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Title page

A single arm, open-label, multicenter Phase 2 study of regorafenib in participants who have been treated in a previous Bayer-sponsored regorafenib study (monotherapy or combination treatment) that has reached the primary completion endpoint or the main data analysis, or has been stopped prematurely.

[Regorafenib rollover study]

Bayer study drug	BAY 73-4506 / Regorafenib		
Study purpose:	Enable patients from the feeder studies to continue treatment		
Clinical study phase:	II	**Date:**	23 JUN 2023
Study No.:	20328	**Version:**	2.0
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The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
ATC	WHO Anatomical Therapeutic Chemical Classification system
CRF	Case Report Form
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

1. Introduction

The primary purpose of the study is to enable participants, currently receiving regorafenib in a Bayer sponsored clinical trial, to continue treatment after their respective study has been completed. A completed study is defined as one that has reached the primary completion endpoint for main data analysis, or has been stopped prematurely, and the respective data have been cleaned. Participants will be able to continue treatment until the treating physician feels the participant is no longer benefiting from treatment.

2. Study Objectives

Primary
• The primary purpose of the program is to enable participants, currently receiving regorafenib in a Bayer sponsored clinical trial and assessed by the principal investigator (PI) to be benefitting, to continue regorafenib treatment after their respective study has met its primary completion date, or main data analysis, or has been stopped prematurely.
Secondary
• Documentation of safety and tolerability

3. Study Design

This is an open label, single arm study.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

Due to the low number of expected patients no subgroup analyses are planned.

4.2 Handling of Dropouts

All data available will be analyzed.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

The number of subjects who prematurely discontinue the study and study treatment for any reason, as well as the reasons for premature discontinuation of study and study treatment, will be reported.

4.4 Interim Analyses and Data Monitoring

Not applicable

4.5 Data Rules

In general all analyses will be performed for the safety set. It is anticipated that the analysis sets will not differ. Otherwise valuable data wich is not available in the safety set will also be analysed. See section 5 for definition of the analysis sets.

4.6 Blind Review

As this is an open label study, no unblinding is necessary. Patients will be assigned to the relevant analysis sets based on the rules described in section 5 for the analysis sets. This will be discussed and documented in the Blind Review Meeting.

5. Analysis Sets

For purposes of statistical analysis, the following analysis sets are defined:

Analysis set	Description
Enrolled	All participants who signed the ICF
Safety	All participants who take at least 1 dose of regorafenib within this rollover study.

5.1 Assignment of analysis sets

Assignment of the subjects to the analysis sets will be made based on the available treatment information (i.e. if there is a record indicating that regorafenib was taken, a patient will be assigned to the safety set).

6. Statistical Methodology

The main objective of the study is to ensure continuation of treatment for eligible patients and only safety data are collected. Beyond summary statistics, no statistical analysis is planned.

6.1 Population characteristics

If applicable, the number of subjects in each analysis set will be presented.

Due to the low number of patients expected in this study, no further summary statistics will be produced. Demographic data will be provided by means of a summary table and individual subject data listingsdisplaying the collected demographic informations as per CRF for all patients enrolled.

6.2 Concomitant medication

Concomitant medication will be analyzed in the safety set.

The frequency of concomitant medications will be summarized by 1st and 3rd level ATC class. This table will be repeated for concomitant anti-cancer therapy, if applicable.

6.3 Study drug exposure

Study drug exposure will be analyzed in the safety set.

Treatment duration will be summarized as well as the number of applications and modifications of the study drug.

6.4 Efficacy

Not applicable

6.5 Pharmacokinetics/pharmacodynamics

Not applicable

6.6 Safety

All analyses will be conducted in the safety set.

AEs will be coded using the latest version of MedDRA during the study. A treatment-emergent adverse event (TEAE) is defined as an AE that increase in severity or that is newly developed after the first study intervention.

If the onset date of an AE is missing/incomplete, it is assumed to have occurred after the first study intervention (i.e., a TEAE) except if the partial onset date or stop date indicates differently.

An overview over all patients experiencing AEs will be given. The total number of patients experiencing TEAEs will be presented and tabulated by SOC and PT and CTCAE grade.

The following categories will be presented:

- TEAEs
- Drug-related TEAEs
- TEAEs leading to discontinuation of study drug
- Treatment-emergent serious adverse events (TESAEs
- Drug-related TESAEs
- TESAEs leading to discontinuation of study drug

All deaths, TESAEs, TEAEs leading to discontinuation and pregnancies will be presented in subject listings, if applicable.

6.7 Subgroup analysis

Due to the low sample size no subgroup analysis will be conducted.

7. Document history and changes in the planned statistical analysis

This is the second version of the SAP. In comparison to the the first version analysis were updated du to the small number of patients entering the study.

8. References

Final study protocol of study 20328, version 2.0, dated 20 NOV 2018

Final CRF of study 20328, dated 11 NOV 2020

SAP version 1, dated 28 MAR 2019