Protocol I4T-MC-JVDU(e)

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

NCT04557384

Approval Date: 26-Feb-2021

Title Page

Protocol Title:

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

Protocol Number: I4T-MC-JVDU

Amendment Number: e

Compound: Ramucirumab (LY3009806)

Study Phase: Phase 1

Short Title:

A Phase 1 Investigation of Subcutaneous Ramucirumab Administration in Participants with Advanced Solid Tumors

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 148078

Approval Date: Protocol Electronically Signed and Approved by Lilly on 21 May 2020.
Protocol Amendment (a) Electronically Signed and Approved by Lilly on 14 September 2020.
Protocol Amendment (b) Electronically Signed and Approved by Lilly on 02 October 2020.
Protocol Amendment (c) Electronically Signed and Approved by Lilly on 05 November 2020.
Protocol Amendment (d) Electronically Signed and Approved by Lilly on 14 January 2021.

Approval Date: 26-Feb-2021 GMT

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

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment d	14-Jan-2021
Amendment c	05-Nov-2020
Amendment b	02-Oct-2020
Amendment a	14-Sep-2020
Original Protocol	21-May-2020

Amendment [e]

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the amendment is to enable investigation of additional dosage regimens. Preliminary interim analysis data from Study I4T-MC-JVDT, a single-site study in healthy participants who received a single dose of SC or IV ramucirumab indicated a 40% bioavailability for ramucirumab following SC administration (bioavailability previously predicted: >50%). A Sub-Cohort B1 has been added to provide a second-dose level (in addition to cohort A), with the goal to generate PK data from at least 6 participants to inform dosing strategy for Sub-Cohort B2 (loading dose and maintenance weekly dose).

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis	Added language to support flat dosing for Study JVDU	Based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 1.1. Synopsis (Overall Design); Section 1.2. Schema; Section 4.1.1. Cohort A	Added language reflecting PK will also be assessed in all cohorts	Clarification
Section 1.1. Synopsis (Number of Participants); Section 9.2. Sample Size Determination	Amended the range of number of study participants from 15-24 to 18-30	To account for the expansion of Cohort B, to investigate additional dosing regimens based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 1.1. Synopsis (Intervention Groups and Duration); Section 6.1. Study Intervention(s) Administered	Amended the Intervention Groups and Duration table and footnotes to reflect the expansion of Cohort B	To account for the expansion of Cohort B, to investigate additional dosing regimens based on preliminary interim analysis data from Study I4T-MC-JVDT

Section # and Name	Description of Change	Brief Rationale
Section 1.2. Schema	Amended Schema and footnotes to reflect the expansion of Cohort B	To account for the expansion of Cohort B, to investigate additional dosing regimens based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 1.3. Schedule of Activities	Amended note above table	Clarification
Section 1.3. Schedule of Activities, Continued Access Schedule of Activities	Added reference to Section 10.3 in the AE collection row	Clarification
Section 1.3. Schedule of Activities	Added language stating an investigator designee may also assess the injection site assessments	To provide flexibility for sites
Section 1.3. Schedule of Activities	Amended instructional language in the Administer ramucirumab row	Clarification
Section 1.3.1. Pharmacokinetic Sampling Schedule	Amended general instructions for PK sampling	Clarification
Section 2.1. Study Rationale	Removed language related to prior dosing rationale Added language referencing clinical outcome and PK parameters of IV and SC dosing of ramucirumab in Study I4T-MC-JVDT Removed sentence referencing Eli Lilly's SC formulation of ramucirumab	Clarification; based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 2.3.1. Risk Assessment	Amended language to allude to recent clinical data for SC ramucirumab	Based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 4.1. Overall Design; Section 9.2.1. Cohort A	Described sub-cohorts and cohorts based on updated study design Removed language about Study JVDT	To account for the expansion of Cohort B, to investigate additional dosing regimens based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 4.1.1. Cohort A	Removed sentence referencing "participants with disease indications where ramucirumab is approved as a monotherapy"	Correction (missed in previous amendment), based on preliminary interim analysis data from Study I4T-MC-JVDT revealing lower bioavailability than the assumption, previously eligible participants for approved ramucirumab monotherapy (2L Gastric, 2L HCC) would have received sub-optimal exposure on starting Cohort A dose

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1. Cohort A	Amended language related to enrolling an additional 3 participants into Cohort A	Clarification that additional enrollment in Cohort A may occur to numerous reasons
Section 4.1.2. Cohort B	Specified additional design elements in Cohort B, which now comprises B1, B2, and B3	To account for the expansion of Cohort B, to investigate additional dosing regimens based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 4.3.2. Rationale for Cohort B (Sub-Cohorts B1, B2, and B3) Dose Selection	Added rationale for dose selection and updated dosing table (based on bioavailability of 40%) for new Sub-Cohorts B1, B2, and B3 Removed rationale for initial Cohort B dose selection	To account for the expansion of Cohort B, to investigate additional dosing regimens based on preliminary interim analysis data from Study I4T-MC-JVDT
Section 5.1. Inclusion Criteria	Amended Inclusion Criterion 3	Clarification
Section 6.1. Study Intervention(s) Administered	Added language specifying dosage in Sub-Cohort B1 Specified when interim analysis will be performed (Sub-Cohort B2) Specified ramucirumab dose may be adjusted in Sub-Cohort B3	To account for the expansion of Cohort B, to investigate additional dosing regimens
Section 6.1. Study Intervention(s) Administered; Section 6.6. Dose Modification	Changed injection site reaction grading threshold and moved to Section 6.1 (from Section 6.6.)	Allowing participants with mild-to-moderate local injection site reactions due to ramucirumab SC administration to continue to receive it
Section 6.6. Dose Modification	Removed language related to pausing study on the basis of a new safety signal	Dose modifications are not relevant for the LD
Section 6.6. Dose Modification	Added fever as an example of a non-threatening and reversible Grade 3 clinical AE Moved language referencing Appendix 3 for AE grading to an earlier paragraph	Clarification
Section 6.6. Dose Modification	Added a dose reduction for the MD of the newly described dosage regimen	To account for a newly added LD of 1750 mg and MD of 875 mg QW based on preliminary interim analysis bioavailability data of 40%
Section 7.3. Lost to Follow up	Removed language related to collection of survival status	Correction, as long-term follow-up and survival status is not being collected for this study
Section 9.1. Statistical Hypotheses	Specified C_{trough} and the approved dose of IV ramucirumab	Clarification
Section 9.2.1. Cohort A	Amended number of participants/duration of PK and safety assessment required before opening enrollment for Cohort B	To account for the expansion of Cohort B, to investigate additional dosing regimens based on preliminary interim analysis data from Study I4T-MC-JVDT

Section # and Name	Description of Change	Brief Rationale
Section 9.2.2. Cohort B (Sub-Cohorts B1, B2, and B3); Section 9.5. Interim Analyses	Changed name from safety review team (SRT) or internal assessment committee to internal review committee	For consistency with other documents
Section 9.2.2. Cohort B (Sub-Cohorts B1, B2, and B3)	Removed language related to PK data providing support for Cohort B dose selection Added language related to Sub-Cohort B2 dosing regimen determination based on Sub-Cohort B1 results	To account for the expansion of Cohort B, to investigate additional dosing regimens
Section 9.2.3. Cohort C	Changed language to ensure flexibility of obtaining sufficient safety/PK data	To provide flexibility in participant enrollment
Section 9.5. Interim Analysis	Removed timing of interim analyses	To provide flexibility for data analysis
Section 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Removed language related to categorization of AE severity grade Added language regarding grading of hepatic labs	This protocol will use the CTCAE v5.0 to assign AE severity grades for all labs except hepatic labs which will use v4.03
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Table of Contents

1. Protocol Summary

1.1. Synopsis

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

Short Title: A Phase 1 Investigation of Subcutaneous Ramucirumab Administration in Participants with Advanced Solid Tumors

Rationale:

In the current approved indications, ramucirumab is administered intravenously either as a single agent or in combination with anti-cancer therapies. Ramucirumab has an established safety profile as a single agent and in combination with chemotherapy in the cancer population. Exposure-response (ER) analyses across Phase 3 ramucirumab studies, where ramucirumab was dosed intravenously at the currently-approved doses of 8 mg/kg every 2 weeks (Q2W) and 10 mg/kg every 3 weeks (Q3W), showed that patients in the highest ramucirumab C_{trough} quartile demonstrated greater treatment benefit (increased overall survival [OS] and progression-free survival [PFS]) than patients in the lowest C_{trough} quartile, and in some studies, in the lowest two C_{trough} quartiles (25% or 50% of the overall patient population, respectively). A subcutaneous (SC) dosing regimen for ramucirumab has the potential to optimize ramucirumab exposure by changing the ramucirumab pharmacokinetic (PK) profile, and thereby may improve patient outcomes compared with an intravenous (IV) dosing regimen. This would be achieved by raising ramucirumab C_{trough} and lowering ramucirumab C_{max} (leading to reduced peak-to-trough fluctuation) and decreasing the time to achieve sustained therapeutic levels (Rummel et al. 2017; Anderson et al. 2019; Dent et al. 2019).

Using PK parameters (from the ramucirumab IV population PK model), an estimated 40% bioavailability and 0.3 day^{-1} absorption rate for SC ramucirumab (based on interim analysis data from Study I4T-MC-JVDT), a simulation of the PK profile for SC ramucirumab was performed. Results indicated similar mean ramucirumab AUC and variability (CV%) of exposure following either flat SC dosing (875 mg QW dosing) or weight-based dosing (10 mg/kg Q2W IV). Thus, it is planned that the SC ramucirumab dose regimen will be flat dosing in this study.

This open-label Phase 1 study will assess the PK profile and safety of SC ramucirumab, alone or in combination with additional anti-cancer therapy, in participants with cancer.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine a recommended ramucirumab SC dosing regimen for future studies by assessing the PK parameters of ramucirumab after SC administration.	• AUC and C_{max} of ramucirumab when administered as monotherapy • C_{trough} (serum trough concentrations)

Objectives	Endpoints
• To determine a recommended ramucirumab SC dosing regimen for future studies by assessing safety of ramucirumab after SC administration.	• Safety including, but not limited to, AEs, TEAEs, and SAEs after SC administration.
Secondary	
• To assess the IG of ramucirumab administered SC.	• Relationship between TE ADA and safety. • Relationship between TE ADA and ramucirumab PK.
• 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.

Abbreviations: AE = adverse event; AUC = area under the plasma concentration versus time curve; C_{max} = maximum blood plasma concentration; C_{trough} = lowest concentration of a drug just before the next dose; IG = immunogenicity; ISR = injection site reaction; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TE ADA = treatment-emergent anti-drug antibody; TEAE = treatment-emergent adverse event.

Overall Design

Protocol I4T-MC-JVDU (JVDU) is a Phase 1, non-randomized, open-label, ongoing investigation of multiple SC ramucirumab administrations in cancer participants, with the first dose being a SC loading dose followed by weekly SC maintenance dosing. The injection site for the SC administration will be the abdomen.

Section 1.2 provides the study schema. Participants with refractory/relapsed solid tumors with evaluable disease and who have exhausted all treatments with proven clinical benefit (all cohorts), as well as participants with a diagnosis where ramucirumab is clinically acceptable treatment as a monotherapy or in combination with additional anti-cancer therapy (Cohorts B and C only), are eligible for Protocol JVDU. Each treatment cycle is either 21-days or 28-days based on the treatment regimen, with SC ramucirumab administered weekly for 3 doses or 4 doses, respectively, within each cycle. Participants in Cohorts B and C who are planned to receive ramucirumab in combination with additional anti-cancer therapy will receive weekly SC ramucirumab as monotherapy for at least 3 weeks for safety and PK assessment, prior to initiation of the combination agent.

Disclosure Statement: This is a single-group treatment study with one arm that is not blinded.

Number of Participants:

Approximately 18 to 30 participants will be treated in this study.

Intervention Groups and Duration:

	Cohorts				
	A	**B**			**C**
Sub-Cohorts		B1	B2	B3 (Optional)	
Planned Number of Participants	3-6[a]	3-6[a]	3-6[b]	6[b]	6
Ramucirumab Monotherapy SC QW (Cohorts A, B, and C) *Note: If participants are on ramucirumab monotherapy, then the cycle duration is 21 days for the entire duration of the study.*					
Ramucirumab					
SC loading dose given in the first week of treatment[e]	700 mg	N/A	TBD[c] (max 1750 mg weekly)	TBD[c] (max 1750 mg weekly)	Same dose from Cohort B[f]
SC weekly maintenance dose starting at Study Week 2 (ie, Study Day 8)	350 mg QW	TBD[c] (max 875 mg weekly)	TBD[c] (max 875 mg weekly)	TBD[c] (max 875 mg weekly)	
Optional Combination Therapy (Cohorts B and C, starting from Cycle 2) *Note: Regardless of whether participants are on ramucirumab monotherapy or combination therapy, Cycle 1 (21 days) is SC ramucirumab QW monotherapy.*					
2L Gastric[d] (28-Day cycle)		Dose for combination therapies (paclitaxel, docetaxel, irinotecan, fluorouracil, and erlotinib) should follow institutional practice.			
Paclitaxel	N/A				
2L NSCLC (21-Day cycle)					
Docetaxel	N/A				
2L CRC (28-Day cycle)					
Irinotecan	N/A				
Fluorouracil	N/A				
1L NSCLC EGFR+ (28-Day cycle)					
Erlotinib	N/A				

Abbreviations: 1L = first line; 2L = second line; CRC = colorectal cancer; EGFR = epidermal growth factor receptor; FOLFIRI = fluorouracil and irinotecan; N/A = not applicable; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; QW = every week; SC = subcutaneous; TBD = to be determined.

[a] Refer to Sections 4.1.1 and 4.1.2 for total enrollment, based on safety and PK data.

[b] Refer to Section 4.1.2 for total enrollment, based on safety and PK data.

[c] Dose selection for Sub-Cohorts B2 and B3 will be based on safety and available PK data (see Sections 4.1 and 9.2.2 for further details).

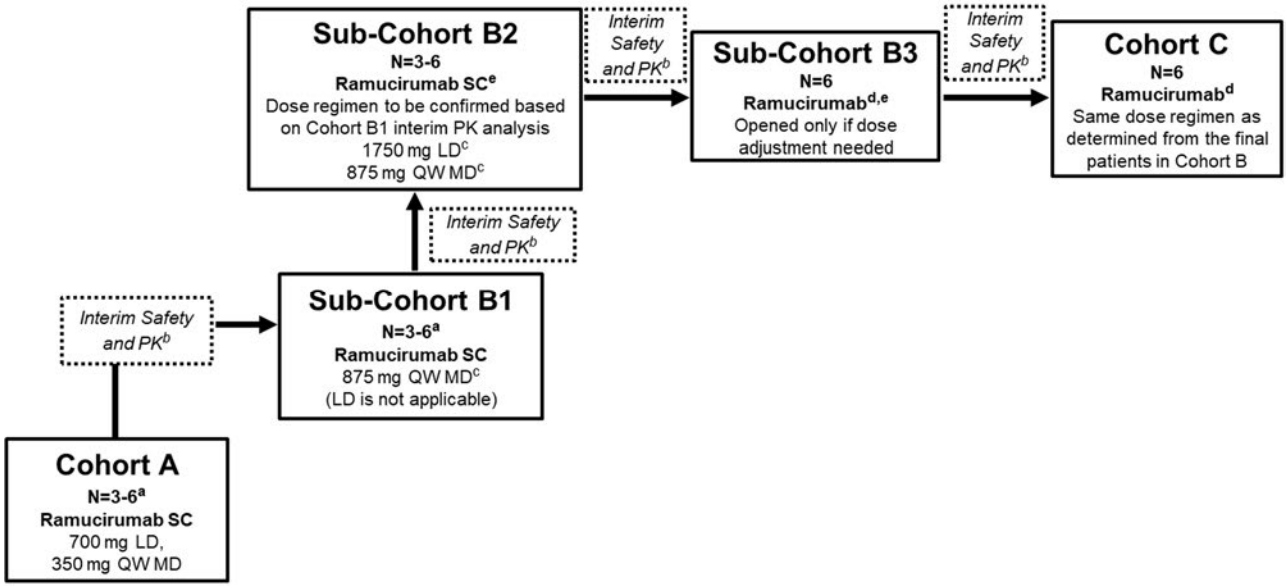
[d] FOLFIRI as an alternative combination is permissible.

[e] Loading dose above 700 mg will use a syringe pump for Cohorts B and C.

[f] Dose meeting PK and safety objectives as described in Section 4.1.3.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: LD = loading dose; MD = maintenance dose; N = number of participants; PK = pharmacokinetic; QW = weekly; SC = subcutaneous.

[a] Refer to Section 4.1.1 for total enrollment, based on safety and PK data.

[b] Refer to Section 4.1.2 for additional details.

[c] Maximal proposed weekly doses are indicated. This dose will be administered once per week, with the LD given on Cycle 1 Day 1, except in Cohort B1 that will start with 875 mg SC QW MD without LD.

[d] Refer to Sections 4.3.2 and 6.1 for the dosing regimen.

[e] Sample size in Sub-Cohorts B2 and B3 (if opened) determined by PK and safety data, per Sections 4.1.2 and 9.2.

1.3. Schedule of Activities (SoA)

Note: For applicable participants who have their combination therapy held while SC weekly ramucirumab is continued, procedures noted in column DX are to be performed at the time of the additional ramucirumab doses.

Screening, On-Study, and Post-Treatment Schedule of Activities																
	Screening		On-Treatment												Post-Treatment	
			Cycle = 21 days			Cycle = 21 days (or 28 days for Cohorts B & C per combination regimen)										
	(Day Relative to C1D1)		Cycle 1			Cycle 2				Cycle 2-n (If combo therapy is held and ramucirumab is given)	Cycle 3-n				Short-term follow-up[a]	Instructions
			(±3 days)			(±3 days)				(±3 days)	(±3 days)				(±3 days)	
	≤28	≤7	D1	D8	D15	D1	D8	D15	D22	DX	D1	D8	D15	D22	V801	D22 for 28-day cycles only.
Procedure																
Informed consent	X															ICF must be signed before any protocol-specific procedures are performed
Inclusion/Exclusion criteria	X															
Medical history	X															Including assessment of preexisting conditions, historical illnesses, and habits (such as tobacco and alcohol use).
Cancer treatment history	X															Record prior anti-cancer therapy
Concomitant medication	X		X													• At baseline, record prior and concurrent medications. • Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.
Physical examination	X		X	X	X	X					X				X	

Screening, On-Study, and Post-Treatment Schedule of Activities																
	Screening		**On-Treatment**												**Post-Treatment**	
			Cycle = 21 days			**Cycle = 21 days (or 28 days for Cohorts B & C per combination regimen)**										
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2**				**Cycle 2-n** (If combo therapy is held and ramucirumab is given)	**Cycle 3-n**				**Short-term follow-up[a]**	**Instructions**
			(±3 days)			(±3 days)				(±3 days)	(±3 days)				(±3 days)	
	≤28	**≤7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D22**	**DX**	**D1**	**D8**	**D15**	**D22**	**V801**	D22 for 28-day cycles only.
Procedure																
Vital signs	X		See instructions			X	X	X	X	X	X	X	X	X	X	Measure vital signs (height [at baseline], weight, temperature, blood pressure, pulse rate, and respiration rate). On days with concurrent ECGs, vital signs, and/or PK sampling, these measurements should occur at approximately the same time. Vital sign measurements will be obtained: • Day 1 at predose (prior to SC ramucirumab dose, but within 90 minutes prior to predose blood draw) • C1D2 (24 hours postdose) • C1D8 • C1D15 • Any time for other specified visits, but prior to SC ramucirumab dose at same visit.
AE collection	X		X												X	• Collect continuously at every visit and throughout the study. • CTCAE Version 5.0 • See Section 10.3 for AE grading for lab investigations.

Screening, On-Study, and Post-Treatment Schedule of Activities																
	Screening		On-Treatment												Post-Treatment	
			Cycle = 21 days			Cycle = 21 days (or 28 days for Cohorts B & C per combination regimen)										
	(Day Relative to C1D1)		Cycle 1			Cycle 2				Cycle 2-n (If combo therapy is held and ramucirumab is given)	Cycle 3-n				Short-term follow-up[a]	Instructions
			(±3 days)			(±3 days)				(±3 days)	(±3 days)				(±3 days)	
	≤28	≤7	D1	D8	D15	D1	D8	D15	D22	DX	D1	D8	D15	D22	V801	D22 for 28-day cycles only.
Procedure																
ECOG PS	X		X			X					X				X	During study treatment, perform ≤3 days prior to treatment.
ECG	X		See instructions												X	Single, local. On days with concurrent measurements, see vital sign row for more details. Times are referenced to the end of dosing. ECGs will be obtained: • C1D1 at predose. • Every 6 weeks thereafter, predose. • Any other time as clinically indicated.
Hematology		X	X	X	X	X	X	X		X	X				X	See Appendix 2.
Coagulation		X				X										See Appendix 2. Perform at baseline, C2D1, D1 of every other cycle afterwards (C4D1, C6D1, etc.), and as clinically indicated.
Clinical chemistry		X	X	X	X	X	X	X		X	X				X	See Appendix 2.
Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Appendix 2. In addition, perform as clinically indicated.
Pregnancy test		X	See instructions												X	• Applies only to women of childbearing potential.

Screening, On-Study, and Post-Treatment Schedule of Activities																
	Screening		On-Treatment												Post-Treatment	
			Cycle = 21 days			Cycle = 21 days (or 28 days for Cohorts B & C per combination regimen)										
	(Day Relative to C1D1)		Cycle 1			Cycle 2				Cycle 2-n (If combo therapy is held and ramucirumab is given)	Cycle 3-n				Short-term follow-up[a]	Instructions
			(±3 days)			(±3 days)				(±3 days)	(±3 days)				(±3 days)	
	≤28	≤7	D1	D8	D15	D1	D8	D15	D22	DX	D1	D8	D15	D22	V801	D22 for 28-day cycles only.
Procedure																
																• Note: During study treatment, perform monthly or as required per local regulations and/or institutional guidelines. See Appendix 2.
Thyroid panel		X	See instructions												X	See Appendix 2. Starting C1D1, then every 3 months thereafter.
Radiologic imaging and measurement of palpable or visible lesions	X		See instructions												X	• Perform according to RECIST 1.1, by the same method used at baseline, every 8 weeks (±7 days) for the first 6 months after C1D1 and every 12 weeks (±7 days) thereafter until radiographic disease progression, death, or study completion, whichever occurs first. Perform as scheduled, even if study treatment is delayed or omitted.
Injection site assessments (solicited)			See instructions			X	X	X	X	X	X	X	X	X		Prior to each injection and at the designated timepoints, the investigator/investigator designee will ask the participant if they have any injection site concerns and record the participant's response. **1.Cycle 1 collection:**

Screening, On-Study, and Post-Treatment Schedule of Activities																
	Screening		On-Treatment												Post-Treatment	
			Cycle = 21 days			Cycle = 21 days (or 28 days for Cohorts B & C per combination regimen)										
	(Day Relative to C1D1)		Cycle 1			Cycle 2				Cycle 2-n (If combo therapy is held and ramucirumab is given)	Cycle 3-n				Short-term follow-up[a]	Instructions
			(±3 days)			(±3 days)				(±3 days)	(±3 days)				(±3 days)	
	≤28	≤7	D1	D8	D15	D1	D8	D15	D22	DX	D1	D8	D15	D22	V801	D22 for 28-day cycles only.
Procedure																
																a.C1D1: 5-15 min after injection is complete and 60 min after injection is complete b.C1D2 (approximately 24 hr after injection) c.C1D4 (± 1 day) d.C1D8: 5-15 min after injection and 60 min after injection e.C1D15: 5-15 min after injection and 60 min after injection **2.Cycle 2-n collection:** a.5-15 min after injection and 60 min after injection The findings from the assessment are recorded on the ISR questionnaire. All positive responses of pain require an additional assessment using the participant-completed Pain VAS. If there are ≥2 injections, the ISR questionnaire will be filled out separately for each site, after all injections have been administered. See Section 8.2.5 for details.

Screening, On-Study, and Post-Treatment Schedule of Activities																
	Screening		**On-Treatment**												**Post-Treatment**	
			Cycle = 21 days			**Cycle = 21 days (or 28 days for Cohorts B & C per combination regimen)**										
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2**				**Cycle 2-n** (If combo therapy is held and ramucirumab is given)	**Cycle 3-n**				**Short-term follow-up[a]**	**Instructions**
			(±3 days)			(±3 days)				(±3 days)	(±3 days)				(±3 days)	
	≤28	**≤7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D22**	**DX**	**D1**	**D8**	**D15**	**D22**	**V801**	D22 for 28-day cycles only.
Procedure																
Injection site assessments (spontaneous)			See instructions													1. ISR questionnaire completed outside of solicited assessment schedule. 2. May be triggered by participant anytime during the cycle based on diary. 3. If the participant indicates presence of pain during spontaneous ISR reporting, no VAS assessment is required.
Participant diary			See instructions													• Participant will assess injection site(s) daily. If any ISR symptoms present, the participant should contact the investigator. • Diary should be returned to the investigator at each weekly visit.
Sample collection																See Section 1.3.1 for PK and IG.
PK				See Section 1.3.1												
IG				See Section 1.3.1												

Screening, On-Study, and Post-Treatment Schedule of Activities																
	Screening		On-Treatment												Post-Treatment	
			Cycle = 21 days			Cycle = 21 days (or 28 days for Cohorts B & C per combination regimen)										
	(Day Relative to C1D1)		Cycle 1			Cycle 2				Cycle 2-n (If combo therapy is held and ramucirumab is given)	Cycle 3-n				Short-term follow-up[a]	Instructions
			(±3 days)			(±3 days)				(±3 days)	(±3 days)				(±3 days)	
	≤28	≤7	D1	D8	D15	D1	D8	D15	D22	DX	D1	D8	D15	D22	V801	D22 for 28-day cycles only.
Procedure																
Administer ramucirumab			See instructions													See Section 6.1. Participants must be closely monitored for a 1-hour observation period following the administration of SC ramucirumab (see Section 6.1).
Administer combination medications, if applicable (Cohorts B and C only)			See instructions								See instructions					Begin Combination anti-cancer therapies along with weekly SC ramucirumab at Cycle-2. See details in Section 6.1. Erlotinib (1L EGFR+ NSCLC), docetaxel (2L NSCLC), paclitaxel (2L gastric), FOLFIRI (2L CRC).

Abbreviations: 1L = first line; 2L = second line; AE = adverse event; C = cycle; CRC = colorectal cancer; CTCAE = common terminology criteria for adverse events; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Score; EGFR = epidermal growth factor receptor; FOLFIRI = fluorouracil and irinotecan; hr = hour; ICF = informed consent form; IG = immunogenicity; ISR = injection site reaction; min = minutes; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SC = subcutaneous; V = visit; VAS = visual analogue scale.

a Short-term follow-up begins when the participant and investigator agree that the participant will no longer continue study treatment and lasts a minimum of 30 days following the last dose of study drug.

Continued Access Schedule of Activities			
Visit	**Study Treatment 501-5XX**	**Follow-Up[a] 901**	
Procedure			**Instructions**
AE Collection	X	X	Grading via CTCAE, Version 5.0. As part of AE collection, monitor vital signs and perform standard laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing) at the same frequency as during the study treatment period. See Section 10.3 for AE grading for lab investigations. All laboratory tests during the continued access period will be performed in the local laboratories only.
PK, IG, and exploratory hypersensitivity			In the event of hypersensitivity, blood samples will be collected for PK, IG, and exploratory hypersensitivity analyses at the following time points, as close as possible to: (i) the onset of the hypersensitivity, (ii) the resolution of the hypersensitivity, and (iii) 30 (±3) days following the hypersensitivity.
Administer ramucirumab	X		See Section 6.1. Participants must be closely monitored for a 1-hour observation period following the ramucirumab injection (see Section 6.1).

Abbreviations: AE = adverse event; CTCAE = common terminology criteria for adverse events (NCI 2018); IG = immunogenicity; NCI = National Cancer Institute; PK = pharmacokinetic.

[a] Continued-access follow-up begins when the participant and the investigator agree that the participant will no longer continue treatment in the continued-access period and lasts a minimum of 30 days following the last dose of study drug. In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

1.3.1. Pharmacokinetic Sampling Schedule

General Instructions:

The pharmacokinetic sampling table applies to all participants irrespective of 21-day or 28-day cycle length.

Adequately record the actual collection date and time (24-hour clock; for example, 16:00, not 4 pm) on the requisition form of the sample.

In case of cycle delay and/or ramucirumab dosing interruption, if possible, collect an additional unscheduled PK samples using the appropriate central lab collection kit:

- at time as close as possible to the onset of the adverse event (AE) (if the cycle delay or ramucirumab dosing interruption is due to an AE).
- at the time when ramucirumab dose should have been administered (if there had not been a delay or dose interruption).
- prior to resuming the ramucirumab dosing after dosing interruption/dosing delay.

Note: If the above time points for unscheduled PK sampling happen to occur at the same time as a scheduled PK time point (see table below), then only the scheduled sample will be taken.

Sample #	Study Cycle	Day within Cycle	Collection Time Point Relative to Ramucirumab Weekly Dose	Ramucirumab PK Collection	Immunogenicity Collection
1	**1**	**1**	-1 hr (predose)	X	X
2	**1**	**2**	24 hrs ± 2 postdose	X	
3	**1**	**4 ± 1**	48-96 hrs postdose window	X	
4	**1**	**8**	-1 hr (predose)	X	
5	**1**	**15**	-1 hr (predose)	X	X
6	**1**	**18 ± 1**	48-96 hrs postdose window	X	
7	**2**	**1**	-1 hr (predose)	X	
8	**2**	**8**	-1 hr (predose)	X	X
9	**2**	**11 ± 1**	48-96 hrs postdose window	X	
10	**3**	**1**	-1 hr (predose)	X	
11	**3**	**15**	-1 hr (predose)	X	
12	**3**	**18 ± 1**	48-96 hrs postdose window	X	
13	**4**	**1**	-1 hr (predose)	X	X
14	**5**	**1**	-1 hr (predose)	X	
End of treatment			30 days post last dose	X	X

Abbreviations: hr = hour; PK = pharmacokinetic.

2. Introduction

2.1. Study Rationale

Ramucirumab, as a single agent or in combination with different chemotherapy regimens, has been approved in the US in the following second-line indications:

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

These approvals were based on 5 global, randomized Phase 3 studies which demonstrated overall survival (OS) benefit. The approved ramucirumab dose and schedule by intravenous (IV) infusion is 8 mg/kg every 2 weeks (Q2W) for gastric or GEJ adenocarcinoma, CRC, and HCC, and 10 mg/kg every 3 weeks (Q3W) for NSCLC (Fuchs et al. 2014; Wilke et al. 2014; Tabernero et al. 2015; Reck et al. 2017; Zhu et al. 2019).

Most recently, RELAY, which evaluated ramucirumab 10 mg/kg Q2W IV in combination with an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), erlotinib, demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS) in first-line treatment in patients with metastatic *EGFR*-mutated NSCLC. The application was approved by Food and Drug Administration (FDA) (Nakagawa et al. 2019).

The safety profile of IV ramucirumab is well established based on an exposure of more than 6400 patients who have received ramucirumab in the development program and more than 125,000 patients who have been treated with ramucirumab worldwide across 5 licensed second-line indications in the post-marketing setting.

For most drugs, the concentration at the site of the receptor determines the intensity of a drug's effect, and one can see that there is a concentration below which no effect is observed, and a concentration above which no greater effect is achieved. Ramucirumab most closely aligns with this mode of activity, being an antibody that targets a receptor (vascular endothelial growth factor [VEGF] Receptor 2). As such, it is common to associate drug effect with C_{trough} (FDA 2003). Exposure-response (ER) analyses across Phase 3 ramucirumab studies, where ramucirumab was dosed intravenously at the currently-approved doses of 8 mg/kg Q2W and 10 mg/kg Q3W, showed that after the first dose administration, patients in the lowest ramucirumab C_{trough} quartile and in some studies, in the lowest 2 C_{trough} quartiles (25% or 50% of the overall patient population, respectively) demonstrated less treatment benefit (lower OS and PFS) than patients in the highest C_{trough} quartiles. These studies demonstrated a greater benefit for patients in the highest exposure quartile who achieved, after the first dose administration, a C_{trough} of approximately 50 μg/ml. The lower ramucirumab C_{trough} values were likely due to a faster ramucirumab clearance in those patients.

In attempts to improve efficacy outcomes in those patients with a lower C_{trough}, efforts were made in 2 postmarketing Phase 2 studies to increase area under the plasma concentration versus time curve (AUC) and C_{trough} at a population level. Various IV doses and dosing regimens were tested in an attempt to produce higher measures of these criteria than what has been achieved

with the approved ramucirumab IV dosing regimens (8 mg/kg Q2W and 10 mg/kg Q3W). While increasing the ramucirumab dose in the second-line gastric cancer population from 8- to 12-mg/kg Q2W IV did not identify new safety concerns, there was no statistical improvement in the PFS with the higher dose other than a modest upward trend (data on file). In these studies, while ramucirumab AUC and C_{trough} were increased by about 50% at 12 mg/kg Q2W compared with 8 mg/kg Q2W, there continued to be a significant overlap in ramucirumab AUC and C_{trough}, and patients with higher clearance were still not able to achieve substantial improvements in C_{trough}. This may explain why substantial improvements in efficacy were not observed. It takes about 8 weeks of treatment with ramucirumab at 12 mg/kg Q2W IV for the majority (95%) of patients to achieve ramucirumab C_{trough} above 50 μg/mL. Thus, increasing the dose of the IV formulation does not appear be an effective way to rapidly increase C_{trough} for an entire population, which is needed to optimize efficacy.

Therefore, in contrast to the above strategy, based on the literature and knowledge of the pharmacokinetics (PK) of monoclonal antibodies (mAbs) following a subcutaneous (SC) administration (Viola et al. 2018), it is hypothesized that introduction of a ramucirumab SC formulation would allow additional optimization of the ramucirumab PK profile. A SC dosing regimen for ramucirumab, with an initial loading dose, has the potential to achieve in almost all patients (including patients with higher clearance) a target C_{trough} equivalent to the fourth quartile of the IV C_{trough} observed across the Phase 3 studies (i.e., C_{trough} above 50 μg/mL after the first dose) and produce an AUC comparable to the approved IV formulation of ramucirumab, which may result in improved efficacy.

For ramucirumab, a more frequent dosing regimen (than Q2W) would produce a less variable exposure over the dosing interval and may provide a new opportunity to further optimize ramucirumab exposure (beyond the exposure following an IV administration). Following a SC administration, ramucirumab would be absorbed over a longer period compared to an IV infusion, leading to a more constant ramucirumab concentration over the dosing interval. This would result in a lower C_{max} and a higher C_{trough}, with a lower peak-to-trough ratio compared with the 10 mg/kg Q2W IV administration. The evidence of any ER relationship for treatment-emergent adverse events (TEAEs) across the Phase 3 studies is minimal. Increased exposure of ramucirumab was associated with Grade ≥3 hypertension and neutropenia observed in some of the second-line studies. A lower C_{max} could result in potentially lower adverse events (AEs) related to severe hypertension and neutropenia that could further improve the benefit-risk profile.

The ramucirumab AUC following 10 mg/kg Q2W IV dosing regimen will be used as the reference exposure for the SC ramucirumab development because it is the highest ramucirumab exposure (tested in the Phase 3 RELAY study) with demonstrated efficacy and manageable safety. In addition, SC ramucirumab clinical investigation is supported by data from the ongoing study I4T-MC-JVDT (JVDT). Study JVDT is a Phase 1, dose-escalation study evaluating the PK profile and safety of single-dose IV and single-dose SC ramucirumab in healthy participants. The results from JVDT led to prediction of similar mean ramucirumab AUC and similar variability (CV%) of exposure following either flat SC dosing (875 mg QW dosing) or weight-based dosing (10 mg/kg Q2W IV). The large clinical safety and PK data base from IV ramucirumab and the data from study JVDT support the dosing regimens to be tested (refer to Section 4.3.2 for further details).

In summary, the development of a SC dosing regimen for ramucirumab has the potential to improve patient outcomes by changing the PK profile, relative to IV dosing, by:

- enabling the majority of patients to more rapidly achieve target C_{trough} (>50 μg/mL) after the first dose,
- achieving an AUC at a steady state at least comparable to a current IV dosing regimen which has demonstrated efficacy and safety, and
- minimizing peak-to-trough fluctuations and high C_{max}, potentially limiting some C_{max}-related toxicities.

The JVDU study is a Phase 1, nonrandomized, open-label, multicohort, multiple-dose study and will evaluate the PK and safety of SC ramucirumab in participants with cancer, alone or in combination with additional anti-cancer therapy.

2.2. Background

Ramucirumab is a human receptor-targeted mAb that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D; Lu et al. 2003; Zhu et al. 2003). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream intracellular signaling components, including extracellular signal-regulated protein kinases 1 and 2 (Erk1/Erk2), neutralizing ligand-induced proliferation, and migration of human endothelial cells (Lu et al. 2003; Zhu et al. 2003; Jimenez et al. 2005; Miao et al. 2006; Goldman et al. 2007; Tvorogov et al. 2010).

Ramucirumab has shown clinical efficacy in terms of PFS and OS for second-line gastric cancer in 2 randomized Phase 3 trials: REGARD (Study I4T-IE-JVBD [Study JVBD] [Fuchs et al. 2014]; ramucirumab monotherapy with best supportive care [BSC]) and RAINBOW (Study I4T-IE-JVBE [Study JVBE] [Wilke et al. 2014]; ramucirumab in combination with paclitaxel). Ramucirumab also demonstrated a statistically significant improvement in investigator-assessed PFS compared with placebo in a controlled Phase 3 study (I4T-MC-JVCU, RAINFALL) in first-line patients with metastatic gastric or GEJ adenocarcinoma, although an OS benefit was not demonstrated.

Ramucirumab has shown efficacy in terms of PFS and OS in randomized Phase 3 trials for NSCLC (Study I4T-MC-JVBA [Study JVBA]; REVEL [Reck et al. 2017]; ramucirumab in combination with docetaxel), CRC (Study I4T-MC-JVBB [Study JVBB]; RAISE [Tabernero et al. 2015]; ramucirumab in combination with FOLFIRI), and HCC (selected patients with an alpha-fetoprotein [AFP] ≥400 ng/mL) ([Study I4T-MC-JVDE]; REACH-2 [Zhu et al. 2019]; ramucirumab monotherapy).

Another Phase 3, placebo-controlled study (I4T-MC-JVDC [Study JVDC], RANGE) (Petrylak et al. 2020) examining ramucirumab plus docetaxel versus placebo plus docetaxel as second-line therapy in locally advanced, unresectable, or metastatic urothelial carcinoma, met its primary endpoint of PFS, demonstrating a statistically significant improvement in the ramucirumab arm compared with the placebo arm.

Most recently, RELAY, which evaluated ramucirumab 10 mg/kg Q2W IV in combination with an oral EGFR TKI, erlotinib, demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of PFS in first-line treatment in patients with metastatic *EGFR*-mutated NSCLC (Nakagawa et al. 2019). The application was approved by FDA.

Ramucirumab is currently approved in the US:

- as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- in combination with docetaxel, for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with EGFR or anaplastic large-cell lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.
- in combination with FOLFIRI, for the treatment of metastatic CRC with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- as a single agent, for the treatment of HCC in patients who have an AFP of ≥400 ng/mL and have been treated with sorafenib.

Details on the safety profile of ramucirumab is available in the Investigator's Brochure (IB).

An SC formulation of ramucirumab is being developed with the goal of optimizing drug exposures based on insights from the prior development program.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ramucirumab may be found in the IB, Participant Information Leaflet, Package Insert, Development Safety Update Report, or Summary of Product Characteristics.

2.3.1. Risk Assessment

The safety profile of IV ramucirumab is well established based on an exposure of more than 6400 patients who received ramucirumab in the development program and more than 125,000 patients who have been treated with ramucirumab worldwide across 5 licensed second-line indications in the post-marketing setting.

The AEs associated with IV ramucirumab across approved indications include specific effects of mAbs (including infusion-related reactions), and class-specific effects related to the mechanism of antiangiogenic agents which inhibit the VEGF/VEGF Receptor 2 signaling pathway (including hypertension, proteinuria, and bleeding/hemorrhage events).

Across the approved indications and in the RELAY study, the safety profile of IV ramucirumab, as a single agent or in combination with chemotherapy or erlotinib, was well tolerated with manageable toxicities.

The key risks for IV ramucirumab either as a single agent or in combination with anti-cancer therapy across currently approved indications of advanced gastric cancer, metastatic CRC, metastatic NSCLC, and HCC with AFP of ≥400 ng/mL are as follows:

a. Gastric cancer: Gastrointestinal (GI) perforation and severe (Grade ≥3) bleeding including GI hemorrhage
b. NSCLC: Grade ≥3 bleeding (including Grade ≥3 pulmonary hemorrhage)
c. HCC: Grade ≥3 bleeding (including GI hemorrhage) and liver failure/liver injury (including hepatic encephalopathy)

The risks associated with ramucirumab are mitigated in the protocol by clearly defined eligibility criteria for enrollment and close monitoring of study participants following ramucirumab dosing and initiation of appropriate treatment as necessary.

Ramucirumab administered intravenously either as monotherapy or in combination with chemotherapy or erlotinib in Phase 3 studies has demonstrated a favorable benefit-risk profile in the treatment of various tumor types.

Results of a single-dose safety study in monkeys indicate that SC administration of ramucirumab has a low potential for injection site irritation. The SC formulation may, by reducing C_{max}, limit toxicities that are C_{max}-driven. Interim results (Section 2.1) from JVDT, to date have shown SC ramucirumab to be safe and tolerable. The AEs observed were transient, monitorable, reversible, and consistent with the known safety profile of IV ramucirumab. In addition, injection site reactions were not reported.

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 ramucirumab should not be administered to pregnant women or women planning to become pregnant.

2.3.2. Benefit Assessment

Ramucirumab, as a single agent or in combination with different chemotherapy regimens has been approved in the US in the following second-line indications:

- gastric or GEJ adenocarcinoma,
- NSCLC,
- CRC, and
- HCC.

Since the ramucirumab SC formulation involves the same drug-product as that mentioned in Section 2.1, an SC dosing regimen for ramucirumab has the potential to optimize ramucirumab exposure by changing the ramucirumab PK profile, and thereby may further improve patient outcomes compared with an IV dosing regimen. This would be achieved by raising ramucirumab C_{trough} and lowering ramucirumab C_{max} while achieving similar ramucirumab AUC and decreasing the time to achieve sustained therapeutic levels compared to IV administration.

2.3.3. Overall Benefit: Risk Conclusion

Ramucirumab IV has demonstrated a favorable benefit-risk profile in a variety of human cancers as a single agent or in combination with other anti-cancer therapies as demonstrated in Sections 2.2 and 2.3. Considering the measures taken to minimize risk to participants participating in this study and for a lower potential for C_{max}-associated toxicities, the potential risks identified in association with SC regimen for ramucirumab are justified by the anticipated benefits that may be afforded to participants with cancer.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine a recommended ramucirumab SC dosing regimen for future studies by assessing the PK parameters of ramucirumab after SC administration.	• AUC and C_{max} of ramucirumab when administered as monotherapy • C_{trough} (serum trough concentrations)
• To determine a recommended ramucirumab SC dosing regimen for future studies by assessing safety of ramucirumab after SC administration.	• Safety including but not limited to AEs, TEAEs, and SAEs after SC administration.
Secondary	
• To assess the IG of ramucirumab administered SC.	• Relationship between TE ADA and safety. • Relationship between TE ADA and ramucirumab PK.
• 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.
Tertiary/Exploratory	
• To document and report efficacy of ramucirumab following SC administration.	• BOR

Abbreviations: AE = adverse event; AUC = area under the plasma concentration versus time curve; BOR = best overall response; C_{max} = maximum blood plasma concentration; C_{trough} = lowest concentration of a drug just before the next dose; IG = immunogenicity; ISR = injection site reaction; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TE ADA = treatment-emergent anti-drug antibody; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Protocol I4T-MC-JVDU (JVDU) is a Phase 1, non-randomized, open-label investigation of multiple, repeated-weekly SC ramucirumab administrations in participants with cancer. The injection site for the SC administration will be the abdomen.

The study comprises sequential dose-escalating cohorts with a third dose-expansion cohort (see Section 1.2 for study schema): Cohorts A, B (Sub-Cohorts B1, B2, and B3), and C (dose-expansion cohort).

4.1.1. Cohort A

Cohort A will recruit 3 participants with refractory/relapsed solid tumors with measurable disease and who have exhausted all treatments with proven clinical benefit. Participants will receive an initial ramucirumab SC loading dose of 700 mg followed by a weekly ramucirumab SC injection maintenance dose of 350 mg (see Section 4.3.1 for more details). Cohort A participants will be followed for a minimum of 3 weeks following initiation of ramucirumab SC treatment prior to opening enrollment in the subsequent Cohort B. The study team will review the totality of available safety data from Cohort A and study JVDT, and based on this, will make a recommendation to open enrollment to Cohort B (please refer to Section 9.2.2). If new or unexpected safety findings are identified relative to the large database of IV ramucirumab, or one or more participants in Cohort A do not have sufficient PK data to inform dose for Cohort B, up to an additional 3 participants may be enrolled into Cohort A. Participants in Cohort A may have the opportunity to adjust their weekly maintenance dose to the maintenance dose selected for Cohort C, based on investigator's discretion.

4.1.2. Cohort B

Cohort B participants must fulfill all inclusion criteria requirements that apply to Cohort A. In addition, Cohort B participants with disease indications where ramucirumab is approved as either monotherapy or in combination with additional anti-cancer therapy are also eligible provided the initiation of the combination partner can be delayed for 3 weeks from the initiation of ramucirumab dosing.

The dose regimen for Cohort B will be selected to achieve a steady state C_{trough} concentration higher than 50 µg/mL in the majority of the population with associated AUC similar to the approved ramucirumab IV regimen (e.g., 10 mg/kg Q2W IV). Initial Cohort B dosing will be determined based on bioavailability calculated using available PK data as shown in Sections 2.1 and 4.3.2.

Cohort B will be comprised of 3 sub-cohorts: B1, B2, and if required B3. Additional details for each sub-cohort will be discussed below.

4.1.2.1. Sub-Cohort B1

The goal of Sub-Cohort B1 is to obtain PK data by investigating a weekly SC ramucirumab maintenance dose (MD) predicted to achieve the desired PK endpoints of C_{trough} and AUC

discussed above. The target C_{trough} and steady-state exposure are predicted to be reached after two to three weeks, respectively following weekly SC ramucirumab. Thus, steady state is reached earlier as compared to the standard IV Q2W ramucirumab dosing which takes six to eight weeks.

Sub-Cohort B1 will open following a review of all available data from Cohort A, as discussed in Section 4.1.1. Initially, 3 participants will be recruited at a proposed maximum dose of 875 mg SC QW. For additional details, refer to Section 4.3.2. Up to an additional 3 participants may be enrolled into Sub-Cohort B1 if warranted by safety or PK data assessed at the interim analysis (please refer to Section 9.2.2 for more details).

The PK data from a minimum of 6 participants treated in both Sub-Cohort B1 and Cohort A along with the data from Study JVDT will be used to determine the dosing regimen for Sub-Cohort B2.

4.1.2.2. Sub-Cohort B2

The goal of Sub-Cohort B2 is to identify a SC ramucirumab dosing regimen that will deliver the safety and PK objectives of the study. Only one dosing regimen will be investigated in Sub-Cohort B2, that will open following Sub-Cohort B1.

Initially, 3 participants will be recruited in Sub-Cohort B2 and receive SC ramucirumab as a LD on Day 1 of the first week (maximum 1750 mg), followed by a weekly MD (maximum 875 mg). For additional details, refer to Section 4.3.2. If a minimum of 3 weeks of PK and safety data reveal that there are no unexpected safety issues and adequate exposure is achieved, an additional 3 participants will be enrolled at the same dose.

This will be followed by an interim analysis of data from all 6 participants before opening Cohort C, at that dose.

If the initial dose for Sub-Cohort B2 **does not** meet the study objectives, an alternate dose may be explored in Sub-Cohort B3, if deemed feasible.

4.1.2.3. Sub-Cohort B3

The goal of the optional Sub-Cohort B3 is the same as Sub-Cohort B2, that is, to identify a SC ramucirumab dosing regimen that will deliver the safety and PK objectives of the study if not achieved in Sub-Cohort B2.

Only one dosing regimen will be investigated with 6 participants enrolled in Sub-Cohort B3 that may open if greater than anticipated target exposure is determined in Sub-Cohort B2 and/or unexpected safety findings warrant a dose reduction. A reduced dose for unexpected safety findings will only be explored if it is predicted to reach target exposure as explained in Section 4.3.2.

A review of the data from Sub-Cohort B3 will be performed as described above for Sub-Cohort B2. If the study objectives are achieved, Cohort C will open at the dosing regimen investigated in Sub-Cohort B3.

Once the dose for Cohort C has been confirmed, if applicable, participants in Cohort B may have the opportunity to adjust their weekly maintenance dose to the maintenance dose selected for Cohort C, based on investigator's discretion.

4.1.3. Cohort C

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

4.2. Scientific Rationale for Study Design

See Section 2.1.

4.3. Justification for Dose

4.3.1. Rationale for Initial Cohort A Dose Selection

The ramucirumab SC dose for the initial Cohort A (n=3 to 6 participants) has been chosen with the intent to match the steady state AUC of the 8 mg/kg Q2W IV regimen, assuming a bioavailability of 80%. The initial ramucirumab SC loading dose will be 700 mg followed by a weekly ramucirumab SC injection maintenance dose of 350 mg.

Ramucirumab IV has demonstrated an acceptable risk/benefit profile at the approved dose regimens of 8 mg/kg Q2W, 10 mg/kg Q2W, and 10 mg/kg Q3W as monotherapy or in combination with anti-cancer treatments. Furthermore, ramucirumab IV at 13 mg/kg every week (QW) (equivalent to 26 mg/kg over two weeks) has been determined to be the maximum tolerated dose under weekly dosing (Study I4T-MC-JVBM). Consequently, the proposed starting dose for JVDU is well below that dose/exposure intensity.

The planned starting dose of ramucirumab is 700 mg loading dose (LD) followed, a week later, by 350 mg maintenance dose (MD) administered once a week. This dosing regimen has been selected to ensure that, in the unlikely event of a bioavailability as high as 80%, the maximum ramucirumab AUC achieved in Cohort A participants will not exceed AUC following IV ramucirumab 8 mg/kg Q2W.

4.3.2. Rationale for Cohort B (Sub-Cohorts B1, B2, and B3) Dose Selection

Cohort B dose selection is intended to deliver a C_{trough} >50 µg/mL and a steady-state AUC similar to the approved IV ramucirumab dose regimen of 10 mg/kg Q2W. This will be accomplished by investigating a loading dose and maintenance dose paradigm, which will deliver target C_{trough} and steady-state concentration rapidly.

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

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

80% to 100%	10 mg/kg	880	440

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

[a] In Sub-Cohort B1, the loading dose will not be given.

Interim data from Study JVDT indicates a bioavailability of 40% and peak concentration occurring at 4 days post administration for SC ramucirumab (consistent with a 0.3 day^{-1} absorption rate constant). With a bioavailability of 40%, a starting regimen of ramucirumab SC LD of 1750 mg and MD of 875 mg in Cohort B is proposed. The proposed maximum ramucirumab SC LD of 1750 mg will deliver exposure equivalent to 10 mg/kg/week and 13 mg/kg/week for participants with body weights of 70 kg and 55 kg, respectively. Assuming the same bioavailability, the proposed maximum ramucirumab SC MD of 875 mg will deliver exposure equivalent to 5 mg/kg/week and 6 mg/kg/week for participants with body weights of 70 kg and 55 kg, respectively. Consequently, the exposure achieved following both proposed LD and MD will be lower than the highest investigated ramucirumab IV doses of 20 mg/kg Q3W IV (Study JVBN) and 13 mg/kg QW IV (maximum tolerated dose in Study JVBM).

The bioavailability in single-dose healthy participants may vary from cancer patients who will receive multiple doses of ramucirumab SC, hence periodic PK and safety analysis will be planned as described in Section 4.1.

The combined PK and safety data from Cohort A and Sub-Cohort B1 will inform the starting dose selection for Sub-Cohort B2 (maximum planned dose ramucirumab SC LD of 1750 mg followed by 875 mg SC MD QW). Subsequent need for Sub-Cohort B3 with an alternate dosing regimen is described in Section 4.1.2.3. The table below shows the proposed dosing regimen for each Sub-Cohort as well as possible alternate dose decisions that could be made based on either bioavailability and/or safety as described in Section 4.1.2.

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

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

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

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

c Only 1 dosing regimen (one LD - MD level) will be investigated in Sub-Cohort B2 and Sub-Cohort B3. Dose will be selected based on PK and safety data as described in Section 4.1.2.

4.3.3. Rationale for Cohort C Dose Selection

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

4.4. End of Study Definition

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. Participants must be 18 years of age inclusive, at the time of signing the informed consent, and are of an acceptable age to provide informed consent according to the local regulations.

Type of Participant and Disease Characteristics

2. Have evaluable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009).
3. Participants must be, in the judgment of the investigator, an appropriate candidate for experimental therapy, and:
    a. **For Cohort A only**: Have exhausted all anti-cancer treatments with proven clinical benefit.
    b. **For Cohorts B and C only**: Any one of the 3 conditions below needs to be fulfilled:
        - have exhausted all anti-cancer treatments with proven clinical benefit, or
        - have HCC or gastric cancer who have received prior treatment, and where IV ramucirumab monotherapy is clinically acceptable treatment after progression, or
        - have a diagnosis for which IV ramucirumab in combination with additional anti-cancer therapy is clinically acceptable treatment. Additionally, it must be clinically acceptable to delay initiation of the combination partner for 3 weeks from the initiation of ramucirumab dosing.
4. Have a Performance Score (PS) of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982).
5. Have venous access sufficient to allow for blood sampling.
6. Have a life expectancy of at least 3 months.
7. Have discontinued all previous treatments for cancer and recovered from the acute effects of therapy. Participants must have discontinued from previous treatments, as shown below:

Previous Treatment	Length of Time Prior to First Dose of Ramucirumab
Endocrine therapies	≥14 days
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥21 days or ≥ 5 half-lives, whichever is shorter

Previous Treatment	Length of Time Prior to First Dose of Ramucirumab
Biologic agents that are large molecules including immunotherapy	≥28 days
Radiotherapy	
Limited-field radiotherapy with palliative intent	≥14 days
Other radiotherapy	≥28 days
Major surgery, excluding biopsy	≥28 days

8. Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9 g/dL
Note: Transfusions to increase a participant's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug. If a participant receives transfusions, erythropoietin, or G-CSF therapy ≥14 days prior to the first dose, the hematologic criteria listed above must be met following the 14-day window and prior to the first dose of study therapy.	
Coagulation[a]	
International Normalized Ratio (INR) or Prothrombin Time (PT)	INR ≤1.5x ULN or PT ≤5 seconds above ULN, unless participant is receiving anticoagulant therapy, where the INR or PT is within therapeutic range of intended use of anticoagulants
Partial Thromboplastin Time (PTT) or Activated Partial Thromboplastin Time (aPTT)	PTT or aPTT ≤5 seconds above ULN, unless participant is receiving anticoagulant therapy, where the PTT or aPTT is within therapeutic range of intended use of anticoagulants
Hepatic	
Total bilirubin	≤1.5x ULN
ALT and AST	AST and ALT ≤2.5x ULN **OR** ≤5x ULN if the liver has tumor involvement
Renal	
Serum creatinine **OR**	<1.5x ULN **OR**
Measured creatinine clearance **OR**	≥50 mL/min/1.73 m^2
Calculated creatinine clearance	
Urine Protein	<2+ on dipstick or routine urinalysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <1 g of protein in 24 hours OR <1 (<100 mg/mmol) on UPCR using a first morning urine sample to allow participation in the study.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; G-CSF = granulocyte-colony stimulating factor; GEJ = gastroesophageal junction; NSCLC = non-small cell lung cancer; ULN = upper limit of normal; UPCR = urine protein to creatinine ratio.

[a] Gastrointestinal-GEJ and NSCLC participants are allowed to be on therapeutic-dose anticoagulation if they are on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the participant must have an INR ≤3.0 and no active bleeding (i.e., no bleeding within 14 days prior to enrollment) nor a pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices). Participants on anticoagulation therapy with an underlying medical condition that increases the risk for bleeding (e.g., local tumor recurrence following resection) are not eligible. Hepatocellular carcinoma participants are only allowed to be on prophylactic treatment with anticoagulants, not therapeutic doses, and their PT, PTT, and INR values must be consistent with the criteria listed in the table above.

Sex

9. Male 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:
Male participants are eligible to participate if they agree to the following during the intervention period and for at least 84 days/12 weeks following completion of study drug administration:
   - Refrain from donating sperm
   PLUS either:
   - Be abstinent from heterosexual or homosexual intercourse, as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), and agree to remain abstinent
   OR
   - Must agree to use contraception/barrier as detailed below:
     - Agree to use a male condom AND
     female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4, when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.
     - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

b. Female participants:
   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
     - Is not a WOCBP
     OR
     - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 84 days/12 weeks, corresponding to the time needed to eliminate any study intervention(s) (e.g., 5 terminal half-lives) ***plus*** 30 days (a menstrual cycle) after the last dose of study intervention, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction

during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
    - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

10. 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

11. Have uncontrolled hypertension defined as systolic blood pressure (BP) >150 mmHg or diastolic BP >90 mmHg despite standard medical management.
12. Have significant bleeding disorders or experienced Grade 3/4 GI bleeding within 3 months prior to enrollment.
13. Have hepatic impairment (such as severe liver cirrhosis Child-Pugh B [or worse], cirrhosis with a history of hepatic encephalopathy, clinically meaningful ascites requiring ongoing treatment with diuretics and/or paracentesis, or history of hepatorenal syndrome).
14. Have experienced any arterial thromboembolic events (ATEs), including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, ≤6 months prior to randomization.
15. The participant has clinically relevant congestive heart failure (CHF; New York Heart Association [NYHA] Grade ≥2) or symptomatic or poorly controlled cardiac arrhythmia.
16. Have a serious concomitant systemic disorder that, in the opinion of the investigator, would preclude participation in the study.
17. Have active infection requiring systemic therapy (e.g., bacterial infection requiring intravenous antibiotics at time of initiating study treatment, systemic fungal infection, or detectable viral infection requiring systemic therapy).

18. Human immunodeficiency virus (HIV) positive participants (HIV 1 and/or 2; screening not required) are excluded unless they are well controlled on highly active antiretroviral therapy with:
    a. No evidence of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections within the last 2 years, and
    b. CD4 count >350 cells/µl.
19. Have chronic active hepatitis B or C virus infection (screening not required).
20. Have prior or second concurrent primary malignancies that, in the judgment of the investigator and the Lilly clinical research physician (CRP)/clinical research scientist (CRS), may affect the interpretation of results. Participants with carcinoma in situ of any origin and participants with prior malignancies who are in remission and whose likelihood of recurrence is very low (such as basal cell carcinoma), as judged by the Lilly CRP/CRS, are eligible for this study.
21. Have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required). Participants with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids (exceeding 10 mg/day prednisone or equivalent) and/or anticonvulsants to treat CNS metastases, and their disease is asymptomatic and radiographically stable for at least 30 days.
22. Have a history of GI perforation and/or fistula within 6 months prior to enrollment.
23. Serious or non-healing wound, ulcer, or bone fracture within 4 weeks prior to enrollment.

Prior/Concomitant Therapy

24. Are receiving chronic therapy with nonsteroidal anti-inflammatory agents (e.g., indomethacin, naproxen, or similar agents) or other antiplatelet agents (e.g., clopidogrel or dipyridamole) within 7 days prior to first dose of study treatment. Aspirin use at doses up to 325 mg/day is permitted (see Section 10.6, Appendix 6).
25. Participants with prior treatment with IV ramucirumab as monotherapy or in combination with chemotherapy or targeted/biological agents on or outside of a clinical trial.

Prior/Concurrent Clinical Study Experience

26. have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed. Exceptions will be considered on a case by case basis by the sponsor CRP/CRS.

Other Exclusions

27. Have tattoos or scars over the abdomen, or other factors (e.g., rash, excessive folds of skin) that, in the investigator's opinion, would interfere with injection site assessments.
28. Have an elective or a planned major surgery during the course of the trial, or have undergone major surgery within 28 days prior to enrollment.
    Note: Central venous access device placement must occur at least 7 days prior to enrollment.

Note: If participant received major surgery, the participant must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

Additional Key Exclusion Criteria specific to NSCLC

29. Have radiologically documented evidence of major blood vessel invasion or encasement by cancer.
30. Have radiographic evidence of intratumor cavitation, regardless of tumor histology.
31. Have a history of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months prior to enrollment.

5.3. Lifestyle Considerations

There are no specific lifestyle restrictions for this protocol.

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. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. 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 re-screened once only. The interval between re-screenings should be at least 2 weeks. Each time re-screening is performed, the individual must sign a new ICF. Repeating of laboratory tests during the screening period or repeating screening tests 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/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

	Cohorts				
	A	B			C
Sub-Cohorts		B1	B2	B3 (Optional)	
Planned Number of Participants	3-6[a]	3-6[a]	3-6[b]	6[b]	6
Ramucirumab Monotherapy SC QW (Cohorts A, B, and C) *Note: If participants are on ramucirumab monotherapy, then the cycle duration is 21 days for the entire duration of the study.*					
Ramucirumab					
SC loading dose given in the first week of treatment[e]	700 mg	N/A	TBD[c] (max 1750 mg weekly)	TBD[c] (max 1750 mg weekly)	Same dose from Cohort B[f]
SC weekly maintenance dose starting Study Week 2 (ie, Study Day 8)	350 mg QW	TBD[c] (max 875 mg weekly)	TBD[c] (max 875 mg weekly)	TBD[c] (max 875 mg weekly)	
Optional Combination Therapy (Cohorts B and C, starting from Cycle 2) *Note: Regardless of whether participants are on ramucirumab monotherapy or combination therapy, Cycle 1 (21 days) is SC ramucirumab QW monotherapy.*					
2L Gastric[d] (28-Day cycle)		Dose for combination therapies (paclitaxel, docetaxel, irinotecan, fluorouracil, and erlotinib) should follow institutional practice.			
Paclitaxel	N/A				
2L NSCLC (21-Day cycle)					
Docetaxel	N/A				
2L CRC (28-Day cycle)					
Irinotecan	N/A				
Fluorouracil	N/A				
1L NSCLC EGFR+ (28-Day cycle)					
Erlotinib	N/A				

Abbreviations: 1L = first line; 2L = second line; CRC = colorectal cancer; EGFR = epidermal growth factor receptor; FOLFIRI = fluorouracil and irinotecan; N/A = not applicable; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; QW = every week; SC = subcutaneous; TBD = to be determined.

[a] Refer to Section 4.1.1 and 4.1.2 for total enrollment, based on safety and PK data.

[b] Refer to Section 4.1.2 for total enrollment, based on safety and PK data.

[c] Dose selection for Sub-Cohorts B2 and B3 will be based on safety and available PK data (see Sections 4.1 and 9.2.2 for further details).

[d] FOLFIRI as an alternative combination is permissible.

[e] Loading dose above 700 mg will use a syringe pump for Cohorts B and C.

[f] Dose meeting PK and safety objectives as described in Section 4.1.3.

For participants on combination IV interventions, on days ramucirumab is to be administered with the combination intervention, ramucirumab is to be administered first. The combination intervention will be administered per local guidelines, following the one-hour ramucirumab observation period.

A delay of a treatment up to 7 days due to administrative reasons, including holidays, weekends, bad weather, or other unforeseen circumstances, will be permitted and not be counted as a protocol deviation.

After the SC administration, a 1-hour observation period will be completed. Any premedication for combination therapy must be administered after the ramucirumab one-hour observation period. All premedication administered must be adequately documented in the case report form (CRF).

Ramucirumab will be initiated with a loading dose of 700 mg SC followed, a week later, by a maintenance dose of 350 mg SC QW (Cohort A), administered in the abdomen. Ramucirumab dose will be escalated in Sub-Cohort B1 to investigate a weekly maintenance SC ramucirumab dose (maximum of 875 mg SC weekly) and thereafter in Sub-Cohort B2 to investigate up to a maximum loading dose of 1750 mg SC followed, a week later, by a maximum weekly maintenance dose of 875 mg SC. For loading doses greater than 700 mg, SC administration will be a SC infusion using a SC infusion pump where ramucirumab is infused at a rate of approximately 0.25 ml/min and duration of infusion will be based on dose and volume of infusion. Interim analysis is planned after the Sub-Cohorts B1 and B2 are enrolled, and ramucirumab dose may be adjusted in the optional Sub-Cohort B3 to further explore whether the safety and PK objective of the study can be achieved (see Section 4.1.2). The ramucirumab dosing regimen in Cohort C will be the same as in Cohort B which answers the safety and PK objective of the study (see Section 4.1.3). The site of administration of each injection will be recorded, and when more than one injection is administered, the same site will not be used but another quadrant utilized. Ideally the site of SC ramucirumab injection should be the abdomen; however, in case of contraindication to abdominal SC injection, such as clinical conditions with dermatitis, cellulitis, or surgical wound, the participant is allowed to rotate the injection site to thigh or upper arms. If the loading dose causes an injection site reaction (>Grade 2), then the sponsor may determine an alternate administration of loading dose for subsequent participants.

6.1.1. Treatment Requirements for Each Treatment Visit and Treatment Delays

Treatment Requirements for each New Cycle

The timing of starting a new cycle of protocol therapy will be as follows:

- Those getting single-agent ramucirumab SC: Each cycle will be 21 days with weekly ramucirumab SC administration. Each new cycle will start 7 days (±3 days) from the last ramucirumab SC.
- Those getting ramucirumab SC with combination anti-cancer treatments: Ramucirumab SC will be given weekly within each cycle.

a. Ramucirumab SC with paclitaxel: Each cycle will be 28 days with paclitaxel administered on Days 1, 8, and 15 and start 14 days (±3 days) from the previous Day 15 paclitaxel administration.

b. Ramucirumab SC with FOLFIRI: Each cycle will be 28 days and start 14 days (±3 days) from the last administration of FOLFIRI.

c. Ramucirumab SC with erlotinib: Each cycle will be 28 days with daily oral erlotinib and start 7 days (±3 days) from the last administration of ramucirumab SC in the previous cycle.

d. Ramucirumab SC with docetaxel: Each cycle will be 21 days with docetaxel administered on Day 1 and start 21 days (±3 days) from the last administration of docetaxel.

Note: For each weekly dose in Cycle 1, the following criteria must be fulfilled to administer ramucirumab SC:

- Total bilirubin ≤1.5x upper limit of normal (ULN) or baseline (whichever is greater)
- ALT and AST ≤3x ULN, if baseline <1.5x ULN
- ALT and AST ≤2x baseline, if baseline ≥1.5x ULN

For each new cycle and every 3 weeks for those in Cohort B and C where combination therapies have been held or discontinued, the following criteria must be fulfilled to administer ramucirumab SC:

- Total bilirubin ≤1.5x upper limit of normal (ULN) or baseline (whichever is greater)
- ALT and AST ≤3x ULN, if baseline <1.5x ULN
- ALT and AST ≤2x baseline, if baseline ≥1.5x ULN
- Absolute neutrophil count (ANC) ≥1.5x 103/µL (≥1.5x 109/L), platelets ≥100x 103/µL (≥100x 109/L)
- Ramucirumab-related AEs that are National Cancer Institute (NCI) common terminology criteria for adverse events, version 5.0 (CTCAE, v5.0) Grade <2 or equivalent severity to baseline (except for alopecia; for hypertension and proteinuria, see Section 6.5.1.8).

Participants not meeting the criterion for total bilirubin may be allowed to continue treatment with ramucirumab or placebo in specific cases (e.g., Gilbert's syndrome) after the Lilly CRP/CRS and investigator agree that it is medically appropriate for these participants. The decisions and supporting rationale must be documented in writing. For participant and study site convenience and safety, treatment decisions will be based upon results of tests performed locally. For dosing decisions, bilirubin, AST, and ALT will be required to be collected locally and centrally; ANC and platelets will be collected locally. The duplicate test results obtained locally will not be collected on the CRF, unless it impacts treatment decision, in which case the critical finding should be documented in the appropriate CRF as part of the rationale for dose modification. Discrepancies between the local and central laboratory that may have an impact on treatment decisions will not be considered protocol violations.

6.1.2. Treatment Delays and Omissions

If the criteria to start a subsequent new cycle listed above are not met, the next ramucirumab SC dosing may be delayed for up to a maximum of 4 weekly doses to allow for recovery. If the participant is on a combination anti-cancer treatment regimen, it should be continued during the delay of ramucirumab SC if the participant does not meet the criteria of delay and/or discontinuation for that regimen per its prescribing information. If a delay of greater than 4 weekly doses is necessary due to ramucirumab-related, unresolved toxicity, ramucirumab SC should be discontinued. The combination anti-cancer treatment may be continued at investigator's discretion with the participant remaining in the study, if clinically indicated. If ramucirumab dose modification is warranted, refer to Section 6.6 for further details.

If participants have discontinued combination anti-cancer therapy, ramucirumab SC may be continued as monotherapy until progressive disease, at the discretion of the investigator.

Treatment delays and omissions due to anti-cancer therapies other than SC ramucirumab are addressed as follows:

- If a participant has an AE found related to chemotherapy/TKI at the start of a new cycle, then the cycle is postponed and re-started once the AE has resolved and can be re-aligned with the weekly ramucirumab SC administration.
- If a participant has an AE found related to chemotherapy/TKI "within" a cycle, that dose is omitted, then the next planned dose is administered once the AE has resolved and can be re-aligned with the weekly ramucirumab SC administration.

Ramucirumab SC can only be administered at investigational site, at-home administration is not permitted in this study. In the event of treatment delays of ramucirumab SC unrelated to AEs but due to unforeseeable circumstances (e.g., COVID-19 pandemic resurgence) and in the principal investigator's discretion the participant has experienced clinical benefit, re-administration of loading dose is required only if ≥30 days has elapsed since the last ramucirumab SC dose. In such a scenario, a discussion with Lilly CRP/CRS should be done before resuming ramucirumab SC. In addition, all on-treatment SoA as in Section 1.3 must resume. On resuming ramucirumab SC the combination anti-cancer treatment can be re-aligned with ramucirumab SC administration.

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 (i.e., receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy 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, and dose modifications).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label non-randomized study.

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 in the 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.

When participants self-administer oral study intervention at home, compliance with oral study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and/or counting returned tablets/capsules during the site visits and documented in the source documents and CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Palliative Medicine and Supportive Care

Palliative radiation therapy is permitted after discussion with and agreement of the Lilly CRP/CRS or designee for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Such areas must not be an identified target lesion and must not constitute progressive disease or meet RECIST criteria for progressive disease. Any symptomatic deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific antitumor systemic therapy, will be cause for discontinuation of study therapy.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the CRF.

Participants should receive full supportive care as appropriate (see Section 10.6, Appendix 6). Prophylactic antibiotic treatment should be consistent with American Society of Clinical Oncology (ASCO) guidelines (Taplitz et al. 2018).

6.5.1.1. Injection Site Reactions

Local reactions at the injection site(s) will be evaluated for erythema, induration, pain, pruritus, and edema. Symptomatic treatment would include acetaminophen, non-sedating antihistamines, and topical emollients, as appropriate.

6.5.1.2. Transfusions

Transfusions of red blood cells, platelets, or other blood products are permitted at the investigator's discretion.

If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Bohlius et al. 2019).

6.5.1.3. Antiemetic Agents

The use of antiemetic agents is permitted at the discretion of the investigator.

6.5.1.4. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator. Opiate and non-opiate analgesic agents are permitted (including acetaminophen/paracetamol); however, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or aspirin is restricted (Section 10.6).

6.5.1.5. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator.

6.5.1.6. Growth Factors

Growth factors should not be administered to enable a participant to satisfy study inclusion criteria.

The use of granulocyte-colony stimulating factor (G-CSF) is permitted at the discretion of the investigator based on ASCO guidelines (Smith et al. 2015).

In the event of Grade 3 or 4 neutropenia >7 days, initiate G-CSF in subsequent cycles, unless determined to be inappropriate for the participant per the investigator.

The as-needed use of erythroid-stimulating factors (e.g., erythropoietin) is permitted at the discretion of the investigator based on ASCO guidelines (Bohlius et al. 2019) (Section 10.6).

6.5.1.7. Other Supportive Care Agents

The use of benzodiazepines, antidepressants, laxatives, and other agents that may be helpful in controlling disease-related symptoms are also permitted and encouraged, except as prohibited in Section 10.6.

6.5.1.8. Supportive Care by Adverse Event of Special Interest

Refer to Section 6.6.1 for adverse event of special interest (AESI) dose-modification guidelines.

6.5.1.8.1. Hypersensitivity Reactions, Including Anaphylaxis

Administration of mAbs such as ramucirumab can result in HSRs, including immediate reactions like anaphylactic reactions or infusion-related reactions and delayed reactions such as those involving the muco-cutaneous system. Monitor participants for symptoms and signs of HSRs during the loading dose SC injection and maintenance SC injection followed by a 1-hour observation period post administration, with resuscitation equipment readily available.

Symptoms and signs that may occur as part of HSRs include, but are not limited to:

- fever,
- chills,
- nausea,
- headache,
- bronchospasm,
- hypotension,
- angioedema,
- throat irritation,
- rash,
- pruritus,
- myalgia, and
- dizziness.

Supportive care should be employed in accordance with the symptoms/signs. Participants should be treated appropriately by the investigator. If a severe (Grades 3 or 4) HSR occurs, discontinue ramucirumab permanently.

In the event of an HSR, a blood sample should be collected for immunogenicity (anti-ramucirumab antibody) and PK (ramucirumab serum concentration) at the following time points: (1) as close to the onset of the reaction as possible, (2) at the resolution of the event, and (3) 30 days following the onset of the event. In addition, blood and urine samples should be collected as described in Section 10.2, Appendix 2 (Hypersensitivity tests).

6.5.1.8.2. Hypertension

An increased incidence of severe hypertension was reported in patients receiving ramucirumab as compared to placebo. In most cases, hypertension was controlled using standard antihypertensive treatment.

Pre-existing hypertension should be controlled before starting ramucirumab treatment. Monitoring of BP is recommended during therapy.

Temporarily suspend ramucirumab for severe hypertension until controlled with medical management. Permanently discontinue ramucirumab if medically significant hypertension cannot be controlled with antihypertensive therapy.

6.5.1.8.3. Proteinuria

Proteinuria is an adverse effect for all therapies targeting the VEGF/VEGF Receptor 2 pathway. Proteinuria has been associated with ramucirumab in clinical studies. The majority of events were of Grades 1 and 2.

Monitoring for the development or worsening of proteinuria during ramucirumab therapy is required. Prior to each dose of study treatment, the participant's urine protein must be ≤2+ on dipstick or routine urinalysis, <2 (or <200 mg/mmol) on urine protein-to-creatinine ratio (UPCR), or <2 g on 24-hour urine collection (Section 6.6.1).

Dose-modification guidelines for participants experiencing proteinuria are provided in Section 6.6.1.

6.5.1.8.4. Thromboembolic Events

6.5.1.8.4.1. Arterial Thromboembolic Events

Serious ATEs, including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have been reported in clinical trials. Permanently discontinue ramucirumab in participants who experience a severe ATE.

6.5.1.8.4.2. Venous Thromboembolic Events

Venous thromboembolic events (VTEs) are associated with cancer; however, the incidence of VTEs likely varies depending on the type of cancer, stage, and intensity of imaging. Additionally, VTEs have been associated with some antiangiogenic therapy, although the incidence varies depending on the type of therapy, use of concomitant chemotherapy agents, and specific disease state. Venous thromboembolic events have been reported from clinical studies investigating ramucirumab, particularly in the context of metastatic disease or in regions adjacent to implanted venous access devices.

Most VTEs lack early warning signs; therefore, awareness and prompt treatment are important, especially in those patients with risk factors and/or previous history of VTEs (Chen and Cleck 2009; Suter and Ewer 2013).

Ramucirumab therapy should be discontinued in the event of any Grade 3 or 4 VTE that is considered by the investigator to be symptomatic and not adequately treated by anticoagulation therapy. In some study protocols, at the investigator's discretion, ramucirumab therapy may be continued in the setting of an incidentally diagnosed, asymptomatic deep vein thrombosis or pulmonary embolism or following a symptomatic deep vein thrombosis or pulmonary embolism when symptoms have resolved with the institution of anticoagulation therapy.
Ramucirumab should also be discontinued in the setting of a deep vein thrombosis or pulmonary embolism that occurs or intensifies while the participant is receiving therapeutic anticoagulation therapy.

6.5.1.8.5. Bleeding/Hemorrhage

Ramucirumab is an antiangiogenic therapy and may increase the risk of severe bleeding. Severe GI hemorrhage was reported in patients with gastric cancer treated with ramucirumab in

combination with paclitaxel and in patients with CRC treated with ramucirumab in combination with FOLFIRI.

Permanently discontinue ramucirumab in participants who experience Grade 3 or 4 bleeding.

6.5.1.8.6. Gastrointestinal Perforation

Ramucirumab is an antiangiogenic therapy and may increase the risk of GI perforations. Cases of GI perforation have been reported in patients treated with ramucirumab.

Permanently discontinue ramucirumab in participants who experience GI perforations.

6.5.1.8.7. Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is an acute neurological disorder characterized by various neurological signs and symptoms in conjunction with distinctive neuroimaging findings reflecting vasogenic edema, often in association with elevated BP (Bartynski and Boardman 2007; Bartynski 2008; Fugate and Rabinstein 2015; Fischer and Schmutzhard 2017). Both clinical and imaging features are usually reversible (Hinchey et al. 1996; Lee et al. 2008; Fugate and Rabinstein 2015).

Cases of PRES, including fatal cases, have been rarely reported in patients receiving ramucirumab. Posterior reversible encephalopathy syndrome symptoms may include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension.

Posterior reversible encephalopathy syndrome should be identified and treated promptly in order to minimize potential for permanent neurological damage. A diagnosis of PRES can be confirmed by brain imaging (e.g., magnetic resonance imaging [MRI]). Treatment encompasses careful control of BP, withdrawal of potentially causative medication, and administration of anti-convulsant agents to those experiencing seizures (Stott et al. 2005).

Permanently discontinue ramucirumab in participants who experience PRES.

6.5.1.8.8. Congestive Heart Failure

An increased risk of CHF has been associated with some antiangiogenic therapeutic agents, particularly in patients with metastatic breast cancer previously treated with anthracyclines or with other risk factors for CHF, including prior radiotherapy to the left chest wall. A small number of CHF events (including fatal) were also reported in patients who had received ramucirumab after prior treatment with anthracyclines in the Phase 2 and Phase 3 studies.

While the mechanism of action is currently unknown, based on the safety data received to date, it is likely that treatment with ramucirumab enhances the cardiotoxicity associated with mitoxantrone and has the potential to enhance cardiotoxicity of other agents within the anthracycline/anthracenedione class of chemotherapy medications.

Participants with risk factors should be closely monitored for signs and symptoms of CHF. Caution should be exercised when treating participants with clinically significant cardiovascular disease, such as pre-existing coronary artery disease or CHF. Participants with symptomatic CHF, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia should

not be enrolled in clinical trials with ramucirumab. Ramucirumab should be discontinued in the event of any Grade 3 and 4 events consistent with CHF.

6.5.1.8.9. Fistula Formation

Gastrointestinal and non-GI fistula formation has been associated with antiangiogenic agents including bevacizumab and sunitinib (Kamba and McDonald 2007). Some fistulas can be resolved with surgery procedures; however, fistulas can be fatal. The impact on the quality of life of having a fistula varies according to the location and extent of the fistula (Chen and Cleck 2009). A small number of fistula events have been reported in ramucirumab clinical trials.

Ramucirumab treatment should be discontinued in participants who develop fistulas.

6.5.1.8.10. Surgery and Impaired Wound Healing

The impact of ramucirumab has not been evaluated in patients with serious or nonhealing wounds. In a study conducted in animals, ramucirumab did not impair wound healing. However, since ramucirumab is an antiangiogenic therapy and may have the potential to adversely affect wound healing, ramucirumab treatment should be withheld prior to scheduled surgery. The decision to resume ramucirumab following surgical intervention should be based on clinical judgment of adequate wound healing.

If a participant develops wound-healing complications during therapy, discontinue ramucirumab until the wound is fully healed.

6.5.1.8.11. Liver Failure and Other Hepatic Impairment

Liver failure or other significant liver injury events, such as hepatic encephalopathy, have been observed in patients receiving ramucirumab. In HCC patients with liver cirrhosis, hepatic encephalopathy was reported at a higher rate in the ramucirumab-treated patients compared to the placebo-treated patients. Use ramucirumab with caution in participants with severe liver cirrhosis (Child-Pugh B or C), cirrhosis with hepatic encephalopathy, clinically significant ascites due to cirrhosis, or hepatorenal syndrome. “Clinically significant ascites” is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis. Use only if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure in these participants.

Ramucirumab should be discontinued in the event of any new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis.

Refer to the appropriate section of each study protocol for detailed information regarding participant eligibility and criteria for discontinuation.

6.6. Dose Modification

Ramucirumab loading dose modification is not allowed as it is a one-time dose.

Dose modifications are permitted only for ramucirumab maintenance dose in the setting of non-life-threatening and reversible Grade 3 clinical AEs (e.g., fever) considered to be at least possibly related to ramucirumab that resolve to Grade ≤1 or pretreatment baseline within 21 to 28 days, based on cycle length.

If a Grade 4 AE occurs and is deemed at least possibly related to ramucirumab, then ramucirumab should be discontinued except in the specific case of Grade 4 fever or Grade 4 laboratory abnormalities (please refer to Section 10.3 for additional details regarding severity grading of laboratory abnormalities).If Grade 4 fever or laboratory abnormalities resolve to Grade ≤1 or pretreatment baseline within 1 treatment cycle for that specific regimen (monotherapy or combination), treatment with ramucirumab may be continued at the discretion of the investigator.

In these settings, ramucirumab may be re-administered at the maintenance dose. If a second instance of such an event occurs, ramucirumab should be subsequently re-administered at the next lower dose level as shown in the table below. A second dose reduction is not permitted for this level of event (Grade 3 or 4 event). If the dose of ramucirumab is reduced because of potentially related AEs, subsequent dose increases are not permitted.

Participants who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE, v5.0 Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator. Except in the case of proteinuria, as described in Section 6.6.1, asymptomatic laboratory abnormalities should not result in dose interruptions, modifications, or discontinuation of study therapy unless determined by the investigator to be clinically significant or life-threatening. Ramucirumab will be permanently discontinued in case of any ramucirumab-related event that is deemed life-threatening, regardless of grade.

In case a dose reduction is necessary, the study intervention will be administered as follows:

In case of AEs that require dose reduction, reduction of the SC ramucirumab dosing regimen should occur as indicated in the table below, according to the dose regimen on which the toxicity was observed.

Cohort	Dose Regimen	Participant Dose Reduction (maintenance dose)
Cohort A	LD 700 mg; MD 350 mg QW	MD 220 mg QW
Cohorts B and C Possible dosing regimen depending on F %	LD 880 mg; MD 440 mg QW	MD 220 mg QW
	LD 1120 mg; MD 560 mg QW	MD 280 mg QW
	LD 1400 mg; MD 700 mg QW	MD 350 mg QW
	LD 1750 mg; MD 875 mg QW	MD 440 mg QW

Abbreviations: F = bioavailability; LD = loading dose; MD = maintenance dose; QW = every week.

Dose modifications for combination treatments (paclitaxel, docetaxel, irinotecan, fluorouracil, and erlotinib) should follow institutional practice.

6.6.1. Ramucirumab Dose Modifications

The ramucirumab dose may need to be modified if the participant experiences an AE, including an AESI (Section 8.3.6). Doses may be delayed, allowing time for the participant to recover from the event. Certain AEs require immediate and permanent discontinuation of study treatment (see table below). If administration of ramucirumab is delayed for more than 4 weekly doses from last planned administration, the participant should be discontinued from ramucirumab treatment, unless a longer suspension has specifically been deemed appropriate for a given participant in discussion with the Lilly CRP/CRS. Any participant who requires a dose reduction will continue to receive a reduced dose until discontinuation from ramucirumab or discontinuation from the study. As per the Section 6.1, only one dose reduction level of ramucirumab is allowed and, if AEs are experienced at the reduced dose level, ramucirumab treatment will be discontinued.

Section 6.6 presents the ramucirumab dose reductions.

The table below presents the criteria for dose modifications and dose discontinuations applicable if the participant experiences a ramucirumab AESI or other AEs at least possibly related to ramucirumab.

Dose-Modification Guidelines for Ramucirumab for Adverse Events at least Possibly Related to Ramucirumab, including Adverse Events of Special Interest

	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 6.5.1.8.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Section 6.6.*** ***Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.***
1.	**Hypersensitivity reaction**		
1.a.	Hypersensitivity reaction	2	Prior to all future injections of ramucirumab, premedicate with: • histamine H1 antagonist, such as diphenhydramine hydrochloride • dexamethasone or equivalent • acetaminophen/paracetamol
1.b.	Hypersensitivity reaction	3-4	Immediately and permanently discontinue ramucirumab.
2.	**Hypertension**		
2.a.	Hypertension (non-life-threatening and associated with symptoms) NOTE: Hypertension should be monitored prior to each SC ramucirumab dose administration.	3	• Omit ramucirumab until the hypertension is controlled with medication and is resolved to Grades 0-2. o If controlled with medication and resolved to Grades 0-2, then may resume ramucirumab at current dose. • If NOT controlled with medication and not resolved to Grades 0-2 within a reasonable timeframe (e.g., 21-28 days), discontinue ramucirumab at investigator's discretion.
2.b.	Uncontrolled hypertension, hypertensive crisis, or hypertensive encephalopathy	4	Immediately and permanently discontinue ramucirumab.
3.	**Proteinuria**		
3.a.	Proteinuria ≤2+ (dipstick or routine urinalysis)		• Administer ramucirumab at the current dose if clinically indicated. • Obtain spot UPCR on first morning urine sample within 3 days prior to the next dose. o If UPCR <2 (or <200 mg/mmol), administer study treatment at the participant's current dose. o If UPCR ≥2 (or ≥200 mg/mmol), modify the dose. See Proteinuria ≥2 (or ≥200 mg/mmol) (UPCR), **line 3.c**.

	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 6.5.1.8.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Section 6.6.*** ***Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.***
3.b.	Proteinuria >2+ (dipstick or routine urinalysis)		• Delay study treatment for up to 14 days (omit 2 doses). • Obtain spot UPCR on first morning urine sample within 3 days prior to the next dose. o If UPCR <2 (or <200 mg/mmol), no further dose delay or dose reduction is required. o If UPCR ≥2 (or ≥200 mg/mmol), modify the dose. See Proteinuria ≥2 (or ≥200 mg/mmol) (UPCR), **line 3.c**.
3.c.	Proteinuria ≥2 (or ≥200 mg/mmol) (UPCR)		Omit ramucirumab dose until UPCR returns to <2 (or <200 mg/mmol). Resume ramucirumab at reduced dose as shown in Section 6.6. If UPCR remains ≥2 (or ≥200 mg/mmol) after 14 days, discontinue study treatment. • **Second occurrence**: Discontinue study treatment.
3.d.	Proteinuria UPCR >3 (or >300 mg/mmol) **or** in the setting of nephrotic syndrome		Discontinue study treatment.
4.	**Arterial thromboembolic events, venous thromboembolic events**	3 or 4	Immediately and permanently discontinue ramucirumab.
5.	**Bleeding/Hemorrhage**		
	Bleeding/Hemorrhage	2	Continue with treatment unless investigator-considered related.
	Bleeding/Hemorrhage	3 or 4	Immediately and permanently discontinue ramucirumab.
6.	**Gastrointestinal perforation**		Immediately and permanently discontinue ramucirumab.
7.	**Posterior reversible encephalopathy syndrome**		Immediately and permanently discontinue ramucirumab.
8.	**Congestive heart failure**		
	Congestive heart failure	2	Continue with treatment unless investigator-considered related.
	Congestive heart failure	3 or 4	Immediately and permanently discontinue ramucirumab.
9.	**Fistula formation**		Immediately and permanently discontinue ramucirumab.
10.	**Impaired wound healing**		
10.a.	Prior to planned surgery		Withhold ramucirumab at least 4 weeks (28 days) prior to scheduled surgery.
10.b	After surgery		Resume ramucirumab based on clinical judgment.

	Adverse Event ***NOTE: All specific adverse events listed are defined as AESIs in Section 6.5.1.8.***	**CTCAE Grade**	**Dose-Modification Guidelines** ***NOTES:*** ***Dose reductions to occur as defined in Section 6.6.*** ***Treating physicians can modify or discontinue ramucirumab more conservatively than in the guidance below.***
10.c.	Wound-healing complications developed during study treatment		Delay ramucirumab dosing until the wound is fully healed.
11.	**Hypothyroidism**		
	Hypothyroidism	2 or 3	Therapy with ramucirumab can be continued while treatment for the thyroid disorder is instituted.
	Hypothyroidism	4	Immediately and permanently discontinue ramucirumab.
12.	**Hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis**		Immediately and permanently discontinue ramucirumab.

Abbreviations: AESI = adverse event of special interest; CTCAE = common terminology criteria for adverse events; NCI = National Cancer Institute; SC = subcutaneous; UPCR = urine protein-to-creatinine ratio.

6.7. Intervention after the End of the Study

The end of study definition is defined in Section 4.4. Investigators will continue to follow the SoA provided in Section 1.3 until notified by sponsor that end of study has occurred.

6.7.1. Intervention after Study Completion

Subcutaneous ramucirumab may be made available after conclusion of the study to participants who are still receiving and benefitting from study treatment in countries where the drug cannot be lawfully prescribed.

6.7.1.1. Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 participant is still on study treatment when study completion occurs. Sponsor will notify investigators when the continued access period begins.

Participants are not required to sign a new ICF before treatment is provided during the continued access period; the initial ICF for this study includes continued access under this protocol.

The participant's continued access to study intervention will end when a criterion for discontinuation is met (Section 7). Continued access follow-up will begin the day after the participant and the investigator agree to discontinue study intervention and lasts approximately 30 days. Follow-up procedures will be performed as shown in the Continued Access SoA.

Participants who are in short-term follow-up when the continued access period begins will continue in short−term follow-up until the 30-day short-term follow-up visit is completed.

In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants will remain on treatment until a discontinuation criterion is met, at which point study intervention is permanently discontinued and the participant will enter the short-term follow-up period. See the SoA 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. Short-term follow-up that includes safety follow-up begins when the participant and the investigator agree that the participant will no longer continue study treatment and will last for a minimum of 30 days following the last dose of study drug.

The discontinuation values required below pertain to participants enrolled with normal or near normal hepatic biochemical tests (ALT <2x ULN, total bilirubin level (TBL) <1.5x ULN, alkaline phosphatase [ALP] <1.5x ULN). In participants with abnormal hepatic biochemical tests at baseline, the discontinuation values may need to be adjusted on a case-by-case basis. For example, in participants enrolled with baseline ALT >1.5x ULN (for example, nonalcoholic fatty liver disease), the discontinuation value may need to be ALT >2x baseline plus symptoms instead of ALT >3x ULN plus symptoms. Similarly, in participants with elevated TBL (for example, Gilbert's syndrome) or elevated ALP (for example, underlying bone disease) at baseline, the discontinuation values will increase and will be based on direct bilirubin levels and hepatic ALP-isoenzyme levels respectively. Consult with the GI & Liver Safety Committee if necessary. If an adjustment is needed, follow the process for changing required language.

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 to be evaluated for safety. See the SoA 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 (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula (QTcF) 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. This review of the electrocardiogram (ECG) printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Possible reasons leading to permanent discontinuation of investigational product:

- Subject Decision
- the participant or the participant's designee, requests to discontinue investigational product.

In addition, participants will be discontinued from the investigational product in the following circumstances:

- the participant becomes pregnant during the study.
- The participant has evidence of progressive disease.

- The participant experiences unacceptable toxicity.
- The participant is noncompliant with study procedures and/or treatment.
- The investigator decides that the participant should be discontinued from study intervention.
- 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 study invention will occur prior to introduction of the new agent.
- The participant has had 1 dose reduction and experiences an AE that would cause a second dose reduction.

See the SoA 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)
- if the participant becomes pregnant during the study. See Section 8.3.5 regarding regulatory reporting requirements on fetal outcome
- if enrollment in any other clinical study involving an investigational product 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.

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 should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (AEs and SAEs) 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.

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. 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.

8.1. Efficacy Assessments

Tumor assessments will be performed for each participant at the times shown in the SoA (Section 1.3).

Computed tomography (CT) scans, including spiral CT, are the preferred methods of assessment (CT scan thickness recommended to be ≤5 mm); however, MRI is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST 1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiologic scan of the thorax, abdomen, and pelvis is required.

In the event of unforeseeable circumstances where participant visits are not able to happen per SoA (e.g., travel restrictions due to Covid-19 pandemic resurgence), participant may opt to have scans done at a local imaging center that is more conveniently located to them. This will need to be orchestrated by the investigator to make sure the participant will remain evaluable per RECIST (contacting the local imaging center and ordering the correct scan/details, as well as thorough documentation of the imaging center location and copies of scans retained as source data at the investigator's site.)

See Section 9.4 for definitions of efficacy endpoints.

8.2. Safety Assessments

For each participant, ECGs, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3).

In the event of unforeseeable circumstances where participant visits are not able to happen per SoA (e.g., travel restrictions due to Covid-19 pandemic resurgence), alternative options for safety assessments need to be performed as given below.

- If delayed visits occur, to ensure participants' safety, the assessments and data collection should continue by remote methods, with the frequency specified in the protocol, including but not limited to AEs/SAEs, concomitant medications, ECOG PS. Serious AE criteria, reporting, and follow-up requirements and procedures remain the same.
- Ensure that all delayed visits and remote-based assessments are documented.
- Labs and other procedures (e.g., imaging, ECG) can be performed locally if a participant is unable to get to their scheduled visit where they were to be collected. The name and address of the performing laboratory or clinic, certification status, and reference ranges also need to be maintained in the participant's files by the site (see Section 8.2.1).

Results from any clinical laboratory test analyzed by a central laboratory (refer to Section 10.2) will be provided to investigative sites by Lilly or its designee.

Refer to Section 8.3 for details on the recording of AEs.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

8.2.1. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA 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 until the completion of Visit 801 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. In the event of unforeseeable circumstances when this is not feasible (e.g., restricted travel due to Covid-19 pandemic resurgence), local or off-site laboratory testing is permissible. In this case, 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. The name and address of the performing off-site laboratory or clinic, certification status, and reference ranges also need to be maintained in the participant's files by the site.
- If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, BP increased, neutrophils decreased, etc.) and it is known to be related to a disease diagnosis (for example, hypertension, neutropenia, etc.) this should be reported in the CRF as an AE. Do not enter the test abnormality, enter the disease diagnosis or categorical term. If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE, AE, or dose modification), then the event(s) must be reported in the CRF as AE(s).

8.2.2. Safety Surveillance

The sponsor has robust safety surveillance processes based on recommendation made by Council for International Organizations of Medical Sciences (CIOMS) Working Group VI - Management of Safety Information from Clinical Trials Report. These processes are in line with FDA's expectations for Safety Assessment Committees and European Medicines Agency expectations for monitoring safety in clinical trials.

Each investigational drug has a Developmental Safety Surveillance Team (DSST) which is responsible for monitoring the safety of participants and overseeing the evolving safety profile of investigational drugs. The DSST will review all available data including but not limited to clinical trial data (cumulative AE and SAE data and laboratory data), non-clinical data (toxicology studies), epidemiology studies and literature. The team will conduct real time review of all SAEs and other incoming expedited safety reports. The DSST is also responsible for review of accumulating safety data across all trials for the investigational drug. The DSST will meet on a timely manner at pre-defined intervals or on an ad-hoc basis as required.

The DSST is a multidisciplinary team which includes a physician/scientist who are well versed in Pharmacovigilance and with the therapeutic area for which the investigational drug is being developed. The roles and responsibilities of this team and the processes are clearly defined in Lilly's internal standard operating procedures.

Each investigational drug has a Developmental Safety Management Team (DSMT) which is a cross-functional, multidisciplinary team and includes DSST members, study team physicians and other members depending on the necessity such as epidemiologist, clinical pharmacologist, toxicologist, and statistician. The DSST and DSMT work together to review clinical data from the clinical trial.

The DSST can make recommendations to the DSMT in order to minimize risk to participants in clinical trials. Such recommendations will include (but are not limited to) changes to conduct of the trial, determination of new adverse drug reactions (ADRs), and determining if event(s) meets the criteria for expedited reporting to regulators (such as investigational new drug [IND] safety reports) and investigators.

In addition, each individual clinical trial study team has clearly defined processes to review all relevant safety data at cohort level and trial level in order to monitor safety of participants in clinical trials and enable trial level decisions such as dose escalation.

Lilly Global Patient Safety (GPS) has a robust process, for expedited communication of SAEs and suspected unexpected serious adverse reactions (SUSARs) per regulatory requirements and other important study information as needed. The protocol gives detailed information to study sites for collection and reporting of AEs and SAEs.

8.2.3. Safety Monitoring

The Lilly CRP/CRS will monitor safety data throughout the course of the study. This will include monitoring and recording all AEs, including all CTCAE v5.0 grades and SAEs. The sponsor will review SAEs within the time frames mandated by company procedures. The Lilly CRP/CRS will periodically review the following data:

- trends in safety data
- review of vital signs, physical exam findings, laboratory analytes including proteinuria, blood chemistry, and hematology labs.
- adverse events, including monitoring of AESIs of ramucirumab (HSRs, hypertension, proteinuria, ATEs, VTEs, bleeding/hemorrhagic events, GI perforation, CHF, wound healing complications, fistula, liver failure/liver injury, and PRES). In addition, injection site reactions (ISRs) related to SC ramucirumab will be evaluated for pain, erythema, induration, swelling, and pruritus.

When appropriate, the sponsor CRP/CRS will consult with the functionally independent GPS therapeutic area physician or CRS.

8.2.4. Hepatic Safety Monitoring

Close hepatic monitoring and evaluation

Liver testing (Section 10.5), including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), gamma-glutamyltransferase (GGT), and creatine kinase (CK), should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:

ALT or AST <1.5x ULN	ALT or AST ≥5x ULN or ALT or AST ≥3x ULN concurrent with TBL ≥2x ULN
ALT or AST ≥1.5x ULN	ALT or AST ≥3x baseline or ALT or AST ≥2x baseline concurrent with TBL ≥2x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, and history of alcohol drinking and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time, international normalized ratio (PT-INR); serological tests for viral hepatitis A, B, C, E; autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan). Additional blood test for glutamate dehydrogenase (GLDH), an exploratory biomarker of drug induced liver injury will be collected for future exploratory analyses.

Based on the participant's history and initial evaluation results, further testing should be considered, in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, and/or a liver biopsy.

Additional Hepatic Safety Data Collection

Additional safety data should be collected via the CRF if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT or AST <1.5 ULN

- Elevation of serum ALT or AST to ≥5x ULN on 2 or more consecutive blood tests
- The combination of elevated ALT or AST ≥3x ULN and elevated TBL ≥2x ULN

In participants enrolled with baseline ALT or AST ≥1.5x ULN

- Elevated ALT or AST ≥3x baseline on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥2x baseline and elevated TBL ≥2x ULN

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be an SAE

8.2.5. Injection Site Reactions

- Injection site assessments using the ISR questionnaire at times specified in the SoA (Section 1.3). If there are ≥2 injection sites, an ISR questionnaire will be filled out separately for each site.
- Symptoms of a local ISR may include erythema, induration, pain, pruritus, and edema that will be assessed at the site by the study team using visual and palpation assessments as appropriate. Injection site findings will be captured on an ISR questionnaire. If any of the symptoms are present, the investigator will characterize using a categorical scale (e.g., intensity and diameter of erythema, diameter of induration, analgesic level requirements for pain, impact of pruritus on sleep, and degree of edema).
- 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 SAEs.
- If an unsolicited ISR is reported by a participant or investigator, the ISR questionnaire 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.
- Participants will be asked to assess injection site(s) daily and record any symptoms in a diary. The diary will be returned to the investigator at each clinic visit. Participants should contact the investigator if any symptoms occur between clinic visits.

8.2.5.1. Injection Site Pain Assessments

- Injection site pain assessments using a 100-mm visual analogue scale (VAS) will be performed at times specified in the SoA (Section 1.3). If there are ≥2 injection sites, VAS pain assessments will be filled out separately for each site.
- The VAS will only be completed by participants if they indicate the presence of pain as investigators complete the ISR questionnaire for solicited/scheduled assessments using the ISR questionnaire. The VAS will not be completed when the ISR questionnaire is used for spontaneous assessments.
- The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection site pain. It is presented as a 100-mm line anchored by verbal descriptors of "no pain" and "worst imaginable pain." Participants will be provided with translations in which they are fluent.

8.2.6. Hypersensitivity Reactions, Including Anaphylaxis

In the event of a suspected systemic HSR, an AE CRF should be completed.

- Each clinical sign or symptom associated with the HSR (e.g. mucocutaneous, cardiovascular, respiratory, GI, CNS, or other) should be entered as a separate AE on the AE CRF form.
- The investigator should indicate whether the event constituted an HSR.

- To fully characterize the HSR, additional information about each event will be captured on the AE CRF form.
  - Each symptom of the event should be assessed. Symptoms may include rash/urticaria, tachycardia, chest pain, fever, flushing, dyspnea, and in severe cases, bronchospasm, angioedema, and hypotension.
  - Timing of the event occurrence is important. The investigator should indicate the timing category that is appropriate.
- In the event of an HSR, blood samples for immunogenicity and PK should be drawn and additional laboratory tests conducted as described in Section 6.5.1.8.1.

8.3. Adverse Events and Serious Adverse Events

The investigator will use CTCAE v5.0 (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 intervention (see Section 7).

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

All SAEs will be collected from the signing of the ICF.

All AEs will be collected from the signing of the ICF until the follow-up visit.

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 study drug. 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. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Serious AEs, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

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 AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 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.

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, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., 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 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.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs.

Pregnancy (maternal or paternal exposure to investigational product) 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 to collect data on the outcome for both mother and fetus.

8.3.6. Adverse Events of Special Interest

Adverse events of special interest for this program include:

a. Hypersensitivity reactions
b. Hypertension
c. Proteinuria
d. Thromboembolic events (ATEs and VTEs)
e. Bleeding/hemorrhage events
f. Gastrointestinal perforation
g. Posterior reversible encephalopathy syndrome
h. Congestive Heart Failure
i. Fistula
j. Wound-healing complications
k. Liver failure/liver injury

Section 6.5.1.8 describes supportive care measures for each ramucirumab AESI. Section 6.6.1 presents the dose-modification guidelines for ramucirumab AESIs. Contact the Lilly CRP/CRS if questions arise concerning AESIs.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. When the ability to use the product safely is impacted, the following are also product complaints:

- Deficiencies in labeling information, and
- Use errors for device or combination products due to ergonomic design elements of the product.

Sponsor collects product complaints on investigational products, medical devices, 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.

Complaints are also collected on comparators and other materials supplied, as required and instructed for the study.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product, medical device, or delivery system, so that the situation can be assessed.

Product complaints will be reported by the investigator to the sponsor per instructions provided on the study specific Product Complaint Form.

With each complaint related to a medical device or delivery system, the investigator will assess and indicate on the complaint form whether the product complaint, deficiency, or problem could have led to an SAE had precautions not been taken. As required by local regulations, the investigator will report to their IRB/IEC any unanticipated adverse device effect (UADE; unanticipated problem that resulted in an SAE), or any product complaint that could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 7 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

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 (LY3009806) as specified in the SoA (see Section 1.3.1 PK sampling schedule).
- A maximum of 5 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 (e.g., 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.
- Genetic analyses will not be performed on these PK samples. Participant confidentiality will be maintained.

Bioanalytical samples collected to measure investigational product concentration 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.

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), venous blood samples will be collected and stored for analysis to determine antibody production against ramucirumab. Antibodies may

be further characterized for their ability to neutralize the activity of 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 (see Section 8.2.6). All samples for immunogenicity should be taken predose when applicable and possible. The detection and characterization of antibodies to ramucirumab will be performed using a validated assay method by or under the supervision of the sponsor. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study to enable further analysis of immune responses to ramucirumab. Immunogenicity will be evaluated as described in Section 9.4.6.2.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

A projected registration dose (PRD) will be identified that is a safe ramucirumab SC dosing regimen leading to a PK profile with similar steady state exposure but higher C_{trough} (>50 µg/mL) and lower C_{max} relative to the PK profile of the approved IV ramucirumab dose of 10 mg/kg Q2W.

9.2. Sample Size Determination

A maximum of approximately 30 participants will receive study intervention such that approximately 12 PK-evaluable participants complete the study at the PRD.

Participants who meet all criteria for enrollment will be assigned to receive ramucirumab in this study. The sponsor will confirm the dose and identification number assignment (and cohort) for each participant. No dose escalations (i.e., to the next cohort) can occur without prior discussion and agreement with the responsible sponsor CRP/CRS.

The primary objectives of this study are to assess the PK parameters of ramucirumab administered SC and to assess safety of ramucirumab administered SC.

9.2.1. Cohort A

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

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

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

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

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

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

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

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

9.2.3. Cohort C

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

If any participant of Cohorts A, B, or C discontinues the therapy prior to the assessment of safety and PK profile at Week 3, a new participant (up to 3) may be enrolled to make sure there will be sufficient data for safety and PK assessment.

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 who receive at least one dose of study treatment.
Efficacy Evaluable	All participants with evaluable disease per their baseline assessment and at least one complete post-baseline assessment.
Safety	All participants who take at least 1 dose of study intervention.
Pharmacokinetic Analysis	All treated participants who received at least 1 dose of study treatment and have at least one evaluable PK sample.

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

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of sponsor or its designee. The primary analysis will happen after all participants complete the PK and safety assessment at Week 3 or discontinue treatment prior to completing Week 3.

This is not a controlled study and statistical tests of clinical outcomes are not feasible. Summaries will be limited to descriptive statistics. Unless otherwise stated, any confidence intervals (CIs) will be given at a 2-sided 95% level.

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. Additional exploratory

analyses of the data will be conducted as deemed appropriate. Principal features of the protocol include any analyses which are regarded critical to registration.

The initial statistical analysis plan will be finalized prior to first participant 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. General Considerations

Any modifications or clarifications to the data analysis methods will be described and justified in the SAP before data analysis. As this is an uncontrolled, open-label study, any modifications to analyses after the initial SAP will be considered post hoc.

The primary analysis of clinical data will occur after all participants have completed the PK evaluation period. Additional updated analyses of efficacy and safety may be conducted at later times if deemed appropriate by the sponsor.

9.4.1.1. Participant Disposition

A detailed description of participant disposition will be provided, according to CONSORT publishing requirements, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated, as well as number and percentage of participants completing the study, as defined in the SAP, or discontinuing prior to study completion (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.4.1.2. Participant Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target participant population considered for regulatory approval.

A summary of baseline participant and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

Other participant baseline characteristics will be summarized by cohort as deemed appropriate.

9.4.1.3. Concomitant Medications

A summary of prior and concomitant medications and transfusions by cohort will be reported.

9.4.1.4. Treatment Compliance

Study treatment compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of doses dispensed and returned over the course of the participant's treatment.

9.4.1.5. Extent of Exposure

The duration on therapy, dose omissions, dose reductions, dose delays, and dose intensity for each drug will be summarized for all treated participants by arms.

9.4.1.6. Post-Study Treatment Therapy

The numbers and percentages of participants receiving post-study-treatment, anti-cancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall, and by line of therapy.

9.4.2. Primary Endpoint

The primary clinical objective is to evaluate the safety and PK profile of ramucirumab administered SC. The safety assessment will include, but not be limited to, summaries of TEAEs, SAEs, abnormal laboratory findings, and dose modifications. See Section 9.4.5 for a detailed description of the safety analyses.

Serum concentration of ramucirumab will be summarized using descriptive statistics per dose and time point of collection. Additional analysis utilizing the population PK approach will also be conducted if deemed appropriate. See Section 9.4.6.1 for details.

9.4.3. Secondary Endpoint(s)

Immunogenicity incidence will be tabulated, and correlation of immunogenicity to ramucirumab drug level, activity, and safety will be assessed as appropriate. See Section 9.4.6.2 for details.

Injection site reactions will be summarized. Details will be described in SAP.

9.4.4. Tertiary/Exploratory Endpoint

Any evidence of clinical activity, including best overall response, will be noted for each participant.

9.4.5. Other Safety Analyses

All safety analyses will be made on the Safety Population. The most current version of MedDRA at the time of analysis will be used when reporting AEs by MedDRA terms and CTCAE (v5.0) will be utilized to assign AE-severity grades.

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study drug
- serious AEs, including possible relationship to study drug
- adverse events leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs and ECGs.

All parameter estimates from the fitted dose-toxicity model used to guide the dose escalation will be provided along with the associated 95% CIs.

A summary overview of all AEs will be provided overall and by cohort. Treatment-emergent AEs, SAEs, and AESIs will be summarized and listed overall and by cohort.

All deaths that occur during the study, within 30 days of the study treatment discontinuation, as well as the cause of death, will be summarized and listed overall and by cohort.

In addition, summary and listing of AEs leading to death, leading to study treatment discontinuation, and leading to study treatment dose modification will be produced overall and by cohort.

All relevant hematology and chemistry laboratory values will be graded according to CTCAE v5.0. The shifts in CTCAE toxicity grading from baseline to worst grade postbaseline (first dose up to 30 days after study treatment discontinuation) will be produced overall and by cohort.

All vital signs including temperature, BP, heart rate, and weight will be listed overall and by cohort.

9.4.6. Other Analyses

9.4.6.1. Pharmacokinetic Analyses

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

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

9.4.6.2. Immunogenicity Analyses

The frequency and percentage of participants with preexisting anti-drug antibody (ADAs) and with treatment-emergent (TE) ADA to ramucirumab will 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 ADAs) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADAs). For the TE ADA+ participants the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated in TE ADA+ participants if assessed.

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

In the event of an HSR, ADAs and ramucirumab serum concentrations will be tabulated (see Section 8.2.6).

9.5. Interim Analyses

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

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 CIOMS International Ethical Guidelines
  - Applicable International Council for Harmonization (ICH) good clinical practice (GCP) Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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 (and/or UADEs) 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 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 CTA.

10.1.2. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. 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.

10.1.4. 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.

10.1.5. Committees Structure

Not applicable.

10.1.6. 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 Lilly 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 Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly 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.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF (eCRF) unless transmitted to the sponsor or designee electronically (e.g., 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.
- 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 (e.g., 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 (e.g., 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 (CTA) 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, 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 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 sources and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (participant-focused outcome instrument) will be collected by the participant, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture system(s) will be stored at third parties. 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 sponsor will be encoded and stored in the global product complaint management system.

10.1.8. 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.

10.1.9. 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 IRBs/IECs, 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 assure appropriate participant therapy and/or follow-up.

10.1.10. 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.

10.1.11. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the indicated laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Hematology – local laboratory

- Leukocytes (WBC)
- Neutrophils, segmented
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Erythrocytes (RBC)
- Hemoglobin (HGB)
- Hematocrit (HCT)
- Platelets (PLT)
- Cell morphology (RBC and WBC)

Coagulation – local laboratory

- Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)
- International normalized ratio (INR) or prothrombin time (PT)

Chemistry –central laboratory

Serum concentrations of:

- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Bilirubin, total
- Blood urea nitrogen (BUN) or blood urea
- Calcium
- Chloride
- Creatinine
- Glucose
- Potassium
- Sodium
- Total protein

Thyroid panel– central laboratory

- Thyroid-stimulating hormone
- Free T4

Pregnancy test (for female participants of childbearing potential) – local laboratory

- Urine pregnancy test at a minimum sensitivity of 25 IU/L or equivalent units of β-hCG. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required

Urinalysis – local laboratory

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

Hypersensitivity Tests[b] – central laboratory	

• Anti-LY antibodies (immunogenicity)
• LY concentration (PK)
• Tryptase[c]
• N-methylhistamine
• Complements
  ○ C3a
  ○ C5a
	• Cytokine Panel
	  ○ IL-6
	  ○ IL-1β
	  ○ IL-10
	• Basophil Activation Test[d]

Abbreviations: PK = pharmacokinetic; RBC = red blood cells; WBC = white blood cells.

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 Test only if dipstick result is abnormal.

b Central laboratory. Additional tests and local laboratory tests may be performed at the discretion of the investigator.

c If a tryptase sample is obtained more than 2 hours after the event (i.e. within 2-12 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 2-12 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.

d 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.

10.3. 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 participant 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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing 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 the 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 (e.g., 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 pre-existing 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 definition above, then it cannot be an SAE even if serious conditions are met (e.g., 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:

c. Results in death

d. 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.

e. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to 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 pre-existing condition that did not worsen from baseline is not considered an AE.

f. 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

g. Is a congenital anomaly/birth defect

h. 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 AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to 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 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 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 use Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (NCI 2018) to assign AE severity grades. Post baseline grading for all laboratory investigations should be done per normal limit references, where specified, regardless of whether the assessment is normal or abnormal at baseline. For example, in hepatic laboratory assessments, the investigator will use CTCAE version 4.03 (NCI 2010) 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 Investigator's Brochure (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 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 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 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 Sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in SAE form.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SAE form.

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 post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., 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 salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., 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, or medical history interview.

3. Postmenopausal female is defined as, women with:
   - 12 months of amenorrhea for women >55, with no need for FSH
   - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that induced amenorrhea)

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

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

b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c.) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

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 including fetal status (presence or absence of anomalies) and 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, including 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 post-study 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. If the participant is discontinued from the study intervention, follow the standard discontinuation process and continue directly to the follow-up phase.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 8.2.4 for guidance on appropriate test selection.

- **For testing selected, analysis is required to be completed by the Lilly-designated central laboratory except for Microbiology.**
- **Local testing may be performed in addition to central testing when required for immediate participant management.**
- **Results will be reported if a validated test or calculation is available.**

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl Alcohol (EtOH)
	Glutamate dehydrogenase (GLDH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (Quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin IgG (Quantitative)
HAV Total Antibody	Immunoglobulin IgM (Quantitative)
HAV IgM Antibody	Phosphatidylethanol (PEth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]

HBV DNA [d]	Anti-actin antibody [b]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA [d]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA [d]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

[a] This is not required if anti-actin antibody is tested.

[b] This is not required if ASMA is tested.

[c] Assayed by investigator-designated local laboratory ONLY; no central testing available.

[d] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.6. Appendix 6: Protocol JVDU Restricted and Prohibited Concomitant Therapy

The table below describes medications, treatments, and drug classes restricted or prohibited, with exceptions and conditions for use during the study treatment period (there are no prohibited therapies during the follow-up period). Participants who, in the assessment by the investigator, require the use of any of the prohibited treatments for clinical management should be removed from the trial. Participants may receive other supportive therapy or vaccinations that the investigator deems to be medically necessary.

Therapy	Allowed as Needed	Allowed for Chronic Use	Exceptions or Conditions for Use
Antiplatelet therapy and NSAIDs	Yes	Yes, with restrictions	Chronic use of aspirin up to 325 mg/day is permitted. Chronic use of NSAIDs is not permitted. However, in certain medical situations, NSAIDs may be the best treatment option (for example, for pain management) and are therefore permitted as needed. Increased risk of bleeding should be considered by the treating physician and the participant.
Anticoagulation therapy	No	Yes, with restrictions	At enrollment, participants on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin or similar agent. If on warfarin, the participant must have an INR ≤3 and no active bleeding or pathological condition present that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).
Anti-cancer biological therapy	No	No	
Chemotherapy	No	No	
Cytochrome P450 metabolizers	Yes	Yes	For participants using ramucirumab with combination treatments as stated in this protocol, please follow local label for prescribing information.
Erythroid growth factors	Yes	No	Follow local guidelines.
Experimental medicines or investigational agents	No	No	Other than ramucirumab, paclitaxel, docetaxel, fluorouracil, irinotecan, and erlotinib.
Glucocorticoids	Yes	Yes, with restrictions	Systemic glucocorticoids are permitted to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Use in participants with contrast allergies is acceptable. A temporary course of corticosteroids will be allowed for other indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note: Inhaled steroids are allowed for management of asthma.
Immunotherapy	No	No	Other than inhaled steroids and vaccinations.
Radiation therapy	No	No	Localized radiation therapy to a symptomatic, solitary lesion or to the brain may be allowed after consultation with the Sponsor.
Live Vaccines	No	N/A	Prohibited as concomitant therapy during the study and for at least 3 months after last dose of study drug.

Abbreviations: INR = international normalized ratio; NSAID = nonsteroidal anti-inflammatory drug.

10.7. Appendix 7: Abbreviations

Term	Definition
2L	Second line
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
ALK	anaplastic large-cell lymphoma kinase
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
AUC	area under the plasma concentration versus time curve
BP	blood pressure
BSC	best supportive care
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMV	cytomegalovirus
CNS	central nervous system
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.
CONSORT	Consolidated Standards of Reporting Trials
CRC	colorectal cancer
CRF	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.
CRS	clinical research scientist
C_{max}	maximum blood plasma concentration
CK	creatine kinase
CT	computed tomography
CTA	Clinical Trial Agreement
CTCAE	common terminology criteria for adverse events
C_{trough}	lowest concentration of a drug just before the next dose
CV	Pharmacokinetic variability
D. Bil	direct bilirubin
DMC	data monitoring committee
DSMT	Developmental Safety Management Team
DSST	Developmental Safety Surveillance Team
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Score
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
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.
ER	exposure-response
ERCP	endoscopic retrograde cholangiopancreatography
Erk1/Erk2	extracellular signal-regulated protein kinases 1 and 2
FDA	Food and Drug Administration

FOLFIRI	fluorouracil and irinotecan
FSH	follicle-stimulating hormone
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
GEJ	gastroesophageal junction
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GPS	Global Patient Safety
HCC	hepatocellular carcinoma
HDV	hepatitis D virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSR	hypersensitivity reaction
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
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.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ISP	injection site pain

ISR	injection site reaction
IV	intravenous
IWRS	interactive web-response system
LD	Loading dose
mAbs	monoclonal antibodies
MD	maintenance dose
MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NSAID	nonsteroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival
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-1	programmed cell death-1
PET	positron emission tomography
PET-CT	positron emission tomography-CT
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PRD	projected registration dose
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
QW	every week
Q2W	every 2 weeks
Q3W	every 3 weeks
QTcF	QT interval corrected using Fridericia’s formula

QW	every week
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
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.
SoA	Schedule of Activities
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TE ADA	treatment-emergent anti-drug antibody
TKI	tyrosine kinase inhibitor
UADE	unanticipated adverse device effect
ULN	upper limit of normal
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event
WOCBP	woman of childbearing potential

10.8. Appendix 8: Protocol Amendment History

Amendment d: 14-Jan-2021

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for the amendment is to make changes based on preliminary data from Study JVDT, to remove hepatocellular carcinoma (HCC) and gastric cancer patients from inclusion in Cohort A and add to Cohorts B and C, and to correct an error in the contraceptive language.

Section # and Name	Description of Change	Brief Rationale
4.1. Overall Design	Introduced Study JVDT earlier in protocol.	Administrative change.
4.3.1. Rationale for Initial Cohort A Dose Selection	Expanded number or participants from n = 3 to n = 3 to 6.	Clarification of sample size for Cohort A.
5.1. Inclusion Criteria	Inclusion criterion 3: Removed HCC and gastric cancer patients from inclusion in Cohort A and added to inclusion in Cohorts B and C.	Ensure HCC and gastric cancer patients do not get sub-optimal dose on starting Cohort A.
	Inclusion criterion 9: Revised "Male participants are eligible to participate if they agree to the following during the intervention period and for at least the duration of the study or for 5 months following completion of study drug administration, whichever is longer:" to " …for at least 84 days/12 weeks following completion of study drug administration:"	Correction of duration language for male participants related to contraceptive use, sperm donation, and sexual abstinence.
6.1.1 Treatment Requirements for Each Treatment Visit and Treatment Delays	Corrected start of each new cycle to ±3 days	Clarification
8.2.5. Injection Site Reactions	Added language to explain how injection site reactions will be assessed.	Clarification.
9.2.1. Cohort A	Added language to be able to expand sample size from 3 to up to 6 in Cohort A based on safety findings from Study JVDT.	Clarification of sample size for Cohort A.
10.6. Appendix 6: Protocol JVDU Restricted and Prohibited Concomitant Therapy	Cytochrome P450 metabolizers allowed as needed or chronic use with exceptions.	Clarification related to use of concomitant therapy.

Amendment c: 05-Nov-2020

Overall Rationale for the Amendment:

The overall rationale for the amendment is to incorporate updates for hepatic safety and to allow participants to adjust their weekly maintenance dose to the maintenance dose of Cohort C once the dose has been confirmed.

Section # and Name	Description of Change	Brief Rationale
4.1.1 Cohort A; 4.1.2 Cohort B	Allowance for participants to adjust weekly maintenance dose to the maintenance dose for Cohort C once the dose has been confirmed	Administrative
6.1.1 Treatment Requirements for Each Treatment Visit and Visit Delays; 8.2.4 Hepatic Safety Monitoring; Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments	Updated criteria for administering ramucirumab SC; added GLDH test for potential future analyses of biomarkers of drug-induced liver injury	Alignment with updated hepatic safety guidance

Amendment b: 02-Oct-2020

Overall Rationale for the Amendment:

The overall rationale for the amendment is to incorporate changes and provide additional clarifications according to regulatory agency interactions.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; 2.3.1 Risk Assessment; 6.1 Study Intervention(s) Administered; 6.5.1 Palliative Medicine and Supportive Care	Removed premedication with antihistamines	Regulatory agency interaction
1.3 Schedule of Activities	Added coagulation collection on C2D1 and every other cycle afterwards	Regulatory agency interaction
1.3 Schedule of Activities; 7.1 Discontinuation of Study Intervention	Clarified that short-term follow-up lasts a minimum of 30 days following the last dose of study drug	Clarification
Throughout	Minor editorial and document formatting revisions.	These are minor changes; therefore,

Section # and Name	Description of Change	Brief Rationale
		they have not been summarized.

Amendment a: 14-Sep-2020

Overall Rationale for the Amendment:

The overall rationale for the amendment is to provide clarifications in the protocol related to schedule of activities, administration of the investigational product namely subcutaneous (SC) ramucirumab and chemotherapy (FOLFIRI) as discussed below. There are no changes in the study-design, inclusion/exclusion criteria, or statistical analysis that would impact participant safety and overall objectives of the study.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Changed D21 to D22 for C2 and C3-n.	Minor clarification.
1.3 Schedule of Activities	Clarified vital sign measurements will be obtained prior to the ramucirumab dose.	Minor clarification.
1.3 Schedule of Activities	Clarified no Pain VAS is required in the case of a positive response to pain question during spontaneous assessment of ISRs between scheduled visits.	Minor clarification.
Throughout	Updated RELAY approval throughout the protocol.	Minor clarification.
4.3.1 Rationale for Initial Cohort A Dose Selection	Clarified use of a syringe pump will not be used for Cohort A.	Minor clarification.
4.3.2 Rationale for Initial Cohort B Dose Selection; 6.1 Study Intervention(s) Administered	Clarified SC loading dose will be administered using a syringe pump.	Minor clarification.
6.1 Study Intervention(s) Administered	Clarified timing of premedication for combination therapy.	Minor clarification.
6.1 Study Intervention(s) Administered	Added infusion rate for SC administration using a syringe pump.	Clarification.
6.1.1 Treatment Requirements	Changed ramucirumab SC with FOLFIRI timing from 28 to	Rectifying error.

Section # and Name	Description of Change	Brief Rationale
for Each Treatment Visit and Treatment Delays	14 days from the last administration of FOLFIRI.	
6.6 Dose Modification	Clarified an alternate administration of loading dose if an injection site reaction occurs.	Minor clarification.
Throughout	Minor editorial and document formatting revisions.	These are minor changes; therefore, they have not been summarized.

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