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

Statistical Analysis Plan (SAP)

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13-Mar-2015	Prior to DB lock	**Creation of final version**	N/A – First version	NA
23-Jan-2024	Prior to final DB lock	**Update based on new template**	Amendment 1	
		Updated “TOSCA registry” to “who were never exposed to any mTOR inhibitors on the CRAD001MIC03 study”		Section 1
		Updated baseline definition “before the start of everolimus” to “before the start of everolimus in the parent study CRAD001M2301”		Section 2.1.4
		Added Sperate Section for the Baseline definition addition to the “Endocrine assessment and Tanner Staging assessments”		Section 2.1.5
		Updated Time window for Endocrine data		Section 2.1.6
		Updated Section 2.1.6.1 for the Endocrine assessment visits		Section 2.1.6.1
		Added: FAS(CRAD001M2305) definition “(who met the inclusion exclusion criteria).” Added to the definition of Full Analysis Set for TOSCA, “nor recorded as prior or ongoing treatment at the baseline visit”.		Section 2.3.1
		Updated “primary safety objective” to “primary objective”		Section 2.4.2
		Updated to add table for PDs		Section 3.3
		Added separate sentence “Concomitant medication ongoing at the time of enrollment in CRAD001M2305 and during the study will be summarized. Medications used at time of CRAD001M2301 will be listed.”		Section 3.7

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Updated "LH, FSH, and estrogen levels for Male/female patients (for the CRAD001M2305/ TOSCA study, collected"		Section 3.8
		Added sentence "The counts and frequencies by region will be provided if sufficient sample size observed within the region in the CRAD001M2305 study."		Section 3.8.1
		Added separate sentence "If the number of CRAD001M2305 patients is sufficient"		Section 3.9
		Added separate sentence "AEs which will be counted for a specific period are those which are treatment-emergent. These events are those with an onset on or after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity or developed into SAEs after the start of the treatment period."		Section 3.9.1
		Updated Sentence "AE summaries will include all AEs starting on or after treatment day 1 (i.e., on or after the start date of everolimus) and no later than 30 days after the last day of everolimus. All AEs will be listed. Starting prior to treatment day 1 will be identified in the listings with a starting treatment day less than day 1" to "AE summaries will include all AEs ongoing at the time of enrollment and during the Study (CRAD001M2305) and no later than 30 days after the last day of everolimus. AEs ongoing at the time of enrollment and during the study will be listed"		Section 3.9.1.3
		Updated to report Adverse events of Special interest instead of Clinically notable AEs		Section 3.9.1.5
		Added section 3.9.1.6 for the AE reporting outputs for the legal requirements of ClinicalTrials.gov and EudraCT		Section 3.9.1.6

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Added Separate Section 4 “Change to protocol specified analyses”		Section 4
		Updated Section 5 Imputation rules of missing dates: “Imatinib” to “Study” Imputation rule for study drug/AE, concomitant medication and other safety assessment table 4-2 title Imputation of end dates (Concomitant Medications) to “Imputation of end dates (Adverse events, Concomitant Medications)”		Section 5.1
		Added Imputation rule for the Endocrine LLOQ/HLOQ values		Section 5.2

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
C_{min}	Minimum (trough) Concentration
CRF	Case Report/Record Form
CTCAE	Common Terminology Criteria for Adverse Events
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
KM	Kaplan-Meier
LH	Luteinizing Hormone
MAP	Master Analysis Plan
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	Mammalian Target of Rapamycin
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDS	Standard Deviation Score
SEGA	Subependymal Giant Cell Astrocytoma
SOC	System Organ Class
TAND	TSC-Associated-Neuropsychiatric-Disorders
TSC	Tuberous Sclerosis Complex
VAP	Validation and Planning

1 Introduction

This Statistical Analysis Plan (SAP) is for the evaluation of the long-term follow-up study to monitor the effect of everolimus on the growth and development of pediatric patients previously treated with everolimus in study CRAD001M2301 (EXIST-LT). Statistical analyses will be primarily descriptive for all endpoints. The planned statistical analysis is described in Section 10 of the protocol.

The data will be analyzed by Novartis.

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

This pooling will allow for the following:

- Obtaining baseline values collected in CRAD001M2301 before start of everolimus
- Calculating the whole exposure to everolimus for patients enrolled in the CRAD001M2305 study
- Considering the whole growth/development course over time from the start of everolimus.

The data of the patients enrolled in the CRAD001M2305 study and a subset of patients who were never exposed to any mTOR inhibitors on the CRAD001MIC03 study (TOSCA, and these patients are referred to as TOSCA patients) will be presented, side by side, whenever similar data were collected in both studies. This is intended to facilitate the interpretation of the CRAD001M2305 results and help differentiate the impact of the TSC condition versus any potential impact of everolimus on growth and sexual development.

If the missing data pattern is not limiting and if the number of patients in each study is sufficient, exploratory indirect comparisons between patients treated by everolimus (enrolled in CRAD001M2305 study) and patients who were never exposed to any mTOR inhibitors (TOSCA patients) will be performed to evaluate the everolimus effect on growth and sexual development.

2 Definitions and general methodology

2.1 Definitions

2.1.1 Date of first administration of everolimus

For CRAD001M2305 patients, the date of first administration of everolimus is defined as the first date when a non-zero dose was administered in the parent study CRAD001M2301. This date was recorded on Study History (HIS) Case Report Form (CRF) of the CRAD001M2305 study.

For the sake of simplicity, the date of first administration of everolimus will also be referred to as the ***start of everolimus***.

2.1.2 Date of last administration of everolimus

For CRAD001M2305 patients, the date of last administration of everolimus is defined as the last date when a non-zero dose was administered and was recorded on the Everolimus prescription record CRF of the CRAD001M2305 study.

2.1.3 Treatment day / Study day

For CRAD001M2305 patients, the treatment day 1 will be the date of start of everolimus. The treatment day of an assessment that occurred on or after the start of everolimus will be calculated as (date of assessment) – (date of start of everolimus) + 1. The treatment day of an assessment that occurred before the start of everolimus will be calculated as (date of assessment) – (date of start of everolimus).

For TOSCA patients, since they were not exposed to any mTOR inhibitors on the TOSCA study, the concept of study day will be used. The study day 1 will be the enrollment date. The study day of an assessment that occurred on or after the enrollment date will be calculated as (date of assessment) – (enrollment date) + 1. The study day of an assessment that occurred before the enrollment date will be calculated as (date of assessment) – (enrollment date). Treatment day/ Study day will be displayed in the data listings.

2.1.4 Baseline

For CRAD001M2305 patients, the baseline value will be the last available assessment on or before the start of everolimus in the parent study CRAD001M2301.

For the TOSCA patients, the baseline value is taken from the first available assessment on or after the enrollment date.

If patients have no value as defined above, the baseline value will be missing.

2.1.5 First available assessment of endocrine test and Tanner Staging for the CRAD001M2305 patients

The original protocol of the parent study CRAD001M2301 did not require collection of the endocrine blood test nor the Tanner Staging data. These assessments were added in the protocol amendment 2 of CRAD001M2301 and required to be collected during screening and at certain frequency during follow-up. As per the CRAD001M2301 protocol, patients who were ongoing at the time protocol amendment 2 was approved should have the endocrine blood tests and Tanner Staging assessed at their next scheduled visit (considered baseline).

Therefore, some CRAD001M2305 patients who were already enrolled into the parent study CRAD001M2301 before the protocol amendment 2 do not have the endocrine blood test nor the Tanner Staging data on or before the start of everolimus in the parent study, and the first available assessments after the protocol amendment 2 of CRAD001M2301 were considered as the baseline data for those patients in the parent study as well as in the CRAD001M2305 study.

2.1.6 Time windows

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

2.1.6.1 Growth data/ Endocrine data

Height and weight were collected at screening/baseline, every 4 weeks until Week 12, every 6 weeks until Week 24, every 12 weeks until EOT in the CRAD001M2301 study. The growth data (height and BMI) will be collected at the enrollment and every year until EOT in the CRAD001M2305 study. The growth data will be collected at the baseline and annually if available in the TOSCA study.

The endocrine data (LH, FSH, testosterone (in males) and LH, FSH, estrogen (in females)) will be collected in the CRAD001M2305 study at the baseline and then yearly, hence corresponding data will be pooled from CRAD001M2301 Study. The endocrine data will be collected in the TOSCA study at enrollment and annually if available.

Table 2-1 summarizes the time windows for Growth data/Endocrine data analyses, where windows are centered at every year after start of everolimus for CRAD001M2305 patients and every year after the enrollment date for TOSCA patients.

Table 2-1 Time windows for Growth data/ Endocrine data

Time Window	Planned Assessment Day		Time Window Definition	
	CRAD001M2305	TOSCA	CRAD001M2305	TOSCA
Baseline	Last available assessment on or before the start of everolimus in the parent study CRAD001M2301	First available assessment after the enrollment date	Before or on Treatment Day 1	Between Study Day 1 and Study Day 182
Year 1	Treatment Day 365	Study Day 365	Treatment Days 183 to 547	Study Days 183 to 547
Year 2	Treatment Day 730	Study Day 730	Treatment Days 548 to 913	Study Days 548 to 913
Year 3	Treatment Day 1096	Study Day 1096	Treatment Days 914 to 1279	Study Days 914 to 1279
Year 4	Treatment Day 1461	Study Day 1461	Treatment Days 1279 to 1644	Study Days 1279 to 1644
Every year thereafter until the end of each study				

Growth data, if more than one assessment is done within the Baseline time window, the assessment closest to study day 1 (for TOSCA) or treatment day 1 (for CRAD001M2301) will be used; if two or more assessments are equidistant from day 1, then the mean value will be used. For all other time windows, the assessment closest to the planned assessment date will be used; if two or more assessments are equidistant from the planned date, then the mean value will be used.

Endocrine data, if more than one assessment is done within the Baseline time window, the assessment closest to study day 1 (for TOSCA) or treatment day 1 (for CRAD001M2301) or first available assessment will be used; if two or more assessments are equidistant from day 1, then the mean value will be used. For all other time windows, the assessment closest to the planned assessment date will be used; if two or more assessments are equidistant from the planned date, then the mean value will be used.

2.2 Data included in the analysis

This Study CRAD001M2305 is a long-term safety follow-up study and statistical analyses will be primarily descriptive for all endpoints. The planned statistical analysis is described in Section 10 of the protocol.

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

- Obtaining baseline values collected in CRAD001M2301 before start of everolimus
- Calculating the whole exposure to everolimus for patients enrolled in the CRAD001M2305 study
- Considering the whole growth/development course over time from the start of everolimus.

The descriptive analyses of data from the CRAD001M2305 study and TOSCA registry will be presented, side by side, whenever similar data are collected in both studies. This is intended to facilitate the interpretation of the CRAD001M2305 results and help describe any potential impact of everolimus on growth and sexual development, in the TSC population, whose growth and sexual development independent of exposure to systemic mTOR inhibitors is not well characterized.

Table 2-2 summarizes the data which will be included in all the analyses described in the SAP.

Table 2-2 Data included in each analysis

Endpoints	Studies			Analysis Set
	CRAD001M2305	CRAD001M2301	TOSCA	
Baseline characteristics	X	X	X	FAS and FAS Puberty
Patient disposition	X			FAS
Protocol deviations	X			FAS
Concomitant therapy	X	X		Safety Set
Height and BMI	X	X	X	FAS
Tanner stage	X	X	X	FAS puberty
Endocrines	X	X	X	FAS
Adverse events	X	X		Safety Set
Age at menarche	X	X		Safety Set
Age at thelarche	X	X		Safety Set
Age at adrenarche	X	X		Safety Set
Potential delayed puberty	X	X		Safety Set
TAND checklist	X		X	FAS
Indirect comparison	X	X	X	FAS and FAS puberty

Endpoints	Studies			Analysis Set
	CRAD001M2305	CRAD001M2301	TOSCA	
Treatment exposure	X	X		Safety Set
Pharmacokinetics	X	X		Safety Set

In order to ensure all data in the trial is captured, the cut-off date for final analysis will be fixed to the date of the last patient last visit. For the purpose of the final analysis, all tables, figures and listings (TFLs) described in this SAP as well as in TFL shells will be produced.

If it is required to impute an end date in order to perform a specific analysis, the imputed date will be displayed and flagged in the listings. For example, if there is a record in the Everolimus prescription record panel with missing end date (or end date after the cut-off date), the cut-off date needs to be imputed as the end date in order to enable treatment exposure duration to be calculated.

Details of imputation of partial dates are provided in the programming specifications (Programming Dataset Specifications).

2.3 Definitions of analysis populations

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

2.3.1 Full Analysis Set

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

- The Full Analysis Set (FAS):
  - for CRAD001M2305, FAS will consist of all patients enrolled in the CRAD001M2305 study.
  - for TOSCA, FAS will consist of all patients enrolled in this TOSCA registry whose age at study entry was below 16 (for female) and 17 (for male) years and who never received an mTOR inhibitor throughout the registry follow-up period nor recorded as prior or ongoing treatment at the baseline visit.

- The Full Analysis Set for sexual development (FAS Puberty):
  - for CRAD001M2305, FAS Puberty will consist of the FAS patients defined above.
  - for TOSCA, FAS Puberty will consist of the FAS patients defined above but restricting from the patients to those aged between 9 to 17 years (for, females 9 to 16 years, males 9 to 17 years) at registry entry. The TOSCA registry is designed to collect Tanner Staging until 2017 (i.e. 4 to 6 years of follow-up). Thus it is considered adequate to select only TOSCA patients aged between 9 to 17 years old at the time of entry to the registry to allow for obtaining puberty data corresponding to the peri-pubertal time frame.

2.3.2 Safety Set

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

The safety set will be the population used in the assessments of safety, such as adverse events (AEs) and everolimus exposure.

2.4 General statistical methodology

2.4.1 Center pooling

All study centers will be combined for the analysis. Due to the expected small size of centers, no center effect will be assessed.

2.4.2 Analysis of percentage rates

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

The rates of sexual maturation will be described as the percentage of patients who have reached Tanner Stage V by age 16 (for females) or age 17 (for males).

2.4.2.1 Hypothesis and test statistic

No statistical tests are planned for any of the percentage rates.

2.4.2.2 Confidence interval for percentage rates

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

2.4.3 Time-to-event analyses

This section presents the general methodology used to analyze time-to-event variables, e.g., age at which each Tanner Stage will be reached, age at thelarche (females), age at menarche (females) and age at adrenarche (males).

2.4.3.1 Kaplan-Meier estimates

An estimate of the time-to-event function will be constructed using the ***Kaplan-Meier (product-limit) method*** as implemented in the procedure LIFETEST with the METHOD=KM option. Median time-to-event will be obtained along with a 95% confidence interval calculated from the procedure LIFETEST using the method of [Brookmeyer & Crowley, 1982].

Kaplan-Meier (KM) estimates of the time-to-event function with 95% confidence intervals every 12 months, where 12 months is defined as 365.25 days, will be presented. The confidence

intervals will be constructed using Greenwood's formula [Collett, 1994] for the standard error of the KM estimate. The log-log transformation of the survivor function [Kalbfleisch and Prentice, 1980] will be used in order to ensure that the confidence limits remain in the interval [0, 1]. The log-log transformation is implemented in the LIFETEST procedure using the option CONFTYPE=LOGLOG.

3 Statistical methods used in reporting

3.1 General presentation of descriptive summaries

Qualitative data (e.g., gender, race, etc.) will be summarized by appropriate descriptive statistics (i.e. frequencies and percentages); a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum).

3.2 Background and demographic characteristics

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301.

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

The summary table will include age, sex, race, weight, height, body mass index (BMI) at baseline.

Age will be summarized by age category (≤12, >12) for both the studies.

All demographic and background data will be listed.

3.3 Protocol deviation summaries

For CRAD001M2305 patients, all protocol deviations which occurred during the CRAD001M2305 study will be analyzed, The number (%) of participants with any protocol deviation will be tabulated by deviation category, PDs that are pandemic related will be summarized by relationship to COVID-19.

All protocol deviations will be listed (as specified in the VAP documents) using the FAS population.

3.4 Grouping for analysis

The number and percentage of patients in each analysis population will be summarized.

3.5 Patient disposition

For the CRAD001M2305 patients, the FAS will be used for the patient disposition summary tables and listings. Information from the CRF page "End of Treatment" and "End of Study" CRAD001M2305 study will be used to provide a summary showing:

- Number (%) of patients who started/ongoing commercial everolimus
- Number (%) of patients with Treatment discontinuation and their discontinuation reason
- Number (%) of patients with study discontinuation and their discontinuation reason

3.6 Study treatment

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301and will be summarized using the safety set.

The participation in this study does not require the administration of everolimus. In such cases in which the patient was taking everolimus, data collection (such as therapeutic drug trough level, duration of everolimus interruptions and everolimus prescribed dose) will only be recorded, when available.

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

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

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

All exposure data will be listed.

3.7 Concomitant therapy

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301. Concomitant medication ongoing at the time of enrollment in CRAD001M2305 and during the study will be summarized. Medications used at time of CRAD001M2301 will be listed.

Concomitant therapy will be described using the safety set.

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides everolimus that were administered to a patient preceding or coinciding with everolimus intake.

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

Concomitant medications and significant non-drug therapies taken concurrently with everolimus will be listed and summarized by ATC class and PT by means of frequency counts and percentages. These summaries and listings will include medications starting on or after the start date of everolimus, or medications starting prior to the start date of everolimus and continuing after the start date of everolimus. Medications starting more than 30 days after the last day of everolimus will be only listed.

3.8 Primary objective

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

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

- Height
- Weight
- Tanner Stage
- LH, FSH, and estrogen levels for female patients (for the CRAD001M2305 study, collected only for patients of 10 years old or older during the study)
- LH, FSH, and testosterone levels for male patients (for the CRAD001M2305 study, collected only for patients of 10 years old or older during the study)

3.8.1 Height and BMI

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301.

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

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

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

where:

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

- SD3*neg* is the cutoff -3SD calculated by the LMS method:
  SD3*pos* = M * $(1 + LS*(-3))^{1/L}$
- SD23*pos* if the difference between the cutoffs 3SD and 2SD:
  SD23*pos* = M * $(1 + LS*3)^{1/L}$ - M * $(1 + LS*2)^{1/L}$
- SD23*neg* if the difference between the cutoffs -2SD and -3SD:
  SD23*neg* = M * $(1 + LS*(-2))^{1/L}$ - M * $(1 + LS*(-3))^{1/L}$

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

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

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

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

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

- The rate of height (respectively BMI) growth abnormality will be described in the different subgroups defined by the duration of everolimus exposure. These subgroups are described in the Section 3.12.
- The duration of exposure and the age at start of everolimus will be summarized using descriptive statistics in the subgroups of patients with and without a height (respectively BMI) growth abnormality.
- A logistic regression including the duration of exposure and the age at the start of everolimus as continuous covariates will also be used to further explore the relationship between the everolimus exposure and the height (respectively BMI) growth notable abnormality. Additional covariates (e.g. time normalized Cmin) might also be included in the model.

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

3.8.2 Tanner Stage

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301.

Tanner Stage will include two components for boys (testis and pubic hair) and two components for girls (breast development and pubic hair).

Percentage of patients who will have reached Tanner Stage V by age 16 (for females) or age 17 (for males) will be provided, side by side, on the FAS Puberty of the studies CRAD001M2305 and TOSCA, along with 95% confidence intervals.

If the number of CRAD001M2305 patients is sufficient and notably high abnormality, the relationship between the everolimus exposure and the Tanner Stage will be further explored as detailed below:

- The percentage of patients who will have reached Tanner Stage V by age 16 (for females) or age 17 (for males) will be described in the different subgroups defined by duration of everolimus exposure. These subgroups are described in the Section 3.12.
- The duration of exposure and the age at start of everolimus will be summarized using descriptive statistics in the subgroups of patients who will reach and who will not reach Tanner Stage V by age 16 (for females) or age 17 (for males).
- A logistic regression including the duration of exposure and the age at the start of everolimus as continuous covariates may also be used to further explore if needed the relationship between the everolimus exposure and the achievement of Tanner Stage V by age 16 (for females) or age 17 (for males). Additional covariates (e.g. time normalized Cmin) might also be included in the model.

3.8.3 Endocrine parameters

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301. Endocrine parameters such as LH, FSH, testosterone levels (in males) and LH, FSH, estrogen levels (in females) will be summarized descriptively, by study, by gender and by age over time on the FAS of the studies CRAD001M2305 and TOSCA.

Individual patient graphs over time will be provided for the CRAD001M2305 patients.

All data will be listed.

3.8.4 Handling of missing values/censoring/discontinuations

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

3.9 Secondary objective

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

Additionally an indirect comparison of CRAD001M2305 and TOSCA will be performed to compare the height, BMI and sexual development (using Tanner Stages) if the number of patients in the studies are sufficient.

The secondary safety objective of the study will be based mainly on the frequency of AEs during the follow-up period of the CRAD001M2305 study.

All safety data will be listed.

3.9.1 Adverse events

AEs which will be counted for a specific period are those which are **treatment-emergent**. These events are those with an onset on or after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity or developed into SAEs after the start of the treatment period.

AEs collected during the CRAD001M2305 study will be described. All listings and tables will be presented for all CRAD001M2305 patients using the Safety Set.

For CRAD001M2305 patients, using the Safety Set, the overall observation period will be divided into two mutually exclusive segments:

1. everolimus exposure period: from day of first commercial dose received in the CRAD001M2305 study to 30 days after the last commercial dose received in the CRAD001M2305 study.
2. post-everolimus exposure period:
   - starting at day 30+1 after the last commercial dose received in the CRAD001M2305 study
     or
   - starting at the enrollment date for patients who will stop everolimus in CRAD001M2301 and who will not start commercial everolimus.

The safety summary tables will include only assessments collected during the everolimus exposure period. The safety listings will include all assessments, with those collected during the post-everolimus exposure period being flagged.

3.9.1.1 Coding of AEs

AEs are coded using the MedDRA terminology.

3.9.1.2 Grading of AEs

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) by using the latest version available at the time of the final analysis. In case of an update of the CTC criteria during the course of the study, some mapping may be necessary.

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

3.9.1.3 General rules for AE Reporting

Summary tables for AEs have to include only AEs that started or worsened during the everolimus exposure period (treatment-emergent AEs). AE summaries will include all AEs ongoing at the time of enrollment and during the Study (CRAD001M2305) and no later than 30 days after the last dose of everolimus. AEs ongoing at the time of enrollment (CRAD001M2305) and during the study will be listed, and AEs starting later than 30 days after the last dose of everolimus will be specifically flagged.

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

Separate AE summaries will be presented by primary system organ class (SOC), PT, and maximum CTC grade (AEVGRD1C). A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

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

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

3.9.1.4 AE summaries

The following AE summaries will be produced:

- AEs, regardless of study drug relationship, by primary SOC, PT, and maximum grade
- AEs, regardless of study drug relationship, by PT, maximum grade
- AEs, with suspected study drug relationship, by primary SOC, PT, and maximum grade
- Serious adverse events (SAEs), regardless of study drug relationship, by primary SOC and PT, maximum grade
- Adverse events leading to study drug discontinuation, regardless of study drug relationship by primary SOC and PT, maximum grade
- Deaths, by primary SOC and PT

All summaries will show ‘All grades’ (including AEs with unknown/missing grade) and ‘Grades ≥ 3’.

AEs will be presented in alphabetical order for SOC, and in descending order of frequency for PT within each SOC.

Deaths and AEs will be listed by patient.

3.9.1.5 Adverse events of special interest/ Grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound Everolimus. These groupings are defined using MedDRA terms, such as SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no MedDRA SMQ available or the available MedDRA SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. These searches will be are defined in the Novartis tool known as eCRS (electronic Case Retrieval Strategy). The most up-to-date version of the eCRS at the time of analysis is used for retrieval of search terms. A listing of search terms will be provided in the CSR.

For each specified AESI, number (%) of participants with at least one AESI occurring during on-treatment period will be summarized by safety topics, maximum grades.

A listing of all terms down to the MedDRA PTs used to define each AESI will be generated.

3.9.1.6 For the legal requirements of ClinicalTrials.gov and EudraCT

Two required tables on treatment emergent AEs which are not SAEs with an incidence greater than 5%, on treatment emergent SAEs and SAE suspected to be related to study treatment will be provided by SOC and PT on the safety set.

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

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

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

Number of deaths resulting from SAEs suspected to be related to study treatment and number of deaths resulting from SAEs irrespective of causality will be provided.

3.9.2 Other safety data

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301 **except** for the TAND checklist as this assessment was not collected in the parent study CRAD001M2301.

The other secondary objectives of the study will be based on sexual and neuropsychological (TAND checklist) development data.

The age when patients reach each Tanner Stage II-V will be summarized on the FAS Puberty of Studies CRAD001M2305 and TOSCA.

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

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

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

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

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

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

If the number of patients in CRAD001M2305 is sufficient, the rates of potential delayed puberty will be described in the different subgroups defined by duration of everolimus exposure. These subgroups are described in the Section 3.12.

If a high rate of potential delayed puberty occurs and if the number of patients in the CRAD001M2305 study is sufficient, the duration of exposure and the age at start of everolimus will be summarized using descriptive statistics in the subgroup of patients with potential delayed puberty.

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

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

All responses to the individual questions from the TAND Checklist will be summarized using descriptive statistics on both studies, side by side, and over time on the FAS of studies CRAD001M2305 and TOSCA (Research Project 4).

All the responses are categorical in nature from the TAND Checklist, if applicable, the frequency of baseline and worst-post baseline will be summarized on both studies, side by side, and over time on the FAS of studies CRAD001M2305 and TOSCA (Research Project 4).

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

3.9.3 Indirect comparison

For CRAD001M2305 patients, all data described below will be pooled with the corresponding data from Study CRAD001M2301.

If the missing data pattern is not limiting and if the number of patients in each study is sufficient, an indirect comparison between patients treated by everolimus (from CRAD001M2305 study) and those who never received an mTOR inhibitor (TOSCA subset of patients) will be performed to evaluate the everolimus effect on growth and sexual development. Due to the observational nature of the TOSCA registry and its limited duration of follow-up, the statistical analysis will be primarily descriptive.

The following steps will be followed:

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

The following should be noted: the above described use of propensity scores is exploratory and highly dependent on the observed data (observed imbalances between groups, observed missingness pattern) and therefore it is not possible to fully pre-specify all aspects of the planned analyses. In addition, whereas a formal randomization guarantees that there should be no systematic differences in observed and unobserved covariates between the groups to be

compared, the propensity scores are conditional only on the observed covariates. Thus, even if the use of propensity scores is intended to reduce bias and increase precision of the treatment effect, these indirect comparisons analyses using the propensity score methodology will be considered exploratory only and should be interpreted with cautious.

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

If the missing data pattern is not limiting, the effect of everolimus on height (respectively BMI) growth abnormality may also be assessed as an exploratory analysis through the use of propensity scores in a logistic regression or matching comparison as detailed before. The same analysis will be performed for the achievement of Tanner Stage V by age 16 (for females) or age 17 (for males).

3.10 Pharmacokinetic analyses

The pharmacokinetic (PK) analyses will be described only for CRAD001M2305 patients under the safety set.

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

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

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

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

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

If a high rate of growth/puberty abnormalities occurs and if the number of CRAD001M2305 patients is sufficient, the potential relationships between Cmin and growth/puberty data will be explored in the Safety Set as follow:

If the number of CRAD001M2305 patients is sufficient, the percentage of patients who will have reached Tanner Stage V by age 16 (for females) or age 17 (for males) will be presented

split by exposure to everolimus, in terms of patient's time-normalized Cmin. As per everolimus label, the target Cmin for pediatric patients is between 5 to 15 ng/mL, the time-normalized Cmin will be categorized as < 5 ng/ml, 5-10 ng/ml and > 10 ng/ml. Note: if there are insufficient numbers of patients in one of the groups, the categories may be collapsed or redefined.

The same descriptive analyses will be performed for the rates of potential delayed puberty and for rate of notably low BMI/height SDS, if a high rate of growth/puberty abnormalities occurs and if the number of CRAD001M2305 patients is sufficient.

Pooled data will be listed.

3.11 Interim analysis

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

3.12 Subgroup analysis

For the CRAD001M2305 patients, if the number of patients is sufficient, the following subgroups by duration of everolimus exposure will be used for some analyses:

- Less than 5 years of everolimus exposure (< 5 years)
- Between 5 years and 10 years of everolimus exposure (≥ 5 years - < 10 years)
- Ten years or more of everolimus exposure (≥ 10 years)

Note: if there are insufficient numbers of patients in one of the groups the categories may be collapsed or redefined.

3.13 Sample size calculation

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

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

The proposed sample size of 50 patients will allow estimating a two-sided 95% confidence interval for rate of patients with growth development abnormality. Table 3-1 below shows the exact binomial 95% confidence interval [Clopper and Pearson 1934] and the precision of the estimate for N=50 for various numbers of observed patients with growth abnormality. Note that the final interval will depend on the final sample size.

Table 3-1 95% confidence interval for different number of observed patients with growth development abnormality during CRAD001M2305 (sample size N = 50)

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

With this sample size of 50, if we observe 4 patients with growth development abnormality (which corresponds to an observed 8% rate) there will be 79% probability of true rate of patients with growth development abnormality ≤ 10%. Probabilities that the true rate of patients with growth development abnormality is lower or equal to 10% with different number of observed patients with development abnormality are illustrated in Table 3-2. These calculations are based on the binomial distribution.

Table 3-2 Probability that the true rate of patients with growth development abnormality is lower or equal to 0.10 as a function of number of observed patients with development abnormality

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

No power calculation was made for secondary analyses.

4 Change to protocol specified analyses

4.1 Pharmacokinetics data

PK data were collected using central lab for parent study CRAD001M2301 however local lab used for study CRAD001M2305. The local lab test processes are not validated by Sponsor, and it is varying among the local labs so the PK data from local lab are not comparable to the central

lab PK data available in CRAD001M2301. Therefore, PK analysis will be performed only on the data collected in CRAD001M2305 Study.

4.2 Indirect Comparison Analysis

Confidence interval was so wide even for 1 patient with growth development abnormality as shown below in the table 1-1. Estimation was not robust due to the small sample size. Sample size of 15 patients is too small for any comparison, Considering the unlikelihood of making a robust analysis with the limited enrolment into CRAD001M2305, indirect comparison is not meaningful.

Table 1-1 95% confidence interval for different number of observed patients with growth development abnormality during M2305

Number of patients with growth development abnormality	Sample size N = 50		Sample size N = 15	
	Rate of patients with growth development abnormality	Exact binomial 95% confidence interval	Rate of patients with growth development abnormality	Exact binomial 95% confidence interval
0	0.00	(0.00, 0.07)	0.00	(0.00, 0.22)
1			0.07	(0.00, 0.32)
2	0.04	(0.00, 0.14)	0.13	(0.02, 0.40)
3			0.20	(0.04, 0.48)
4	0.08	(0.02, 0.19)	0.27	(0.08, 0.55)
5			0.33	(0.12, 0.62)
6	0.12	(0.04, 0.24)	0.40	(0.16, 0.68)
7			0.47	(0.21, 0.73)
8	0.16	(0.07, 0.29)	0.53	(0.27, 0.79)
9			0.60	(0.32, 0.84)
10	0.20	(0.10, 0.34)	0.67	(0.38, 0.88)
11			0.73	(0.45, 0.92)
12	0.24	(0.13, 0.38)	0.80	(0.52, 0.96)
13			0.87	(0.60, 0.98)
14	0.28	(0.16, 0.42)	0.93	(0.68, 0.998)

5 Appendix

5.1 Imputation Rule

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the participant is considered as on-going:

The participant should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

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

Use Dec31yyyy

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

Use EOT date

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

Use last day of the Month (mm)

Case 5: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm = the month of EOT date:

Use EOT date

All other cases should be considered as a data issue and should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Participants with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 Duration of exposure

Duration of exposure (days) = (last date of exposure to investigational drug) – (date of first administration of investigational drug) + 1

Table 5-1 Imputation of Last dates date of exposure

Scenario	Rule
Investigational drug with a period administration	The planned end date of the last period in which the last non-zero dose of the investigational drug was last administered. Note: If the subject died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last contact, respectively. If the derived last date of exposure goes beyond the data cutoff date, it should be truncated to the date of data cutoff.
Daily administration of the investigational drug	Date of last administration of a non -zero dose of the investigational drug

5.1.3 Cumulative dose

Defined as the sum over the daily doses of all days between first and last dose.

Cumulative dose = sum of (daily dose at a visit * (end date of dose – start date of dose +1).

- The planned cumulative dose total planned dose as per the protocol up to the last administration of study treatment.
- The actual cumulative dose refers to the total actual dose administered, over the duration for which the subject is on the as documented in the Dose Administration eCRF.

For subjects who did not take any drug the cumulative dose is by definition equal to zero.

The actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

5.1.4 AE, concomitant medication and other safety assessment date imputation

Every effort will be made to get the missing information on partial dates. However, despite best efforts, some partial dates might still exist in the database. They will be listed as is. If needed in a calculation (e.g. duration), the standard Novartis Oncology imputation rules will be used.

Table 5-2 Imputation of start dates (Adverse events, Concomitant Medications)

Missing Element	Rule
day, month, and year	No imputation will be done for completely missing dates
day, month	If available year = year of study treatment start date then If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY Else set start date = study treatment start date. If available year > year of study treatment start date then 01JanYYYY If available year < year of study treatment start date then 01JulYYYY
Day	If available month and year = month and year of study treatment start date then If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. Else set start date = study treatment start date. If available month and year > month and year of study treatment start date then 01MONYYYY If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-3 Imputation of end dates (Adverse events, Concomitant Medications)

Missing Element	Rule For patients who discontinued study: *=last treatment date plus 30 days not > (death date, cut-off date) For patients still on study: *= last contact date on study
day, month, and year	No imputation will be done for completely missing dates
day, month	If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period*
day	If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'continuing' rather than the end date provided.

5.2 Endocrine parameters derivations

5.2.1 Handling of test values below LLOQ and above HLOQ

For numerical laboratory parameters, test values below the lower limit of quantification (LLOQ) and above the higher limit of quantification (HLOQ) may show "<n" (or "<=n") and ">n" (or ">=n") in the datasets respectively, where "n" can be any number.

The time point summary tables will follow this data handling rules: prior to conversion of laboratory values to SI unit, a value which shows "<n" (or "<=n") will be handled as zero; a value which shows ">n" (or ">=n") will be handled as "n". These values will be presented in the listing as it is.

6 References

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