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Title page

Sorafenib Long Term Extension Program (STEP)

Bayer study drug	Sorafenib/Nexavar® BAY 43-9006		
Study purpose:	The primary purpose of program is to enable patients, currently receiving sorafenib (Nexavar) in a Bayer/Onyx sponsored clinical trial, to continue sorafenib treatment after their respective study has met its primary endpoint and/or has reached the end as defined in the original protocol.		
Clinical study phase:	IIIb	**Date:**	22 JUN 2021
Study No.:	12311	**Version:**	1.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
GMS	Global Medical Standards
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
SAE	Serious adverse event
SAP	Statistical Analysis Plan
STEP	Sorafenib Long-Term Extension Program
TAS	Therapeutic Area Standards

1. Introduction

Experience has shown that in nearly all clinical trials with sorafenib (Nexavar®) there are patients who are continuing to receive sorafenib after the study has met its primary endpoint. The only process to provide sorafenib to these patients who have a non-approved/reimbursed tumor type is through a clinical trial. The intention of this program is to enable patients who are still benefiting from treatment in a completed clinical trial to continue to receive treatment.

This SAP is based on the integrated clinical study protocol amendment 8, version 7.0, dated 26 MAY 2020, and describes the final statistical analysis methods for the STEP study.

All feeder trials, providing patients to this study are listed in below table.

Table 1–1: Patient numbers of study 12311 by feeder trial

Feeder trial number	Number of Patients, n (%)
100375	3 (1.5)
100554	24 (11.7)
100557	1 (0.5)
10874	1 (0.5)
10916	1 (0.5)
11213	18 (8.7)
11538	3 (1.5)
11546	1 (0.5)
11559	1 (0.5)
11718	1 (0.5)
11721	6 (2.9)
11848	12 (5.8)
11849	1 (0.5)
11868	5 (2.4)
11941	65 (31.6)
11961	7 (3.4)
11988	3 (1.5)
12007	4 (1.9)
12347	2 (1)
12782	4 (1.9)
12913	7 (3.4)
12917	7 (3.4)
12918	4 (1.9)
13266	5 (2.4)
14295	7 (3.4)
14898	13 (6.3)
Total	206 (100)

2. Study Objectives

The primary purpose of this program is to enable patients, currently receiving sorafenib (Nexavar) in a Bayer/Onyx sponsored clinical trial, to continue sorafenib treatment after their respective study has met its primary endpoint and/or has reached the end as defined in the original protocol.

Patients will be able to continue treatment until (i) the treating physician feels the patient is no longer benefiting from the treatment or (ii) the treatment becomes commercially available and reimbursed for the respective indication as applicable in the country in which the patient lives and the patient can obtain suitable amounts of drug for treatment through standard mechanisms of commercial availability (i.e., there should be no interruption in the patient's treatment schedule when switching to commercially available product) or (iii) the patient can join a Post-Trial-Access Program, another study or can receive sorafenib through any other mechanism (e.g. local access program) in accordance with local legal and compliance rules, with no cost to the patient with respect to sorafenib.

An additional objective is the assessment of the safety of Nexavar or Nexavar combination treatment.

3. Study Design

This is an open label program that will enable patients receiving sorafenib (Nexavar) in a completed Bayer/Onyx sponsored clinical trial to continue treatment. A completed study is one that has passed the official statistical and regulatory endpoints and/or has reached its end, as outlined in that protocol. The patients in this open-label program will continue receiving sorafenib treatment at the same dose and schedule as in their original Clinical Trial.

Patients will continue receiving treatment, as long as the treating physician feels the patient is continuing to benefit from treatment or until treatment becomes commercially available and reimbursed for the respective indication in the country in which the patient lives or until being switched to any other form of drug supply with no interruption in the patient's treatment schedule. The patient may also continue treatment until he/she withdraws consent, is non-compliant, is lost to follow up, or if an unacceptable toxicity occurs.

Further details can be found in the protocol.

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).

The creation of tables will follow the Bayer Therapeutic Area Standards (TAS) for Oncology and the Global Medical Standards (GMS).

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.

The analysis is limited to the data coming from this study.

Tables will be created by treatment group (sorafenib monotherapy, sorafenib+erlotinib). For the disposition data, baseline data and ECOG data, the total will also be displayed. Safety data (adverse events, laboratory data) will not be combined across the treatment groups. Since there is only one patient with sorafenib+erlotinib treatment, safety data from the patient with sorafenib+erlotinib will only be listed.

4.2 Handling of Dropouts

Not applicable.

4.3 Handling of Missing Data

Missing data will not be imputed for statistical analysis.

4.4 Interim Analyses and Data Monitoring

Not applicable.

4.5 Data Rules

Baseline value for laboratory measurements and ECOG performance status are the last non-missing values documented before or on the day of first study medication administration in the STEP study.

In this study, adverse events (AEs) ongoing from previous study could also be documented in addition to newly occurring AEs. Since the STEP data are not combined with data from the feeder trials, the start and stop dates of sorafenib treatment in the feeder trial are not available and it cannot be derived if the ongoing AEs are treatment-emergent or not. The ongoing AEs will therefore be analyzed separately and not termed ‘treatment-emergent’. AEs in STEP are considered as treatment-emergent, if they start or worsen from enrolment date in STEP and up to 30 days after the last sorafenib dose. New non-treatment emergent AEs are those that start later than 30 days after last sorafenib treatment.

The investigator should document the AE start date and additionally tick if an AE was ongoing from previous study or not. The assignment if an AE is ongoing or new will be primarily based on the AE start date and will be done according to the following rules:

- Any AE documented on or after enrolment date in STEP will be considered as new.
- Any AE with start date before STEP enrolment date will be considered as ongoing.
- In case the AE start is partially missing (i.e. day and/or month are missing), the date will be imputed as specified below.
- If the AE start date is completely missing, the answer to the question ‘Ongoing from previous study’will be used – ‘yes’ indicates the AE is ongoing, ‘No’ indicates the AE is new.

The following imputation will be used for partially missing AE start date, whenever it is necessary to assign the AE to the ‘ongoing’ or ‘new’ category:

- If only the day is missing, the first of the month will be used, except if the start month/year are equal to enrolment month/year, then the start day of enrolment will be used.
- If day and month are missing, then 1st of July will be used, except if the start year is equal to the enrolment year, then the start day/month of enrolment will be used.

4.6 Blind Review

The results of the final data assessment will be documented in the validity findings and assignment to analysis sets. Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of the study data and documented in the validity findings and analysis sets (see Section 4.6).

Full analysis set (FAS) = All enrolled subjects

All subjects who signed informed consent for STEP are contained in the FAS. This analysis set will be used for disposition tables and subject data listings.

Safety analysis set (SAF)

The population for safety analysis will be comprised of all subjects who received at least one dose of study medication. The SAF will be used for the analyses of the population characteristics and baseline variables, treatment duration, ECOG performance status, and all safety parameters.

6. Statistical Methodology

6.1 Population characteristics

The number and percentage of subjects enrolled will be displayed by feeder trial. The number and percentage of subjects enrolled as well as the reason for termination of treatment will be summarized.

Baseline characteristics and demographics (age, sex, race, diagnosis of cancer, and ECOG performance status) will be summarized for the time point entering this study 12311; as documented in 12311. Age will also be categorized as 15-17, 18–64, 65-74, 75-84, ≥85 years, as applicable.

6.2 Efficacy

Not applicable.

6.3 Pharmacokinetics/pharmacodynamics

Not applicable.

6.4 Safety

Descriptive statistics will be calculated for the treatment duration. Duration of study treatment within STEP will be calculated in days as the date of the last dose of any study treatment – date of the first dose of any study treatment + 1. Duration in months will be presented in months, calculated by dividing days by 30.4. In addition to the descriptive statistics referenced in section 4.1, the sum of all treatment durations will also be calculated.

Adverse Events (AEs) will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). AE grading will be documented using version 3.0 of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

In STEP, AEs ongoing from previous study as well as new AEs occurring during STEP were collected. AEs will be classified as ‘ongoing AE’, ‘new treatment-emergent AE’ or ‘new non treatment-emergent AEs after 30 days after last sorafenib dose’ (see Section 4.5). Tables will be created for ongoing AE, new treatment-emergent AE, and the combination of both. New non treatment-emergent AEs after 30 days after last sorafenib dose will only be listed.

AEs will be summarized by counts and incidence proportions, and grouped by MedDRA system organ class, MedDRA preferred term, and worst CTCAE grade, for the following:

- New TEAEs in STEP:
    - TEAE
    - Drug-related TEAE
    - TEAE leading to dose reduction
    - Drug-related TEAE leading to dose reduction
    - TEAE leading to dose interruption
    - Drug-related TEAE leading to dose interruption
    - TEAE leading to drug discontinuation
    - Drug-related TEAE leading to drug discontinuation
    - TESAE
    - Drug-related TESAE
    - TEAEs leading to death
    - Drug-related TEAEs leading to death
- Ongoing AEs from feeder studies:

  - AEs
  - Drug-related AEs
  - SAEs
  - Drug-related SAEs
- All AEs in STEP (ongoing AEs from feeder studies + new TEAEs in STEP)
  - AEs
  - Drug-related AEs
  - SAEs
  - Drug-related SAEs

The numbers of deaths and the primary cause of death (as reported by the investigator) will be tabulated and listed.

Hematology and blood chemistry values will be summarized according to their worst CTCAE grade, where applicable. Hematology and blood chemistry values will be graded based on the applicable laboratory threshold values outlined in NCI CTCAE version 3.0.

Individual time courses of ECOG performance status will be displayed graphically. Frequencies of the ECOG performance status categories will be summarized for baseline and per 6-month time interval, using the last value per 6-month time interval.

7. Document history and changes in the planned statistical analysis

Not applicable.

8. References

Not applicable.