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Clinical Development

Afinitor®/Votubia® (everolimus)

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A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures

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List of abbreviations

AE	Adverse Event
AED	Anti-epileptic drug
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AMH	Anti-Mullerian Hormone
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BSA	Body surface area
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
C_{min}	Minimum (trough) pre-dose concentration
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Reporting Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Human cytochrome P450 3A4
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
DMPK/BA	Drug Metabolism and Pharmacokinetics / Bioanalytics
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EEG	Electroencephalogram
EIAED	Enzyme inducing anti-epileptic drug
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	Intrauterine Device
IUS	Intrauterine System
LDL	Low Density Lipoprotein
mTOR	mammalian Target Of Rapamycin
PgP	P-glycoprotein
PK	Pharmacokinetics
PPS	Per Protocol Set
QOL	Quality of life
QOLCE	Quality of Life in Childhood Epilepsy
QOLIE-31-P	Quality of Life in Epilepsy Inventory-31-Problems

[redacted]

QOLIE-AD-48	Quality of Life in Epilepsy Inventory for Adolescents-48
RAD001	Everolimus
RAP	Report and Analysis Plan
RBC	Red blood cell
SAE	Serious Adverse Event
SC	Steering Committee
SDQ	Strengths and Difficulties Questionnaire
SEC	Safety event category
SEGA	Subependymal giant cell astrocytoma
SOP	Standard Operating Procedure
TDM	Therapeutic drug monitoring
TSC	Tuberous sclerosis complex
ULN	Upper limit of normal
VABS-II	Vineland Adaptive Behavior Scales 2nd Edition
VEGF	Vascular endothelial growth factor
VNS	Vagal nerve stimulator
WBC	White blood cell
WNV	Wechsler Non-Verbal Scale of Ability

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient randomization into the study; informed consent must be obtained prior to screening (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Amendment 3 (25-Mar-2016)

Amendment rationale

As of February 26, 2016, 366 patients have been randomized, 87 patients discontinued treatment and 279 patients are still ongoing in the Extension phase.

In December 2015, the primary analysis of study data (data cutoff: October 2, 2015) was performed. The primary endpoint of the study was met when a clinically and statistically significant reduction in seizure frequency and increase in response rate, during the maintenance period of the Core Phase, was observed among patients randomized to the high everolimus Cmin range treatment arm (HT) and to patients randomized to the low everolimus Cmin range arm (LT), when compared to patients randomized to placebo. Safety for the 3 treatment arms was also assessed. The Study Steering Committee assessed the results and concluded that everolimus treatment offered study patients a positive and compelling Benefit/Risk.

Protocol Amendment 3 to this Study has been prepared for the following reasons:

Major changes

1. To create a new phase of the study (Post-Extension phase) that will permit the opportunity for patients remaining in the study to receive ongoing treatment with everolimus and for the study to extend the monitoring and collection of everolimus exposure, as well as safety measures during this longer study participation and drug exposure phase.
    - As patients were receiving a benefit from participation in the study, it was decided to extend the End of the Study until a date when either, everolimus could be commercially available to study participants or until it would be reasonable to expect that a roll over protocol could be opened at study sites, so that patients benefiting from continued treatment with everolimus, prior to the commercial availability of the drug, could exit this study, and enter the rollover protocol (as referenced in Sections 4.1.3 and 4.1.4). This strategy will allow closure of this study by October 30, 2017 (approximately 13 months after what would have been the end of study, had the study been closed at the completion of the Extension phase), and the creation of a final CSR.
    - To permit the completion of the Extension Phase and the generation of a Clinical Study Report covering Extension phase, as originally envisioned.
2. To provide investigators with independent control of patient dosing, targeting a trough level within 5-15 ng/ml, subject to safety and tolerability. This allows for more personalized and clinically relevant increases or decreases in dose titrations to more rapidly and effectively permit titration of the everolimus dose to a level that creates a desired Cmin.

Minor changes

1. While making the necessary changes in the protocol to facilitate the objectives described above, some additional clarifying language was included.
2. To clarify protocol text
3. To update pregnancy section based on the revised pregnancy follow up language.

[redacted]

4. To update the DTI sub-study to take account of the fact that only about 15 patients were enrolled, somewhat less than the planned number of 50 patients. As a consequence, the originally planned statistical analyses have been simplified to descriptive analyses only, and no attempt will now be made to correlate findings with the primary outcome measure of seizure frequency.

Changes to the protocol

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

Major changes

- Changes due to the addition of the Post Extension phase and continued monitoring of dosing, exposure, and safety as a result of the extension of treatment
  - Protocol summary, Section 2.2, 4.1, 4.1.3, 4.1.4, 4.1.5, 6.1.1, 6.1.2, 6.1.3, 6.2.2, 6.2.4, 6.5.2, 7.1, 7.1.5, 7.1.6, 7.1.6.1, 7.2.3, 7.2.3.4, 7.2.3.5, 7.2.3.6, 7.2.3.7, 7.2.3.8, 7.2.3.10, 7.2.3.11.1, 7.2.3.11.2, 7.2.3.11.3, 7.2.3.11.4, 7.2.3.11.6, 7.2.4, 10, 10.1.4, Figure 4-1, Table 7-1, Table 7-2, Table 7-5, Table 7-6
- Updates to allow Investigators to request more personalized and clinically relevant dosing
  - Section 4.1.4, 6.1.1, 6.2.2, 6.2.4, 7.1.5

Minor changes

- Corrections made related to clarify protocol text
  - Glossary of terms, Section 4.1, 4.1.3, 6.2.3, 6.3.1.1, 7.1.2, 7.1.4, 7.2.1.2, 7.2.3.1, 7.2.3.11.6, 7.2.3.4, 7.2.4, 7.2.5, 8.6, Table 6-11, Table 6-12
- Updates to pregnancy language
  - Section 7.2.3.11.6
- Corrections made to update the DTI sub-study to take account of the lower than expected sample size (n≈15 instead of n=50)
  - Appendix A, Section 14.1, 14.2, 14.3.1, 14.3.4.1, 14.4.1.1

IRB/IEC

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

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

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

[redacted]

Summary of previous amendments

Amendment 2

Amendment rationale

As of February 27, 2014, 116 patients have been randomized, 3 patients discontinued treatment and with 36 patients still in the baseline phase.

Amendment 2 has been prepared for the following reasons.

Major Changes

1. To include an additional 10 patients to the everolimus 9 to 15 ng/ml trough range arm, to account for a potential loss in power
    - A human error was identified resulting in the failure of the IRT system to perform dose titrations in the presence of C_{min} values outside the targeted trough ranges for patients randomized to everolimus (high trough range: 9-15ng/ml and low trough range: 3-7ng/ml). The error was corrected, but it is estimated that some patients randomized to the high trough range may not have achieved the targeted exposure to everolimus. As a result, it was decided to increase the sample size in the everolimus 9 to 15 ng/ml trough range arm by 10 patients, to account for the potential loss of power in comparing this arm to the placebo arm for the primary efficacy endpoint. In addition, an independent PK expert will be appointed to oversee interaction between PK vendor and IRT vendor to ensure appropriate dose titration recommendations are being made by the IRT system through the rest of the study.
2. Inclusion criteria 3 updated to expand the definition of partial onset seizures (POS) and include sensory seizures as the sole seizure type if confirmed to be partial onset by ictal EEG
    - Associated eligibility criteria are updated as a result of this change which include the updated definition of partial onset seizures for Inclusion criteria 4 and the removal of Exclusion criteria 2
    - Sensory seizures had been excluded from the counting of partial onset seizures. The intent for this exclusion was to limit seizure counting to objectively assessable seizures (i.e., motor events that can be observed by another person). Yet, investigators have noted that sensory events confirmed to be seizures by ictal EEG would represent a seizure as least as “probable” as a motor event, not confirmed by ictal EEG. As a consequence, this amendment includes the expansion of the definition of partial onset seizures suitable for counting in this study, to include sensory seizures confirmed by ictal EEG. By permitting the counting of these events, it has become necessary to expand the definition of sensory seizures to two subcategories (those confirmed by ictal EEG and those not confirmed by EEG).

[redacted]

3. Exclusion criteria 4 clarified to exclude patients < 2 years of age with untreated infantile spasms
    - It has been recognized over the course of the trial that many patients with epileptic spasms, following effective treatment for infantile spasms, may be inadvertently excluded from the study, based on the exclusion criteria of "infantile spasms" Therefore, the exclusion is herein modified to "untreated infantile spasms". This modification will clarify the eligibility of patients with residual epileptic spasms to be included in the study, as originally intended.
4. Addition of Exclusion criteria 26 related to patients on a ketogenic diet defined as < 40g of carbohydrate a day
    - The amendment adds ketogenic diet, defined as "< 40 g of carbohydrate/day". Ketogenic diet, a type of anti-epilepsy therapy, may mediate its effect through mTOR inhibition. Because the potential interaction of similarly acting therapies may pose risks to patients, it was determined that treatment with a low carbohydrate ketogenic diet should be an exclusion criterion.
5. Allowing investigator discretion to manage everolimus titrations in the extension phase.
    - The modifications preserve blinding of the Core Phase randomization among patients, investigators and the sponsor, and provide freedom for dose adjustments that neurologists are typically accustomed to (in the extension phase of multi-dose vs placebo randomized trials of anti-epileptic drugs).
    - Investigators have expressed a desire to know the everolimus Cmin values of their patients after the Core phase of the study, and to be permitted to make dose adjustments (increases or decreases), during the Extension phase. To accomplish this, patients are first transitioned towards an everolimus trough concentration range of 6-10 ng/ml, which preserves the blinding of the original randomization. After this transition (week 26 for newly enrolled patients) Cmin values will be revealed to investigators who will have the option to modify the dose of study drug. If investigators choose not to modify dosing, the dose will be determined by the IRT to maintain the everolimus trough concentration range between 3-15 ng/ml for all patients.
6. Updates to Exclusion Criteria 25 and additional assessment of self-injury and mood and/or behavior changes
    - The study requires patients 13 years and over to complete the eC-SSRS themselves and for caregivers to complete the eC-SSRS on behalf of patients under the age of 13 or patients with cognitive impairment. The amendment now requires that the investigator discuss episodes of self-injury and changes in the patient's mood and/or behavior with the patient and caregiver, for all patients. For patients ≥ 13 years of age who do not complete the scale via IRT, the investigator will proactively assess the patient for the presence of suicidality. These changes help ensure a relevant mental safety assessment has been performed on behalf of patients for whom the eC-SSRS has not been completed. The exclusion criteria was also updated to harmonize with the guidance provided throughout the protocol, namely that a score of 4 or 5 could be addressed in a discussion with a healthcare professional.

7. Updates to Data collection, Data management and quality control
    - The Vineland scale raw scores would be collected in a separate database and not in clinical OC-RDC database. This is the first protocol amendment since the final license agreement for the Vineland scale, therefore additional information regarding the collection of the Vineland data has been included in this amendment.
8. Correction to definition of Safety Population
    - The Safety Population in the original protocol was planned to be defined using actual Cmin values, however that approach has since been recognized as inappropriate. That is, there will be no attempt to reassign patients from one everolimus arm to the other everolimus arm based on observed everolimus concentrations during the Core phase. This is because increases in the dose of everolimus would have been recommended during the Core phase in order to reach the targeted trough range of 9-15 ng/ml, and any associated toxicity should therefore be attributed to the 9-15 ng/ml arm and not the 3-7 ng/ml arm.

Minor Changes

1. To provide corrections to protocol text
2. To include clarifications related to Study Procedures, Timing of Visits and Assessments, updated Reference list and other typographical Errors
3. To include anti-Mullerian Hormone (AMH) in all newly enrolled female patients ≥10 years of age
    - AMH is a gonadotrophin independent, paracrine hormone, involved in the recruitment of primordial follicles. It measures ovarian function and may be useful in assessing conditions such as polycystic ovary syndrome and premature ovarian failure. One of the noted risk factors of everolimus is amenorrhea, and whether amenorrhea represents a consequence of endocrine dysfunction related to everolimus, remains unclear. It has been suggested that patients with tuberous sclerosis may have, as a consequence of mTOR over-activation, a higher rate of primordial follicle recruitment, with premature ovarian failure leading to amenorrhea. In short, it is unclear whether amenorrhea is a comorbid condition associated with TSC or a consequence of everolimus treatment. The measurement of AMH before and during treatment with everolimus, in female patients near puberty can help address this question. Only female patients ≥10 years of age will be evaluated for AMH, because the goal is to capture baseline and post-treatment levels in TSC patients near puberty until menopause.

Changes to the Protocol

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

Major Changes

- **Sample size increase of 10 additional patients**
    - Section 5.1, 6.4.2, 10.8

[redacted]

- **Updates to Inclusion criteria 3 and 4**
  - Section 5.2
- **Updates to Exclusion criteria 2, 4 and 26**
  - Section 5.3
- **Investigator-led titration**
  - Section 4.1, 4.1.3, 4.1.4, Fig. 4-1, Table 4-3, 6.1.1, 6.2.2, 6.5.2, Table 6-14, Table 7-1, 7.1.4, Table 7-4
- **Updates to Exclusion criteria 25 and additional assessment of self-injury and mood and/or behavior changes**
  - Section 5.3 and 7.2.3.10
- **To include Data collection and Database management language relating to the paper component of the trial**
  - Section 9.3, 9.4
- **Correction to definition of Safety Population**
  - Section 10.1.2

Minor Changes

- **Corrections related to Protocol Text**
  - Section 6.1.3, 6.2.5.8, 7.1.1, 7.1.2, 7.1.3, 7.1.4, 7.1.6, 7.2.2.3, 7.2.3.6, 7.2.3.11.6, 7.2.4, 7.2.4.1, 10.1.3, 10.5.1, 10.5.2.1, Table 7-2
- **Clarifications related to Study Procedures, Timing of Visits and Assessments and updated Reference list**
  - Section 2.2, 4.1.1, 4.1.3, 4.1.5, 5.2, 5.3, 6.1.1.1, , 6.2.2, 6.2.5.1, 6.3, 6.3.1, 6.4.3, 6.5.1, 6.5.4.1, 7.1.5.1, 7.2.1.5, 7.2.2.1, 7.2.3.1, 7.2.3.8, 7.2.3.9, 7.2.3.10, 7.2.4.2.2, 7.2.5, 8.1.3, 10.5.2.4, 13, 14, Table 6-5, Table 6-6, Table 6-7, Table 7-1, Table 7-3, Table 7-4
- **To include anti-Mullerian Hormone (AMH) in all newly enrolled female patients ≥10 years of age**
  - Section 7.2.3.11.7, Table 7-1, Table 7-2
- **Corrections of typographical errors**
  - Figure 1-1, Fig 1-3, Table 3-1, Table 7-6, and throughout the protocol

IRB/IEC

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

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

Amendment 1

Amendment Rationale

This study is still in planning stages, and no patients have yet been enrolled. No patients are planned to be enrolled until after this amendment is approved and in place. The changes identified in this protocol amendment address feedback to the protocol provided by the EMA (European Medicines Agency) and FDA, and includes clarifications of instructions and corrections of typographical errors. The rationale for the major changes are as follows:

The exclusion criterion regarding Lennox Gastaut Syndrome (LGS) is removed. Patients with TSC may have multiple seizure types that must include partial onset seizure to be enrolled in the study. The diagnosis of LGS includes multiples seizure types, intellectual disability and a slow-spike wave pattern on EEG. Therefore, because patients carrying the diagnosis of TSC and LGS are viewed as patients with TSC whose disease has progressed to cause intellectual disability and a characteristic LGS EEG wave pattern, there is no reason to exclude patients who have LGS as long as they have an underlying diagnosis of TSC and partial onset seizures.

The volume of blood drawn in the study was reviewed and modified to make it compliant with the "ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use" The volume of blood collected from pediatric patients during all phases of the is now limited to ensure that not more than 1% of the patient's total blood volume (i.e., 0.8mL/kg) is collected on any visit, and not more than 3% of the patients total blood volume (i.e., 2.4mL/kg is collected in any 3 week period. To accomplish this two changes are incorporated:

- Patients weighing less than 12 kg will not be enrolled in the study, because of the inability to collect adequate volumes of blood to monitor their safety and evaluate PK
- Patients weighing 12 to 20 kg will not be required to provide PK AED and it will be recommended that TSC1/2 genetic mutation samples instead be collected on Visit 4 to decrease the collection of blood on Visit 2.

EMA requested that the study include patients down to age 1 year of age. Inclusion criteria, and all stratification specifications are changed to reflect this. The protocol now includes patients age 2 to 65, except for Europe, where the inclusion is 1 to 65. For stratifications, the first group is 1 to <6.

FDA specifically requested a sensitivity analysis of the primary endpoint where seizure frequency is determined across the entire Core phase (i.e., titration period as well as maintenance period). This analysis is already included in Section 10.4.4 of the protocol, however the wording is improved to make it more explicit.

In order to ensure that patients remain in their target trough range, clarification was made that titration may occur during both the Core and the Extension Phases. Language is added to Section 4.1.3, and rows in Tables 4-1 and 4-2 to indicate that titration may occur outside a 'scheduled' time, and what actions must happen if this occurs.

[redacted]

Missing information about whether or not patients may take rescue medication during the Baseline Phase is updated in the exclusion criteria, and in withdrawal criteria.

To improve internal consistency in the protocol the dosing age group for the >18 is changed to ≥ 18.

Clarifications on the inclusion criteria have been added. These focus primarily on the definition of partial onset seizures. Seizures in patients with TSC are focal in origin, due to the underlying pathophysiology of the disease which drives neuronal hyperexcitability in or near tubers and possibly other areas of the brain. Therefore, for the purpose of this study being conducted in patients with TSC, any seizure with a motor component is deemed to be a partial onset seizure, unless that seizure type is demonstrated to be a primary generalized seizures on an ictal EEG. Clarification to the definition of partial onset seizures have been captured in Inclusion Criteria 3. Additionally, further subcategories to categories IB (Complex partial seizures) and IC (secondarily generalized partial seizures) were added in order to capture the different clinical presentations of this seizure type.

Three items are added under criteria for premature withdrawal (7.1.5.1) to ensure that patients who should no longer be included in the study are removed. 1) an interruption from study drug that lasts for more than 28 days; 2) an interruption of one or more of the concomitant AEDs for more than 7 days; 3) In patients who have their dose interrupted for toxicity, if restarting study drug upon resolution of the toxicity requires dose reduction, and that reduction results in instruction to take 0 tablets for placebo patients during the core phase, or 0 mg of everolimus for active drug patients in the Core phase, or 0 mg everolimus for all patients in the Extension phase.

Appendix A is replaced with an updated Substudy summary that includes the collection of HFO EEGs.

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.

Changes to the Protocol

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

1. **Changes to List of Abbreviations and Glossary of Terms**
   - Abbreviations updated to reflect deletion of C-SSRS.
   - Terms updated to clarify patient number.
2. **Changes to Study Design (Protocol section 4)**
   - Figure 4-1: Footnote changed to clarify that after the titration period, patients are maintained on their treatment for 12 weeks.
   - Section 4.1.1: Randomization stratification updated to include patients starting at age 1.
   - Section 4.1.2: Description of titration and PK sampling updated for clarity. The volumes of PK blood samples per age group were also added to this section.
   - Table 4-1: Table on PK sampling and dose titration updated to reflect the possibility of additional PK sampling and potential for titrations.

[redacted]

- Section 4.1.3: Text regarding length of extension phase clarified.
- Section 4.1.3: Description of titration and PK sampling in the extension phase updated for clarity. Blood volume to be taken was clarified and a sentence was added to specify that patients weighing 12-20 kg would not be required to provide blood samples for PK AED testing.
- Table 4-2: Table on PK sampling and dose titration in extension phase updated to reflect the possibility of additional PK sampling and potential for titrations.
- Table 4-2: The heading of "table" is changed to "week".

3. Changes to Patient Population (Protocol section 5)

- Section 5.1: Patient population was changed to include patients starting at age 1 for Europe and patients starting at age 2 for rest of world.
- Section 5.2: Inclusion criteria number 1 modified to include patients starting at age 1 for Europe and patient starting at age 2 for rest of world.
- Section 5.2: Inclusion Criterion #1, the minimum number of pediatric patients to be randomized in the age group 1 to <6 years has changed to 40 patients, in the age group 6 to <12 years has changed to 40 patients, and in the age group 12 to <18 years has changed to 40 patients.
- Section 5.2: Inclusion Criterion #7, the requirement for sexually active males to use a condom during intercourse has been increased to 8 weeks after stopping study treatment.
- Section 5.3: The exclusion criteria have been modified to exclude patients who require rescue medication during the Baseline Phase for 7 or more consecutive days or 7 or more cumulative days.
- Section 5.3: The exclusion criteria regarding Lennox Gastaut Syndrome (LGS) has been removed.
- Section 5.3: Additional exclusion criteria was added stating that patients who weigh less than 12kg cannot be enrolled.

4. Changes to Treatment (Protocol section 6)

- Section 6.1.1: The change allows for clarification regarding color coding of the study medication in order to maintain the blind.
- Section 6.1.1: Packaging of medication boxes clarified as color labeled boxes will be provided separately and not as a "kit".
- Table 6-2: The age of the patients that receive a starting dose of 5.0 mg/m2/day has been changed to patients aged 10 to less than (<) 18 and age of patients receiving a starting dose of 3.0 mg/m^2/day has been modified to greater than or equal to (≥) 18 years.
- Section 6.1.2: Clarification added to rescue medication section that they are only allowed for a period that does not exceed 6 days during the baseline period.
- Section 6.1.3: Dose reduction due to toxicity to zero tablets during the core phase and pregnancy were added to possible reasons for treatment withdrawal.

[redacted]

- Table 6-3: The changes allow for clarification on the age group of patients whose pre-dose concentrations have been predicted after the per protocol starting dose. The middle age group was changed to 10 to less than (<) 18 years age group and ≥ 18 years for the highest age group.
- Section 6.2.3: Under titration the change allows for further clarification on the different age groups listed in table 6-4.
- Section 6.2.4: Reason of interruption of study drug for more than 28 days was added as a possible reason for treatment withdrawal.
- Tables 6-5, 6-6, 6-7, and 6-9: Clarification on the guidelines for Everolimus dose modification for patients that do, or do not take CYP3A4 inducers.
- Section 6.2.5.5: Additional section was added for the management of amenorrhea.
- Table 6-10: The guideline for the management of hepatitis C flare has changed to the patient being excluded from the study.
- Section 6.4.2: Randomization stratification updated to include patients starting at age 1.
- Section 6.5.2: Packaging of medication boxes clarified as color labeled boxes will be provided separately and not as a "kit".
- Table 6-13 and Table 6-14: Packaging of medication boxes clarified as color labeled boxes will be provided separately and not as a "kit". Additional option added for low trough range group.

5. Changes to Visit Schedule and Assessments (Protocol Section 7)

- Table 7-1: In the visit evaluation schedule, the inclusion and exclusion criteria that will be recorded, has been changed to category "D" indicating that this data will be entered into the database.
- Table 7-1: Seizure history has been added to the visit evaluation schedule to be performed at screening.
- Table 7-1: Further clarification in the form of a footnote was added for timing of WNV, Vineland, and QOL after the end of core visit.
- Table 7-1: Assessment for endocrine tests at EOT Core was added.
- Table 7-1: Clarification added to study drug administration assessment.
- Table 7-1: A footnote was added to give the option for patients between 12-20 kg to have the TSC 1/2 genetic sampling on visit 4, to decrease the blood collection amount on visit 2. This information is also included in section 7.1.2 under the description of the baseline visit.
- Table 7-1: AED PK sampling was added at the screening visit.
- Section 7.1.1: The section on screening has been amended to further clarify the requirements for certain procedures, collection of patient data, and the methods of maintaining and recording this data, including IRT procedures.
- Section 7.1.1: The statement on permitting reassessment of screening criteria has been moved from the sub-heading of screening for hepatitis C to the main heading of screening.

[redacted]

- Section 7.1.2: The baseline phase and baseline visit has been amended to further clarify the requirements during this phase, especially seizure diaries, the use of rescue medication, data recording and collection, requirements for determining eligibility, IRT procedures and MRI sub-study details.
- Section 7.1.2: The paragraph detailing the screening visit has been removed from the baseline phase section as the details are covered under section 7.1.1.
- Section 7.1.3: The core phase section has been amended to further clarify the requirements during this phase, including procedures performed during this phase.
- Section 7.1.4: The extension phase section has been amended to further clarify the requirements during this phase, including procedures performed during this phase.
- Section 7.1.5: The end of treatment section has been amended to further clarify the requirements during this visit.
- Section 7.1.5.1: Three additional criteria for premature withdrawal of the patient from the study have been added - An interruption of study drug that lasts for more than 28 days, an interruption of one or more of the concomitant AEDs for more than 7 days, and in patients who have their dose interrupted for toxicity, if restarting study drug upon resolution of the toxicity requires dose reduction, and that reduction results in instruction to take 0 tablets for placebo patients during the core phase, or 0 mg of everolimus for active drug patients in the Core phase, or 0 mg everolimus for all patients in the Extension phase.
- Section 7.2.1.1: Seizure history and TSC history added to patient history description.
- Section 7.2.3.1: Clarifications made to descriptions of neurobehavioral, neurodevelopmental, and neurocognitive assessments.
- Section 7.2.3.4: The tanner staging section regarding pubic hair stages has been amended to provide further clarity on this assessment.
- Section 7.2.3.6: Pregnancy history, menstrual history and monitoring section was updated to include description of the menstruation diaries and how data will be collected.
- Section 7.2.3.8: Clarification was added for collection of pre-baseline height and weight and collection of parental height.
- Section 7.2.3.10: Instructions for who completed the eC-SSRS was clarified.
- Table 7.2.3.11: The table detailing the central clinical laboratory parameters collection plan and the following test-categories have been amended to accurately list all the laboratory evaluations that are required.
- Section 7.2.3.11.2: Description of clinical chemistry was amended to reflect the laboratory evaluations to be performed.
- Section 7.2.3.11.5: Description of urinalysis was amended to reflect the laboratory evaluations to be performed.
- Section 7.2.3.11.6. Timing and procedures for monthly pregnancy tests were clarified.

[redacted]

- Section 7.2.4: The pharmacokinetic section was updated to include blood sample clarifications for pediatric patients, and to define the timing of a trough sample
- Section 7.2.5: Clarification statement was added indicating that the parent/caregiver of patients <10 years old will be completing the three quality of life questionnaires on behalf of the patient.

6. Changes to Statistical Methods and Data Analysis (Protocol section 10)

- Section 10.4.1: Changed the word supportive to sensitivity when describing the analysis of the primary outcome.
- Section 10.4.1.1: The change to the EMA primary variable: response rate includes the change of "exclusion criteria" to "inclusion criteria" as the criteria where counting of partial-onset seizures is defined.
- Section 10.4.4: "Supportive analyses" has been changed to "Sensitivity analyses".

7. Changes to References (Protocol section 13)

- Changes to this section include re-formatting of all the reference articles.

8. Changes to Appendix A (Protocol section 14)

- Changes were made to Appendix A to include EEGs and clarifications were made to the MRI section.

IRB/IEC

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

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

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Protocol summary

Study title: A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures

Study phase: III

Study objectives:

Primary objective: To compare the reduction in frequency of partial-onset seizures on each of two trough ranges of everolimus (3-7 ng/mL and 9-15 ng/mL) versus placebo in patients with TSC who are taking one to three AEDs.

Key secondary objective: To compare each of the two everolimus trough ranges versus placebo with respect to:

1. Ability to completely suppress partial-onset seizures.
2. Proportion of patients with ≥ 25% reduction from baseline in average weekly frequency of partial-onset seizures.
3. Distribution of reduction from baseline in seizure frequency
4. Seizure-free days
5. Treatment duration
6. Quality of life

Study population: The target population is comprised of approximately 355 male or female patients, with TSC who have refractory partial-onset seizures. Patients between ages of 1 and 65 years will be enrolled.

Number of patients: 355

Overview of study design: This is a three-arm, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of two trough-ranges of everolimus given as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures.

The study consists of 4 phases for each patient [Baseline phase: From Screening Week -8 (V1) to randomization visit at Week 0 (V2)], Core phase [Double-blind, placebo-controlled, from randomization at Week 0 (V2) to Week 18 (V11)], Extension phase [All patients receiving everolimus from Week 18 (V11) until 48 weeks after the last patient has completed the core phase], and Post Extension Phase [after the end of the Extension phase until October 30, 2017].

Eligibility criteria will be assessed subsequently at the end of the baseline phase (V2, Week 0), prior to randomization. All patients who continue to meet eligibility criteria, including demonstrating the minimum seizure frequency during the 8-week baseline phase (see Section 5.2 and 5.3), will be randomized in a 1:1:1.09 ratio to one of the three treatment arms as described in Section 6.1. Randomization will be stratified by age subgroup at randomization as follows: 1 to <6 years; (ii) 6 to <12 years; (iii) 12 to <18 years; and (iv) ≥ 18 years.

Statistical considerations: The data cut-off date for the primary efficacy and safety analyses will be when all patients have completed the Core phase or have discontinued early. At that time, all data from the Core phase will be available as will a part of the Extension phase data. The analyses for the reports will thus cover both periods:

- The main focus will be on descriptive and inferential comparisons of both everolimus arms versus placebo on efficacy and safety in the Core phase.
- Descriptive efficacy and safety analyses on Extension phase data will also be conducted in order to explore the longer term effects of everolimus.

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The second data cut-off will be at the end of the extension phase, which is planned 48 weeks after the last patient completes the Core phase, and which will be used for the study report of the Extension phase. Earlier updates of the Extension phase data are not currently planned, but may be performed if needed. The final data cut off will be at the end of the Post Extension phase (October 30, 2017).

1 Background

1.1 Overview of Tuberous Sclerosis and current treatment options

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). Clinical disease spectrum is highly variable, with manifestations ranging from mild skin 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 disease (Curatolo et al 2002, Levine et al 2006). Despite this broad range of clinical findings, a limited number of features are responsible for the decreased life expectancy associated with the disease. These include neurologic disorders (SEGAs and seizures), renal disease (angiomyolipomas and renal cell carcinoma [RCC]), pulmonary disease (lymphangioleiomyomatosis), and cardiovascular disease (rhabdomyoma) (Goh et al 2004).

1.1.1 Epilepsy associated with TSC

TSC represents one of the most common genetic causes of epilepsy. Eighty to 90% of individuals with TSC are affected by epilepsy that manifests usually very early during the first year of life. In a retrospective study of 291 TSC patients treated at Massachusetts General Hospital, 84.5% of the patients developed epilepsy (Chu-Shore et al 2010).

Seizures with partial-onset are observed in most TSC patients. A variety of seizure types have been reported including infantile spasms, simple partial, complex partial and generalized tonic-clonic seizures (Holmes 2007; Wong 2010; Orlova and Crino 2010). In the Massachusetts General Hospital study that included both children and adults, the most common seizures observed were complex partial seizures (86.9%, including those with secondary generalization) and infantile spasms (46.4%) (Chu-Shore et al 2010).

Patients with seizure onset before the age of 4 years, particularly when the seizures are frequent or refractory to treatment, have a substantially increased risk of subsequent mental retardation or autism. In a study that evaluated the intellectual abilities in 108 patients with TSC using standardized assessment tools and compared these with other features of TSC, including seizures, reported that infantile spasms and severe intractable seizures are highly correlated with global intellectual impairment (Joinson et al 2003). Studies have also found a higher incidence of autism in children with TSC who have intractable epilepsy at early onset (Bolton et al 2002). Children with TSC are particularly prone to epileptic encephalopathies such as Lennox-Gastaut syndrome. Goh evaluated intellectual outcomes in children with TSC and infantile spasms and found that the length of uncontrolled seizure activity and poor control of other seizure types after infantile spasms were associated with increased risk of mental retardation (Goh et al 2005).

A retrospective chart review of all patients with TSC seen between January 2002 and October 2008 by (Chu-Shore, et al 2010) reported that the onset of seizures typically occurred in the first year of life (with 82% before 3 years of age); however, adults remain at risk. Notably, in

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this review 12% of adult patients with TSC without prior history of seizure developed epilepsy subsequently, indicating that TSC patients are at an increased risk of epilepsy throughout their lifetime.

Seizure control

Seizures may be controlled by medication such as antiepileptic drugs (AEDs) or methods such as epilepsy surgery, vagal nerve stimulation (VNS) or ketogenic diet (Wong 2010; Jobst 2009). However, between 20-60% of patients with TSC-associated epilepsy fail to demonstrate improvement in seizure frequency with available therapies (Franz 2000; Franz 2001; Collins 2006). One study found only 14% of epilepsy remission rate in its TSC population; furthermore, of these patients, about 25% relapsed after a mean follow-up of 5.5 years (Sparagana 2003).

Refractory seizures

Refractory or intractable epilepsy is generally defined as failure to control partial-onset seizures despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs (Berg 2006; Chu-Shore 2010; Kwan 2010). Many patients with TSC continue to have intractable seizures with a poor response to both established and new anti-epileptic therapies. In the (Chu-Shore study 2010), 155 out of 248 (62.5%) TSC patients with epilepsy developed refractory epilepsy. Furthermore, in patients with a history of infantile spasms, 75.4% developed refractory epilepsy compared to 39.8% in patients without a history of infantile spasms ($p < 0.0001$).

Surgery may constitute a valuable option for refractory seizures, however, surgery is not feasible for all patients either because the removal of epileptic zone will result in unacceptable deficit (for example when motor or language areas are involved) or because of the multifocal origin of seizures (Granata 2009). Furthermore, it is reported that around one third of patients with TSC still experience seizures even after surgical treatment (Curatolo 2006; Jansen 2007; Napolioni 2009).

Attempts to determine why some TSC patients fail to respond to conventional AEDs and develop intractable epilepsy have been inconclusive. One possible explanation is that the available AEDs target neuronal over-excitability through alteration in neurotransmitter release, receptor activation, or ion channel function; therefore such AEDs act primarily on the molecular mechanism that mediates the end stage of epilepsy (i.e., seizures). Such AEDs are considered “antiepileptic” therapies that suppress seizures and thus affect symptoms only, and not “antiepileptogenic” therapies that affect the underlying cause of epilepsy.

1.1.2 Role of mTOR in TSC and epileptogenesis

Neurological manifestations associated with TSC including epilepsy are thought to be caused by cerebral cortical tubers, which are present in over 80% of patients (Crino, et al 2006). However the relationship between tubers and seizures is not totally well understood. Among other questions still unanswered, it is not known whether seizures originate within or near tubers, whether the pathophysiology of seizures in TSC differs from other epilepsy syndromes, or how the development of tubers affects the maturation of brain circuits. Unresolved

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questions also include how the specific gene mutation leads to tuber formation, the exact cells of tuber origin, and the factors that determine tuber location and number.

The protein products of the TSC1 (hamartin) and TSC2 (tuberin) genes are part of the PI3K/PKB(Akt)/S6K1 signaling pathway that regulates cell growth and proliferation via the mammalian target of rapamycin (mTOR) (Dan et al 2002; El-Hashemite et al 2003; Goncharova et al 2002; Manning et al 2002). A precise interaction between tuberin and hamartin appears to be critical at different stages of central nervous system development, including morphogenesis, cell adhesion/migration, and cell fate determination (Wong 2009). In the brain, TSC1 and TSC2 messenger RNA (mRNA) and proteins have been detected in cerebral cortex, hippocampus, cerebellum, brainstem, choroid plexus epithelium, and spinal cord of immature and mature brain (Marcotte and Crino 2006).

mTOR exists as two complexes, designated mTORC1 (mammalian target of rapamycin complex 1) and mTORC2 (mammalian target of rapamycin complex 2). The hamartin/tuberin complex targets specifically regulation of mTORC1 through the inhibition of Ras homolog enriched in brain (Rheb) (Zhang et al 2003). Rheb is a small GTP-binding protein whose activation results in upregulation of mTORC1. Cortical tubers and other hamartomatous lesions found in patients with TSC demonstrate abnormal mTORC1 activation and upregulation of downstream targets including p70 S6 kinase (S6K1), 4E binding protein (4EBP1), and S6 ribosomal protein (Baybis et al 2004; Ma et al 2005). These proteins play a major role in the translational regulation of mRNAs in diverse processes, including proteins involved in G1-phase cell cycle progression in many different cell types (Huang et al 2008). Less is known regarding the mTORC2 complex, but evidence suggests hamartin and tuberin have a role in mTORC2-mediated signaling as well (Huang et al 2008).

In addition to contribution to cortical tuber formation, emerging evidence suggests a major role of mTOR in neuronal function and neuronal disease pathogenesis. Widespread neuropathological changes have been shown to be present in radiologically normal parenchymal structures in addition to TSC cerebral hamartomas (such as SEGA or subependymal nodules (SENs)). mTOR is known to regulate cell size, arborization and function of dendritic spines, as well as synthesis and density of glutamate receptors (Meikle et al 2007; Kwon et al 2006; Lenz 2005; Wiersma-Meems et al 2005). Tavazoie identified anatomic changes in dendritic spines in neurons, more severe in homozygous and less severe in heterozygous neurons for TSC mutations, indicating a so-called genetic “dose effect” (Tavazoie et al 2005). This is relevant for the potential epileptic involvement of peri-tuberal cortex. Individual progenitor neurons sharing a common mutation in either TSC1 or TSC2 give rise to cortical tubers. The process responsible for inactivation of the other copy of the TSC gene can differ for each neuronal progenitor cell, resulting in the markedly different biologic activity of various tubers, even within the same patient.

Nutrient deprivation, specifically that of carbohydrates, serves to inhibit mTOR and results in many of the same effects as treatment with rapamycin (Peng et al 2002). This may be one of the mechanisms of action of the ketogenic diet, a therapy that is particularly efficacious in TSC patients (Kossoff et al 2005).

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Neurotransmitter responses are also impacted by mTOR-dependent signaling in addition to morphological changes in neurons. TSC2+/- rats exhibited memory differences compared to wild-type controls and also more rapidly developed stage five seizures in one model of chemically-induced kindling (Waltereit et al 2006). Glutamatergic neurotransmission has been shown to enhance activity of mTOR and S6K1 that serve to stimulate protein synthesis, including the synthesis of glutamate receptors (Gong et al 2006). In another study, mTOR inhibition by rapamycin altered synaptic protein synthesis during induced plasticity of cultured neurons and long-term consolidation of auditory cortex-dependent memory in gerbils (Tischmeyer et al 2003). Protein synthesis and microanatomic changes that underlie both synaptic long term potentiation and long term depression, processes thought to contribute to epileptogenesis and seizure susceptibility, are also regulated by mTOR (Ess 2006). Alterations in glutamatergic neurotransmission are associated with these changes, as is modulation of voltage-dependent potassium channels (Raab-Graham et al 2006). Additionally, glutamate itself can activate mTOR and S6K1 (Narayanan et al 2007). In this way subclinical epileptiform discharges, such as are those commonly seen in TSC children, could cause epileptogenesis through a localized activation of mTOR independent of TSC1 or TSC2 mutation. This is supported by study reporting inhibition of kindling in wild type mice by mTOR inhibition (Zeng et al 2008). Finally, activation of mTOR is important in the development of chronic epilepsy after closed head injury in animal models not having TSC mutations (Erlich et al 2007).

Apart from the direct effect of mTOR signaling on epileptogenesis, de Vries and Howe proposed that the molecular disruption caused by TSC mutations are sufficient to lead to the neurocognitive and neurodevelopmental deficits seen in tuberous sclerosis, given that many of the upstream and downstream protein targets have key roles in the neurobiology of learning and memory (de Vries and Howe 2007). As illustrated in the figure below (Napolioni et al 2009), the mutation of TSC genes, through downstream effect on neuronal and synaptic structures/neurotransmission, results in fundamental alterations in network properties as well as an imbalance in excitation and inhibition, acting as a common pathway toward epilepsy, intellectual development, and autism.

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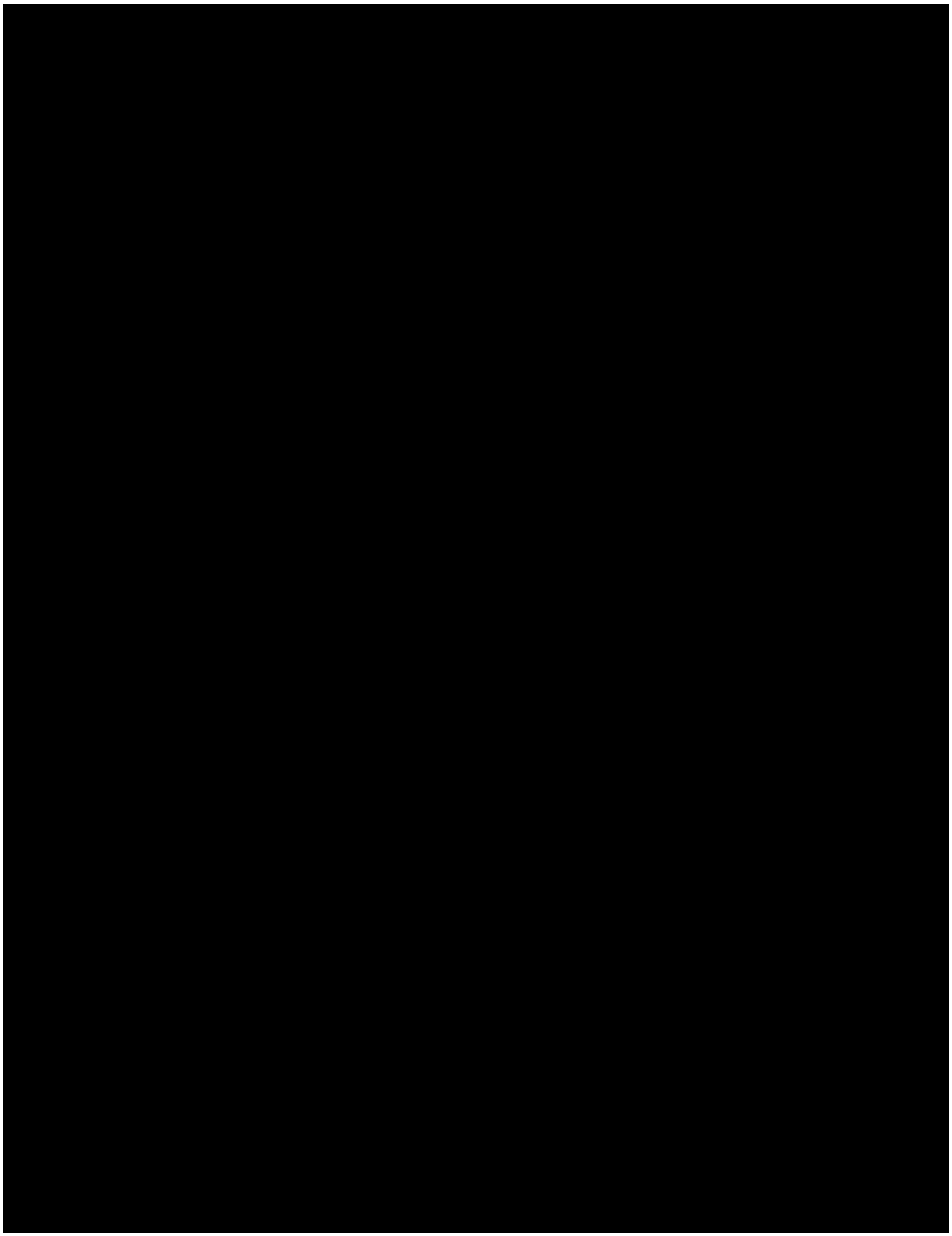
Impact of seizures on neurodevelopment and cognition is also well recognized. Poorly controlled seizures represent significant risk factors for adverse neurocognitive and neurodevelopmental outcome. Recent findings in an Eker Rat model of TSC2 showed an additive effect between molecular and seizure factors. In the study by (Waltereit et al 2011), Eker rats showed some specific social deficits, and gained additional social deficits through the onset of seizures. The combination of poorly controlled seizures and TSC genotype therefore represents a significant risk factors for poor neurocognitive and neurodevelopmental outcomes in TSC. It is well known that the neuropsychiatric manifestations of TSC (including intellectual disability, autism and other neurocognitive deficits) represent some of the greatest contributions to the burden of care in TSC (Hunt et al 1983; de Vries 2010).

1.1.3 Rapamycin and everolimus (RAD001) in TSC-epilepsy

1.1.3.1 Nonclinical investigation

Nonclinical research using animal models, either due to genetic modification or treatment with seizure-inducing agents, has demonstrated a reduction in seizure activity with mTOR inhibitors. For example, a neuronal-specific conditional knockout of *TSC1* experienced spontaneous seizure activity that caused death by day 35 (Figure 1-2). This could be completely blocked by treatment with the mTOR inhibitors rapamycin or everolimus (RAD001), allowing survival to more than 100 days (Meikle 2007 and Meikle 2008).



Zeng et al also reported that early treatment with rapamycin prevented the development of epilepsy and premature death observed in Tsc*1*GFAPCKO mice. Late treatment with rapamycin suppressed seizures and prolonged survival in Tsc*1*GFAPCKO mice that had already developed epilepsy (Zeng 2008).

In summary, the nonclinical research demonstrates that mTOR inhibitors, rapamycin and everolimus, have efficacy for preventing seizures and prolonging survival in TSC mice. The effects of mTOR inhibition in mouse models of TSC are considered to be extremely important as they are more consistent with an anti-epileptogenic effect rather than seizure suppression alone (Wong 2010).

1.1.3.2 Clinical experience in TSC

Everolimus has been investigated in one phase II study (28 patients) in patients with TSC who have SEGA ([RAD001C2485]). Additionally two phase III studies have been conducted in patients with TSC: study [RAD001M2301] in patients with TSC who have SEGA (117 patients) and study [RAD001M2302] in patients with renal angiomyolipoma (118 patients), of which 113 had TSC.

Study RAD001C2485, an open-label phase II study (Clinicaltrials.gov Identifier NCT00411619) of everolimus in patients with TSC who have SEGA, is ongoing at the [redacted] Twenty-eight patients between the ages of 3 and 34 years with TSC who have SEGA were enrolled between 07-Jan-2007 and 18-Dec-2008. The starting daily dose of everolimus was 3.0 mg/m^2, with subsequent titration to attain a target trough level of 5-15 ng/mL. The primary efficacy endpoint of the trial is reduction in SEGA volume. The effect of everolimus on seizure frequency was assessed as a secondary endpoint (Krueger 2010).

A 24-hour video electroencephalogram (EEG) was performed at baseline and at 24 weeks on all patients with uncontrolled epilepsy (defined as those having at least one seizure per month prior to study enrollment), and seizure frequency was also assessed and followed using patient/caregiver report at study visits. Neuro-psychometric function was assessed using a battery of age appropriate tests. Eighteen out of the 28 enrolled patients (64%) had active seizures at baseline. Mean (median) number of seizures/24 hours (by video-EEG) was 6.3 (1.0) at baseline and 2.75 (0.0) at 6 months (median change: -0.99, P=0.022). Nine patients experienced decreases in seizure frequency (across all types of seizure) relative to baseline. Furthermore, the proportion of patients experiencing seizures on a daily basis (caregiver observation) improved from 27% at baseline to 8% at Month 6 (Krueger 2010).

Preliminary data from another ongoing phase II trial that included 23 patients, [average age 8.3 years (range 2-21)], has shown that everolimus can reduce seizure frequency in TSC patients with medically-refractory epilepsy, and may allow concurrent AEDs to be reduced or discontinued [redacted] Clinicaltrials.gov Identifier NCT00411619).

Change in seizure frequency using video EEG was evaluated as a secondary endpoint in Study M2301, a randomized, double-blind, placebo-controlled trial of everolimus in 117 patients with TSC who have SEGA (median age 9.5 years; range 0.8 to 26.6). Frequency of seizures

[redacted]

was measured at baseline and at Week 24 by 24-hour EEG. There was no observed difference between the two treatment arms in change from baseline in total seizure frequency. However, from a clinical viewpoint, analysis of the change in seizure frequency was inconclusive, as seizure diary was not used and a single 24-hour EEG did not appropriately capture the high variability in daily seizure frequency. Although 103 patients (88%) were receiving AEDs at study entry, only 40 patients (34.2%) were captured as having clinical or sub-clinical seizures using single 24-hour EEG [redacted] Clintrials.gov Identifier NCT00789828).

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

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®).

Everolimus was approved by the United States (US) Food and Drug Administration (FDA) under the trade name Afinitor for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib, and for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. The European Commission approved Afinitor for the treatment of patients with advanced RCC, whose disease has progressed on or after treatment with vascular endothelial growth factor-targeted therapy, and for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors (NET) of pancreatic origin in adults with progressive disease.

More recently, an application was submitted for Afinitor in the treatment of patients with hormone receptor-positive advanced breast cancer in combination with an aromatase inhibitor, in postmenopausal women previously treated with endocrine therapy. On 21-Jan-2012, Afinitor was approved in Argentina for this indication.

In addition, everolimus received accelerated approval for the treatment of patients with tuberous sclerosis (TSC) who have subependymal giant cell astrocytoma (SEGA) who require therapeutic intervention but are not candidates for curative surgical resection (as Afinitor) in the US, and received conditional approval in the EU (as Votubia) for the treatment of patients aged 3 years and older with TSC who have SEGA who require therapeutic intervention but are not amenable to surgery.

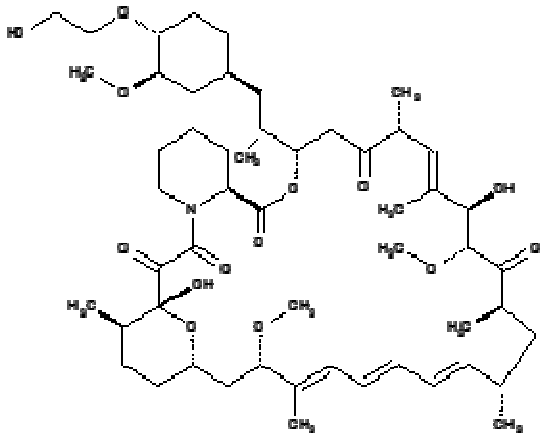
Furthermore, marketing authorization applications have been submitted for Afinitor/Votubia in the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

[redacted]

Table 1-1 Everolimus – Drug Substance

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

Figure 1-4 Chemical Structure of Everolimus



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 (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with everolimus showed a significant reduction in blood vessel density when compared to controls.

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.

[redacted]

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

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

1.2.1.2 Pharmacokinetics of RAD001 in patients with TSC

During Study RAD001M2301, in patients with TSC who have SEGA, pre-dose (C_{min}) and 2-hour post-dose (C_{2h}) PK blood samples were collected at steady-state. Ages of patients in the everolimus arm of study ranged from 1 to 23.9 years. Patients in this study received a starting dose of 4.5 mg/m^2 daily which was subsequently titrated to a whole blood trough concentration of 5-15 ng/mL. This was the starting dose and trough range approved for this indication.

Everolimus C_{min} within individual patients was approximately dose-proportional (dose-proportionality coefficient = 1.107; 90% CI = 1.03, 1.19). This was based on fitting the mixed-effect model to data in the dose range of 1.35 mg/m^2-14.43 mg/m^2.

The geometric mean C_{min} values normalized to mg/m^2 dose in patients of ages < 10 years and 10-18 years were statistically lower than that of adults (> 18 years), suggesting that everolimus clearance normalized to body surface area was higher in younger patients:

- Geometric mean C_{min} (for values not associated with co-administration of CYP3A4/PgP inhibitor and/or inducer):
  - 18 years of age (A): 2.13 ng/mL per mg/m^2 dose (n=46)
  - 10-18 years of age (B): 1.27 ng/mL per mg/m^2 dose (n=92)
  - < 10 years of age (C): 0.97 ng/mL per mg/m^2 dose (n=194)
  - B:A geo-mean ratio [90% CI] = 0.60 [0.38, 0.92]
  - C:A geo-mean ratio [90% CI] = 0.46 [0.31, 0.68]

Co-administration of inducer of CYP3A4 decreased everolimus exposure as indicated by the geometric mean C_{min} values normalized to mg/m^2 dose in patients with TSC who have SEGA in different age groups:

- Geometric mean computed out of C_{min} associated with co-administration of CYP3A4/PgP inducer (without inhibitor of CYP3A4):
  - 18 years of age: 0.72 ng/mL per mg/m^2 dose (n=7)
  - 10-18 years of age: 0.80 ng/mL per mg/m^2 dose (n=118)
  - < 10 years of age: 0.61 ng/mL per mg/m^2 dose (n=122)

Results of a linear mixed model analysis indicated that the relationship between absolute change from baseline in SEGA volume and C_{min} was statistically significant with a slope of -0.304 (95%CI= -0.42, -0.19), corresponding to a 0.211 cm^3 reduction in SEGA volume with a 2-fold increase in C_{min}. Results of another linear mixed model analysis indicated that the relationship between percent change from baseline in SEGA lesion volume and C_{min} was statistically significant with a 12.98% (95% CI= 7.46%, 18.16) further tumor size reduction

[redacted]

for a 2-fold C_{min} increase. Subgroup analysis of selected AEs by everolimus trough concentration was not indicative of an increased risk with higher C_{min} within the C_{min} range observed in the studies.

2 Rationale

2.1 Study rationale and purpose

The primary goal of this study is to assess the efficacy and safety of everolimus as adjunctive therapy in patients with TSC who have partial-onset refractory seizures. Such seizures (often "refractory") are known to be experienced commonly in patients with TSC, as described in Section 1.1.1. Epileptogenesis in these patients has been attributed in part to the overexpression of mTOR. As noted above, the TSC1/TSC2 protein complex is a negative regulator of the mTOR pathway. Hence, mutation or loss of either of these gene products in nonclinical models is associated with increased mTOR pathway activation and heightened sensitivity to mTOR inhibitors (Astrinidis and Henske 2005; Inoki et al 2005; Kwiatkowski and Manning 2005). mTOR pathway upregulation has also been observed in lesions derived from TSC patients (Astrinidis and Henske 2005; Kwiatkowski and Manning 2005), and TSC1 or TSC2 defective experimental animal models exist which recapitulate the pathology, behavioral and neurological aspects of the TSC disease (Onda et al 1999; Kwiatkowski and Manning 2005; Uhlmann et al 2002; Kenerson et al 2005) and are sensitive to mTOR inhibition (Kenerson et al 2005; Astrinidis and Henske 2005; Kwiatkowski and Manning 2005).

Encouraging anti-epileptogenic and antiepileptic, nonclinical and preliminary clinical evidence, discussed in Section 1.1.3, illustrates that two different mTOR targeting drugs (rapamycin and everolimus), can limit the development of new onset seizures and increase survival in genetically engineered models of TSC associated seizures. Rapamycin has been shown to decrease the seizure frequency after the development of seizures in these animals. In the clinical setting, although the M2301 phase III findings were inconclusive, 2 phase II studies provided proof of concept for the activity of everolimus in seizure control. These findings justify the clinical evaluation of the mTOR inhibitor, everolimus, for an indication of seizure reduction. Traditionally, seizure reduction can be most accurately described when an individual seizure type, such as Partial Onset Seizures is pre-defined as the seizure type of interest in the primary endpoint of the study. Finally, because epilepsy in TSC often seems to follow a progressive, intractable course, TSC patients with seizures are in high need of a novel type of intervention that is not only symptomatic "anti-seizure" but may be "anti-epileptogenic" by targeting the primary signaling pathway that triggers epileptogenesis in this group of patients (Crino 2010; Wong 2010; Marcotte and Crino 2006). Taking all these data into account, there is strong rationale for evaluating the use of mTOR inhibitors such as everolimus for the treatment of refractory partial-onset seizures associated with TSC.

[redacted]

2.2 Rationale for the study design

This study will investigate the efficacy and safety of everolimus, as adjunctive treatment, in patients with TSC who have refractory partial-onset seizures. This is a randomized, double-blind, parallel-group study comparing two target trough concentration ranges of everolimus versus placebo.

The use of placebo as the control arm is ethically acceptable because study treatment will be added to other anti-epileptic medications already used by the patients (1-3 AEDs). The presence of a placebo arm allows efficacy/safety changes attributable to treatment to be differentiated from those attributable to underlying disease, with any possible placebo effect being taken into account. Moreover, this design is consistent with clinical trial methodology used for evaluation of other AEDs as adjunctive treatment for refractory partial onset seizures.

Therapeutic dose monitoring is being used since it is expected that most of the patients enrolled will be pediatric, with a broad age range, hence, it will allow to tailor the dose based on BSA and potential concomitant use of medications that interact with everolimus metabolism.

The use of two trough ranges of everolimus is based on the following rationale: in a previous trial of everolimus in TSC patients (Study M2301), therapeutic drug monitoring was used to individualize the dose of everolimus to a targeted trough range of 5 to 15 ng/mL. However, results of this study indicated that acceptable efficacy (defined as $\geq$ 50% reduction in total target SEGA volume in at least 40% of patients) was obtained with trough levels as low as 3 ng/mL below which efficacy is not expected. Therefore, the lower limit of the trough range in the proposed study is 3 ng/mL, with an upper limit of 15 ng/mL. In order to determine the most appropriate trough level range, and to gain insight into whether C_{min} values at the lower end of this range are as effective as higher values, this trial will assess two separate ranges (3-7 ng/mL and 9-15 ng/ mL). The primary comparisons will be between each everolimus arm and placebo.

Additionally, safety will be presented by treatment arm thus allowing for determination of whether tolerability differs between the two everolimus trough levels.

The study includes a prospective baseline phase during which patients complete a seizure diary for a total of 8 weeks, which is considered long enough to provide reliable data on the baseline seizure frequency of patients taking one to three AEDs. At the end of this baseline phase, if all eligibility criteria are still met (lab results from the Screening visit), patients will continue their baseline phase AED medications and be randomized in a 1:1:1.09 fashion to receive adjunctive: 1) placebo; 2) everolimus to attain a trough level 3-7 ng/mL; or 3) everolimus to attain a trough level 9-15 ng/mL. Following randomization, patients enter a core phase, which starts with a 6 week titration period during which up to 3 dose adjustments could be made in order to reach the targeted everolimus trough range. This is followed by a maintenance period of 12 weeks' duration, as recommended in the EMA guidance on anti-epileptics (EMA 2010) as being long enough to establish efficacy. After completing the maintenance period, patients will be offered to continue in an extension phase; this extension phase will allow for longer-term safety and efficacy data to be obtained. Once the Extension phase is completed, patients deriving clinical benefit will be offered continued treatment in

[redacted]

the Post Extension phase which will allow for additional long term safety data to be obtained, while ensuring availability of everolimus.

For the primary efficacy variable of this study, the regulatory requirements differ between Europe and US, with EMA preferring response rate and FDA preferring percentage reduction in seizure frequency. Therefore, both variables will be analyzed for the primary objective, and without correction for multiplicity since it is understood that each Agency will only use their preferred variable to make a decision on the primary objective.

Both primary efficacy variables are based on the change from baseline in seizure frequency during the 12-week maintenance phase, with sensitivity analyses included that count seizures over the entire core phase (titration period plus maintenance period).

2.3 Rationale for dose and regimen selection

The starting dose in both Study C2485 and M2301 was based on the patients' body surface area (BSA). Therapeutic drug monitoring (TDM) of everolimus was used with a targeted trough concentration range in whole blood to determine the optimal therapeutic dose.

In Study M2301, an everolimus trough (C_{min}) level of 3-15 ng/mL has shown superior efficacy versus placebo in patients with TSC who have SEGA, with an acceptable safety profile. In addition, there was a significant correlation between SEGA volume reduction and C_{min} while higher C_{min} did not result in more adverse events. However, it is unknown if a C_{min} in the range of 3-15 ng/mL will lead to a reduction in seizure frequency, or if a correlation between reduction in seizure frequency and C_{min} exists. Therefore, two trough levels, 3-7 ng/mL (low) and 9-15 ng/mL (high), will be investigated.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below. Note that for the primary objective there are separate primary variables and analyses planned for EMA and FDA, in accordance with their differing preferences for demonstrating efficacy of an anti-epileptic medication. See Section 10.4.1 for further details.

Also note that the analyses provided in Table 3-1 mainly apply to data from the core phase of the trial, and at the data cutoff the extension phase will not be complete (see Section 10).

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To compare the reduction in frequency of partial-onset seizures on each of two trough ranges of everolimus (3-7 ng/mL and 9-15 ng/mL) versus placebo in patients with TSC who are taking one to three AEDs.	EMA: Response rate, where response means at least a 50% reduction from baseline in partial-onset seizure frequency during maintenance period of the core phase FDA: Percentage reduction from baseline in partial onset seizure frequency during maintenance period of the core phase	EMA: Cochran-Mantel-Haenszel (CMH) chi-square tests FDA: Rank analysis of covariance (ANCOVA)
Secondary		Refer to Section 10.5
To compare each of the two everolimus trough ranges versus placebo with respect to: (1) Ability to completely suppress partial-onset seizures. (2) Proportion of patients with ≥ 25% reduction from baseline in average weekly frequency of partial-onset seizures. (3) Distribution of reduction from baseline in seizure frequency (4) Seizure-free days (5) Treatment duration (6) Quality of life	(1) Seizure-free rate, where seizure-free means a 100% reduction in partial-onset seizure frequency during maintenance period of the Core phase (2) Proportion of patients with at least a 25% reduction from baseline in partial-onset seizure frequency during maintenance period of the core phase (3) Categorical variable of six levels of reduction from baseline in partial-onset seizure frequency during maintenance period of the core phase (≤ -25% (exacerbation); > -25% to < 25% (no change); ≥ 25% to < 50%; ≥ 50% to < 75%; ≥ 75% to < 100%; 100% (seizure-freedom)). (4) Frequency of seizure-free days during maintenance period of the Core phase (5) Time from randomization until treatment discontinuation in the Core phase (6) Overall QOL global scores from the 3 age-specific questionnaires	Descriptive statistics

[redacted]

Objective	Endpoint	Analysis
To assess everolimus in relation to neurocognitive, neurobehavioral and neurodevelopmental measures using the Vineland Adaptive Behavior Scales-II and the Wechsler Non-Verbal Scale of Ability	Change from baseline of sub-test scores	Descriptive statistics
To assess the relationship between everolimus concentration and efficacy / safety endpoints	Percentage reduction in seizure frequency / frequency of selected AEs	Mixed models and descriptive statistics
To evaluate the impact of everolimus on the pre-dose exposure of antiepileptic drugs	Pre-dose concentrations of AEDs at Baseline (AEDs alone) and at post-Baseline (AEDs plus everolimus)	Mixed models and descriptive statistics
To evaluate the effect of everolimus on long-term seizure reduction	50% response rate, percent reduction from Baseline and seizure free-days in partial onset seizure by time interval over the extension phase	Descriptive statistics
To evaluate the safety and tolerability of each everolimus trough range in the study population	Frequency of AEs / abnormal laboratory values	Descriptive statistics
To evaluate the impact of everolimus on the risk of suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)	Frequency C-SSRS outcomes, frequency of SAEs referring to a positive suicidal evaluation	Descriptive statistics

4 Study design

4.1 Description of study design

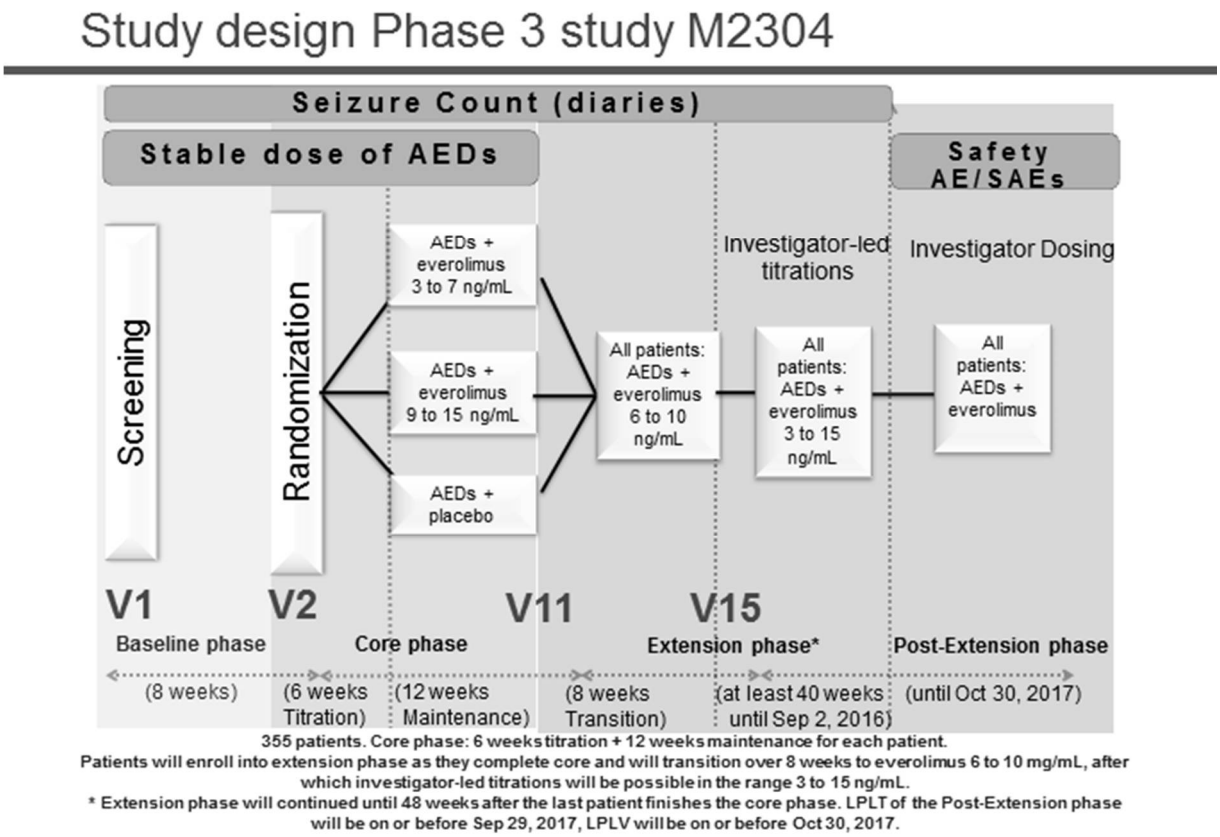
This is a three-arm, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of two trough-ranges of everolimus given as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures.

The study consists of 4 phases for each patient (see Figure 4-1 below):

- Baseline phase: From Screening Week -8 (V1) to randomization visit at Week 0 (V2). For baseline seizure frequency calculations, the 8-week prospective period counts will be totaled.
- Core phase: Double-blind, placebo-controlled, from randomization at Week 0 (V2) to Week 18 (V11).
- Extension phase: From Week 18 (V11) until 48 weeks after the last patient has completed the core phase, with all patients receiving everolimus.
- Post Extension phase: From the end of the extension phase until everolimus is commercially available for the indication, a rollover protocol is available locally, or October 30, 2017, whichever occurs first (on a per patient basis).

[redacted]

Figure 4-1 Study Design



4.1.1 Baseline phase

The Baseline phase is 8 weeks/56 days (+ 2 weeks for scheduling purposes) and begins with the Screening Visit and ends with the Baseline Visit. Patients/caregivers will record seizures in a seizure diary beginning at the Screening Visit. The most recent 56 days prior to the baseline visit must be used for determining eligibility.

Screening visit

During the Screening visit (V1, Week -8), the history of prior seizure type and antiepileptic drug use will be assessed.

The patient must provide a signed informed consent form (ICF) prior to any study related procedure.

Baseline visit

Patients who meet the eligibility criteria will then enter a prospective, eight-week Baseline phase during which the seizure type and frequency and antiepileptic drug use will be assessed. Patients are required to be on a stable dose of 1-3 AEDs (stable dose defined as no change for at least 4 weeks prior to the screening visit and through the entire study). Patients/caregivers

[redacted]

will be instructed on how to count seizures and to complete a daily seizure diary for the entire eight-week Baseline phase.

Eligibility criteria will be assessed subsequently at the end of the baseline phase (V2, Week 0), prior to randomization. All patients who continue to meet eligibility criteria, including demonstrating the minimum seizure frequency during the last 8-weeks of the baseline phase (see Section 5.1), will be randomized in a 1:1:1.09 ratio to one of the three treatment arms as described in Section 6.1. Randomization will be stratified by age subgroup at randomization as follows: (i) 1 to <6 years; (ii) 6 to <12 years; (iii) 12 to <18 years; and (iv) ≥ 18 years.

4.1.2 Core phase

The Core phase of the study includes both a titration period (V2, Week 0 to V8, Week 6) and a maintenance period (V8, Week 6 to V11, Week 18).

During the Core phase of the study, there will be visits at weeks 0 (V2), 1 (V3), 2 (V4), 3 (V5), 4 (V6), 5 (V7), 6 (V8), 10 (V9), 14 (V10), and 18 (V11).

Everolimus will be dosed based on TDM with dose titration to attain one of the two target C_{min} ranges (3 to 7 ng/mL or 9 to 15 ng/mL). Starting doses of study drug are defined in Section 6.1.1.1.

During the 6 week titration period, three pre-dose PK blood samples (0.5 mL for 1 to < 2 years of age; 1 mL for 2 to ≤ 6 years of age; and 2 mL for > 6 years of age) will be taken for potential dose adjustments as described in Table 4-1. The high frequency of visits during the beginning of the Core phase is essential to ensure that titration is being performed effectively, and also helps to ensure that seizures are being counted properly, and provides an opportunity to remind patients of the importance of good compliance.

The titrations are implemented as follows. A local lab (at the treating center) will collect the blood samples and send them to a central laboratory for determination of everolimus concentrations. The site will receive recommendations from the central Interactive Response Technology (IRT) on dose adjustment (to maintain, increase or decrease the number of the 2-mg tablets) for each patient, based on concentration values of the pre-dose PK samples. It is expected that all patients will achieve the planned target pre-dose trough level (C_{min}) during this period. In order to keep the blind, the IRT will also instruct the site to adjust the dose for patients in the placebo arm based on a random scheme of dose changes.

After the completion of the titration period, the vast majority of patients are expected to continue at their current dose level during the entire 12 week maintenance period. However, the possibility of further titration does still exist, based on the planned pre-dose PK blood samples that will be collected every 4 weeks during the maintenance period. In addition, pre-dose PK blood samples should be collected **two weeks after any everolimus dose adjustment**, and so a patient having a titration at week 6 (end of titration period) would need to have a pre-dose PK sample collected at week 8 (2 weeks into the maintenance period). This PK sample could then lead to a dose adjustment at the next planned visit at week 10, which if implemented would then necessitate a further pre-dose PK sample at week 12. Few patients are expected to need these extra titrations, but the possibility exists in order to keep patients in their targeted trough range as assigned at randomization.

[redacted]

Table 4-1 PK sampling and dose titration events during Core phase

Week	Action	Potential for titration
0	Start dosing	
1	PK sample 1	
2	PK result	X
3	PK sample 2	
4	PK result	X
5	PK sample 3	
6	PK result	X
8 (only if titration occurred at week 6)	Additional PK sample	
10	Preplanned PK sample 4	X
12 (only if titration occurred at week 10)	Additional PK sample	
14	Preplanned PK sample 5	X
16 (only if titration occurred at week 14)	Additional PK sample	
18	Preplanned PK sample 6	X

4.1.3 Extension phase

The extension phase of this study will allow further evaluation of the long-term safety profile and efficacy of everolimus in this patient population.

All patients who complete the Core phase will be offered continuation on the extension phase, during which all the patients will receive everolimus at Week 18 [(V11) same visit as end of Core and start of Extension)]. Patients will enter into this phase upon completion of the core phase, and will continue until 48 weeks after the last patient completes the core phase. (Patients enrolled earlier in the study may remain in the Extension phase for more than 48 weeks.)

The intention is to allow investigators to decide appropriate dose changes themselves, based on everolimus concentrations at trough (C_{min}) obtained during the extension phase. However, in order to avoid compromising the blinded nature of the study (including for the investigator, patient and sponsor) in the earlier Core phase, all patients will first be transitioned towards a common targeted trough range of 6 to 10 ng/ml before any C_{min} value is shared with the investigator. Note that no individual patient unblinding will be performed at entry into extension.

During the Extension phase, visits will be at Weeks 18 (V11), 19 (V12), 20 (V13), 22 (V14), 26 (V15), and 30 (V16), and then every 12 weeks thereafter, unless additional visits are clinically indicated. Pre-dose blood samples will be collected at weeks 19 and 22 to allow possible titrations at Weeks 20 and 26. In addition, patients randomized to one of the two everolimus arms will be transitioned at week 18. Patients are expected to approach or be within the planned target trough range of 6 to 10 ng/ml after the week 20 titration. This will serve to preserve the blinding of the prior Core phase. At the Week 26 visit, investigators will be provided with the C_{min} result from Week 22 PK, and they will be permitted to make their own dose titration decisions. Further titrations are possible based on the planned pre-dose PK samples collected every 12 weeks from Week 30, and any additional pre-dose PK blood sample collected two weeks after any everolimus dose adjustment (see Table 4-2).

[redacted]

Table 4-2 PK sampling and dose titration events during Extension phase

Week	Action	Potential for titration
18	Switch to extension	
19	Pre-planned PK sample E1	
20	PK result	X
22	Pre-planned PK sample E2	
26	Pre-planned PK sample E3	X
28 (only if titration occurred at week 26)	Additional PK sample	
30	Pre-planned PK sample E4	X
32 (only if titration occurred at week 30)	Additional PK sample	
42, 54, 66, etc.	PK sample E5, E6, E7, etc.	X

For patients who signed informed consent for Amendment 2 of the protocol after completing their week 18 visit, a modified transition schedule will be permitted in the Extension Phase. This schedule will begin at week 26, 30 or at any subsequent scheduled visit (every 12 weeks thereafter). At the first such visit, the everolimus dose will be transitioned based on the prior PK value using a targeted trough range of 6-10 ng/ml. The patient will return the following week for an everolimus PK sample, and the following week, for disclosure of the PK value. The investigator may begin to make his/her own dose adjustment decisions or rely on the IRT system to prescribe a dose that will maintain the everolimus trough within 3-15 ng/ml. (see Section 4.1.3.1).

At the start of the Extension Phase, during the transition to investigator control of everolimus dosing, and while the everolimus Cmin value is still not shared with the investigator, the investigator should consider managing clinical deterioration in seizure control (as judged by the investigator) by modifying AED doses or adding or subtracting AEDs. Starting at week 26, when everolimus Cmin values are made available to the investigator, the investigator may manage a patient's clinical deterioration by modifying AED doses, adding and or subtracting AEDs and modifying everolimus dosing in whatever order or combination the investigator chooses.

When the last patient completes the Core phase, the data will be analyzed. If the results are positive, patients will continue on study treatment until the end of the Extension phase. Patients deriving clinical benefit will also be offered continued treatment in a Post Extension phase. If the results are negative, the study will be terminated.

When results of the Core phase of the study become available, if a more favorable risk-benefit ratio is identified for one of the two trough ranges, the protocol may be amended and patients will be offered to be titrated to the preferred trough range.

The last Extension phase visit for a patient will be the last scheduled visit that occurs prior to or on September 2, 2016, at which point the patient will then enter the Post Extension phase. After the Post Extension phase is completed, if the Core study results are positive and patients continue to receive benefit, everolimus will continue to be provided free of charge in a roll over protocol until the drug is approved and commercially available for use in TSC-associated refractory partial onset seizures, or until the patient stops receiving everolimus for any reason, whichever occurs first. If this is prohibited by local regulations (e.g., in UK and Norway) the patient will exit the study when the Post Extension phase is completed (see Section 4.1.4).

[redacted]

Additional Everolimus PK sampling

In addition to the time points described above in the Core, Extension and Post Extension sections, pre-dose blood samples for everolimus concentration determination should be collected two weeks after the following events:

- Any everolimus dose adjustment
- Starting or changing the dose of a CYP3A4/PgP inducer/inhibitor

Anti-epileptic drug PK sampling

Everolimus is metabolized by the CYP3A4 pathway in the liver, and to some extent in the intestinal wall. Many of the concomitantly administered AEDs are also metabolized by the CYP3A4 pathway, which results in a potential for drug-drug interaction between the AEDs and everolimus. Therefore, levels of the AEDs listed below (considered to be CYP3A4 substrates and /or inducers) will be measured to investigate the effect of everolimus on the AED level (i.e., if AED + everolimus leads to higher levels of AED compared to AED alone).

Inducers:

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Primidone

Substrates:

- Clobazam
- Clonazepam
- Diazepam
- Felbamate
- Topiramate
- Valproic acid
- Zonisamide

Pre-dose blood samples of 6 mL (5.2 mL for patients 6 and under) will be collected at Visits 1, 2, 3, and 5 for the measurement of antiepileptic drug (AED) concentration. Patients weighing 12 to 20 kg will not be required to provide PK AED blood samples due to the high overall blood volume required at the early visits. Effects of everolimus on the exposure of anti-epileptic drugs will be assessed by comparing the anti-epileptic drug concentrations at Visits 1 and 2 (AEDs alone) and at Visits 3 and 5 (AEDs plus everolimus). A list of commonly prescribed AEDs that are used in this population is provided in Section 6.1.1.1.

4.1.3.1 Investigator-led dosing in patients past week 22

Patients who have completed week 18 of the study at the time of signing informed consent for protocol amendment 2, will have an opportunity to have their everolimus concentrations revealed after a transition process that can begin at any scheduled visit beginning from week

[redacted]

26. At week 26, 30 or any other scheduled visit (every 12 weeks), the patient would first be transitioned using a targeted trough range of 6-10 ng/ml (Transition visit A). The IRT system would recommend dose instructions using the previous PK result (week 22, 26, etc). The patient would return at least 5 days later to provide an additional transition PK trough sample (Transition visit B), and then again at least one week later for a clinic visit (Transition visit C), when the investigator would be informed of the everolimus concentration. The investigator would then be permitted to modify the patient's dose of study drug by 2mg daily (patients not on CYP3A4/PgP inducers) or 4mg daily (patients on CYP3A4/PgP inducers) to a minimum dose of 2 mg/day. A dose increase will not be permitted if the everolimus concentration exceeds 15 ng/ml. If the investigator chooses not to modify dosing, the dose will be maintained by the IRT system in the range of 3-15 ng/ml. Table 4-3 outlines the visits and actions to be taken. Additional assessments to be performed at unscheduled Transition visit C are outlined in Table 7-1.

Table 4-3 Dose transition of everolimus to 6-10 ng/ml beginning at Week 26

Visit	Week	Action
14	22	Pre-planned PK sample
15	26 transition visit A	Transition dose change by IRT based on PK from W22
201	27 transition visit B	Additional transition PK sample
202	28 transition visit C	Cmin revealed, Investigator-led dosing may begin
16	30 transition visit A	Transition dose change by IRT based on PK from W26
201	31 transition visit B	Additional transition PK sample
202	32 transition visit C	Cmin revealed, Investigator-led dosing may begin
17+	42, 54, 66, etc. transition visit A	Transition dose change by IRT based on PK from W30, 42, 54, etc
201	43, 55, 67, etc. transition visit B	Additional transition PK sample
202	44, 56, 68, etc. transition visit C	Cmin revealed, Investigator-led dosing may begin

4.1.4 Post Extension Phase

All patients who complete the Extension phase will be offered continued participation in the Post Extension phase. Investigators will determine patient's daily dosing at their sole discretion based on guidance provided (see Section 6). The IRT system will respond to the investigator's request and provide kit numbers to be dispensed to supply the patient. In the Post Extension phase, the IRT system will no longer provide daily dosing recommendations.

During the Post Extension phase, visits will occur every 12 weeks, unless additional visits are clinically indicated. The first scheduled Post Extension phase visit will occur 12 weeks after the patient's last scheduled Extension phase visit. Additional pre-dose blood samples for everolimus concentration determination should be collected two weeks after the following events:

- Any everolimus dose adjustment
- Starting or changing the dose of a CYP3A4/PgP inducer/inhibitor

Investigators will confirm the Cmin value from the last PK drawn and make a decision on dosing. The investigator will enter the chosen daily dose into the IRT system and the IRT system will dispense the appropriate number of kits to supply the patient until the next scheduled visit.

[redacted]

4.1.5 Definition of end of the study

The end of the Core phase of the study will occur when the last patient reaches Visit 11 (Week 18). At this point, the core data will be analyzed and, if the results are positive, all patients in the Extension phase will continue. If one trough level is found to be superior to the other, the protocol may be amended and all patients will be offered to be titrated to that trough level. The Extension phase of the study will end 48 weeks after the last patient enters the Extension Phase. At that point, long term safety and efficacy data will be analyzed. The last treatment in a patient's Post Extension phase will be on or before September 29, 2017, and the end of the study will be on or before October 30, 2017.

A follow up visit should be performed by either phone or in person, depending on whether adverse events are ongoing at time of the previous visit for all patients who permanently discontinue treatment. Patients will be followed for 30 days after end of treatment for continuing or new adverse events and for serious adverse events until resolution of the AE. At the time when the last patient completes their follow-up visit, the data will be cleaned and locked, and a final study report written.

4.2 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient will be contacted, requested to discontinue taking study treatment, and be seen as soon as possible. The same assessments should be performed as described in Section 7.1.6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial according to ICH-GCP and local regulations.

5 Population

5.1 Patient population

The target population is comprised of approximately 355 male or female patients, with TSC who have refractory partial-onset seizures. Patients between the ages of 2 and 65 years will be enrolled, except in Europe where the minimum age will be 1 based on EMA request.

Refractory seizures are defined as prior history of failure to control partial-onset seizures despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs.

Partial-onset seizures are defined as simple partial seizures with motor signs, complex partial seizures, and complex partial seizures with secondary generalization or a combination of these types.

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

5.2 Inclusion criteria

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

[redacted]

1. Male or female between the ages of 2 and 65 years (except in Europe where the minimum age will be 1 at the request of the EMA). (A minimum number of pediatric patients will be randomized in the following age groups: 1 to <6 years [40 patients], 6 to <12 years [40 patients], and 12 to <18 years [40 patients].)
2. Clinically definite diagnosis of TSC see Table 5-1 (modified Gomez criteria, Gomez 1999). Note: positive genetic test without definite diagnosis of TSC as per the modified Gomez criteria is not allowed.

Table 5-1 Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features
Facial angiofibromas or forehead plaque
Nontraumatic ungual or periungual fibroma
Hypomelanotic macules (three or more)
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cortical tuber[a]
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma, single or multiple
Lymphangiomyomatosis[b]
Renal angiomyolipoma[b]
Minor Features
Multiple, randomly distributed pits in dental enamel
Hamartomatous rectal polyps[c]
Bone cysts[d]
Cerebral white matter radial migration lines[a,d]
Gingival fibromas
Non-renal hamartoma[c]
Retinal achromic patch
'Confetti' skin lesions
Multiple renal cysts[c]
Definite Tuberous Sclerosis Complex: Either two Major Features or one Major Feature plus two Minor Features.

a. The co-occurrence of cerebral cortical dysplasia and cerebral white matter radial migration lines should be considered as one major feature of TSC.
b. In patients with both lymphangiomyomatosis and renal angiomyolipoma, another feature of TSC must be identified before a definite diagnosis is assigned.
c. Histological confirmation of these features is suggested.
d. Radiographic confirmation of these features is sufficient.

[redacted]

3. Diagnosis of partial-onset epilepsy according to the classification of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) and revised in 2009 (Berg 2010). This classification is further modified for the purpose of capturing clinical details, and defines partial onset seizures in patients with TSC on the basis of the pathophysiology of TSC as either:
   - any seizure that has been definitively shown to be partial onset on ictal EEG, or
   - any probable seizure with motor signs (non-sensory) that has NOT been documented to be a primary generalized seizure on ictal EEG.

Seizure Classification:

I. Partial Onset Seizures
   A. Without impairment of consciousness or awareness
      1. With observable motor or autonomic components. (Formerly known as "simple partial seizures") ''Focal motor'' and ''autonomic'' are terms that may adequately convey this concept depending on the seizure manifestations
      2. Involving subjective sensory or psychic phenomena only.(This corresponds to the concept of an aura).
         a. With ictal EEG confirmation
         b. Without ictal EEG confirmation
   B. With impairment of consciousness or awareness. (Formerly known as "complex partial seizures", or partial onset seizures with Absence-like features)
      1. Typical Absence features
      2. Atypical Absence features
      3. NOS (not otherwise specified)
   C. Evolving to a bilateral, convulsive seizure (Formerly known as "secondarily generalized seizure")
      1. Myoclonic features
      2. Clonic features
      3. Tonic features
      4. Tonic-clonic features (Older term: grand mal)
      5. Atonic features
      6. NOS

II Primary Generalized seizures
   A. Absence seizures
      1. Typical absence seizures
      2. Atypical absence seizures
   B. Myoclonic seizures
   C. Clonic seizures
   D. Tonic seizures
   E. Tonic-clonic seizures (Older term: grand mal)
   F. Atonic seizures

[redacted]

G. NOS

4. Uncontrolled partial-onset seizures; must meet the following:
   a. At least 16 reported quantifiable (no cluster or innumerable seizures) partial-onset seizures (as defined in Inclusion Criteria 3) over the Baseline period (56 days, 8 weeks) with no continuous 21-day seizure-free period between Visit 1 (Screening Visit) and Visit 2 (Randomization visit), as per data captured in daily seizure diaries.
   b. Prior history of failure to control partial-onset seizures despite having been treated with two or more sequential regimens of single or combined antiepileptic drugs
   c. Prior or concurrent use of vagal nerve stimulator (VNS) is allowed. If the patient is using VNS, device stimulator parameters must remain constant throughout the study.
   d. Prior epilepsy surgery is allowed if performed at least 12 months before study entry.
5. Must be receiving one, two, or three AEDs at a stable dose for at least 4 weeks at the start of the 8-week prospective Baseline phase, remain on the same regimen throughout the Baseline phase, and intend to continue the same regimen throughout the 18-week double blind Core phase (rescue medications are permitted, as defined in the Rescue Medications Section 6.1.2). No more than ***one*** of these can be a strong CYP3A4 inducer (e.g., Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Primidone)
6. If female of child bearing potential, documentation of negative pregnancy test at time of informed consent. Females of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:
   - Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
   - Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male partner sterilization, at least 6 months prior to screening visit, (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomized male partner should be the sole partner for that subject].
   - Use of a combination of any two of the following (a+b or a+c or b+c):
     a. Use of oral, injected or implanted hormonal methods of contraception
     b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
     c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the oral agent before taking study treatment for at least 3 months.

[redacted]

7. Sexually active males must use a condom during intercourse while taking study drug, and for 8 weeks after stopping study treatment. They should not father a child during this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
8. Hepatic, renal and blood laboratory values within the following range at screening:
   - AST and ALT levels < 2.5 x ULN
   - serum bilirubin <1.5 × ULN (this limit does not apply to patients with an elevated indirect bilirubin, if they have Gilbert's Syndrome),
   - serum creatinine < 1.5 x ULN,
   - hemoglobin ≥ 9 g/dL,
   - platelets ≥ 80,000/mm^3,
   - absolute neutrophil count ≥ 1,000/mm^3
9. Written informed consent. Subjects or their legal guardians must have the ability to comprehend the informed consent form and be willing to provide informed consent. For subjects who are too young or unable to comprehend the written consent, a legal guardian who is able to describe and provide an understanding of the informed consent to the subject must sign the consent form on behalf of the subject. In all cases, the informed consent process will follow the local rules and regulations.
10. Patient or caregiver must be able to reliably record seizures and keep a daily diary and recall adverse events.

5.3 Exclusion criteria

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

1. Patients with seizures secondary to metabolic, toxic, infectious or psychogenic disorder or drug abuse or current seizures related to an acute medical illness.
2. Presence of only non-motor partial seizures (**Criteria Not Applicable per Amendment 2**)
3. Patients with TSC who have SEGA in need of immediate surgical intervention.
4. Patients under 2 years of age with untreated infantile spasms.
5. Within 52 weeks prior to study entry, an episode of status epilepticus, defined as:
   a. in adults and children 5 years and older -- continuous or intermittent, convulsive seizures lasting more than 10 minutes and requiring additional medical intervention such as with rescue medication not commonly used in the home (i.e., a convulsive seizure or series of convulsive seizures not within the patient's typical seizure pattern and management).
   b. in children less than 5 years of age -- continuous or intermittent, convulsive seizures lasting more than 10 minutes and requiring significant additional medical intervention such as hospitalization (note: It is recognized that some young patients may be sent for emergency care despite having experienced a seizure within their typical seizure pattern and management. Only the more severe episodes of prolonged convulsive seizures in such patient, such as those leading to hospitalization, would qualify as status epilepticus).

[redacted]

6. Patients with history of seizure clusters (where individual seizures cannot be accurately counted according to the judgment of the investigator) occurring within 26 weeks prior to study entry.
7. Patients who require rescue medication during the Baseline phase for more than 6 days.
8. Patients with non-TSC related progressive encephalopathy.
9. Patients who weigh less than 12 kg.
10. Patients with coexisting malignancies within the 3 years prior to randomization, except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.
11. Patients with any severe and/or uncontrolled medical conditions at randomization such as:
    a. Symptomatic congestive heart failure of New York Heart Association Class III or IV, history of left ventricular ejection fraction (LVEF) < 50%, QTc interval >460ms, congenital QT syndrome, unstable angina pectoris, myocardial infarction within 6 months of study entry, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease.
    b. Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O_2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates.
    c. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, malabsorption syndrome or small bowel resection).
    d. liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA),
    e. Uncontrolled diabetes as defined by fasting serum glucose > 1.5 × ULN.
    f. Active skin, mucosa, ocular or GI disorders of Grade > 1.
    g. Active (acute or chronic) or uncontrolled severe infections.
    h. A known history of HIV seropositivity or other active viral infections.
12. Patients with an active, bleeding diathesis.
13. Patient with uncontrolled hyperlipidemia: fasting serum cholesterol > 300 mg/dL OR >7.75 mmol/L AND fasting triglycerides > 2.5 x ULN.
14. Patients who have had a major surgery or significant traumatic injury within 4 weeks of study entry. Patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia), or patients that may require major surgery during the course of the study.
15. Patients with a prior history of organ transplant.
16. Patients receiving more than 3 antiepileptic drugs at any time in the baseline phase or at randomization or who change the dose of the AEDs during 4 weeks before screening or during the baseline period.
17. Patients being treated with felbamate, unless treatment has been continuous for ≥ 1 year.
18. Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of study entry (including chemotherapy, radiation therapy, antibody based therapy, etc.).

[redacted]

19. Prior treatment with any investigational drug within the preceding 4 weeks prior to study entry.
20. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent at study entry. Topical or inhaled corticosteroids are allowed.
21. Patients who have received prior treatment with a systemic mTOR inhibitor (sirolimus, temsirolimus, everolimus) within 24 months of study entry. Patients who have received prior treatment with a topical mTOR inhibitor (sirolimus, temsirolimus, everolimus) within 4 weeks of study entry.
22. Patients with a known hypersensitivity to everolimus or other rapamycin-analogues (sirolimus, temsirolimus) or to its excipients.
23. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study.
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
25. Patients with a Score of 4 or 5 on the Suicidal Ideation item within 2 years of Screening, or any "yes" on the Suicidal Behavior item of the Columbia-Suicide Severity Rating Scale at Screening or Baseline who upon follow up with a healthcare professional are found to be severely depressed or suicidal.
26. Maintenance of a diet consisting of <40 g of carbohydrate per day within 3 months of screening.

6 Treatment

6.1 Study treatment

Patients will be randomized to one of the following three treatment arms:

Investigational therapy:

- Everolimus tablets for oral suspension (dispersible tablets) with titration to trough range of 3-7 ng/mL
- Everolimus tablets for oral suspension with titration to trough range of 9-15 ng/mL

Control therapy:

- Placebo

6.1.1 Dosing Regimen

Table 6-1 Dose and Treatment Schedule

Study drugs	Pharmaceutical form and route of administration	Frequency	Route of administration
Everolimus	2 mg tablets for oral suspension	daily (qd)	Oral
Placebo	Matching placebo tablets	daily (qd)	Oral

[redacted]

Study drug (everolimus or matching placebo) will be dispensed by study center personnel on an outpatient basis at Weeks 0, 2, 4, 6, 10, 14 in the Core phase, and at 18, 20, 22, 26, 30 and every twelve weeks thereafter in the Extension phase and Post Extension phase. Patients will be provided with an adequate supply of study drug for self-administration at home, with exception of the days when PK sampling will be performed and drug will be administered at the site after the blood draw. The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). The patient will take the first dose of study drug (Day 1) at the center. All dosages prescribed and administered to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Study drug will be packaged in blister packs, and placed in boxes with color-coded labels of color 1 or color 2 in order to maintain the blind. At each visit a patient will receive one or multiple boxes of medication of **one or both** color labeled boxes with either active drug or placebo, depending on the arm they were randomized to. During the Post Extension phase, only everolimus will be dispensed. See Section 6.5.2.

At the start of the Core phase, IRT will inform the investigator how many tablets from each of the Color 1 and Color 2 labeled boxes should be taken to administer the starting dose, as per Section 6.1.1.1. Then at Weeks 1, 3 and 5 of the Core phase, all patients will have blood samples drawn and sent to a PK lab for determination of the trough level of everolimus, with results forwarded to IRT. In turn, IRT will inform the investigator of the dosing for the following 2 weeks, in terms of number of tablets to be taken from each of the Color 1 and Color 2 labeled boxes, based on the observed everolimus trough level and the targeted trough range of the patient's randomization arm. That is, the dose could be increased, maintained or decreased in order to reach and maintain the targeted trough range. For patients in the placebo arm, the starting dose will be increased, maintained or decreased according to a randomization list, designed to resemble possible titrations on the everolimus arms. PK samples will also be taken at weeks 10 and 14 for all patients to monitor whether the targeted trough level is being maintained with IRT giving appropriate instructions to change the dose if necessary.

The potential for unmasking the blind is minimized because all patients in each treatment arm can receive either or both Color 1 and Color 2 labeled boxes at each visit except Randomization, and because patients randomized to the Everolimus Low group (target trough 3-7 ng/mL) will sometimes have placebo in the Color 1 labeled box and sometimes in the Color 2 labeled box. At Randomization only one color labeled box will be dispensed because it would be possible to ascertain which box contained active drug due to the formula for the starting dose.

At the start of the Extension phase, patients will be assigned to new kit types (see Section 6.5.2). From Weeks 18-26 all patients will be transitioned towards a common targeted trough range of 6 to 10 ng/ml to avoid compromising the blind in the earlier Core phase. Starting at Week 26, investigators will be provided with the Cmin results and will be permitted to make their own titration decisions.

Patients randomized to one of the two everolimus arms will be transitioned at Week 18 based on the prior PK value.

[redacted]

Placebo patients will start everolimus at Week 18, and be dosed according to the starting dose instructions in Section 6.1.1.1. The targeted trough range will be 6 to 10 ng/mL. PK will be taken at Week 19 with appropriate titration dosing instructions given at the Week 20 visit. Patients are expected to approach or be within the planned target trough range of 6 to 10 ng/ml after the Week 20 titration.

At the Week 26 visit, investigators will be provided with the Week 22 C_{min} result, and IRT will recommend a dose change using a wider targeted trough range of 3 to 15 ng/ml. Investigators will be able to override the IRT recommendation subject to the rules defined in Section 6.2.2, although dose increases will not be allowed if C_{min} >= 15 ng/ml. Investigator-led titrations will be possible at all future visits in the extension phase, based on PK samples taken at Weeks 26, 30 and every 12 weeks thereafter, until the Core phase results are available, and a preferred trough range can be recommended.

For patients who sign informed consent for Amendment 2 of the protocol after completing their Week 18 visit, a modified transition schedule will be permitted in the Extension Phase. This schedule may begin at week 26, 30 or at any subsequent scheduled visit (every 12 weeks thereafter). At the first such visit, the everolimus dose will be transitioned based on the prior PK value using a targeted trough range of 6-10 ng/ml (Transition visit A). The patient will return the following week for an everolimus PK sample (Transition visit B), and the following week, for disclosure of the PK value (Transition visit C). The investigator may begin to make his/her own dose adjustment decisions or rely on the IRT system to prescribe a dose.

For any patient participating in the Post Extension phase, the investigator will have complete control over the dosing, although dose increases should not be made if Cmin > 15 ng/ml. Investigators will confirm the Cmin value from the last PK drawn and make a decision on dosing. The investigator will enter into the IRT, the chosen total daily dose in mg units and the IRT system will calculate how many and which kits to dispense to supply the patient until the next scheduled visit.

The results of the Core phase analysis should be considered by investigators participating in investigator led titrations in the Extension phase and/or Post Extension phase. Based on the analysis of the Core phase, it is recommended that the everolimus trough be maintained within 5-15 ng/ml, subject to safety and tolerability.

Dosing

Tablets for oral suspension are to be taken as a suspension only, and should not be swallowed whole, chewed, or crushed. The suspension can be prepared in an oral syringe or in a small drinking glass. Care should be taken to ensure the entire dose is administered. See Section 6.5.1.

Everolimus and/or the matching placebo should be administered after a light breakfast in the morning. If vomiting occurs, no attempt should be made to replace the vomited dose.

On the days of PK sampling, patients should **not** take the daily study drug dose **until AFTER** blood work is drawn so that an accurate trough level of everolimus can be obtained. **On days of scheduled visits, patients should bring their daily dose of study drug into the clinic with them for administration after blood work is drawn.**

[redacted]

During the titration periods, in absence of any other reason for holding study drug, study drug will be continued for up to 2 weeks while awaiting central PK lab results, which will be used to determine if a modification of the dosing regimen is indicated.

Patients should be requested to bring their unused study drug, including the empty blister packs, to the clinic at each visit. Compliance should be verified by the investigator's staff by counting the number of tablets consumed between visits. The investigator (or his/her designee) will document dosage administration and all dose changes during the study in the eCRF. The site must maintain an overall drug accountability log for the study, as well as individual accountability records for each patient. The dose, amount dispensed, amount received, and amount remaining unused must be recorded in the source document. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. The patient will return all unused study drug at each dispensing visit and at the end of the study.

6.1.1.1 Starting Dose

Everolimus or matching placebo will be provided to the patient, and the first dose will be taken at the site on the day of the Baseline visit (V2) after eligibility is confirmed. Starting dose will be determined by the IRT based on the patient's age and concomitant use of CYP3A4/PgP inducers is presented below in Table 6-2.

Patients with TSC associated epilepsy are often treated with CYP3A4 enzyme-inducing antiepileptic drugs (EIAEDs) which lead to an increase of everolimus apparent clearance. Some of these EIAEDs could also be inducers of PgP.

Different starting doses, taking into account increased everolimus clearance in young patients and the use CYP3A4/PgP inducers (regardless of number), will be used as follows:

Table 6-2 Starting dose

Age	Not receiving CYP3A4/PgP inducer	Receiving CYP3A4/PgP inducer
Patients under the age of 10	6.0 mg/m^2/day	9.0 mg/m^2/day
Patients age 10 to 18	5.0 mg/m^2/day	8.0 mg/m^2/day
Patients age ≥18	3.0 mg/m^2/day	5.0 mg/m^2/day

The investigator will enter the patient's age, height, weight, and CYP3A4/PgP inducer status into the IRT system, and the system will calculate the appropriate starting dose. Body surface area (BSA), in m^2, will be calculated by IRT using the following formula, where weight (W) is in kilograms and height (H) is in centimeters (Dubois and Dubois 1916):

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

Once the dose is calculated, the system will instruct the investigator which kit number to assign to the patient, and how many tablets should be taken from each color labeled box.

Commonly prescribed EIAEDs that are used in this population include:

- Phenytoin (Dylantin®, Dilantin® Kapseals®, Dilantin® Infatabs®, Eptoin®, Epanutin®, Diphenin®, Dipheninum®, Phenytek®)
- Carbamazepine (Tegretol®, Biston®, Calepsin®, Carbatrol®, Epitol®, Equetro®, Finlepsin®, Sirtal®, Stazepine®, Telesmin®, Teril®, Timonil®, Trimonil®, Epimaz®, and Degranol®)
- Phenobarbital (Luminal®)

[redacted]

- Pentobarbital (Nembutal®)
- Primidone (Mysoline®)
- Oxcarbazepine (Trileptal®)

6.1.2 Rescue medication

In patients with refractory epilepsy, it is known that sometimes patients experience transient increases in seizure activity despite best medical management. In such cases, rescue medications are permitted.

No new AEDs or changes to existing AED treatment (medication, dose, or frequency) are permitted from 28 days prior to screening and throughout the Baseline and Core phase of the study. In addition, the study drug should not be increased beyond the protocol-defined limits to treat any emerging/increasing epilepsy symptoms.

The choice of rescue medications (e.g., buccal midazolam, rectal diazepam and other benzodiazepines) to provide additional seizure control should follow the local institution's practice. For the purpose of this study, rescue medications are only allowed for a period that does not exceed 6 cumulative days during the Baseline phase of the study; and does not exceed 7 consecutive days or a total of 14 cumulative days during the Core phase of the study. During the Extension and Post Extension phases, rescue medications should not be taken for more than 14 cumulative days in any 12 week period. Use of rescue medications for a longer duration will be considered as a treatment failure and the patient will be discontinued from trial therapy.

All rescue medications will be captured on the rescue medications eCRF page.

6.1.3 Treatment duration

Treatment will continue until any of the following take place during the Core Phase the study:

1. Loss of seizure control defined as an increase of 100% in the average weekly number of partial-onset seizures for a minimum of 4 consecutive weeks as compared to the average weekly number of partial-onset seizures during the 8 weeks baseline period.
2. An episode of status epilepticus, defined as:
    a. in adults and children 5 years and older -- continuous or intermittent, convulsive seizures lasting more than 10 minutes and requiring additional medical intervention such as with rescue medication not commonly used in the home (i.e., a convulsive seizure or series of convulsive seizures not within the patient's typical seizure pattern and management).
    b. in children less than 5 years of age -- continuous or intermittent, convulsive seizures lasting more than 10 minutes and requiring significant additional medical intervention such as hospitalization (note: It is recognized that some young patients may be sent for emergency care despite having experienced a seizure within their typical seizure pattern and management. Only the more severe episodes of prolonged convulsive seizures in such patient, such as those leading to hospitalization, would qualify as status epilepticus)

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3. A single generalized tonic clonic seizure (non-febrile), if none occurred during the baseline period, and if one has not occurred within the past year.
4. Use of rescue medications longer than the maximum duration described in Section 6.1.2.
5. Treatment duration completed as per protocol: completion of the Core phase (if patients do not accept to start the extension phase), completion of the Extension phase or completion of the Post Extension phase.
6. An interruption of one or more of the concomitant AEDs for more than 7 days

Other criteria for withdrawal from the study at any time are:

- Discovery of failure of randomization or blinding
- Discovery of patient ineligibility
- An interruption of study drug that lasts for more than 28 days
- Intolerable toxicity.
- Pregnancy.
- Withdrawal of consent.
- In patients who have their dose interrupted for toxicity, if restarting study drug upon resolution of the toxicity requires dose reduction, and that reduction results in instruction to take 0 tablets for placebo patients during the core phase, or 0 mg of everolimus for active drug patients in the Core phase, or 0 mg everolimus for all patients in the Extension phase and Post Extension phase.

6.2 Dose modification guidelines

6.2.1 Starting dose rationale

The starting doses shown in Table 6-2 for patients in the different age groups were estimated based on data from Study M2301. In this study, the geometric mean C_{min} values normalized to mg/m^2 dose were 0.97, 1.27, and 2.13 ng/mL per mg/m^2 dose for patients not taking CYP3A4/PgP inducer and of ages < 10 years, 10 to <18 years, and ≥ 18 years, respectively, suggesting a higher clearance of everolimus (normalized to BSA) in younger children. Based on these dose normalized C_{min} values, starting doses of 6.0, 5.0, and 3.0 mg/m^2/day for patients in the respective age groups are expected to lead to C_{mins} of 5.82, 6.35, and 6.39 ng/mL, respectively.

Table 6-3 presents the predicted pre-dose concentration by actual starting dose in each of the three age groups for different levels of BSA, for patients not taking CYP3A4/PgP inducers. The starting dose is calculated based on BSA and then rounded to the nearest multiple of 2 (everolimus is provided in 2-mg tablets) as described in Section 6.2.3.

The starting dose for patients receiving CYP3A4/PgP inducers will be increased as per Table 6-4.

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Table 6-3 Predicted pre-dose concentrations in patients of different age groups after the per protocol starting dose

For patients without concomitant use of CYP3A4/PgP Enzyme Inducers (EI):

Age group	BSA m^2	Starting dose (mg/m^2)	Starting dose in mg (calculated dose)	Starting dose rounded to the nearest multiple of the 2-mg tablet (actual dose)*	Predicted C_{min} after the rounded starting dose (ng/mL)
< 10 yr	0.4	6	2.40	2 mg (1 x 2-mg tablet)	4.85
< 10 yr	0.5	6	3.00	4 mg (2 x 2-mg tablet)	7.76
< 10 yr	0.6	6	3.60	4 mg (2 x 2-mg tablets)	6.47
< 10 yr	0.7	6	4.20	4 mg (2 x 2-mg tablets)	5.54
< 10 yr	0.8	6	4.80	4 mg (2 x 2-mg tablets)	4.85
< 10 yr	0.9	6	5.40	6 mg (3 x 2-mg tablets)	6.47
< 10 yr	1.0	6	6.00	6 mg (3 x 2-mg tablets)	5.82
< 10 yr	1.1	6	6.60	6 mg (3 x 2-mg tablets)	5.29
< 10 yr	1.2	6	7.20	8 mg (4 x 2-mg tablets)	6.47
< 10 yr	1.3	6	7.80	8 mg (4 x 2-mg tablets)	5.97
10 to <18 yr	0.9	5	4.50	4 mg (2 x 2-mg tablets)	5.64
10 to <18 yr	1	5	5.00	6 mg (3 x 2-mg tablets)	7.62
10 to <18 yr	1.1	5	5.50	6 mg (3 x 2-mg tablets)	6.93
10 to <18 yr	1.2	5	6.00	6 mg (3 x 2-mg tablets)	6.35
10 to <18 yr	1.3	5	6.50	6 mg (3 x 2-mg tablets)	5.86
10 to <18 yr	1.4	5	7.00	8 mg (4 x 2-mg tablets)	7.26
10 to <18 yr	1.5	5	7.50	8 mg (4 x 2-mg tablets)	6.77
10 to <18 yr	1.6	5	8.00	8 mg (4 x 2-mg tablets)	6.35
10 to <18 yr	1.7	5	8.50	8 mg (4 x 2-mg tablets)	5.98
10 to <18 yr	1.8	5	9.00	10 mg (5 x 2-mg tablets)	7.06
10 to <18 yr	1.9	5	9.50	10 mg (5 x 2-mg tablets)	6.68
10 to <18 yr	2.0	5	10.00	10 mg (5 x 2-mg tablets)	6.35
≥ 18 yr	1.5	3	4.50	4 mg (2 x 2-mg tablets)	5.68
≥ 18 yr	1.6	3	4.80	4 mg (2 x 2-mg tablets)	5.33
≥ 18 yr	1.7	3	5.10	6 mg (3 x 2-mg tablets)	7.52
≥ 18 yr	1.8	3	5.40	6 mg (3 x 2-mg tablets)	7.10
≥ 18 yr	1.9	3	5.70	6 mg (3 x 2-mg tablets)	6.73
≥ 18 yr	2.0	3	6.00	6 mg (3 x 2-mg tablets)	6.39

*This is the dose of active drug. During the study patients may have placebo tablets added and subtracted to maintain the blind.

6.2.2 Dose Titration

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial.

Dose will be titrated via Interactive Response Technology (IRT) in a blinded fashion until each patient reaches their assigned target trough range. The IRT will indicate from which of the 2 labeled boxes (color 1 or color 2) the tablet/s should be titrated or down titrated (to attain trough level or adverse events management).

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The titration will be performed as follows:

- Any age, **NO** CYP3A4/PgP inducers: one tablet (2 mg) total increments, **regardless of BSA**
- Any age, **WITH** CYP3A4/PgP inducers: two tablets (4 mg) total increment, **regardless of BSA**. (In cases where a patient is taking 4 mg/day and requires a dose reduction, the reduction would be by one tablet (2 mg).)

For example, a 4 year old patient not taking CYP3A4/PgP inducers with a BSA of 0.65: calculated as 0.65 × 6.0 = 3.9 mg, rounded up to 4 mg (2 tablets). If this patient's first C_{min} is below 3 ng/mL, his dose would be adjusted up from 4 mg (2 tablets) by one increment of 2 mg (1 tablet), for a **total** daily dose of 6 mg (3 tablets).

Patients on placebo will have random increases and decreases in number of tablets taken to simulate titration and to maintain the blind. Patients in the low trough group will also have random increases and decreases in placebo tablets to simulate titration for the high trough group.

During the extension phase, placebo dose changes will be possible at the start of dose transition. Starting at the visit at which everolimus concentrations may be disclosed, placebo tablets will no longer be dispensed.

In the Extension phase, from Week 26 onwards when investigator-led dose titration is possible, dose changes should continue to be in units of 1 tablet (2 mg) for patients not taking CYP3A4/PgP inducers, and 2 tablets (4 mg) for patients taking CYP3A4/PgP inducers. The investigator will be allowed full discretion to increase the dose, as long as C_{min} does not exceed 15 ng/ml and to decrease the dose to a minimum of 1 tablet (2mg) per day. A dose and frequency of less than 2 mg/day requires study treatment discontinuation (see Section 7.1.6.1).

In the Post Extension phase, the investigator will have independent control over the dosing to increase or decrease the dose. Dose increases should not be attempted if C_{min} is ≥ 15 ng/ml.

6.2.3 Rounding of doses

Starting dose

The starting dose should be rounded up or down to the nearest multiple of 2 mg in order to use whole 2-mg tablets. For example:

Table 6-4 Examples for how to dose a patient

Patient age	BSA m^2	CYP3A4/PgP inducers?	Starting dose (mg/m^2)	Calculation	Starting dose in mg	Round	Starting dose rounded to nearest multiple 2-mg tablet*
2	0.5	No	6	0.5 x 6	3.0	Up	4 mg (2 x 2-mg tablet)
9	1.2	Yes	9	1.2 x 9	10.8	Down	10 mg (5 x 2-mg tablets)
22	1.8	No	3	1.8 x 3	5.4	Up	6 mg (3 x 2-mg tablets)

*This will be the active dose. Additional placebo tablets may be added or subtracted to maintain the blind.

If the starting dose in mg is an odd integer (i.e., 1, 3, 5, etc.), then the dose should be rounded up to the nearest multiple of 2 mg tablets (e.g., a starting dose of 3 mg would be rounded up to 4 mg, corresponding to two 2 mg tablets).

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Titration

Titration will be done by whole increments of 2 mg (patients not taking CYP3A4/PgP inducers) and 4 mg (patients taking CYP3A4/PgP inducers), so rounding will not be necessary. In the examples above in Table 6-4, patients illustrated in rows 1 and 3 (2 and 22 years of age) will be titrated by 1 tablet, whereas the patient in row 2 (9 years old) will be titrated by 2 tablets.

During the Core phase and Extension phase, trough PK levels will be assessed for the purpose of dose titration and assessment of any potential interactions with antiepileptic drugs. For the first 6 weeks of the core phase, bi-weekly PK samples are to drawn and analyzed to assist in titration. However, in the absence of adverse events requiring a site visit (as assessed by the investigator and the patient through telephone contact), and if there are circumstances that make it difficult for the patient to go to the site, the PK samples can be taken at a local facility and sent to the central laboratory for analysis, provided the study PK kit is used and proper labeling, handling, and shipment procedures are followed. This will be done on an exception basis only.

6.2.4 Dose reduction or delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Please see Table 6-5, Table 6-6 and Table 6-7 below for specific guidelines. In all cases, intended dose adjustments must be communicated to the IRT. The IRT will give instructions as to the new number of tablets to be taken from each blister pack in order to implement the dose adjustment through the end of the Extension phase.

The following guidelines need to be applied:

- All changes in dose must be recorded on the Dosage Administration Record eCRF.
- The study drug at the day of treatment can be administered at full dose, at reduced dose or held according to the below dose adjustment Table 6-5, Table 6-6, Table 6-7, Table 6-8, Table 6-9 and Table 6-10 and according to the actual instructions from IRT as to the new number of tablets to be taken from each blister pack (Core and Extension phases only). During the Post Extension phase, IRT will dispense kit packs based on the dose determined by the investigator.
- If the study drug cannot be administered on the scheduled day, the administration of the study drug will be skipped until the next day.
- If the interruption of study drug lasts for more than 28 days, the patient must be withdrawn from the study.

[redacted]

Table 6-5 Everolimus dose modification guidelines for non-hematologic toxicities

Toxicity	Action
Pneumonitis	Please refer to Section 6.2.5.7
Reactivation of HBV or HCV flare	Please refer to Section 6.2.5.8
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)*	Interrupt study drug administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, study drug should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold study drug until recovery to ≤ grade 1 or baseline grade / value and reintroduce study drug 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers
AST or ALT elevation Grade 4 (> 20 x ULN)* Recurrence of grade 4 after dose reduction or toxicity requiring study drug interruption for > 28 days	Interrupt study drug administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, study drug should be re-started at 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers. If resolution takes > 7 days, discontinue study drug. Discontinue study drug.
Intolerable grade 2 mucositis (see Section 6.2.5.3), or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 6.2.5.6)	Interrupt study drug administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, study drug should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold study drug until recovery to ≤ grade 1 or baseline grade / value and reintroduce study drug 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days.
Any other grade 4	Hold study drug until recovery to grade ≤ 1 or baseline value Reintroduce study drug at one 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue study drug
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose by 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers. The lowest possible dose level of study drug is 2 mg daily. Below this level, study drug must be discontinued.
Recurrence of grade 4 after dose reduction	Discontinue study drug
Any non-hematologic toxicity requiring study drug interruption for > 28 days	Discontinue study drug
* Should HCV flare be confirmed, the guidelines for flare must take precedence	

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

Toxicity	Action
Grade 2 thrombocytopenia	No action
Grade 3 thrombocytopenia	Interrupt study drug until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce study drug at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce study drug reduced 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available.
Grade 4 thrombocytopenia	Interrupt study drug until recovery to grade ≤ 1. Then reintroduce study drug at 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available.
Grade 3 neutropenia or anemia	Interrupt study drug until resolution to grade ≤1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce study drug at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce study drug 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available.
Grade 4 neutropenia or anemia	Interrupt study drug until recovery to grade ≤ 1 or baseline value. Reintroduce study drug at 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available.
Febrile neutropenia	Interrupt study drug until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce study drug 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available.
Recurrence of grade 3 toxicity after dose reduction	Reduce dose 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers. The lowest possible dose level of study drug is 2 mg. Below this level, study drug must be discontinued.
Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction	Discontinue study drug
Any hematologic toxicity requiring study drug interruption for > 28 days	Discontinue study drug

6.2.5 Management of specific toxicity

Adverse events most frequently observed with everolimus are rash, stomatitis /oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2). Recommendations for dose adjustments, should any of these treatment-related adverse events occur, are given in Table 6-5, Table 6-6, Table 6-7, Table 6-9 and Table 6-10.

6.2.5.1 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive

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fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

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

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

6.2.5.2 Management of skin toxicity

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

6.2.5.3 Management of stomatitis / oral mucositis / mouth ulcers

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

Stomatitis/oral mucositis/mouth ulcers due to study drug should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be

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avoided in all patients due to their strong inhibition of everolimus metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

6.2.5.4 Management of diarrhea

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

6.2.5.5 Management of amenorrhea

Investigators should be aware of the identified risk of secondary amenorrhea in post-adolescent females. No changes in study drug treatment or treatment with concomitant medications was implemented in prior cases. Nearly all previous cases of amenorrhea for patients on study resolved without treatment action. Amenorrhea did not result in any treatment discontinuations. If an amenorrhea event of at least 6 months is seen, consultation with an endocrinologist, gynecologist or other appropriate medical personnel is recommended.

6.2.5.6 Management of hyperlipidemia and hyperglycemia

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

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of study drug and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on study drug.

6.2.5.7 Management of non-infectious pneumonitis

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

Individuals participating in this trial will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. Chest X-ray or CT/MRI scan can be performed if clinically indicated. If non-infectious pneumonitis develops, the guidelines in Table 6-7 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

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

Table 6-7 Management of non-infectious pneumonitis

Worst grade pneumonitis	Required investigations	Management of pneumonitis	Study drug dose adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required	Administer 100% of study treatment dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, D_LCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Reduce study treatment dose by 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers until recovery to < Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤ Grade 1 within 4 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, D_LCO, and room air O_2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart study treatment within 4 weeks at a reduced dose (2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers) if evidence of clinical benefit. If toxicity recurs at grade 3, consider discontinuation of study drug.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, D_LCO, and room air O_2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

[redacted]

6.2.5.8 Management of hepatitis reactivation / flare

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 6-8 provides details of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Table 6-8 Action to be taken based on screening hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HbsAg	+ or -	+	-	-	-
HbsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HbcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Excluded from the study		No prophylaxis Monitor HBV-DNA every 4 weeks (from Visit 2 and onwards)		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. For HBV reactivation definition and management guidelines, see Table 6-9.

Table 6-9 Guidelines for the management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA OR positive HBsAg --- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]	Excluded from study
For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBsAb (with no prior history of vaccination against HBV), OR positive HBcAb] --- Reactivation is defined as: New appearance of measurable HBV-DNA	Treat : Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ undetectable (negative) HBV-DNA levels If resolution occurs within ≤ 28 days, study drug should be re-started at 2 tablets less for patients taking CYP3A4/PgP inducers, or 1 tablet less for patients NOT taking CYP3A4/PgP inducers, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.
* All reactivations of HBV are to be recorded as grade 3 (CTCAE Version 4.03 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.	

[redacted]

Monitoring for hepatitis C flare

The following category of patients should be monitored every 8 to 12 weeks for HCV flare:

- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured')

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to Table 6-10.

Table 6-10 Guidelines for the management of hepatitis C flare

Baseline results	HCV flare definition*	HCV flare management
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Excluded from study
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue study drug
* All flares of HCV are to be recorded as grade 3 (CTCAE Version 4.03 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).		

6.3 Concomitant medications

Patients must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken from the screening visit through the 30-day safety follow up visit must be reported on the Concomitant Medication/Significant Non Drug Therapies eCRF.

6.3.1 Permitted concomitant therapy requiring caution and/or action

6.3.1.1 CYP3A4 and P-glycoprotein inhibitors/inducers/substrates

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Everolimus is also a substrate of PgP.

For this study patient population, many patients will be taking concomitant CYP3A4/PgP enzyme inducing drug. Therefore, their PK trough levels will be monitored closely.

Therefore:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.

[redacted]

- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of study drug to half the currently used dose. If the inhibitor is discontinued, consider a washout period of at least 2-3 days (average for the most commonly used moderate inhibitors), before the study drug dose is returned to the dose used prior to initiation of the moderate CYP3A4 and/or PgP inhibitor.
- Seville oranges, star fruit, grapefruit and their juices affect CYP3A4 and PgP activity. Concomitant use should be avoided.
- For patients who require co-administration of strong CYP3A4/PgP inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), the starting dose will be increased per Section 6.1.1.1, and titration will be done by 4 mg increments.
- This dose adjustment of study drug is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving CYP3A4/PgP inducers. If the inducer is discontinued, consider a washout period of at least 3-5 days (reasonable time for significant enzyme de-induction), before the study drug dose is returned to the dose used prior to initiation of the CYP3A4/PgP inducer.
- Anytime there is a change in inducers or inhibitors of CYP3A4 and/or PgP, trough PK levels will be checked and study drug dose will be adjusted accordingly.

Please refer to Table 6-11 listing relevant inducers and inhibitors of CYP3A4 and to Table 6-12 for a list of relevant substrates, inducers, and inhibitors of PgP. These tables are not all inclusive and are only provided as guidance to the investigator.

Everolimus may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines, or contact with other who recently received live vaccines, should be avoided while a patient is treated with study drug. Everolimus should not be administered within 2 weeks of receiving a live vaccine, //cdc.gov/mmwr/pdf/rr/rr6002.pdf.

[redacted]

Table 6-11 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A4

Inducers
avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, rifabutin, phenobarbital, mitotane, enzalutamide, bosentan, efavirenz, etravirine, modafinil, nafcillin, genistein, ritonavir, thioridazine, tipranavir, semagacestat, talviraline, lopinavir, lersivirine, amprenavir, aprepitant, armodafinil bexarotene, clobazam, danshen, dexamethasone, echinacea, garlic, gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, pleconaril, primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, troglitazone, vinblastine, eslicarbazepine, ginseng, vemurafenib, boceprevir, sulfinpyrazone, ticagleror, vicriviroc/ritonavir, ritonavir, ticlopidine, brivacetam, Stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), quercetin.
Inhibitors
Strong inhibitors: boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, cobicistat, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir
Moderate inhibitors: amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, nilotinib imatinib, tofisopam, cyclosporin, ciprofloxacin, verapamil, dronedarone, crizotinib, casopitant, amprenavir, atazanavir/ritonavir, duranavir, netupitant, schisandra sphenanthera, cimetidine, lomitapide

Table 6-12 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A4 dual inhibitors

Substrates
digoxin, quinidine, paclitaxel, cyclosporine, sirolimus, tacrolimus, fentanyl, pphenytoin
Inducers
avasimibe, carbamazepine, efavirenz, genistein, phenytoin, quercetin, rifampin, St. John's wort extract
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, clarithromycin, conivaptan, cremophor RH40, curcumin, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fluvoxamine, ginko, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lapatinib, lopinavir/ritonavir, mibefradil, milk thisle, mirabegron, nelfinavir, nifedipine, nitredipine, paroxetine, propafenone, quercetin, quinidine, ranolazine, rifampin, ritonavir, sequinavir/ritonavir, schisandra chinesis extract, simepravir, St. John's wort extract, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir/ritonavir, tolvaptan, valspodar, vandetanib, verapamil voclosporin
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated 2015, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

6.3.2 Prohibited concomitant therapy

No new AEDs or changes to existing AED treatment (medication, dose, or frequency) are permitted from 28 days prior to screening and throughout the Baseline and Core phase of the study. In addition, the study drug should not be increased beyond the protocol-defined limits to treat any emerging/increasing epilepsy symptoms.

Patients may not take any other mTOR inhibitors while on study.

[redacted]

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the study. 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 to the investigator.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Log eCRF. IRT must be notified within 2 days of the Baseline visit, that the patient was not randomized.

6.4.2 Treatment assignment or randomization

Patients will be assigned to one of the three treatment arms (Section 6.1) in order to obtain 115 patients in the placebo arm, 115 patients in the everolimus 3-7 ng/ml trough arm and 125 patients in the everolimus 9-15 ng/ml trough arm, which corresponds to a ratio of approximately 1 : 1 : 1.09. See Section 10.8 for explanation of why 10 additional patients will be randomized in the everolimus 9-15 ng/ml arm.

Randomization will be stratified by age subgroup at randomization as follows: (i) 1 to <6 years; (ii) 6 to <12 years; (iii) 12 to <18 years; and (iv) ≥ 18 years.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and will enter the patient's age, height, weight, and CYP3A4/PgP inducer status. The IRT system will then calculate the appropriate starting dose. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

[redacted]

6.4.3 Treatment blinding

This is a double-blind study. Patients, investigators, site personnel and the Novartis trial team will make every effort to remain blinded to the identity of the treatment from the time of randomization until database lock for the Core phase, using the following methods: (1) randomization data are kept strictly confidential until the time of treatment unblinding. This information will not be accessible to anyone involved in the conduct of the study with the exception of the DMC who will perform periodic safety reviews. The DMC independent statistician and programmers, producing outputs for the DMC, will remain semi-blinded to the treatment groups. (2) the identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, labeling, schedule of administration and appearance. The following Novartis personnel, all non-members of the study team, will be unblinded: PK DMPK/BA (BA monitor), Drug Supply Manager, IRT Trials Account Manager, Independent Randomization Expert and Independent PK Expert. In addition, the following CRO vendors will be unblinded: for IRT [redacted] and for PK bioanalysis ([redacted].

Unblinding will only occur in the case of patient emergencies (Section 8.3), during safety review in the DMC if required (Section 8.6), for regulatory reporting purposes (if requested) and at the conclusion of the study.

6.5 Study Drug Supply

6.5.1 Study drug preparation and dispensation

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

Everolimus Dispersible Tablets are to be taken as a suspension only and should not be swallowed whole, chewed, or crushed. The suspension can be prepared in an oral syringe or in a small drinking glass. Care should be taken to ensure the entire dose is administered. Enteric feeding tubes may be used.

Administer the suspension immediately after preparation. Discard the suspension if not administered within 60 minutes of preparation. Prepare the suspension in water only.

1. **Using an oral syringe:** The required number of tablets for oral suspension (maximum of five 2-mg tablets) should be placed into a 10 mL oral syringe. Do not break or crush tablets. The plunger should be inserted and pushed inward to make contact with the dispersible tablet(s).
2. A sufficient volume of water (approximately 5 mL) should be drawn up from a glass to cover the dispersible tablet(s). In addition, approximately 4 mL of air should be drawn up into the oral syringe. The filled oral syringe should be placed in a glass (tip up) and the contents left to disintegrate for 3 minutes, until the Everolimus Dispersible Tablets are in suspension.

[redacted]

3. Prior to administration, the oral syringe should be inverted gently five times. While holding the oral syringe in an upright position (tip up), excess air should be removed carefully. The full contents of the oral syringe should be immediately dispensed into the mouth of the patient, slowly and gently.
4. The same volume of water and air should then be drawn up into the oral syringe, and the contents should be swirled to suspend any remaining particles. The full contents of the syringe should be dispensed into the mouth of the patient, slowly and gently.

If more than five tablets are to be dispersed, steps 1 and 2 should be repeated with the additional tablets to ensure the entire dose is administered. Step 3 should be repeated after the last dispersion.

Using a small drinking glass or cup:

1. The required number of tablets for oral suspension (maximum of five 2-mg tablets) should be placed into a small drinking glass (maximum size 100 mL or 3.38 oz.) containing approximately 25 mL (.85 oz.) of water. Do not break or crush tablets.
2. The tablets should be left to disintegrate for 3 minutes. The contents should be stirred gently with a spoon, immediately prior to drinking.
3. After administering the suspension, the glass should be rinsed with the same volume of water and stirred with the same spoon to suspend any remaining tablet particles. The rinse should be swallowed to ensure the entire dose is administered.

If more than five tablets are to be dispersed, steps 1 and 2 should be repeated with the additional tablets to ensure the entire dose is administered. Step 3 should be repeated after the last dispersion.

Of note, anyone who prepares the suspensions for another person should wear gloves to avoid possible contact with the drug.

6.5.2 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the labels. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Accountability Log) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

Study drug will be packaged in blister packs, and placed in boxes with color-coded labels color 1 or color 2 in order to maintain the blind. At each visit a patient will receive one or multiple boxes of medication of **one or both** color labels and the contents of each labeled box will be as follows:

[redacted]

Table 6-13 Core Phase Treatment

Patients randomized to:	Core Phase Treatment
Everolimus High (target trough 9-15 ng/ml)	Color 1 Labeled box = everolimus 2mg tablets & Color 2 Labeled box = everolimus 2mg tablets
Everolimus Low (target trough 3-7 ng/ml)	Color 1 Labeled box = everolimus 2mg tablets & Color 2 Labeled box = matching placebo tablets, or Color 1 Labeled box = matching placebo tablets & Color 2 Labeled box = everolimus 2mg tablets
Placebo	Color 1 Labeled box = placebo 2mg tablets & Color 2 Labeled box = matching placebo tablets

The potential for unmasking the blind is minimized because all patients in each treatment arm receive either one or both Color 1 and Color 2 labeled boxes at each visit, and because patients randomized to the Everolimus Low group (target trough 3-7 ng/ml) will sometimes have placebo in the Color 1 labeled boxes and sometimes in the Color 2 labeled box.

At the start of the Extension phase, patients who were receiving placebo will receive everolimus. At Week 26 and thereafter, investigators will be permitted to make their own dose titrations and only everolimus tablets will be dispensed.

For patients already having completed week 18 of the study at the time of signing the informed consent for protocol amendment 2, investigators will also be permitted to make their own dose changes, but only after a 2 week titration process that can begin at any upcoming scheduled visit on or after week 26. Such patients may continue to receive everolimus and placebo tablets, although only everolimus tablets will be dispensed once the Cmin value has been shared with the investigator.

Table 6-14 Extension Phase Treatment

Patients originally randomized to:	Dispensing Visit	Extension Phase Treatment
Any treatment arm	Before the first visit when Cmin is provided to the investigator	Color 1 Labeled box = everolimus 2mg tablets & Color 2 Labeled box = matching placebo tablets or Color 1 Labeled box = matching placebo tablets & Color 2 Labeled box = everolimus 2mg tablets or Color 1 Labeled box = everolimus 2mg tablets & Color 2 Labeled box = everolimus 2mg tablets
	On or after the first visit when Cmin is provided to the investigator	Color 1 Labeled box = everolimus 2mg tablets or Color 2 Labeled box = everolimus 2mg tablets

The dosing in the extension phase is designed to minimize the potential for unmasking the blind in the earlier Core phase. This is achieved by transitioning all patients to a common trough range of 6 to 10 ng/ml before any C_{min} value is provided to the investigator, and by adding the possibility of placebo tablets being administered to patients in any of the three treatment groups during the transition period.

[redacted]

Table 6-15 Post Extension Phase Treatment

Patients originally randomized to:	Dispensing Visit	Extension Phase Treatment
Any treatment arm	Any dispensing visit	everolimus 2mg tablets with Open Label design

As soon as the site is approved for the Post Extension Phase and the patient has signed the Informed Consent Form for the Post Extension Phase and related actions are completed in the IRT, the system will assign only Open Label boxes to patients based on the selected dose. The system is managing the number of kits needed by the patient.

6.5.3 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Investigator's Brochure].

6.5.4 Study drug compliance and accountability

6.5.4.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Log. Information will be collected on the DAR eCRF as to how many tablets each patient is taking from the Color 1 blister and the Color 2 blister. This information must be captured in the source document at each patient visit. Study site personnel will also affix the medication labels to the appropriate source document each time drug is dispensed to a patient.

6.5.4.2 Study drug accountability

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

At study close-out, and as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the field monitor or to the Novartis address provided in the investigator folder at each site.

[redacted]

6.5.4.3 Handling of other study treatment

Not applicable.

6.5.5 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 list all of the assessments and indicate 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 eCRF will be used as a source document. The category in table indicates which data are entered into the database (D) or remain in source documents only (S).

Tests, procedures and visits should occur on schedule whenever possible. However, test, procedures and visit that occur within the prescribed allowance windows indicated in Table 7-1 and Table 7-2 will not constitute protocol deviations.

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening	Baseline	Core Phase								EoT Core (11)	Extension Phase (visits every 12 weeks after #16)					Transition Visits[8]		End of treatment Extension (EoT)	Follow up/Study Completion
Visit Number			1	2	3	4	5	6	7	8	9	10	777	12	13	14	15	16+	201	202	778	779
			-8	0	1	2	3	4	5	6	10	14	18	19	20	22	26[8]	30[8]+			within 7 days of stopping study drug	30 days after EOT
Study Week			-2 to +4 wks*	56 to 70 days after V1*	± 2 days						± 7 days		± 2 days[5]	± 2 days		± 7 days						
Obtain Informed Consent	D	11.3	X																			
IRT Registration	S	7.2.4.2.1	X																			
Demography	D	7.1.1.3	X																			
Inclusion/exclusion criteria	D	7.2.1.5	X	X[4]																		
Screen failure log as needed	D	7.1.1.2	X	X																		
Relevant medical history/current medical conditions	D	7.2.1.1	X																			
Diagnosis of TSC	D	7.2.1.2	X																			
Prior anti-TSC therapy	D	7.2.1.3	X																			
Seizure history	D	7.2.1.1	X																			
Previous AED therapy	D	7.2.1.4	X																			

[redacted]

	Category	Protocol Section	Screening	Baseline	Core Phase								EoT Core (11)	Extension Phase (visits every 12 weeks after #16)					Transition Visits[8]		End of treatment Extension (EoT)	Follow up/Study Completion
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**777**	**12**	**13**	**14**	**15**	**16+**	**201**	**202**	**778**	**779**
			-8	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**	**14**	**18**	**19**	**20**	**22**	**26[8]**	**30[8]+**			**within 7 days of stopping study drug**	**30 days after EOT**
Study Week			**-2 to +4 wks***	**56 to 70 days after V1***	**± 2 days**						**± 7 days**		**± 2 days[5]**	**± 2 days**			**± 7 days**					
Current AED therapy	D	7.2.2.3	X																			
Concomitant medications	D	7.2.3.9	X	X		X		X		X	X	X	X		X	X	X	X		X	X	X
Rescue medications	D	7.2.2.4		X		X		X		X	X	X	X		X	X	X	X		X	X	X
IRT Randomization	S	7.2.1.6		X																		
Physical examination	S	7.2.3.2	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Neurological exam	S	7.2.3.3	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Contact Epilepsy Study Consortium	S	7.1.1	X																			
Distribute Seizure Diary	S	7.2.2.1	X	X		X		X		X	X	X	X		X	X	X	X				
Seizure data from diary	D	7.2.2.1		X		X		X		X	X	X	X		X	X	X	X			X	
Height[7]	D	7.2.3.8	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Parental height	D	7.2.3.6		X																		
Weight	D	7.2.3.8	X	X		X		X		X	X	X	X		X	X	X	X		X	X	

[redacted]

	Category	Protocol Section	Screening	Baseline	Core Phase								EoT Core (11)	Extension Phase (visits every 12 weeks after #16)					Transition Visits[8]		End of treatment Extension (EoT)	Follow up/Study Completion
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**777**	**12**	**13**	**14**	**15**	**16+**	**201**	**202**	**778**	**779**
			-8	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**	**14**	**18**	**19**	**20**	**22**	**26[8]**	**30[8]+**			**within 7 days of stopping study drug**	**30 days after EOT**
Study Week			**-2 to +4 wks***	**56 to 70 days after V1***	**± 2 days**						**± 7 days**		**± 2 days[5]**	**± 2 days**			**± 7 days**					
Vital signs	D	7.2.3.7	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Tanner Staging[6]	D	7.2.3.4		X								X					X	X[2]			X[2]	
Developmental milestones[6]	D	7.2.3.5		X								X					X	X[2]			X[2]	
EOT (Core and Extension)	D	7.1.6											X								X	
Pregnancy History, Menstrual History	D	7.2.3.6		X																		
Distribute Menstrual Diary	S	7.2.3.6	X	X		X		X		X	X	X	X		X	X	X	X				
Menstrual Monitoring	D	7.2.3.6		X	X			X		X	X	X	X			X	X	X			X	
Laboratory assessments		7.2.3.11																				
Hematology	D	7.2.3.11.1	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Chemistry	D	7.2.3.11.2	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Endocrine tests	D	7.2.3.11.3		X								X	X					X			X	

[redacted]

	Category	Protocol Section	Screening	Baseline	Core Phase								EoT Core (11)	Extension Phase (visits every 12 weeks after #16)					Transition Visits[8]		End of treatment Extension (EoT)	Follow up/Study Completion
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**777**	**12**	**13**	**14**	**15**	**16+**	**201**	**202**	**778**	**779**
			-8	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**	**14**	**18**	**19**	**20**	**22**	**26[8]**	**30[8]+**			**within 7 days of stopping study drug**	**30 days after EOT**
Study Week			**-2 to +4 wks***	**56 to 70 days after V1***	**± 2 days**						**± 7 days**		**± 2 days[5]**	**± 2 days**			**± 7 days**					
Lipid Panel	D	7.2.3.11.4	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Hepatitis testing	D	7.2.3.12, 7.2.3.13	X	X				X			X	X	X			X	X	X			X	X
Urinalysis	D	7.2.3.11.5	X	X		X		X		X	X	X	X		X	X	X	X			X	
Urine Pregnancy test	D	7.2.3.11.6	X					X		X	X	X				X	X	X			X	X
Serum Pregnancy test	D	7.2.3.11.6		X									X								X	
Anti-Mullerian Hormone	D	7.2.3.11.7		X									X					X[9]			X[9]	
ECG	D	7.2.3.16.1	X																			
MRI[1]	D	7.2.3.14		X									X									
EEG[1]	D	7.2.3.15		X									X									
Safety																						
Adverse events	D	8.1		X		X		X		X	X	X	X		X	X	X	X	X	X	X	X
Patient reported Outcomes		7.2.5																				

[redacted]

	Category	Protocol Section	Screening	Baseline	Core Phase								EoT Core (11)	Extension Phase (visits every 12 weeks after #16)					Transition Visits[8]		End of treatment Extension (EoT)	Follow up/Study Completion
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**777**	**12**	**13**	**14**	**15**	**16+**	**201**	**202**	**778**	**779**
			-8	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**	**14**	**18**	**19**	**20**	**22**	**26[8]**	**30[8]+**				
Study Week			**-2 to +4 wks***	**56 to 70 days after V1***	**± 2 days**						**± 7 days**		**± 2 days[5]**	**± 2 days**		**± 7 days**					**within 7 days of stopping study drug**	**30 days after EOT**
Seizure diaries	S	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WNV[2]	D	7.2.3.1		X									X					X[2]			X	
Vineland[2]	D	7.2.3.1		X									X					X[2]			X	
QOL	D	7.2.5		X									X								X	
eC-SSRS	D	7.2.3.10	X	X		X		X		X	X	X	X		X	X	X	X		X	X	
Study Drug administration via IRT recorded on Everolimus/Placebo DAR	D	7.2.2.2		X		X		X		X	X	X	X		X	X	X	X		X	X	
AED administration recorded on AED DAR	D	7.2.2.3		X`		X		X		X	X	X	X		X	X	X	X		X	X	
[redacted]																						
Everolimus PK sampling	D	7.2.4			X		X		X		X	X	X	X		X	X	X	X		X	
AED PK sampling	D	7.2.4	X	X	X		X															

[redacted]

	Category	Protocol Section	Screening	Baseline	Core Phase								EoT Core (11)	Extension Phase (visits every 12 weeks after #16)					Transition Visits[8]		End of treatment Extension (EoT)	Follow up/Study Completion
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**777**	**12**	**13**	**14**	**15**	**16+**	**201**	**202**	**778**	**779**
			-8	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**	**14**	**18**	**19**	**20**	**22**	**26[8]**	**30[8]+**			**within 7 days of stopping study drug**	**30 days after EOT**
Study Week			**-2 to +4 wks***	**56 to 70 days after V1***	**± 2 days**						**± 7 days**		**± 2 days[5]**	**± 2 days**		**± 7 days**						
Offer inclusion into extension phase	S	4.1.3, 7.1.4											X									
Offer inclusion into the post extension phase	S	4.1.4, 7.1.5																			X	

[redacted]

	Category	Protocol Section	Screening	Baseline	Core Phase								EoT Core (11)	Extension Phase (visits every 12 weeks after #16)					Transition Visits[8]		End of treatment Extension (EoT)	Follow up/Study Completion
Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**777**	**12**	**13**	**14**	**15**	**16+**	**201**	**202**	**778**	**779**
			-8	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**10**	**14**	**18**	**19**	**20**	**22**	**26[8]**	**30[8]+**				
Study Week			**-2 to +4 wks***	**56 to 70 days after V1***	**± 2 days**						**± 7 days**		**± 2 days[5]**	**± 2 days**		**± 7 days**					**within 7 days of stopping study drug**	**30 days after EOT**
Study completion CRF	D	7.1.7																				X

* All procedures for screening visit must be performed within -2 weeks to + 4 weeks of Visit 1. All procedures for Baseline visit must be performed within -2 days of Baseline visit (V2) and occur prior to first dose.
[1] MRI and EEG will only be performed at select sites during the study. Please refer to protocol Appendix A for more information
[2] WNV, Vineland, Tanner Staging, Developmental milestones, will be completed every 6 months after End of Core, i.e., Week 42, Week 66 etc. Although there is an "X" in the Visit 16+ column, these assessments will not be done at Visit 16 because 6 months will not have passed since EOT Core Visit 11 (777).
[3] [redacted]
[4] Eligibility related to lab criteria will be based on central lab results from the Screening visit.
[5] +/- 7 days for permanent discontinuation.
[6] Tanner staging is not required after 2 consecutive assessment scores of Stage 5 on both assessments. Tanner Staging will occur at Baseline only for patients who enter the study with Stage 5 for both assessments. Developmental milestones will be completed at the same time and frequency as Tanner Staging.
[7] Height is to be performed for adults at full development only at screening visit. Patients who are still growing will measure height at all visits.
[8] Please refer to Section 4.1.3 for details and actions to be performed when transitioning patients to 6 to 10 ng/ml starting at visits 26, 30+ in the Extension Phase
[9] AMH will be tested in females ≥10 years of age at Baseline, EOT core, Week 54 and every 48 weeks thereafter.

[redacted]

Table 7-2 Visit Evaluation Schedule: Post Extension Phase

	Category	Protocol Section	Post Extension Phase Visits (every 12 weeks)	End of treatment Post Extension (EoT)	Follow up/Study Completion
Visit Number			**401, 402, 403+ ±7 days**	**780 ±7 days**	**779**
Obtain Informed Consent [1]	S	11.3	X		
Physical examination	S	7.2.3.2	X	X	
Tanner Staging[2]	D	7.2.3.4	X		
Development Milestones[2]	D	7.2.3.5	X		
Neurological exam	S	7.2.3.3	X	X	
Height	D	7.2.3.8	X	X	
Weight	D	7.2.3.8	X	X	
Vital signs	D	7.2.3.7	X	X	
EOT (Post Extension)	D	7.1.6		X	
Laboratory assessments		7.2.3.11			
Hematology	D	7.2.3.11.1	X	X	
Chemistry	D	7.2.3.11.2	X	X	
Endocrine tests	D	7.2.3.11.3	X	X	
Lipid Panel	D	7.2.3.11.4	X	X	
Hepatitis testing (if indicated)	D	7.2.3.12, 7.2.3.13	X	X	X
Urinalysis	D	7.2.3.11.5	X	X	

[redacted]

	Category	Protocol Section	Post Extension Phase Visits (every 12 weeks)	End of treatment Post Extension (EoT)	Follow up/Study Completion
Visit Number			**401, 402, 403+ ±7 days**	**780 ±7 days**	**779**
Urine Pregnancy test	D	7.2.3.11.6	X		X
Serum Pregnancy test[3]	D	7.2.3.11.6	X*	X	
Anti-Mullerian Hormone	D	7.2.3.11.7	X	X	
ECG	D	7.2.3.16.1	If clinically indicated		
Safety					
Adverse events	D	8.1	X	X	X
eC-SSRS/ Assessment of Mood and behavior	D	7.2.3.10	X	X	
Assessment of changes in seizure presentation	D	7.2.3	X		
Study Drug administration via IRT recorded on Everolimus DAR	D	7.2.2.2	X		
AED administration recorded on AED DAR	D	7.2.2.3	X	X	
Everolimus PK sampling [4]	D	7.2.4	X		
Concomitant medications	D	7.2.3.9	X	X	X

[redacted]

	Category	Protocol Section	Post Extension Phase Visits (every 12 weeks)	End of treatment Post Extension (EoT)	Follow up/Study Completion
Visit Number			**401, 402, 403+ ±7 days**	**780 ±7 days**	**779**
Rescue medications	D	7.2.2.4	X	X	X
Study completion CRF	D	7.1.7			X

[1] Amendment 3 informed consent to be signed prior to first Post Extension phase visit.
[2] Tanner staging is not required after 2 consecutive assessment scores of Stage 5 on both assessments. Tanner staging and developmental milestones will continue to be completed every 6 months.
[3] Serum pregnancy test required to confirm any positive urine test
[4] Additional PK required as per Section 4.1.4

[redacted]

7.1.1 Screening

The informed consent must be signed prior to any screening procedure. The informed consent will provide information on study requirements and study procedures.

During the Screening visit (V1 /Week -8), the patient demographics and medical history, including TSC diagnosis, prior anti-TSC therapy, seizure history and prior AED use will be assessed. A physical and neurological examination will be performed, as well as assessments for height, weight, vital signs, and risk of suicide using the eC-SSRS. Laboratory tests for hematology, chemistry, hepatitis, lipids, urinalysis, and pregnancy will be assessed. Also, PK sampling for the specified AEDs will be collected. An ECG will also be performed at screening. For applicable patients, all available pre-baseline height and weight data should be collected in order to adequately represent the patient's rate of growth prior to starting the study.

In addition, inclusion and exclusion criteria will be evaluated. The patient should also be registered into the IRT system as described in the IRT Manual.

The Epilepsy Study Consortium

As part of screening, investigators will be asked to complete a detailed description of each patient's seizures along with the seizure classification on a form that will be faxed to the Epilepsy Study Consortium.

A reviewer at the Consortium will review the form and provide feedback about the patient's seizure classification to the Investigator.

Rescreening

Reassessment of any screening criteria is permitted for previously screen failed patients. Patients who did not meet the required seizures counts during the baseline phase would need to wait at least 3 months before re-screening. Reassessment of screening criteria is permitted for patients whose laboratory values changed since initial screening as long as all screening procedures are performed within the specific screening time window. The re-test value must be normal at least two weeks prior to randomization.

Screening for hepatitis B

Prior to randomization, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

- All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal and Greece. [nc.cdc.gov/travel/yellowbook/2010/chapter-2/hepatitis-b.aspx#849]
- Patients with any of the following risk factors:
  - known or suspected past hepatitis B infection,
  - blood transfusion(s) prior to 1990,
  - current or prior IV drug users,
  - current or prior dialysis,

[redacted]

- household contact with hepatitis B infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos,
- mother known to have hepatitis B,
- history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.

- Additional patients at the discretion of the investigator

Patients with serological markers indicative of prior hepatitis B will be excluded from the study.

The management guidelines, in Section 6.2.5.8, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

Screening for hepatitis C

Patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR:

- known or suspected past hepatitis C infection (including patients with past interferon 'curative' treatment),
- blood transfusions prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact of hepatitis C infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos.

At the discretion of the investigator, additional patients may also be tested for hepatitis C.

The management guidelines, in Section 6.2.5.8, are provided according to the results of the baseline assessment of hepatitis C viral load.

For other screening assessments refer to Table 7-1.

7.1.1.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be randomized for any reason will be considered a screen failure. The reason for not being randomized will be entered on the Screening Failure Log. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Baseline Phase (see Section 8 for SAE

[redacted]

reporting details). Any data other than these that are entered by the site into the database will not be deleted, but they will not be included for analysis. If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

7.1.1.3 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics, including demographic information (age, sex, ethnicity, race, weight) and other background or relevant medical history (seizure type and frequency, date of epilepsy diagnosis, and treatment history). Information will also be collected regarding child-bearing potential, TSC diagnosis, TSC genetic testing, and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical and neurological examination, vital signs, hematology and blood chemistry, urinalysis, pregnancy test, ECG, and suicide risk assessed by the eC-SSRS). The prior and current AED and concomitant medication use, including VNS and ketogenic diet, will also be collected and recorded. For further details on eligibility assessments, please see Table 7-1.

7.1.2 Baseline phase

The baseline phase consists of a screening visit (V1) at week -8 through the baseline visit (V2) at week 0. For more information on the screening visit, please see Section 7.1.1. During this phase, patients should keep track of any seizures in the seizure diaries and any change in AEDs taken during this time.

Baseline visit

During the baseline visit, inclusion and exclusion criteria will be re-assessed, (central lab results from the Screening visit), along with other assessments outlined in Table 7-1. performed prior to first dose The use of seizure rescue medication from time of screening to baseline will also be collected. If a patient requires rescue medication for 7 or more cumulative days during the Baseline phase, they will not be able to continue to the Core phase of the study. A physical and neurological exam will be performed, as well as assessments for height, weight, vital signs, tanner staging, and laboratory tests (hematology, chemistry, lipids, hepatitis, endocrine function, urinalysis, and pregnancy). [redacted] The patient's seizure history and AED use from screening to baseline will be assessed from the seizure diaries. In addition, assessments for developmental milestones, suicidality, quality of life and neuropsychological assessments will be performed. Also, pregnancy history, menstrual history, and mother's reproductive history, and assessment of parental height will be conducted.

Adverse events and concomitant medications will also be assessed at this visit. For patients participating in the MRI substudy, an MRI and EEG will also be conducted at the Baseline visit. For more information on the MRI and EEG substudy, please see Appendix A.

All patients who continue to meet eligibility criteria at the baseline visit (V2), including demonstrating the minimum seizure frequency during the 8-week baseline phase (see Section 5.2), will be randomized in a 1:1:1.09 ratio to one of the three treatment arms as described in Section 6.1. The patient should be randomized via the IRT system as described in the IRT [redacted]

manual. At that time, study medication pack details and administration guidelines will be provided. Also, the first dose of study drug should be administered.

7.1.3 Core phase

The Core phase begins at the baseline visit (Visit 2) and continues up to and includes Visit 11 (week 18), at which time the patient would be offered inclusion into the extension phase.

At Weeks 2 (V4), 4 (V6), 6 (V8), 10 (V9), 14 (V10), and 18 (V11); assessments will include seizure diaries, use of AED medications, and suicidality risk. Other assessments include use of rescue medications, physical and neurological exams, and height, weight, vital signs, and laboratory tests (hematology, chemistry, lipids, hepatitis, and urinalysis). If applicable, pregnancy testing and/or hepatitis testing will be assessed approximately every month. Endocrine testing will be done every 12 weeks.

At each visit during the Core phase, study drug titration (if applicable) and dosing will also occur. Adverse events, concomitant medications, and drug accountability will also be assessed at each visit.

Pharmacokinetic testing will be performed at various visits throughout the core phase for dosing and titration purposes. For more information on PK testing, see Section 7.2.4. Only at the Week 14 (V10) visit during the Core Phase, development milestones and Tanner staging will be assessed.

The end of treatment (EOT) in the Core Phase is at Week 18 (Visit 11). In addition to the assessments above, at this visit, neuropsychological and quality of life assessments will be performed.

For more information about assessments, please see Table 7-1.

7.1.4 Extension phase

All patients who complete the Core phase will be offered continuation on the Extension phase, during which all the patients will receive everolimus at Week 18 [(V11) same visit as end of Core and start of extension)]. Patients will enter into this phase upon completion of the core phase, and will continue in the Extension phase until 48 weeks after the last patient completes the core phase. (Patients enrolled earlier in the study may remain in the Extension phase for more than 1.5 years.)

During the Extension phase, visits will be at Weeks 18 (V11), 19 (V12), 20 (V13), 22 (V14), 26 (V15), and 30 (V16), and then every 12 weeks thereafter, unless additional visits are clinically indicated. For patients signing the informed consent for Amendment 2 after completing the week 18 visit, at least two additional visits will be added for the purpose of transitioning towards a trough concentration range of 6-10 ng/ml.

Assessments during the extension phase should be performed pre-dose and include seizure diaries, use of AED medications, and suicidality risk will also be assessed and recorded. Other assessments include use of rescue medications, physical and neurological exams, and height, weight, vital signs, and laboratory measurements (including pregnancy tests). Pharmacokinetic testing for everolimus will be performed at all visits throughout the extension phase, except at Week 20.

[redacted]

In the Extension phase, development milestones and Tanner staging will be done as outlined in Table 7-1. Menstrual monitoring will be assessed every month (if applicable).

At each visit during the Extension phase, study drug titration (if applicable) and dosing will also occur. Adverse events, concomitant medications, and drug accountability will also be assessed at each visit.

At the end of the Extension phase, an end of treatment visit will occur as described in Section 7.1.6 and Table 7-1.

For more information about assessments, please see Table 7-1.

7.1.5 Post Extension phase

All patients continuing to receive clinical benefit at the completion of the Extension phase will be offered continued treatment in the Post Extension phase. During the Post Extension phase, visits will occur every 12 weeks unless additional visits are clinically indicated. Investigators will have control over patient dosing and should follow the guidance outlined in Section 6. Modified safety assessments will be performed as described in Table 7-2.

7.1.6 End of treatment visit and premature withdrawal

Premature withdrawal

Patients may voluntarily withdraw from the study or be dropped from the study at the discretion of the investigator at any time. For more detailed information, please see Section 7.1.6.1

End of treatment (EOT)

There are three time points at which an EOT eCRF can be completed for each patient. One will be at Visit 11/Week 18, marking the end of the Core phase of the study. A second will be when the patient completes the study treatment in the Extension Phase and the third will be when the patient completes the Post Extension phase. At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed (Core, Extension or Post Extension as applicable). An End of Treatment eCRF page should be completed, giving the date and reason for stopping the study treatment.

During the EOT visits, assessments will include collection of concomitant and rescue medications, physical and neurological exam, height, weight, vital signs, and laboratory tests assessments, including a pregnancy test, the use of AED medications, and the risk of suicidality. For the Core and Extension phase EOT visits, seizure diary review, quality of life and neuropsychological assessments will also be performed, and menstrual monitoring will be reviewed as applicable.

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

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

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

The Investigator must contact the IRT to register the subject's discontinuation.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

7.1.6.1 Criteria for premature patient withdrawal

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

- Pregnancy
- Discovery of failure of randomization or blinding
- Discovery of patient ineligibility
- An interruption of study drug that lasts for more than 28 days.
- Intolerable toxicity
- Withdrawal of Consent
- In patients who have their dose interrupted for toxicity, if restarting study drug upon resolution of the toxicity requires dose reduction, and that reduction results in instruction to take 0 tablets for placebo patients during the core phase, or 0 mg everolimus for active drug patients in the Core phase, or 0 mg everolimus for all patients in the Extension and Post Extension phases.

In addition to the general withdrawal criteria, the following study specific criteria will also require study treatment discontinuation during the Core Phase:

- Loss of seizure control defined as an increase of 100% in the average weekly number of partial-onset seizures for a minimum of 4 consecutive weeks as compared to the average weekly number of partial-onset seizures during the 8 weeks baseline period.
- An episode of status epilepticus, defined as: in adults and children older than 5 years -- continuous or intermittent, convulsive seizures lasting more than 10 minutes and requiring additional medical intervention such as with rescue medication not commonly used in the home (i.e., a convulsive seizure or series of convulsive seizures not within the patient's typical seizure pattern and management).
- A single generalized tonic clonic seizure (non-febrile), if none occurred during the baseline period, and if one has not occurred within the past year.
- Use of rescue medications longer than the maximum duration described in Section 6.1.2.
- An interruption of one or more of the concomitant AEDs for more than 7 days.

[redacted]

- Treatment duration completed as per protocol: completion of the Core phase (if patients do not accept to start the extension phase), completion of the Extension phase (if patients do not accept to start the post extension phase) or completion of the Post Extension phase.

At the start of the Extension Phase, during the transition to investigator control of everolimus dosing, and while the everolimus Cmin value is still not shared with the investigator, the investigator should consider managing clinical deterioration in seizure control (as judged by the investigator), if it should occur, by modifying AED doses or adding or subtracting AEDs. Starting at week 26, when everolimus Cmin values are made available to the investigator, the investigator may manage a patient's clinical deterioration by modifying AED doses, adding and or subtracting AEDs and modifying everolimus dosing in whatever order or combination the investigator chooses.

Patients who are withdrawn prematurely will have an End of Treatment visit as close as possible to the day that study drug is stopped. There will then be a follow-up visit 30 days after study drug is stopped.

7.1.7 Follow up/Study completion

All patients will be followed for adverse events and serious adverse events for at least 30 days following the last dose of study treatment. At the end of this period, the investigator should follow up with the patient about any adverse event observed/concomitant medication taken during this period either in person (for patients who have continuing adverse events) or via a phone visit (for patients who do not have continuing adverse events. Also, patients who are being followed for possible hepatitis flare ups will have an office visit where they will be tested for hepatitis for the final time in the study. Female patients of child bearing potential will perform a urine pregnancy test at home and report the results at this follow up.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first. In case the patient has any abnormal laboratory values at end of treatment that are considered clinically significant by the investigator, the patient needs to come to the site for repeat blood analysis until resolution or stabilization including at least a site visit with respective analyses 30 days after end of treatment.

For more information on follow up procedures, please refer to Table 7-1.

Patients lost to follow up should be recorded as such on the eCRF. 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 Eligibility assessments

7.2.1.1 Patient History

A detailed patient history will be taken, to include seizure history, TSC history and any TSC-related problems, major illness, surgeries, concomitant conditions. This information, including dates of diagnosis and whether or not the condition is still present will be recorded on the Relevant Medical History eCRF.

7.2.1.2 Diagnosis of TSC

Each patient must have a documented diagnosis of TSC per the modified Gomez criteria. See Section 5.2, Inclusion criterion #2. This diagnosis will be recorded on the TSC Diagnosis eCRF.

7.2.1.3 Prior anti-TSC therapy

A history should be taken from each patient to document any previous anti-TSC therapy taken. This information will be recorded on the Prior TSC therapy eCRF. Patients may not have been on prior anti-TSC therapy within 24 months of randomization, unless they were treated with a topical mTOR inhibitor, in which case the washout time is 4 weeks.

7.2.1.4 Prior AED therapy

Each patient will be questioned to get a history of prior anti-epileptic drug therapy to ensure that the inclusion criterion 4B is met, and the failed therapies recorded. These prior therapies will be documented on the Prior AED therapy eCRF.

7.2.1.5 Inclusion/Exclusion criteria

Once all screening procedures have been completed, and the laboratory results are back from the central lab, the patient's results should be compared with the list of Inclusion/Exclusion Criteria in Section 5.2 and Section 5.3. If all criteria aremet at the Baseline visit (using lab results from screening visit), the patient may be randomized to receive study drug. The eligibility questionnaire must be completed per the IRT manual in order to initiate therapy.

7.2.1.6 IRT randomization

When screening procedures are complete, and eligibility is confirmed, the patient will be entered into the IRT system to be randomized and have their first drug package assigned. This will be done per the IRT manual.

[redacted]

7.2.2 Efficacy assessments

7.2.2.1 Seizure diaries and counts

The investigator will review patient-specific seizure types and descriptions with the patient or caregiver at the screening visit, in order to ensure that all events are appropriately recorded throughout the study (the investigator may believe that some stereotypical events are not likely to be seizures, but for patient safety, and to limit patient confusion, the investigator may instruct the patient to record and count such events as well). Events will be counted daily by the patient or caregiver, following the Screening Visit, and entered into the diary by date, with seizures lasting more than 10 minutes being noted. The investigator will define a list of "probable seizures" in consultation with the Epilepsy Study Consortium (see Section 7.1.1) after the Screening Visit. Only events characterized as "probable seizures" by the investigator will be entered with their frequencies into the investigator portion of the diary, which will then be entered into the eCRF.

7.2.2.2 Study drug administration

At each study visit, the site will log into the IRT system to get the next drug assignment for each patient. The assigned number package will be dispensed to the patient. The tear off portion of the label will be affixed to the patient-specific drug accountability log. The specifics of the drug administration will be recorded on DAR eCRF.

7.2.2.3 AED therapy and administration

Patients must be taking one to three concomitant AEDs during the baseline and core phases of the study. These medications will be recorded on the AED DAR eCRF. The specific drugs and doses of these medications may not change 28 days prior to the screening visit and through the core phase of the study.

The name, dose, and frequency of concomitant AED therapy will be asked about at every visit. Any changes will be recorded on the AED DAR eCRF.

7.2.2.4 Rescue medications

Rescue medications are permitted as per Section 6.1.2. Any use of rescue medications will be recorded on the Rescue Medications eCRF.

7.2.3 Safety and tolerability assessments

Safety will be monitored by assessing as well as collecting the adverse events at every visit until the study completion visit. For details on AE collection and reporting, refer to Section 8. Risk of suicide will be assessed at each visit until the End of Treatment Visit of the Post Extension phase. Neurobehavioral, neurodevelopment, and neurocognitive assessments, will also be collected and assessed as part of safety monitoring during the Core and Extension phases only. In the Post Extension phase, as part of safety monitoring, assessments of changes in seizure presentation (i.e. frequency, intensity and/or development of new seizure types) will be collected.

[redacted]

7.2.3.1 Neurobehavioral, neurodevelopmental, and neurocognitive assessments

Wechsler Non-Verbal Scale of Ability

All patients aged ≥4 and <22 will undergo three subtests from the WNV 4-Subtest Battery at Baseline, at completion of the Core phase (EoT Core/Visit 11/Week 18), and then every 6 months (24 weeks) through the End of Treatment Visit of the Extension phase. If the last assessment before the EOT Visit of the Extension phase was less than 3 months prior to the EOT visit, the assessment does not need to be repeated.

For children ≥4 and <8 years of age, the following 3 subtests will be administered at the aforementioned visits in the following order: Matrices, Coding, and Recognition.

For children and young adults ≥8 and <22 years of age, the following 3 subtests will be administered at the aforementioned visits in the following order: Matrices, Coding, and Spatial Span.

The instructions for this scale will be provided in English, German, Spanish, French, Chinese and Dutch.

Vineland II Adaptive Behavior Scale

The Vineland is a scale that measures changes in certain behaviors. There are two forms which can be used to complete this scale. One is the **Survey Interview Form**, which a physician completes while interviewing/observing the patient. This form will be used when the investigator assesses that the patient is able to provide the information for the scale. The preference is for the Survey Interview Form to be used. The second form is the **Parent/Caregiver Form** which is completed by the Parent or Caregiver. This form will be used when the physician assesses that the patient cannot provide the information for the scale. The Parent/Caregiver Form should only be considered for parents/caregivers who are likely to complete the form accurately. Whichever form is used for the first assessment will be used throughout the study.

The appropriate Vineland Scale (Survey Interview or Parent/Caregiver) will be completed at Baseline (Visit 2), completion of the Core phase (EOT Core/Visit 11/Week 18), and then every 6 months (24 weeks)through the End of Treatment Visit of the Extension phase. If the last assessment before the EOT Extension were to be less than 3 months prior to the EOT visit, the assessment need not be repeated. The Vineland aids in diagnosing and classifying intellectual and developmental disabilities and other disorders, such as Autism, Asperger Syndrome, and developmental delays. The Vineland will be provided in the following languages: Dutch, Dutch (BELG), English (Australian), English (UK), English (US), English (CA), French, French (BELG), French (CA), German, German (BELG), Italian, Japanese, Polish, Spanish, Spanish (COL), and Spanish (US). These are the only countries in which the Vineland Scale will be used. Other countries will skip the Vineland, and only complete the other scales. Scoring by the site is not required for Vineland scales.

[redacted]

7.2.3.2 Physical examination

Physical examination must include a total body examination including: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and basic neurological exam. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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

7.2.3.3 Neurological examination

Neurological examination must include level of consciousness, mental status, speech, vision, cranial nerves III, IV, and VI, motor, sensory and gait/limb ataxia assessments.

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

7.2.3.4 Tanner staging

Tanner staging will be performed as described in Table 7-1 and Table 7-2 and will consist of the parameters below for both males and females.

7.2.3.4.1 Males

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.

Pubic Hair Stages:

Stage 1: Pre-adolescent, 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.

[redacted]

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 pattern and present along the inner borders of the thighs.

7.2.3.4.2 Females

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.

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.

7.2.3.5 Developmental milestones

Developmental milestones will be assessed at the visits listed in Table 7-1 and Table 7-2 and will include questions related to the expected secondary sexual characteristics such as body hair, breast development and voice change. Females will also be assessed on date of thelarche, which is the first stage of secondary (postnatal) breast development. Males will be assessed on date of adrenarche, which includes changes in sweat composition, pubic hair growth, and increasing skin oiliness or acne.

[redacted]

7.2.3.6 Pregnancy History, Menstrual History and Monitoring

In order to provide additional follow-up on cases of amenorrhea, increased hormonal evaluation will be performed and supplemental medical history will be collected.

Additional menstrual history (previous cases of amenorrhea or menstrual disorders, biological mother's age at menopause) and pregnancy history (pregnancies, full-term gestations, abortions, live births, living children) will be collected at baseline. Patients will be distributed menstrual diaries starting at the screening visit. Menstrual monitoring will be collected monthly at baseline and then every 4 weeks through Week 30. After Week 30, menstrual status will be collected monthly until the End of Treatment Extension via patient menstrual diary for source documentation, data from the patient menstrual diary will be collected during patient's visit at clinical site for eCRF entry. Pregnancy testing will be performed as described in Table 7-1 and Table 7-2. It is recommended that study coordinators contact patients monthly for the first 3 months to remind patients to document menstrual status in patient diary.

7.2.3.7 Vital signs

Vital signs include blood pressure, temperature, pulse and respiratory rate measurements. The results will be recorded on source documents, repeated at each visit and entered in eCRF starting at the screening visit and until the 30-day Safety Follow-up as described in Table 7-1 and Table 7-2.

7.2.3.8 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as described in Table 7-1 and Table 7-2. Weight will be recorded on the eCRF at each visit starting at the Screening Visit until the Post Extension Phase End of Treatment Visit. Pre-baseline height and weight will also be collected with a goal of collecting a minimum of three data points each 6 months apart for patients who enter the study with a Tanner Stage of less than 5. Parental height will also be captured at baseline for purposes of comparing children's height.

7.2.3.9 Concomitant medications

Each patient will be queried at each visit regarding the use of any medication other than study drug. These drugs will be listed on the Concomitant Medications eCRF. The start date, stop date, and reason for each drug should be recorded. If the reason for a concomitant medication constitutes an adverse event after signing informed consent, this AE should be added to the AE eCRF.

7.2.3.10 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior using a semi-structured interview to probe patient responses. The electronic version of this scale (eC-SSRS) will be administered via the IVR system and will be completed at every visit as outlined in Table 7-1 and Table 7-2.

[redacted]

Patients 13 years and over will complete this scale for themselves. Patients under 13 years, or with cognitively impairment which renders them unable to understand and complete the scale, will have it completed by their Parent/Caregiver.

If at any assessment after Screening and/or Baseline the score is 4 or above on the Suicidal Ideation item or any "yes" on the Suicidal Behavior item, the patient must be referred to a health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the health care professional to whom the patient is referred.

Per health authority recommendations, it is important to closely monitor the mental well-being of patients taking medications actively targeting their central nervous system. In the event that a patient ≥13 years of age does not complete the scale via the IVR system, the investigator will proactively assess the patient for the presence of suicidality and mood disturbance as part of the monitoring of adverse events. The investigator should ask the patient whether he or she has thought about hurting himself/herself and whether the patients wished they were dead, using words appropriate to the understanding of the individual patient. For all patients, the investigator will also ask the caregiver whether the patient has done anything to seriously injure himself/herself (but excluding behaviors previously associated with frustration, like hand biting, head banging etc.), or has expressed or exhibited significant changes in mood or behavior. These questions will be asked at every visit during the study as described in Table 7-1 and Table 7-2, with the caregiver also present in the room, so that both parties can answer. Any positive response will be further investigated, and appropriate medical treatment initiated and recorded as an adverse event on the AE eCRF

In the event of a successful suicide, the investigator will complete the Supplemental Data for Suicidal Ideation and Behavior Categories eCRF.

The use of the eC-SSRS to detect suicidal ideation or behavior is currently mandated in studies of CNS active drugs.

The eC-SSRS system is available in various languages including but not limited to Chinese, Danish, Dutch, Dutch (BELG), English (Australian), English (UK), English (US), English (CA), French, French (BELG), French (CA), German, German (BELG), Greek, Hungarian, Italian, Japanese, Korean, Norwegian, Polish, Russian, Spanish, Spanish (MEX), Spanish (US), Swedish, Turkish and Thai.

[redacted]

7.2.3.11 Laboratory evaluations

Table 7-3 Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, WBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), ANC
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol (fasting), LDL, HDL, Glucose (fasting), LDH (lactate dehydrogenase), Magnesium, Phosphate, Potassium, Total Protein, Sodium, Triglycerides, Blood Urea Nitrogen (BUN), Uric Acid, Creatinine Clearance (calculated)
Urinalysis	Macroscopic Panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, Protein, pH, Urobilinogen)
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR
Endocrine tests	FSH, LH, estradiol, β-HCG and testosterone, Anti-Mullerian Hormone

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [Laboratory Manual]. If a central lab result comes back that requires stat re-testing for safety, a local lab may be used. However, the central lab must be used for all study visits.

7.2.3.11.1 Hematology

Hematology tests are to be performed as indicated in Table 7-1 and Table 7-2. These must include: hemoglobin, hematocrit, platelets, red blood cell (RBC) count, total white blood cell (WBC) count and differential including lymphocytes, monocytes, neutrophils, eosinophils, basophils. Absolute Neutrophil Count (ANC) will be calculated by the laboratory.

7.2.3.11.2 Clinical chemistry

The following tests will be performed as indicated in Table 7-1 and Table 7-2: sodium, potassium, chloride, bicarbonate, creatinine, LDH, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, indirect bilirubin, direct bilirubin, alkaline phosphatase, uric acid, BUN, calcium, magnesium, phosphate, and fasting glucose. Creatinine clearance will also be calculated.

7.2.3.11.3 Endocrine tests

Endocrine tests will be performed at baseline, Visit 10, every 12 weeks, and EOT visits (Core, Extension and Post-Extension). Tests will include LH, FSH, estradiol, and testosterone. Please refer to Table 7-1 and Table 7-2 for more information.

7.2.3.11.4 Lipid profile

A lipid profile (total cholesterol, triglycerides, LDL, HDL) will be determined at screening and repeated at the same time points in Table 7-1 and Table 7-2. A final assessment will be performed at EOT Visits. The patient must be in a fasting state at the time of blood sampling for the lipid profile evaluation.

[redacted]

7.2.3.11.5 Urinalysis

Dipstick measurements for protein, ketones, bilirubin, leukocyte esterase, nitrites, urobilinogen, glucose, pH and blood will be performed. Any significant findings on dipstick will be followed up with a microscopic evaluation, where WBC and RBC sediments will also be measured. In the case where a urine sample cannot be obtained, this test can be omitted.

7.2.3.11.6 Pregnancy and assessments of fertility

Pregnancy testing is required for females of childbearing potential at screening, baseline and monthly until the end of the trial. β-HCG serum pregnancy testing will be performed at baseline and at the end of the treatment for the Core, Extension and Post-Extension phases. Urine pregnancy testing will be performed at screening, monthly at clinic visits, and at home when visits are greater than one month apart. Patients should be instructed to inform the site of a positive urine pregnancy result. β-HCG serum pregnancy testing will be performed for confirmation of a positive urine pregnancy test. Patients with a positive serum pregnancy test should be withdrawn from the study. For further guidance see Section 8.4.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 8 weeks after stopping study treatment. Highly effective contraception methods include:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Female Sterilization: Have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception
- or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormonal contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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

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

[redacted]

A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via semen.

7.2.3.11.7 Anti-Mullerian Hormone test

Female patients ≥10 years of age will perform AMH at Baseline, EOT core, Week 54 and every 48 weeks thereafter. Patients who are beyond the Baseline visit at the time of signing the Amendment 2 informed consent should not collect AMH.

7.2.3.12 HBV testing

Prior to randomization, the categories of patients listed in Section 7.1.1 should be tested for hepatitis B serologic markers and viral load (local results are acceptable for screening only):

- HBV-DNA, HBsAg, HBc Ab, and HBs Ab.
- During the treatment period, HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 6-8.
- The final monitoring visit for HBV will be at the 30-day safety follow-up.

7.2.3.13 HCV testing

Patients with hepatitis C risk factors and at the discretion of the investigator should be tested for HCV RNA prior to randomization (local results are acceptable for screening only). For a list of hepatitis C risk factors, refer to Section 7.1.1.

Follow-up testing will be performed, as per the visit schedule, only if the patient has a history of Hepatitis C. The final monitoring visit for HCV will be at the 30-day safety follow-up.

7.2.3.14 Radiological examinations

Magnetic Resonance Imaging (MRI) with diffuse tensor imaging (DTI) will be performed at select sites during the study. These scans will be performed at baseline, or within 7 days prior to the baseline visit and again at the end of the Core phase (V11) or within 7 days prior to the end of Core phase. Please refer to protocol Appendix A for more information.

7.2.3.15 Electroencephalogram (EEG) assessments

High frequency oscillation EEGs will be performed at selected sites during the study. These tests will be performed at baseline, or within 7 days prior to baseline visit, and again at the end of Core phase (V11) or within 7 days prior to the end of Core phase. Please refer to protocol Appendix A for more information.

[redacted]

7.2.3.16 Cardiac assessments

7.2.3.16.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed during screening and if medically indicated during the treatment period.

Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF.

7.2.4 Pharmacokinetics

During the 6 week titration period, three pre-dose PK blood samples will be taken for potential dose adjustments as described in Table 4-1. A local lab (at the treating center) will collect the blood samples and send them to a central laboratory for determination of everolimus concentrations. The site will receive recommendations from the central Interactive Response Technology (IRT) on dose adjustment (to maintain, increase or decrease the number of the 2-mg tablets) for each patient, based on concentration values of the pre-dose PK samples. **A sample of blood collected immediately prior to dosing on the study day and at 22-26 hours after the patient's last daily dose of study drug following 5 days of consistent (daily dose and timing of dose) dosing is a valid trough PK blood sample. Any sample collected outside of these parameters is not considered a true trough and therefore should not be used as a basis for adjusting the patient's dose.** It is expected that all the patients will achieve the desired target pre-dose trough level (Cmin) during this period. In order to keep the blind, the IRT will also instruct the site to adjust the dose for patients in the placebo arm.

After the completion of the titration period, patients will continue their current dose level during a 12 weeks maintenance period. Pre-dose PK blood samples will be collected every 4 weeks during the maintenance period.

In order to minimize total blood samples taken from pediatric patients, the amount of blood required for everolimus PK samples will be 0.5 mL for patients from 1 to < 2 years of age, and 1 mL for patients 2 to ≤ 6 years of age. For patients > 6 years of age, the amount will be 2 mL.

Additional Everolimus PK sampling

In addition to the time points described above in the Core, Extension and Post Extension phase sections, pre-dose blood samples for everolimus concentration determination should be collected two weeks after the following events:

- Any everolimus dose adjustment
- Starting or changing the dose of a CYP3A4/PgP inducer/inhibitor

[redacted]

Anti-epileptic drug PK sampling

Everolimus is metabolized by the CYP3A4 pathway in the liver, and to some extent in the intestinal wall. Many of the concomitantly administered AEDs are also metabolized by the CYP3A4 pathway, which results in a potential for drug-drug interaction between the AEDs and everolimus. Therefore, levels of the AEDs listed in Section 4.1.3 (considered to be CYP3A4 substrates and /or inducers) will be measured to investigate the effect of everolimus on the AED level (i.e., if AED + everolimus leads to higher levels of AED compared to AED alone).

Pre-dose plasma samples will be collected at Visits 1, 2, 3, and 5 for the measurement of antiepileptic drug (AED) concentration. Effects of everolimus on the exposure of anti-epileptic drugs will be assessed by comparing the anti-epileptic drug concentrations at Visits 1 and 2 (AEDs alone) and at Visits 3 and 5 (AEDs plus everolimus). A list of commonly prescribed AEDs that are used in this population is provided in Section 6.1.1.For a list of inducers and inhibitors, please refer to Section 4.1.3 and Table 6-11 and Table 6-12.

Table 7-4 Everolimus/Placebo PK Sample Log Table for Study core phase, Visits 0-11(777)

Study visit	Study Week	Time	PK Collection Number[b]	PK Sample Number[c]	Sample Volume[d] (mL)
Visit 3	Week 1	Pre-dose	401/501	401	2 mL (blood)
Visit 5	Week 3	Pre-dose	402/502	402	2 mL (blood)
Visit 7	Week 5	Pre-dose	403/503	403	2 mL (blood)
Visit 9	Week 10	Pre-dose	404/504	404	2 mL (blood)
Visit 10	Week 14	Pre-dose	405/505	405	2 mL (blood)
Visit 11(777)	Week 18	Pre-dose	406/506	406	2 mL (blood)
Additional[a]		Pre-dose	40401/50501 40402/50502 40403/50503 . . .	3001, 3002, 3003, . . .	2 mL (blood)

[a] additional visit at two weeks after any everolimus dose adjustment or start/change in dose of the CYP3A4/PgP inhibitor/inducer
[b] The first PK collection number refers to the first dose of everolimus received after collection of the PK sample, while the second PK collection number is the last dose the subject received prior to the collection of the PK sample
[c] The PK sample number uniquely identifies the PK sample for a particular visit and should be written on the tube label of samples sent to the central PK lab.
[d] Sample volume is dependent on patient's age. 0.5 mL for 1 to <2, 1 mL for 2 to ≤ 6, and 2 mL for > 6

During the Extension phase, Everolimus PK samples will be drawn at Weeks 19 (V12), 22 (V14), 26 (V15), and 30 (V16), and then every 12 weeks thereafter, unless additional visits are clinically indicated. Pre-dose blood samples will be collected per Table 4-2. After the target trough level is achieved, PK blood draws will be performed every 12 weeks through the Post Extension phase.

[redacted]

Table 7-5 Everolimus PK Sample Log Table for Study extension phase, starting at Visit 12

Study visit	Study Week	Time	PK Collection Number[b]	PK Sample Number[c]	Sample Volume[d] (mL)
Visit 12	Week 19	Pre-dose	601/701	601	2 mL (blood)
Visit 14	Week 22	Pre-dose	602/702	602	2 mL (blood)
Visit 15	Week 26	Pre-dose	603/703	603	2 mL (blood)
Visit 16	Week 30	Pre-dose	604/704	604	2 mL (blood)
	Every 12 weeks after	Pre-dose	605/705, 606/706, 607/707….	605,606, 607….	2 mL (blood)
End of Treatment Extension (V778)		Pre-dose	699/799	699	2 mL (blood)
Visit 201	Transition B: Week 27, 31, 43, 55, 67, etc	Pre-dose	801/901	801	2 mL (blood)
Additional[a]		Pre-dose	60601/70701, 60602/70702, 60603/70703,…	4001, 4002, 4003, . . .	2 mL (blood)

[a] additional visit at two weeks after any everolimus dose adjustment or start/change in dose of the CYP3A4/PgP inhibitor/inducer
[b] The first PK collection number refers to the first dose of everolimus received after collection of the PK sample, while the second PK collection number is the last dose the subject received prior to the collection of the PK sample
[c] The PK sample number uniquely identifies the PK sample for a particular visit and should be written on the tube label of samples sent to the central PK lab.
[d] Sample volume is dependent on patient's age. 0.5 mL for 1 to <2, 1 mL for 2 to ≤ 6, and 2 mL for > 6

Table 7-6 Everolimus PK Sample Log Table for Study Post-Extension phase

Study visit	Study Week in Post-Extension Phase[e]	Time	PK Collection Number[b]	PK Sample Number[c]	Sample Volume[d] (mL)
Visit 401	Week n+12	Pre-dose	1101/1201	1101	2 mL (blood)
Visit 402	Week n+24	Pre-dose	1102/1202	1102	2 mL (blood)
Visit 403	Week n+36	Pre-dose	1103/1203	1103	2 mL (blood)
Visit 404	Week n+48	Pre-dose	1104/1204	1104	2 mL (blood)
Visit 405	Week n+60	Pre-dose	1105/1205	1105	2 mL (blood)
Additional[a]		Pre-dose	11801/12901, 11802/12902, 11803/12903,…	11001, 11002, 11003, . . .	2 mL (blood)

[a] Additional visit at two weeks after any everolimus dose adjustment or start/change in dose of the CYP3A4/PgP inhibitor/inducer
[b] The first PK collection number refers to the first dose of everolimus received after collection of the PK sample, while the second PK collection number is the last dose the subject received prior to the collection of the PK sample
[c] The PK sample number uniquely identifies the PK sample for a particular visit and should be written on the tube label of samples sent to the central PK lab.
[d] Sample volume is dependent on patient's age. 0.5 mL for 1 to <2, 1 mL for 2 to ≤ 6, and 2 mL for > 6
[e] n = the week at which the patient's last scheduled Extension phase visit occurred

[redacted]

Table 7-7 PK Sample Log Table for Carbamazepine

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	1/201	1	~1mL (plasma)
Visit 2	Week 0	Pre-dose	2/202	2	~1mL (plasma)
Visit 3	Week 1	Pre-dose	3/203	3	~1mL (plasma)
Visit 5	Week 3	Pre-dose	4/204	4	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-8 PK Sample Log Table for Oxcarbazepine

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	11/211	11	~1mL (plasma)
Visit 2	Week 0	Pre-dose	12/212	12	~1mL (plasma)
Visit 3	Week 1	Pre-dose	13/213	13	~1mL (plasma)
Visit 5	Week 3	Pre-dose	14/214	14	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-9 PK Sample Log Table for Clonazepam

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	21/221	21	~1mL (plasma)
Visit 2	Week 0	Pre-dose	22/222	22	~1mL (plasma)
Visit 3	Week 1	Pre-dose	23/223	23	~1mL (plasma)
Visit 5	Week 3	Pre-dose	24/224	24	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b]Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-10 PK Sample Log Table for Diazepam

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	31/231	31	~1mL (plasma)
Visit 2	Week 0	Pre-dose	32/232	32	~1mL (plasma)
Visit 3	Week 1	Pre-dose	33/233	33	~1mL (plasma)
Visit 5	Week 3	Pre-dose	34/234	34	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

[redacted]

Table 7-11 PK Sample Log Table for Clobazam

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	41/241	41	~1mL (plasma)
Visit 2	Week 0	Pre-dose	42/242	42	~1mL (plasma)
Visit 3	Week 1	Pre-dose	43/243	43	~1mL (plasma)
Visit 5	Week 3	Pre-dose	44/244	44	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-12 PK Sample Log Table for Felbamate

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	51/251	51	~1mL (plasma)
Visit 2	Week 0	Pre-dose	52/252	52	~1mL (plasma)
Visit 3	Week 1	Pre-dose	53/253	53	~1mL (plasma)
Visit 5	Week 3	Pre-dose	54/254	54	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-13 PK Sample Log Table for Phenobarbital

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	61/261	61	~1mL (plasma)
Visit 2	Week 0	Pre-dose	62/262	62	~1mL (plasma)
Visit 3	Week 1	Pre-dose	63/263	63	~1mL (plasma)
Visit 5	Week 3	Pre-dose	64/264	64	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

[redacted]

Table 7-14 PK Sample Log Table for Phenytoin

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	71/271	71	~1mL (plasma)
Visit 2	Week 0	Pre-dose	72/272	72	~1mL (plasma)
Visit 3	Week 1	Pre-dose	73/273	73	~1mL (plasma)
Visit 5	Week 3	Pre-dose	74/274	74	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-15 PK Sample Log Table for Primidone

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	81/281	81	~1mL (plasma)
Visit 2	Week 0	Pre-dose	82/282	82	~1mL (plasma)
Visit 3	Week 1	Pre-dose	83/283	83	~1mL (plasma)
Visit 5	Week 3	Pre-dose	84/284	84	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-16 PK Sample Log Table for Topiramate

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	91/291	91	~1mL (plasma)
Visit 2	Week 0	Pre-dose	92/292	92	~1mL (plasma)
Visit 3	Week 1	Pre-dose	93/293	93	~1mL (plasma)
Visit 5	Week 3	Pre-dose	94/294	94	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

[redacted]

Table 7-17 PK Sample Log Table for Valproic acid

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	101/301	101	~1mL (plasma)
Visit 2	Week 0	Pre-dose	102/302	102	~1mL (plasma)
Visit 3	Week 1	Pre-dose	103/303	103	~1mL (plasma)
Visit 5	Week 3	Pre-dose	104/304	104	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

Table 7-18 PK Sample Log Table for Zonisamide

Study visit	Study Week	Time	PK Collection Number[a]	PK Sample Number	Sample Volume[b]
Visit 1	Week -8	Pre-dose	111/311	111	~1mL (plasma)
Visit 2	Week 0	Pre-dose	112/312	112	~1mL (plasma)
Visit 3	Week 1	Pre-dose	113/313	113	~1mL (plasma)
Visit 5	Week 3	Pre-dose	114/314	114	~1mL (plasma)

[a] The first PK collection number is for current dose, while the second PK collection number is for last dose the subject received prior to the collection of the PK sample
[b] Sample collection is dependent on patient's weight. Patients weighing ≥ 12 kg to ≤ 20 kg will not have AED PK samples taken. Patients ≤ 6 will have 5.2 mL blood taken to yield 2.6 mL plasma for three .87 mL aliquots of plasma. Patients > 6 will have 6 mL blood taken to yield 3 mL plasma for 3 1 mL aliquots of plasma.

7.2.4.1 Analytical method

Everolimus concentrations in whole blood will be determined by a LC-MS/MS method following solid phase extraction. The method has a lower limit of quantification (LLOQ) of 0.300 ng/mL.

Plasma concentrations of Clobazam, N-desmethyl Clobazam; Clonazepam and Diazepam will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) 1, 1, 1 and 2 ng/mL, respectively.Plasma concentrations of Felbamate, Phenytoin will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) 50 and100 ng/mL, respectively.

Plasma concentrations of Primidone and Zonisamide will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) 10 and 20 ng/mL, respectively.

Concentrations below the LLOQ will be reported as 0 ng/mL or 0 μM or 0 μg/mL and missing samples will be labeled accordingly.

Additional details regarding the analytical Method for quantification of everolimus (and other analytes, as applicable) shall be described in the Bioanalytical Report issued at the final of the Clinical Study Report.

[redacted]

7.2.4.2 Other assessments

7.2.4.2.1 IRT Registration

After a patient signs the informed consent form, they must be registered into the IRT system to obtain the patient number, and enter the patient to the study. Instructions should be followed as per the IRT manual.

7.2.4.2.2 TSC genetic testing

In addition to the safety and efficacy assessments described above, blood will be taken at the Baseline visit to measure TSC genetic markers (TSC1 / TSC2) if they have not been tested prior to entering the trial. If these tests have been analyzed and reported prior to study start, the date of testing, results of those tests, and the lab that performed the test will be collected.

7.2.5 Patient reported outcomes

The following scales will be completed used to assess all health-related quality of life (HRQoL) issues. One instrument will be used per subject determined by the subject's chronological age at Baseline. These questionnaires should be completed only by the person who has epilepsy or the parent/caregiver for children <10 years old. The same questionnaires completed at Baseline will continue to be completed throughout the study. This will be collected at Baseline, Week 18 (End of Core) and End of Treatment for the Extension phase, see Table 7-1.

- Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) for children ≤10 years old with epilepsy
- Quality of Life in Epilepsy Inventory for Adolescents – 48 (QOLIE-AD-48) for Adolescents 11-17 years old with epilepsy
- Quality of Life in Epilepsy Inventory -31- Problems (QOLIE-31-P) for adults ≥ 18 years old with epilepsy

In situations where completion of the instrument (QOLIE-AD-48 and QOLIE-31-P) by the subject is required, but the subject is either a) unable to sign the instrument, or b) capable of indicating the correct response but physically incapable of marking the score sheet, the subject may be assisted by a parent or caregiver in completing the instrument. No other assistance is permissible in order to maintain the validity of the results.

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.

[redacted]

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

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

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

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 the EOT eCRF.

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

As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates or ongoing at end of study)
- Its relationship to the study treatment (suspected or not suspected)
- Action taken with respect to study or investigational treatment (no action taken, study drug dosage adjusted/ temporarily interrupted or permanently discontinued).
- Whether medication or therapy was given (concomitant medication/non-drug therapy given)
- 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 the study treatment, the interventions required to treat it, and the outcome.

[redacted]

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

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

8.1.3 Adverse events of special interest

In clinical trials, everolimus has been associated with infections (including exacerbation, aggravation or reactivation of pre-existing infections), and serious cases of hepatitis B reactivation, including fatal outcome. Infections and reactivation of infections is an expected event during periods of immunosuppression.

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal ones) and proteinuria. Renal function will be monitored throughout the study.

Also in clinical trials, everolimus has been associated with noninfectious pneumonitis, stomatitis, hyperglycemia, hypophosphatemia, and dyslipidemia. These events will be monitored throughout the study as described in Section 6.2.5.

Additional events associated with everolimus in clinical trials include hemorrhages, thrombotic and embolic events, cytopenias, cardiac failure, amenorrhea, male infertility, and hypersensitivity reactions. Potential risks also include intestinal obstruction/ileus, pancreatitis, and cholelithiasis.

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect

[redacted]

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

8.2.2 Reporting

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

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. 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 each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, except for countries applied with local Novartis operation procedure in local languages, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department as managed by local organizations.

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 investigator folder 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 study 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 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

8.4 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the 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 study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

[redacted]

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

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be constituted prior to the randomization of the first patient. The DMC is an external independent group including at least two physicians with expertise in epilepsy and/or TSC and one statistician. The DMC will perform the first safety review using a data cutoff 6 months after randomization of the first patient or when 100 patients have received treatment for 4 weeks (whichever occurs first), and every 6 months thereafter until the Core Database Lock, unless otherwise requested by the Chairman of the DMC. The DMC will also receive reports on a regular basis on all SAEs reported for this trial. No interim analysis is planned. Recruitment will not be interrupted unless otherwise requested by the Chairman of the DMC.

Details on the membership, responsibilities and working procedures of the DMC will be described in the DMC Charter.

8.7 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial (i.e., not members of the DMC) and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in the SC Charter.

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

[redacted]

- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

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

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

9.2 Site monitoring

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

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

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

9.3 Data collection

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.

In this study the Vineland Scales are considered paper CRFs, designated investigator staff must record the information required by the protocol onto the Vineland Scales that are printed on multi-

[redacted]

part, non-carbon-required paper. Field monitors will review the Vineland Scales for completeness and accuracy and instruct site personnel to make any required corrections or additions. The harvested Vineland Scales will be forwarded to Novartis (or designated CRO). The carbon copies will remain on site as source document.

The Principal Investigator is responsible for assuring that the data entered into eCRFs and on Vineland Scales is complete, accurate, and that entry and updates are performed in a timely manner.

An IRT system will be used for drug dispensing and titration purposes for this study. There will be regular reports of enrollment at site activity. In order to maintain the blind, there will data transfers of operational details only from IRT until analysis of the Core data. After the Core data have been analyzed, regular full data transfers will be established.

Safety labs will be collected centrally and data transferred to the study database, at regular intervals. The C-SSRS will be administered via IVRS, and there will be regular transfers of these data. PK analysis will also be done at a central lab. In order to maintain the blind, the PK results will only be transferred at the time of analysis of the Core data. DTI MRI and EEG performed will be transmitted by the sites to the CRO designated by Novartis to undergo central review. Refer to Appendix A for further details.

9.4 Database management and quality control

For Vineland Scales used in this study, data will be entered into a fully validated study database by Novartis Data Management personnel (or designated CRO). Following entry from the Vineland Scales, the data are systematically checked by Novartis Data Management personnel (or designated CRO) using programmed checks and data review tools/reports. 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 on the corresponding eCRF. Designated investigator site staff are required to respond promptly to queries. Novartis Data Management personnel (or designated CRO) will make any necessary changes to the data.

For the eCRFs used in this study, 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.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an IRT. The system will be supplied by a

[redacted]

vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

10 Statistical methods and data analysis

The data cut-off date for the primary efficacy and safety analyses will be when all patients have completed the Core phase or have discontinued early. At that time, all data from the Core phase will be available as well as part of the Extension phase data. The analyses for the reports will thus cover both periods:

- The main focus will be on descriptive and inferential comparisons of both everolimus arms versus placebo on efficacy and safety in the Core phase.
- Descriptive efficacy and safety analyses on Extension phase data will also be conducted in order to explore the longer term effects of everolimus.

The second data cut-off will be at the end of the extension phase, which is planned 48 weeks after the last patient completes the Core phase, and which will be used for the final report of the Extension phase. Earlier updates of the Extension phase data are not currently planned, but may be performed if needed. A final data cutoff will be at the end of the Post Extension phase, which is planned on October 30, 2017.

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure. This will be the primary analysis set for all Core phase efficacy analyses.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication in the Core Phase, and had at least one post-baseline safety assessment in the Core Phase (where the statement that a patient had no adverse event (on the Adverse Events CRF) constitutes a safety assessment). Patients will be analyzed according to the study treatment (regimen) they actually received. This will be the primary analysis set for all Core phase safety analyses.

[redacted]

A precise definition of "actually received", will be added in the Report and Analysis Plan (RAP).

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the CSP.

Protocol deviations leading to exclusion from the PPS are:

- Absence of diagnosis of TSC or partial-onset epilepsy.
- Baseline phase with less than 16 partial-onset seizures or at least 21 days seizure-free.
- Previously failed less than two sequential regimens of single or combined AEDs.
- Use of more than 3 concomitant AEDs in the baseline phase or the core phase AEDs.
- Non-use of concomitant AEDs in the baseline phase or the core phase.
- Use of a different 1 to 3 concomitant AEDs in the Core phase to that in the Baseline phase.
- Rescue medication during the Core phase modified beyond the accepted limits defining rescue medication.
- Study treatment received different from treatment assigned by randomization.
- Missing seizure information on > 50% of days in the Core phase.

10.1.4 Long-Term Evaluation Set

The Long-Term Evaluation Set is intended to capture all data on everolimus in the trial, from the Core Phase, the Extension Phase and the Post Extension Phase. It consists of all patients who received at least one dose of everolimus in the trial and have at least one efficacy/safety measure. Patients will be analyzed as a single everolimus group as well as separately according to their randomized treatment arm in the Core phase (i.e., everolimus trough ranges of 9-15 ng/ml and 3-7 ng/ml, or for patients originally randomized to placebo who enter the extension phase, everolimus trough range of 3-15 ng/ml). This analysis set will be used for long-term efficacy and safety analyses.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics will be summarized descriptively by treatment group for the FAS. Categorical data will be presented by frequencies and percentages. For continuous data the mean, standard deviation (SD), median, 25^{th} and 75^{th} percentiles, minimum and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies)

10.3.1 Study medication

Duration of study treatment exposure, cumulative dose (mg/m^2) and dose intensity (mg/m^2/day) will be summarized by treatment group. The number of patients with dose changes/interruptions will be presented by treatment group, along with reasons for the dose change. These analyses will be conducted over the Core phase on the Safety set, and over the extension phase on the Long-Term Evaluation set.

[redacted]

10.3.2 Concomitant medication

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and treatment arm by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. These summaries will be presented separately for anti-epileptic drugs versus other types of concomitant medications.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed. The Safety Set and the Long-Term Evaluation Set will be used for all above-mentioned concomitant medication tables and listings.

10.4 Primary objective

The primary objective is to compare the reduction in frequency of partial-onset seizures on each of two trough ranges of everolimus (3-7 ng/mL and 9-15 ng/mL) versus placebo in patients with TSC who have refractory partial-onset seizures and are already receiving one to three AEDs.

10.4.1 Variable

The regulatory requirements for demonstrating efficacy of an anti-epileptic medication differ between Europe and US: whereas the EMA prefers response rate to be the primary variable, the FDA prefers percentage reduction in seizure frequency. It is understood that each Agency will use their preferred variable as the primary variable, with the other (non-primary) variable being used in a supportive analysis. As each Agency will only use their preferred primary variable to make a decision on the primary objective, the full alpha level can be used for each Agency's primary variable, without correction for multiplicity.

10.4.1.1 EMA primary variable: response rate

The EMA primary variable is response rate in the maintenance period of the Core phase, determined using counts of partial-onset seizures (as defined in **Inclusion Criterion 4a**) from patient seizure diaries (see Section 7.2.2.1) and the following definitions:

- Average weekly seizure frequency in the Baseline phase (SF_B) = 7 × number of partial-onset seizures recorded over the 8 week prospective Baseline phase ÷ number of days with evaluable seizures in the prospective Baseline phase.
- Average weekly seizure frequency in the maintenance period of the Core phase (SF_M):
  - If patient does not discontinue during the 6 week titration phase, SF_M = 7 × number of partial-onset seizures recorded during the maintenance period of the Core phase ÷ number of days with evaluable seizures in the maintenance period of the Core phase.
  - Otherwise, SF_M = 7 × number of partial-onset seizures recorded during the titration period of the Core phase ÷ number of days with evaluable seizures in the titration period of the Core phase.

[redacted]

That is, patients who discontinue prior to the maintenance period have seizure frequency determined using their data from the titration period, thereby assuring that all patients with seizure data in the Core phase have a value for SF_M.

- Percentage reduction from baseline in average weekly seizure frequency during the maintenance period of the Core phase (% Red) = $100 \times (SF_B - SF_M) \div SF_B$.

A responder is a patient with ≥ 50% reduction from baseline in average weekly partial-onset seizure frequency during the maintenance period of the Core phase, that is, when % Red ≥ 50.

10.4.1.2 FDA primary variable: percentage reduction in seizure frequency

The FDA primary variable is percentage reduction from baseline in average weekly frequency of partial-onset seizures during the maintenance period of the Core phase, and is defined by the variable % Red in Section 10.4.1.1 above.

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 EMA primary variable: response rate

Response rate in the maintenance period of the Core phase will be compared between each everolimus arm versus the placebo arm, according to a Bonferroni-Holm procedure, assuring an overall experiment-wise alpha level of 2.5% one-sided. Cochran-Mantel-Haenszel (CMH) chi-square tests will be used (implemented via SAS procedure FREQ with CMH option in the TABLES statement), stratified by age subgroup at randomization (the randomization stratification factor, consisting of 4 subgroups: 1 to < 6, 6 to < 12, 12 to < 18, ≥18 years). The p-value will be obtained from the "General association" CMH statistic.

The statistical hypotheses are

H_{01}: $RR_{EVE1} \leq RR_{PLB}$ versus H_{11}: $RR_{EVE1} > RR_{PLB}$, and

H_{02}: $RR_{EVE2} \leq RR_{PLB}$ versus H_{12}: $RR_{EVE2} > RR_{PLB}$

where RR_{EVE1} is the probability of response on the everolimus 3-7 ng/mL trough arm, RR_{EVE2} is the probability of response on the everolimus 9-15 ng/mL trough arm, and RR_{PLB} is the probability of response on the placebo arm.

Response rates will be provided with exact 95% confidence intervals (Clopper and Pearson, 1934).

In addition, the odds ratio will be used as a measure of association between treatment and response. It will be derived for each everolimus arm versus placebo from a logistic regression model (implemented using SAS procedure LOGISTIC, with treatment specified as an explanatory variable in the CLASS statement), stratified by age subgroup at randomization. The two odds ratios will be presented with two-sided 95% Wald confidence limits.

10.4.2.2 FDA primary variable: percentage reduction in seizure frequency

Percentage reduction in seizure frequency in the maintenance period of the Core phase will be compared between each everolimus arm versus the placebo arm, according to a Bonferroni-Holm procedure, assuring an overall experiment-wise alpha level of 2.5% one-sided. Rank ANCOVA will be used (implemented via SAS procedures RANK, REG and FREQ), with

[redacted]

baseline average weekly seizure frequency as covariate, and stratified by age subgroup at randomization.

The statistical hypotheses are:

H_{01}: $\mu_{EVE1} \leq \mu_{PLB}$ versus H_{11}: $\mu_{EVE1} > \mu_{PLB}$, and

H_{02}: $\mu_{EVE2} \leq \mu_{PLB}$ versus H_{12}: $\mu_{EVE2} > \mu_{PLB}$

where μ_{EVE1} is the population mean of the reduction in seizure frequency for the everolimus 3-7 ng/mL trough arm, and where μ_{EVE2} and μ_{PLB} are the equivalent quantities for the everolimus 9-15 ng/mL trough arm and the placebo arm.

The median percentage reduction from baseline will be presented for each everolimus arm versus the placebo arm, along with 95% confidence intervals computed using the bootstrap percentile method.

10.4.3 Handling of missing values/censoring/discontinuations

Patients with no data in their seizure diary during the Core phase will be assumed to be non-responders for the EMA primary analysis, and to have a percentage reduction from baseline in seizure frequency of 0% for the FDA primary analysis. In addition, in case of one or more individual days with missing seizure information within a period, those days are excluded from the period duration when computing the standardized seizure frequency over the period (e.g. in case 3 seizures have been reported over a period of 28 days, but one of those 28 days had missing seizure evaluation, the seizure frequency will be computed as 3 seizures over 27 days and not 3 seizures over 28 days).

10.4.4 Supportive and sensitivity analyses

For the EMA primary variable on response rate, a supportive analysis will be the FDA primary analysis on percentage reduction in seizure frequency, and vice versa.

The primary analysis of both the EMA and FDA primary variables will be repeated in the Per Protocol Set.

In addition, sensitivity analyses will be conducted in the FAS to assess robustness of the primary analysis to (i) patient discontinuation before the end of the Core phase, and (ii) the calculation of seizure frequency across the entire Core phase (i.e., titration period as well as maintenance period).

For (i), the sensitivity analysis will assume no change from baseline in seizure frequency for patients discontinuing in the Core phase, whereas the primary analysis uses the actual seizure frequency calculated up to the day of discontinuation. Response rate and percentage change from baseline in seizure frequency will be recalculated for this sensitivity analysis and analyzed per the primary analysis.

For (ii), the sensitivity analysis will use the average weekly seizure frequency over the entire Core phase, that is, over the 6-week titration period plus the 12-week maintenance period. This compares with the primary analysis where titration period data is not used to calculate average weekly seizure frequency if the patient continues into the maintenance period. The variable used in the sensitivity analysis, labeled SF_{TM} is defined as follows:

[redacted]

- Average weekly seizure frequency in the entire Core phase (SF_{TM}) = 7 × number of seizures recorded over the entire Core phase (titration plus maintenance) ÷ number of days with evaluable seizures in the entire Core phase (titration plus maintenance).

Response rate and percentage reduction in seizure frequency will be re-calculated using SF_{TM} instead of SF_M, and analyzed as per the primary analysis.

Table 10-1 Supportive and sensitivity analyses for primary objective

	Variable	Population	Time Period	Variable for seizure frequency	Rule for discontinuations
EMA	% reduction in seizure frequency	FAS	Maintenance	SF_M	None
	Response rate	PPS	Maintenance	SF_M	None
	Response rate	FAS	Maintenance	SF_M	$SF_M = SF_B$
	Response rate	FAS	Titration + maintenance	SF_{TM}	None
FDA	Response rate	FAS	Maintenance	SF_M	None
	% reduction in seizure frequency	PPS	Maintenance	SF_M	None
	% reduction in seizure frequency	FAS	Maintenance	SF_M	$SF_M = SF_B$
	% reduction in seizure frequency	FAS	Titration + maintenance	SF_{TM}	None

FAS = Full Analysis Set, PPS = Per Protocol Set, SF_M = average weekly seizure frequency in the maintenance period of the Core phase, SF_{TM} = average weekly seizure frequency in the entire Core phase (titration + maintenance), SF_B = average weekly seizure frequency in the Baseline phase.

10.5 Secondary objectives

Secondary objectives are described below, separated into sections for efficacy, safety, pharmacokinetics and patient-reported outcomes.

10.5.1 Efficacy objectives

Seizure freedom

The ability to completely suppress partial-onset seizures will be assessed by determining the proportion of patients remaining seizure-free during the maintenance period of the Core phase. A patient will be considered seizure-free if the percentage reduction from baseline in average weekly frequency of partial-onset seizures during the maintenance period of the Core phase is 100%, that is, if % Red = 100 using the definitions given in Section 10.4.1.1. Patients with no data in their seizure diary during the Core phase will be assumed not to be seizure-free.

The seizure-free rates for each treatment arm will be presented along with exact 95% confidence intervals (Clopper and Pearson, 1934). The odds ratio for each everolimus arm versus placebo, plus the Wald 95% confidence interval, will be derived from a logistic regression model stratified by age subgroup at randomization.

A sensitivity analysis will be performed where patients who discontinue during the Core phase are assumed not to be seizure-free even if % Red = 100.

[redacted]

Proportion of patients with at least 25% reduction in seizure frequency

This objective is assessed by determining the proportion of patients in each treatment arm with at least a 25% reduction from baseline in average weekly frequency of partial-onset seizures during the maintenance period of the Core phase, defined by % Red ≥ 25 using the definitions given in Section 10.4.1.1. Patients with no data in their seizure diary during the Core phase will be assumed to have less than a 25% reduction.

The proportion of patients with at least a 25% reduction will be presented in each treatment arm along with exact 95% confidence intervals (Clopper and Pearson, 1934). The odds ratio for each everolimus arm versus placebo, plus the Wald 95% confidence interval, will be derived from a logistic regression model stratified by age subgroup at randomization.

Distribution of reduction from baseline in seizure frequency

The reduction from baseline in average weekly frequency of partial-onset seizures in the maintenance period of the core phase will be categorized into six levels using the variable % Red defined in Section 10.4.1.1. The six levels will be: (≤ -25% (exacerbation); > -25% to < 25% (no change); ≥ 25% to < 50%; ≥ 50% to < 75%; ≥ 75% to < 100%; 100% (seizure-freedom)). Patients with no seizure diary data in the Core phase will be assigned as missing.

The proportions of patients in each category will be presented for each treatment arm.

Seizure-free days

The frequency of partial-onset seizure-free days per 28 days during the maintenance period of the Core phase will be obtained for each patient, calculated as 28 × number of partial-onset seizure-free days in the maintenance period of the Core phase ÷ number of non-days with evaluable seizures in the maintenance period of the Core phase. A similar quantity will be calculated for the Baseline phase. Patients with no seizure data in the Core phase will be assumed to have the same number of seizure-free days as during the Baseline phase.

The change from baseline in frequency of partial-onset seizure-free days per 28 days will be summarized by treatment arm (mean, standard deviation, range). Mean differences between each everolimus arm and the placebo arm in change from baseline in frequency of seizure-free days will presented, along with 95% confidence intervals.

Treatment duration

Treatment duration is defined as the time from randomization until the date of permanent study treatment discontinuation (for any reason) during the entire Core phase (i.e., including the titration period and the maintenance period). Patients who complete the Core phase without discontinuing will have treatment duration censored on the last day of the Core phase.

The treatment duration distributions in each arm will be presented descriptively in the FAS using Kaplan-Meier curves, from which summary statistics will be determined, including the median treatment duration and the proportions of patients on treatment at 6 and 12 weeks. These statistics will be given as point estimates with 95% confidence intervals. The hazard ratio (and two sided 95% confidence interval) for each everolimus arm versus placebo will be obtained from a Cox proportional hazards model stratified by age subgroup at randomization.

[redacted]

Long-term efficacy evaluation over the extension phase

Descriptive statistics on percent reduction from baseline in partial onset seizure-frequency, responder rate and seizure-free days will be computed by time interval over the extension phase on the Long-Term Evaluation Set.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined normal ranges. Other safety data (e.g., electrocardiogram, vital signs) will be considered as appropriate. All safety data will be listed.

For the analysis of safety data from the Core phase of the study, the overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication in Core phase
2. on-treatment period: from day of first dose of study medication in the Core phase until 30 days after last dose of study medication in the Core phase, except for patients who enter the Extension phase, for whom the on-treatment period lasts until the day before starting everolimus in the Extension phase
3. post-treatment period: starting the day after the end of the on-treatment period.

10.5.2.2 Adverse events (AEs)

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

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

Specific safety event categories (SECs) will be monitored during the study, consisting of one or more well-defined adverse events which are similar in nature and for which there is a specific clinical interest to epilepsy/TSC or the study treatment. SECs of interest include for example CNS-related events, stomatitis/oral mucositis, infections, renal events and amenorrhea. This list is not exhaustive and all the principles guiding the definition and use of those categories will be further documented in the Report and Analysis Plan (RAP).

For each specified SEC, number and percentage of patients with at least one event that is part of the SEC will be reported.

[redacted]

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high
- classification to compare baseline to the worst on-treatment value
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the RAP.

10.5.2.4 Other safety data

Neuropsychological assessments

Changes from baseline in neurodevelopmental, neurobehavioral and neurocognitive assessments and tests of cognitive function will be listed and summarized descriptively by treatment group. The instruments/questionnaires that will be used include:

- Vineland Adaptive Behavior Scales 2nd Edition (VABS-II)
- Wechsler Non-Verbal Scale of Ability

Vital signs

Definitions of notably abnormal results will be defined in the RAP. Analysis will consist of

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

Columbia Suicide Severity Reporting Scale (C-SSRS)

C-SSRS data will be mapped to Columbia Classification Algorithm for Suicide Assessment (C-CASA) as per FDA guidance on suicidality (Food and Drug Administration 2010). The proportion of patients who have completed suicide, suicide attempt, preparatory actions toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior without

[redacted]

suicidal intent will be summarized by treatment group. The number of patients with SAEs referring to a positive suicidal evaluation will be summarized by treatment group.

Growth Data

Growth data will only be analyzed as part of the long-term evaluation of everolimus among patients under the age of 18, i.e., using patients from the LTE Safety Set who were under 18 years of age on the start date of everolimus. Growth data will be summarized descriptively for each treatment group at each time point. These data consist of height, height velocity, weight, weight velocity, the age at thelarche and menarche for girls, the age at adrenarche for boys as well as the Tanner stage assessment. In addition, based on height data collected during the study and published reference height information, the height standard deviation score (SDS, also called z-score) will be computed for each patient at each time point as:

(height - mean height for that age category) / SD of height for that age category.

The same approach will be used to compute height velocity SDS, weight SDS and weight velocity SDS.

Descriptive statistics of these endpoints will be presented by time point and the z-scores will allow identification of potential outliers. Growth velocity during the trial will also be compared with growth velocity at baseline (if sufficient pre-baseline data are available).

10.5.2.5 Tolerability

Not applicable for this study.

10.5.3 Pharmacokinetics

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the lower limit of quantitation (LLOQ) or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Validity of PK samples will be confirmed by checking sampling time window and vomiting. Only confirmed PK concentrations will be used in the analyses.

Drug concentrations for each treatment group (for core phase only) and each visit will be summarized by descriptive statistics. Descriptive statistics of drug concentration will include arithmetic and geometric mean, median, SD, coefficient of variation (CV), geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation.

To evaluate the effects of everolimus on exposure of AEDs descriptive statistics will be used to compare the pre-dose concentrations of AEDs at Visits 1 and 2 (AED alone) with those at Visits 3 and 4 (AED plus everolimus).

To evaluate the impact of EIAED/CYP3A4 inducer and inhibitor on everolimus PK, a linear mixed model will be fitted to log-transformed C_{min} concentration at steady state including log-transformed dose, use of EIAED/CYP3A4 inducer and inhibitor and other factors as appropriate as covariates.

[redacted]

To explore the relationship between everolimus C_{min} and the response rate as defined for the primary analysis, a logistic regression model will be used to fit the response data using averaged C_{min} levels in the maintenance period of the core phase, stratifying by age subgroup at randomization and adjusting for additional risk factors if appropriate.

The relationship between everolimus C_{min} and selected safety endpoints will also be explored by an appropriate model-based approach.

10.5.4 Patient-reported outcomes

Quality of life will be assessed using three age-specific questionnaires as follows:

- Patients aged ≤ 10 years: Quality of Life in Childhood Epilepsy (QOLCE)
- Patients aged 11-17 years: Quality of Life in Epilepsy Inventory for Adolescents-48 (QOLIE-AD-48)
- Patients aged ≥ 18 years: Quality of Life in Epilepsy Inventory-31-Problems (QOLIE-31-P)

Descriptive statistics for the overall quality (QOL) score and subscale scores will be presented by time point and treatment group in the FAS for each questionnaire.

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

No interim analysis is planned for this study.

10.8 Sample size calculation

The sample size was chosen to provide adequate power for the primary objective comparing seizure frequency between each everolimus arm and the placebo arm. The sample size calculation provided here is based exclusively on response rate, the primary endpoint used by the EMA, but it is also expected to provide sufficient patients for the power of the FDA primary endpoint, percentage reduction in seizure frequency. This is because response rate is a binary transformation of percentage reduction in seizure frequency, and therefore likely to be less sensitive owing to the loss of information going from a continuous variable to binary.

It was assumed that response rates would be 15% in the placebo arm and 35% in each of the two everolimus arms. That is, there was no *a priori* strong expectation that the higher targeted trough everolimus arm 9-15 ng/mL would deliver a higher response rate than the lower targeted trough everolimus arm 3-7 ng/mL, as better efficacy may be mitigated by worse tolerability. For this reason, the testing strategy was to simultaneously compare each pairwise comparison, splitting the significance level, rather than testing hierarchically starting with the higher trough arm for example.

Using nQuery version 6.1 it was determined that a sample size of 355 patients would ensure 90% power for each of the primary comparisons of each everolimus arm versus placebo, assuming one-sided 1.25% significance levels for each CMH chi-square test, and assuming balanced randomization (i.e., 115 patients per randomization arm).

Table 10-2 Sample size and power for primary objective

Comparison	One-sided alpha	Response rates under alternative hypothesis	Sample Size	Power
Everolimus 3-7 ng/mL arm versus Placebo arm	1.25%	35% vs. 15%	230 (115 vs. 115)	90%
Everolimus 9-15 ng/mL arm versus Placebo arm	1.25%	35% vs. 15%	230 (115 vs. 115)	90%

Approximately 5 months after the first patient was randomized, a human error was identified which caused the IRT system not to perform dose titrations despite C_{min} values outside the targeted trough range. The IRT system was updated the same day. By that time a total of 47 patients had already passed their Week 2 assessment, the point at which the first dose titration could have been made.

After an investigation into the potential impact of this error on the study power, it was noted that placebo patients would be unaffected, and in all likelihood, the majority of patients in the everolimus 3 to 7 ng/ml arm would be expected to achieve everolimus concentrations within the targeted range. However, since few patients randomized to the everolimus 9 to 15 ng/ml arm would be expected to achieve adequate dosing, it was decided to increase the sample size in the everolimus 9 to 15 ng/ml arm by 10 patients.

[redacted]

The choice of 10 patients was made on the following grounds. Based on the pattern of complete and incomplete blocks, up to 18 of the 47 potentially affected patients may have been on the everolimus 9 to 15 ng/ml arm. As a worst case, assume all 18 patients were under-dosed and achieved everolimus concentrations in the 3-7 ng/ml range, and assume that this trough range is no better than placebo. Then at the end of the study, among the 115 planned patients on the everolimus 9 to 15 ng/ml arm, 18 patients will have a 15% chance of being responders (i.e., as placebo arm patients) and 97 will have a 35% chance. Overall this makes an expected response rate in the everolimus 9 to 15 ng/ml arm of 31.9%, in which case the power for the comparison with the placebo arm drops to 78%. Other more realistic scenarios lead to a smaller loss in power, for example with 12 patients under-dosed and subject to placebo arm response rate, the power is 83%, with 6 patients it is 87%. The sample size increase was chosen to protect against loss in power for these more realistic scenarios, where the addition of 10 patients to the everolimus 9-15 ng/ml arm improves power to 85% for 12 under-dosed patients and to 88% for 6 under-dosed patients.

The sample size increase of 10 patients will be made by inserting a number of blocks with randomization ratio of 1:1:2 in favor of the everolimus 9 to 15 ng/ml arm, with the planned sample size becoming 355 patients (115 on placebo arm, 115 patients on everolimus 3 to 7 ng/ml arm and 125 patients on everolimus 9 to 15 ng/ml arm; overall randomization ratio of 1:1:1.09). The required modification of the randomization list will be overseen by an Independent Randomization Expert, a Novartis employee who is not part of the study team.

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

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

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.2.

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.

[redacted]

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.

13 References (available upon request)

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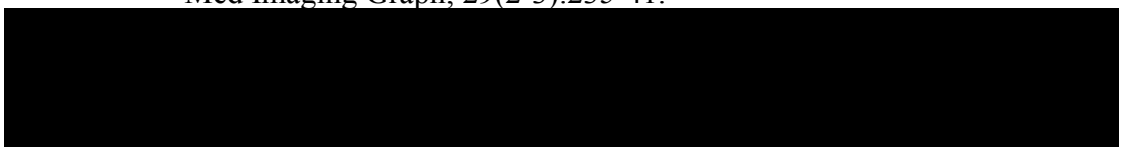

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14 Appendix A: Using Diffusion Tensor Imaging (DTI) with Tractography to Measure the Treatment Effect of Everolimus in Tuberous Sclerosis Complex (TSC) Patients with Epilepsy: An EXIST-3 Sub-study

14.1 SUMMARY OF DTI SUB-STUDY OBJECTIVES AND RATIONALE

Tuberous sclerosis complex (TSC) is a genetic disorder with an incidence at birth of 1 in 6000. This disorder is characterized by the development of benign tumors in multiple organ systems, including the brain. The primary neurological manifestations of TSC are epilepsy, mental retardation and autism. Epilepsy is most common, occurring in 80-90% of patients, and often the seizures are severe, unremitting, and uncontrolled by current anticonvulsant medications. Strong preclinical evidence and more recent phase II human clinical trials reveal that treatment with the mTOR inhibitor everolimus can improve seizure control in TSC patients who are refractory to conventional anticonvulsant treatments. EXIST-3 is a phase III randomized, placebo-controlled, double-blind clinical trial designed to confirm these findings. We hypothesize that improvement in white matter integrity and connectivity, in conjunction with reduced tuber epileptogenicity, by everolimus is an important if not essential mechanism of the everolimus anti-seizure effect. We propose to assess this hypothesis through analysis of white matter integrity and connectivity using diffusion tensor imaging (DTI) with tractography and advanced EEG technology in a subset of EXIST-3 participants through the following aims:

- **Assess the hypothesis that DTI measures of white matter integrity improve after treatment with everolimus in epilepsy patients with TSC.** Regions of interest (ROI) will be determined and analyzed for before and after treatment changes in the everolimus and placebo arms.
- **Assess the hypothesis that overall and specific tuber epileptogenicity improves with treatment with Everolimus.** 1 hour EEG utilizing a customized EEG protocol for recording high frequency oscillations (HFO) will be obtained at time points coinciding with MRI DTI studies. HFO measures (gamma, ripples, fast ripples) will be determined.

14.2 BACKGROUND

Previous clinical trials have demonstrated clear efficacy and favorable clinical tolerability of everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR) in the treatment of subependymal giant cell astrocytoma (SEGA) and angiomyolipoma (AML) in patients with tuberous sclerosis complex (TSC)(Bissler et al 2012; Franz et al 2012). FDA approval for these indications occurred in 2010 and 2012, respectively. Relevant to the current proposal, improvement in seizure frequency and other neurological and behavioral aspects of TSC has been seen in SEGA patients treated with everolimus(Krueger et al 2010). We recently completed a phase II clinical trial confirming these earlier results in TSC epilepsy patients without SEGA, in which seizure frequency was reduced in 17 of 20 subjects (median reduction = 73%) after 12 weeks of therapy (*clinicaltrials.gov:* NCT01070316, Krueger et al 2013). The current phase III double-blind randomized placebo controlled trial (EXIST-3, CRAD001 M2304) is designed to confirm these earlier phase II results. This sub-study of

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EXIST-3 subjects is designed to evaluate the value of diffusion tensor imaging (DTI) tractography accompanied by high frequency oscillations (HFO) EEG analysis as an exploratory measure of clinical benefit in TSC patients with epilepsy treated with everolimus.

As our understanding of TSC matures, it is becoming clear that non-tuber abnormalities, especially in the white matter (WM) and subcortical areas, are strongly associated with neurological outcome (Wong 2008; Tsai 2011). Diffusion tensor imaging (DTI), a specialized type of magnetic resonance imaging (MRI) of the brain that can be combined with tractography to determine fascicle structures and connections in matching brain anatomy (Ciccarelli et al 2008; Mori et al 1999), has been used to detect abnormities in TSC that appeared normal with conventional MRI techniques (Garaci et al 2004; Peng et al 2004; Luat et al 2007; Arulrajah et al 2009; Krishnan et al 2010, Simao et al 2010; Widjaja et al 2010). Furthermore, we have shown that DTI measures, such as fractional anisotropy (FA), radial diffusivity (RD), and mean diffusivity (MD), improve in TSC patients with SEGA treated with everolimus (Tillema et al 2012). Comparing baseline values with those acquired after 12-18 months of treatment, a significant change in FA was observed in the corpus callosum, internal capsule, and geniculocalcarine region ($p < 0.05$). Mean change in FA was 0.04 ($p < 0.01$), driven primarily by a significant decrease in RD, and was independent of SEGA response to treatment. These findings suggest that WM integrity can be improved with mTOR inhibition in TSC individuals and encourage systematic analysis of the relationship between DTI and everolimus treatment response in epilepsy patients with TSC.

Analysis of DTI with tractography in the current context can be further enhanced when accompanied with current state of the art advanced EEG analysis that includes high frequency oscillations (HFO EEG). HFO EEG is a powerful technique for examining the energy in any single frequency band as an indicator of oscillatory synchrony and therefore local functional integration. In preliminary experiments, we examined HFO patterns in children with TSC and epilepsy and found that HFO EEG analysis revealed a particularly high predictive value of epilepsy in otherwise asymptomatic individuals in TSC when compared to traditional EEG (Wu, Bebin, unpublished). Specifically, traditional EEG demonstrated a sensitivity of 83% and specificity of 50% (n=10), whereas HFO EEG was associated with 100% sensitivity and specificity (n=8)

EXIST-3 (CRAD001M2304) is a three-arm, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of two trough-ranges of everolimus given as adjunctive therapy in patients with TSC who have refractory partial-onset seizures. The study consists of three phases (1) baseline observation period x 8 weeks; (2) core treatment phase from randomization to primary endpoint x 18 weeks; and (3) extension phase from week 18 until up to 48 weeks after last patient has completed the core phase. Target enrollment for the overall study is approximately 355 subjects between ages 2 and 65 (or 1 and 65 in Europe), with partial-onset seizures refractory to current medical therapy (failed 2 or more anti-epileptic regimens), and diagnosis of TSC. The study will be conducted globally, involving 100-120 different sites. Evaluation of a subset of EXIST-3 patients (about 15 patients) will be used to assess the benefit of DTI tractography combined with HFO EEG analysis as an independent biomarker of everolimus efficacy.

A number of important considerations must be accounted for in ensuring the successful acquisition of comparable data at multiple sites. These include logistical factors such as study

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protocol compliance, compliance with HIPAA regulations, and technical performance factors of imaging equipment (Smith et al 2004; Zhou and Liu 2005: Keator et al 2008). For MRI, differences in scanner make, model, field strength, field homogeneity, slew rates, and image reconstruction may influence data acquisition (Friedman and Glover 2006a; Friedman and Glover 2006b). The quantitative assessment of acquired data may be influenced by the nature and sophistication of the post-acquisition image analysis, including approaches for identifying and compensating for certain image artifacts. Recent publications have described successful multi-site diffusion imaging protocols, with effective assessment and management of inter-site and intra-site variability related to site-dependent and time-varying characteristics of imaging equipment (Zhu et al 2011; Evans 2006). Best practice for data quality assessment is to estimate accuracy with respect to a gold-standard phantom, and to characterize measurement precision via one of test-retest imaging, imaging with multiple replications, or bootstrap estimation.

It became clear during the 2011 International TSC Research Conference in Washington DC that single site clinical trials in TSC were going to be limited in their impact and ability to move TSC clinical care forward, due to their limited size and scope. To address this need, the TSC-CRC was created, consisting of geographically-distributed medical centers across the USA each with a large TSC clinic directed by clinician with advanced expertise in TSC . [redacted]. The TS Alliance patient-advocacy organization provides some monetary support and also has key involvement aimed at helping identify areas of unmet need in TSC-related research and encouraging patient recruitment into TSC-CRC clinical trials. The success of the TSC-CRC is already demonstrated in the first 12 months of existence, having been awarded more than $12.5M from the National Institutes of Health for clinical trials targeting epilepsy and autism in TSC.

One of the current NIH-funded clinical trials of the TSC-CRC includes sophisticated DTI imaging and advanced HFO EEG analysis. As part of the study, the TSC-CRC already has identified personnel at each site familiar with acquisition and tasked specifically to ensure quality control. 3T MRI scanners at each of the sites will be calibrated every 6 months using both the American College of Radiology (ACR) and 'live human' (live volunteer who undergo repeated imaging at each site) phantoms to ensure DTI accuracy across all the sites (Friedman 2006; Zhu et all 2011; Evans 2006; Nagy et al 2007; Delakis et al 2004; Tofts et al 2000; Zou et al 2005). Similar standardization and quality assurance procedures are in place at each location for HFO EEG. The advantage of utilizing TSC-CRC sites to conduct this DTI sub-study in EXIST-3 is that this standardization across sites will not have to be newly created and supervised by Novartis and avoids duplicative effort and cost.

14.3 RESEARCH STRATEGY

14.3.1 Sub-Study Subjects

Up to 15 patients enrolled in EXIST-3 from US TSC-CRC sites will be eligible for participation in the DTI sub-study. Enrollment will be competitive across the US TSC-CRC sites until the target is achieved. Participation in the DTI sub-study will be considered optional, and not prevent enrollment into EXIST-3 if DTI sub-study participation is declined.

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14.3.2 Sub-Study Participation Criteria

Only patients enrolled in EXIST-3 will be eligible for participation in the DTI sub-study and same inclusion/exclusion criteria for EXIST-3 will apply for this DTI sub-study.

Inclusion criteria for participation in DTI sub-study:

- Meet all inclusion criteria for enrollment in EXIST-3
- Provide written, informed consent for participation in the optional DTI sub-study analysis

Exclusion criteria for participation in DTI sub-study:

- Ensure no exclusion criteria for enrollment in EXIST-3 apply
- Contraindications to MRI scanning, such as metal implants/non-compatible medical devices or medical conditions

14.3.3 Sub-Study Procedures

14.3.3.1 Overview

EXIST-3 consists of an 8 week baseline phase, 6 week titration phase, and 12 week maintenance phase. The DTI sub-study analysis entails two MRI sessions and two 1-hour EEG sessions. The first EEG and MRI will be performed prior to randomization and study drug initiation (visit 2, week 0) and will serve as the baseline. The follow-up EEG and MRI will be performed at the end of the core phase (visit 11, week 18). Blinding rules in place for EXIST-3 will remain in effect for the DTI sub-study analysis (DTI investigators will remain blinded to treatment group of participating subjects until final unblinding and analysis of entire EXIST-3 dataset).

14.3.3.2 Informed Consent

All prospective subjects and their families will have the DTI sub-study explained by a member of the research team or a member of their staff. Participation in the DTI sub-study will be optional and not required for participation in EXIST-3. The nature of sub-study tests and procedures will be explained together with potential hazards and possible adverse reactions. The written informed consent, and patient assent with parental permission, if applicable, will be obtained prior to the performance of any screening evaluation, per each site's IRB guidelines.

14.3.3.3 DTI Acquisition

Both structural and diffusion images will be acquired. Sedation will be used if needed to limit motion artifact during image acquisition. DTI data will be pre-processed with alignment to T1-weighted MPRAGE images to help compensate for eddy currents and patient motion to ensure maximum data quality. 3-Telsa MRI scanners will be used at all sites for all subject imaging in the DTI sub-study. Image acquisition protocols will be the same as those for the TACERN (TSC Autism Center of Excellence Network) study conducted by the TSC-CRC, to minimize need for duplicative standardization, allow comparison of results across studies, and to provide recommended TSC clinical standard of care brain surveillance imaging. Specific sequences will include anatomical imaging, diffusion tensor imaging, functional imaging, and post-gadolinium imaging.

14.3.3.4 HFO EEG Acquisition

As for DTI, EEG acquisition and recording protocols will be the same as those for the TACERN study conducted by the TSC-CRC, to minimize need for duplicative standardization, allow comparison of results across studies, and to provide recommended TSC clinical standard of care EEG recording. One hour of recording is generally sufficient for HFO analysis and negates the need for 24-hour EEG used in previous TSC everolimus clinical trials. Data will be acquired utilizing a 23 electrode enhanced version of the International 10-20 System, with 9mm gold-disc electrodes to yield a frequency resolution of 0.5Hz. Sedation for EEG is not allowed and if performed on the same day as MRI requiring sedation, EEG should be obtained prior to the MRI or on a different day. Subjects should be sleep-deprived as much as tolerated and scheduled for early to mid-morning or around subjects' usual nap times to increase the likelihood of both awake and sleep epochs being captured during the recording session.

14.3.3.5 Data Transfer for Central Analysis

Local sites will be able to review imaging and EEG studies for clinical and safety purposes, where previous examinations will be available for comparison. For the DTI sub-study, imaging and EEG data will be transferred to [redacted] for centralized analysis. Prior to transfer, all data will be anonymized at the local site with the study type, subject ID, and acquisition date as the only identifiers. The local site will retain a copy of the entire study data (MRI and EEG) until receipt by [redacted] is confirmed. Standard redundancy and backup procedures will be followed at [redacted] to ensure data is not lost or compromised until analysis is complete. TSC-CRC investigators involved in DTI and HFO EEG analysis will be given secure access to [redacted] servers with the relevant anonymized data sets necessary for the analyses outlined in Section 14.3.3.4.

14.3.4 Sub-Study Analysis and Statistical Considerations

14.3.4.1 Analytical Methods

Specific, reproducible, regions of interest (ROI) will be determined, following known anatomy, to evaluate multiple white matter regions. These will include (i) the genu and splenium of the corpus callosum, (ii) anterior and posterior limb of the internal capsule, and (iii) the geniculocalcarine tract. The following four tensor parameters will be determined for each of the three ROIs: fractional anisotropy, radial diffusivity, axial diffusivity and mean diffusivity, making a total of 12 different analyses. HFO EEG will be quantified in three frequency bands, by region corresponding to electrode and frequency, for gamma (30-100Hz), ripple frequencies (100-250Hz), and fast ripple frequencies (250-500Hz). Data from the regions will be combined, providing three EEG parameters for gamma, ripple and fast ripple frequencies.

Change from baseline in the 12 DTI parameters and the 3 EEG parameters will be summarized using appropriate descriptive statistics between the pooled everolimus arms and the placebo arm. Other endpoints include change from baseline in tuber burden, and change from baseline in number of regions of the brain with EEG abnormalities.

[redacted]

The sample size of about15 patients in this sub-study was chosen for practical reasons rather than on the basis of statistical power.

14.4 POTENTIAL BENEFITS, RISKS, AND PRECAUTIONS

14.4.1 Potential Benefits of the DTI Sub-study

14.4.1.1 Potential direct benefit to class

EXIST-3 is a randomized, placebo-controlled, double-blinded, phase III clinical trial using the investigational drug everolimus to evaluate its clinical effectiveness as a treatment of refractory epilepsy in TSC. The DTI sub-study, using advanced non-invasive imaging and electroencephalography (EEG) technologies, provides additional objective assessment approaches to assess treatment efficacy and safety. The DTI sub-study will do so without the need to involve the entire study population (n=15 vs n=355 for EXIST-3), improving study feasibility and limiting patient time and effort within the group. The results of the DTI sub-study may further support IND application for FDA approval of everolimus for the treatment of refractory epilepsy in this study population by providing mechanistic and objective evidence of treatment effect. It would also provide supporting evidence for the use of DTI and HFO EEG in the future as non-invasive, objective measures of everolimus treatment effect should everolimus be approved for this indication.

14.4.1.2 Potential direct benefit to subjects

TSC patients already undergo MRI surveillance annually to monitor for the emergence or progression of subependymal giant cell astrocytoma (SEGA) (2012 International TSC Consensus Conference, manuscript in preparation). More frequent MRI may be indicated if SEGA is present and being followed clinically before implementing medical or surgical intervention. In the process of DTI acquisition for the present study, MRI obtained has the potential to identify SEGA emergence or progression sooner than what would be realized otherwise. Like MRI, conventional EEG in TSC is recommended-at time of diagnosis and periodically thereafter according to clinical need in refractory epilepsy patients. The purpose of conventional EEG is to assess for epileptiform activity and characterize ictal events, both of which will be frequent in patients participating in EXIST-3. Participation in the DTI sub-study will provide such patients two opportunities to non-invasively assess for these findings that in turn may have important secondary impact on development, cognitive function, and behavior that can directly influence medical decision-making for the same.

Participants also will have potential for benefit after DTI and HFO analysis is completed. The previously discussed Phase II Everolimus for SEGA in TSC clinical trial is now in extension phase, with patients treated now out to 5+ years. At the time of most recent analysis, in which all patients were treated at least 2 years, patient-reported seizure frequency demonstrated improvement at 12 and 24 months that was not evident in all participants at the conclusion of the main study phase (6 months) (Krueger et al 2013). In fact, improvement seems to be more evident the longer treatment is continued (Krueger et al 2013). Thus evidence of DTI or HFO EEG improvement within individual study participants could provide compelling evidence to pursue continued treatment with everolimus on a clinical basis even if clear improvement in seizure frequency is not immediately evident.

[redacted]

14.4.2 Potential Risks of the DTI Sub-study

MRI and EEG used to acquire DTI and HFO EEG data for the sub-study are routine clinical procedures considered safe and carry negligible risk. Both procedures are routinely performed in the TSC population eligible for participation in EXIST-3.

EEG has minor risk of skin irritation from the adhesive used for application of the electrodes.

MRI utilizes electromagnetic signals to generate non-invasive images internal organs of patients, including the brain. MRI itself does not affect body tissues, but can interfere or cause discomfort in patients with non-compatible surgical implants and devices. MRI contrast agent (gadolinium) can rarely cause hypersensitivity or skin reactions in susceptible individuals and individuals with severely compromised renal clearance. In both instances (incompatible medical devices or medical conditions), such patients are excluded from participation in the EXIST-3 DTI sub-study.

EEG will be obtained without sedation. In contrast, MRI in TSC refractory epilepsy patients often requires sedation to obtain suitable images for clinical interpretation and analysis (Curatolo et al 2002; Jansen et al 2008). This is particularly true for DTI acquisition, which is additionally susceptible to motion artifact and eddy currents and other distortions. Complications with sedation are rare (Karian et al 2002), but include risk of over-sedation, respiratory depression, and post-sedation effects on mental status, behavior, and cognitive performance (Schulte-Uentrop and Goepfert 2010; Edwards and Arthurs 2011).

14.4.3 Additional Precautions

Inclusion and exclusion criteria already outlined in the main EXIST-3 protocol will apply to the DTI Sub-study as well, with the few additional criteria defined in Section 14.3.2. Adverse event reporting, subject removal, safety monitoring, emergency unblinding, stopping rules, data quality assurance and handling, patient confidentiality, and all other safety and regulatory rules detailed in the main EXIST-3 protocol will continue to apply and be adhered to for all DTI sub-study activities.

14.4.4 Cost

Neither third party payers, subjects, nor their families will be charged for the performance of MRI scans and EEG studies to be used for the DTI sub-study.

14.4.5 Analysis of Benefit and Risk for DTI Sub-study Participation

In summary, TSC patients with medically refractory epilepsy and having failed previously multiple AED medications have limited options for improved seizure control using currently available anticonvulsant medications and are at highest risk of poor long-term neurological outcome. EXIST-3 is a phase 3 clinical trial designed to evaluate the safety and efficacy of everolimus for seizure control in this population. EXIST-3 participation is considered to be of more than minimal risk with potential for direct patient benefit. The only additional risk of DTI sub-study participation is encountered with sedation required for MRI during the acquisition of DTI. This risk is countered by the DTI sub-study's potential to provide an objective measures to treatment effect and establish evidence for everolimus mechanism of action in treating epilepsy Thus there is benefit to class while minimizing the number of

[redacted]

subjects needed for the analysis (direct benefit to overall study and indirect benefit to subjects). Direct benefit to DTI sub-study participants is also possible through heightened MRI surveillance for SEGA emergence/progression and EEG monitoring for epileptiform activity and seizures. DTI and HFO analysis may also provide direct evidence of treatment benefit on an individual basis that may prove useful for future treatment decisions involving patient care with everolimus after completion of EXIST-3. Altogether, both EXIST-3 main study and DTI sub-study represent more than minimal risk, with the potential for direct and indirect patient benefits.