NOVARTIS

Clinical Development

RAD001, everolimus

Clinical Trial Protocol CRAD001C1X01B / NCT02017860

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

RAP Module 3 – Detailed Statistical Methodology

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1.0	20Apr2015	First version

Table of contents

1 Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Novartis according to the data analysis section 10 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided.

Statistical analysis will be performed when all patients discontinued the trial or the 30-day safety follow-up was completed, whichever comes earlier. Those analyses results will be used to document the summary of the safety.

1.1 Subjects and treatments

1.1.1 Analysis sets

Full Analysis Set (FAS): The Full Analysis Set (FAS) comprises all patients who received at least one dose (partial or complete) of everolimus. The FAS will be used for all listings of raw data.

Safety Set: The Safety Set includes all patients who received at least one dose (partial or complete) of everolimus, and have at least one valid post-baseline safety assessment. The statement that a patient had no AEs (on the AEs CRF) constitutes a valid safety assessment.

1.1.2 Patient disposition

The number of patients ongoing at the time of analysis as well as the primary reason for end of treatment will be summarized for FAS.

1.1.3 Patient demographics and other baseline characteristics

Demographic data, like age and gender as well as the parent study number will be summarized descriptively.

Patient demographics and baseline characteristics will be listed by patient.

1.1.4 Treatments (study treatment, concomitant therapies, compliance)

Exposure to everolimus will be summarized for FAS 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.

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 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.

Everolimus dose administration will be listed by patient.

1.2 Safety evaluation

For all safety analyses, the safety set will be used.

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

1. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
2. post-treatment period: starting at day 30 after last dose of study medication.

1.2.1 Adverse events (AEs)

Summary tables for AEs have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, 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 incidence of all treatment-emergent AEs (number and percentage) will be summarized by system organ class (SOC), preferred term, and maximum severity, relation to study treatment.

Deaths reportable as SAEs and non-fatal serious AEs will be listed by patient.

1.3 Determination of sample size

No formal sample size calculation is required for this trial since only patients who are still on treatment in the parent study will be enrolled in this trial.

2 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

No appendix 16.1.9 will be provided.