NOVARTIS

Clinical Development

RAD001/Everolimus/Afinitor®

Oncology Clinical SAP CRAD001C2X01B / NCT01789281

An open-label, multi-center everolimus roll-over protocol for patients who have completed a previous Novartis-sponsored everolimus study and are judged by the investigator to benefit from continued everolimus treatment

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous version of SAP

Version	Date	Changes
1.0	08Nov2013	Final version
2.0	07Feb2020	To update the SAP per protocoal amendment 1 • To change the primary endpoint from number of patients receiving everolimus to frequency and severity of AEs/SAEs to better characterize the long-term safety of the compound • To include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit. In addition, SAP is also updated to follow Novartis SAP template.
	09Jun2020	To update the SAP on the basis of amendment 1 and the change of safety data collection in protocol amendment 1 • Safety data from both ARGUS safety database and RDC clinical database will be analyzed seperately for comprehensive and transparent safety data reporting in final CSR. • To include global protocol amendment date 18-Mar-2016 as a general cutoff date to analyze safety data from RDC clinical database.

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
BSC	Best Supportive Care
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
EC	European Commission
eCRS	Electronic Case Retrieval Strategy
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IIT	Investigator-initiated Trial
IRB	Institutional Review Board
OGD&GMA	Oncology Global Development and Global Medical Affairs
PI	Principal Investigator
PT	Preffered Term
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure

1 Introduction

This document provides the detailed statistical analysis plan (SAP) for the data from study CRAD001C2X01B. Data analysis will be performed by Novartis personnel or a designated third party.

The original RAP Module 3 for study CRAD001C2X01B was finalized in November 2013 after the initial protocol was released. Subsequently clinical study protocol (CSP) amendment 1 was released in March 2016 to change the primary endpoint from number of patients receiving everolimus to frequency and severity of AEs/SAEs to better characterize the long-term safety of the compound. In addition, the CSP has been amended to include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit. This SAP amendment is to incoporate the impact of CSP amendment 1 on the analysis.

1.1 Study design

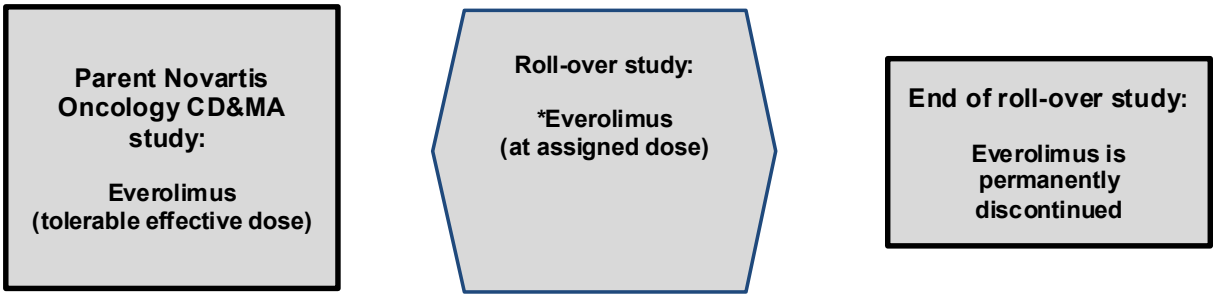
This is a multi-center, open label study to better characterize the long-term safety of everolimus in patients currently being treated in a Novartis-sponsored Oncology Global Development and Global Medical Affairs (OGD&GMA) study and who are not progressing on the current study treatment as judged by the investigator.

Parent studies eligible to participate in the roll-over study will be decided by Novartis. Investigator initiated trials (IIT) will not be included. The primary objective of the parent study must have been reached and the parent study must be in the process of being completed and reported. Patients may be allowed to continue combination therapy with Sandostatin LAR® Depot if they are currently receiving this combination therapy on the parent protocol and at the discretion of the investigator.

Patients will continue to be treated in the roll-over protocol until they are no longer benefiting from their everolimus treatment as judged by the investigator (disease progression), they develop unacceptable toxicities, they withdraw consent, they are non-compliant to the protocol, the investigator feels it is no longer in the patient's best interest to continue everolimus therapy or the patient dies, whichever comes first. At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. A patient will reach the end of study when everolimus treatment is permanently discontinued.

The study is expected to remain open until such time that enrolled patients no longer need treatment with everolimus or are able to obtain commercial supply according to local regulations for their medical condition.

Figure 1-1 Study design



*Note: The starting everolimus (and Sandostatin LAR® Depot, if applicable) dose will be the same as the last dose received in the parent study.

1.2 Study objectives and endpoints

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

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate long term safety data	Frequency and severity of AEs/SAEs	Refer to Section 2.5 & 2.8
Secondary		
To evaluate clinical benefit as assessed by the investigator	Proportion of patients with clinical benefit as assessed by the investigator at scheduled visits	Refer to Section 2.7

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis using SAS Version 9.3. Only data reported in the database of this protocol will be included in the analyses. Patient data from the parent study will not be taken into account.

Summary tables will be provided for patient disposition, demographic data and treatment exposure. All data collected on the database will be listed, using all patients enrolled in this study.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented, unless otherwise stated.

The original protocol was released on 07-Dec-2012. Protocol amendment 1 (PA1) was released on 18-Mar-2016. In this amendment the primary endpoint was changed to safety to better characterize the long-term safety of the compound. In addition, the protocol has been amended to include the collection of all AEs (including non-serious AEs) and an investigator attestation of continued clinical benefit. Additional eCRFs were added to collect data related to

- Investigator attestation of clinical benefit at every quarterly visit
- All adverse events (based on original protocol only SAEs were collected and all SAEs were only collected in ARGUS safety database)
- Relevant medical history/current medical conditions
- Monthly at home pregnancy testing for female patients of child bearing potential (serum/urine)
- Study evaluation completion at the end of the 30 day safety follow up
- Related imaging, drug use 6 months prior to liver event, pathology, medical history possibly contributing to liver dysfunction, local laboratory results (viral serology, autoimmune, immunoglobulin, liver function tests), overview, potential impact of alcohol use, acetaminophen/paracetamol pertaining to liver event (only when drug-induced liver injury (DILI) cases occur)

However, at the time of global protocol amendment was released, 32 out of 34 patients were enrolled; 21 patients ongoing; 11 patients had already discontinued the study. Only 2 patients consented after PA1 approval. Therefore, 32/34 patients did not have AEs collected in eCRFs before PA1, ~30% of enrolled patients had AEs reported in RDC clinical database after PA1, and ~50% of SAEs occurred before PA1 were not reported in RDC. Due to this, safety data from both ARGUS safety database and RDC clinical database will be analyzed seperately for comprehensive and transparent safety data reporting in final CSR. See section 2.8.2 in detail.

2.1.1 General definitions

Study drug = RAD001 = everolimus = Afinitor®.

Study treatment is defined as everolimus or everolimus + Sandostatin LAR if patients are allowed to continue combination therapy.

Date of first administration of study drug is defined as the first date when a nonzero dose of study drug was administered and recorded on eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred as start of study drug.

Date of last administration of study drug is defined as the last date when a nonzero dose of study drug was administered and recorded on the database of this protocol.

The date of first and last administration of sandostatin LAR is defined in the same way.

Date of first administration of study treatment is defined as the first date when a nonzero dose of study treatment was administered and recorded on the database of this protocol.

Date of last administration of study treatment is defined as the last date when a nonzero dose of study drug was administered and recorded on the database of this protocol.

Study day is calculated as: date of the event (onset date of an event, assessment date...) – first date of the first administration of study treatment + 1. Therefore, the first day of study treatment is study day 1.

Baseline is defined when appropriate as the the non-missing record with the latest assessment date on or before the date of first administration of study treatment.

2.2 Analysis sets

The safety set will be used for statistical analysis and data reporting.

The Safety Set includes all patients who received at least one dose of study drug after enrolling into the roll-over protocol.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients ongoing, completed and discontinued from the treatment at the time of analysis as well as the primary reason for end of treatment will be summarized.

2.3.2 Patient demographics and other baseline characteristics

For patients that are eligible to participate in this roll-over study, demographic data, like gender, age, previous study, site/center and subject number, and relevant medical history will be summarized descriptively.

2.3.3 Protocol deviation

Protocol deviation data will be summarized.

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

2.4.1 Study treatment/compliance

Exposure to everolimus and sandostatin LAR will be summarized for all treated patients and will be based only on dose administered within this protocol. Study treatment administered during the parent study will not be taken into account.

The following algorithm will be used to calculate the duration of exposure in days:

- Duration of exposure to everolimus (days) = (date of last administration of everolimus) – (date of first administration of everolimus) + 1.
- Duration of exposure to sandostatin LAR (days) = (date of last administration of sandostatin LAR + 27 days) – (date of first administration of sandostatin LAR) + 1.
- Duration of exposure to everolimus + sandostatin LAR (days) = max(date of last administration of everolimus, date of last administration of sandostatin LAR + 27 days) – min(date of first administration of everolimus, date of first administration of sandostatin LAR) + 1.

The date of first administration of everolimus is derived as the first date when a nonzero dose of everolimus was administered and recorded on the database of this protocol. The date of last administration of everolimus is defined as is the last date when a nonzero dose of study drug was administered and recorded on the database of this protocol. The date of first and last administration of sandostatin LAR is defined in the same way.

The duration of exposure in years is calculated by dividing the duration of exposure in days by 365.25. The duration includes the periods of temporary interruption.

- Duration of exposure in years for everolimus = (Last dosing date – First dosing date + 1)/365.25
- Duration of exposure in years for sandostatin LAR = (Last dosing date + 27– First dosing date + 1)/365.25
- Duration of exposure in years for everolimus + sandostatin LAR (days) = [max(date of last administration of everolimus, date of last administration of sandostatin LAR + 27 days) – min(date of first administration of everolimus, date of first administration of sandostatin LAR) + 1] /365.25.

2.4.2 Prior, concomitant, and post therapies

Prior and post medication/thearpies are not applicable in this roll-over study. The information of concomitant medication is not collected.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary objective is to evaluate long term safety as assessed by the occurrence of AEs/SAEs.

Varaibles see Section 2.8

2.5.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested.

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.5.4 Supportive analyses

No supportive analysis is planned.

2.6 Analysis of the key secondary objective

No key secondary efficacy objectives are analyzed.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The secondary objective of the study is to evaluate clinical benefit as assessed by the investigator. The secondary endpoint is the proportion of patients with clinical benefit as assessed by the investigator at scheduled visits.

2.7.2 Statistical hypothesis, model, and method of analysis

No statistical analyses will be performed on secondary endpoint. Data will be used only for descriptive summary of patients remaining on drug – as needed during the conduct of the study. SAEs reported to the safety database will be reviewed and reported as part of the regular pharmacovigilance activities.

2.7.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 Safety analyses

The assessment of safety will be based mainly on the frequency of AEs and SAEs.

Analysis set and grouping for the analyses:

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

1. on-treatment period: from day of first dose of study medication in the roll-over study to 30 days after last dose of study medication

2. post-treatment period: starting at day 30+1 after last dose of study medication.

2.8.1 Exposure to study treatment

Exposure will be assessed for both Everolimus and Everolimus + Sandostatin LAR.

The following analyses will be performed to assess study treatment exposure:

- Duration of study drug exposure in years;
- Cumulative dose;
- Actual dose intensity;
- Dose adjustments and discontinuation;

Seperate table and plot for on-treatment period and AEs/SAEs collection period in clinical database on patient level will be generated to reflect the proportion of safety data collection within the overall treatment period.

2.8.2 Adverse events (AEs)

Verbatim terms will be coded to lower-level terms in the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA. An assessment of severity grade will be made using NCI-CTCAE v4.03.Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by System Organ Class (SOC) and or Preferred Term (PT), severity (CTC Grade 1-4, 5 Death is exluded), type of adverse event, relation to study treatment.

Since safety data collection was changed in the protocol amendment released on 18-Mar-2016, CTC grade were captured in the RDC clinical database only after the protocol amendment. All SAEs including AESIs reported as SAEs were captured in ARGUS safety database throughtout the study.

Thorough manual review was implemented to ensure SAEs reported both in ARGUS and RDC databases were uniquetly matched without any missing or overlapped inputs.

Hence, AEs/SAEs from both ARGUS safety database and RDC clinical database will be summarized seperately to ensure comprehensive and transparent safety data reporting. Global protocol amendment date (18-Mar-2016) as a general cutoff date will be applied to analyze safety data from RDC clinical database.

The following AE summary tables will be provided:

I. from Safety Database (ARGUS):

- All SAEs throughout the study
    - SAEs regardless of study treatment relationship by primary system organ class and preferred term
    - SAEs suspected to be study treatment relationship by primary system organ class and preferred term

- All AESI reported as SAEs as per protocol throughout the study
  - Serious AESIs regardless of study treatment relationship by safety topic and preferred term

II. from Clinical Database (RDC):

- AEs (non-serious AE and AESI) after protocol amendment
  - AEs regardless of study treatment relationship
    a. by primary system organ class, preferred term and maximum CTC grade
    b. by primary system organ class and preferred term
  - AEs suspected to be study treatment related
    a. by primary system organ class, preferred term and maximum CTC grade
    b. by primary system organ class and preferred term
  - AEs leading to study drug discontinuation regardless of study drug relationship by primary system organ class and preferred term
  - AEs resulting in dose adjustment or interruption regardless of study drug relationship by primary system organ class and preferred term
  - AEs requiring additional therapy and concomitant medication regardless of study drug relationship by primary system organ class and preferred term
  - AESIs regardless of study treatment relationship
    c. by primary system organ class, preferred term and maximum CTC grade
    d. by primary system organ class and preferred term
  - AESIs suspected to be study treatment related
    c. by primary system organ class, preferred term and maximum CTC grade
    d. by primary system organ class and preferred term
  - AESIs leading to study drug discontinuation regardless of study drug relationship by primary system organ class and preferred term
  - AESIs resulting in dose adjustment or interruption regardless of study drug relationship by primary system organ class and preferred term
  - AESIs requiring additional therapy and concomitant medication regardless of study drug relationship by primary system organ class and preferred term
- SAEs after protocol amendment
  - SAEs regardless of study treatment relationship by primary system organ class and preferred term
  - SAEs suspected to be study treatment relationship by primary system organ class and preferred term

For legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment-emergent non-serious AEs with an incidence greater than 5% in clinical database, and on-treatment deaths and treatment-emergent SAEs in ARGUS safety database will be provided by

system organ class and preferred term using the safety set. The rule for the calculation of the number of occurrences is detailed in the Appendix section 5.2.

All of these tables will display the number and percent of patients that experience the given event and will display events by MedDRA. Events will be displayed alphabetically for SOC and PT. All safety data (including those from the post-treatment periods) will be listed and those collected during the post-treatment period are to be flagged.The following listings will also be generated:

- Listing of AEs leading to study drug discontinuation
- Listing of AEs leading to dose adjustment or interruption
- Listing of SAEs in ARGUS safety database
- Listing of SAEs in RDC clinical database

2.8.2.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) will be summarized by risk group and preferred term defined below. AESIs in RDC clinical database and serious AESI in ARGUS safety database will also be listed.

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

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure.

In addition to all serious adverse events reported on a continuous basis throughout the study, the investigator should use the SAE form to report the following medically significant potential risks noted in the Novartis Risk Management Plan for everolimus:

- Development toxicity
- Reproductive (teratogenicity) toxicity
- Intestinal obstruction /ileus
- Male infertility
- Pancreatitis
- Cholelithiasis
- Muscle-wasting/Muscle-loss

All AESIs are defined through the use of MeDRA terms, Standardized MedDRA Queries (SMQ), Preferred Terms (PT), System Organ Classes (SOC), or through a combination of these components. At the project level, a SAS dataset named Case Retrieval Strategy (eCRS) contains the exact composition of the adverse events groupings will be used to map reported adverse events to the adverse events groupings of special interest. This dataset may be updated (i.e., it is a living document) based on review of accumulating trial data, and it is the most up to date version at the time of DBL that will be used. Safety topics flagged in the

eCRS are adjusted to use RMP update flag (RM) instead of core safety flag (SP), with 2 study-specific groupings of "Cholelithiasis" and "Intestinal obstruction ileus" using other flag (OS) to generate protocol-defined AESIs from both RDC clinical and ARGUS safety databases. Note that certain adverse events may be reported within multiple groupings.

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

2.8.3 Deaths

CTC Grade 5 will not be used in this study; rather, information about deaths will be collected on the CRF End of Treatment (EOT) page. Deaths reportable as SAEs will be listed by patient and tabulated by type of adverse event.

All deaths will be summarized. Following summaries will be provided:

- On-treatment death in RDC clinical database by primary system organ class and preferred term
- All deaths in ARGUS safety database by system organ class and preferred term

Listing of all deaths in ARGUS safety database will also be provided.

2.8.4 Laboratory data

Lab data of hepatic laboratory values will be listed only when DILI cases occur.

2.8.5 Other safety data

Pregnancy test results for safety monitoring is collected locally and will be listed.

Following liver event data will be listed only when DILI cases occur.

- Related imaging of liver event
- Pathology of liver event
- Overview of liver event
- Liver event associated with clinical signs/symptoms
- Potential impact of alcohol use of liver event

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

No exploratory analyses are planned.

2.14 Interim analysis

No interim analyses are planned for this study. Nevertheless it may be possible that different analyses may be necessary to descriptively summarize patients on drug at regular intervals.

3 Sample size calculation

The sample size is not based on any statistical considerations.

The purpose of this study is to allow continued use of everolimus in patients who are currently receiving everolimus treatment in a Novartis-sponsored, Oncology Clinical Development & Medical Affairs (CD&MA) study that has reached its study objectives, are not progressing on the current study treatment as defined by the parent protocol and are unable to access everolimus treatment outside of a clinical study.

The total sample size will be determined by the number of patients entering the study.

4 Change to protocol specified analyses

No change from protocol specified analysis is planned.

5 Appendix

5.1 Imputation rules

Not applicable.

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Not applicable.

5.1.3 Concomitant medication date imputation

Not applicable.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

AEs will be coded using the latest MedDRA version available at time of database lock while National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 will be used for reporting AE severity.

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

CTCAE grade 5 (death) will not be used in this study; rather, this death information will be collected on the EOT CRF page (Panel: CMP). Grading is applicable in dada collected in RDC clinical database but not ARGUS safety database.

The rule for the calculation of the number of occurrences that is provided in the summary of serious and non serious adverse events required for the legal requirements of ClinicalTrials.gov and EudraCT is the following:

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

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Not applicable.

6 Reference (available upon request)

Not applicable.