Protocol I4T-MC-JVDT(c)

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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Approval Date: 21-Oct-2020

Title Page

Protocol Title: 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

Protocol Number: I4T-MC-JVDT

Amendment Number: (c)

Compound: LY3009806

Study Phase: Phase 1

Short Title: Single-Dose Study in Healthy Participants to Characterize Ramucirumab Pharmacokinetics and Safety after Subcutaneous Administration in Comparison to Intravenous Infusion

Acronym: JVDT

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 148078

Approval Date: Protocol Electronically Signed and Approved by Lilly: 15 May 2020

Protocol Amendment(a) Electronically Signed and Approved by Lilly: 26 June 2020

Protocol Amendment(b) Electronically Signed and Approved by Lilly: 14 July 2020

Protocol Amendment(c) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 21-Oct-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment(b)	*14-Jul-2020*
Amendment(a)	*26-Jun-2020*
Original Protocol	*15-May-2020*

Amendment(c):

Overall Rationale for the Amendment:

This amendment addresses the sponsor's and investigator's decision to allow doses to be reduced for remaining groups, as required.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Based on the safety review of Groups 1 and 2: • clarified that SC ramucirumab dosing will consist of up to 3 dose levels, • removed sentinel dosing for Group 3 IV dosing, • reduced dose from 700 mg IV to a maximum dose of 350 mg IV and reduced IV infusion volume from 70 mL to 35 mL for Group 3, • indicated that Group 6 will be optional and reduced maximum dose to 350 mg, • indicated that subsequent dose levels may be reduced, and • indicated that IV and SC doses will not exceed 350 mg for remaining groups.	To enhance the safety of the participants. The 700 mg dose was deemed unacceptable based on cases of asymptomatic transaminase increases, so the dose capped was at 350 mg.
1.2 Schema	Updated schema to reflect dose level changes based on safety data from Groups 1 and 2 and revised Group 6 to be optional.	To enhance the safety of the participants.
2.1 Study Rationale	Clarified that SC ramucirumab dosing will consist of up to 3 dose levels for subsequent dose-escalation groups.	To enhance the safety of the participants based on safety review of Groups 1 and 2.
4.1 Overall Design	Based on the safety review of Groups 1 and 2: • removed sentinel dosing for Group 3 IV dosing, • reduced dose from 700 mg IV to a maximum 350 mg IV for Group 3, • indicated that Group 6 may be dosed at a maximum dose of 350 mg according to the pharmacy manual if safety results are acceptable and of scientific value, • clarified that SC ramucirumab dosing will consist of up to 3 dose levels, • indicated that subsequent dose levels may be adjusted based on safety reviews, • removed Group 6 data for further implementation of loading dose regimen, and	To enhance the safety of the participants.

Section # and Name	Description of Change	Brief Rationale
	• indicated that exclusion criteria will be revised based on transaminase increases.	
4.1 Overall Design	Indicated that participants should follow local guidance and CRU precautions to minimize the risk for COVID-19.	To minimize the risk for COVID-19 infection.
4.3 Justification of Dose	Based on the safety review of Groups 1 and 2: • reduced dose from 700 mg IV to a maximum dose of 350 mg IV for Group 3, • reduced maximum dose level from 1400 mg to 350 mg for Group 6, • indicated Group 6 may not be needed based on emerging data, • capped maximum dose at 350 mg for all subsequent groups because of the acceptable safety profile, and • added explanation that margin of safety table was based on originally planned doses.	To enhance the safety of the participants.
5.2 Exclusion Criteria	For Exclusion Criterion [14]: • removed 1.5-fold for ULN, and • added AST and GGT.	To enhance the safety of the participants based on safety review of Groups 1 and 2.
5.2 Exclusion Criteria	For Exclusion Criterion [15]: • removed 1.5-fold for ULN, and • removed isolated bilirubin >1 fold ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%.	To enhance the safety of the participants based on safety review of Groups 1 and 2.
5.2 Exclusion Criteria	For Exclusion Criterion [16]: • removed with exception of Gilbert's syndrome or asymptomatic gallstones, and • specified that Gilbert's syndrome is not acceptable.	To enhance the safety of the participants based on safety review of Groups 1 and 2.
6.1 Study Intervention(s) Administered	Based on the safety review of Groups 1 and 2: • reduced dose from 700 mg IV to a maximum of 350 mg IV for Group 3, • removed 1400 mg SC dose, and • removed reference to approximately 30 minute duration for SC infusion (with pump) and added reference to the pharmacy manual.	To enhance the safety of the participants.

Section # and Name	Description of Change	Brief Rationale
8.2.3 Electrocardiograms	Removed reference to Section 7 for QTc withdrawal criteria and any additional QTc readings.	To remove a reference that was inadvertently included in the protocol.
9.4.2.2 Pharmacokinetic Statistical Inference	Modified the dose range investigated from 350 mg to 1400 mg to 350 mg to 700 mg based on safety review of Groups 1 and 2.	To reflect dose level changes based on safety review of Groups 1 and 2.
9.5 Interim Analyses	Indicated that PK data may be reviewed for Groups 1 and 2 if timing permits.	To add flexibility for reviewing PK data if needed.
Throughout	Minor editorial and formatting revisions	Minor and therefore have not been summarized

Abbreviations: AST = aspartate aminotransferase; COVID-19 = coronavirus disease 2019; CRU = clinical research unit; GGT = gamma-glutamyl transferase; IV = intravenous; PK = pharmacokinetic; QTc = corrected QT interval; SC = subcutaneous; ULN = upper limit of normal.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: 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

Short Title: Single-Dose Study in Healthy Participants to Characterize Ramucirumab Pharmacokinetics and Safety after Subcutaneous Administration in Comparison to Intravenous Infusion

Rationale:
Ramucirumab (Cyramza®; LY3009806) drug substance (hereafter referred to as ramucirumab), administered as an intravenous (IV) infusion, is approved for several cancer indications. There may be an opportunity to optimize the ramucirumab pharmacokinetic (PK) profile using a subcutaneous (SC) formulation. The clinical development of IV ramucirumab has been exclusively done in cancer patients. The large clinical data with IV ramucirumab, together with the nonclinical toxicology data, support investigating single IV and SC doses of ramucirumab in a healthy human population.

For the new, proposed ramucirumab SC route of administration, the important biopharmaceutic questions (such as PK and bioavailability) will be more efficiently investigated in the healthy human population.

The proposed study (I4T-MC-JVDT [JVDT]) will be the first-in-human study investigating single administration of IV ramucirumab (1 dose level) and SC ramucirumab (up to 3 dose levels) to establish the PK and safety profiles in healthy participants. This will allow both safe dosing of the new SC formulation and provide single-dose ramucirumab safety and PK profiles (both IV and SC) on which to build the remainder of the program.

In order to ensure safety, the doses planned in the proposed study will aim to not exceed the plasma concentrations (maximum drug concentration [C_{max}] and area under the concentration versus time curve [AUC]) tested in previous studies with ramucirumab IV. Furthermore, it is understood that SC administration of a monoclonal antibody leads to lower plasma levels (C_{max} and AUC) than the same dose administered IV. Comprehensive details on the Study JVDT design is presented in the overall study design section.

Objectives and Endpoints

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

Overall Design

Study JVDT will be the first-in-human study investigating single SC or IV administration of ramucirumab in healthy participants. The study will be at a single site. 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. The reason for randomizing 10 participants per group is to ultimately ensure that at least 8 participants (6 ramucirumab:2 placebo) in each group complete the study (that is, complete the first 40 days of study procedures per the schedule of events; see Section 4.4). Replacement participants may be enrolled if needed to reach the planned number of completers.

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 the first dose of SC (Group 1).

Participants may receive either a single dose of IV ramucirumab or a single dose of SC ramucirumab (up to 3 increasing/escalating dose levels) to establish the PK and safety profiles. It is planned that maximum 6 groups will be sequentially enrolled and the doses envisioned are those below:

- Group 1: SC ramucirumab 350 mg (1 injection of 2 mL×175 mg/mL)
- Group 2: SC ramucirumab 700 mg (2 injections of 2 mL×175 mg/mL)
- Group 3: IV ramucirumab to a maximum of 350 mg (60-minute IV infusion; maximum 35 mL×10 mg/mL)
- Group 4: SC ramucirumab 350 mg (2 injections of 2 mL×87.5 mg/mL)
- Group 5: SC ramucirumab 350 mg (2 injections of 1 mL×175 mg/mL)
- Optional Group 6: SC ramucirumab (maximum planned dose level, 350 mg, given as slow SC infusion).

Groups 4 and 5 are planned to investigate single SC ramucirumab dose of 350 mg with different volume of injection (2 injections of 1 mL×175 mg/mL) and different concentration of the drug product (2 injections of 2 mL×87.5 mg/mL) compared to the first group dosed at 350 mg (1 injection of 2 mL×175 mg/mL). Data from these groups will provide insight about the effect of injection volumes and ramucirumab concentration on the PK and tolerability of SC ramucirumab.

The initial dose planned for Groups 3 and 6 are to be modified based on emerging data discussed at the safety review between sponsor and investigator (see Section 4.3 for rationale).

More precisely, following the emerging data from Groups 1 and 2, the study doses are modified downwards. This is pending the full safety review of all data from Groups 1 and 2. The IV dose (Group 3) will not exceed 350 mg, and the subsequent SC doses will be capped at 350 mg (Groups 4 through 6). In Section 4.3 (Justification for Dose), Groups 1 and 2 safety data justifying that change are presented in more detail.

Disclosure Statement: This is a PK and safety study to test both the marketed ramucirumab IV formulation and a novel ramucirumab SC formulation in healthy participants with the objective of comparing PK exposure and safety following both routes of administration.

Number of Participants:

Approximately 60 participants will be enrolled and randomly assigned to study intervention to obtain at least 48 evaluable participants for an estimated total of at least 8 evaluable participants per intervention group (Section 9.2).

Intervention Groups and Duration:

Participants will be screened within 28 days prior to Day 1 of dosing for each group. Within 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 dosing groups or treatment intervention are as stated in the study design:

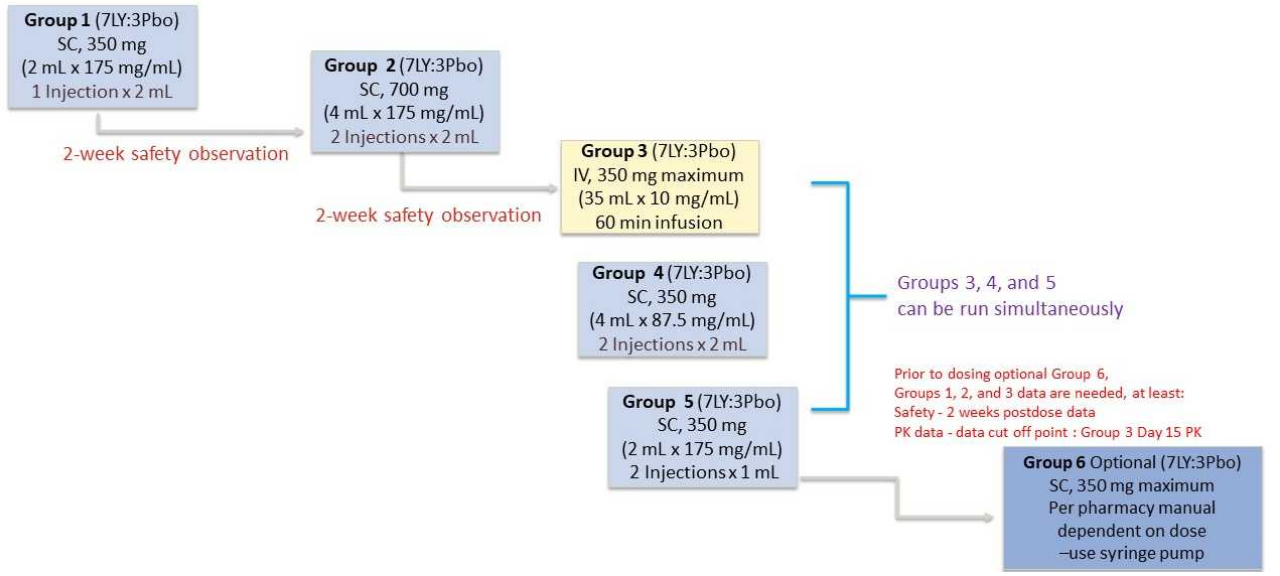
- Group 1: SC ramucirumab 350 mg (1 injection of 2 mL×175 mg/mL)
- Group 2: SC ramucirumab 700 mg (2 injections of 2 mL×175 mg/mL)
- Group 3: IV ramucirumab to a maximum of 350 mg (60-minute IV infusion; maximum 35 mL×10 mg/mL)
- Group 4: SC ramucirumab 350 mg (2 injections of 2 mL×87.5 mg/mL)
- Group 5: SC ramucirumab 350 mg (2 injections of 1 mL×175 mg/mL)
- Optional Group 6: SC ramucirumab (maximum planned dose level, 350 mg, given as slow SC infusion).

The 3 dosing groups will be sequentially enrolled/dosed after at minimum 2-week safety observation from the previous group has been reviewed. However, Groups 4 and 5 receiving the same SC ramucirumab dose as Group 1 may be dosed simultaneously to Group 3.

Participants will be admitted to the clinical research unit (CRU) as part of an inpatient visit on Day -1. Participants will be discharged from the CRU on Day 8 at the end of the inpatient visit after all study assessments for that visit have been completed and in agreement with the investigator. Participants will return thereafter to the CRU for clinical assessments and blood samples on an outpatient basis (according to the protocol Schedule of Activities) until the final follow-up visit approximately 12 weeks following the IV infusion or SC injection.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: IV = intravenous; LY = ramucirumab (LY3009806); Pbo = placebo; PK = pharmacokinetic(s); SC = subcutaneous.

1.3. Schedule of Activities (SoA)

Procedures/ Assessments	Screening	Baseline	Inpatient								Outpatient		EoT	F/U				Comments
			Dosing														ED	
Visit	**1**	**2**	**3**								**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
Informed consent	X																	
Review/confirm I/E criteria	X		P															
Complete medical history	X																	
Review preexisting conditions/AEs	X	X	P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE grading will be via CTCAE version 5.0.
Concomitant medications	X	X	P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Substance use (alcohol, tobacco)	X	X																Breath ethanol testing will be performed.
Physical examination	X	X					X							X			X	Complete physical examination will be performed at screening; brief physical examination at other time points. Symptom-directed physical examinations may be conducted at any time, as deemed necessary by the investigator.
Weight	X	X	P											X			X	
Height	X																	

Schedule of Activities (SoA)

Procedures/ Assessments	**Screening**	**Baseline**	**Inpatient**							**Outpatient**		**EoT**	**F/U**				**Comments**
			Dosing													**ED**	
Visit	**1**	**2**	**3**							**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
Vital signs (PR, BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.2 for details. Vital sign measurements will be measured after at least 5 minutes in the supine position (except body temperature). Blood pressure and heart rate will be collected in triplicate. On days with concurrent ECGs, vital signs, and/or PK sampling, these measurements should occur at approximately the same time. ECGs and vital sign measurements should occur prior to blood draw. Vital sign measurements will be obtained: • Day 1 at predose (prior to IV or SC dose, but within 90 minutes prior to predose blood draw) • End of infusion (IV group only) • 6 hours after end of infusion (IV group only) • Day 2 (24 hours postdose for IV and SC groups) • Any time for other specified visits (prior to blood draws at same visit).

Schedule of Activities (SoA)

Procedures/ Assessments	**Screening**	**Baseline**	**Inpatient**								**Outpatient**		**EoT**	**F/U**				**Comments**
			Dosing														**ED**	
Visit	**1**	**2**	**3**								**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
ECGs	X	X	X	X			X			X				X			X	On days with concurrent measurements, see vital signs row for more details. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Times are referenced to the end of dosing. ECGs will be obtained: • Day 1 at predose (prior to IV or SC dose, but within 90 minutes prior to predose blood draw) • End of infusion (IV group only) • 6 hours after end of infusion (IV group only) • Day 2 (24 hours postdose for IV and SC groups) • Any time for other specified visits (prior to blood draws at same visit)
Chest x-ray (posterior-anterior view)	X																	Investigator-designated/local. Performed at screening unless performed within the past 6 months, and x-ray/reports are available.
QuantiFERON®-TB Gold test or TST	X																	Investigator-designated/local. Follow-up TST will occur 2 to 3 days after screening.

Schedule of Activities (SoA)

Procedures/ Assessments	**Screening**	**Baseline**	**Inpatient**								**Outpatient**		**EoT**	**F/U**				**Comments**
			Dosing														**ED**	
Visit	**1**	**2**	**3**								**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
Admission to CRU		X																
Discharge from CRU										X								Following completion of Day 8 assessments.
Ramucirumab administration (IV or SC)			X															
HIV/Hepatitis B (surface antigen and core antibody)/Hepatitis C	X																	
Serum immunoglobulins (IgG, IgM, IgA)	X						X						X	X			X	Investigator-designated/local.
Urinary drug screen	X	X																
FSH	X																	For women not of childbearing potential, FSH will be drawn to confirm status as defined in Inclusion Criterion [7b] and to be exempt for pregnancy tests.
Pregnancy test	X	X												X			X	Investigator-designated/local. Serum pregnancy test will be conducted at screening only. Urine pregnancy test will be conducted at all other time points. A beta-human chorionic gonadotropin test may be performed to confirm a result that is positive or in the postmenopausal range.

Schedule of Activities (SoA)

Procedures/ Assessments	**Screening**	**Baseline**	**Inpatient**							**Outpatient**		**EoT**	**F/U**				**Comments**
			Dosing													**ED**	
Visit	**1**	**2**	**3**							**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
Clinical chemistry	X	X		X	X		X			X	X	X	X	X			X	Investigator-designated/local
Hematology	X	X		X	X		X			X	X	X	X	X			X	Investigator-designated/local
Thyroid-stimulating hormone (including free T4)	X												X				X	Investigator-designated/local.
Coagulation		X																Investigator-designated/local. Perform as clinically indicated.
Urinalysis	X	X	X		X		X			X			X	X			X	Investigator-designated/local
Pharmacogenetics			P															

Schedule of Activities (SoA)

Procedures/ Assessments	**Screening**	**Baseline**	**Inpatient**								**Outpatient**		**EoT**	**F/U**				**Comments**
			Dosing														**ED**	
Visit	**1**	**2**	**3**								**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
PK sample			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See PK and immunogenicity sampling table (Section 1.3.1) for details. In the event of drug hypersensitivity reactions (immediate or nonimmediate), up to 3 additional samples will be collected for PK at the following time points: • as close to the onset of the reaction event as possible • at the resolution of the event • approximately 90 days following the event If more than 1 laboratory blood draw is scheduled at the same time, blood draws should be obtained in the following order: • safety laboratory tests • PK samples • immunogenicity samples

Schedule of Activities (SoA)

Procedures/ Assessments	**Screening**	**Baseline**	**Inpatient**								**Outpatient**		**EoT**	**F/U**				**Comments**
			Dosing														**ED**	
Visit	**1**	**2**	**3**								**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
Immunogenicity			P									X		X			X	See PK and immunogenicity sampling table (Section 1.3.1) for details. In the event of drug hypersensitivity reactions (immediate or nonimmediate), up to 3 additional samples will be collected for immunogenicity at the following time points: • as close to the onset of the reaction event as possible • at the resolution of the event • approximately 90 days following the event

Schedule of Activities (SoA)

Procedures/ Assessments	Screening	Baseline	Inpatient							Outpatient		EoT	F/U				Comments
			Dosing													ED	
Visit	**1**	**2**	**3**							**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3 ±1**	**4 ±1**	**5 ±1**	**6 ±1**	**7 ±1**	**8 ±1**	**12 ±1**	**15 ±1**	**22 ±1**	**31 ±2**	**40 ±2**	**50 ±3**	**90 ±3**	
Week	**-4**		**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	
Injection site reaction assessments			X (Predose; 1 min ± 1 min, 10 min ± 2 min, 30 min ± 5 min, and 240 min ± 10 min postdose)	X (24 hr ± 4 hr postdose)	X	X	X	X	X	X	X	X	X	X	X	X	X	Injection site assessments will be performed at the indicated time points on each study day. The findings from the assessment are recorded on the ISR questionnaire. Injection site pain (ISP) assessments are part of the solicited and spontaneous ISR assessments. All positive responses of pain require an additional assessment using the Pain Visual Analog Scale (Pain VAS). If there are 2 injections, the ISR questionnaire will be filled out separately for each site, after both injections have been administered. The exploratory tool for injection site assessment (Scarletred) will be performed after each time the ISR questionnaire is administered for each injection. ISR assessments will be performed for the SC groups only. See Section 8.2.5 for details.

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ED = early discontinuation; EoT = end of treatment; F/U = follow-up; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; Ig = immunoglobulin; ISP = injection site pain; ISR = injection site reaction; IV = intravenous; P = predose; PK = pharmacokinetic; PR = pulse rate; SC = subcutaneous; TB = tuberculosis; TST = tuberculin skin test; VAS = visual analog scale.

1.3.1. Pharmacokinetic and Immunogenicity Sampling

Sample #			Day	Collection Time Point Relative to Ramucirumab Single Dose	Lower Limit For Collection Time	Upper Limit For Collection Time	Pharmacokinetic Analysis Ramucirumab/Placebo		Immunogenicity ADA Assessment
IV	**SC**	**ADA**					**IV**	**SC**	**IV and SC**
		1	1	-1 hr ± 5 mins (predose)	-65 mins	-55 mins			X
1			1	1 hr ± 5 mins (end of infusion)	55 mins	65 mins	X		
2			1	4 hrs ± 10 mins	3 hrs 50 mins	4 hrs 10 mins	X		
3	1		1	8 hrs ± 30 mins	7.5 hrs	8.5 hrs	X	X	
4	2		2	24 hrs ± 1 hr	23 hrs	25 hrs	X	X	
5	3		3	48 hrs ± 6 hrs	42 hrs	54 hrs	X	X	
6	4		4	72 hrs ± 6 hrs	66 hrs	78 hrs	X	X	
7	5		5	96 hrs ± 6 hrs	90 hrs	112 hrs	X	X	
8	6		6	120 hrs ± 6 hrs	114 hrs	126 hrs	X	X	
9	7		7	144 hrs ± 6 hrs	138 hrs	150 hrs	X	X	
10	8		8	168 hrs ± 6 hrs	162 hrs	174 hrs	X	X	
	9		12	264 hrs ± 24 hrs	240 hrs	288 hrs		X	
11	10	2	15	336 hrs ± 24 hrs	312 hrs	360 hrs	X	X	X

Sample #			Day	Collection Time Point Relative to Ramucirumab Single Dose	Lower Limit For Collection Time	Upper Limit For Collection Time	Pharmacokinetic Analysis Ramucirumab/Placebo		Immunogenicity ADA Assessment
IV	**SC**	**ADA**					**IV**	**SC**	**IV and SC**
	11		22	End of Therapy Visit 504 hrs ± 24 hrs	480 hrs	528 hrs		X	
12	12	3	31	30-day Follow-up	-	-	X	X	X
13	13		40	40 days ± 2 days	-	-	X	X	
14	14		50	50 days ± 3 days	-	-	X	X	
15	15	4	90	90 days ± 3 days ~ 12 weeks	-	-	X	X	X

Abbreviations: ADA = antidrug antibody; IV = intravenous; SC = subcutaneous.

The actual date and exact 24-hour clock time of sample collection should be recorded on the requisition form. Samples are requested to be taken at the specified time; however, aberrations to the specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. It is essential that the actual times of doses and samples are recorded accurately on the appropriate forms.

2. Introduction

Ramucirumab is a human receptor-targeted monoclonal antibody (mAb) that specifically binds vascular endothelial growth factor (VEGF) receptor 2. Ramucirumab has been marketed worldwide as an intravenous (IV) formulation since 2014 and is well-established treatment, as a single agent and/or in combination with chemotherapy, for the following second-line indications:

- gastric or gastroesophageal junction (GEJ) adenocarcinoma
- non-small cell lung cancer (NSCLC)
- colorectal cancer (CRC), and
- hepatocellular carcinoma (HCC)

The data generated by the proposed Study I4T-MC-JVDT (JVDT) will be used to recommend a subcutaneous (SC) dosing regimen for ramucirumab to be used in further clinical development with the expectation to improve patient outcomes by changing the pharmacokinetic (PK) profile, relative to IV dosing, as follows:

- achieve and maintain higher trough concentrations (C_{trough}) with lower peak concentrations (C_{max}) while producing comparable overall exposure at steady state as the IV formulation (10 mg/kg every 2 weeks [Q2W] IV),
- increase the proportion of patients achieving target C_{trough} (>50 μg/mL), and
- with an initial loading dose, ensure C_{trough} >50 μg/mL is achieved quickly in therapy.

This protocol will study both IV and SC ramucirumab in healthy participants to establish PK and safety after single-dose administration.

Section 2.1 and Section 4.3 provide more details about the study rationale, and dose justification and margin of safety, respectively.

2.1. Study Rationale

Ramucirumab presents a biphasic disposition PK following IV administration, with a distribution apparent terminal elimination half-life ($t_{1/2}$) of approximately 20 hours and elimination $t_{1/2}$ of approximately 10 days to 2 weeks. Consequently, there is an initial 2-fold decline in ramucirumab concentration during approximately the first 3 days postdose before reaching the terminal phase where the ramucirumab concentration declined more slowly.

Hence, there may be an opportunity to optimize the ramucirumab PK profile using an SC formulation. An SC formulation would enable ramucirumab to be absorbed over a longer period of time than the 60-minute IV infusion, leading to a more constant ramucirumab concentration over the dosing interval with a higher C_{trough}, lower C_{max}, and lower peak-to-trough ratio under SC administration compared to IV administration.

The clinical development of IV ramucirumab has been exclusively done in cancer patients. However, for the new proposed SC route of administration, the important biopharmaceutic

questions (such as PK and bioavailability) will be more efficiently investigated in the healthy human population (questions such as PK characteristics may be answered prior to formally investigating the efficacy of SC ramucirumab). The large clinical data with IV ramucirumab, together with the nonclinical toxicology data, support investigating single IV and SC doses of ramucirumab in a healthy human population. Section 2.3 (Benefit/Risk Assessment) and Section 4.3 (Dose Justification) provide details to support the clinical investigation of a single dose of ramucirumab in healthy participants.

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. Section 1.2 provides the study schema. Section 4.1 presents the study design and the different group/dose levels.

The study will provide the critical SC ramucirumab PK area under the concentration versus time curve (AUC) data to enable the determination of the bioavailability by comparison to the AUC following IV administration. It will also help further clinical development in terms of choice of dosing regimen and administration condition (in particular by assessing the effect of changing the volume injected, or changing the concentration of SC ramucirumab solution on the exposure and/or tolerability). The SC ramucirumab dosing will consist of subsequent dose-escalation groups (up to 3 dose levels predicted to be ultimately used for therapeutic intent [see Section 4.3 for dose rationale]) to assess both safety and PK behavior (exposure and bioavailability).

2.2. Background

See Section 2 and Section 2.1.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of ramucirumab may be found in the Investigator's Brochure (IB).

The safety profile of ramucirumab given IV in adults with advanced cancers across a number of indications is well established. Adverse events of special interest (AESIs) identified for ramucirumab monotherapy include infusion-related reactions (IRRs), hypertension, proteinuria, arterial thromboembolic events (ATEs), bleeding/hemorrhage and gastrointestinal (GI) perforation. Analysis of Cycle 1 data from ramucirumab monotherapy Phase 3 studies in patients with advanced gastric and hepatocellular carcinoma showed the majority of TEAEs reported were reversible Grade 1 and 2 events, occurring at similar rates in both ramucirumab and placebo arms. The commonly reported TEAEs were hypertension, fatigue, abdominal pain, and anemia. In addition to hypertension, other AESIs reported were proteinuria, bleeding/hemorrhage events, and IRRs. Hypertension, anemia, and anaphylaxis were the events to be reported as Grade 3 events in the ramucirumab arm. Given that the duration of treatment in this study is a single dose, much shorter than the duration of treatment received by cancer patients, and the trial population is healthy, and therefore lacking risk factors for the majority of these events

(excluding IRRs), the risk to participants of experiencing these toxicities is reduced. These risks are considered manageable in a clinical research unit (CRU) setting and are mitigated in the protocol, as the participants will be closely monitored following the single-dose administration. This will enable prompt identification of AEs and treatment as needed. Premedication is also considered to help reduce the severity of potential immediate cutaneous reactions.

The nonclinical safety profile of IV-administered ramucirumab has been evaluated in repeat-dose toxicity studies of up to 39-weeks duration in cynomolgus monkeys. The local irritation potential of a single SC administration of ramucirumab, as formulated for presentation in this clinical protocol, has also been evaluated in monkeys. Taken together, the results of these studies support the safe administration of single SC doses of ramucirumab in this protocol, with exposure-based safety margins of 11X to 12X with respect to the maximum planned dose (see Section 4.3 for details).

More precisely, in nonclinical repeat-dose studies, IV ramucirumab was well tolerated and no adverse effects were observed after once-weekly (QW) administration of ramucirumab doses up to 40 mg/kg in a 5-week study, or after 11 weekly administrations of doses up to 50 mg/kg in a 39-week study in cynomolgus monkeys. Section 4.3 presents the margin of safety of the highest proposed single IV and SC ramucirumab dose in Study JVDT relative to the nonclinical no-observed-adverse-effect level (NOAEL) in the 5-week monkey study.

In the 39-week study in monkeys, renal toxicity and effects on the epiphyseal growth plate were observed. Because these effects emerged only after a long duration of repeated exposures, they are not expected following a single dose in this trial.

In the single-dose study of ramucirumab administered SC in monkeys, doses of up to 10-mg/kg ramucirumab were well-tolerated with no clinical signs or gross evidence of injection site reactions (ISRs). Non-adverse effects consisting of minimal fibroblast hypertrophy at >1 mg/kg, and minimal macrophage infiltrate at 10 mg/kg, were observed microscopically at the injection site; these effects are expected outcomes of introduction of foreign protein into the SC space and indicate a low potential for irritation at the injection site.

Because ramucirumab is a biotherapeutic, no genotoxicity studies have been conducted. No genotoxicity is expected based on the mechanism of action. No reproductive toxicity studies have been conducted. Based on the mechanism of action, fetal harm would be expected and therefore in this study, women of childbearing potential (WOCBP) are excluded and male participants with partners of childbearing potential must use contraception for the required time period to mitigate this risk.

There is no anticipated therapeutic benefit for the participants in this trial. However, participants may benefit from the screening procedures (through detection of unknown health issues) even if they receive no therapeutic benefit from the trial.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate ramucirumab safety following a single dose in healthy participants	• Incidence of AEs, TEAEs, and serious adverse events (SAEs) after IV administration and SC administration in healthy participants
• Assess ISRs following SC administration of ramucirumab using ISR questionnaire	• Characterization and measurement of incidence and severity of ISRs (including injection site pain) 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 drug concentration (C_{max}), time of maximum concentration (t_{max}) o SC: $AUC_{(0-\infty)}$, C_{max}, t_{max} after SC administration

Exploratory	
• 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

4. Study Design

4.1. Overall 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 the first dose of SC (Group 1).

In Section 4.2, additional rationale is presented for the selection of healthy participants for this investigation.

Participants will be screened within 28 days prior to Day 1 of dosing for each group. Participants will be admitted to the 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).

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 groups (Groups 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 may be dosed with an infusion pump once the sponsor has reviewed both the safety and PK data (Groups 1 through 3) if the safety results are acceptable and if there is scientific value for investigating an additional group. The dose for Group 6 will be determined (maximum dose 350 mg). The plan for periodic reviews is presented Section 9.5.

The dose levels are provided below and may be adjusted based on safety reviews for preceding groups.

The participants receiving ramucirumab in each group will be administered the following dose level (up to 3 dose levels predicted to be ultimately used for therapeutic intent [see Section 4.3 for dose rationale]):

- **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 (maximum 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, to further understand SC ramucirumab PK and safety in healthy participants**
    - 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. See Section 6.1 for details.

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 that 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 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 (see Section 4.3 for further details).

Injection site pain (ISP) 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 (according to the protocol Schedule of Activities) until the final follow-up visit approximately 12 weeks following the IV infusion or SC injection. The sample size is provided in Section 9.2.

Participants should follow local guidance and CRU precautions to minimize risk for coronavirus disease 2019 (COVID-19) infection.

4.2. Scientific Rationale for Study Design

The healthy population was selected to participate in this study because it is the most optimal setting to gather intensive PK information over an extended period of time. This PK data are needed to answer the scientific objectives of the study, which are to assess the bioavailability of ramucirumab following SC administration. Furthermore, conducting the study in healthy participants mitigates the potential confounding effects of disease state and concomitant medications in patients on the primary objective (PK and safety) of the study. It is very difficult to achieve the study objective in a cancer patient population. Accurate estimation of AUC is critical for robust estimation of bioavailability. Consequently, ramucirumab PK sampling over at least 12 weeks is needed to achieve that goal because of the long terminal half-life of ramucirumab.

Ramucirumab IV administration is important in this study to accurately estimate the bioavailability, because it is not known whether ramucirumab clearance (hence exposure) is similar in healthy participants and cancer patients.

Ramucirumab has not been studied in healthy human participants. However, the large clinical safety database of IV ramucirumab in cancer patients and the preclinical studies with ramucirumab administered IV and SC support investigating single IV and SC ramucirumab doses in healthy participants (see margin of safety in Section 4.3).

Placebo will be used as a comparator to allow optimal interpretation of safety and tolerability data following ramucirumab administration.

The dose justification is provided in Section 4.3.

The rationale for sample size is provided in Section 9.2.

4.3. Justification for Dose

The overall principle for the choice of SC ramucirumab dose levels to be tested in this single-ascending dose study in healthy participants is:

- To support appropriate dose selection in subsequent studies in cancer patients with multiple repeated SC ramucirumab administration
- To support subsequent safe administration, in cancer patients, of ramucirumab SC dosing regimen leading to
  - Higher C_{trough} (target 50 µg/mL) and lower C_{max} for ramucirumab compared to IV ramucirumab 10 mg/kg Q2W
  - Similar steady-state AUC as achieved following IV ramucirumab 10 mg/kg Q2W.

Simulations of PK profiles following SC dosing were performed, taking into account different constraints (for example, maximum possible drug product concentration and maximum possible injectable volume and dose frequency), and the most conservative (worse-case scenario) assumptions for bioavailability and rate of absorption (0.6 bioavailability with coefficient of variation [CV] 20% and rate of absorption of 0.3/day). Those assumptions are based on literature report about mAb PK following SC administration which indicate that 60% bioavailability is in the lower end of reported bioavailability (Viola et al. 2018). The 20% CV on bioavailability lead

to a bioavailability of 0.6 (0.44-0.79), mean (90% population prediction interval), used in these simulations.

All of the outcomes from those simulations, graphs, and tables are presented in Appendix 6 (Section 10.6).

To prepare for future investigation of the above-mentioned ramucirumab SC dosing regimen in cancer patients, the proposed study (Study JVDT) in healthy participants will investigate single doses of SC ramucirumab 350 and 700 mg (with a maximum of 2 mL per injection site and a maximum of 2 injection sites per dose administration). The starting 350-mg SC ramucirumab dose is half the highest approved therapeutic dose (10 mg/kg Q2W IV). To prepare for the need of a loading dose in cancer patients, a ramucirumab dose of 350 mg administered SC (as a slow SC infusion with a pump) may also be investigated in Study JVDT.

The top planned SC ramucirumab dose in Group 6 was initially planned as a maximum dose level of 1400 mg in a previous protocol version. Since then, Groups 1 and 2 (350 mg and 700 mg SC) have been enrolled and received study treatment, and 2-week postdose safety data from those groups were reviewed. Consequently, after the safety review, the maximum dose is to be capped at 350 mg as this dose was associated with an acceptable safety profile. This edict applies to all subsequent groups.

The emerging data suggests Group 6 may not be needed given the planned collection of information at the 350 mg SC dose (Groups 1, 4, and 5).

In addition to those SC ramucirumab dose levels, a single dose of up to 350-mg ramucirumab administered IV (via 60-minute infusion) is planned to enable determination of the absolute bioavailability following SC administration.

The initial ramucirumab SC doses will be determined from the safety data from previous clinical experience with IV ramucirumab, as it is understood that the IV administration leads to higher plasma levels and it is expected that tolerability will be better with the SC administration.

In summary, ramucirumab dose levels that are proposed for Study JVDT are:

- ramucirumab IV, originally 700 mg dose level and subsequently modified to 350 mg IV following safety review of Groups 1 and 2
- ramucirumab 350 mg SC
- ramucirumab 700 mg SC

The table below presents the margin of safety (based on C_{max} or AUC) relative to the toxicology monkey study. The table uses the originally planned maximum ramucirumab dose IV and SC, in the absence of any ramucirumab data in healthy participants and based on the assumption that ramucirumab IV PK properties are similar in healthy participants and in patients and the assumption for bioavailability following SC as stated above.

Predicted Margin of Safety at Maximum Dose in Study JVDT

Study	Dose (mg/kg) and Route of Administration	C_{max} (µg/mL)	Margin of Safety	AUC_{0-168} (mg.h/mL)	Margin of Safety
SNBL 023.04 (5-week monkey)	40 (IV)[a] NOAEL	1460	-	189	-
JVDT (SAD in healthy participants)	10 (IV)[b]	211	7X	18.6	10X
	20 (SC)[c]	139	11X	15.3	12X

Abbreviations: AUC_{0-168} = area under the curve during the dosing interval; C_{max} = maximum observed concentration; IV = intravenous; PK = pharmacokinetics; popPK = population pharmacokinetics; SAD = single ascending dose; SC = subcutaneous.

a 40 mg/kg was the no-adverse-effect level in this study.

b 700 mg is equivalent to 10 mg/kg in a 70-kg human. Exposure values from RELAY popPK model report the mean, as the toxicology data report the mean, which is consistent with the median values reported in Appendix 6.

c 1400 mg is equivalent to 20 mg/kg in a 70-kg human. The human PK model simulation of SC regimen indicates a mean C_{max} of 139 µg/mL and mean AUC over the first week AUC_{0-168} of 15.3 mg.h/mL following a ramucirumab 1400-mg SC administration. Appendix 6 reports median value (very close to these mean values).

A NOAEL of 40 mg/kg was established in a 5-week repeat dose study in monkey. At this dose, C_{max} and AUC values are 11-fold and 12-fold higher than the anticipated systemic exposure following a single SC dose of 1400 mg in Study JVDT. At this dose, C_{max} and AUC values are 7-fold and 10-fold higher than the anticipated systemic exposure following a single IV dose of 700 mg in Study JVDT.

Therefore, nonclinical data provides support for the safety of the IV and SC dose of ramucirumab to be investigated in normal, healthy human participants (Section 10.6).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the first 40 days of study procedures as per the schedule of events. If a participant does not complete the 40 days procedure, he/she maybe replaced.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the trial globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be between the ages of 18 and 60 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, vital sign measurements, including electrocardiogram (ECG), and laboratory tests
3. Have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator; have a urinary protein value <2+ on dipstick urinalysis
4. Have venous access sufficient to allow for blood sampling and/or administration of study intervention for IV administration as per the protocol
5. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

Weight

6. Body weight within ≥70 kg and body mass index (BMI) within the range of 18 to 32 kg/m^2 (inclusive)

Sex

7. Male and/or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants:

- regardless of their fertility status, with a partner of childbearing potential, must for the duration of the study or for 5 months following completion of study drug administration, whichever is longer, agree to either:
    - remain abstinent, if this is their preferred and usual lifestyle (periodic abstinence [for example, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception), **or**

- use condoms, **and** ensure the partner uses
  - one highly effective (<1% failure rate) method of contraception, such as combination oral contraceptives, implanted contraceptives, or intrauterine devices, **or**
  - one effective method of contraception, such as diaphragms with spermicide or cervical sponges with spermicide

- with pregnant partners should use condoms during intercourse for the duration of the study or for 5 months following completion of study drug administration, whichever is longer
- who are in exclusively same-sex relationships (as their preferred and usual lifestyle) or with female partners of nonchildbearing potential are not required to use contraception
- should refrain from sperm donation for the duration of the study or for 5 months following completion of study drug administration, whichever is longer.

b) Female participants:

- will not be breastfeeding or planning to breastfeed during the study
- must have a negative pregnancy test at the time of screening
- must be of nonchildbearing potential defined as:
  - infertile due to surgical sterilization (bilateral oophorectomy, tubal ligation, or hysterectomy) or having a congenital anomaly (mullerian agenesis), **or**
  - postmenopausal, as evidenced by spontaneous amenorrhea for at least 12 months, **or**
  - a woman ≥55 years of age who is not on hormone therapy and who has had at least 12 months of spontaneous amenorrhea, or with a diagnosis of menopause prior to starting hormone replacement therapy

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have known allergies to ramucirumab, any components of the formulation buffer matrix or related compounds, or history of significant atopy

2. Have an abnormal blood pressure (>140/90 mmHg) and/or pulse rate as determined by the investigator
3. Have a history or presence of cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, psychiatric, or neurological disorders that could significantly alter the absorption, metabolism, or elimination of drugs; or constituting a risk when taking the study intervention; interfere with the evaluation of injection site assessments, or any other medical condition that, in the judgement of the investigator, could interfere with the interpretation of data
4. Regularly use known drugs of abuse and/or show positive findings on urinary drug/alcohol screening
5. Have evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies
6. Show evidence of hepatitis C and/or positive hepatitis C antibody
7. Show evidence of hepatitis B and/or positive hepatitis B surface antigen
8. Have self-perceived dullness or loss of sensation on either side of the body or the abdomen
9. Have donated blood of more than 500 mL within the previous 30 days of study screening
10. Have a history or presence of a bleeding disorder
11. Have had a serious or nonhealing wound, ulcer, or bone fracture within 28 days prior to enrollment
12. Have undergone major surgery within 28 days, or have postoperative bleeding complications or wound complications from a surgical procedure performed in the last 2 months
13. Have a history of GI perforation, peptic ulceration, diverticular disease, and/or fistulae within 6 months prior to enrollment
14. Have alanine transaminase, aspartate aminotransferase, and gamma-glutamyl transferase > upper limit of normal (ULN)
15. Have bilirubin > ULN
16. Have current or chronic history of liver disease or known hepatic or biliary abnormalities (Gilbert's syndrome is not acceptable)
17. Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to participant safety. Participants on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.
18. Have experienced any arterial thromboembolic events, including but not limited to myocardial infarction, stroke, transient ischemic attack, cerebrovascular accident, or unstable angina, ≤6 months prior to randomization.

Prior/Concomitant Therapy

19. Are currently using aspirin or other nonsteroidal anti-inflammatory drugs

20. Have participated, within the last 30 days, in a clinical study involving a study intervention. If the previous study intervention has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.
21. Have previously completed or withdrawn from this study or any other study investigating ramucirumab
22. Have used or intend to use over-the-counter or prescription medication for pain or inflammation within 7 days prior to Day 1 or during the study

Prior/Concurrent Clinical Study Experience

23. Are currently enrolled in a clinical trial involving a study intervention or off-label use of a drug or device, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this trial
24. Have been treated with biologic agents (such as mAbs, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing

Diagnostic Assessments

25. Have tattoos or scars over the abdomen, or other factors (for example, rash, excessive folds of skin) that, in the investigator's opinion, would interfere with injection site assessments

Other Exclusions

26. Are deemed unsuitable for inclusion in the trial in the opinion of the investigator or sponsor
27. Have an average weekly alcohol intake that exceeds 21 units per week (males ≤65 years old) and 14 units per week (females [and males >65 years old, if applicable]);
    1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirit(s)
28. Are unwilling to stop alcohol consumption during study visits/time in the research unit
29. Smoke more than 10 cigarettes per day or are unable to abide by CRU smoking restrictions

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

There are no dietary restrictions for this study.

5.3.2. Caffeine, Alcohol, and Tobacco

1. During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (for example, coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic (PD) sample.
2. During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or PD sample.

3. Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the CRU.

5.3.3. Activity

1. Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (for example, watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study and were not alternates.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Alternates may also be rescreened if out of the screening window. Rescreened participants should be assigned a new participant number. When rescreening, some screening tests and procedures may be repeated at the investigator's discretion. Individuals may be rescreened once only. The interval between rescreenings should be at least 2 weeks. With rescreening, the individual must sign a new ICF. Repeating of laboratory tests once during the screening period or repeating screening tests once to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Intervention Name	Ramucirumab IV (marketed IV formulation)	Ramucirumab SC	Placebo for SC	Placebo for IV
Type	Drug	Drug	Matching placebo	Matching placebo
Dose Formulation	Vial	Vial	Vial	Vial
Unit Dose Strength(s)[a]	Experimental	Experimental	Placebo	Placebo
Dosage Level(s)[a]	350 mg	350 or 700 mg	NA	NA
Route of Administration[a]	IV infusion (Group 3)	SC injection (Groups 1, 2, 4, 5) SC infusion with a pump (Group 6)	SC injection (Groups 1, 2, 4, 5) SC infusion with a pump (Group 6)	IV infusion (Group 3)
Use[a]	Experimental	Experimental	Placebo	Placebo
IMP and NIMP[a]	IMP	IMP	NIMP	NIMP
Sourcing[a]	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling[a]	Study intervention will be provided in a vial. Each vial will be labeled as required per country requirement.	Study intervention will be provided in a vial. Each vial will be labeled as required per country requirement.	Placebo will be provided in a vial. Each vial will be labeled as required per country requirement.	Placebo will be provided in a vial. Each vial will be labeled as required per country requirement.
Current/Former Names or Aliases[a]	Ramucirumab, Cyramza®, LY3009806	Ramucirumab, Cyramza®, LY3009806	Placebo	Placebo

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NA = not applicable; NIMP = noninvestigational medicinal product; SC = subcutaneous.

a Information provided in this table (dose formulation, sourcing, packaging and labeling, current/former names or aliases) may change throughout the study or may vary by country.

The study intervention will be administered as a slow, IV infusion over at least 60 minutes in Group 3; and as an SC infusion (with a pump) in Group 6 per pharmacy manual; or SC injection in Groups 1, 2, 4, and 5. Sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the IV or SC infusion/SC injection and for at least 1 hour after participants have completed the IV or SC infusion/SC injection.

The SC injection site will be the abdomen. The study intervention will be given in the CRU by qualified CRU personnel as designated by the investigator. Study injections should be given by a

limited number of personnel for consistency. The site of administration of each injection will be recorded; when there is more than 1 injection, the same site will not be used but another quadrant will be used.

6.1.1. Special Treatment Considerations

6.1.1.1. Premedication for Infusions and Subcutaneous Injections

Premedication (with IV histamine H_1 antagonists such as diphenhydramine hydrochloride) is planned prior to ramucirumab IV infusion as specified per label for IV administration. Participants receiving SC infusion/injection will also receive oral premedication such as oral diphenhydramine. After the IV infusion/or SC infusion/injection, a 1-hour observation period will be completed. This will follow the label instructions to be used with the IV marketed material.

Any premedications given will be documented as a concomitant therapy (see Section 6.5).

6.1.1.2. Management of Infusion Reactions

There is a risk of infusion reactions and anaphylaxis with any biological agent; therefore, all participants should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, the infusion will be discontinued.

Supportive care should be employed in accordance with the symptoms/signs. Participants should be treated appropriately by the investigator.

In the event of an IRR, every effort should be made to collect a blood sample for an antiramucirumab antibody determination as well as for ramucirumab serum concentration as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the onset of the event. In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Appendix 2 (Clinical Laboratory Tests)

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

5. Investigators should consult the study drug information provided in the Pharmacy Manual or label for the specific administration information (including warnings, precautions, contraindications, adverse reactions).

6.3. Measures to Minimize Bias: Randomization and Blinding

Study using Precoded Randomization provided to site	On Day 1, participants will be assigned a unique number (randomization number). The randomization number encodes the participant's assignment to the study, according to the randomization schedule. Each participant will be dispensed study intervention, labeled with his/her unique randomization number, throughout the study. Participants will be sequentially enrolled to groups. Within each group, participants will be randomized to receive a single dose of IV or SC ramucirumab or placebo (7 ramucirumab:3 placebo per group).

Blinded study with unblinded site pharmacist who is dispensing drug	Participants will be randomly assigned in a 7:3 ratio (ramucirumab:placebo) to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately. Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan. Emergency codes will be available to the investigator. A code, which reveals the study intervention group for a specific study participant, may be opened during the study only if the participant's well-being requires knowledge of the participant's treatment assignment. If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from an Eli Lilly and Company (Lilly) clinical pharmacologist (CP) or clinical research physician (CRP) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

6.3.1. Package and Labeling

Ramucirumab will be provided as a 10-mg/mL (IV) or 175-mg/mL (SC) preservative-free, sterile solution for injection in vials. The Pharmacy Manual will provide instructions for the preparation of 87.5-mg/mL SC ramucirumab. Placebo will be provided as a preservative-free, sterile solution for injection in vials (SC).

Ramucirumab and placebo vials should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) with protection from light.

The study intervention will be labeled according to the country's regulatory requirements

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the case report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤3 grams/day, is permitted for use any time during the study. Premedications for IRRs are permitted for use. Other concomitant medication may be considered on a case-by-case basis, by the investigator in consultation with the Medical Monitor, if possible.

6.6. Dose Modification

If moderate or severe AEs are consistently observed across participants in a group or if unacceptable pharmacological effects, reasonably attributable to ramucirumab administration in the opinion of the investigator, are observed in more than 2 of the participants in a group, then no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the Medical Monitor/Sponsor, relevant personnel, and the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will take place before resumption of dosing.

If the SAE occurs in 1 participant in a group, then dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the Medical Monitor, relevant personnel, and the IRB/IEC will take place before resumption of dosing.

Refer to Section 10.3.5 of Appendix 3 for additional information about the sponsor's surveillance process for dose escalation and group expansion.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per the SoA (Section 1.3) of the protocol.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study for additional data collection consistent with routine safety monitoring. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving a study intervention or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant may continue to follow study procedures dependent on the cause for the incorrect enrollment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product (IP). The documented approval must contain the benefit/risk assessment and a robust clinical justification that continuing in the study will not jeopardize the participant's safety. All inadvertently enrolled participants will complete safety follow-up as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get IP. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented and the participant will not be considered lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time has to be correctly recorded in the CRF. Failure or being late (that is, outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (for example, equipment technical problems, venous access difficulty, or participant defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations, but the CRU will still be required to notify the sponsor in writing via a file note.
- Appendix 2 lists the laboratory tests that will be performed for this study.
- Section 10.2.1 of Appendix 2 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.
- Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems. Height and weight will also be measured and recorded at screening.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations included in a Manual of Operations for the study. Vital sign measurements will be recorded before collecting any blood samples.
- Blood pressure and pulse rate should be measured after at least 5 minutes supine, and taken in triplicate.
- If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes.
- If the participant feels unable to stand, supine vital signs only will be recorded.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

8.2.3. Electrocardiograms

- Single, 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and corrected QT intervals (QTc).
- For each participant, ECGs should be collected according to the SoA (Section 1.3) and the study-specific recommendations included in the Manual of Operations for the study.
- Any clinically significant findings from ECGs that result in a diagnosis, and that occur after the participant receives the first dose of the study intervention, should be reported to the sponsor or its designee as an AE via electronic case report form (eCRF)
- Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

- Electrocardiograms will be interpreted by a qualified investigator (the physician or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 28 days after the last dose of study intervention, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If laboratory values from nonprotocol-specified laboratory assessments, performed at the institution's local laboratory, require a change in participant management or are considered clinically significant by the investigator (for example, SAE, AE, or dose modification), then the results must be recorded in the CRF.

8.2.5. Injection Site Reactions

- Injection site assessments using the ISR questionnaire and an exploratory tool (Scarletred) will be performed at times specified in the SoA (Section 1.3).
- Manifestations of a local ISR may include erythema, induration, pain, pruritus, and edema. Injection site findings will be captured on the eCRF.
- Injection site reactions, whether recorded as a result of the prespecified (or solicited) assessment or spontaneously reported reactions, will be recorded as AEs only if they qualify as severe AEs.

- If a spontaneous (or unsolicited) ISR is reported by a participant or investigator, the ISR CRF will be used to capture additional information about this reaction (for example, degree and area of erythema) at additional visits until resolution of the event.
- Injection site pain assessments are part of the solicited and spontaneous ISR assessments. All positive responses of pain will require an additional assessment using the Pain Visual Analog Scale (Pain VAS). The VAS will be performed at times specified in the SoA (Section 1.3). If there are 2 injections, timing will relate to the second injection. Pain measurements will be quantified using the 100-mm VAS pain score for all participants, regardless of whether they report ISP. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess ISP; it is presented as a 100-mm line anchored by verbal descriptors, usually "no pain" and "worst imaginable pain." The participant will be asked to rate any pain at the injection site on a scale of 0 to 100 mm on the line immediately (within 1 minute) following the injection.
- In addition, the exploratory tool (Scarletred) will be used to acquire exploratory ISR data at each of the time points where the ISR data is being collected by administration of the ISR questionnaire. Failure to take this assessment at any of the indicated time points will not result in a protocol deviation.

8.2.6. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study. This will include monitoring and recording of all AEs, including all National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grades and SAEs.

The sponsor will review SAEs within time frames mandated by company procedures. The sponsor CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes including proteinuria, reduced red blood cells, and decreased neutrophil count
- AEs, including monitoring of AESIs; see Section 8.3.6

When appropriate, the sponsor CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.2.6.1. Hypersensitivity Reactions

In the event of a suspected systemic allergic/hypersensitivity reaction, additional safety data should be collected using the Infusion-related reaction/Hypersensitivity/Anaphylaxis follow-up form or documented via the eCRF.

- Hypersensitivity/Infusion-Related Reactions eCRFs are used to capture additional characteristics of the hypersensitivity/anaphylaxis/injection-related reaction that cannot be captured on the AE eCRF.
- Each symptom of the event (for example, mucocutaneous, cardiovascular, GI, CNS, other) should be assessed.

- If any of the above symptoms are observed during the assessment, a single generalized AE record should be entered on the AE eCRF (do not include symptoms in AE Term/description).
- Timing of the event occurrence is important. The investigator should indicate the timing category that is appropriate.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs are provided in Appendix 3 (Section 10.3). The investigator will use CTCAE version 5.0 (NCI 2018) to assign AE severity grades.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting the sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until participation in the study has ended.

All AEs will be collected from the signing of the ICF until participation in study has ended.

Adverse events that begin before the start of study intervention, but after signing of the ICF, will be recorded on the AE CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received the study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving ramucirumab, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants, will be collected after the start of study intervention and until at least 12 weeks after the last dose.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Pregnancy (maternal or paternal exposure to IP) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Appendix 4 (Section 10.4) to collect data on the outcome for both mother and fetus.

8.3.6. Adverse Events of Special Interest

The sponsor CP or CRP will periodically review AESIs for this program, which include:

- bleeding/hemorrhagic events
- liver failure/liver injury
- hypertension
- proteinuria
- fistula
- GI perforation
- IRR (including hypersensitivity reactions)
- wound healing complications
- posterior reversible encephalopathy syndrome (PRES)
- ATEs
- venous thromboembolic events (VTEs)
- congestive heart failure

When appropriate, the sponsor CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

Sponsor collects product complaints on IP and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3) of the protocol.

8.3.7.1. Time Period for Detecting Product Complaints

- Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug is used.
- If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

8.3.7.2. Prompt Reporting of Product Complaints to Sponsor

- Product complaints will be reported to the sponsor using the Product Complaint Form within 24 hours after the investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the sponsor by the method provided in the form. If the primary method is unavailable, then an alternative method provided in the form should be utilized.

8.3.7.3. Follow-Up of Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, any dose of ramucirumab greater than a single dose of study intervention within a 24-hour time period will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose. Participants should receive appropriate supportive care measures for AESIs or other AEs, as deemed necessary by the investigator.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until study intervention can no longer be detected systemically (at least 28 days).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

- Whole blood samples will be collected for measurement of serum concentrations of ramucirumab as specified in the SoA (Section 1.3), Section 1.3.1, and Section 10.2.1.
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the PK of ramucirumab.
- Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.
- Pharmacokinetic samples will be retained for a maximum of 1 year following the last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, and/or bioanalytical method cross-validation.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of ramucirumab will be assayed using a validated method. Analyses of samples collected from placebo treated participants are not planned.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last participant visit for the study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

A blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants.

See Appendix 5 (Section 10.5) for information regarding genetic research and Appendix 1 (Section 10.1.9) for details about sample retention and custody.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3) and Section 1.3.1, venous blood samples will be collected to determine antibody production against ramucirumab. Antibodies may be further characterized for their ability to neutralize the activity of the ramucirumab. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of ramucirumab. All samples for immunogenicity should be taken predose when applicable and possible.

Additionally, blood samples for the determination of ramucirumab concentration and antiramucirumab antibodies are to be collected at the 30-day and 90-day follow-up visits (see SoA [Section 1.3]).

In the event of an IP-related IRR, see Section 6.1.1.2.

Antiramucirumab antibodies may be determined using a validated immunoassay at a laboratory designated by the sponsor or designee. Samples may be stored for a maximum of 15 years after the last participant visit for the trial, at a facility selected by the sponsor, to enable further analysis of immune responses to ramucirumab. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Treatment-emergent antidrug antibodies (TE ADAs) are defined in Section 9.4.4.

The detection and characterization of antibodies to ramucirumab will be performed using a validated assay method at a laboratory under the supervision of the sponsor.

Refer to Appendix 1 (Section 10.1.9) for details on Sample Retention.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

Formal statistical hypothesis testing is not planned. Therefore, adjustments for multiple testing do not apply.

9.2. Sample Size Determination

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.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF
Enrolled/Intent-to-Treat	All participants assigned to treatment, regardless of whether they take 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.
Dose Evaluable	All participants who completed treatment
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All treated participants who received 1 dose of study intervention and have sufficient evaluable PK samples.

Abbreviations: ICF = informed consent form; PK = pharmacokinetic.

9.3.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

9.3.2. Study Participant Characteristics

Demographic and baseline characteristics will be summarized by treatment group.

9.3.3. Treatment Compliance

No analyses of treatment compliance are planned.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor or its designee. The primary analysis of the study will occur when there are at least 8 evaluable participants (6 ramucirumab:2 placebo) per intervention group.

Pharmacokinetic analyses will be conducted on data from all participants who receive 1 dose of IP and have evaluable PK.

Safety analyses will be conducted in the safety population.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety and population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to first participant, first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1. Safety Analyses

9.4.1.1. Clinical Evaluation of Safety

All IP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with IP as perceived by the investigator. Adverse events reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

All SAEs will be reported.

9.4.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital sign measurements, and ECG parameters. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for ramucirumab will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be t_{max}, C_{max}, and AUC of ramucirumab following IV and SC administration and bioavailability following SC administration. Other noncompartmental parameters, such as half-life, IV clearance, volume of distribution, apparent clearance, and volume of distribution following IV and SC ramucirumab administration may be reported.

In addition to noncompartmental analysis, non-linear mixed-effect modelling analysis of the Study JVDT PK data will be performed. This model will enable to estimate mean and variability (variance) of ramucirumab PK parameters following SC administration and to investigate potential covariate explaining that variability.

9.4.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate ramucirumab AUC and C_{max} dose proportionality following SC administration in the dose range investigated. Log-transformed ramucirumab C_{max} and AUC 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). The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).

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.

Ramucirumab bioavailability will be estimated (see Section 9.4.2.1).

Comparison of AUC and C_{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 C_{max} and AUC will be the response variable, and the drug product concentration (that is, Group 1 and Group 4) is the explanatory variable.

Comparison of AUC and C_{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 C_{max} and AUC will be the response variable, and the volume injected (that is, Group 1 and Group 5) is the explanatory variable.

9.4.3. Other Safety Analyses

All safety analyses will be made on the Safety Population. The most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of analysis will be used when reporting AEs by MedDRA terms, and CTCAE version 5.0 will be used to assign AE severity grades.

All relevant hematology and chemistry laboratory values will be graded according to CTCAE version 5.0.

9.4.4. Immunogenicity Assessments

The frequency and percentage of participants with preexisting antidrug antibodies (ADAs) and with TE ADAs to ramucirumab may be tabulated.

Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADAs).

The frequency of neutralizing antibodies may also be tabulated in TE ADA-positive participants, when available.

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

9.4.5. Other Analyses

Other analyses may include analyses of assessments, which are not defined as endpoints, that need to be prespecified and not necessarily be reported in the CSR such as, but not limited to, immunogenicity, biomarkers, population PK, health care utilization endpoints and health technology assessment-related endpoints.

9.5. 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.
- PK data may be reviewed for Groups 1 and 2 if timing permits.
- PK data will be reviewed once Group 1 through 3 PK samples have been collected (cutoff 2-week sample collection in Group 3).

9.6. Data Monitoring Committee (DMC)

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by the sponsor to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by the sponsor personnel prior to any further planned dosing. If a dose is planned imminently, the sponsor personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This might include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system(s) will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.7.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.8. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.9. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of ramucirumab.

Sample Type	Custodian	Retention Period After Last Participant Visit
Long-term storage samples	Sponsor or Designee	15 years
Biomarkers	Sponsor or Designee	15 years
PK	Sponsor or Designee	1 year
Genetics/PD	Sponsor or Designee	15 years
Immunogenicity	Sponsor or Designee	15 years

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing (Section 5.1)

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative site or other blinded personnel.

Safety Laboratory Tests

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets
- Differential WBC (absolute counts) of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils

Coagulation
- Prothrombin time (PT or INR)
- Partial thromboplastin time (PTT or aPTT)

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Microscopic examination of sediment[d]

Serum Immunoglobulins
- IgG
- IgM
- IgA

QuantiFERON®-TB Gold Test or Tuberculin Skin Test

Clinical Chemistry
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium (ionized/total)
- Phosphorus/Phosphate
- Magnesium
- Glucose (fasting)
- Blood urea nitrogen (BUN)
- Creatinine
- Uric acid
- Total cholesterol
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyl transferase (GGT)

- Thyroid-stimulating hormone
- Free thyroxine (T4)
- Hepatitis B surface antigen[a,b]
- Hepatitis C antibody[a,b]
- HIV[b]
- Urine drug screen[c]
- Breath ethanol testing[c]
- FSH
- Beta human chorionic gonadotropin
- Pregnancy test[e]

Hypersensitivity Tests[f]
- Anti-LY antibodies (immunogenicity)
- LY concentration (PK)
- Tryptase[g]
- N-methylhistamine
  - Complements
  - C3a
- C5a
  - Cytokine Panel
  - IL-6
  - IL-1β
- IL-10
- Basophil Activation Test[h]

Abbreviations: aPTT = activated partial thromboplastin time; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; Ig = immunoglobulin; IL = interleukin; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

[a] Performed at screening only.

[b] These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review" for Hepatitis B and C and HIV.

[c] Urine drug screen and breath ethanol level will be performed at screening and repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.

[d] Test only if dipstick result is abnormal.

[e] Investigator-designated/local. Serum pregnancy test will be conducted at screening only. Urine pregnancy test will be conducted at all other time points. A beta human chorionic gonadotropin test may be performed to confirm a result that is positive or in the postmenopausal range.

[f] Central laboratory. Additional tests and local laboratory tests may be performed at the discretion of the investigator.

[g] If a tryptase sample is obtained more than 2 hours after the event (i.e. within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine for *N*-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

[h] Antidrug antibody testing should include drug-specific IgE or the basophil activation test. The basophil activation test is an in vitro cell-based assay that only requires a serum sample. It is a surrogate assay for drug-specific IgE but is not specific for IgE.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	35.7	1	35.7
Clinical laboratory tests[a]	12.5	10	125
Coagulation[a] (PT or INR; PTT or aPTT)	2.7	1	2.7
Serum immunoglobulins (IgG, IgM, IgA)	3.5	4	14
Thyroid-stimulating hormone (including T4)	3.5	3	10.5
Pharmacokinetics	2.5	15	37.5
Immunogenicity	10	4	40
Hypersensitivity/Infusion-related reaction[b]	24	3	72
Pharmacogenetics	10	1	10
Total			347.4
Total for clinical purposes (rounded up to nearest 10 mL)			350

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio; PT = prothrombin; PTT = partial thromboplastin time.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Only in the event of drug hypersensitivity reactions (immediate or nonimmediate).

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to the hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is

appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information on the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will use CTCAE version 5.0 (NCI 2018) to assign AE severity grades.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post mortem findings, including histopathology.
- New or updated information will be recorded on the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting SAEs

SAE Reporting
• The investigator or site must alert Lilly CRP/CP, or its designee, of any SAE as soon as practically possible. • Additionally, the investigator or site must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24−hour notification requirement refers to the initial SAE information and all follow-up SAE information. • Facsimile transmission of the SAE Form is the preferred method to transmit this information to the sponsor or designee. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE Form sent by overnight mail or courier service, or email. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Form within the designated reporting time frames. • Contacts for SAE reporting can be found in the SAE Form.

10.3.5. Sponsor Surveillance Process for Dose Escalation or Group Expansion

The sponsor has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with Food and Drug Administration's (FDA's) expectations for safety assessment committees (SACs) (FDA 2012, 2015, 2018a, 2018b). This includes processes with clearly described roles and responsibilities that are owned by the sponsor's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (that is, review of cumulative SAEs, other important safety information) by designated cross-functional teams in a timely manner at predefined intervals or on an ad hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program is reviewed on a regular basis and that important new safety information, such as the need for protocol modification or other relevant safety-related material, is identified and communicated to regulators and investigators appropriately and in a timely fashion. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any serious adverse reactions (SARs) are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing report of suspected unexpected serious adverse reactions (SUSARs) is created and distributed to investigators on a biannual (twice yearly) basis. Any significant potential risk/safety concerns that are being monitored, as well as any results being reported in other periodic reports for the

compound, SAC decisions, and other significant safety data (for example, nonclinical and clinical findings, removal of SARs) are included in the report.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - documented hysterectomy
   - documented bilateral oophorectomy
   - documented tubal ligation

For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, medical history interview, or prior documented medical history at the site, and may be documented in the medical history.

3. Postmenopausal female is defined as women with:
   - at least 6 weeks postsurgical bilateral oophorectomy with-or-without hysterectomy, confirmed by operative note/medical records
     OR
   - with spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced the amenorrhea).
     AND
   - if ≤ age 55, has a follicle-stimulating hormone of ≥40 mIU/mL

Contraception Guidance:

See Section 5.1.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

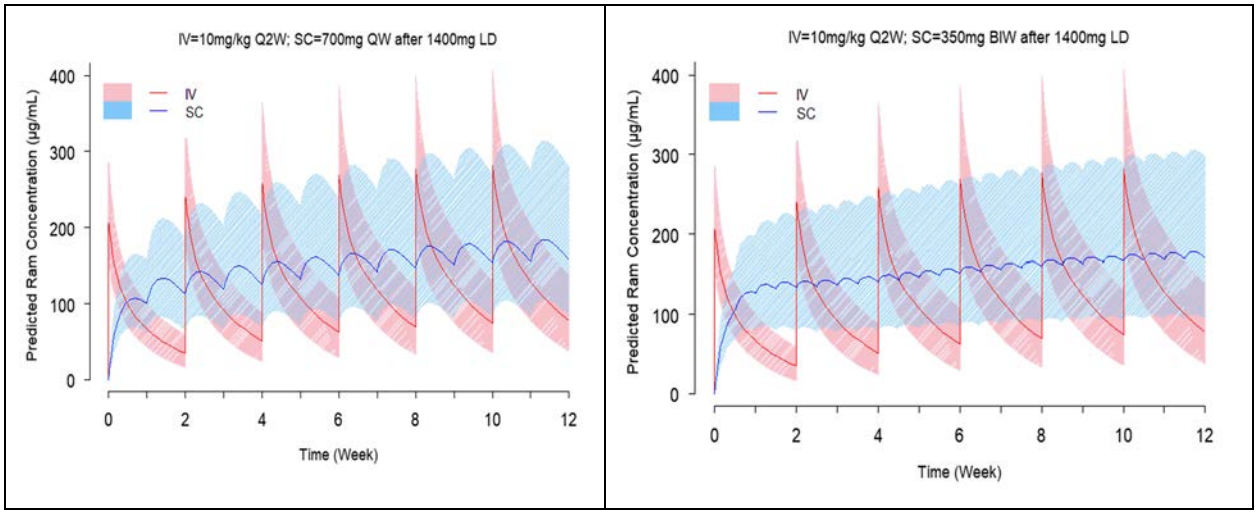
10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRBs/IECs allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to study intervention or cancer and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study intervention and/or interventions of this drug class and cancer. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention or study interventions of this class or indication continues but no longer than 15 years or other time period as per local requirements.

10.6. Appendix 6: Pharmacokinetic Profile Simulation (Intravenous versus Subcutaneous)

The PK profile for IV (10 mg/kg Q2W) and SC administration of ramucirumab (Left panel: 1400-mg SC loading dose on Day 1 followed by QW SC 700 mg; Right panel: 1400-mg SC loading dose on Day 1 followed by twice-weekly [BIW] SC 350 mg) is shown in the figure below.



Abbreviations: BIW = twice weekly; IV = intravenous; LD = loading dose; Q2W = every 2 weeks; QW = once weekly; Ram = ramucirumab; SC = subcutaneous.

Model-Simulated Ramucirumab AUC, Average, Trough, and Peak Concentrations Following Intravenous (10 mg/kg Q2W) and Subcutaneous Administration of Ramucirumab (1400-mg SC loading dose on Day 1 followed by either weekly [QW] SC 700 mg or twice weekly [BIW] SC 350 mg)

	10 mg/kg Q2W IV RELAY		SC LD 1400 mg + SC MD 350 mg BIW		SC LD 1400 mg + SC MD 700 mg QW		RATIO SC 350 / IV 10	RATIO SC 700 / IV 10
	Median	5^{th}-95^{th} percentile	Median	5^{th}-95^{th} percentile	Median	5^{th}-95^{th} percentile	Median	Median
Week 1&2 PK parameters								
AUC1 mg.h/mL	18.1	13.2-25.4	16.3	10.6-25.1	14.8	9.61-22.9	0.90	0.82
AUC2 mg.h/mL	26.2	18.2-38.2	39.2	24.8-61.5	35.8	22.6-56.2	1.50	1.37
C_{av} µg/mL Week1	108	79-151	97	63-149	88.1	57-136	0.9	0.82
C_{av} µg/mL Week2	48	30-76	136	85-217	125	77-198	2.83	2.59
C_{max} µg/mL	206	153-285	141	87-227	134	83-212	0.68	0.65
C_{trough} µg/mL	35	16-58	133	80-218	112	66-184	3.86	3.25
Steady state SS PK parameters								
AUC_{ss} mg.h/mL	48.0	30-75	59	33-102	59	34-102	1.23	1.23
C_{av} µg/mL	143	90-223	176	99.4-305	176	100-305	1.23	1.23
C_{max} µg/mL	285	200-412	178	100-308	186	106-318	0.62	0.65
C_{trough} µg/mL	77	38-138	170	96-296	157	86-278	2.21	2.04
Ratio C_{trough} SS/WEEK1&2	2.23		1.28		1.40			
$C_{average}$ to trough WEEK2	1.38		1.02		1.12			
Peak to trough at SS	3.7		1.05		1.18			

Abbreviations: AUC_{ss} = area under the curve at steady state over 2 weeks; AUC1 = area under the curve during the first week of treatment; AUC2 = area under the curve during the first 2 weeks of treatment; BIW = twice weekly; C_{av} = average concentration; C_{max} = maximum concentration; C_{trough} =trough min concentration at the end of the dosing interval; IV = intravenous; LD = loading dose; MD = maintenance dose; PK = pharmacokinetic; SC = subcutaneous; SS = steady state; Q2W = every 2 weeks; QW = once weekly.

Model-Simulated Ramucirumab AUC, Average, Trough, and Peak Concentrations Following Intravenous (13 mg/kg QW) and Subcutaneous Administration of Ramucirumab (1400-mg SC loading dose on Day 1 followed by either weekly [QW] SC 700 mg or twice weekly [BIW] SC 350 mg)

	13 mg/kg IV QW MTD		SC LD 1400 mg + SC MD 350 mg BIW		SC LD 1400 mg + SC MD 700 mg QW		RATIO-MOS IV 13 mg/kg QW/SC700	RATIO-MOS IV 13 mg/kg QW/SC350
	Median	5th-95th percentile	Median	5th-95th percentile	Median	5th-95th percentile	Median	Median
Week 1&2 PK parameters								
AUC1 mg.h/mL	23.5	17.1-33.1	16.3	10.6-25.1	14.8	9.61-22.9	1.6	1.4
AUC2 mg.h/mL	58	41.2 – 83	39.2	24.8-61.5	35.8	22.6-56.2	1.6	1.5
C_{av} µg/mL Week1	140	101-197	97	63-149	88	57-136	1.6	1.5
C_{av} µg/mL Week2	205	143-297	136	85-217	125	77-198	1.6	1.5
C_{max} µg/mL	353	259-495	141	87-227	134	83-212	2.6	2.5
C_{trough} µg/mL	135	82-207	133	80-218	112	66-184	1.2	1.0
Steady state SS PK parameters								
$AUC_{,ss}$ mg.h/mL	125	78-194	59	33-102	59	34-102	2.11	2.11
C_{av} µg/mL	371	233-578	176	99.4-305	176	100-305	2.11	2.11
C_{max} µg/mL	540	366-804	178	100-308	186	106-318	2.9	3.03
C_{trough} µg/mL	270	153-433	170	96-296	157	86-278	1.72	1.59

Abbreviations: AUC_{ss} = area under the curve at steady state over 2 weeks; AUC1 = area under the curve during the first week of treatment; AUC2 = area under the curve during the first 2 weeks of treatment; BIW = twice weekly; C_{av} = average concentration; C_{max} = maximum concentration; C_{trough} =trough min concentration at the end of the dosing interval; IV = intravenous; LD = loading dose; MD = maintenance dose; PK = pharmacokinetic; SC = subcutaneous; SS = steady state; QW = once weekly.

10.7. Appendix 7: Abbreviations

Term	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ATE	arterial thromboembolic event
AUC	area under the concentration versus time curve
BIW	twice weekly
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BMI	body mass index
C_{av}	average drug concentration during the dosing interval for a single dose
C_{max}	maximum drug concentration
C_{trough}	minimal/predose concentration before the next dose
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, GCP, and applicable regulatory requirements.
COVID-19	coronavirus disease 2019
CP	clinical pharmacologist
CRC	colorectal cancer
CRF/eCRF	case report form/electronic case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

CRU	clinical research unit
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GI	gastrointestinal
HCC	hepatocellular carcinoma
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction

ISP	injection site pain
ISR	injection site reaction
IV	intravenous(ly)
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
participant	equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRES	posterior reversible encephalopathy syndrome
Q2W	every 2 weeks
QTc	corrected QT interval
QW	once weekly
SAC	safety assessment committee
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERM	selective estrogen receptor modulator
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of maximum concentration

TE ADA	treatment-emergent antidrug antibody
TE ADA+	treatment-emergent antidrug antibody positive
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event
WOCBP	woman/women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment(b): 14 July 2020

Overall Rationale for the Amendment:

This amendment addresses feedback from the United States Food and Drug Administration (FDA).

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Indicated that AE grading will be via CTCAE version 5.0	To address FDA feedback
8.2.6 Safety Monitoring	Indicated that safety monitoring will include monitoring and recording of all AEs, including all CTCAE version 5.0 grades and SAEs	To address FDA feedback
8.3 Adverse Events and Serious Adverse Events	Indicated that the investigator will use CTCAE version 5.0 to assign AE severity grades	To address FDA feedback
9.4.3 Other Safety Analyses	Indicated that the most current version of MedDRA will be used to report AEs and that CTCAE version 5.0 will be used to assign AE severity grades. Indicated that all relevant hematology and chemistry laboratory values will be graded according to CTCAE version 5.0.	To address FDA feedback
10.3.3 Recording and Follow-Up of AEs and/or SAEs	Indicated that the investigator will use CTCAE version 5.0 to assign AE severity grades	To address FDA feedback
11 References	Added reference for CTCAE version 5.0	To address FDA feedback
Throughout	Minor editorial and formatting revisions	Minor and therefore have not been summarized

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; FDA = United States Food and Drug Administration; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Amendment(a): 26 June 2020

Overall Rationale for the Amendment:

Due to the COVID-19–related increased risks, extending the participant's inpatient visits at the clinical research unit would reduce the exposure and risks.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Modified the enrollment ratio to 10 participants (7 ramucirumab:3 placebo per group) to complete at least 8 participants	To capture that 10 participants per group will be enrolled
1.1 Synopsis	Added language to indicate that replacements may be enrolled	To add flexibility because replacements may be needed to reach the planned number of completers
1.1 Synopsis	Revised dosing for the remaining participants in the sentinel group from later in the morning to the next day	To reflect that dosing will be on the next day for the remaining participants in the sentinel group
1.1 Synopsis	Clarified that at least 48 evaluable participants will be enrolled and randomized for at least 8 evaluable participants per group	To add clarity on number of evaluable participants
1.1 Synopsis	Changed CRU discharge to Day 8 from Day 5	To reduce the risk of infections, changed outpatient visits for Days 6, 7, and 8 to inpatient visits
1.2 Schema	Modified schema to include 7 ramucirumab:3 placebo participants per group instead of 6 ramucirumab:2 placebo participants per group	To reflect the change in enrollment ratio and clarify that Group 6 will be randomized
1.3 Schedule of Activities	Changed outpatient visits for Days 6, 7, and 8 to inpatient visits	To minimize the procedures for check-ins/check-outs due to COVID-19
1.3 Schedule of Activities	Indicated that breath ethanol testing will be performed	To clarify that breath testing will be done for alcohol

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Clarified that a complete physical examination will be performed at screening and brief physical examinations will be performed at other time points	To provide clarification on physical examinations
1.3 Schedule of Activities	Changed CRU discharge to Day 8 from Day 5	To reduce the risk of infections, changed outpatient visits for Days 6, 7, and 8 to inpatient visits
2.1 Study Rationale	Modified the enrollment ratio to 10 participants (7 ramucirumab:3 placebo per group) to complete at least 8 participants	To capture that 10 participants per group will be enrolled
4.1 Overall Design	Modified the enrollment ratio to 10 participants (7 ramucirumab:3 placebo per group) to complete at least 8 participants	To capture that 10 participants per group will be enrolled
4.1 Overall Design	Revised dosing for the remaining participants in the sentinel group from later in the morning to the next day	To reflect that dosing will be on the next day for the remaining participants in the sentinel group
4.1 Overall Design	Changed CRU discharge to Day 8 from Day 5	To reduce the risk of infections, changed outpatient visits for Days 6, 7, and 8 to inpatient visits
5.1 Inclusion Criteria	Under inclusion criterion [7a], added with spermicide	To add clarity that cervical sponges will be used with spermicide
5.1 Inclusion Criteria	Under inclusion criterion [7b], removed regardless of childbearing potential	To remove unnecessary language because females must be of nonchildbearing potential
6.1 Study Intervention(s) Administered	Under the placebo for IV column, removed reference to SC injection (Groups 1, 2, 4, 5) and SC infusion with a pump (Group 6)	To remove duplicate information that was inadvertently populated under the placebo for IV column. The placebo for SC is captured under the placebo for SC column.

Section # and Name	Description of Change	Brief Rationale
6.3 Measures to Minimize Bias: Randomization and Blinding	Modified the enrollment ratio to 10 participants (7 ramucirumab:3 placebo per group) to complete at least 8 participants	To capture that 10 participants per group will be enrolled
6.3 Measures to Minimize Bias: Randomization and Blinding	Revised ratio for randomization to 7:3 from 3:1	To capture that 10 participants per group will be enrolled
9.2 Sample Size Determination	Clarified that participants will be randomly assigned (10 per group/dose level; 7 ramucirumab:3 placebo) to obtain at least 8 evaluable participants per group (6 ramucirumab:2 placebo)	To capture that 10 participants per group will be enrolled to complete at least 8 evaluable participants
9.2 Sample Size Determination	Revised to indicate that the participant will be considered evaluable instead of a completer when the participant completes up to 40 days of study procedures	To capture the number of evaluable participants needed for the analysis
9.2 Sample Size Determination	Added language to indicate that the sponsor will be consulted if a participant needs to be replaced	To add flexibility because replacements may not be needed if there are sufficient evaluable participants
9.4 Statistical Analyses	Added timeline for primary analysis of the study	To add clarity for primary analysis
9.5 Interim Analysis	Revised dosing for the remaining participants in the sentinel group from later in the morning to the next day	To reflect that dosing will be on the next day for the remaining participants in the sentinel group
10.2 Appendix 2 Clinical Laboratory Tests	Revised ethanol testing to breath ethanol testing	To clarify that breath ethanol testing is acceptable
Throughout	Minor editorial and formatting revisions	Minor and therefore have not been summarized

Abbreviations: COVID-19 = coronavirus disease 2019; CRU = clinical research unit; IV = intravenous.

11. References

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