# STATISTICAL ANALYSIS PLAN

## CRESTONE: A Phase 2 Study of Seribantumab in Adult Patients with Neuregulin-1 (NRG1) Fusion Positive Locally Advanced or Metastatic Solid Tumors

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| **Protocol Number:** | ELVCAP-001-01 |
| **Development Phase:** | Phase 2 |
| **Sponsor:** | Elevation Oncology, Inc.<br>101 Federal Street<br>Suite 1900<br>Boston, MA 02110 |
| **Protocol Version Number/ Date:** | v7.0/ 21 September 2022 |
| **SAP Version/ Date:** | v1.0/ 11 March 2024 |

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| **Protocol Version:** | V7.0 |
| **SAP Version:** | V1.0 |

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# TABLE OF CONTENTS

# LIST OF TABLES



# LIST OF FIGURES

# Version History

| Version and Date | Description |
|---|---|
| Version 1.0 (11 March 2024) | Initial version |

# LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| CBR | Clinical Benefit Rate |
| CI | Confidence Interval |
| CR | Complete Response |
| CRF | Case Report Form |
| CT | Computerized Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose Limiting Toxicity |
| DoR | Duration of Response |
| ECOG | Eastern Cooperative Oncology Group |
| ECG | Electrocardiogram |
| EGF | Epidermal Growth Factor |
| EORTC | European Organization for Research and Treatment of Cancer |
| EOT | End of Treatment |
| ERBB | Epidermal Growth Factor Family of Receptor Tyrosine Kinases |
| MedDRA | Medical Dictionary for Regulatory Activities |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| HER3 | Human Epidermal Growth Factor Receptor 3 |
| IV | Intravenous |
| MoST | Molecular Screening and Therapeutics Study |
| NCI | National Cancer Institute |
| NE | Not Evaluable |
| NON-CR | Non Complete Response |
| NON-PD | Non Progressive Disease |
| NRG1 | Neuregulin-1 |
| NSCLC | Non-Small Cell Lung Cancer |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PCM1 | Pericentriolar Material 1 |
| PD | Progressive Disease |
| PFS | Progression-free Survival |
| PK | Pharmacokinetic |
| PMEPA1 | Prostate Transmembrane Protein, Androgen Induced 1 |
| PR | Partial Response |
| PT | Preferred Term |
| QTcF | QT Interval Corrected According to Fredericia's Method |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Stable Disease |

| ABBREVIATION | DEFINITION |
|---|---|
| SOC | System Organ Class |
| STMN2 | Stathmin 2 |
| TEAE | Treatment-Emergent Adverse Event |
| TESAE | Treatment-Emergent Serious Adverse Event |
| WHO | World Health Organization |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methodology and analyses to be conducted for Elevation Oncology, Inc. protocol ELVCAP-001-01 (Version 7.0). Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report. The clinical study report will include all planned analyses defined in this SAP and any deviations from the planned analyses.

# 2. STUDY OBJECTIVES

Primary Objective: the primary objective of this study is to determine the objective response rate (ORR) by independent radiologic review to single agent seribantumab (anti-HER3 monoclonal antibody therapy; 3,000 mg IV weekly) in patients with centrally confirmed Neuregulin-1 (NRG1) gene fusion positive advanced cancer according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Objectives: the secondary objectives of this study include the following:

- To determine the overall efficacy of single agent seribantumab in NRG1 gene fusion positive patients with various solid tumors through the assessment of the following clinical outcome parameters:
- Duration of Response (DoR) by independent radiologic review
- ORR and DoR by investigator assessment
- Progression-free Survival (PFS) by independent radiologic review and investigator assessment
- Overall Survival (OS)
- Clinical Benefit Rate (CBR) [Complete Response (CR), Partial Response (PR), Stable Disease (SD) ≥24 weeks] by independent radiologic review and investigator assessment
- To describe the safety profile of seribantumab

Exploratory Objectives: the exploratory objectives for this study are:

- To evaluate the pharmacokinetics (PK) of the seribantumab dosing schedule in patients with NRG1 gene fusion positive advanced solid tumors
- To evaluate if mechanistically linked exploratory biomarkers from tumor tissue or blood samples correlate with clinical outcomes
- To evaluate changes from baseline in quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)

# 3. STUDY OVERVIEW

## 3.1. Study Design

This study is an open-label, international, multi-center, Phase 2 study in adult patients with advanced or metastatic solid tumors, which harbor the NRG1 gene fusion based upon local testing. The design of the study is summarized in Figure **1**.

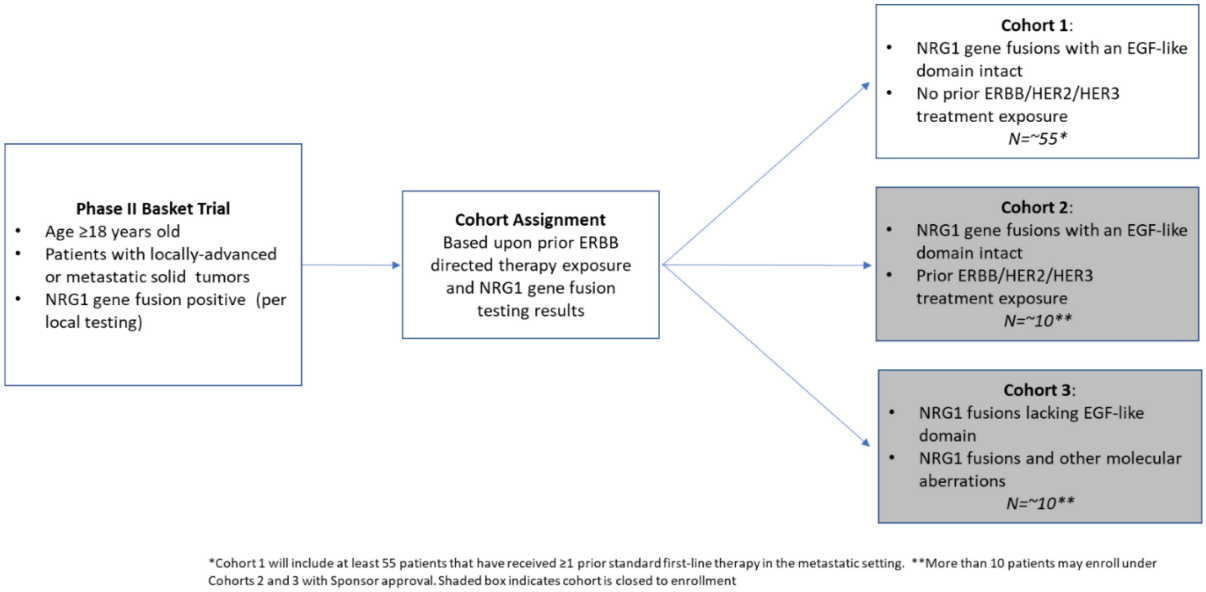
All patients will be determined to be NRG1 gene fusion positive based on local testing of tumor tissue per local laboratory directed analyses prior to initiating further screening procedures. After all screening procedures and determination of eligibility for study treatment have been completed, eligible patients will be assigned by the Sponsor to the appropriate cohort based upon prior treatment history. Patients will be assigned to Treatment Cohorts as follows:

**Cohort 1:** Patients with NRG1 gene fusions who are ERBB/HER2/HER3 treatment-naïve AND harbor NRG1 gene fusions with an EGF-like domain intact. Cohort 1 will include at least 55 patients with tumors that progressed on or are intolerant to ≥1 prior standard first-line therapy in the metastatic setting.

**Cohort 2:** Enrollment to Cohort 2 was closed under Protocol Version 5.0/Protocol Administrative Letter 8.0. Patients with NRG1 gene fusions with an EGF-like domain intact, who received ≥ 1 prior standard first-line therapy in the locally advanced or metastatic setting including at least one ERBB/HER2/HER3 directed treatment are ineligible for study participation.

**Cohort 3:** Enrollment to Cohort 3 was closed under Protocol Version 5.0 and later. Patients with NRG1 fusions without an EGF-like domain (including but not limited to NRG1-PMEPA1, NRG1-STMN2, PCM1-NRG1 and INTS9-NRG1) and patients with NRG1 fusions and other molecular aberrations lacking standard treatment options, AND patients unable to provide tissue for central confirmation of NRG1 gene fusion status are ineligible for study participation under Protocol Version 5.0.

**Figure 1:** Study Schema of Patient Flow in the CRESTONE Clinical Study




*Cohort 1 will include at least 55 patients that have received ≥1 prior standard first-line therapy in the metastatic setting. **More than 10 patients may enroll under Cohorts 2 and 3 with Sponsor approval. Shaded box indicates cohort is closed to enrollment

EGF = epidermal growth factor; ERBB = receptor tyrosine-protein kinase erbB-3; HER = human epidermal growth factor receptor; NRG1 = Neuregulin-1

## 3.2. Seribantumab Dosing

Starting with Protocol Version 4.0 and later, eligible patients will receive seribantumab 3,000 mg 1-h IV once weekly until patients meet one or more protocol specific study treatment discontinuation criteria.

Prior to Protocol Version 4.0, treatment for all eligible patients consisted of an initial Induction (Induction Regimen 1: 3,000 mg x 1 week followed by 2, 000 mg once weekly dosing x 3 weeks; Induction Regimen 2: 3,000 mg once weekly dosing x 4 weeks) followed by Q2W maintenance dosing with 3,000 mg seribantumab.

## 3.3. Randomization and Blinding

This is an open-label non-randomized study.

## 3.4. Sample Size Determination

The trial is designed to provide statistically persuasive evidence of a clinically meaningful effect of seribantumab if the lower boundary of a 2-sided 95% exact binomial confidence interval (CI) about the estimated ORR exceeds a minimal threshold of 20%. This threshold for level of evidence for benefit would be consistent with the standard used for approved targeted therapies for genomically defined populations of patients who stop responding to previous standard therapies. A sample size of 55 patients with central confirmation of NRG1 gene fusion status, who have been enrolled and treated with either the 12-Week Target Induction Regimen and transitioned without interruption to weekly dosing (Clinical Protocol Version 3.0), or once weekly dosing from the time of enrollment (Clinical Protocol

Version 4.0 or later) is planned in the cohort 1 primary efficacy analysis population. Patients in the safety run-in (enrolled under Clinical Protocol Version 2.0 or earlier) will be included if they received seribantumab at 3,000 mg QW beyond induction/re-induction. This sample size will provide approximately 90% power for the lower bound of the 95% CI to exclude the pre-specified threshold of 20% for positivity assuming the ORR is 40% with seribantumab treatment.

## 3.5. Duration of Study

The expected duration of the study is 3 years.

## 3.6. Disease Assessments

For all consented patients assigned to one of the treatment cohorts after eligibility confirmation, treatment must start within 7 days following cohort assignment. Patients are expected to be treated until investigator-assessed progressive disease or unacceptable toxicity. Tumor assessments will be measured and recorded by the local radiologist beginning at weeks 6, 12, 18 and 24 (+/- 2 weeks) and subsequently every 8 weeks (+/- 2 weeks) through Week 48, followed by every 12 weeks (+/- 2 weeks) thereafter until disease progression and evaluated using the RECIST guidelines (version 1.1). All patients that discontinue treatment for reasons other than disease progression will have a scan performed at the time of the End of Treatment (EOT) visit.

In addition, an independent central review of scans may be conducted for patients assigned to cohort 1. All images may be submitted to a central imaging facility and may be assessed by independent reviewers in accordance with the Imaging Charter. After patients discontinue seribantumab treatment, survival information and information about subsequent therapies will be collected until death or study closure, whichever occurs first.

# 4. ANALYSIS POPULATIONS

This section defines the analysis populations to be used for the planned statistical analyses.

## 4.1. Efficacy Analysis Populations

**Cohort 1 primary efficacy analysis population**

The population will be used for the primary analysis of efficacy for registration purpose. It will include cohort 1 subjects enrolled in this study who meet all criteria listed below:

- Centrally confirmed NRG1 gene fusion
- Received at least one dose of seribantumab with the 3,000 mg IV QW dosing regimen (starting with Protocol Version 3.0 and later). Patients in the safety-run in (enrolled under Protocol Version 2.0 or earlier) will be included if they received seribantumab at 3,000 mg QW beyond induction/re-induction.
- Received at least one prior standard therapy in the locally advanced or metastatic setting
- At least one measurable lesion at baseline as assessed per RECIST Version 1.1

## 4.2. Safety Population

The Safety Population includes patients receiving at least one dose of seribantumab therapy across any of the three treatment cohorts (e.g., cohort 1, 2 and 3) and across any of the seribantumab dosing regimens. The safety population will be used for the overall safety analysis.

## 4.3. Pharmacokinetic Evaluable Population

The PK Evaluable Population includes all eligible patients who have at least one dose of seribantumab therapy, and from whom results of plasma concentrations are obtained for at least one sampling point which is suitable for analysis. The PK Evaluable Population will be used for PK analysis.

# 5. CLINICAL OUTCOME VARIABLES

This section provides endpoint definitions. For endpoints based on tumor assessments, such as ORR, DoR, PFS, and CBR, the definitions are the same for each endpoint whether the independent radiographic review assessments or investigator assessments are used per RECIST v1.1.

## 5.1. Primary Efficacy Endpoint

### 5.1.1. Objective Response Rate (ORR)

ORR is defined as the proportion of patients whose overall response is a confirmed CR or PR per RECIST v1.1. To be assigned a status of confirmed PR or CR, changes in tumor measurements must be confirmed by repeated assessments at least 4 weeks (28 days) after the criteria for response are first met. Tumor assessments after the initiation of new anticancer therapy should not be used to derive the ORR.

Patients with no evaluable post-baseline disease assessments (i.e., NE) will be considered non-responders and included in the denominator in the calculation of the ORR.

ORR based on independent radiologic review assessments is the primary efficacy endpoint in this study.

## 5.2. Secondary Efficacy Endpoints

### 5.2.1. Duration of Response (DoR)

Duration of response is defined as the time from the start date of CR or PR (whichever response status is observed first and subsequently confirmed), to the date of first documented radiographical progression of disease using RECIST v1.1, or death from any cause, whichever comes first. DoR will be calculated for patients who are responders, i.e., those who achieve a confirmed CR or PR.

DoR in days will be calculated as:

- DoR (days) = Date of PD or death (whichever is earlier) or Date of censoring – first date of PR/CR + 1

DoR in months will be calculated as:

- DoR (months) = 12*DoR (days)/365.25

DOR will follow the same censoring rules as PFS primary analysis in Table 1 in section 5.2.2.

### 5.2.2. Progression-free Survival (PFS)

Progression-free survival is defined as the time from the date of seribantumab treatment initiation (Dose 1) to the first documented radiographical progression of disease using RECIST v1.1, or death from any cause, whichever comes first.

PFS in days will be calculated as:

- PFS (days) = Date of PD or death (whichever is earlier) or Date of censoring – first dose date + 1

PFS in months will be calculated as:

- PFS (months) = 12*PFS (days)/365.25

The following table summarizes the PFS censoring rules:

**Table 1: Progression Free Survival Censoring Rules**

| | **Primary analysis (Censoring rules)** | **Sensitivity analysis (Censoring rules)** |
|---|---|---|
| No PD, no death, no NACT initiated | Censored at last tumor assessment. If no evaluable tumor assessment, censored on the first dose date. | Censored at last tumor assessment. If no evaluable tumor assessment, censored on the first dose date. |
| No PD, no death, NACT initiated | Censored at the last tumor assessment prior to NACT. If no evaluable tumor assessment, censored on the first dose date. | Censored at last tumor assessment regardless of NACT. If no evaluable tumor assessment, censored on the first dose date. |
| PD or death, no NACT initiated | PFS event at the date of PD or death | PFS event at the date of PD or death |
| PD or death prior to or on date NCAT initiated if patient received the NACT | PFS event at the date of PD or death | PFS event at the date of PD or death |
| PD or death after NACT | Censored at the last tumor assessment prior to NACT | PFS event at the date of PD or death |
| PD or death after 1 missed tumor assessment | PFS event at the date of PD or death | PFS event at the date of PD or death |
| PD or death after 2 or more missed tumor assessment | Censored at last tumor assessment prior to PD or death | PFS event at the date of PD or death |
| Abbreviations: PD = progressive disease; PFS = progression-free survival; NACT = new anticancer therapy | | |

### 5.2.3. Overall Survival (OS)

Overall survival is defined as the time from the date of seribantumab treatment initiation (Dose 1) to the date of death from any cause.

OS in days will be calculated as:

- OS (days) = Date of death – first dose date + 1

OS in months will be calculated as:

- OS (months) = 12*OS (days)/365.25

Patients who are alive at the time of database lock or lost to follow-up will be censored on the date the patient was last known to be alive based on data collected in the database.

### 5.2.4. Clinical Benefit Rate (CBR)

Clinical benefit rate is defined as the proportion of patients who achieve PR, CR, or SD which is maintained through at least 24 weeks per RECIST v1.1. Tumor assessments after the initiation of new anticancer therapy should not be used to derive the CBR.

Patients with no evaluable post-baseline disease assessments (i.e., NE) or with ongoing SD but short of 24 weeks at the time of analysis will be considered as not having attained clinical benefit and included in the denominator in the calculation of the CBR.

## 5.3. Safety Endpoints

### 5.3.1. Treatment-emergent Adverse Events (TEAEs)

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary v26.0 or later. Severity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All AEs, complaints, or symptoms that occur from the time that written informed consent has been obtained through the EOT visit are to be recorded on the appropriate case report form (CRF).

TEAEs are defined as any event that occurred after the first dose of study drug and 28 days after the last dose of seribantumab that was not present prior to study drug administration or worsened in severity after study drug administration. TEAEs will be summarized in the safety analysis.

### 5.3.2. Dose Limiting Toxicities (DLTs)

Patients will be monitored during weekly dosing for a period of 28 days (i.e., throughout C1W1, C1W2, C1W3, and C1W4) for the occurrence of dose limiting toxicities (DLTs). Any Grade 3 or 4 hematologic or non-hematologic toxicity considered related to seribantumab will be considered dose limiting. A DLT is defined as any AE meeting specific criteria, occurring during weekly treatment with seribantumab, where the relationship to seribantumab cannot be ruled out. The full list of criteria for determination of DLTs is given in Section 5.2.4.1 of Clinical Protocol Version 7.0.

Any toxicity, regardless of CTCAE grade, resulting in discontinuation or dose reduction of seribantumab treatment during the 28-day DLT evaluation period, except for symptoms related to PD, will be considered a DLT.

### 5.3.3. Exposure to Study Drug

Seribantumab dosing will consist of weekly dosing until study treatment discontinuation criteria are met.

Total treatment duration:

- Total treatment duration (days) = date of last dose – date of first dose + 1
- Total treatment duration (months) = 12*Total treatment duration (days)/365.25

Actual numbers of completed seribantumab infusions:

- Actual numbers completed = actual numbers of completed seribantumab infusions from the first dose to last dose

Actual dose of administered seribantumab infusions (mg):

- Actual dose administered (mg) = actual cumulative dose of administered seribantumab up to the date of last dose

Relative dose intensity (RDI) is the percentage of actual dose administered relative to the intended dose planned through to treatment discontinuation.

RDI will be calculated as follows:

- RDI = 100% * d/D

where d (mg) is actual total dose administered and D (mg) is cumulative dose planned. D is the total dose that would be administered if there were no modification to dose or schedule.

## 5.4. Pharmacokinetics

The PK of seribantumab will be assessed from plasma samples taken at time indicated in the Schedule of Assessments.

# 6. STATISTICAL ANALYSES

This section describes the statistical analyses to be conducted in relation to the primary, secondary, and exploratory objectives of the study.

## 6.1. General Statistical Considerations

In general, analyses specified will follow the multi-cohort nature of the study design. Specifically, analysis of safety (Section 6.4) will be presented by cohort (cohort 1 primary efficacy analysis population, cohort 1, cohort 2, cohort 3) and all cohorts combined based on the safety analysis population. Analysis of patient population (Section 6.2) will be summarized similarly, except for Patient Disposition, which will be summarized for all patients who have signed the informed consent regardless of seribantumab treatment. The efficacy analysis (Section 6.3) primary focus will be on the cohort 1 primary efficacy analysis population patients. Safety and efficacy analysis will also be performed for non-small cell lung cancer (NSCLC) vs other tumors within cohort 1 primary efficacy analysis population.

For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided as summary statistics. The mean and median will be reported to one additional decimal place compared to the original data. The standard deviation will be reported to two additional decimal places compared to the original data and the minimum and maximum will be reported to the same number of decimal places as the original data.

For categorical variables, the frequency and percentage in each category will be displayed. Percentages (e.g., for AEs and concomitant medications) will be calculated out of the population total for each cohort. Footnotes will clarify the denominator used in each output if other than the analysis set stated in the title. Percentages will be reported to one decimal place throughout unless the percentage is 100 (in which case no decimal places will be presented) or if the frequency count is zero (in which case no percentage will be presented).

For time to event data, unless otherwise noted, the median value, 25th percentile and 75th percentile will be calculated using the Kaplan-Meier method. In addition, the minimum and maximum values of the time to event data will be calculated with an indication of whether that value is an event or censored. However, if both an event and a censored observation contributes to the minimum or maximum then in the case of the minimum the value would be indicated as an event and in the case of a maximum the value would be indicated as censored. Furthermore, the Brookmeyer and Crowley method will be used to calculate the CI of the median value estimated using the Kaplan-Meier method (Brookmeyer and Crowley 1982). Also, the Greenwood formula will be used to calculate the CI of the survival rate (or the rate of interest pertaining to the time to event data), at a given time point estimated using the Kaplan-Meier method for the time to event data (Kalbfleisch and Prentice 2002).

### 6.1.1. Baseline Definition

Unless stated otherwise, the baseline value is defined as the last non-missing measurement prior to the first administration of seribantumab. Study Day 1 will be considered as the date

of the first dose of seribantumab. The change from baseline for a parameter is calculated as (observed value at visit - baseline value).

### 6.1.2. Multiple Comparisons

No multiple comparisons adjustment will be applied to the efficacy analysis.

### 6.1.3. Handling of Dropouts or Missing Data

Unrecorded data values will be recorded as missing. Only recorded (i.e., complete) data values will be used for statistical analyses. In general, invalid or missing values will not be imputed unless stated otherwise.

In cases of missing or incomplete dates (e.g., AEs and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original CRFs will be presented in the data listings.

To be conservative in the case of missing causality assessment for AEs after data querying, AEs will be assumed to be related to study drug. If the CTCAE grade is missing after data querying it will not be imputed and the patient will be presented in table summaries based on the maximum CTCAE grade of all other recorded AEs meeting applicable criteria.

## 6.2. Analysis of Study Population

### 6.2.1. Patient Disposition

Patient disposition will be summarized in terms of counts and percentages for all patients who have signed the informed consent regardless of seribantumab treatment. The following patient disposition categories will be summarized:

- Patients screened
- Patients who enrolled in the study
- Patients treated with seribantumab
- Patients discontinued from seribantumab
- Patients who terminated the study

For patients who discontinued study treatment, or terminated the study, a summary will be provided by reason.

The number and percentage of patients in each defined analysis population may also be tabulated.

All patient disposition data will be listed.

### 6.2.2. Protocol Deviations

Protocol deviations will be identified and reported by the process described in the current version of the study Protocol Deviation Plan. Protocol deviations considered reportable in the clinical study report per the study Protocol Deviation Plan will be summarized and listed by-patient.

### 6.2.3. Demographics and Baseline Characteristics

Demographic characteristics will be collected during the Screening period. Gender, race, and ethnicity will be summarized using frequencies and percentages. If female, the frequencies and percentages of childbearing potential will be summarized. Age at Screening will be summarized using descriptive statistics. Demographic and baseline characteristics will be summarized based on the safety population. Additional summaries based on other analysis populations may also pe performed.

Baseline height (cm), body weight (kg) will be summarized with descriptive statistics and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized using frequencies and percentages.

Demographics and baseline characteristics will be listed by-patient.

### 6.2.4. Medical History

A medical history will be collected during Screening. All pertinent prior medical conditions, surgeries or other medical procedures, allergies, and concomitant medications will be collected.

The reported medical history terms will be coded using the MedDRA v26.0 or later. Summary analyses for medical history will be based on Safety Population and will be summarized by system organ class (SOC) and preferred term (PT). Patients may have more than one reported medical history event for each SOC and PT but will be only counted once within each SOC and PT classification.

Reported medical history data will be presented in a by-patient listing.

### 6.2.5. Primary Cancer History

Primary cancer history will be collected during Screening. Continuous variables including time from initial histologic/cytologic diagnosis (months) and time from last progression will be summarized with descriptive statistics. Categorical variables including primary cancer type, tumor stage at time of diagnosis, histology/cytology, grade, tumor stage at trial entry, NRG1 Fusion detected, NRG1 testing method, and other genomic findings will be summarized in count and percentage.

Primary cancer history data will be presented in a by-patient listing.

### 6.2.6. Prior Cancer Therapies

The analyses will be based on Safety Population. The prior systemic anti-cancer treatments, prior cancer radiation therapy, and prior cancer surgery will be collected during Screening.

For systemic anti-cancer treatments, the number and percentage of patients, the line of therapy setting, duration of therapy, best overall response (defined in order of CR, PR, SD, PD, NON-CR/NON-PD, NE), and reason for discontinuing will be summarized. The reported cancer therapy terms will be coded using the World Health Organization (WHO) Drug Dictionary (Version Global B3, March 2020 or later). Prior cancer therapies will be summarized by Anatomical Therapeutic Chemical (ATC) and PT. A patient will be counted only once within an ATC classification but may contribute to two or more PTs in the same classification.

For prior radiation therapy and prior cancer surgery, the number and percentage of patients, the radiation location, duration of radiation therapy, total dose in Gy, surgery intention will be summarized. The type of surgery will be coded using MedDRA v26.0 or later. The surgeries will be summarized by SOC and PT. A patient will be counted only once within a SOC classification but may contribute to two or more PTs in the same classification.

All prior therapies will be listed, including prior systemic anti-cancer treatments, prior radiation therapy and prior cancer surgery.

### 6.2.7. Prior & Concomitant Medications

The medications collected will be coded using WHO Drug Dictionary (Version Global B3, March 2020 or later). The prior and concomitant medications will be summarized by ATC and PT. A patient will be counted only once within an ATC classification but may contribute to two or more PTs in the same classification. Frequency ordering will be used for the table presentation (i.e. order by the overall grouping in descending frequency for each ATC and for each PT within each ATC).

All prior and concomitant medications will be presented in listings.

### 6.2.8. Concomitant Medical Procedures

The number and percentage of patients will be summarized. All medical procedures will be coded by using MedDRA v26.0 or later. The medical procedures will be summarized by SOC and PT. A patient will be counted only once within a SOC classification but may contribute to two or more PTs in the same classification. Frequency ordering will be used for the table presentation (i.e. order by the overall grouping in descending frequency for each SOC and for each PT within each SOC).

All concomitant medical procedures will be presented in a data listing.

### 6.2.9. Subsequent Cancer Therapies

Subsequent cancer therapies (subsequent cancer therapy, cancer surgery and radiation therapy) will be collected during every survival follow-up.

For subsequent cancer therapy, regimen start/stop dates, and ongoing status will be recorded. The number and percentage of patients treated with a subsequent cancer regimen will be

summarized. The reported cancer therapy terms will be coded using WHO Drug Dictionary (Version Global B3, March 2020 or later). Subsequent cancer therapies will be summarized by ATC and PT. A patient will be counted only once within an ATC classification but may contribute to two or more PTs in the same classification.

For subsequent cancer surgery, the number and percentage of patients who have surgery therapies, palliative/curative intent will be summarized. For subsequent radiation therapy, the number and percentage of patients who have radiation therapies, palliative/ curative intent, therapy location, total dose in Gy will be summarized.

The surgery procedures will be summarized by SOC and PT. A patient will be counted only once within a SOC classification but may contribute to two or more PTs in the same classification.

All the subsequent therapies will be listed.

## 6.3. Efficacy Analyses

All efficacy analyses will be performed by cohort. Analyses for the cohort 1 primary efficacy analysis population will be intended to support a potential registration With the exception on the handling of tumor assessments after the initiation of new anticancer therapy as described in Sections 5.1 and 5.2, all data from scheduled or unscheduled assessments will be included in the efficacy analyses.

All efficacy analysis will be analyzed by investigator assessments only, independent radiographic review was not done due to Sponsor decision to end the study prior to full enrollment.

### 6.3.1. Objective Response Rate

The point estimate of the ORR along with the 2-sided 95% exact Clopper-Pearson CI will be presented.

The best overall response (CR, PR, SD, PD, NE) will also be tabulated to show the number and percentage of patients in each response category.

### 6.3.2. Progression-free Survival

PFS will be estimated using the Kaplan-Meier method and will be presented graphically. Sensitivity analysis based on the alternative censoring rules described in Table 1 will be provided.

The number and percentage of patients experiencing a PFS event and patients censored will be summarized. The median, 25th percentile, 75th percentile, minimum and maximum will be provided along with the 95% CI for the median. The proportion and 95% CI for the number of patients progression-free at clinically significant time points (e.g., 6 months, 12 months) from the date of the first dose will be provided. Other clinically relevant timepoints may also be included if data warrant.

### 6.3.3. Overall Survival

OS will be estimated using the Kaplan-Meier method along with the Kaplan-Meier plot. The number and percentage of deaths and patients censored will be summarized. The median, 25th percentile, 75th percentile, minimum and maximum will be provided along with the 95% CIs for the median. The proportion and 95% CI for the number of patients alive at clinically significant time points (e.g., 6 months, 12 months) from first treatment will be provided. Other clinically relevant timepoints may also be included if data warrant.

### 6.3.4. Duration of Response

DoR will be estimated using the Kaplan-Meier method along with the Kaplan-Meier plot. The number and percentage of patients experiencing a DoR event and patients censored will be summarized. The median, 25th percentile, 75th percentile, minimum and maximum will be provided along with the 95% CI for the median. The proportion and 95% CI for the number of patients with durable responses at 6 months and 12 months from the onset of response will be provided. Other clinically relevant timepoints may also be included if data warrant.

### 6.3.5. Clinical Benefit Rate

The CBR along with exact Clopper-Pearson 95% CI will be presented.

### 6.3.6. Interim Futility Analysis

A pre-planned interim futility analysis based on investigator assessed ORR will be conducted after 20 patients are enrolled in the cohort 1 primary efficacy analysis population and have been followed for at least one tumor assessment (i.e., 6 weeks +/- 2 weeks). Should four or more objective responses be observed at the time of the interim analysis, enrollment to cohort 1 for the primary analysis population will continue until a minimum of 55 patients. The futility analysis will be considered non-binding as factors other than ORR may be factored in (such as depth of response, duration of response, tumor type and fusion partner).

## 6.4. Safety Analyses

The assessment of the incidence of adverse events during the study will consist of the recording of any AEs, SAEs, DLTs, etc. Safety will also be assessed through clinical laboratory evaluations, immunogenicity assessments, vital signs, electrocardiograms (ECGs), physical examinations, ECOG performance status, and prior and concomitant medication reporting.

The safety analysis will be based on the Safety Population and will be presented by cohort (cohort 1 primary efficacy analysis population, cohort 1, cohort 2, cohort 3) and all cohorts combined.

### 6.4.1. Extent of Exposure

Descriptive statistics will be provided for total treatment duration, total dose planned, actual total dose administered, and relative dose intensity.

The number and percentage of patients initiating a given number of treatment cycles and seribantumab infusions will be summarized. A cycle will be defined as 28 days. In addition, the number and percentage of patients with dose modification, dose interruption, or missed dose will be summarized, along with the reason.

The seribantumab administration data will be presented in a by-patient listing.

### 6.4.2. Adverse Events

Patient incidence will be summarized in tables. Frequency ordering will be used for the table presentation (i.e. order by the overall grouping in descending frequency for each SOC and for each PT within each SOC).

An overview of adverse events will be provided which summarizes the patient incidence of the following. This overview will include the number and percentage of patients with:

- Any AEs;
- Any TEAEs;
- Any drug related TEAEs;
- Any serious adverse events (SAEs);
- Any serious TEAE (TESAEs);
- DLTs;
- CTCAE grade 3/4/5 TEAEs;
- CTCAE grade 3/4/5 TEAEs related to seribantumab;
- TEAEs leading to dose reduction or interruption of study drug;
- TEAEs leading to discontinuation of study drug;
- TEAEs resulting in Death.

The number and percentage of patients with AEs will be tabulated by the highest CTCAE Grade, SOC, and PT. DLTs, TEAEs, TEAEs related to study drug will be summarized in the same manner.

TEAEs will also be summarized by SOC and PT. DLTs, CTCAE Grade 3/4/5 TEAEs, TESAEs, drug-related TEAEs, drug-related CTCAE Grade 3/4/5 TEAEs, AEs leading to dose reduction or interruption of study drug, and AEs leading to discontinuation of study drug will be summarized in the same manner.

For all above summaries, patients with multiple adverse events will be counted only once per SOC and PT.

Listings will be presented for TEAEs and TESAEs.

### 6.4.3. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be summarized using descriptive statistics for select laboratory parameters (e.g. serum or plasma chemistry, complete blood count) including

absolute measurements and changes from baseline by scheduled time of evaluation. Changes from baseline by scheduled time of evaluation will include EOT visit, maximum post-treatment value, and minimum post-treatment value. Both scheduled and unscheduled post-treatment visits will be considered for the summaries of the maximum and minimum post-treatment values.

Abnormal laboratory results will be graded according to NCI CTCAE v5.0 as applicable.

Clinical laboratory evaluations will be listed by patient and abnormal values will be flagged.

### 6.4.4. Vital Signs

Descriptive statistics will be provided for vital signs measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and weight). Actual observed values and changes from baseline by scheduled evaluation, and maximum and minimum post-treatment values will be presented.

Both scheduled and unscheduled post-treatment values until the EOT will be considered for summaries of the minimum and maximum on-treatment values. In addition, box plots of change from baseline values by visit for systolic and diastolic blood pressure and pulse rate will be produced.

All vital signs assessments will be presented in a by-patient listing.

### 6.4.5. Electrocardiograms

Note that the mean of the triplicate readings will be obtained at Screening for each patient prior to summarizing.

Continuous ECG parameters (Cardiac Rate, PR, RR, QRS, QT, QTcF) will be summarized using descriptive for actual values and for changes from baseline by scheduled time of evaluation, including the maximum post-treatment value. Both scheduled and unscheduled post-treatment values will be considered for summaries of the maximum post-treatment values.

The Fridericia-corrected QT interval (QTcF) will be calculated as QTcF = QT/(RR)^1/3 for the above summaries.

- Increase from baseline QTcF > 30 ms
- Increase from baseline QTcF > 30 ms and QTcF ≤ 60 ms
- Increase from baseline QTcF > 60 ms

Box plots or other graphical summaries may be produced for QTcF absolute and change from baseline values if warranted after data review.

Overall evaluation of ECG is also collected at each visit in terms of normal or abnormal, and the relevance of the abnormality is termed as “clinically significant” or “not clinically significant”, this information may be summarized.

### 6.4.6. Physical Examinations

The overall physical examination result at each time point (including scheduled and unscheduled will be listed by-patient.

### 6.4.7. ECOG Performance Status

For patients with ECOG performance status assessments, the performance status at each visit on study and worst post-baseline assessment will be presented using frequencies and percentages. Both scheduled and unscheduled visits will be considered in determination of the worst post-baseline assessment.

ECOG performance status results will be presented in a by-patient listing.

### 6.4.8. Other Safety Assessments

Results from other safety assessments (e.g. pregnancy test) will be presented in by-patient listings if applicable.

## 6.5. Covariates and Subgroups

The following covariates and subgroups are of interest:

- Tumor type (NSCLC vs other tumors)
- Fusion partner (ADAM9, AGRN, APP, ATP1B1, BAG4, CD74, CDH1, COX10-AS1, DIP2B, DPYSL2, FUT10, GDF15, HMBOX1, IL1RL2, ITGB1, MDK, MRPL13, NOTCH2, PARP8, POMK, RBPMS, RNF169, ROCK1, SDC4, SETD4, SLC3A2, TMPRSS3, TNC, TSHZ2, VAMP2, VTCN1, WHSC1L1, ZMYM2)

Additional efficacy and safety analysis may be performed by subgroups for cohort 1 primary efficacy analysis population. Waterfall plot of responses will be provided by fusion partner.

## 6.6. COVID-19

Due to the COVID-19 pandemic, additional analyses (e.g., sensitivity analysis) may be performed to assess the impact of COVID-19 on clinical trial data.

Applicable data collected in relation to COVID-19 on the CRF will be summarized as appropriate and/or included in data listings.

Protocol deviations resulting from COVID-19 will be recorded and included in the protocol deviation listing.

## 6.7. Pharmacokinetic Analysis

Plasma concentrations by patient, cycle, day, and time will be obtained and documented at various time points during the treatment with seribantumab.

If applicable, additional PK analysis and methods will be described in a standalone PK analysis plan.

PK concentration results will be presented in a by-patient listing.

# 7. GENERAL INFORMATION

## 7.1. Statistical Software

The creation of analysis datasets and statistical analyses will be done using SAS® version 9.4 or higher. The Medpace standard operating procedures (Medpace Standard Operating Procedures GL-DS-02-S4 and GL-DS-03-S3, or newest version at the time of analysis if applicable) will be followed for the validation of all SAS programs and outputs.

## 7.2. Format of Tables, Listings, and Figures

The format of tables, listings, and figures will be described in a stand-alone programming specifications document. The programming specification document will be prepared before database lock (or interim data lock for analyses presented at interim analysis).

# 8. CHANGES FROM PROTOCOL-SPECIFIED ANALYSIS

An independent central review of scans was not done due to Sponsor decision to end the study prior to full enrollment. Therefore, the primary efficacy endpoint and secondary efficacy endpoints utilizing independent radiologic review will not be analyzed.

The following exploratory endpoints in Protocol 7.0 will not be analyzed:

- To evaluate if mechanistically linked exploratory biomarkers from tumor tissue or blood samples correlate with clinical outcomes
- To evaluate changes from baseline in quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)

For Cohort 1 Primary Efficacy Analysis Population definition, “based on independent central reviews” was removed from the last criteria.

Cohort 2 and Cohort 3 Efficacy Analysis Population, intended for exploratory efficacy analysis, will not be analyzed.

# 9. REFERENCES

Brookmeyer, R., & Crowley, J. (1982). A confidence interval for the median survival time. *Biometrics*, 29-41.

Kalbfleisch, J. D. & Prentice, R. L. (2002). *The statistical analysis of failure time data* (2nd ed.). Hoboken, NJ: John Wiley & Sons, Inc.