STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7080-G000-604
Study Protocol Title:	An open-label, multi-center, roll-over study to assess long term safety of lenvatinib monotherapy or lenvatinib combination regimen or comparator treatment arm to cancer patients in Eisai sponsored lenvatinib trials
Date:	28 Feb 2024
Version:	Version 2.0

1 TABLE OF CONTENTS

2 VERSION HISTORY

Version	Description	Date
1.0	Initial version	05 Jun 2019
2.0	• Revised the scope of the statistical analysis plan to reflect the decision by the team to prepare only 1 clinical study report which would present all analyses by region (China, Rest of World). • Clarified that adverse events are considered treatment emergent in this rollover study if they occurred on or after the first dose date of study drug and on or before 28 days after the last dose date of study drug. • Reduced the number of TLGs to only present major adverse event categories, eg, TEAEs, treatment-related TEAEs, SAEs, AEs CTCAE Grade ≥3, AEs leading to discontinuation.	28 Feb 2024

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADaM	Analysis Data Model
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
WHO	World Health Organization

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report the results for Eisai Protocol E7080-G000-604. This is a long term, open-label extension study to roll over eligible subjects from Eisai-sponsored lenvatinib studies. This study was conducted in China and several other countries including Australia, Belgium, Germany, Italy, Netherlands, Poland, Romania, South Korea, Thailand, and the United States; summaries will be prepared by region (China vs Rest of World) and across all subjects.

4.1 Study Objectives

4.1.1 Primary Objective

The primary objective is to assess the long-term safety of study drug(s) in subjects who were enrolled in Eisai-sponsored lenvatinib studies.

4.2 Overall Study Design and Plan

This is an open-label extension study to roll over eligible subjects from Eisai-sponsored lenvatinib studies. Subjects are enrolled in the rollover study for the purpose of long-term safety data collection. The transition from the parent study to the extension study would occur after the completion and evaluation of the primary endpoint of the parent studies or after all study data for the primary outcome measure were evaluated for the parent study. The parent study is defined as the Eisai-sponsored lenvatinib clinical study in which the subject was receiving lenvatinib either as monotherapy or as combination therapy, or was receiving any other comparator therapy.

The subjects willing to participate in the rollover study have to sign the informed consent form (ICF) for Study E7080-G000-604. The "End-of-Treatment" assessments in the parent study are to be completed and reviewed by the investigator prior to subject enrollment into Study E7080-G000-604. The eligibility for the rollover study is to be established based on meeting all inclusion and exclusion criteria described in Section 9.3 of the protocol. The intention is that the subject will not be without study drug during the transition from the parent study to the rollover study. The subjects in Study E7080-G000-604 should receive the first dose of the study drug the following day after the last dose of the study drug in the parent study. All treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the rollover study ICF for up to 28 days after the last dose of study drug(s) (or 5 × half-life of study drug[s], whichever is longer). SAE management and reporting requirements specific to study drugs will be addressed as per the instructions in the parent study protocol. Ongoing AEs in the parent study will remain ongoing at the time of discontinuation in the parent study, and the rollover study will capture only new or worsening TEAEs occurring after signing the rollover study ICF.

Screening period:

From approximately Day -30 to Day -1, subjects may remain on the parent study.

Subjects will be enrolled into the study under the following cohort definitions.

Cohort A: Subjects who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study will continue to receive lenvatinib monotherapy.

Cohort B: Subjects who received lenvatinib combination therapy or who crossed over from a comparator arm to receive lenvatinib combination therapy in their parent study will continue to receive lenvatinib combination therapy.

Cohort C: Subjects who received comparator treatment in their parent study will continue to receive comparator treatment, with the exception of subjects receiving placebo. Subjects who received placebo in their parent study and who were either not permitted to cross over or who opted not to cross over to active treatment will not be eligible to enroll in this study.

Treatment Phase:

During the Treatment Phase, subjects still on treatment will continue the same treatment they received upon discontinuation of the parent study. Subjects will remain on treatment in consecutive cycles as per the parent study protocol until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, discontinuation of Study E7080-G000-604 by the sponsor, use of non-permitted concomitant drugs, unacceptable noncompliance with the protocol, or if the subject is lost to follow-up.

This is a rollover open-label study with no control group. Subjects will enter the study at the same doses of study drug of lenvatinib or the combination regimen, or any other comparator therapy (except placebo), upon discontinuation of the parent study.

Discontinuation criteria are as follows: progression of disease, unacceptable toxicity, subject request, withdrawal of consent, termination of study by sponsor, use of non-permitted concomitant drugs, unacceptable non-compliance with the protocol, subject lost to follow-up. Subjects will be permitted to continue study drug(s) beyond initial disease progression as long as the treating investigator considers that there is continued clinical benefit after discussing with the sponsor and if the subject is tolerating the study drug(s).

5 DETERMINATION OF SAMPLE SIZE

This is a rollover open-label safety study; no formal sample size calculations were performed. It is expected that approximately 50 subjects will be initially rolled over to the study. It is anticipated that additional subjects may also roll over to the study in the future. Subjects who meet all of the inclusion criteria and none of the exclusion criteria, with no evidence of progressive disease, and who have tolerated study drug(s) in their parent study without significant toxicities will be rolled over to this study. Subjects with evidence of disease progression but who continue to derive clinical benefit, as determined by the

investigator, would require discussion with the sponsor on an individual case-by-case basis prior to enrollment in this study.

6 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

6.1 Study Assessments

6.1.1 Demographics

Subject demographic information will be collected and recorded in the electronic case report form (eCRF). Demographic information includes age, sex, and race/ethnicity.

6.1.2 Medical History and Physical Examinations

Initial physical examination and any therapeutic area-specific assessments will be performed as per local standard of care or as clinically indicated. Results of these examinations will not be recorded in the eCRF and will not be summarized.

6.1.3 Efficacy Assessments

Tumor assessments will be performed as per local standard of care. Results of these assessments will not be recorded in the eCRF and will not be summarized.

6.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all TEAEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for both increasing and decreasing severity), and SAEs. Long-term safety information will be collected at the time study drug is dispensed to the subject.

Monitoring of laboratory measurements, vital signs, and performance of electrocardiograms or physical examinations will be done per local standard of care or as clinically indicated.

6.2 Study Subjects

6.2.1 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug(s).

6.2.2 Subject Disposition

The number of subjects enrolled, treated, and prematurely discontinued from study treatment will be summarized. The reason for study drug discontinuation will be summarized according to the categories in the eCRF.

6.2.3 Protocol Deviations

Not applicable.

6.2.4 Demographic and Other Baseline Characteristics

Demographic characteristics (age, sex, race, ethnicity) for the Safety Analysis Set will be summarized using descriptive statistics.

6.2.5 Prior and Concomitant Therapy

Concomitant medications are not collected in the eCRF. If the subject takes a concomitant medication in response to an AE, the AE will be recorded in the Adverse Events eCRF.

6.3 Data Analysis General Considerations

Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation (SD), median, Q1, Q3, and range (minimum, maximum). Categorical variables will be summarized by reporting the number and percentage of subjects. In most cases, the denominator for calculating percentages will be the number of subjects in the column header. Whenever a different subset is used to define the denominator, a footnote will be provided to describe the set of subjects to be used as the denominator. The reporting number of decimal places will be provided in the table shells.

6.4 Efficacy Analyses

Not Applicable

6.5 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

6.5.1 Extent of Exposure

The length of time on treatment (months), and the quantity of study drug administered [dose intensity (mg/day)] will be summarized.

6.5.2 Adverse Events

The adverse event (AE) verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory

Activities (MedDRA). The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

AEs collected in this study must be treatment-emergent adverse events (TEAE). This is defined as an AE that emerges during treatment in the rollover study, having been absent before the time the subject signs the rollover study ICF or

- Re-emerges during treatment in the rollover study, having been present before signing the ICF but stopped before signing the ICF, or
- Worsens in severity during treatment in the rollover study relative to the pre-ICF state, when the AE is continuous.

Only those AEs that are treatment emergent will be included in summary tables. TEAEs are those occurring on or after the first dose date of study drug and on or before 28 days after the last dose of study drug. All TEAEs will be presented in subject data listings.

An overview table, including the number and percentage of subjects with TEAEs, SAEs, deaths, and those with TEAEs that led to study drug discontinuation, interruption, or dose reduction will be provided. The number (percentage) of subjects with TEAEs will be summarized by SOC and PT, by relationship to study drug (Yes [related] and No [not related]), and by CTCAE toxicity grade as follows:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by decreasing frequency of PT
- TEAEs with CTCAE Grade ≥3 by decreasing incidence of PT
- Treatment-emergent serious AEs by decreasing incidence of PT
- Overview of treatment-related TEAEs
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by decreasing frequency of PT
- Treatment-related TEAEs with CTCAE Grade ≥3 by decreasing incidence of PT
- Treatment-related treatment–emergent serious AEs by decreasing incidence of PT
- Fatal TEAEs by decreasing incidence of PT
- TEAEs leading to treatment discontinuation of lenvatinib

The following listings will be provided for the subjects in the Safety Analysis Set:

- Demographics

- Disposition
- Lenvatinib dosing
- All AEs
- All SAEs
- Adverse events with CTCAE Grade 3 or above
- All AEs leading to study drug discontinuation
- All fatal AEs

6.5.3 Laboratory Values

Clinical laboratory tests including hematology, chemistry, and urinalysis will be performed per local standard of care or as clinically indicated. Laboratory values will not be collected in the eCRF, but any laboratory abnormalities that meet the definition of a TEAE (see protocol section 9.5.7.1) will be recorded on the Adverse Events eCRF. These will be summarized as TEAEs along with all other TEAEs.

6.5.4 Vital Signs

Vital signs measurements will be performed as per local standard of care or as clinically indicated. Only changes from screening vital signs findings that meet the definition of a TEAE will be recorded on the Adverse Events eCRF. These will be summarized as TEAEs along with all other TEAEs.

6.5.5 Physical Examinations

Physical examinations will be performed as per local standard of care or as clinically indicated. Only changes from screening physical examination findings that meet the definition of a TEAE will be recorded on the Adverse Events eCRF. These will be summarized as TEAEs along with all other TEAEs.

6.5.6 Electrocardiograms

Complete, standardized, 12-lead ECG recordings (if required) will be performed as per local standard of care. Only changes from screening ECG findings that meet the definition of a TEAE (see protocol section 9.5.7.1) will be recorded on the Adverse Events eCRF. These will be summarized as TEAEs along with all other TEAEs.

6.6 Other Analyses

Not Applicable

6.7 Exploratory Analyses

Not Applicable

7 INTERIM ANALYSES

No interim analyses are planned for this study.

8 CHANGES IN THE PLANNED ANALYSES

No changes to planned analyses are expected.

9 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

Statistical programming and analyses will be performed using SAS® (SAS institute, Inc., Cary, NC, USA), Version 9.4 or higher.

In general, missing or partial dates for adverse events will be imputed in order to assign treatment emergent status. The details on data handling will be provided in Analysis Data Model (ADaM) Specification Documents.

10 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

11 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v 9.4 or later. Statistical summaries will be prepared by Eisai or its designee.

12 MOCK TABLES, LISTINGS, AND GRAPHS

The study table, listing and graph (TLG) shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

13 REFERENCES

Not applicable

14 APPENDICES

Not Applicable

SIGNATURE PAGE

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