Statistical Analysis Plan: I4T-MC-JVDT (version 2)

A Single-Dose Study in Healthy Participants to Characterize Ramucirumab Pharmacokinetics and Investigate Injection Site Reactions Following an Intravenous Infusion or Subcutaneous Administration of Ramucirumab

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STATISTICAL ANALYSIS PLAN

A Single-Dose Study in Healthy Participants to Characterize Ramucirumab Pharmacokinetics and Investigate Injection Site Reactions Following an Intravenous Infusion or Subcutaneous Administration of Ramucirumab

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Clinical Phase I

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
ADA	Anti-drug antibody
AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BQL	Below the lower limit of quantitation
CL	Apparent total body clearance of drug calculated at intravenous administration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
ECG	Electrocardiogram
F	Bioavailability based on AUC(0-∞)
ICH	International Conference on Harmonisation
ISP	Injection site pain
ISR	Injection site reaction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation

$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TE ADA	Treatment-emergent antidrug antibody
TE ADA+	Treatment-emergent antidrug antibody positive
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
VAS	Visual analog scale
Vss	Volume of distribution at steady state following intravenous administration
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z	Volume of distribution during the terminal phase after intravenous administration (IV administration only)
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration (SC administration only)
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 15 May 2020), Protocol Amendment (a) (final version dated 26 June 2020), Protocol Amendment (b) (final version dated 14 July 2020), and Protocol Amendment (c) (final version dated 21 October 2020).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objectives and Endpoints

Primary Objectives	Primary Endpoints
• Evaluate ramucirumab safety following a single dose in healthy participants	• Incidence of adverse events (AEs), treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs) after intravenous (IV) administration and subcutaneous (SC) administration in healthy participants
• Assess injection site reactions (ISRs) following SC administration of ramucirumab using ISR questionnaire	• Characterization and measurement of incidence and severity of ISRs (including injection site pain [ISP]) using data collected from the ISR questionnaire
• Assess ramucirumab PK following a single dose of IV or SC administration	• PK parameters: o IV: area under the concentration versus time curve (AUC) from zero to infinity ($AUC_{[0-\infty]}$), maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}) o SC: $AUC_{(0-\infty)}$, C_{max}, t_{max} after SC administration

4.2 Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
• Immunogenicity	• The frequency and percentage of participants with preexisting antidrug antibodies (ADA) and with treatment-emergent antidrug antibody positive (TE ADA+) to ramucirumab will be tabulated and any difference after IV administration versus SC administration • For the TE ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies will also be tabulated in TE ADA+ participants • The relationship between the presence of antibodies and the PK parameters, including safety, to ramucirumab after IV versus SC administration
• Assess ISRs following SC administration of ramucirumab using Scarletred tool	• Characterization and measurement of incidence and severity of ISRs using data collected from the exploratory tool

5. STUDY DESIGN

This is a single-site study in healthy participants who will receive a single dose of SC or IV ramucirumab. The study will be participant- and investigator-blinded, randomized, and placebo-controlled (7 ramucirumab:3 placebo per group/dose level). Placebo will be used as a comparator for both IV and SC to allow interpretation of safety and tolerability data following administration.

There will be sentinel dosing in this protocol, the initial 2 participants will be randomized/dosed (1 ramucirumab:1 placebo), and subsequently (the next day), the remaining participants in the group will be dosed. This will be subject to a satisfactory safety review by the investigator. This will occur on both the first dose of SC (Group 1).

Participants will be screened within 28 days prior to Day 1 of dosing for each group. Participants will be admitted to the clinical research unit (CRU) as part of an inpatient visit on Day -1 and will be sequentially enrolled. In each group, participants will be randomized to receive a single dose of IV or SC ramucirumab or placebo (7 ramucirumab:3 placebo per group).

The participants receiving ramucirumab in each group will be administered the following dose level (3 dose levels predicted to be ultimately used for therapeutic intent):

- Group 1 will test a ramucirumab 350-mg SC dose
  - administered at a concentration of 175 mg/mL as 1×2-mL injection.
- Group 2 will test a ramucirumab 700-mg SC dose
  - administered at a concentration of 175 mg/mL as 2×2-mL injections.
- Group 3 will test a ramucirumab IV dose (maximum of 350 mg)
  - administered as a 60-minute infusion (35 mL×10 mg/mL)
  - Analysis of safety and PK data from Groups 1 to 3 will allow initiation of Group 6.
- Group 4 will test a ramucirumab 350-mg SC dose
  - administered at a concentration of 87.5 mg/mL as 2×2-mL injections
  - The purpose is to investigate the effect of a different drug product concentration on PK and safety and Group 1 will be the reference comparison group.
- Group 5 will test a ramucirumab 350-mg SC dose
  - administered at a concentration of 175 mg/mL as 2×1-mL injections
  - The purpose is to investigate the effect of a different volume administered at the injection site on PK and safety and Group 1 will be the reference comparison group.
- Optional Group 6 may test SC ramucirumab dose, maximum 350 mg
  - administered at a concentration of 175 mg/mL administered via an infusion pump according to the pharmacy manual

The SC injection site will be the abdomen.

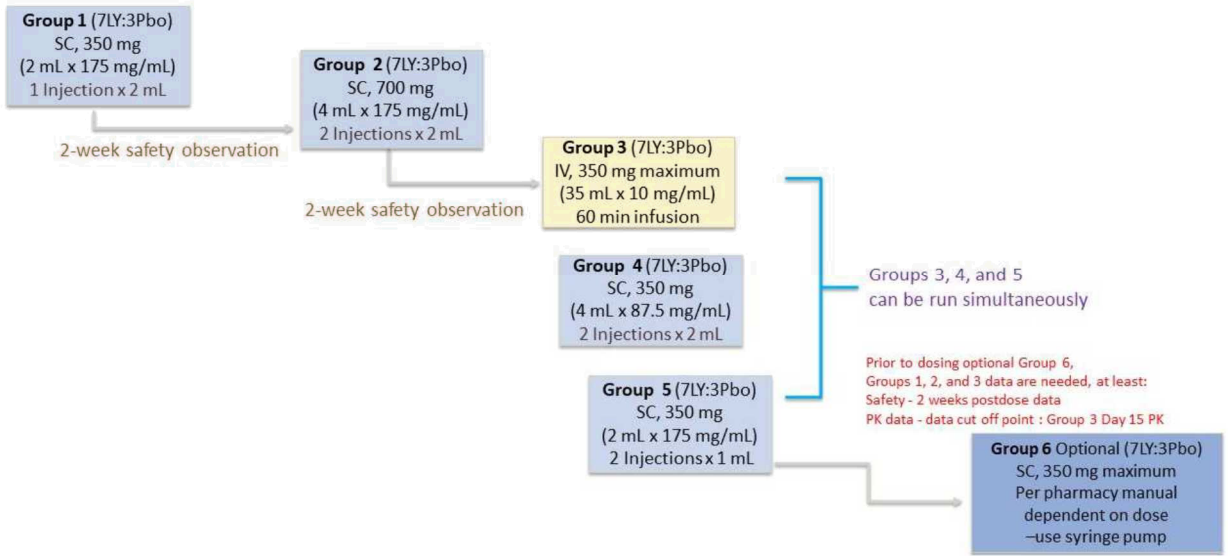
There will be at least a 2-week safety observation period between the titrating SC injection groups (Groups 1 and 2), and between the SC and IV 700-mg groups (Group 2 and 3) while local laboratory data is reviewed by the sponsor and investigator. If the safety review is acceptable, Groups 4 and 5 may be dosed simultaneously to Group 3, as no dose escalation is occurring in those groups. Group 6 will be dosed with an infusion pump once the sponsor has reviewed both the safety and PK data (Groups 1 through 3) and thus confirm the dose for Group 6 (maximum dose 1400 mg).

Following the safety review of Groups 1 and 2, the sponsor and investigator agreed to allow doses to be reduced for remaining groups. This may mean less groups may need to be studied. The asymptomatic transaminase increases observed during the safety review have also lead to a change in the exclusion criteria to further enhance the safety of the participants. In view of these findings, subsequent doses will be capped at 350 mg. Lower doses may also be studied. These decisions will be based on emerging data.

Injection site pain and ISRs will be monitored in each group, and a comparison of scorings will be used. The severity of ISP and ISRs reported across all participants will be evaluated. The data from Group 1, in comparison to Groups 4 and 5, will provide insight about the effect of injection volumes and ramucirumab concentration on ISP and ISR.

Participants will be discharged from the CRU on Day 8 after all study assessments have been completed and in agreement with the investigator. Participants may be required to remain in the CRU longer than Day 8, at the investigator's discretion. Participants will be required to return to the CRU for clinical assessments and blood samples on an outpatient basis until the final follow-up visit approximately 12 weeks following the IV infusion or SC injection.

The study schema is shown below.



6. TREATMENTS

The following is a list of the study treatment names that will be used in the TFLs.

Study Treatment Name	Abbreviations	Treatment order in TFL
Placebo IV	A	1
Placebo SC	B	2
350 mg ramucirumab IV	C	3
350 mg ramucirumab SC (1x2 mL)	D	4
350 mg ramucirumab SC (2x2 mL)	E	5
350 mg ramucirumab SC (2x1 mL)	F	6
700 mg ramucirumab SC (2x2 mL)	G	7
XX mg ramucirumab slow SC infusion	H	8

7. SAMPLE SIZE JUSTIFICATION

Approximately 60 participants will be enrolled and randomly assigned to study intervention (10 per group/dose level; 7 ramucirumab:3 placebo) to obtain at least 48 evaluable participants overall for an estimated total of at least 8 evaluable participants per intervention group (6 ramucirumab and at least 2 placebo). The sample size is not powered on the basis of statistical hypothesis testing. A participant will be considered evaluable when the participant completes up to 40 days of study procedures. When a participant does not complete up to 40 days of study procedures, the sponsor will be consulted if the participant will need to be replaced.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Enrolled/Intent-to-Treat" population will consist of all participants assigned to treatment, regardless of whether they took any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.

The "Safety" population will consist of all participants who received at least one dose of ramucirumab or placebo.

The "Pharmacokinetic" population will consist of all participants who received at least one dose of ramucirumab and have sufficient evaluable PK data.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum and N; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric coefficient of variation will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized by treatment group and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

Plasma concentrations of ramucirumab (LY3009806) will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	h*µg/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	h*µg/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	µg/mL	maximum observed drug concentration
t_{max}	H	time of maximum observed drug concentration
$t_{1/2}$	H	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
CL	L/h	total body clearance of drug calculated after intravenous administration
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (SC administration only)
V_z	L	volume of distribution during the terminal phase after intravenous administration (IV administration only)
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration
Vss	L	volume of distribution at steady state following intravenous administration
F	%	bioavailability based on AUC(0-∞) $$F = \frac{AUC\ [SC]}{AUC\ [IV]} \times 100$$

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the CSR.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on observed last quantifiable drug concentration will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

  - The compound is non-endogenous.
  - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.
  - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.
- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time outside sampling time window specified in Section 1.3.1 in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the CSR.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the CSR.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile
A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values
Individual values excluded as outliers will be documented in the CSR. Approval of the CSR will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

Ramucirumab bioavailability will be estimated. PK parameters will be evaluated to estimate ramucirumab $AUC_{(0-\infty)}$ and C_{max} dose proportionality following SC administration in the dose range investigated. Log-transformed ramucirumab C_{max} and $AUC_{(0-\infty)}$ parameters will be evaluated in a linear mixed effects model with fixed effects for dose (Groups 1, 4, and 5 who received 350 mg will be combined if appropriate). The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval.

For ramucirumab SC dosing PK parameters, the t_{max} will be analyzed using a Wilcoxon rank-sum test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated to assess similarity or not in t_{max} between dose level groups 1, 4, 5 combined compared to group 2 and group 6.

The above-mentioned analysis investigating the relationship (e.g. linearity/proportionality) between ramucirumab PK parameters and dose may be adjusted/repeated in the event of significant difference in PK between the 350 mg SC groups (Group 1, 4, 5). Such difference would indicate significant impact of either injection volume or drug product concentration on the PK. In this scenario, the analysis, investigating the relationship (e.g. linearity/proportionality) between ramucirumab PK parameters and dose, may be repeated by excluding the data from one or two of the 350 mg SC group.

Comparison of $AUC_{(0-\infty)}$, C_{max} and t_{max} between Group 1 and Group 4 will enable to assess the effect of changing the drug product concentration on the exposure. The log-transformed $AUC_{(0-\infty)}$, C_{max} and t_{max} will be the response variable, and the drug product concentration (that is, Group 1 and Group 4) is the explanatory variable.

Comparison of $AUC_{(0-\infty)}$, C_{max} and t_{max} between Group 1 and Group 5 will enable to assess the effect of changing the volume injected at one site of injection on the exposure. The log-transformed $AUC_{(0-\infty)}$, C_{max} and t_{max} will be the response variable, and the volume injected (that is, Group 1 and Group 5) is the explanatory variable.

Example SAS Code:

```
proc mixed data=data alpha=0.1;
by parameter;
class dose;
model logpk = dose / ddfm=kr residual cl;
lsmeans dose / pdiff=control('1') alpha=0.1;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A TEAE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose. For Group 6 with SC infusion, the onset time of the AE will be relative to the start of infusion.

All AEs will be listed. TEAEs will be summarized by treatment, group, dose level, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of TEAEs will be summarized by treatment, group, dose level, Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. CTCAE version 5.0 will be used to assign AE severity grades. Any SAEs will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version March 2020 B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter, treatment, group, and dose level, together with changes from baseline, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

Coagulation and thyroid-stimulating hormone data will be listed.

Samples for serum immunoglobulins, and their derived total, will be summarized and listed by parameter and treatment.

9.4.4 Vital signs

Where supine blood pressure and pulse rate are measured in triplicate, the mean value will be calculated and used in all subsequent calculations.

Vital signs data will be summarized by treatment, group, and dose level, together with changes from baseline, where baseline is defined as the mean of the triplicate Day 1 predose assessment.

Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

9.4.5 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

9.4.6 Immunogenicity Assessments

The frequency and percentage of participants with preexisting ADAs and with treatment-emergent ADAs (TE ADA) to ramucirumab will be tabulated and listed by treatment.

For participants who are ADA negative at baseline, TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay (1:10). For participants who are ADA positive at baseline, TE ADAs are defined as those with a 4-fold (2 dilution) increase in titer compared to baseline. The frequency and percentage of participants with neutralizing antibodies will also be tabulated for participants with TE ADA+.

The relationship between the presence of antibodies and the PK parameters, including safety to ramucirumab, may be assessed. All immunogenicity analysis will be performed and reported by Eli Lilly.

9.4.7 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the patient's medical history, alternative causes, and symptoms.

These data will be listed.

9.4.8 Injection-Site Reactions

Injection-site reaction data (including erythema, induration, pain, pruritus, edema, and bleeding) will be listed and summarized by treatment in frequency tables. The exploratory ISR data collected from the Scarletred tool at the same timepoints will be reported separately.

9.4.9 Injection-Site Pain Assessment

Intensity of pain data will be quantified using a 100-mm validated VAS where 0 mm represents "no pain" and 100 mm represents "worst possible pain". The data will be summarized and listed by treatment and timepoint.

9.4.10 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

9.4.11 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

However, there will be periodic reviews of data to assess safety, tolerability, and PK data. There will be sentinel dosing in this protocol, the initial 2 participants will be randomized/dosed (1 ramucirumab:1 placebo), and subsequently (the next day), the remaining participants in the group will be dosed. The following information belongs in this section:

- Safety reviews are planned prior to dose escalation after 2-week safety data are available.
- The Lilly PK team will review the PK data for Groups 1 and 2 if timing permits.
- The Lilly PK team will review the PK data once Group 1 through 3 PK samples have been collected (cutoff 2-week sample collection in Group 3).

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

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