I4T-MC-JVDU Statistical Analysis Plan Version 2

A Phase 1, Nonrandomized, Open-Label Investigation of Subcutaneous Ramucirumab Administration in Participants with Advanced Solid Tumors

NCT04557384

Approval Date: 2-Jun-2021

1. Statistical Analysis Plan: I4T-MC-JVDU: A Phase 1, Nonrandomized, Open-Label Investigation of Subcutaneous Ramucirumab Administration in Participants with Advanced Solid Tumors

Subcutaneous Ramucirumab (LY3009806)

Phase 1, nonrandomized, open-label study of subcutaneous ramucirumab administration in participants with advanced solid tumors.

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Protocol I4T-MC-JVDU
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 02-September-2020
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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved prior to the first visit when a subject receives study drug.

Statistical analysis plan Version 2 was approved after the internal review of Cohort A. Sample size in Cohort B was changed to reflect the safety and PK information collected from Cohort A.

4. Study Objectives

4.1. Primary Objective

The primary objective of the study is to determine a recommended ramucirumab subcutaneous (SC) dosing regimen for future studies by assessing the pharmacokinetic (PK) parameters and safety of ramucirumab after SC administration.

4.2. Secondary Objectives

The secondary objectives are as follows:

- to assess the immunogenicity of ramucirumab after SC administration
- to assess injection site reactions (ISRs) following SC administration of ramucirumab using ISR questionnaire.

4.3. Exploratory Objectives

The exploratory objective of the study is to explore the antitumor activity of ramucirumab following SC administration.

5. Study Design

5.1. Summary of Study Design

The study comprises 3 sequential dose cohorts: Cohorts A, B, and C. Participants with refractory/relapsed solid tumors with evaluable disease and who have exhausted all treatments with proven clinical benefit, as well as participants with a diagnosis where ramucirumab is clinically acceptable treatment as a monotherapy (all cohorts) or in combination with additional anti-cancer therapy (Cohorts B and C only), are eligible for Study I4T-MC-JVDU (JVDU). Each treatment cycle is either 21 days or 28 days based on the treatment regimen, with SC ramucirumab administered weekly for 3 doses or 4 doses, respectively, within each cycle. Participants in Cohorts B and C who are planned to receive ramucirumab in combination with additional anti-cancer therapy will receive weekly SC ramucirumab as monotherapy for at least 3 weeks for safety assessment, prior to initiation of the combination agent.

5.2. Determination of Sample Size

A maximum of approximately 30 participants will be treated in this study.

5.2.1. Cohort A

Three participants will be enrolled in Cohort A and followed for a minimum of 3 weeks prior to opening enrollment to Cohort B. If new or unexpected safety findings are identified relative to the large database of intravenous (IV) ramucirumab, or if 1 or more participants do not have sufficient PK data to inform dose for Cohort B, up to an additional 3 participants may be enrolled into Cohort A.

5.2.2. Cohort B (Sub-Cohorts B1, B2, and B3)

The internal review committee will review the totality of available safety data from Cohort A and Study I4T-MC-JVDT (JVDT), and based on this, will make a recommendation to open enrollment to Sub-Cohort B1.

Sub-Cohort B1 will initially recruit 3 participants to receive the maintenance weekly regimen, and based on the review of the first 3 weeks of safety and PK data, the following may be decided:

- to enroll up to 3 additional participants in Sub-Cohort B1, if new or unexpected safety findings are identified relative to the large database of IV ramucirumab at an alternate dose
- to enroll up to 3 additional participants in Sub-Cohort B1, if 1 or more participants in Cohort B1 do not have a sufficient PK data to inform dose for Cohort B2, or
- to open Sub-Cohort B2 at the determined loading and maintenance dosing regimen based on the available data.

Sub-Cohort B2 will recruit a minimum of 3 participants but will not exceed 6 participants. The number of participants in Sub-Cohort B2 will depend on the dosing decisions made at the data reviews after the first 3 and 6 participants have completed 3 weeks of treatment in

Sub-Cohort B2. If either analysis reveals that the Sub-Cohort B2 dosing regimen is not optimal, then the optional Sub-Cohort B3 (N=6) may be opened to investigate an alternative dose, if deemed appropriate.

Overall, the maximum number of participants in Cohort B is approximately 18.

5.2.3. Cohort C

Cohort C will initiate recruitment of 6 participants once 3 weeks of dosing safety data from Cohort B (in at least 6 participants) and initial PK data support pursuing further enrollment at the same dosing regimen. The study population will be the same as Cohort B. The dose regimen for Cohort C is anticipated to be the same as the preceding 6 participants in Cohort B. This expanded number of participants will provide additional PK and safety data to inform potential further development of SC ramucirumab.

5.3. Method of Assignment to Treatment

5.3.1. Cohort A Dose Selection

The ramucirumab SC dose for the initial Cohort A (n=3 to 6 participants) has been chosen with the intent to match the steady-state area under the plasma concentration versus time curve (AUC) of the 8-mg/kg every 2 weeks IV regimen, assuming a bioavailability of 80%. The initial ramucirumab SC loading dose will be 700 mg followed by a weekly ramucirumab SC injection maintenance dose of 350 mg.

5.3.2. Cohort B (Sub-Cohorts B1, B2, and B3) Dose Selection

Cohort B dose selection is intended to deliver a trough concentration (C_{trough}) >50 µg/mL and a steady-state AUC similar to the approved IV ramucirumab dose regimen of 10 mg/kg every 2 weeks. This will be accomplished by investigating a loading dose and maintenance dose paradigm, which will deliver target C_{trough} and steady-state concentration rapidly.

Table 5.1 below indicates the anticipated ramucirumab SC dosing regimen for Cohort B, as a function of estimated bioavailability.

Table 5.1. Initial Dose Level Options for Cohort B

Bioavailability (Mean F)	AUC at steady state eq to (Q2W IV)	SC LD one dose (mg)[a]	SC MD (mg) QW
40% to 50%	10 mg/kg	1750	875
50% to 65%	10 mg/kg	1400	700
65% to 80%	10 mg/kg	1120	560
80% to 100%	10 mg/kg	880	440

Abbreviations: AUC = area under the plasma concentration versus time curve; eq = equivalent; F = bioavailability; IV = intravenous; LD = loading dose; MD = maintenance dose; SC = subcutaneous; Q2W = every 2 weeks; QW = every week.

a In Sub-Cohort B1, no loading dose will be given.

Interim data from Study JVDT indicates a bioavailability of 40% and peak concentration occurring at 4 days postadministration for SC ramucirumab. With a bioavailability of 40%, a starting regimen of ramucirumab SC loading dose (LD) of 1750 mg and maintenance dose (MD) of 875 mg in Cohort B is proposed. The proposed maximum ramucirumab SC LD of 1750 mg will deliver exposure equivalent to 10 mg/kg/week and 13 mg/kg/week for participants with body weights of 70 kg and 55 kg, respectively. Assuming the same bioavailability, the proposed maximum ramucirumab SC MD of 875 mg will deliver exposure equivalent to 5 mg/kg/week and 6 mg/kg/week for participants with body weights of 70 kg and 55 kg, respectively. Consequently, the exposure achieved following both proposed LD and MD will be lower than the highest investigated ramucirumab IV doses of 20 mg/kg every 3 weeks IV (Study I4T-IE-JVBN [IMCL CP12-0402]) as well as the maximum tolerated dose exposure of 13 mg/kg once weekly IV (as determined in Study I4T-IE-JVBM [IMCL CP12-0401]).

The combined PK and safety data from Cohort A and Sub-Cohort B1 will inform the starting dose selection for Sub-Cohort B2 (maximum planned dose ramucirumab SC LD of 1750 mg followed by 875 mg SC MD once weekly). Table 5.2 shows the proposed dosing regimen for each sub-cohort as well as possible alternate dose decisions that could be made based on either bioavailability and/or safety as described in Section 5.2.

Table 5.2. Dose Options for Cohort B

Sub-Cohort	Proposed LD[a]	Proposed MD[b]	Possible Dose Decision Based on Either Bioavailability and/or Safety
B1	Not Applicable	875 mg SC QW	e.g., MD 700 mg SC QW e.g., MD 560 mg SC QW e.g., MD 440 mg SC QW
B2[c]	1750 mg SC infusion	875 mg SC QW	e.g., LD 1400 mg SC; MD 700 mg SC QW e.g., LD 1120 mg SC; MD 560 mg SC QW e.g., LD 880 mg SC; MD 440 mg SC QW
B3[c] (Optional)	<1750 mg SC infusion	<875 mg SC QW	e.g., LD 1400 mg SC; MD 700 mg SC QW e.g., LD 1120 mg SC; MD 560 mg SC QW e.g., LD 880 mg SC; MD 440 mg SC QW

Dose Options for Cohort B

Abbreviations: LD = loading dose; MD = maintenance dose; PK = pharmacokinetic; QW = every week; SC = subcutaneous.

a LD: During Week 1 administered as 1 dose on Day 1.

b MD: Weekly dosing starting on Week 2 (Cycle 1 Day 8) except for B1 when it will be starting on Week 1 (Cycle 1 Day 1).

c Only 1 dosing regimen (1 LD - MD level) will be investigated in Sub-Cohort B2 and Sub-Cohort B3. Dose will be selected based on PK and safety data as described in Section 5.2.

5.3.3. Cohort C Dose Selection

Cohort C will evaluate, in 6 participants, the dose regimen identified in Cohort B which answers the safety and PK objective of the study. Cohort C may open if 3-week dosing safety data from Cohort B (in at least 6 participants) and initial PK data support pursuing enrollment at the same dosing regimen.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of sponsor or its designee. The study PK scientist will be responsible for designing, conducting, and interpreting the PK analysis and delivering PK parameters. The interpretation of final study results will be the responsibility of the clinical research physician (CRP), the study statistician, and PK scientist. The primary analysis will happen after all participants complete the PK and safety assessment at Week 3 or discontinue treatment prior to completing Week 3.

This is not a controlled study and statistical tests of clinical outcomes are not feasible. Summaries will be limited to summary statistics. Unless otherwise stated, any confidence intervals (CIs) will be given at a 2-sided 95% level. Exploratory statistical analysis procedures not specified in the present document will be executed if deemed appropriate.

The following general terms will be used globally in the SAP:

- Unless otherwise specified, summary statistics stand for the number of participants with an observation (n), mean, standard deviation, median, minimum, and maximum for continuous variables; and population size (N), the number of subjects with events (n) and the proportion of subjects with events (p=n/N) for categorical variables.
- **Entered population** will consist of all participants who sign the informed consent form.
- **Enrolled/Intent-to-Treat population** will consist of all participants who receive at least 1 dose of study drug.
- **Efficacy population** will consist of all participants with evaluable disease per their baseline assessment and at least 1 complete postbaseline assessment.
- **Safety population** will consist of all participants who take at least 1 dose of study drug. The safety population will be used for all analyses of dosing, exposure, and safety.
- **Pharmacokinetic analysis population** will consist of all treated participants who receive at least 1 dose of study drug and have at least 1 evaluable PK sample.

6.2. Handling of Dropouts or Missing Data

For patient data listings, observed data will be used and missing data will not be imputed.

General rules for imputing dates related to adverse events (AEs) or concomitant therapy:

- Onset date of an AE or start date of a concomitant therapy:
    - If only the day is missing, the date will be set to:
        - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment.

        - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of first study treatment.
    - If both the day and month are missing, the complete date will be set to:
        - January 1 of the year of onset, if the onset year is after the year of the first study treatment.
        - The date of the first dose, if the onset year is the same as the year of the first study treatment.

- Resolution date of an AE or end date of a concomitant therapy:
    - If only the day is missing, the date will be set to the last day of the month of the occurrence, or to the date of death of the patient died in the same month.
    - If both the day and month are missing, the date will be set to December 31 of the year of occurrence, or to the date of death of the patient died in the same year.

If a date is completely missing, then the AE will be considered as treatment emergent. In case of additional therapies, the therapy will be considered concomitant.

General rule for imputing other dates: If a date variable is needed for an analysis, use the following general rule to impute incomplete date:

- If the day of a date is missing, but not the month or year, then assign Day 1 of the month to the day.
- If the month of a date is missing, but not the day or the year, then assign January to the month.

After imputation, the imputed date should be logically consistent with other relevant date variable(s).

6.3. Participant Disposition

All patient discontinuation data will be listed, including the extent of the patient participation in the study. If known, a reason for their discontinuation from treatment and from study will be listed and summarized overall and by dose level (if appropriate). All participants entered in the study will be included in the summary and listing.

6.4. Participant Characteristics

The following patient demographic and other baseline characteristics will be summarized overall and by dose level (if appropriate):

- patient demographics: age (years), gender, race, ethnicity, weight (kg), height (cm), Eastern Cooperation Oncology Group Performance Status (ECOG PS), alcohol use and tobacco use
- baseline disease characteristics: pathological diagnosis type at initial diagnosis, duration of disease (months), disease stage and histopathological diagnosis grade at study entry

- prior cancer therapies
- historical illness by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), including infusion-related reaction (IRR) and hypersensitivity, presented in decreasing frequency

Patient listings of demographic data and baseline characteristics will be provided. Patient listings of prior cancer therapies (surgery, radiotherapy, and systemic therapy) will be provided.

6.5. Treatment Compliance

Ramucirumab SC and other intravenously administered study drugs will be administered at the investigational sites. As a result, patient compliance is ensured.

The number of tablets taken relative to the number expected to be taken may be summarized for other study drugs such as erlotinib, if appropriate.

6.6. Concomitant Therapy

The following concomitant medications used in study treatment period or the 30-day postdiscontinuation follow-up period will be summarized by numbers and percentages overall and by dose level (if appropriate), presented in decreasing frequency of the World Health Organization (WHO) drug term:

- All concomitant medications
- Supportive care and select medications including growth factors

  Note: such drugs to be used for programming will be identified through reviewing of the unique drug terms collected in the study
- Premedication for study drug

Patient listing of all concomitant therapies and premedications will be provided.

The number and percentage of participants with blood transfusions experienced in study treatment period or the 30-day postdiscontinuation follow-up period will be summarized overall and by dose level (if appropriate).

6.7. Efficacy Analyses

The efficacy of ramucirumab following SC administration is an exploratory objective of the study. The planned analyses of efficacy are detailed in Section 6.12.

6.8. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

All PK/pharmacodynamic (PD) analysis will be the responsibility of Lilly Global PK/PD and Pharmacometrics group based on applicable Global PK/PD and Pharmacometrics Standard Operating Procedures and software approved by Global PK/PD and Pharmacometrics group's management.

6.8.1. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on all data from all participants who received at least 1 dose of investigational product and have sufficient evaluable PK samples.

Ramucirumab concentration will be summarized by standard summary statistic per dose level and collection time point. Additionally, PK data may be added to the large IV ramucirumab PK database in cancer participants to estimate, using non-linear mixed-effect modelling, the post-hoc individual PK-parameter estimate for Study JVDU participants.

6.8.2. Immunogenicity Analyses

Treatment-emergent antidrug antibody (TE ADA) evaluable: A patient is evaluable for TE ADA if there is at least 1 non-missing test result for ramucirumab ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of subjects evaluable for TE ADA in each cohort.

TE ADA positive (+): A patient evaluable for TE ADA is considered to be TE ADA+ if the subject has at least 1 postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment-boosted). If baseline result is ADA Not Present, then the subject is TE ADA+ if there is at least 1 postbaseline result of ADA Present with titer >= 20 (treatment-induced).

TE ADA inconclusive: A patient evaluable for TE ADA is considered TE ADA Inconclusive if 20% of the subject's postbaseline samples, drawn pre-dose, are ADA Inconclusive and all remaining postbaseline samples are ADA Not Present.

TE ADA negative (-): A patient evaluable for TE ADA is considered TE ADA- if not TE ADA+ and not TE ADA Inconclusive.

The frequency and percentage of participants with preexisting ADAs and with TE ADA to ramucirumab will be tabulated. For the TE ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated in TE ADA+ participants if assessed.

The relationship between the presence of antibodies to ramucirumab, the PK parameters, and PD response, including safety and efficacy, to ramucirumab may be assessed.

In the event of a hypersensitivity, ADAs and ramucirumab serum concentrations will be tabulated.

6.9. Safety Analyses

All participants who receive at least 1 dose of study drug will be summarized for exposure and safety.

6.9.1. Extent of Exposure

The following exposure-related variables will be reported using summary statistics overall and by dose level (if appropriate):

- Exposure: duration of treatment; number of cycles received; number of participants completing ≥1 cycle, ≥2 cycles, …, ≥6 cycles, and mean, standard deviation; number of participants with dose adjustments: dose reduction, dose delay, and dose omission;
- Reasons for dose adjustments;
- Dose intensity: cumulative dose; weekly dose intensity; relative dose intensity; overall weekly dose intensity; overall relative dose intensity.

Details of study drug administration will be included in participants listings.

6.9.2. Adverse Events

The National Cancer Institute - Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v5.0 criteria, the investigator will be responsible for selecting the appropriate system organ class (SOC) and assessing severity grade based on the intensity of the event.

Unless otherwise specified, when summarized by PT, AEs will be presented in decreasing frequency of PT; when summarized by SOC and PT, AEs will be presented in decreasing frequency of PT within SOC; and when summarized by NCI-CTCAE term, AEs will be presented in decreasing frequency of NCI-CTCAE term. If more than 1 AE is recorded for a patient within any SOC or PT term or NCI-CTCAE term, the patient will only be counted once on the most severe grade and the closest relationship to treatment.

Summary will be presented overall and by dose level (if appropriate).

6.9.2.1. *Overall Summary of Adverse Events*

A treatment-emergent adverse event (TEAE) is defined as any untoward medical occurrence that either occurs or worsens at any time after treatment and that does not necessarily have to have a causal relationship with this treatment.

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages overall and by dose level (if appropriate):

- participants with at least 1 TEAE, serious adverse event (SAE), or NCI-CTCAE Grade ≥3 TEAE
- participants with AEs that led to death (on study treatment, within 30 days of discontinuation from study treatment) or discontinuation
- participants with SAEs that led to discontinuation

The summary will be provided regardless of study drug causality, and repeated for events deemed by the investigator to be possibly related to study treatment.

A participants listing of all AEs will be provided.

6.9.2.2. *Treatment-Emergent Adverse Events*

The following summaries of TEAEs will be provided overall and by dose level, if appropriate ([*]repeat for events deemed by the investigator to be possibly related to study medication, [†]include consolidated summary):

- by PT[*†]
- CTCAE Grade ≥3 TEAE by PT[*†]
- by SOC and by PT[*]
- by maximum NCI-CTCAE grade and by PT[*†]

6.9.2.3. *Injection Site Reactions (ISRs)*

In addition to the typical AE analyses, the following analysis of the ISRs, which is of special interest in the study, will be provided overall and by dose level, if appropriate:

- participants with at least 1 ISR
- ISR details: anatomical location; directionality of the administration; injection site erythema; injection site induration; injection site pain; injection site pruritus; injection site edema

6.9.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

Reasons for deaths (study disease, AE [any study drug-related, procedural-related]) will be summarized and listed separately for 1) all deaths, 2) deaths on therapy, 3) deaths within 30 days of treatment discontinuation, and 4) deaths on therapy or within 30 days of treatment discontinuation, 5) deaths after 30 days of treatment discontinuation.

Serious adverse events will be summarized by PT and repeated for events deemed by the investigator to be possibly related to study medication, with consolidated summary performed if needed. A listing of SAEs will be produced.

In addition, the following analyses will be performed ([*]repeated for events deemed by the investigator to be possibly related to study medication, [†]include consolidated summary):

- AEs leading to death by PT[†]
- AEs leading to study treatment discontinuation by PT[†]
- AEs leading to study treatment dose adjustment by PT[†]
- Adverse events of special interest (AESIs) by PT[*]
- Listing of AESIs

6.9.4. Clinical Laboratory Evaluation

The severity of laboratory results will be classified according to CTCAE Version 5.0. The shifts in CTCAE toxicity grading from baseline to worst grade postbaseline (first dose up to 30 days after the last dose of study treatment) will be produced.

A participant listing of all laboratory data will be provided with a flag for values outside of the laboratory normal range as well as investigator site, patient identifier, age, gender, race, weight, and visit.

6.9.5. Vital Signs and Other Physical Findings

Weight at baseline will be presented using summary statistics. Change from baseline to on-treatment weight assessments will be presented. For systolic and diastolic blood pressure, shift from baseline will be provided. All vital signs including weight, temperature, blood pressure, heart rate, and respiratory rate will be listed for all enrolled participants. Hospitalizations during study or within 30 days of treatment discontinuation will be summarized and listed.

6.9.6. Electrocardiograms

Listing of ECG data will be provided.

6.10. Protocol Violations

All significant protocol violations will be listed by predetermined categories specified in the Trial Issue Management Plan.

6.11. Interim Analyses and Data Monitoring

An internal assessment committee will review the data on a cohort-by-cohort basis during the study to identify the dose providing the appropriate PK profile, and to assess whether safety findings inconsistent with the IV ramucirumab profile are observed. The investigators and the sponsor study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol. Furthermore, access to PK data will be planned in the course of the study to inform on dose selection particularly prior and during Cohort B (after the initial 3 participants in Cohort B complete 3-week sampling).

6.12. Planned Exploratory Analyses

The exploratory objective of the study is to explore the efficacy of ramucirumab following SC administration, specifically the best overall response. Best overall response is the best response recorded from the start of treatment until disease progression, in the order of complete response, partial response, stable disease, and progressive disease. Best overall response will be summarized for all participants evaluable for efficacy whose disease is assessable by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

If appropriate, best overall response will be estimated and reported overall and by dose level.

6.13. Annual Report Analyses

The following reports are needed for a Development Update Safety Report (DSUR):

- estimated cumulative subject exposure
- cumulative exposure to investigational drug, by demographic characteristics for ongoing unblinded clinical trials and completed clinical trials
- exposure information for ongoing clinical trials and clinical trials that completed during the reporting period
- listing of subjects who died during the DSUR reporting period
- discontinuations due to AEs during the DSUR reporting period

6.14. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.
- An AE is considered 'Serious' whether or not it is a TEAE.
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participants in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (for example, the clinical study report, manuscripts, and so forth).

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