NOVARTIS

Clinical Development

RAD001 (everolimus)

Protocol CRAD001M2305 / NCT02338609

Long-term follow-up study to monitor the growth and development of pediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT)

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List of abbreviations

AE	Adverse Event
µM	Micro mole
AKT	Protein Kinase B
ATC	Anatomical-Therapeutic-Chemical
BMI	Body Mass Index
CCHMC	Cincinnati Children's Hospital Medical Center
CHMP	Committee for Medicinal Products for Human Use
Cm	Centimeter
Cmax	Maximum Concentration
Cmin	Minimum (trough) Concentration
CNAE	Clinically Notable Adverse Event
CPO	Country Pharmaceutical Organization
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
CTH	Clinical Trial Head
DS&E	Drug Safety & Epidemiology
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EIAED	Enzyme Inducing Antiepileptic Drugs
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Patient First Visit
GCP	Good Clinical Practice
HUVEC	Human Umbilical Vein Endothelial Cell
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
In	Inch
IN	Investigator Notification
IRB	Institutional Review Board
Kg	Kilogram
Lb	Pound
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	Mammalian target of Rapamycin
NCI	National Cancer Institute
nM	Nano mole

PASS	Post-Authorization Safety Study
PD	Progressive Disease
PHI	Protected Health Information
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic
p-S6	Phosphorylated S6
RCC	Renal Cell Carcinoma
REB	Research Ethics Board
SAE	Serious Adverse Event
SD	Standard Deviation
SDS	Standard Deviation Score
SEC	Study Evaluation Completion
SEGA	Subependymal Giant Cell Astrocytoma
SEN	Subependymal Nodule
SI	Système International
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Event
TAND	TSC-Associated-Neuropsychiatric-Disorders
TDM	Therapeutic Drug Monitoring
TS	Tanner Stage
TSC	Tuberous Sclerosis Complex
UK	United Kingdom
US	United States of America
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

Amendment 1

Amendment rationale

At the time of this amendment, enrollment into this study has not yet started.

This protocol is being amended in order to address comments received from the reviewers at the Committee for Medicinal Products for Human Use (CHMP). In light of these comments from the Health Authority, the protocol is being amended to clarify operational activities that are planned for each visit. Additional details regarding the analysis plan were added.

The specific issues addressed in this amendment include:

1. To more completely capture the trajectory of growth and sexual development, the maximum age of follow up is increased from age 15 years (female) and 16 years (male), to 16 years (female) and 17 years (male).
2. To better evaluate the physiological basis of potential delays in growth or sexual development, annual endocrine laboratory testing for FSH, LH, and estrogen (females) or testosterone (males) will be performed.
3. To provide a more detailed description of growth and sexual development in the study population, the age of attainment of each Tanner stage will be evaluated.
4. To better track everolimus exposure and dosing, investigators will be asked to estimate the duration of interruptions by the patient in the prior reporting period.
5. Sample size determinations have been added as well as other clarifications of the analysis plan.
6. Data collected in the follow-up M2305 study will be pooled with the corresponding patient's data collected in the parent CRAD001M2301 study. Inclusion of baseline values collected in M2301 before the start of everolimus will be used to calculate the whole exposure to everolimus for patients enrolled in the M2305 study and in considerations pertaining to the entire growth/development course over time from the start of everolimus.
7. To be able to differentiate the impact of the TSC condition and the impact of the everolimus treatment on growth and sexual development a data set from peri-pubertal patients with TSC, who have not been exposed to everolimus will be used as a reference. These patients are a subset of the patient population that is currently being enrolled into the TOSCA registry (CRAD001MIC03). By end of enrollment TOSCA will have collected the data of approximately 1700 patients from 31 countries around the world. The descriptive analyses will present, side by side, the results from the CRAD001M2305 patients and those from the TOSCA registry patients not treated with an mTOR inhibitor, whenever similar data are collected in both studies. Detailed definition of the TOSCA subset of patients that will be used as a TSC-untreated reference population is provided in this amendment. If the missing data pattern is not limiting, exploratory indirect comparisons between patients treated by everolimus (from M2305 study) and those who never received an mTOR inhibitor (TOSCA subset of patients) will be performed to evaluate the everolimus effect on growth and sexual development (through the use of propensity scores).

8. The WHO growth charts will be used as reference data representing the average global population. Since no weight-for-age references are available from the WHO above 10 years of age, the WHO BMI-for-age references from 0 to 19 years of age will be used and the BMI standard-deviation scores (SDS) will be analyzed instead of weight SDS.
9. The long-term brain development and in particular the occurrence of TSC associated neurocognitive disorders will be assessed through the collection of the TAND Checklist, whenever available. Brain MRI scans may be evaluated, provided that scientific or technological advancements allow these data to be used for assessing brain functions.
10. The window to allow patients entering the study was extended from 3 to 6 months after end of treatment in study CRAD001M2301.
11. The language regarding evaluation of adverse event data was aligned with Novartis data directory requirements.

Changes to the protocol

1. Section 1.1.2, Section 1.2.1: Updated with newest regulatory and approval information
2. Section 1.1.3: Deleted sentence regarding TSC and development delays. Updated regarding toxicology and amenorrhea see in preclinical and clinical studies to-date
3. Section 2.1, Figure 4-1, Section 10. Updated to clarify patient population.
4. Section 2.1, Figure 4-1, Section 6, Section 7.1.3, Section 10.3, Section 10.4: Clarifications made to remove implication that everolimus/study treatment mandatory for study participation (including changes made to sub-section headers)
5. Section 2.2, Section 3, Table 3-1, Section 4.1, Figure 4-1, Section 5, Table 7-1, Section 7.2.2.3, Section 10.4.1, Section 10.4.2.3: Added endocrine laboratory values as part of development monitoring
6. Section 2.1, Section 2.2, Section 3, Table 3-1, Section 4.1, Figure 4-1, Section 4.3, Section 5: Updated study completion age to 16 (female) and 17 (male).
7. Section 2.2, Section 3, Table 3-1, Section 4.1, Figure 4-1, Section 5, Section 6.3.2, Table 7-1, Section 10.3, Section 10.5.2: Clarified the data collection and analysis regarding everolimus dose exposure and dose interruptions
8. Section 3, Section 10.4.2.2, Section 10.5.1.3: Updated the activities relating to collection and analysis of Tanner Stage data
9. Section 4.1: Updated frequency and activities that will be completed at each respective visit
10. Section 4.1, Section 7.2.2.1, Section 10.4.2.1: Clarified data collection and analysis for height and weight
11. Section 4.3: Updated potential LPLV to 2026 since age for study completion is now later
12. Section 7.1.3: Clarifications added regarding end of study activities.
13. Section 10.5.3.1: Added analysis and definition for potential delayed puberty
14. Section 10.8: Updated the analysis for sample size calculations
15. Section 1.1.3: Deleted sentence regarding recent growth surveys and trends in growth and development of children. Deleted sentence stating that TSC and SEGA and not everolimus therapy could be the cause of delayed development.

16. Section 2.2, Section 4.1, Figure 4-1, Table 7-1, Section 7.2.2.4 and 7.2.2.5: Annual brain MRI status collection and TAND Checklist added.
17. Section 2.2, Section 10: Added that data of CRAD001M2305 will be pooled with data from parent protocol CRAD001M2301 and clarification of how data will be reported side by side.
18. Section 3, Table 3-1: Primary endpoints updated: Weight replaced by BMI, height and BMI SDS by year since baseline.
19. Section 3, Table 3-1: Secondary endpoints: added brain development as assessed by TAND and indirect comparison of CRAD001M2305 and CRAD001MIC03 (TOSCA).
20. Section 4.1, Figure 4-1, Section 5.1, Section 5.2: Enrolment window extended from 3 to 6 months after last treatment in CRAD001M2301.
21. Section 8.1.1: Updated adverse events evaluation.
22. Section 10: Update that statistical analyses will primarily be descriptive.
23. Section 10: Added paragraph about data comparison with data from TOSCA registry.
24. Section 10.1.1: Definition of analysis sets updated to reflect addition of TOSCA patients who are younger than 17 and have not received any mTOR inhibitor.
25. Section 10.1.2: Clarification added that all patients have received everolimus in study CRAD001M2301.
26. Section 10.2: Demographics and baseline characteristics updated to reflect addition of TOSCA data. Baseline values were updated accordingly.
27. Section 10.3: Updated to describe how cumulative duration and dose of everolimus will be calculated/estimated for the time prior to CRAD001M2305 and during CRAD001M2305.
28. Section 10.4.2.2: Section fully revised. Weight replaced by BMI and formulas updated.
29. Section 10.4.2.2: Safety Set replaced by FAS of both studies CRAD001M2305 and TOSCA. Clarification for which patients the relationship between the everolimus exposure and the Tanner Stage will be done.
30. Section 10.4.2.3: Safety Set replaced by FAS of both studies CRAD001M2305 and TOSCA. Clarification for which patients graphs will be provided.
31. Section 10.4.3: Updated to include data from TOSCA registry.
32. Section 10.5.1.3: Clarified statistical analysis of age when patients reach each Tanner Stage. Clarification that FAS instead of Safety Set will be used.
33. Section 10.5.1.3: Statistical section regarding TAND assessments added.
34. Section 10.5.1.4: Section added to describe how the indirect comparison will be performed.
35. Section 10.5: Addition of TAND assessments and indirect comparison with TOSCA.
36. Section 10.5.1.1: Clarification that adverse events will be described only for CRAD001M2305.
37. Section 10.5.2: Weight SDS replaced by BMI SDS in the last paragraph.

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 underlined for insertions.

IRB

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. In addition, if 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 amended protocol.

Protocol summary:

Protocol number	CRAD001M2305
Title	Long-term follow-up study to monitor the growth and development of pediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT)
Brief title	Long-term monitoring of growth and development of pediatric patients previously treated with everolimus
Sponsor and Clinical Phase	Novartis Phase IIIb/IV
Investigation type	Post Authorization Safety Study (PASS)
Study type	Interventional
Purpose and rationale	The results from CRAD001M2301 have shown that a significant proportion of patients with advanced TSC-associated SEGA benefited from continuous treatment with the mTOR inhibitor everolimus which led to volume reduction of the SEGA lesions. Patients with TSC-associated SEGA are typically young children at pre-pubertal age whose physical and sexual maturation is ongoing. mTOR has been shown to be an important regulator of cell growth and proliferation. Additionally, it is possible that mTOR is also a regulator of sexual development and maturation. As many patients treated in CRAD001M2301 were young at the time of their exposure to everolimus (an mTOR inhibitor) and/or have experienced prolonged exposure to the drug from a young age, patients exposed to everolimus as part of CRAD001M2301 may present an appropriate study population in which to track the long term impact of everolimus exposure on growth and development. Therefore this safety extension-study is implemented to continue monitoring growth and development of pediatric patients previously enrolled in CRAD001M2301 who have been treated or are being treated with everolimus.
Primary Objective(s)	The primary objective of this study is to monitor the growth and development of pediatric patients with TSC-associated SEGA, previously enrolled in CRAD001M2301, who had received everolimus as part of study CRAD001M2301 and may or may not be continuing treatment with everolimus by annual assessments of: 1. Height 2. Weight for BMI 3. Tanner Stage 4. Endocrine laboratory values (FSH, LH, and estrogen or testosterone)
Secondary Objectives	• Long-term safety • Age at menarche (females) • Age at thelarche (females) • Age at adrenarche (males) • Age at Tanner Stages II-V • Assess neuropsychological development by TAND Checklist • Compare CRAD001M2305 and CRAD001MIC03 on height, BMI and sexual development (using Tanner Stages)
Study design	This is a prospective, multi-center, long-term follow-up, Post-Authorization Safety Study (PASS) evaluating the growth and development of pediatric

	patients who are currently being treated with everolimus and have been treated with everolimus for TSC-associated SEGA. The study will include all consenting pediatric patients who at the time of completion of study CRAD001M2301 have not achieved Tanner Stage V and are younger than 16 years (for females) or 17 years (for males), and were receiving treatment with everolimus in study CRAD001M2301 within 6 months before enrollment into CRAD001M2305. According to CRAD001M2301 enrollment figures, it is anticipated that at the time of the start of study CRAD001M2305, approximately 50 patients may be eligible for this study, if they consent to participate.
Population	The target population is comprised of pediatric female and male patients who have previously participated in the study CRAD001M2301 and have not, prior to enrollment into CRAD001M2305, reached age 16 for females, or age 17 for males. Additionally, these patients will not yet have achieved Tanner Stage V. Study treatment in study CRAD001M2301 must have been completed within 6 months prior to enrollment into CRAD001M2305.
Inclusion criteria	1. Pediatric female patients who were on study treatment in study [CRAD001M2301] within the past 6 months and have not reached Tanner Stage V or age 16 at the time of completion of [CRAD001M2301] or 2. Pediatric male patients who were on study treatment in study [CRAD001M2301] within the past 6 months and have not reached Tanner Stage V or age 17 at the time of completion of [CRAD001M2301]. 3. Written informed consent according to local guidelines.
Exclusion criteria	1. Pediatric female patients who were on study treatment in [CRAD001M2301] and have not reached Tanner Stage V but are within 3 month of turning age 16 or 2. Pediatric male patients who were on study treatment in [CRAD001M2301] and have not reached Tanner Stage V but are within 3 months of turning age 17 3. Any patient who was pregnant prior to start of CRAD001M2305
Investigational and reference therapy	Not applicable
Efficacy assessments	Not applicable
Safety assessments	Safety assessments will consist of monitoring and recording adverse and serious adverse events.
Other assessments	To monitor the growth and the development of pediatric patients the following assessments will be performed annually: • Height • Weight • Tanner Stage • LH, FSH, and estrogen levels (female patients) • LH, FSH, and testosterone levels (male patients)Furthermore, the timing of menarche, thelarche (females) and adrenarche (males) and age at each Tanner Stage (II-V) will also be determined if achieved before study completion. • TAND Checklist

	• Date of brain MRI scans

Data analysis	This is a long-term safety follow-up study and statistical analyses will be primarily descriptive for all endpoints.
	Data collected in this CRAD001M2305 study will be pooled with the corresponding patient's data collected in the parent CRAD001M2301 study, in particular, background information on the disease history, demographics and baseline characteristics, everolimus exposure, sexual and growth development data.
	To facilitate the interpretation of the CRAD001M2305 results and help differentiate the impact of the TSC condition versus the impact of everolimus on growth and sexual development, a descriptive statistical comparison will be performed using data from patients with comparable clinical characteristics, enrolled in the TOSCA registry (CRAD001MIC03) and not treated with any mTOR inhibitor. The descriptive analyses will present, side by side, the results from the CRAD001M2305 patients and those from the TOSCA patients not treated with any mTOR inhibitor, whenever similar data are collected in both studies.
	Categorical data will be presented as frequencies, percentages, and 95% confidence intervals. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.
	If the missing data pattern is not limiting, exploratory indirect comparisons between patients treated by everolimus (from M2305 study) and those who never received an mTOR inhibitor (TOSCA subset of patients) will be performed to evaluate the everolimus effect on growth and sexual development (use of propensity scores).
	In order to describe data from the CRAD001M2305 patients and those from the TOSCA registry side by side, the following analyses sets will be used.
	• The Full Analysis Set (FAS):
	  • for CRAD001M2305, FAS will consist of all patients enrolled in this study.
	  • for TOSCA, FAS will consist of all patients enrolled in this TOSCA registry whose age at study entry was below 17 years and who never received an mTOR inhibitor throughout the registry follow-up period.
	• The Full Analysis Set for sexual development (FAS Puberty):
	  • for CRAD001M2305, FAS Puberty will consist of the FAS patients defined above.
	  • for TOSCA, FAS Puberty will consist of the FAS patients defined above but restricting from the patients to those aged between 9 to 17 years at study entry. The TOSCA registry is designed to collect Tanner Staging until 2017 (i.e. 4 to 6 years of follow-up). Thus it is considered adequate to select only TOSCA patients aged between 9 to 17 years old at the time of entry to the registry to allow for obtaining puberty data corresponding to the peri-pubertal time frame.
	The Safety Set (SS) will include all patients enrolled in this follow-up CRAD001M2305 study who have at least one-post baseline safety assessment. It should be noted that all patients enrolled in the CRAD001M2305 study have been exposed to everolimus in the parent study CRAD001M2301 (and may or may not continue receiving

	commercial everolimus while on CRAD001M2305). For CRAD001M2305 patients, the duration of everolimus exposure and cumulative everolimus dose will be described using descriptive statistics on the Safety Set. The total duration of everolimus exposure will be calculated as the total duration of everolimus exposure received while on CRAD001M2301 plus the total duration of (commercially supplied) everolimus exposure reported in CRAD001M2305. In the CRAD001M2305 study, the duration of (commercially supplied) everolimus exposure will be estimated using the dates of the first and last everolimus doses and investigator summary of treatment interruptions between each visit. The primary safety objective of this study is to report the effect of everolimus treatment on height, BMI and sexual development (using Tanner Stages) in children and adolescents with TSC-associated SEGA who are taking everolimus or have taken everolimus. The height and BMI standard deviation scores (SDS) will be calculated based on data collected during the study and published reference information. The SDS (also called z-scores) will be computed for a particular patient at each time point. The time-course of height and BMI SDS will be summarized on the FAS using descriptive statistics by year since the enrollment date. Growth charts for height and BMI will be presented for each patient. Percentage of patients who will have reached Tanner Stage V by age 16 (for females) or age 17 (for males) will be provided on the FAS Puberty, along with 95% confidence intervals. Endocrine parameters such as LH, FSH, testosterone levels (in males) and LH, FSH, estrogen levels (in females) will be summarized descriptively by gender and by age over time on the Safety Set. The following secondary objectives will be described: the long term-safety, the age at Tanner Stage V, the age at thelarche and menarche for females, and the age at adrenarche for males. The secondary safety objective of the study will be based mainly on the frequency of adverse events. The overall observation period will be divided into two mutually exclusive segments to analyse the adverse events on the Safety Set in the M2305 study: 1. everolimus exposure period: from day of first commercial dose received in the M2305 study to 30 days after the last commercial dose received in the M2305 study 2. post-everolimus exposure period: • starting at day 30+1 after the last commercial dose in the M2305 study or • starting at the enrollment date for patients who will stop everolimus in M2301 and who will not start everolimus in M2305. Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the everolimus exposure period. However, all safety data will be listed and those collected during the post-everolimus exposure period are to be flagged. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

	Clinically notable AEs (CNAE) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with everolimus. The other secondary safety objectives of the study will be based on sexual and neuropsychological development data. The age when patients reach each Tanner Stage II-V will be summarized on the FAS Puberty. The following variables will be summarized on the Safety Set (those are only collected in the CRAD001M2305 study) using descriptive statistics: • age when females will start thelarche • age when females will have their first menses • age when males will reach adrenarche Potential delayed puberty will be defined based on Tanner stage and also on onset of menarche for girls. Potential cases identified through this algorithm, will then be clinically reviewed by assessing all available information in order to conclude the clinical relevance of the delay: • Potential delayed puberty in girls is defined as failure to attain Tanner Stage II by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner Stage II • Potential delayed puberty in boys is defined as failure to attain Tanner Stage II by age 14 All responses to the individual questions from the TAND Checklist (collected in both studies) will be summarized using descriptive statistics on both studies, side by side, and over time on the FAS. Everolimus blood trough levels (Cmin), collected at investigator discretion in compliance with local product information, should be recorded if available. The time-normalized Cmin value will be estimated for the entire treatment period using recorded everolimus Cmin values and prescribed doses in that treatment period. Cmin will be summarized with descriptive statistics over time. No formal interim analysis is planned for this study. However, safety outputs may be generated for regulatory safety updates.
Key words	Pediatric Study, Growth and Development, Height, Weight, BMI, Tanner Stage, Tuberous Sclerosis Complex (TSC), TSC SEGA, Everolimus

1 Background

1.1 Overview of subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC) and growth and development

The long term effects of everolimus on the growth and development of pediatric patients treated for TSC-associated SEGA are unknown. This study is designed to monitor the long term growth and development of pediatric patients who had previously been treated with everolimus in a randomized, placebo controlled clinical trial of everolimus in this indication (CRAD001M2301).

1.1.1 SEGA-associated with TSC

TSC is an autosomal dominant genetic disorder caused by inactivating mutations in the *TSC1* or *TSC2* genes, with a prevalence ranging from 1 in 6000 to 1 in 25,000 (Morrison 2009, Crino 2006, Osborne 1991). TSC affects approximately 1 million people worldwide (Anon 2010). The disease is characterized by benign, highly vascular, hamartoma growth and variable clinical manifestations ranging from mild dermatologic findings to seizures (which affect up to 90% of patients), learning disabilities (38% to 80%), mental retardation (50% to 70%), autism (20% to 60%), and fatal renal, cardiac, or pulmonary diseases (Curatolo 2002, Levine 2006).

Despite this broad range of clinical findings, a limited number of features are responsible for the morbidity and decreased life expectancy associated with this disease. These include neurologic disorders such as SEGAs and seizures, renal diseases such as angiomyolipomas and renal cell carcinoma (RCC), pulmonary disease (lymphangioleiomyomatosis), and cardiovascular disease (rhabdomyoma) (Goh et al 2004).

The incidence of SEGA in TSC varies from 5 to 15% (Shepherd et al 1991). SEGA lesions are usually associated with TSC. They arise in the subependymal layer of the lateral ventricle and are usually located near the foramen of Monro and enhance homogeneously with contrast on MRI with no evidence of surrounding edema. These are slow-growing lesions that are typically unapparent clinically until they reach sufficient size to produce ventricular obstruction and hydrocephalus. By the time symptoms are noted, they are often irreversible even by emergent surgical intervention. They arise deep within the brain in the region of the foramen of Monro, which hampers their surgical resection, as the approach to the lesion entails removal of substantial amounts of viable cerebral tissue. Surgery, even when successful, often results in significant morbidity.

1.1.2 Treatments for SEGA-associated with TSC

For SEGAs that exhibit serial growth, cause hydrocephalus, or produce any clinical symptoms, resection, until recently, was the only recommended treatment for these patients (Torres 1998, Sinson 1994, Cuccia 2003). The lack of reported spontaneous regression or subsequent stabilization in SEGAs supported this recommendation (Franz 2007). In addition, SEGAs do not typically respond to radiation therapy or chemotherapy (Franz 2007). Given

the genetic basis of TSC, the risk of inducing second malignancies through utilization of standard chemotherapeutic agents or radiation therapy has been noted (Matsumura et al 1998).

Everolimus first received accelerated approval from FDA on 29-Oct-2010 based on data from CRAD001C2485 under the trade name Afinitor® for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection based on data from CRAD001C2485. The effectiveness of Afinitor 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 FDA based on results of study CRAD001M2301 and with the approval of the dispersible tablet to "Afinitor® Tablets and Afinitor® Disperz are indicated in pediatric and adult patients with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The effectiveness of Afinitor Tablets and Afinitor Disperz 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 the EU, under the trade name Votubia®, everolimus first received conditional approval on 02-Sep-2011 based on the data from CRAD001C2485 for the treatment of patients aged 3 years and older with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated. Based on data from CRAD001M2301, the European Commission decision was received on 15-Nov-2013 for removal of the age restriction and inclusion of the dispersible tablets.

1.1.3 Growth and development

Growth

Childhood growth and development are routinely monitored as part of child preventive health care in many countries. The assessment whether a child's growth pattern deviates from that of the reference population is intended to detect childhood illnesses that manifest themselves through abnormal growth, ideally before any other signs or symptoms of the disease have appeared.

Close monitoring of growth and development may be even more important when children are treated over long periods of time with drugs like everolimus that interfere with complex intracellular signaling pathways. Everolimus is an inhibitor of mTOR, a key player in a multifunctional, intracellular signal transduction pathway which has been shown to be essential for various vital processes. mTOR senses cellular nutrient and energy levels, and is one of many regulators of the cell cycle and proliferation. At present, it is unknown if long term treatment with everolimus affects the growth and development of children. Under certain circumstances everolimus is the only treatment option for children with SEGA associated with TSC. In this study, the height and weight for BMI of pediatric patients who take or have taken everolimus will be assessed on an annual basis to detect possible abnormalities.

WHO (World Health Organization) growth charts and other population-specific growth data have been used to establish cut-off values that define abnormal growth. The most commonly used parameter is height-for-age [expressed as height SD score (SDS) or height percentile].

Standard deviations scores (SDS) give an indication of the stature of the subject relative to a normal population of that age, a value of 0 being average and + and - values representing degrees of tallness and shortness, respectively.

Development

In animal studies it was shown that signaling through mTOR was at least partially involved in the control of puberty onset. Chronic blockade of mTOR by rapamycin had a strong inhibitory impact on puberty onset in female rats. Preliminary results suggested that also male rat puberty is sensitive to mTOR inactivation. Toxicology studies performed with everolimus demonstrate that treatment with everolimus may be associated with decreased weight in rodent pups and a delay in descent of testes in male pups.

Additionally, the safety profile of everolimus in Study [CRAD001M2301] was consistent with that observed in the phase II study [CRAD001C2485] in patients with TSC with the exception of three cases of secondary amenorrhea. Secondary amenorrhea is thought to be an indicator of end-stage ovarian dysfunction. It has been speculated that this finding may be a consequence of TSC-related-mTOR over-expression or mTOR inhibition.

Due to these preclinical and clinical findings further investigation of possible effects of long-term everolimus treatment on the onset of puberty and development of TSC patients is imperative. This study is designed to address these questions. The timing of puberty onset and development through the different stages to full maturation will be monitored by assessment of Tanner Stage and if achieved prior to study completion timing of menarche and thelarche (females) or adrenarche (males).

In addition, many of the patients who will be enrolled in this study have previously received and will be taking antiepileptic drugs (or enzyme-inducing antiepileptic drugs [EIAED]). While in general it is not thought that antiepileptic drugs impact ultimate height, the studies have not been comprehensive (Macardle et al 1986). Additionally, some antiepileptic drugs (e.g., valproic acid, topiramate) may affect weight in the peri-pubertal period (Novak et al 1999). As a consequence, this study may generate some observations about the dual exposure of patients to antiepileptic drugs and everolimus.

1.2 Introduction to everolimus

1.2.1 Overview of everolimus (RAD001)

Everolimus (Afinitor®/Votubia®; RAD001) is a selective inhibitor of mTOR, specifically targeting mTORC1. Everolimus was initially developed to prevent allograft rejection following solid organ transplantation, and is approved in more than 80 countries worldwide for use in this indication (Certican®/Zortress®).

In the oncology setting, everolimus has been approved, under the trade name Afinitor, in the US, in EU and many countries worldwide for the treatment of patients with advanced renal cell carcinoma (>100 countries), for the treatment of patients with advanced neuroendocrine

tumors of gastrointestinal, lung or pancreatic origin (>80 countries) and for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer in combination with an aromatase inhibitor, after prior endocrine therapy (>80 counties). Indications vary by country.

In the TSC setting, everolimus has received approval in more than 70 countries, under the trade names Afinitor and Votubia, for the treatment of patients with TSC who have SEGA not requiring immediate surgery and for the treatment of adult patients with renal angiomyolipoma associated with TSC, not requiring immediate surgery.

1.2.1.1 Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to µM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVEC) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The antiangiogenic 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.

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. In nonclinical 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 antiproliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

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

1.2.1.2 Clinical experience

Interventional studies in patients with tuberous sclerosis complex:

Everolimus has been investigated in one phase I/II study (28 patients) in patients with TSC who have SEGA [CRAD001C2485]. Additionally, two phase III studies have been conducted in patients with TSC: study [CRAD001M2301] in patients with TSC who have SEGA (117 patients) and study [CRAD001M2302] in patients with renal angiomyolipoma

(118 patients). [CRAD001MIC02] is an ongoing, expanded access phase IIIb study for patients with TSC associated SEGA. Currently there is a fourth phase III study [CRAD001M2304] ongoing in which everolimus will be tested to evaluate whether its use as adjunctive treatment results in reducing seizure frequency in patients with TSC who have refractory seizures.

Data on a small series of TSC patients who had systematic SEGAs which were treated with daily rapamycin therapy showed tumor size reduction by 46-63% within 2.5 to 5 months (Franz et al 2006). All lesions exhibited regression and, in one case, necrosis. Interruption of therapy for one patient resulted in regrowth of the SEGA, but further regression of another 62-75% was seen upon the resumption of therapy. These results represented a new therapeutic paradigm for the treatment of SEGAs in the TSC patients with rapamycin and related agents.

Therefore, in 2007, everolimus entered clinical development for TSC. Study C2485, conducted by Cincinnati Children's Hospital Medical Center (CCHMC), is a prospective, non-randomized, open-label, investigator-initiated, single-center 28-patient trial designed to evaluate the safety and efficacy of everolimus in patients ≥ 3 years of age with SEGA associated with TSC. The primary efficacy endpoint is the change from baseline in volume of primary SEGA lesion at 6 months as determined by central radiology review. At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. The median duration of response for these 9 patients was 11.8 months (range 3.2 to 39.1 months). Response rate continues to improve as 58.3% of patients (14 of 23) who took everolimus for at least four years have experienced a reduction of ≥ 50% in the size of their largest SEGA relative to baseline. One patient has experienced a SEGA progression (defined as an increase of at least 25% to a value greater than baseline). The median time from first response to progression/censoring was 37 months (range: 6-63 months). No patient developed a new lesion and none required surgical resection or other therapy for SEGA.

The safety and efficacy of everolimus in patients with TSC who have SEGA was studied further in [CRAD001M2301], a randomized (2:1), double-blind, placebo-controlled trial of everolimus conducted in 117 pediatric and adult patients with SEGA and TSC. The main efficacy outcome measure was SEGA response rate based on independent central radiology review. After 6-months of study treatment, 35% of the patients treated with everolimus had at least a 50% reduction in SEGA volume compared to none in the placebo group (Franz et al 2013). Based on recent data, the response rate after at least 12-months of everolimus treatment has increased to 48%. SEGA progression was seen in nine of the all patients treated with everolimus (8.1%). In five patients, progression occurred after cessation of treatment or was associated with Cmin values which were markedly reduced or at zero. In one case of progression, the patient developed hydrocephalus that was successfully treated, in the absence of SEGA growth. In one case, progression reversed with further treatment.

Non-interventional studies:

A total of three non-interventional studies relevant for the TSC setting ([CRAD001MIC03], [CRAD001MCO05], and [CRAD001M1401]) have been initiated and are ongoing (Table 1-1). These three studies have so far not shown any unexpected or unusual safety findings.

Table 1-1 Non-interventional studies

Non interventional studies			
Study no.	**CRAD001MIC03**	**CRAD001MCO05**	**CRAD001M1401**
Title	TOSCA	Epidemiological follow-up	Survey
Population	Patients, any age with TSC diagnosed within last 12 months	Patients with confirmed diagnosis of TSC	TSC Patients <15-years-old
Study design	International, observational disease registry, retrospective and prospective	Epidemiological, monographic registry model with open follow-up, retrospective and prospective; competitive recruitment	Observational, site survey; patient registration

For additional efficacy and safety information, please refer to the most recent edition of the Investigator's Brochure as well as the Afinitor/Votubia prescribing information.

2 Rationale

2.1 Study rationale and purpose

The results from [CRAD001M2301] have shown that a significant proportion of patients with advanced TSC-associated SEGA benefited from continuous treatment with the mTOR inhibitor everolimus which led to volume reduction of the SEGA lesions. Patients with TSC-associated SEGA are typically young children at pre-pubertal age whose physical and sexual maturation is ongoing. mTOR has been shown to be an important regulator of cell growth and proliferation. Additionally, it is possible that mTOR is also a regulator of sexual development and maturation. As many patients treated in [CRAD001M2301] were young at the time of their exposure to everolimus (an mTOR inhibitor) and/or have experienced prolonged exposure to the drug from a young age, patients exposed to everolimus as part of CRAD001M2301 may present an appropriate study population in which to track the long term impact of everolimus exposure on growth and development.

Upon request by the EMA (during the procedure EMEA/H/C/002311/II/0004), this safety extension-study, classified as Post-Authorization Safety Study (PASS), is implemented to continue growth and development monitoring of pediatric patients enrolled in CRAD001M2301 who have been treated or are being treated with everolimus.

The study will monitor the growth and development of pediatric patients with TSC-associated SEGA, previously enrolled in CRAD001M2301until they reach Tanner Stage V, or until age 16 for females or 17 for males whichever occurs first. After completion of [CRAD001M2301] continued treatment with everolimus is at investigator discretion and is not required for participation in CRAD001M2305. It is expected that some patients will cease treatment with everolimus upon completion of study CRAD001M2301, but most will opt for continued treatment with everolimus. Under either circumstance, the patients will be eligible for enrolment in study CRAD001M2305.

The primary objective of CRAD001M2305 is to report the long-term effects of everolimus treatment on height, BMI and sexual development (using Tanner Stages) in children and adolescents with TSC-associated with SEGA. Additionally, it is possible that the presence of TSC and SEGA and non-everolimus therapy could affect growth and sexual development. To be able to differentiate the potential impact of the TSC condition and the potential impact of the everolimus treatment on growth and sexual development a second data set from peri-pubertal patients with TSC, who have not been exposed to everolimus will be used as a reference. These patients are a subset of the patient population that is currently being enrolled into the TOSCA registry.

Height and BMI data obtained in this study will be compared against the WHO reference growth charts (representing the average global population). Recent growth surveys in both developed and developing countries have reported increases in mean height and earlier sexual maturation, suggesting that current WHO growth charts, may not be representative of the general population in the future. Therefore if, over the course of the next 10 years, a more appropriate reference data set is developed, the study may compare the growth and sexual development of its subjects to such a data set.

Monitoring of patient safety, brain development as assessed by TAND Checklist and the timing of menarche, thelarche (females), and adrenarche (males), and the age at Tanner Stage V will be determined as secondary objectives.

2.2 Rationale for the study design

CRAD001M2305 is a prospective, multi-center phase IIIb/IV study. This study will investigate if the physical and sexual development of pediatric patients is affected by previous or ongoing treatment with everolimus.

Growth (height, weight), sexual development (Tanner Stages, sex hormone levels, age at menarche, thelarche (females) and adrenarche (males)), and brain development (assessed by TAND Checklist, dates of brain MRI) of patients participating in this long-term follow-up study will be followed at annual visits to the site until patients achieve Tanner Stage V or age 16 (females), age 17 (males) whichever occurs first.

Adverse events, concomitant medication, appearance of menarche, will be monitored and data collected every 3 months (“3-monthly”). As per local product information, all patients should be receiving periodic Therapeutic Drug Monitoring (TDM) to monitor the blood trough concentration of everolimus, any available everolimus blood trough levels with date of sample collection, will be recorded every 3-months. Unless clinically indicated these 3-monthly visits can be performed per telephone.

Of note: the participation in this study does not require the administration of everolimus. In such cases in which the patient is taking everolimus, data collection (such as TDM, trough level, duration of everolimus interruptions and everolimus prescribed dose) will only be recorded, when available. Everolimus treatment, should it be continued during CRAD001M2305, will be based on the local product information.

Blood samples will be collected annually for assessment of endocrine levels at a local lab for all patients, starting at age 10 until study participation is ended.

Data collected in this CRAD001M2305 study will be pooled with the corresponding patient's data collected in the parent CRAD001M2301 study, in particular background information on the disease history, demographics and baseline characteristics, everolimus exposure, sexual and growth development data.

To facilitate the interpretation of the CRAD001M2305 results and help differentiate the impact of the TSC condition versus the impact of everolimus on growth and sexual development, a descriptive statistical comparison will be performed using data from patients with comparable clinical characteristics, enrolled in the TOSCA registry and not treated with an mTOR inhibitor.

CRAD001M2305 results will be reported, side by side, with those from the TOSCA registry patients not treated with an mTOR inhibitor, whenever similar data are collected in both studies.

3 Objectives and endpoints

Primary objective:

The primary objective of this study is to monitor the growth and development of pediatric patients with TSC-associated SEGA, previously enrolled in CRAD001M2301, who had received everolimus as part of study CRAD001M2301 and may or may not be continuing treatment with everolimus. Annual measurements of the following will be collected:

- Height
- Weight for BMI
- Tanner Stage
- Endocrine laboratory values (FSH, LH, and estrogen or testosterone)

Secondary objectives:

- Long-term safety
- Age at menarche (females)
- Age at thelarche (females)
- Age at adrenarche (males)
- Age at Tanner Stage II-V
- Assess neuropsychological development by TAND Checklist
- Compare CRAD001M2305 and CRAD001MIC03 on height, BMI and sexual development (using Tanner Stages)

Primary endpoints:

Growth and development of pediatric patients with TSC-associated SEGA who are taking everolimus or have previously taken everolimus will be monitored via:

- Percentage of patients who achieved Tanner Stage V by age 16 (for females) or age 17 (for males)
- Height, standard deviation score by year since baseline

- BMI, standard deviation score by year since baseline
- Mean endocrine laboratory values (FSH, LH, and estrogen or testosterone) by age

Secondary endpoints:

- Safety assessments will consist of monitoring and recording adverse events, including serious adverse events. Safety will be assessed by the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0 (//ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).
- Age at Tanner Stage II-V
- Age at start of menses (menarche) – for females
- Age at thelarche – for females
- Age at adrenarche – for males
- TAND Checklist - individual responses over time since the enrollment date
- Indirect comparison between CRAD001M2305 and CRAD001MIC03 will be performed on the following endpoints:
    - Percentage of patients who achieved Tanner Stage V at or before age of 16 (females) or 17 (males).
    - Height/BMI standard deviation score by year since baseline

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary objective:		
Monitoring growth and development of pediatric patients with TSC-associated SEGA who are taking everolimus or have taken everolimus by annual measurements of height, weight for BMI, and Tanner Stage	Percentage of patients who achieved Tanner Stage V at or before age of 16 (females) or 17 (males). Height/BMI standard deviation score by year since baseline Mean endocrine laboratory values (FSH, LH, and estrogen or testosterone) by age	Refer to Section 10.4.
Secondary objectives:		
Determine timing of developmental milestones: menarche (females), thelarche (females), adrenarche (males), Tanner Stage II-V	Age at start of menses (menarche) – for females Age at onset of breast development (thelarche) – for females Age at pubic hair development (adrenarche) – for males Age at Tanner Stage II-V - all patients	Refer to Section 10.5.1.
Assess neuropsychological development	TAND Checklist individual responses over time since the enrollment date	
Compare CRAD001M2305 and CRAD001MIC03 on height, BMI and sexual development (using Tanner Stages)	Indirect comparison between CRAD001M2305 and CRAD001MIC03 will be performed on the following endpoints: Percentage of patients who achieved Tanner Stage V at or before age of 16 (females) or 17 (males). Height/BMI standard deviation score by year since baseline.	
Safety as assessed by the NCI Common Toxicity Criteria, version 3.0.	Safety will be assessed by the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0 (//ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Notes: • Safety assessments will consist of monitoring and recording adverse and serious adverse events • Safety follow-up as per product information	

4 Study design

4.1 Description of study design

This is a prospective, multi-center, long-term follow-up, Post-Authorization Safety Study (PASS) evaluating the growth and development of pediatric patients who are currently being treated with everolimus or who have previously been treated with everolimus for TSC-associated SEGA in [CRAD001M2301]. The study will include all consenting pediatric patients who at the time of completion of study CRAD001M2301 have not achieved Tanner Stage V and are younger than 16 years (for females) or 17 years (for males), and were receiving treatment with everolimus in study [CRAD001M2301] within 6 months before enrollment into CRAD001M2305.

According to [CRAD001M2301] enrollment figures, it is anticipated that at the time of the start of study CRAD001M2305, approximately 50 patients may be eligible for this study, if they consent to participate.

Enrollment

Enrollment into CRAD001M2305 will start at the conclusion of the parent protocol ([CRAD001M2301]). Investigators will identify study patients who qualify for enrollment into CRAD001M2305 and assign each a unique patient number (refer to Section 6.3).

All pediatric patients and his/her parents or legal guardian must be thoroughly informed about the study. The Informed Consent Form(s) for CRAD001M2305 must be signed prior to performing any study procedures.

Once Informed Consent has been obtained and eligibility is confirmed (Tanner Stage and age have been verified) by the investigator, the patient may be enrolled in the study.

Monitoring

For patients taking everolimus, dosing should follow the local product information.

Patient visits will occur every 3 months (± 14 days) for collection of adverse events, any Afinitor/Votubia-related SAEs, and date of menarche (females). This information will be obtained from the patient or their parents/caregiver, depending on the patient's age and cognitive abilities.

Visits will also occur annually (± 30 days) for measurement of growth (height, weight), development (Tanner staging, age at thelarche, age at menarche for females, age at adrenarche for males), and pregnancy testing. Height and weight should be measured with the same calibrated equipment and in the same manner, preferably with the patient wearing minimal clothing and no shoes at every respective visit. If possible these measurements should be obtained by the same site personnel throughout the study.

A blood sample will be taken at the annual visits for assessment of hormone levels at a local laboratory, starting at age 10 until study participation is ended. Estrogen, luteinizing hormone,

and follicular stimulating hormone will be tested for females and testosterone, luteinizing hormone, and follicular stimulating hormone for males.

Adverse events should be collected, by the investigator, according to the protocol requirements. Afinitor/Votubia-related SAEs should be collected throughout the study until 30 days after last everolimus dose.

Additionally, medications and therapies/non-drug therapies should be recorded on the CRFs designated to record concomitant medications at every 3-month and annual visit until the end of the study.

The date of the first dose and the date of the last dose of systemic everolimus treatment will be recorded, as available. The patient's recent everolimus Cmin (i.e. obtained since the last visit as per local product information) with collection date and current prescribed everolimus dose should be recorded. The time-normalized Cmin value will be estimated for the entire treatment period using recorded everolimus Cmin values and prescribed doses in that treatment period (Section 10.5.2). Additionally, a summary of everolimus interruptions (an estimate of the duration of the interruptions) will be collected at each study visit.

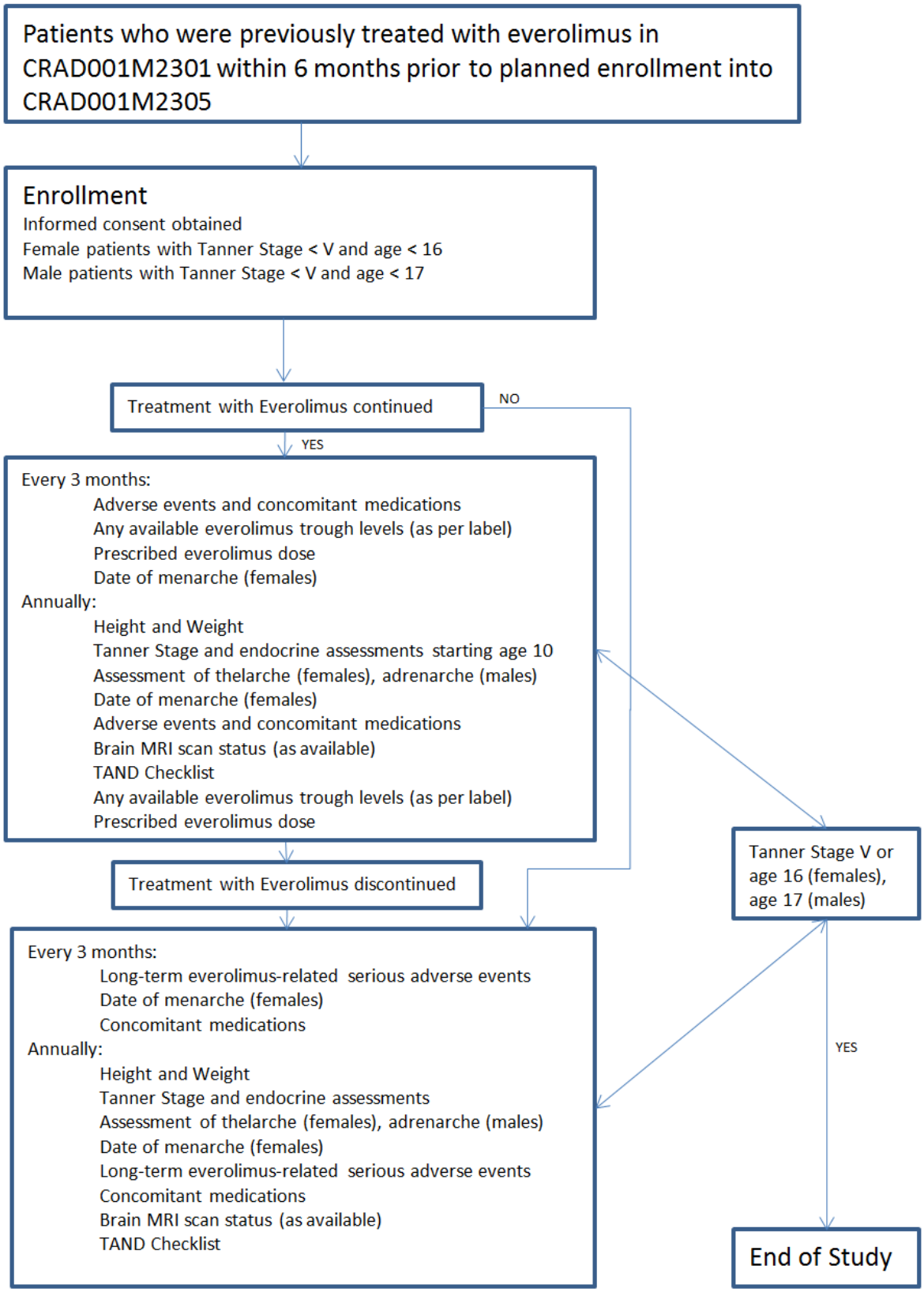
The dates of all performed brain MRI scans that are done in the scope of the regular TSC SEGA follow-up will be collected at the annual visits. Brain MRI data will not be collected at this point but may be retrieved at a later date if technological advancements pertaining to predicting future cognitive abilities such as the development of the working memory arise.

Brain development will be assessed by determining the occurrence of TSC-Associated-Neuropsychiatric-Disorders (TAND) with an appropriate TAND Checklist at each annual visit.

The first study visit will occur 3 months after enrollment in CRAD001M2305 and the first annual visit one year (± 30 days) after enrollment in CRAD001M2305. The 3-monthly visits can be performed per telephone unless a visit to the site is clinically indicated.

Patient participation in the study will be completed once the patient has achieved Tanner Stage V or age 16 for females, age 17 for males, whichever occurs first.

Figure 4-1 Study flowchart



4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned for this study. However, safety outputs may be generated for regulatory safety updates.

4.3 Definition of end of the study

The study will end when all patients have either reached Tanner Stage V, or age 16 for females, age 17 for males, or when the last patient is discontinued. The latest possible LPLV date is expected to take place in September-2026.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. The investigator may be informed of 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 target population is comprised of pediatric female and male patients who have previously participated in the study [CRAD001M2301] and have not, prior to enrollment into CRAD001M2305, reached age 16 for females, or age 17 for males. Additionally, these patients will not yet have achieved Tanner Stage V. Study treatment in study [CRAD001M2301] must have been completed within 6 months prior to enrollment into CRAD001M2305.

The investigator or designee must ensure that only patients who meet all inclusion are offered participation in the study. No additional exclusions can be applied by the investigator, in order that the study population will be representative of all eligible patients. All screening assessments must be completed and reviewed by the investigator (or designee) prior to starting study participation in CRAD001M2305.

All pediatric study patients and their parent(s) or legal guardian must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations, and all regulatory requirements in order to ensure informed consent. The written informed consent must be obtained prior to performing any CRAD001M2305 study procedures. If the patient is unable to read, an impartial witness and/or the patient's parent or legal guardian must be present during the entire informed consent discussion. The following criteria apply to all patients enrolled into the study.

5.2 Inclusion criteria

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

1. Pediatric female patients who were on study treatment in study [CRAD001M2301] within the past 6 months and have not reached Tanner Stage V or age 16 at the time of

completion of [CRAD001M2301]
or

2. Pediatric male patients who were on study treatment in study [CRAD001M2301] within the past 6 months and have not reached Tanner Stage V or age 17 at the time of completion of [CRAD001M2301].
3. Written informed consent according to local guidelines.

Tanner Staging results that were obtained and documented within 6 months prior to enrollment into CRAD001M2305 may be used for enrollment decisions.

5.3 Exclusion criteria

1. Pediatric female patients who were on study treatment in CRAD001M2301 and have not reached Tanner Stage V but are within 3 month of turning age 16
or
2. Pediatric male patients who were on study treatment in CRAD001M2301 and have not reached Tanner Stage V but are within 3 months of turning age 17
3. Any patient who was pregnant prior to start of CRAD001M2305

6 Treatment

This study does not require treatment with any medication.

6.1 Monitoring everolimus dosing

At the discretion of the investigator, patients may be treated with commercially available everolimus, as per local product information / standard of care. Dosing will be based on locally performed PK analyses. Novartis will not perform any PK analyses. Treatment duration and dose modifications will be at the investigator's discretion, as per the local product information.

Table 6-1 Dose and treatment schedule (if continuing on everolimus)

Everolimus treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Commercially available everolimus	Tablet for oral use or dispersible tablet for oral use	As per local product information/ investigator discretion	As per local product information / investigator discretion

6.2 Concomitant medications

Concomitant medications should be collected, by the investigator, according to the protocol requirements.

6.3 Patient numbering, everolimus exposure

6.3.1 Patient numbering

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

6.3.2 Everolimus exposure

For patients being prescribed Afinitor/Votubia, the sponsor will monitor the exposure by requesting that the investigator record in the CRF the current prescribed dose, a summary of everolimus interruptions, and any available everolimus trough concentration levels (completed as per label) that have been recorded in the patient chart. This information must also be recorded in the source document at each patient visit.

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.

No CRF will be used as a source document.

Table 7-1 Visit evaluation schedule

	Day 1 / Enrollment	Every 3 months after Day 1 (3-monthly visits that coincide with the annual visits are skipped (every 4th 3-monthly visit))			First annual visit	Every 3 months after each consecutive year (3-monthly visits that coincide with the annual visits are skipped (every 4th 3-monthly visit))	Annually after first year	Study completion
Time Point (months)	**0**	**3**	**6**	**9**	**12**	**15, 18, 21, 27…**	**24, 36…**	**Last**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6, 7, 8, 10…**	**9, 13…**	**778**
Visit Window		**± 14 days**			**± 30 days**	**± 14 days**	**± 30 days**	
Obtain Informed Consent (D)	X							
Inclusion/exclusion criteria (D)	X							
Demography (D)	X							
Prior study information (D)	X							
Physical examination								
Height (D)	X				X		X	X
Weight (D)	X				X		X	X
Tanner Staging (D)	X				X		X	X
Developmental Milestones								
Menarche (females) (D)	X	X	X	X	X	X	X	X
Thelarche (females) (D)	X				X		X	X
Adrenarche (males) (D)	X				X		X	X
Urine pregnancy testing (D)	X				X		X	X
Endocrine assessments (D)	X				X		X	X
Concomitant medications (D)	X	X	X	X	X	X	X	X
Adverse events (D)	X	X	X	X	X	X	X	X
Serious adverse event reporting (D)	X	X	X	X	X	X	X	X
Pregnancy reporting (D)	X	X	X	X	X	X	X	X

	Day 1 / Enrollment	**Every 3 months after Day 1 (3-monthly visits that coincide with the annual visits are skipped (every 4th 3-monthly visit))**			**First annual visit**	**Every 3 months after each consecutive year (3-monthly visits that coincide with the annual visits are skipped (every 4th 3-monthly visit))**	**Annually after first year**	**Study completion**
Time Point (months)	**0**	**3**	**6**	**9**	**12**	**15, 18, 21, 27…**	**24, 36…**	**Last**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6, 7, 8, 10…**	**9, 13…**	**778**
Visit Window		**± 14 days**			**± 30 days**	**± 14 days**	**± 30 days**	
Any available everolimus blood trough levels (C_{min}) as per label (D) (only while on everolimus treatment)	X	X	X	X	X	X	X	X
Prescribed everolimus dose (D) (only while on everolimus treatment)	X	X	X	X	X	X	X	X
Summary of dose interruptions (D) (only while on everolimus treatment)	X	X	X	X	X	X	X	X
Brain MRI scan dates (as available) (D)					X		X	
TAND Checklist (D)	X				X		X	
End of everolimus treatment (D)		X (as applicable, complete follow-up for safety 30-days after last dose)						

7.1.1 Eligibility enrollment

Patients have to be thoroughly informed about the study by the investigator and have to sign the informed consent form before study enrollment can be performed. The inclusion/exclusion criteria should be verified within 28 days before Day 1. If Tanner Staging was done in the scope of [CRAD001M2301] within 3 months prior to enrollment into CRAD001M2305, these results may be used for enrollment decisions. In this case, Tanner Staging does not have to be repeated. The patient's age should be verified prior to enrollment into CRAD001M2305.

7.1.1.1 Patient demographics and other characteristics at study start

At time of enrollment, patients' demographic and previous study identification from the parent protocol (CRAD001M2301) will be collected. Furthermore patients will undergo Tanner Staging, height, weight, and developmental milestone (adrenarche, thelarche, menarche) assessments.

Data pertaining to ongoing adverse events and concomitant medications will be transferred from the parent study into CRAD001M2305.

For details of assessments, refer to Table 7-1.

7.1.2 Study participation

At the discretion of the investigator, patients may continue treatment of their TSC-associated SEGAs with commercially-supplied everolimus. Everolimus does not need to be actively in use for the entire duration of the patient's study participation.

7.1.3 Study completion

Patients will meet the criteria for study completion upon demonstrating Tanner Stage V, or reaching age 16 (females) or age 17 (males), whichever comes first. Upon meeting the criteria for study completion, the patient should schedule an End of Study visit at the site. The End of Study visit cannot be completed via telephone contact.

Patients who discontinue commercial everolimus should continue study participation until meeting any of the aforementioned criteria for study completion. The discontinuation of everolimus will be recorded on the End of Treatment CRF page. Safety monitoring should be continued for at least 30 days following the last dose of everolimus.

Patients who complete the study, or discontinue the study early, should have the reason for exiting the study recorded on the Study Phase Completion Disposition CRF (SEC) page.

7.1.3.1 Criteria for early study discontinuation

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients must be withdrawn from the study if any of the following occur:

- Protocol deviation(s) that impact eligibility
- Patient withdrew consent
- Lost to follow-up

- Administrative problems
- Death

7.1.4 Post-study follow up period

All patients must have safety evaluations 30 days after the last dose of everolimus.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.2 Assessment types

7.2.1 Efficacy assessments

Not applicable

7.2.2 Safety and tolerability assessments

Safety will be monitored by collecting data about growth, development, and adverse events. For details on AE collection and reporting, refer to Section 8.1.

7.2.2.1 Height and weight

Height and body weight (with minimal clothing, without shoes) will be measured annually. Note: CRFs are designed to collect the data in the units they are measured in; e.g., height in centimeters (cm) or inches (in) and weight in kilograms (kg) or pounds (lb). Height and weight should be measured with the same calibrated equipment and in the same manner at every respective visit. If possible these measurements should be obtained by the same site personnel throughout the study.

7.2.2.2 Tanner staging

For all male patients, Tanner Stage V will be achieved once the patient has demonstrated either stage 5 genitalia development or stage 5 pubic hair development. For all female patients, Tanner Stage V will be achieved once the patient has demonstrated either stage 5 breast development or stage 5 pubic hair development (Marshal 1969, Marshal 1970).

Male: Genitalia stages:

Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.

Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.

Stage 3: Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.

Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin.

Stage 5: Genitalia adult in size and shape. No further enlargement takes place after Stage 5 is reached.

Male: Pubic hair stages:

Stage 1: Pre-adolescent. The vellus over the pubesis no further developed than that over the abdominal wall, i.e. no pubic hair.

Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly at the base of the penis.

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs but not up the linea alba or elsewhere above the base of the inverse triangle.

Female: Breast stages:

Stage 1: Pre-adolescent; elevation of papilla only.

Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.

Stage 3: Further enlargement of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

Female: Pubic hair stages:

Stage 1: Pre-adolescent; the vellus over the pubes is not further developed than that over the anterior abdominal wall, i.e. no pubic hair.

Stage 2. Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia.

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle.

7.2.2.3 Endocrine testing

A blood sample for analysis of luteinizing hormone (LH), follicular stimulating hormone (FSH), and estrogen (females) or total testosterone (males) will be collected on day 1, annually, and at end of study for endocrine assessment at a local laboratory for all patients, starting at age 10 until study participation is ended. In the event that amenorrhea is reported in between scheduled assessments, hormone evaluations should be completed at that time.

7.2.2.4 Brain imaging

The dates of all brain MRI scans that were performed since the last annual visit will be collected annually. Actual MRI data will only be retrieved if future technological advancements allow MRI data to be used for prediction of cognitive abilities, diagnosing neuropsychological disorders, and assessing the speed of cognitive development.

7.2.2.5 TSC-associated-neuropsychiatric-disorders (TAND)

A TAND Checklist will be completed by an appropriate clinician at the clinical site at each annual visit.

7.2.2.6 Pregnancy testing

For all female patients who have achieved Tanner Stage II or higher, urine pregnancy testing will be completed annually as part of the assessments for growth and development. In the event of positive urine pregnancy test, results should be verified by serum pregnancy testing.

7.2.2.7 Pregnancy and assessments of fertility

When effective contraception is required, pregnancy testing is recommended at enrollment and at the end of the trial. All patients should follow instructions for contraception as per local label.

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception. Discontinuation of everolimus should be considered in case of pregnancy.

All pregnancies should be followed up to determine outcome (Section 8.3). Patient participation in this study for monitoring of growth and development should be continued.

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.

Adverse events that begin or worsen after informed consent may be recorded in the Adverse Events CRF. Adverse events that were ongoing from CRAD001M2301 will be transferred to the AE CRFs for CRAD001M2305. Adverse event monitoring should be continued for at least 30 days following the last dose of everolimus 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 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form

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

- The severity grade (CTCAE Grade 1-4)
- Its duration (start and end dates or ongoing at end of study)
- Its relationship to the everolimus treatment (suspected/not suspected)
- Action taken with respect to everolimus treatment (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken)
- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event 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 everolimus treatment, the interventions required to treat it, and the outcome.

Progression of TSC may be reported as an adverse event. Progression of TSC will not necessarily end patient participation in this study unless the patient meets any of the other reasons for early study discontinuation.

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

8.2 Serious adverse events

8.2.1 Definitions

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

1. Is fatal or life-threatening
2. Results in persistent or significant disability/incapacity
3. Constitutes a congenital anomaly/birth defect
4. 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
5. 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 of TSC
- 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 until at least 30 days after the patient has stopped everolimus must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to everolimus. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. 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.

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 treatment with everolimus, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

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

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

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

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on everolimus 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 Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the commercial supply of everolimus and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took everolimus 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 local product information.

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, and the progress of enrollment and study conduct. 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, such as 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

For studies using Electronic Data Capture (EDC), 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.

9.4 Database management and quality control

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

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.

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

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or a designated CRO.

This is a long-term safety follow-up study and statistical analyses will be primarily descriptive for all endpoints.

Data collected in this CRAD001M2305 study will be pooled with the corresponding data collected in the parent CRAD001M2301 study, in particular, background information on the disease history, demographics and baseline characteristics, everolimus exposure, sexual and growth development data. This pooling will allow for the following:

- Obtaining baseline values collected in M2301 before start of everolimus
- Calculating the whole exposure to everolimus for patients enrolled in the M2305 study
- Considering the whole growth/development course over time from the start of everolimus.

The descriptive analyses of data from the CRAD001M2305 study and TOSCA registry will be presented, side by side, whenever similar data are collected in both studies. This is

intended to facilitate the interpretation of the CRAD001M2305 results and help differentiate the impact of the TSC condition versus the impact of everolimus on growth and sexual development.

Categorical data will be presented as frequencies, percentages and 95% confidence intervals. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

If the missing data pattern is not limiting, exploratory indirect comparisons between patients treated by everolimus (from M2305 study) and those who never received an mTOR inhibitor (TOSCA subset of patients) will be performed to evaluate the everolimus effect on growth and sexual development. The proposed statistical methodology for these indirect comparisons is described in Section 10.5.1.4.

In addition to the statistical methods outlined below, further details and any additional exploratory analyses that may be performed will be described in the Report and Analysis Plan (RAP).

10.1 Analysis sets

10.1.1 Full Analysis Set

In order to describe data from the CRAD001M2305 patients and those from the TOSCA registry side by side, the following analyses sets will be used.

- The Full Analysis Set (FAS):
  - for CRAD001M2305, FAS will consist of all patients enrolled in this study.
  - for TOSCA, FAS will consist of all patients enrolled in this TOSCA registry whose age at study entry was below 17 years and who never received an mTOR inhibitor throughout the registry follow-up period.
- The Full Analysis Set for sexual development (FAS Puberty):
  - for CRAD001M2305, FAS Puberty will consist of the FAS patients defined above.
  - for TOSCA, FAS Puberty will consist of the FAS patients defined above but restricting from the patients to those aged between 9 to 17 years at study entry. The TOSCA registry is designed to collect Tanner Staging until 2017 (i.e. 4 to 6 years of follow-up). Thus it is considered adequate to select only TOSCA patients aged between 9 to 17 years old at the time of entry to the registry to allow for obtaining puberty data corresponding to the peri-pubertal time frame.

10.1.2 Safety Set

The Safety Set (SS) will include all patients enrolled in this follow-up CRAD001M2305 study who have at least one-post baseline safety assessment. It should be noted that all patients enrolled in the CRAD001M2305 study have been exposed to everolimus in the parent study CRAD001M2301 (and may or may not continue receiving commercial everolimus while on CRAD001M2305).

10.1.3 Per-Protocol Set

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics will be described by study (CRAD001M2305 and TOSCA), side by side, on the two Full Analysis Sets (FAS and FAS-Puberty).

The baseline value will be the last available assessment on or before the start of everolimus for CRAD001M2305 patients and the first available assessment after the enrollment date for the TOSCA patients.

10.3 Treatments (everolimus treatment, concomitant therapies, exposure)

For patients in Study CRAD001M2305, the duration of everolimus exposure and cumulative everolimus dose will be described using descriptive statistics on the Safety Set.

The total duration of everolimus exposure will be calculated as the total duration of everolimus exposure received while on Study CRAD001M2301 plus the total duration of (commercially supplied) everolimus exposure reported in Study CRAD001M2305.

Similarly the cumulative dose of everolimus will be calculated as the cumulative everolimus dose received while on CRAD001M2301 plus the cumulative everolimus (commercially supplied) dose reported in CRAD001M2305.

In the CRAD001M2305 study:

- the duration of (commercially supplied) everolimus exposure will be estimated based on the dates of the first and last everolimus doses and the investigator summary of treatment interruptions (estimation of number of missed doses) between each visit.
- the cumulative dose will be estimated through the prescribed doses recorded at each visit. Between two consecutive visits, the prescribed dose will be assumed constant taking into account the investigator summary of treatment interruptions between each visit.

All exposure data will be listed.

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

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

10.4 Primary objective

The primary safety objective of this study is to report the effect of everolimus on height, BMI and sexual development (using Tanner Stages) in children and adolescents with TSC-associated SEGA who are taking everolimus or have taken everolimus.

10.4.1 Variable

To monitor the growth and the development of pediatric patients the following measurements will be performed annually:

- Height
- Weight
- Tanner Stage
- LH, FSH, and estrogen levels (female patients) starting age 10
- LH, FSH, and testosterone levels (male patients) starting age 10

10.4.1.1 Statistical hypothesis, model, and method of analysis

10.4.1.2 Height and BMI

The height standard deviation score (SDS) will be calculated based on height data collected during the study and published reference height information. The height SDS (also called z-score) will be computed for a particular patient at each time point. The same approach will be used to compute BMI SDS. BMI will be calculated as weight (in kg) / squared height (in m). The z-scores will allow identification of potential outliers.

SDS will be calculated using the current formulae provided by the WHO as follows:

1. Calculate $z_{ind} = \frac{\left(\frac{X}{M}\right)^{L} - 1}{LS}$
2. If $|z_{ind}| \leq 3$, $SDS = z_{ind}$
   If $z_{ind} > 3$, $SDS = 3 + (X - SD3pos) / SD23pos$
   If $z_{ind} < -3$, $SDS = -3 + (X - SD3neg) / SD23neg$

where:

- X is height in centimeters or BMI in kilograms/m^2,
- L, M and S are height or BMI-, sex- and age-specific reference values from the WHO Growth Charts.
- SD3*pos* is the cutoff 3SD calculated by the LMS method:
  $SD3pos = M * (1 + LS*3)^{1/L}$
- SD3*neg* is the cutoff -3SD calculated by the LMS method:
  $SD3pos = M * (1 + LS*(-3))^{1/L}$
- SD23*pos* if the difference between the cutoffs 3SD and 2SD:
  $SD23pos = M * (1 + LS*3)^{1/L} - M * (1 + LS*2)^{1/L}$
- SD23*neg* if the difference between the cutoffs -2SD and -3SD:
  $SD23neg = M * (1 + LS*(-2))^{1/L} - M * (1 + LS*(-3))^{1/L}$

Height-for-age and BMI-for-age L, M and S reference values for boys and girls are available under http://www.who.int/childgrowth/standards/en/ (for patients aged between 0 to 5 years old) and http://www.who.int/growthref/en/ (for patients aged between 5 to 19 years old). These correspond to the latest available international references available at the time of this protocol and described in the 2007 Bulletin of the World Health Organization (Mercedes de

Onis et al 2007). However these references may be revised according to new available standards at the time of the analysis.

The age category immediately above the patient's exact age should be used. SDS is actually a Z score that measures the distance from the population mean in units of standard deviations. That is, SDS < 0 refers to values lower than the population mean, and for example SDS ≤ -1.645 refers to values in the lowest 5%. (The usual percentile more commonly used in the clinical practice can be derived from the Z-score by a normal distribution).

The time-course of height and BMI SDS will be summarized, side by side, on the FAS of the studies CRAD001M2305 and TOSCA using descriptive statistics by year since the enrollment date (for TOSCA patients) or since the start of everolimus (for CRAD001M2305 patients). The counts and frequencies of patients with height and BMI SDS values lower than the 5th percentile (notably low) or higher than the 95th percentile (notably high) will be described on the FAS, overall and by region.

The rate of height (respectively BMI) growth notable abnormality will be calculated as the rate of patients with a height SDS < 5th percentile at the last time point where height is reported.

If a high rate of notably height (respectively BMI) growth abnormality occurs in the CRAD001M2305 patients, the relationship between the everolimus exposure and the height growth abnormality will be further explored as detailed below:

- The rate of height (respectively BMI) growth abnormality will be described in the different subgroups defined by the duration of everolimus exposure. These subgroups will be defined in the Report and Analysis Plan.
- The duration of exposure and the age at start of everolimus will be summarized using descriptive statistics in the subgroups of patients with and without a height (respectively BMI) growth abnormality.
- A logistic regression including the duration of exposure and the age at the start of everolimus as continuous covariates will also be used to further explore the relationship between the everolimus exposure and the height (respectively BMI) growth notable abnormality. Additional covariates (e.g. time normalized Cmin) might also be included in the model.

In addition, individual patient graphs for height and BMI over time will be provided for CRAD001M2305 patients.

10.4.1.3 Tanner Stage

Tanner Stage will include two components for boys, namely testis and pubic hair; and two components for girls: breast development and pubic hair.

Percentage of patients who will have reached Tanner Stage V by age 16 (for females) or age 17 (for males) will be provided, side by side, on the FAS Puberty of the studies CRADM2305 and TOSCA, along with 95% confidence intervals.

The relationship between the everolimus exposure and the Tanner Stage will be further explored in the CRAD001M2305 patients as detailed below:

- The percentage of patients who will have reached Tanner Stage V by age 16 (for females) or age 17 (for males) will be described in the different subgroups defined by duration of everolimus exposure. These subgroups will be defined in the Report and Analysis Plan.
- The duration of exposure and the age at start of everolimus will be summarized using descriptive statistics in the subgroups of patients who will reach and who will not reach Tanner Stage V by age 16 (for females) or age 17 (for males).
- A logistic regression including the duration of exposure and the age at the start of everolimus as continuous covariates may also be used to further explore if needed the relationship between the everolimus exposure and the achievement of Tanner Stage V by age 16 (for females) or age 17 (for males). Additional covariates (e.g. time normalized Cmin) might also be included in the model.

10.4.1.4 Endocrine parameters

Endocrine parameters such as LH, FSH, testosterone levels (in males) and LH, FSH, estrogen levels (in females) will be summarized descriptively, side by side, by gender and by age over time on the FAS of the studies CRADM2305 and TOSCA.

In addition individual patient graphs over time will be provided for the CRAD001M2305 patients.

All data will be listed.

10.4.2 Handling of missing values/censoring/discontinuations

All missing data will simply be described as missing on appropriate tables/listings in particular for patients who will not have reached Tanner Stage V or the age of 16 years (for females) or the age of 17 years (for males) at the end of the CRAD001M2305 study or at the end of the TOSCA registry using the FAS Puberty.

10.4.3 Supportive analyses

Not applicable

10.5 Secondary objectives

The following secondary objectives will be described: the long term-safety, the age at Tanner Stage II-V, the age at thelarche and menarche for females, the age at adrenarche for males and the TAND Checklist responses.

Additionally an indirect comparison of CRAD001M2305 and TOSCA will be performed to compare the height, BMI and sexual development (using Tanner Stages).

10.5.1 Safety objectives

The secondary safety objective of the study will be based mainly on the frequency of adverse events. All safety data will be listed.

10.5.1.1 Analysis set and grouping for the analyses

All listings and tables will be presented for all CRAD001M2305 patients using the Safety Set for adverse events.

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

1. everolimus exposure period: from day of first commercial dose received in the M2305 study to 30 days after the last commercial dose received in the M2305 study.
2. post-everolimus exposure period:
   - starting at day 30+1 after the last commercial dose received in the M2305 study or
   - starting at the enrollment date for patients who will stop everolimus in M2301 and who will not start commercial everolimus.

10.5.1.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the everolimus exposure period, the treatment-emergent AEs. However, all safety data will be listed and those collected during the post-everolimus exposure period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to everolimus treatment and by year since the enrollment date.

The prevalence over time of treatment-emergent adverse events will be described by system organ class and or preferred term.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

Clinically notable AEs (CNAE) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with everolimus.

For each CNAE, number and percentage of patients with at least one event part of the CNAE will be reported by categories regrouping the relevant preferred terms, as appropriate.

10.5.1.3 Other safety data

The other secondary safety objectives of the study will be based on sexual and neuropsychological development data.

The age when patients reach each Tanner Stage II-V will be summarized on the FAS Puberty of the studies CRADM2305 and TOSCA.

The following variables will be summarized on the Safety Set (SS) (those are only collected in the CRAD001M2305 study) using descriptive statistics:

- age when females will start thelarche
- age when females will have their first menses
- age when males will reach adrenarche

For the age at which Tanner Stage II will be achieved, summary statistics from the Kaplan-Meier distribution will be determined on the FAS puberty, including the median age and the proportions of patients reaching this milestone at some given ages. These statistics will be given as point estimates with 95% confidence intervals. The same analyses will be performed for the following variables: age at which each Tanner Stage III, IV and V will be reached. Age at thelarche (females), age at menarche (females) and age at adrenarche (males) will be described similarly on the SS.

Potential delayed puberty will be defined based on Tanner stage and also on onset of menarche for girls. Potential cases identified through this algorithm, will be then clinically reviewed by assessing all available information in order to conclude the clinical relevance of the delay.

Potential delayed puberty in girls is defined as failure to attain Tanner Stage II (for both breast development and pubic hair) by age 13, or absence of menarche by age 15 or within 5 years of attainment of Tanner Stage II (Fenichel 2012) Potential delayed puberty in boys is defined as failure to attain Tanner Stage II (for both testis and pubic hair) by age 14 (Traggiai 2002, Tanner 1962)

Rates of potential delayed puberty will be described for boys and girls separately among the patients at risk of delayed puberty along with 95% confidence intervals. The patients at risk are patients who may potentially present an event of potential delayed puberty at baseline.

The rates of potential delayed puberty will be described in the different subgroups defined by duration of everolimus exposure. These subgroups will be defined in the Report and Analysis Plan.

The duration of exposure and the age at start of everolimus will be summarized using descriptive statistics in the subgroup of patients with potential delayed puberty.

If a high rate of potential delayed puberty occurs, a logistic regression including the duration of exposure and the age at the start of everolimus as continuous covariates will also be used to further explore the relationship between the everolimus exposure and the rate of potential delayed puberty. Additional covariates (e.g. time normalized Cmin) might also be included in the model.

These patients will be clinically reviewed by assessing all available information in order to evaluate their puberty development.

All responses to the individual questions from the TAND Checklist (collected in both studies) will be summarized using descriptive statistics on both studies, side by side, and over time on the FAS of studies CRAD001M2305 and TOSCA.

Safety data from other assessments will be listed, notable values flagged, and any other information collected will be listed as appropriate.

10.5.1.4 Indirect comparison

If the missing data pattern will not limiting, an indirect comparison between patients treated by everolimus (from CRAD001M2305 study) and those who never received an mTOR inhibitor (TOSCA subset of patients) will be performed to evaluate the everolimus effect on

growth and sexual development. Due to the observational nature of the TOSCA registry and its limited follow-up time, the statistical analysis will be primarily descriptive.

The following steps will be followed:

- The following non-exhaustive list of baseline characteristics will be used to assess potential imbalances between the two groups of patients: age at baseline, race, country, gender, age at first diagnosis of TSC, height abnormality at baseline, BMI abnormality at baseline, TSC mutation, type of TSC lesions, endocrine abnormality at baseline, Tanner Stage at baseline.
- If any imbalances that are deemed to affect the comparison of the two groups are identified in the step above, propensity scores will be calculated using the appropriate statistical model according to the observed missing data pattern. The propensity score is the conditional probability of being a member of one of the groups to be compared (i.e. probability of being from the CRAD001M2305 study) given the patient's covariates (D'Agostino 1998, Rosenbaum 1984).
- Strata defined by the propensity scores (e.g. quintiles) will be then created and the balance between the groups within those strata will be examined.
- If deemed relevant, the estimated propensity scores may then be used to obtain estimates for the effect of everolimus on growth (respectively sexual) development, through matching and/or logistic regression adjustment, using the CRAD001M2305 and TOSCA FAS (respectively FAS-Puberty) analysis sets. Matching will be considered if there is a much larger sample size of untreated (TOSCA) patients as compared to the CRAD001M2305 patients. In regression adjustment the propensity score may be included either as its raw score or as per the defined strata. In addition to the propensity score a subset of the other baseline characteristics covariates may be included.

The following should be noted: the above described use of propensity scores is exploratory and highly dependent on the observed data (observed imbalances between groups, observed missingness pattern) and therefore it is not possible to fully pre-specify all aspects of the planned analyses. In addition, whereas a formal randomization guarantees that there should be no systematic differences in observed and unobserved covariates between the groups to be compared, the propensity scores are conditional only on the observed covariates. Thus, even if the use of propensity scores is intended to reduce bias and increase precision of the treatment effect, these indirect comparisons analyses using the propensity score methodology will be considered exploratory only and should be interpreted with cautious.

For each covariate used to investigate the imbalances between the two groups (and then calculate the propensity score) the missing-data mechanism will be explored. If relevant (depending on the number of patients in the TOSCA Full Analysis Sets, amount of missing data, missing-data mechanism), specific methods like Multiple Imputation or ECM algorithms may be considered to estimate the propensity scores in presence of missing data. Handling of missing data is an evolving field of research and additional methods may be considered at the time of the availability of these long-term data. This will be further detailed in the Report Analysis Plan.

If the missing data pattern will not limiting, the effect of everolimus on height (respectively BMI) growth abnormality may also be assessed as an exploratory analysis through the use of

propensity scores in a logistic regression or matching comparison as detailed before. The same analysis will be performed for the achievement of Tanner Stage V by age 16 (for females) or age 17 (for males).

10.5.2 Pharmacokinetics

Blood trough levels collected at investigator discretion in compliance with local product information should be recorded, if available.

The time-normalized Cmin value will be estimated for the entire treatment period using recorded everolimus Cmin values and prescribed doses in that treatment period. Cmin will be summarized with descriptive statistics over time in the SS.

Time-normalized Cmin (Cmin,TN) will be calculated over each assessment interval (t1, t2). The time-normalized Cmin is defined as:

$$Cmin,TN = (Cmin,t1*p1 + Cmin,t2*p2) / (p1+p2)$$

- Cmin is considered to be the same within the same dosing interval (Cmin,ti is the mean Cmins if multiple Cmins are available within a dosing interval)
- The dosing interval Pi is number of days in which the patient is treated with the same dose (in mg).
- If there is no valid Cmin value available within a dose interval, the following imputation rule will be applied: the last Cmin,ti value will be taken and multiplied by the ratio of the dose given in the current dose interval to that of the previous dose interval.
- The dose refers to the prescribed dose.

If a high rate of growth/puberty abnormalities occurs, the potential relationships between Cmin and growth/puberty data will be explored in the SS as follow:

Percentage of patients who will have reached Tanner Stage V by age 16 (for females) or age 17 (for males) will be presented split by exposure to everolimus, in terms of patient's time-normalized Cmin. As per everolimus label the target Cmin for pediatric patients is between 5 to 15 ng/mL, the time-normalized Cmin will be categorized as < 5 ng/ml, 5-10 ng/ml and > 10 ng/ml. Note: if there are insufficient numbers of patients in one of the groups the categories may be collapsed.

The same descriptive analyses will be performed for the rates of potential delayed puberty and for rate of notably low BMI/height SDS.

10.6 Exploratory objectives

Not applicable

10.7 Interim analysis

No formal interim analysis is planned for this study. However, safety outputs may be generated for regulatory safety updates.

10.8 Sample size calculation

No formal sample size calculation has been performed in this non-comparative study which consists in the long-term safety follow-up of CRAD001M2301 paediatric patients. It is anticipated that approximately 50 patients who have participated in CRAD001M2301 would be eligible to enter CRAD001M2305.

Based on the safety findings in study CRAD001M2301 in terms of growth development where the estimated rate of patients with growth development abnormality was between 5 – 10% as of 11-Jan-2013 cutoff, it can be expected that the proportion of patients with growth development abnormality in this study would be in the same range, between 5 - 10%. The growth development abnormality would be defined as rate of notably low height SDS at the cut-off date of the analysis.

The proposed sample size of 50 patients will allow estimating a two-sided 95% confidence interval for rate of patients with growth development abnormality. Table 10-1 below shows the exact binomial 95% confidence interval (Clopper and Pearson 1934) and the precision of the estimate for N=50 for various numbers of observed patients with growth abnormality. Note that the final interval will depend on the final sample size.

Table 10-1 95% confidence interval for different number of observed patients with growth development abnormality during M2305 (sample size N = 50)

Number of patients with growth development abnormality	Rate of patients with growth development abnormality	Exact binomial 95% confidence interval
0	0.00	(0.00, 0.07)
2	0.04	(0.00, 0.14)
4	0.08	(0.02, 0.19)
6	0.12	(0.04, 0.24)
8	0.16	(0.07, 0.29)
10	0.20	(0.10, 0.34)
12	0.24	(0.13, 0.38)
14	0.28	(0.16, 0.42)

With this sample size of 50, if we observe 4 patients with growth development abnormality (which corresponds to an observed 8% rate) there will be 79% probability of true rate of patients with growth development abnormality $\leq$ 10%. Probabilities that the true rate of patients with growth development abnormality is lower or equal to 10% with different number of observed patients with development abnormality are illustrated in Table 10-2. These calculations are based on the binomial distribution.

Table 10-2 Probability that the true rate of patients with growth development abnormality is lower or equal to 0.10 as a function of number of observed patients with development abnormality

Number of observed patients with growth development delay	Observed rate of patients with growth development delay	P(true rate of patients with growth development delay ≤ 0.10 | observed rate)
0	0.00	1.00
2	0.04	0.99
3	0.06	0.92
4	0.08	0.79
5	0.10	0.62
6	0.12	0.44
8	0.16	0.17
10	0.20	0.05

10.9 Power for analysis of key secondary variables

No power calculation was made for secondary analyses.

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, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is

capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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(s), proposed informed consent form(s) (ICF) that are considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement.

11.5 Publication of study protocol and results

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

11.6 Study documentation, record keeping and retention of documents

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

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

subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site 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.

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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