose intensity will be summarized.

Dose reductions and interruptions

The number of patients with dose reductions or interruptions, and the reasons, will be summarized. Dose reductions and interruptions will be determined programmatically using the rules defined below.

Interruption: An interruption is defined as a 0 mg/0 tablets dose given on one or more days.

If the start and end dates of dose interruption are incomplete (partial date), no imputation method will be applied to the date. It will be considered as no dose interruption.

Reduction: A reduction is defined as a decrease in dose to a non-zero dose from the protocol planned dose (10 mg/day), or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. For example, in the sequence 10 mg daily – 0 mg – 5 mg daily, the 5 mg daily dose will be counted as a reduction. In the sequence 10 mg daily – 2.5 mg daily – 5 mg daily, two reductions will be counted since the 5 mg daily dose is still lower than the protocol planned dose and is, therefore, counted as a second reduction. A decrease in frequency of administration which results in a lower cumulative dose is also counted as a reduction, e.g., in the sequence 10 mg daily – 5 mg daily – 5 mg every other day, two reductions will be counted.

If a patient moves from a higher than protocol planned dose down to the planned dose then this is not counted as a reduction. However, if they move directly from a higher than planned dose down to a lower than protocol planned dose, or the planned dose on a less frequent regimen, then this is counted as a reduction.

The number of dose reductions and interruptions per patient will be tabulated. The reasons for reductions and interruptions will be summarized, where only reasons that correspond to programmatically determined dose reductions and interruptions will be presented.

2.4.2 Prior, concomitant and post therapies

Prior, concomitant and post therapies entered into the database will be coded using the WHO Drug Reference List to allow for categorization by preferred term. In addition to categorizing therapies data by preferred term, drugs are classified according to their ATC classification in order to present how they are being utilized. The ATC classification allows for a summary of medications by a high-level common drug class.

Concomitant medications and significant non-drug therapies/procedures taken concurrently with the study drug everolimus will be listed and summarized by ATC class and preferred term by means of frequency counts and percentages.

These summaries and listings will include medications starting on or after the start date of everolimus, or medications starting prior to the start date of everolimus and continuing after the start date of everolimus. Medications starting more than 30 days after the last day of everolimus will not be included. Any prior concomitant medications or significant non-drug therapies/procedures starting and ending prior to the start of everolimus will be listed.

Systemic anti-angiomyolipoma medication since discontinuation of study treatment will be listed and summarized by ATC class and preferred term by means of frequency counts and percentages.

The Safety Set will be used for all the above-mentioned tables and listings.

2.5 Analysis of the 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. For further details on safety analysis, please see safety analyses in section 2.8.

2.5.1 Primary endpoint

The primary endpoints are incidence of adverse events and laboratory abnormalities. For further details, please see safety analyses in section 2.8.

2.5.2 Statistical hypothesis, model, and method of analysis

Not applicable

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable

2.5.4 Supportive analyses

Additional sensitivity analyses might be further conducted if needed to assess the impact of missing assessments and/or evaluate the effect of baseline demographic and disease characteristics of potential prognostic value on study objectives.

Additional sensitivity analysis can be done to assess the impact of COVID19.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

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 baseline.

2.7.1 Secondary endpoints

The efficacy endpoints will be based on the independent central radiology review of CT/MRI assessments of the kidneys to determine the volumes of target lesions in the kidneys.

The efficacy analysis will be performed using the FAS.

Definition

Each post baseline CT/MRI assessment of the kidneys will be classified by the Independent Central Radiology Review as either angiomyolipoma response, stable disease, angiomyolipoma progression or not evaluable, based on the combined radiological assessments of target angiomyolipoma volume, kidney volumes and new angiomyolipoma lesions.

An overall angiomyolipoma response will then be calculated by Novartis combining the angiomyolipoma radiological assessment as provided by the Independent Central Radiology Review and angiomyolipoma-related bleeding reported by the investigator on the Adverse

Events CRF page. Clinical review is required in order to identify all occurrences of angiomyolipoma-related bleeding reported by the investigators.

Angiomyolipoma response is 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 angiomyolipomata identified at screening.

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

- No new angiomyolipomata $\geq$ 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 baseline)
- The patient does not have any angiomyolipoma-related bleeding of grade $\geq$ 2 (as defined by NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03).

Angiomyolipoma progression is 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 angiomyolipomata identified at baseline and where nadir is the lowest angiomyolipoma volume achieved by the patient previously in the trial (including screening)
- The appearance of a new angiomyolipoma $\geq$ 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 $\geq$ 2 as defined by NCI CTCAE, version 4.03.

Stable disease (SD): insufficient shrinkage in angiomyolipoma volume to qualify for response and the absence of progression.

Not evaluable (NE): CT/MRI performed but not readable (e.g., not all designated target lesions are included in a follow up image due to technical error).

The ***best overall angiomyolipoma response*** is the best response recorded from treatment until the first to occur out of (i) angiomyolipoma progression, (ii) the cut-off date for the final analysis, (iii) the date when a further systemic anti-angiomyolipoma medication is started, (iv) the date of an angiomyolipoma-related surgery, or (v) the date of death.

Angiomyolipoma response rate

Angiomyolipoma response rate, is defined as the proportion of patients with best overall angiomyolipoma response status of “angiomyolipoma response” (as defined as above) during maximum treatment duration of 48 weeks 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 an exact 95% confidence interval for all patients.

Overall angiomyolipoma response (either angiomyolipoma response, stable disease, angiomyolipoma progression or not evaluable) at each assessment will be summarised by frequency and percentage.

Supportive analyses will include descriptive summaries of the sum of the volumes of target angiomyolipoma lesions from both kidneys (mean, standard deviation, 25th and 75th percentiles, median, minimum and maximum) at each assessment, using the time windows defined in Section 2.1.1.7. Change from baseline (actual and percentage) in the sum of volumes of target angiomyolipoma lesions will also both be summarized descriptively at each assessment.

A waterfall plot will present the best percentage change from baseline in target angiomyolipoma volume at each assessment.

Note that patients with best overall angiomyolipoma response of Not Evaluable will be treated as non-responders in the calculation of the best overall angiomyolipoma response rate in the FAS, but will be excluded from the denominator for the waterfall plots.

Angiomyolipoma progression

Angiomyolipoma progression, is defined as the proportion of patients with an angiomyolipoma progression during maximum treatment duration of 48 weeks, as defined as above, 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 progression rate will be calculated based on the FAS and presented together with an exact 95% confidence interval for all patients.

Time to angiomyolipoma progression

Time to angiomyolipoma progression (TTAP) is defined as the time from the start date of everolimus to the date of the first documented angiomyolipoma progression, where angiomyolipoma progression is defined as above. TTAP will be censored if angiomyolipoma progression is not observed before the first to occur out of

(i) the cut-off date for the analysis, or

(ii) the date when a further systemic anti-angiomyolipoma medication is started, or

(iii) the date of a angiomyolipoma-related surgery or

(iv) the date of death.

The censoring date will be the date of the last adequate CT/MRI assessment occurring before the first of any of these four events to have occurred, or treatment day 1 if there were no adequate CT/MRI assessments performed post-baseline.

TTAP will be presented in months and is calculated as:

> (Date of angiomyolipoma progression/censoring – Start date of everolimus + 1) × 12 ÷ 365.25.

The TTAP distribution will be presented descriptively in the FAS using a Kaplan-Meier curve. Summary statistics from the Kaplan-Meier distribution will be determined, including the

median TTAP and the proportions of patients remaining progression-free at 3, 6, and 12 months. These statistics will be given as point estimates with 95% confidence intervals.

Per protocol, tumor assessment was done at Week 4, 12, 24 and 48. At database lock, it was observed that most patients were censored at treatment completion at the time of their Week 48 assessment, and only 3 out of the 40 patients had angiomyolipoma progression observed. 9 patients were discovered to have TTAP greater than the maximum treatment duration of 48 weeks + 7 day window, among which one patient had progressed; this patient had the longest TTAP in the analysis set.

Kaplan-Meier estimates up to 48 weeks can be interpreted as fully valid. However, beyond that point where censoring was occurring due to treatment completion, the estimates are extremely undependable due to the high variability introduced by the small number of patients remaining in the risk set. In particular, the progression event in the patient with the longest TTAP causes the KM curve to drop to zero which is not meaningful; it is just an artifact of the KM calculation. In order to perform a somewhat interpretable analysis at this late timepoint, a revised analysis was introduced in which all patient outcomes (censoring or event) occurring after the maximum treatment duration will be considered to have occurred at the same timepoint. Specifically:

For TTAP exceeding the maximum treatment duration of 48 weeks + 7day window (11.268 months), the TTAP will be reassigned to 11.268 months. Then the Kaplan-Meier curve will be re-computed using this revised time definition.

It should be kept in mind that the KM event rate at the end of the study using this approach is very likely still over-estimated: the KM curve still drops noticeably because there were only 9 patients in the risk set beyond the end of treatment. Nevertheless, there was no signal in the data of a likely large increase in that narrow timeframe. Although this revised estimate ignores an event when it actually occured, it does allow incorporation of that single late event in a more reasonable manner than using the raw data. Therefore, it is reasonable to say that the estimates up to the end of the Week 48 assessment window can be interpreted as fully valid.

Time to angiomyolipoma response

Time to angiomyolipoma response is defined as the time from the start date of everolimus until the date of the first documented angiomyolipoma response, where angiomyolipoma response is as defined as above. Time to angiomyolipoma response applies only to patients who achieve an angiomyolipoma response, i.e., patients in the analysis will have known times to angiomyolipoma response and there will be no censored times.

Time to angiomyolipoma response is calculated in months as

$$(\text{Date of first AML response} - \text{Start date of everolimus} + 1) \times 12 \div 365.25.$$

The median time to angiomyolipoma response will be presented along with a 95% confidence interval, and the proportions of angiomyolipoma responders who respond by 3, 6, and 12 months will be provided.

Duration of angiomyolipoma response

Duration of angiomyolipoma response is defined as the time from the date of the first documented angiomyolipoma response until the date of the first documented angiomyolipoma progression, where angiomyolipoma response and angiomyolipoma progression are as defined as above. Duration of angiomyolipoma response applies only to patients who achieve an angiomyolipoma response.

Duration of angiomyolipoma response will be censored if angiomyolipoma progression is not observed before the first to occur out of

(i) the cut-off date for the analysis, or

(ii) the date when a further systemic anti-angiomyolipoma medication is started, or

(iii) the date of a angiomyolipoma-related surgery, or

(iv) the date of death.

The censoring date will be the date of the most recent CT/MRI assessment before the first of any of these four events occurred.

Duration of angiomyolipoma response is calculated in months as

> (Date of angiomyolipoma progression/censoring – Date of first angiomyolipoma response + 1) × 12 ÷ 365.25.

A Kaplan-Meier curve will be constructed, and the median duration of angiomyolipoma response will be presented along with 95% confidence intervals. In addition, the Kaplan-Meier estimates with 95% confidence intervals will be presented at 3, 6, and 12 months.

Change from baseline in renal function

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). In addition, the proportion of patients with NCI CTCAE grade 3/4 serum creatinine will be determined.

For creatinine clearance, changes from baseline will be summarized descriptively (mean, standard deviation, 25th and 75th percentiles, median, minimum and maximum) at each assessment in FAS. The proportions of patients with severe renal impairment and NCI CTCAE grade 3/4 serum creatinine will be summarized by means of frequency counts and percentage at each assessment. Creatinine and CrCl values will be listed at patient level by visit from FAS.

2.7.2 Statistical hypothesis, model, and method of analysis

This study has a single treatment arm and there are no statistical tests planned for any of the response rates.

Response rates

Responses will be summarized in terms of percentage rates with exact 95% confidence intervals. An exact binomial confidence interval (Clopper and Pearson, 1934) will be used, implemented using SAS procedure FREQ with the EXACT statement for one-way tables.

Time-to-event analyses

This section presents the general methodology used to analyze time-to-event variables, e.g., TTAP, time to angiomyolipoma response and duration of response.

An estimate of the time-to-event function will be constructed using the Kaplan-Meier (product-limit) method as implemented in the procedure LIFETEST with the METHOD=KM option. The Kaplan-Meier curve will be displayed.

Median time-to-event will be obtained along with a 95% confidence interval calculated from the procedure LIFETEST using the method of (Brookmeyer and Crowley, 1982).

Kaplan-Meier estimates of the time-to-event function with 95% confidence intervals at 3, 6, and 12 months, where 1 month is defined as (365.25/12)=30.4375 days, will be presented. The confidence intervals will be constructed using Greenwood's formula (Collett, 1994) for the standard error of the Kaplan-Meier estimate. The log-log transformation of the survivor function (Kalbfleisch and Prentice, 1980) will be used in order to ensure that the confidence limits remain in the interval [0, 1]. The complementary log-log transformation is implemented in the LIFETEST procedure using the option CONFTYPE=LOGLOG.

2.7.3 Handling of missing values/censoring/discontinuations

Patients with unknown angiomyolipoma response status will be treated as non-responders in the calculation of the angiomyolipoma response rate in the Full Analysis Set at the end of the trial.

If an AML progression is documented after two or more missing assessments or non-adequate assessments, then the date of AML progression will be censored at the date of the last adequate assessment. If an AML response is observed after a single missing or non-adequate assessment, the actual date of event will be used.

TTAP will be censored if angiomyolipoma progression is not observed before the first to occur out of (i) the cut-off date for the analysis, or (ii) the date when a further systemic anti-angiomyolipoma medication is started, (iii) the date of a angiomyolipoma-related surgery or (iv) the date of death. The censoring date will be the date of the most recent MRI assessment before the first of any of these four events occurred.

Time to angiomyolipoma response applies only to patients who achieve an angiomyolipoma response, i.e., patients in the analysis will have known times to angiomyolipoma response and there will be no censored times.

Duration of angiomyolipoma response will be censored if angiomyolipoma progression is not observed before the first to occur out of (i) the cut-off date for the analysis, or (ii) the date when a further systemic anti-angiomyolipoma medication is started, (iii) the date of a angiomyolipoma-related surgery or (iv) the date of death. The censoring date will be the date of the most recent MRI assessment before the first of any of these four events occurred.

Other missing data will simply be noted as missing on appropriate tables/listings.

2.8 Safety analyses

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., vital signs and special tests) will be considered as appropriate.

All safety outputs will use the Safety Set.

The safety summary tables will include only assessments collected no later than 30 days after the date of last administration of everolimus. The safety summary listings will include all assessments, with those collected later than 30 days after date of last everolimus being flagged.

2.8.1 Adverse events

General rules for AE Reporting

AE summaries will include all AEs starting on or after treatment day 1 (i.e., on or after the start date of everolimus) and no later than 30 days after the last day of everolimus. All AEs will be listed. AEs starting prior to treatment day 1 will be identified in the listings with a starting treatment day less than day 1, and AEs starting later than 30 days after the last day of everolimus will be specifically flagged.

AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary system organ class, and for each preferred term using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the AE category.

Separate AE summaries will be presented by primary system organ class, preferred term, and maximum common toxicity criteria (CTC) grade. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The frequency of CTC grade 3 and 4 AEs will be summarized separately.

Any information collected (e.g., CTC grades, relationship to study drug, action taken) will be listed as appropriate.

AE summaries

The following adverse event summaries will be produced:

- Adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events, with suspected relationship to study drug, by primary system organ class and preferred term
- Adverse events, regardless of study drug relationship, by preferred term
- Adverse events, regardless of study drug relationship, by primary system organ class, preferred term and maximum CTC grade
- Adverse events, with suspected study drug relationship, by primary system organ class, preferred term and maximum CTC grade

- CTC grade 3 or 4 adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- CTC grade 3 or 4 adverse events, with suspected study drug relationship, by primary system organ class and preferred term
- Deaths, by primary system organ class and preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Serious adverse events, with suspected study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation, regardless of study drug relationship, by preferred term
- Adverse events requiring dose adjustment or study drug interruption, regardless of study drug relationship, by preferred term
- Adverse events requiring additional therapy, regardless of study drug relationship, by preferred term

Adverse events will be presented in alphabetical order for system organ class, and in descending order of frequency for preferred term within each system organ class.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables for on treatment emergent AEs which are not SAEs with an incidence greater than and equal to 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.1 Adverse events of special interest (AESI)/ grouping of AEs

For each specified AESI, the number and percentage of patients with at least one event of the AESI occurring during the on-treatment period will be summarized. Summaries of these AESIs will be provided grouped by CTCAE grades, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, etc.

Such groups consist of adverse events for which there is a specific clinical interest in connection with everolimus treatment (i.e., where everolimus may influence a common mechanism of action responsible for triggering them), or adverse events which are similar in nature (although not identical). A non-exhaustive list of AE groupings includes “Stomatitis and related events”, “Infections”, “Amenorrheas” and “Non-infectious pneumonitis”. All notable adverse event groupings are defined through the use of Standardized MedDRA Queries (SMQ), Preferred Terms (PT), High Level Terms (HLT), or System Organ Classes (SOC), or through a combination of these four components. At the project level, a SAS dataset named eCRS contains the exact composition of the adverse events groupings will be used to map reported adverse events to the notable adverse events groupings. This dataset may be updated (i.e., it is a living document) based on review of accumulating trial data, and it is the most up to date version at the time of DB lock that will be used. Note that certain adverse events may be reported within multiple groupings.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by system organ class and preferred term.

All deaths will be listed for the safety set, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

The laboratory assessments include hematology, biochemistry, coagulation , urinalysis, hepatitis markers, and pregnancy test. Data from all sources (central and local laboratories) will be listed, but summary tables will only include data from the central laboratory (except urinalysis, where most assessments were done in local lab).

The frequency of notable laboratory abnormalities will be displayed by parameter.

The following summaries will be produced for laboratory data (by laboratory parameter – except for coagulation parameters):

- Number and percentage of patients with worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

Note: As a project standard, shift tables using the low/normal/high classifications based on laboratory reference ranges to compare baseline to the final on-treatment laboratory value will not be produced.

The following listings will be produced for laboratory data:

- Listing of patients with laboratory values outside the laboratory reference ranges with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

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.

Data from electrocardiogram will be listed at screening and unscheduled visits.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The parameters collected are height (cm), weight (kg), body temperature (°C), respiratory rate (breaths per minute), pulse (beats per minute) and both systolic and diastolic blood pressure (mmHg).

The criteria for clinically notable abnormalities are defined below in Table 2-1.

The following summaries will be produced for each vital sign parameter:

- Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e., both elevated and below normal values).

In addition, the following two listings will be produced:

- Patients with clinically notable vital sign abnormalities.
- All vital sign assessments listed by patient and vital sign parameter.

In both listings, the clinically notable values will be flagged and the assessments collected later than 30 days after the last treatment date will also be flagged.

Table 2-1 Clinically notable values for vital signs

Vital Sign		Criteria for clinically notable abnormalities
Systolic BP (mmHg)	High	>=180 mmHg and increase >=20 mmHg from baseline
	Low	<= 90 mmHg and decrease >=20 mmHg from baseline
Diastolic BP (mmHg)	High	>=105 mmHg and increase >=15 mmHg from baseline
	Low	<= 50 mmHg and decrease >=15 mmHg from baseline
Body temperature (°C)	High	>=39.1°C
	Low	<=35.0°C
Weight (kg)	High	Increase from baseline of >= 10%
	Low	Decrease from baseline of >= 10%
Pulse (beats per minute [bpm])	High	≥ 120 bpm with increase from baseline of ≥ 15 bpm
	Low	≤ 50 bpm with decrease from baseline of ≥ 15 bpm

2.8.4.3 WHO performance Status

The WHO performance scale (Table 2-2) is an instrument designed by the World Health Organization and is used to describe the physical health of patients, ranging from 0 (most active) to 4 (least active).

Table 2-2 WHO Performance Scale

Score	Description
0	Able to carry out all activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to do light work.
2	Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

The WHO performance status will be analyzed for patients from the safety set. Frequency counts and percentages will be used to summarize performance status descriptively over time. A Listing of performance status will be presented.

2.8.4.4 Pulmonary function test

Change from baseline in pulmonary function tests by time point will be presented. Lung function parameters including FEV1, FVC and DL_{CO} and changes from baseline will be summarized descriptively (mean, standard deviation, 25th and 75th percentiles, median, minimum and maximum) at each assessment in sporadic LAM and LAM patients only from safety set. Listing of pulmonary function test will also be presented for LAM patients.

2.9 Pharmacokinetic endpoints

Not applicable

2.10 PD and PK/PD analyses

Not applicable

2.11 Patient-reported outcomes

Not applicable

2.12 Biomarkers

Not applicable

2.13 Other Exploratory analyses

Not applicable

2.14 Final analysis

A 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.

3 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.

4 Change to protocol specified analyses

No change to protocol.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely or partially missing and the end of treamtent (EOT) eCRF page is available (prior to any death date or withdrawl of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Use the start date of that record.

Subjects with missing start dates are to be considered missing for all study treatment component related calculations described in Section 2.4.1 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE date imputation

Adverse event end date

No imputation of partial date or missing date was done except for imputation to handle events spreading over the cut-off date.

Adverse event start date

If the adverse event start date was missing no imputation was done.

If the adverse event start date was partial (missing day) and the month occurred prior to the study medication start month and the year occurred prior to the study medication start year, the 15th of the specified month was used.

If the adverse event start date was partial (missing day), and the adverse event start month was greater than or equal to the study medication start month and the adverse event start year was greater than or equal to the study medication start year, the maximum of the first of the month of the adverse event start date or the study medication start date plus one day was used.

The table below presents the algorithm used to impute the partial AE start date:

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	_null_	_null_	_null	_null_
YYYY < TRTY	01JULYYYY	15MONYYYY	15MONYYYY	15MONYYYY
YYYY = TRTY	TRTSTD+1	15MONYYYY	MAX(01MONYYYY, TRTSTD+1)	MAX(01MONYYYY, TRTSTD+1)
YYYY > TRTY	01JANYYYY	MAX(01MONYYYY, TRTSTD+1)	MAX(01MONYYYY, TRTSTD+1)	MAX(01MONYYYY, TRTSTD+1)

Where:

MON = Month of Partial Adverse Event Start Date

YYYY =Year of Partial Adverse Event Start Date

TRTM= Month of Treatment Start Date

TRTY= Year of Treatment Start Date

TRTSTD = Treatment Start Date

5.1.3 Concomitant medication date imputation

Medication/therapy end date

If the medication/therapy end day or day/month was missing and the partial date indicated that the medication/therapy clearly started prior to or equal to the year of study treatment start - Impute the last day of the month or 31 December.

If the medication/therapy end date is completely missing - Check to see if medication is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then we assume that medication is still being taken (i.e. no imputation is done).

If the medication is not ongoing and medication start date is prior to first dose date of study treatment then impute the study treatment end date as medication end date. Similarly, if medication started on or after first dose date then impute the last date of either the last dose date of study treatment or a day after medication/therapy start date.

Medication/therapy start date

If the medication/therapy start day or day/month was missing and the partial date indicated that the medication/therapy clearly started prior to or equal to the year of study treatment start, the 1st of the month or January 1 was used as the medication/therapy start date.

If the medication/therapy start day was missing, and the partial date did not indicate if the date was before or after first dose of study treatment, the medication/therapy start date was imputed to:

- 01JAN CMDEND1Dyyyy if the medication/therapy end date was before the start of study treatment (where CMDEND1D is the medication/therapy end date).
- Start of study treatment otherwise.

5.1.3.1 Prior therapies date imputation

Not applicable

5.1.3.2 Post therapies date imputation

Not applicable

5.1.3.3 Other imputations

Not applicable

5.2 AEs coding/grading

Coding of AEs

Adverse events are coded using the MedDRA terminology.

Grading of AEs

AEs will be assessed according to the CTCAE version 4.03. In case of an update of the CTC criteria, some mapping may be necessary.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of TSC treatments. CTCAE v4.03 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). 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, grades 1 – 5 corresponding to the severity of mild, moderate, severe, life-threatening, and death related to the AE will be used.

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in <Novartis internal criteria for CTC grading of laboratory parameters>. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version 4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned when the value is within normal limits. In the case when a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero. Grade 5 will not be used.

5.3.1 Handling of test values below LLOQ and above HLOQ

For numeric laboratory parameters, test values below the lower limit of quantification (LLOQ) and above the higher limit of quantification (HLOQ) may show “<n” (or “<=n”) and “>n” (or “>=n”) in the database respectively, where n can be any number. The classification of CTC grades, the low/normal/high groups, and time point summary tables will follow this data handling rule: a value which shows “<n” (or “<=n”) will be handled as zero; a value which shows and “>n” (or “>=n”) will be handled as n. These values will be presented in the listing as it is.

5.4 Statistical models

5.4.1 Primary analysis

Primary analysis is safety analysis, so no model will be used for analysis.

5.4.2 Key secondary analysis

Not Applicable

5.5 Rule of exclusion criteria of analysis sets

Not Applicable

6 Reference

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