Protocol H8H-MC-LAIO (b)

An Open-Label, 2-Part Study to Investigate the Effect of Lasmiditan on the Pharmacokinetics of Dabigatran and Rosuvastatin in Healthy Volunteers

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Approval Date: 06-Nov-2020

Title page

Protocol Title:

An Open-Label, 2-Part Study to Investigate the Effect of Lasmiditan on the Pharmacokinetics of Dabigatran and Rosuvastatin in Healthy Volunteers

Protocol Number: H8H-MC-LAIO

Amendment Number: H8H-MC-LAIO(b)

Compound: Lasmiditan (LY573144)

Study Phase: Phase 1

Short Title: A DDI Study of Lasmiditan with Dabigatran etexilate and Rosuvastatin in Healthy Volunteers

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company

Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 103420

Approval Date: Protocol Electronically Signed and Approved by Lilly on 11 September 2020.

Amendment (a) Electronically Signed and Approved by Lilly on 16 September 2020.

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

Approval Date: 06-Nov-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	*16-Sep-2020*
Original Protocol	*11-Sep-2020*

Amendment [b]

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Criterion #4 has been updated to specify renal and liver function cut-off values.	This addition was made to provide additional clarity.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: An Open-Label, 2-Part Study to Investigate the Effect of Lasmiditan on the Pharmacokinetics of Dabigatran and Rosuvastatin in Healthy Volunteers.

Short Title: A DDI Study of Lasmiditan with Dabigatran etexilate and Rosuvastatin in Healthy Volunteers

Rationale:

Lasmiditan (LY573144) is a highly selective and potent agonist at the 5-hydroxytryptamine 1Freceptor. Lasmiditan has been developed by Eli Lilly and Company, and approved by the US Food and Drug Administration (FDA), for the acute treatment of migraine attacks, with or without aura, in adults.

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are membrane-bound, efflux transporters located in the small intestine, colon, and liver (among other tissues), serving to limit the absorption of drugs from the gastrointestinal tract and to increase biliary secretion of drugs and their metabolites (Maliepaard et al. 2001, International Transporter Consortium et al. 2010). Certain substrates of BCRP or P-gp have been shown to have clinically significant drug interactions when administered with inhibitors of BCRP or P-gp, respectively (International Transporter Consortium et al. 2010).

The potential for lasmiditan and its metabolites to inhibit efflux transporters P-gp and BCRP was assessed in vitro. The intestinal drug-drug interaction (DDI) index (dose/250 mL [I2]/concentration of drug causing half-maximal inhibitory effect [IC50]) was determined for both P-gp and BCRP inhibition in context of a 200-mg dose, the maximum approved dose for lasmiditan (FDA 2020a). The calculated DDI index was 16 for BCRP and 25 for P-gp. Both these values exceed the FDA cutoff value of 10, indicating that lasmiditan has the potential to inhibit P-gp and BCRP in the clinic.

This study aims to evaluate the safety, tolerability, and pharmacokinetics of rosuvastatin and dabigatran in the presence of lasmiditan. Dabigatran etexilate and rosuvastatin are sensitive substrates of efflux transporters, P-gp and BCRP, respectively (FDA 2020b).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of lasmiditan on P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) activity in healthy participants	• C_{max} and AUC(0-∞) of dabigatran to assess P-gp activity and rosuvastatin to assess BCRP activity

Secondary	
• To evaluate the safety and tolerability of dabigatran etexilate or rosuvastatin in combination with lasmiditan in healthy participants • To evaluate the pharmacokinetics of lasmiditan and M8	• A summary of the number of treatment-emergent adverse events and serious adverse events • C_{max}, t_{max}, and AUC(0-∞) of lasmiditan and M8

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; BCRP = breast cancer resistance protein; C_{max} = maximum observed drug concentration; P-gp = p-glycoprotein; t_{max} = time of maximum observed drug concentration.

Overall Design

This is a Phase 1, two-part, two-period, open-label study in healthy participants. Part 1 will study dabigatran P-gp DDI with lasmiditan. Part 2 will study rosuvastatin BCRP DDI with lasmiditan. Parts 1 and 2 will have a similar design, i.e., dabigatran etexilate or rosuvastatin administration alone in Period 1 (Day 1) followed by a brief washout, then lasmiditan on Days 8, 9, and 10 (Period 2) with coadministration of dabigatran etexilate or rosuvastatin with lasmiditan on Day 10. Each part will consist of different participants and the 2 parts may run in parallel.

Disclosure Statement: This is an open-label, parallel-group DDI study with 2 parts.

Number of Participants:

Approximately 72 participants will be enrolled to Part 1 of the study to ensure that at least 62 evaluable participants complete that part. Approximately 32 participants will be enrolled to Part 2 to ensure that at least 28 evaluable participants complete that part.

Intervention Groups and Duration:

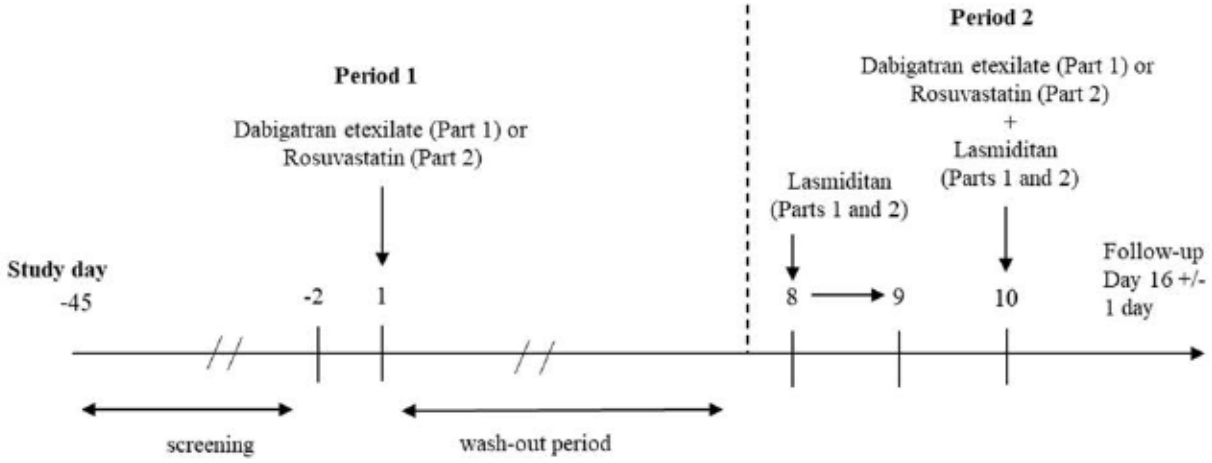
This study consists of 2-parts and 2-periods. Part 1 will consist of single oral doses of dabigatran etexilate (Period 1), followed by 3 daily doses of lasmiditan with coadministration of a single oral dose of dabigatran etexilate given at the same time as the third dose of lasmiditan (Period 2). Part 2 will consist of single oral doses of rosuvastatin (Period 1) followed by 3 daily doses of lasmiditan with coadministration of a single dose of rosuvastatin given at the same time as the third dose of lasmiditan (Period 2).

Part 1: Dabigatran etexilate/Lasmiditan		
Period 1 (Day 1)	Period 2	
	(Days 8-9)	(Day 10)
Dabigatran etexilate (150 mg)	Lasmiditan (200 mg 1x per day)	Dabigatran etexilate (150 mg) + Lasmiditan (200 mg)

Part 2: Rosuvastatin/Lasmiditan		
Period 1 (Day 1)	Period 2	
	(Days 8-9)	(Day 10)
Rosuvastatin (10 mg)	Lasmiditan (200 mg 1x per day)	Rosuvastatin (10 mg) + Lasmiditan (200 mg)

Data Monitoring Committee: No

1.2. Schema


Period 1
Dabigatran etexilate (Part 1) or Rosuvastatin (Part 2)
Period 2
Dabigatran etexilate (Part 1) or Rosuvastatin (Part 2)
+
Lasmiditan (Parts 1 and 2)
Lasmiditan (Parts 1 and 2)
Study day
-45
-2
1
8
9
10
Follow-up Day 16 +/- 1 day
screening
wash-out period

1.3. Schedule of Activities (SoA)

Part 1 – Dabigatran etexilate/Lasmiditan

	Screening	Days													ED/ Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	
Informed consent	X																
Inclusion and exclusion criteria	X																
Demography	X																
Participant admission to CRU		X							X								
Participant discharge from CRU					X									X			At the investigator's discretion, participants may remain inpatient after Day 3 or 12.
Past and current medical history (includes substance usage [and family history of premature cardiovascular disease])	X																
Full physical examination including height and weight	X																A symptom-directed physical examination may be performed at other times at the discretion of the investigator.
Serum or urine pregnancy test (women of childbearing potential only)	X	X							X							X	Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at every admission period and at poststudy, if applicable.

	Screening	Days													ED/ Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	
Human immunodeficiency virus, hepatitis B and C screening	X																
12-lead electrocardiogram (ECG)	X		P		X							P		X			
Vital signs (supine)	X		P, 1, 2 h	24 h						P		P, 1, 2 h	24h			X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Clinical laboratory assessments (including liver chemistries)	X		P	24 h						P			24 h			X	See Appendix 10.2, Clinical Laboratory Tests, for details. Urinalysis performed at screening, follow-up and ED only.
C-SSRS and Self-Harm Supplement	X								X							X	"Baseline" questionnaire to be used at screening, all other time points use "Since Last Visit" questionnaire. The Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Self-Harm Follow-Up form will be used to collect additional information. The Day 7 assessment can be performed up to pre-dose on Day 8.

	Screening	Days													ED/ Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	
Genetic sample			X														
PK samples - dabigatran (plasma)			P, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 h	24, 36 h	48 h	72 h						P, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 h	24, 36 h	48 h	72 h		72-hour blood draw to be performed at outpatient visit.
PK samples - lasmiditan/M8 (plasma)												P, 0.5, 1, 1.5, 2, 4, 8, 12 h	24, 36 h	48 h	72 h		72-hour blood draw to be performed at outpatient visit.
Study intervention administration			X							X	X	X					Dabigatran etexilate to be given on Day 1 (Period 1). Lasmiditan to be given on Days 8, 9, and 10 with a single dose of dabigatran etexilate co-administered with lasmiditan on Day 10 (Period 2).
Adverse event/serious adverse event review		X	←═══════════════════════════════════→													X	
Concomitant medication review		X	←═══════════════════════════════════→													X	

	Screening	Days													ED/ Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	

Abbreviations: CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; P = predose; PK = pharmacokinetics.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture. Where venipuncture and other procedures take place at the same time point, the following time windows for obtaining blood samples should be maintained: >0 to 2 hours postdose: ±5 minutes; 2.5 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; 24 to 48 hours postdose: ±30 minutes; ≥72 hours postdose: ±120 minutes. Where repeats of supine vital sign measurements are required, repeats should be performed after venipuncture.

Part 2 – Rosuvastatin/Lasmiditan

	Screening	Days													ED Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	
Informed consent	X																
Inclusion and exclusion criteria	X																
Demography	X																
Participant admission to CRU		X							X								
Participant discharge from CRU					X									X			At the investigator's discretion, participants may remain inpatient after Day 3 or 12.
Past and current medical history (includes substance usage [and family history of premature cardiovascular disease])	X																
Full physical examination including height and weight	X																A symptom-directed physical examination may be performed at other times at the discretion of the investigator.

	Screening	Days														ED Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	
Serum or urine pregnancy test (women of childbearing potential only)	X	X							X							X	Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at every admission period and at poststudy, if applicable.
Human immunodeficiency virus, hepatitis B and C screening	X																
12-lead electrocardiogram (ECG)	X		P		X							P		X			
Vital signs (supine)	X		P, 1, 2h	24 h						P		P, 1, 2h	24 h			X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Clinical laboratory assessments (including liver chemistries)	X		P		X					P				X		X	See Appendix 10.2, Clinical Laboratory Tests, for details. Urinalysis performed at screening, follow-up and ED only.
C-SSRS and Self-Harm Supplement	X								X							X	"Baseline" questionnaire to be used at screening, all other time points use "Since Last Visit" questionnaire. The Self-Harm Supplement should be completed every time the C-SSRS is

	Screening	Days														ED Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	
																	administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Self-Harm Follow-Up form will be used to collect additional information. The Day 7 assessment can be performed up to pre-dose on Day 8.
Genetic sample			X														
Transporter genotyping	X																
PK samples - rosuvastatin (plasma)			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 h	24 h	48 h	72 h						P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 h	24 h	48 h	72 h		Blood draw at 72hours will be performed at an outpatient visit.
PK samples - lasmiditan/M8 (plasma)												P, 0.5, 1, 1.5, 2, 4, 8, 12 h	24, 36 h	48 h	72 h		Blood draw at 72 hours will be performed at outpatient visit.
Study intervention administration			X							X	X	X					Rosuvastatin to be given on Day 1 (Period 1).

	Screening	Days													ED Follow-Up	Comments
Procedure	-45 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	Day 16 +/-1 day	
																	Lasmiditan to be given on Days 8, 9, and 10 with a single dose of rosuvastatin co-administered with lasmiditan on Day 10 (Period 2).
Adverse event/serious adverse event review		X	←═══════════════════════════════════→													X	
Concomitant medication review		X	←═══════════════════════════════════→													X	

Abbreviations: CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; P = predose; PK = pharmacokinetics.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture. Where venipuncture and other procedures take place at the same time point, the following time windows for obtaining blood samples should be maintained: >0 to 2 hours postdose: ±5 minutes; 2.5 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; 24 to 48 hours postdose: ±30 minutes; ≥72 hours postdose: ±120 minutes. Where repeats of supine vital sign measurements are required, repeats should be performed after venipuncture.

2. Introduction

Lasmiditan (LY573144) is a highly selective and potent agonist at the 5-hydroxytryptamine 1F (5-HT1F) receptor. Lasmiditan has been developed by Eli Lilly and Company (Lilly), and approved by the US Food and Drug Administration (FDA), for the acute treatment of migraine attacks, with or without aura, in adults. Full details of the preclinical and clinical safety and tolerability data are contained in the Investigator's Brochure (IB).

2.1. Study Rationale

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are membrane-bound, efflux transporters located in the small intestine, colon, and liver (among other tissues), serving to limit the absorption of drugs from the gastrointestinal tract and to increase biliary secretion of drugs and their metabolites. Certain substrates of BCRP or P-gp have been shown to have clinically significant drug interactions when administered with inhibitors of BCRP or P-gp, respectively (International Transporter Consortium et al. 2010).

The potential for lasmiditan and its metabolites to inhibit efflux transporters P-gp and BCRP was assessed in vitro. The intestinal drug-drug interaction (DDI) index (dose/250 mL [I2]/concentration of drug causing half-maximal inhibitory effect [IC_{50}]) was determined for both P-gp and BCRP inhibition in the context of a 200-mg dose, the maximum approved dose (FDA 2020a). The calculated DDI index was 16 for BCRP and 25 for P-gp. Both these values exceed the FDA cutoff value of 10, indicating that lasmiditan has the potential to inhibit P-gp and BCRP in the clinic.

This study aims to evaluate the safety, tolerability, and pharmacokinetics (PK) of rosuvastatin and dabigatran in the presence of lasmiditan. Rosuvastatin and dabigatran etexilate are sensitive substrates of efflux transporters, BCRP and P-gp, respectively (FDA 2020b).

2.2. Background

In previous studies, following single oral dose administration of lasmiditan to adult participants, lasmiditan was absorbed with a median time of maximum observed drug concentration (t_{max}) of 1.8 hours, and rapidly eliminated with a mean half-life associated with the terminal elimination phase ($t_{1/2}$) of approximately 5.7 hours. Lasmiditan undergoes extensive hepatic and extrahepatic metabolism with ketone reduction to inactive metabolite M8 as the major biotransformation pathway. No accumulation of lasmiditan was observed with daily dosing. More detailed information about the PK and absorption, distribution, metabolism, and excretion properties of lasmiditan may be found in the IB.

Dabigatran etexilate, a competitive, direct thrombin inhibitor, is a P-gp substrate. Following absorption, dabigatran etexilate is hydrolyzed to form dabigatran, the active moiety. Dabigatran concentrations reach t_{max} within 2 hours of administration, and then concentrations decline in a biphasic manner, with a terminal $t_{1/2}$ of 12 to 17 hours. Dabigatran is primarily eliminated through renal excretion and does not appear to be a substrate for renal transporters based on the reported renal clearance of 89 mL/min (Stangier 2008). Dabigatran itself is not a substrate for the cytochrome P450 (CYP) family of metabolizing enzyme nor a substrate for P-gp, meaning that

changes in dabigatran exposure following administration of a P-gp inhibitor would be anticipated to only reflect the activity of the inhibition of dabigatran etexilate transport at the intestinal wall (Stangier 2008). Previous studies have investigated the effect of P-gp inhibitors on dabigatran PK. Dabigatran area under the concentration versus time curve (AUC) increased by 58% and 53% when co-administered with amiodarone and quinidine, respectively (Pradaxa® Prescribing Information, 2010). Ketoconazole, a strong P-gp inhibitor, increased dabigatran AUC and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple daily 400-mg doses (Pradaxa Prescribing Information, 2010).

Rosuvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor indicated for patients with primary hyperlipidemia, is a BCRP substrate. After dose administration, rosuvastatin concentrations reach t_{max} approximately 3 to 5 hours postdose and then concentrations decline with $t_{1/2}$ of approximately 19 hours. Approximately 72% of total rosuvastatin clearance is hepatic, with the majority of this clearance occurring through biliary excretion; approximately 10% of an administered dose of rosuvastatin is metabolized, primarily via CYP2C9. Unlike many other BCRP substrates, however, rosuvastatin is neither metabolized by CYP3A to a clinically significant extent, nor is it a substrate for P-gp (Crestor® Prescribing Information, 2020). Previous studies have investigated the effect of BCRP inhibitors on rosuvastatin PK. Rosuvastatin AUC increased by 60% and 610% when co-administered with BCRP inhibitors, eltrombopag and cyclosporine (Crestor Prescribing Information, 2020).

2.3. Benefit/Risk Assessment

The dose of lasmiditan to be given in this study is 200 mg. In previous healthy volunteer studies, doses of lasmiditan up to 400 mg have been given as single or multiple doses up to 7 days. Lasmiditan has been associated with a mean decrease in heart rate of 5 to 10 bpm compared to 2 to 5 bpm for placebo. Additionally, in nonelderly healthy volunteers a slight mean increase in blood pressure of 2 to 3 mmHg was observed 1 hour after dosing. No additional findings on vital signs were noted following once-daily dosing for 7 days (H8H-MC-LAHE). Nervous system disorders, including dizziness, fatigue, and paresthesia and sedation were commonly reported as adverse events (AEs) (≥5% and > placebo) in the Phase 2/3 pool, especially at higher dose levels; they were generally mild or moderate in intensity. Overall, in previous healthy volunteer studies these changes were well tolerated. Further information about adverse drug reactions can be found in the US Prescribing Information (Reyvow Prescribing Information, 2020).

Driving should be avoided for at least 8 hours, and participants will remain in the clinical research unit (CRU) for 48 hours postdose.

Dabigatran etexilate and rosuvastatin doses to be administered in this study (150 mg and 10 mg, respectively) are within the therapeutic range (see Section 4.3), and have previously been administered to healthy volunteers with no tolerability concerns in other DDI studies (Study I8D-MC-AZEE [AZEE]; NCT02568397 and Study I8D-MC-AZEB [AZEB]; NCT03019549)].

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

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lasmiditan may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of lasmiditan on P-gp and BCRP activity in healthy participants	• C_{max} and AUC(0-∞) of dabigatran to assess P-gp activity and rosuvastatin to assess BCRP activity
Secondary	
• To evaluate the safety and tolerability of dabigatran etexilate or rosuvastatin in combination with lasmiditan in healthy participants • To evaluate the pharmacokinetics of lasmiditan and M8	• A summary of the number of treatment-emergent adverse events and serious adverse events • C_{max}, t_{max}, and AUC(0-∞) of lasmiditan and M8

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; BCRP = breast cancer resistance protein; C_{max} = maximum observed drug concentration; P-gp = p-glycoprotein; t_{max} = time of maximum observed drug concentration.

4. Study Design

4.1. Overall Design

This is a Phase 1, two-part, two-period, open-label study in healthy participants. Part 1 will study dabigatran P-gp DDI with lasmiditan. Part 2 will study rosuvastatin BCRP DDI with lasmiditan. Parts 1 and 2 will have a similar design, i.e., dabigatran etexilate or rosuvastatin administration alone in Period 1 (Day 1) followed by a brief washout, then lasmiditan on Days 8, 9, and 10 (Period 2) with coadministration of dabigatran etexilate or rosuvastatin with lasmiditan on Day 10. Each part will consist of different participants and the 2 parts may run in parallel. Participants for both Part 1 and Part 2 will be consented with a single consent form, and both genotyping and coagulation tests will be performed for both parts during screening. Part 2 will be prioritized to complete first due to an anticipated screen fail rate of ~50% secondary to genotype criteria. Once Part 2 has achieved last participant dosed, no further genotyping will be needed for LAIO screening. Participants who failed Part 2 screening due to genotyping only and have a normal coagulation profile will automatically be eligible for Part 1.

4.1.1. Number of Participants

Approximately 72 participants will be enrolled to Part 1 of the study to ensure that at least 62 evaluable participants complete that part. Approximately 32 participants will be enrolled to Part 2 to ensure that at least 28 evaluable participants complete that part. For the purposes of this study, a participant completes the study when all scheduled procedures shown in the Schedule of Activities (Section 1.3) have been finished.

4.2. Scientific Rationale for Study Design

The study has an open-label, fixed-sequence, 2-part design in which each subject receives either dabigatran etexilate or rosuvastatin alone (Parts 1 and 2, respectively), and lasmiditan alone for 2 consecutive days followed by lasmiditan co-administered with either dabigatran etexilate or rosuvastatin, allowing each subject to act as his/her own control for safety and PK comparisons. The washout period between dabigatran etexilate or rosuvastatin doses of 7 days is considered sufficient based on the half-life of dabigatran of 12 to 17 hours, and the half-life of rosuvastatin of approximately 19 hours. A 200-mg dose of lasmiditan was selected as it is the highest potential recommended dose for lasmiditan. Data from multiple doses of lasmiditan demonstrated that steady state was achieved by 48 hours after dose with no accumulation with once-daily dosing. Given that patients may take lasmiditan on consecutive days, 3-day dosing with lasmiditan is deemed to be appropriate.

Human BCRP (encoded by the gene ABCG2) is polymorphic. Participants with the c.421C>A and c.34G>A polymorphisms, specifically the c.34AA, c.421AA, and c.34GA/421CA genotypes, will be excluded because these genetic polymorphisms are associated with impaired BCRP activity (Furukawa et al. 2009; Keskitalo et al. 2009; Wan et al. 2015). Because the activity of BCRP is impaired with these participants, it would be anticipated that even complete inhibition of BCRP would not result in a substantial change in rosuvastatin exposure. Accordingly, excluding participants with these polymorphisms will ensure that the "worst-case" interaction between lasmiditan and rosuvastatin will be evaluated in this study.

The human organic anion-transporting polypeptide 1B1 (OATP1B1) transporter (also known as SLCO1B1) is also polymorphic. To evaluate worst-case interactions between lasmiditan and rosuvastatin, participants with the c.521TC or c.521CC polymorphisms will be excluded from this study because these genetic polymorphisms are associated with decreased transporting activity of OATP1B1 (Niemi et al. 2011) and higher plasma rosuvastatin concentrations (Crestor Prescribing Information, 2020).

4.2.1. Participant Input into Design

Throughout this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, either as a recipient of an investigational intervention or as a control. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials.

4.3. Justification for Dose

Dabigatran etexilate is currently approved in the US to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of deep venous thrombosis and pulmonary embolism, and to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism (Pradaxa Prescribing Information, 2010). The recommended dose for dabigatran etexilate is 150 mg twice daily for patients with creatinine clearance >30 mL/min (Pradaxa Prescribing Information, 2010). Single oral doses of 10 to 400 mg dabigatran etexilate have been administered to healthy participants and were well tolerated (Stangier et al. 2008). Coadministration of dabigatran etexilate with lasmiditan may increase dabigatran exposure. The selected 150-mg dose for this study should provide adequate plasma dabigatran concentrations to address the study objectives with minimal risk of AEs (Härtter et al. 2013).

Rosuvastatin is currently approved in the US as an adjunct to diet for the treatment of adult patients with primary hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia or primary dysbetalipoproteinemia (Type III hyperlipoproteinemia), and for the slowing the progression of atherosclerosis, risk reduction of myocardial infarction, stroke, and arterial revascularization procedures in patients without clinically evident chronic heart disease, but with multiple risk factors (Crestor Prescribing Information, 2020). Rosuvastatin is commonly administered to adults at an oral dose of 5 to 40 mg once-daily, with the majority of the clinical DDI or pharmacogenetic studies conducted using a 10- or 20-mg dose (Lee et al. 2015; Crestor Prescribing Information, 2020). Rosuvastatin administered orally at a dose of 10 mg is suggested as a good clinical probe for both hepatic and intestinal BCRP function (Lee et al. 2015). Coadministration of rosuvastatin with lasmiditan may increase rosuvastatin exposure. The 10-mg rosuvastatin dose selected for this study should provide adequate plasma rosuvastatin concentrations to address the study objectives with minimal risk of AEs.

The dose level of 200 mg is the highest approved for lasmiditan. Doses up to 400 mg have been well tolerated in previous studies in healthy participants.

The doses will be administered at approximately the same time on each treatment day. The actual time of all dose administrations will be recorded in the participant's electronic case report form (CRF).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study shown in the Schedule of Activities (SoA) with sufficient PK for analysis.

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 SoA for the last participant in the trial globally.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG).

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only, and not continuously throughout the trial.

Screening may occur up to 45 days prior to enrollment. Participants who are not enrolled within 45 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, repeat the following screening tests and procedures: clinical laboratory assessments and vital signs.

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 at screening. Continued eligibility will be assessed through serum pregnancy (females only) on the day of admission to the CRU.

Type of Participant and Disease Characteristics

1. must be aged 21 to 70 years, inclusive, at the time of signing the informed consent
2. have a body mass index of 18.5 to 35.0 kg/m2, inclusive, at the time of screening
3. who are overtly healthy as determined through medical evaluation including medical history, physical examination, and vital signs
4. have clinical laboratory test results within normal reference range for the population or CRU or results with acceptable deviations that are judged to be not clinically significant by the investigator (for example, estimated glomerular filtration rate >60 ml/min/1.73m^2 and liver function tests <2x ULN)
5. have a hemoglobin level of ≥12.5 g/dL for males or ≥11.4 g/dL for females at the time of screening
6. have venous access sufficient to allow for blood sampling as per the protocol
7. are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

Sex

8. 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.

Male participants:

- are not required to adhere to contraceptive requirements

Female participants:

- Female participants of childbearing potential (see Appendix 10.4) who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- Female participants of childbearing potential, who are not abstinent as described earlier, must agree to use a highly effective method of contraception (i.e., one with less than 1% failure rate) such as combination or oral contraceptives, implanted/injected contraceptives, intrauterine devices, or sterile partner until 30 days after the last dose of study medication.
- Female participants not of childbearing potential are not required to use contraception. This includes females who are:
  - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or congenital anomaly (e.g., Müllerian agenesis)
  - postmenopausal as defined in Appendix 10.4.

Informed Consent

9. capable of giving signed informed consent as described in Appendix 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

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

Medical Conditions

1. have a positive pregnancy test at screening or Day -1 of each period
2. are planning to become pregnant during the study or within 1 month of study completion
3. are women who are lactating
4. have known allergies to lasmiditan, dabigatran, rosuvastatin-related compounds or any components of the formulation of lasmiditan, dabigatran, rosuvastatin, or a history of significant atopy
5. a history of significant allergic reactions to medications or food products
6. have an abnormal blood pressure and/or pulse rate as determined by the investigator
7. clinically significant abnormalities on ECG as determined by investigator
8. have a history or presence of cardiovascular, respiratory, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the

study interventions; or of interfering with the interpretation of data. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable

9. show a history of central nervous system conditions such as strokes, transient ischemic attacks, significant head trauma, seizures, central nervous system infections, migraine, brain surgery, or any other neurological conditions that, in the opinion of the investigator, increase the risk of participating in the study
10. have a history or presence of neuropsychiatric disease (e.g., manic depressive illness, schizophrenia, depression) considered as clinically significant by the investigator
11. are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk of suicide
12. have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) **or** have answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS, **and** the ideation or behavior occurred within the past month
13. regularly use known drugs of abuse
14. show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies
15. presence of hepatitis B surface antigen at screening or within 6 months prior to first dose of study intervention
16. positive hepatitis C antibody test result at screening or within 6 months prior to first dose of study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained
17. positive hepatitis C RNA test result at screening or within 6 months prior to first dose of study intervention. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing
18. blood donation of 450 mL or more, or participation in a clinical study that required a blood volume of 400 mL or more since the last study visit within the past 3 calendar months.
19. have any medical conditions, medical history, or are taking any medications that are contraindicated in the dabigatran etexilate or rosuvastatin label

Prior/Concomitant Therapy

20. have participated, within the past 30 days of admission, in a clinical study involving any study intervention. If the previous study intervention has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed
21. have previously completed or withdrawn from this study or any other study investigating lasmiditan, and have previously received the investigational product
22. use of monoamine oxidase-A inhibitors and other drugs associated with serotonin syndrome (i.e., selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and 5-HT1 agonists) within the 3 months prior to the first dosing occasion

23. are intending to use over-the-counter or prescription medication, including dietary supplements, traditional medicines, and herbal supplements, within 14 days prior to dosing and until study discharge (apart from occasional acetaminophen, hormonal contraception, or hormone replacement therapy)

Prior/Concurrent Clinical Study Experience

24. are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

Other Exclusions

25. have an average weekly alcohol intake that exceeds 21 units per week (males aged ≤65 years) and 14 units per week (females [and males aged >65 years); 1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirit(s), or have a positive ethanol test at screening or admission
26. are unwilling to stop alcohol consumption 48 hours prior to admission in Periods 1 and 2, and while resident at the CRU. At all other times, participants must agree to consume no more than 2 units per day
27. are smokers of more than 10 cigarettes or e-cigarettes, or 3 cigars or 3 pipes per day, and are unable to refrain from smoking while resident at the CRU
28. consume excessive amounts of coffee, tea, cola, or other caffeinated beverages per day. Excessive amount is defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine)
29. currently use or show evidence of substance abuse (including alcohol abuse) or dependence within the past 6 months based on history at screening visit
30. inability to comply with the dietary regimen of the clinical research center
31. are Lilly employees or are an employee of any third-party involved in the study who require exclusion of their employees.
32. are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
33. in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

Part 1 Only (Dabigatran etexilate arm)

34. have known bleeding disorder including prior personal or familial history of abnormal bleeding, hereditary or acquired coagulation or platelet disorder or abnormal coagulation test (prothrombin time/international normalized ratio [INR] or partial thromboplastin time/activated partial thromboplastin time greater than upper limit of normal [ULN]) result at screening

Part 2 Only (Rosuvastatin arm)

35. have c.34AA, c.421AA, or c.34GA/421CA genotypes of ABCG2 as determined through genotyping

36. have c.521TC or c.521CC genotypes as determined through genotyping

5.3. Lifestyle Considerations

1. Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study

5.3.1. Meals and Dietary Restrictions

1. During each confinement period, participants will consume only food and beverages that are provided to them by the CRU staff. Standard meals (e.g., breakfast, lunch, dinner, and snack) will be provided to the participants while resident at the CRU.
2. Dabigatran, rosuvastatin, and lasmiditan will be administered after an overnight fast of at least 8 hours. In the morning of each treatment day, participants will abstain from water 1 hour before and after dosing (except for water given with the dose). Participants will remain fasting for approximately 3 hours postdose, at which time a meal will be served.

5.3.2. Caffeine, Alcohol, and Tobacco

1. During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
2. During each dosing session, participants will abstain from alcohol for 48 hours prior to admission until after collection of the final PK and/or pharmacodynamic sample.
3. Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the CRU.

5.3.3. Activity

1. Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention.

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. While rescreening, all screening tests and procedures should be repeated: Individuals may be rescreened up to 1 time. The interval between screening and rescreening should be at least 1 week. Each time rescreening is performed, the individual must sign a new ICF. Repeating laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening. Participants who are deemed a screen failure for Part 1 may still be considered eligible for Part 2 (or vice versa) if all eligibility criteria are met (e.g. if a participant is excluded from Part 2 due to exclusion criteria 35 or 36, they may still be enrolled in Part 1).

6. Study Intervention

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

6.1. Study Intervention(s) Administered

This study involves a comparison of dabigatran etexilate administered once orally with dabigatran etexilate and lasmiditan administered once orally. This study also involves a comparison of rosuvastatin administered once orally with rosuvastatin and lasmiditan administered once orally. Table LAIO.1 shows the treatment regimens.

Table LAIO.1. Study Interventions Administered

Study Intervention	Lasmiditan	Dabigatran etexilate	Rosuvastatin
Dosage Formulation	Tablet	Capsule	Tablet
Unit dose strength(s)/Dosage Level(s)	(2 × 100-mg) tablet/ 200-mg lasmiditan	150-mg capsule	10-mg tablet
Route of Administration	Oral	Oral	Oral
Dosing instructions	2 tablets taken on Days 8, 9, and 10	1 capsule taken on Day 1 and 1 capsule taken on Day 10	1 tablet taken on Day 1 and 1 tablet taken on Day 10

6.1.1. Administration Details

For the dabigatran etexilate cohort, a single oral dose of dabigatran etexilate 150 mg will be administered in the morning of Period 1 (Study Day 1). On the morning of Study Days 8 and 9 (Period 2), a dose of lasmiditan 200 mg will be administered. On the morning of Study Day 10 (Period 2), a single dose of dabigatran etexilate 150 mg and lasmiditan 200 mg will be administered. All treatments should be administered orally with approximately 240 mL of room temperature water in the morning to the participants in a sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

For the rosuvastatin cohort, a single oral dose of rosuvastatin 10 mg will be administered in the morning of Period 1 (Study Day 1). On the morning of Study Days 8 and 9 (Period 2), a dose of lasmiditan 200 mg will be administered. On the morning of Study Day 10 (Period 2), a single dose of rosuvastatin 10 mg and lasmiditan 200 mg will be administered. All treatments should be administered orally with approximately 240 mL of room temperature water in the morning to the participants in a sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions 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 CRU staff may supply or administer study intervention. All study interventions 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 CRU 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. The investigator or designee will return all unused study interventions to Lilly or its designee at the end of the study.
5. Note: In some cases, sites may destroy the material if, during the CRU selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. There is no bias as the primary endpoint is PK and objective in measure.

6.3.1. Packaging and Labeling

Each tablet of lasmiditan contains 100 mg of active ingredient and is provided as bulk supply in bottles. Dabigatran etexilate capsules (150 mg) and rosuvastatin tablets (10 mg) may be provided by the CRU or sponsor.

6.4. Study Intervention Compliance

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 CRU staff other than the person administering the study intervention. CRU personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, traditional medicines, and/or dietary 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
- Dosage information including dose and frequency for concomitant therapy of special interest

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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

Acetaminophen at doses of ≤3 g/24 hours, may be administered at the discretion of the investigator for the treatment of headache, etc. Contraceptive medication is permitted as per the inclusion criteria. Hormone replacement therapy is also allowed. Use of statins is not allowed other than rosuvastatin administration as described in Section 1.3.

If the need for concomitant medication (other than acetaminophen, hormonal contraception, or hormone replacement therapy) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist (CP), clinical research physician (CRP), or designee. Any medication used during the course of the study must be documented.

6.6. Dose Modification

Dose modification will not be allowed during the study.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study 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.

Discontinuation of the study intervention for abnormal liver test results **should be considered** by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- alanine aminotransferase (ALT), aspartate aminotransferase (AST) >5X ULN
- ALT or AST >3X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or INR >1.5 or
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Participants who discontinue from study intervention due to the abnormal liver test results will undergo monitoring as described in Appendix 10.6.

In addition, study drug may be discontinued if participants

- answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
- answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant from the study.

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

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 (e.g., parents or legal guardian)

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

Discontinuation is expected to be uncommon. At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study intervention and from the study at that time. Enrolled participants who discontinue from the study without study intervention will not be required to attend the early discontinuation visit.

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 receiving study intervention unless there are extenuating circumstances that make it medically necessary for the participant to continue on study intervention. If the investigator and the sponsor CP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CP to allow the inadvertently enrolled participant to continue in the study with or without treatment with study intervention.

The documented approval must contain the benefit-risk assessment and a robust clinical justification that continuing in the study will not jeopardize the participant's safety.

All inadvertently enrolled participants will complete safety follow up as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the CRU. 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 10.1.

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.

- Section 1.3 lists the SoA, detailing the study procedures and their timing (including tolerance limits for timing).
- The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time has to be correctly recorded in the CRF. Failure or being late (i.e., outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (e.g., equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note.
- Appendix 10.2 lists the laboratory tests that will be performed for this study.
- Appendix 10.2.1 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.
- Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3)
- Blood pressure and pulse rate should be measured singly after at least 5 minutes supine. For each individual subject, the same cuff size should be used throughout the study for the measurements of blood pressure. The cuff should, when possible, be attached to the subject's dominant arm.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Where orthostatic measurements are required, participants should be supine for at least 5 minutes and then participants will stand, and standing blood pressure will be measured after 2 minutes; no longer than 3 minutes. If the subject feels unable to stand, supine vital signs only will be collected. Additional vital signs may be measured during each study period if warranted.

8.2.3. Electrocardiograms

- For each participant, a single 12-lead digital ECG will be collected according to the SoA. Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.
- Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.
- If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 10.2 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 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 10.2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event [SAE] or AE or dose modification), then the results must be recorded in the CRF.
- If a central vendor is used for the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, unless the safety laboratory test results may unblind the study.

8.2.5. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study.

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

- trends in safety data
- laboratory analytes including hematology and chemistry

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 10.6), including ALT, AST, ALP, TBL, and direct bilirubin, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 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 ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

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 (e.g., heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 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 ≥3x ULN with hepatic signs/symptoms*, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms*, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

*** Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.**

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined earlier, as well as tests for prothrombin time-INR; tests for viral hepatitis A,

B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, 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, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver test results during the study

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevation of TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study intervention due to a hepatic event

Note: the interval between the 2 consecutive blood tests should be at least 2 days.

8.2.5.2. Suicidal Ideation and Behavior Risk Monitoring

Lasmiditan is considered to be a central nervous system-active drug.

Participants being treated with lasmiditan should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

C-SSRS

C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group (Treatment of Adolescent Suicide Attempters) for

the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

8.3. Adverse Events and Serious Adverse Events

Product complaints are covered in Section 8.3.6.

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 or study (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 until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the start of intervention until the follow-up visit.

Medical occurrences that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event 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 patient has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving study intervention, 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 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE 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.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS.

If a suicide-related event is discovered during the C-SSRS but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

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 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed up 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 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward 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, if indicated, female partners of male participants will be collected after the start of study intervention and until follow-up visit.
- 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 10.4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Pregnancy (maternal or paternal exposure to study intervention) 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 10.4 to collect data on the outcome for both mother and fetus.

8.3.6. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.
Sponsor collects product complaints on study interventions and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

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

8.3.6.1. Time Period for Detecting Product Complaints

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

8.3.6.2. Prompt Reporting of Product Complaints to Sponsor

- Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the sponsor through email. If email is unavailable, then fax should be utilized.

8.3.6.3. Follow-up of Product Complaints

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

8.3.6.4. Regulatory Reporting Requirements for Product Complaints

- The investigator will promptly report all device-related product complaints to the sponsor to facilitate timely regulatory reporting.
- As required by local regulations, the investigator will report to their IRB/IEC any unanticipated adverse device effect (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

For the purposes of this study, and overdose of lasmiditan, dabigatran etexilate, or rosuvastatin is considered any dose higher than the dose assigned. There is no specific antidote for lasmiditan, or rosuvastatin.

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 until study intervention can no longer be detected systemically (at least 2 days).
3. document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. in the case of emergency uncontrolled bleeding as a direct consequence of dabigatran, urgent referral for treatment with idarucizumab should be considered.

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

At the visits and times specified in the SoA, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of lasmiditan, metabolite M8, rosuvastatin, and dabigatran. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

8.5.1. Bioanalysis

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

Concentrations of lasmiditan, metabolite M8, rosuvastatin, and dabigatran will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

Bioanalytical samples collected to measure study intervention concentrations will be retained for a maximum of 2 years following last participant visit for the study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

A blood or saliva sample for DNA isolation will be collected from participants.

See Appendix 10.5 for information regarding genetic research and Appendix 10.1.10 for details about sample retention and custody.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Not applicable for this study.

8.10. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

There is no direct control for multiplicity but both primary objective variables will be tested as co-confirmatory variables. All other tests and/or estimation statistics will not be confirmatory but will contribute to a body of evidence to support final conclusions.

No significant DDI for dabigatran or rosuvastatin will be concluded if the respective 90% confidence interval for AUC from time zero to infinity (AUC[0-∞]) and C_{max} is completely contained within the no-effect boundaries (0.80, 1.25). A description of each test is provided in Section 9.4.

9.2. Sample Size Determination

Approximately 72 participants will be enrolled to Part 1 of the study to ensure that at least 62 evaluable participants complete that part. With 62 participants, we expect the two 1-sided t-tests (TOSTs) for equivalence applied to the lognormal mean ratio to have a power of at least 80% for the AUC(0-∞) and C_{max} tests in Part 1. This assumes a nominal expected mean ratio of 1.05, a coefficient of variation (CV) of 39.3%, and a significance level of 0.05 of each 1-sided test when testing against an upper limit of 1.25 and a lower limit of 0.80. The tests will be displayed in the form of 90% confidence intervals, which are equivalent to the according TOST. The source of the CV is Boehringer Ingleheim bioequivalence study (EudraCT number 2007-005765-35), and the higher intrasubject CV observed in the second-generation dabigatran arm was chosen.

Approximately 32 participants will be enrolled to Part 2 to ensure that at least 28 evaluable participants complete that part. With 28 participants, we expect the two 1-sided t-tests for equivalence applied to the lognormal mean ratio to have a power of at least 80% for the AUC(0-∞) and C_{max} tests in Part 2. This assumes a nominal expected mean ratio of 1.05, a CV of 25.1%, and significance level of 0.05 of each 1-sided test when testing against an upper limit of 1.25 and a lower limit of 0.80. The tests will be displayed in the form of 90% confidence intervals which are equivalent to the according TOST. The source of the CV is Study AZEB, and the higher of the rosuvastatin AUC(0-∞) and C_{max} intrasubject CVs was chosen.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF
Enrolled	All participants assigned to treatment, regardless of whether they take any doses of study intervention, or if they took the correct treatment.
Safety	All participants assigned to dabigatran etexilate or rosuvastatin and who take at least 1 dose of 1 of those products. Participants will be analyzed according to the product they actually received.

Pharmacokinetic Analysis	All participants who receive at least 1 dose of dabigatran etexilate or rosuvastatin and have evaluable PK.

9.3.1. Study Participant Disposition

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

9.3.2. Study Participant Characteristics

The subject's age, sex, and other demographic characteristics will be recorded and summarized. Demographic characteristics may be considered in the interpretation of PK and safety analyses.

9.3.3. Treatment Compliance

The date and time of dosing will be recorded and listed.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Pharmacokinetic analyses will be conducted on data from all participants who receive at least 1 dose of lasmiditan and have evaluable PK. Statistical inference of PK parameters will utilize participants in the PK analysis population which have evaluable PK, both before and after the introduction of lasmiditan.

Safety analyses will be conducted for all enrolled participants who received at least 1 dose of dabigatran etexilate or rosuvastatin, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.1. Safety Analyses

9.4.1.1. Clinical Evaluation of Safety

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

The incidence of AEs for each treatment will be presented by severity and by association with study intervention as perceived by the investigator. Adverse events reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of study intervention-related SAEs will be reported.

9.4.1.2. Statistical Evaluation of Safety

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

9.4.2. Pharmacokinetic Analyses

9.4.2.1. PK Parameter Estimation

Pharmacokinetic parameter estimates will be calculated using standard noncompartmental methods. The primary PK parameters for analysis of dabigatran and rosuvastatin will be C_{max} and AUC(0-∞). Other noncompartmental parameters, such as $t_{1/2}$, apparent total body clearance of drug calculated after extravascular administration, and apparent volume of distribution during the terminal phase after extravascular administration, may be reported as appropriate. Noncompartmental PK parameters will also be calculated for lasmiditan and M8.

9.4.2.2. PK Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate drug interaction for dabigatran and rosuvastatin with lasmiditan. Log-transformed C_{max} and AUC(0-∞) parameters for dabigatran and rosuvastatin will be evaluated separately. The treatment differences will be back transformed to present the ratios of geometric means and the corresponding 90% confidence interval.

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% confidence intervals and p-values from the Wilcoxon test will be calculated.

The effect of polymorphisms in genes coding for certain transporters (e.g., ABCG2, ABCB1, ABCC2, SLCO1B3, NTCP, and SLCO2B1) on the magnitude of the interaction between rosuvastatin and lasmiditan may be explored. For each subject, the ratio of rosuvastatin exposures with and without concomitant lasmiditan exposures will be calculated. A graphical analysis of these ratios between participants with and without SNPs of interest is intended. Additional analyses may be conducted as warranted.

9.4.3. Pharmacodynamic Analyses

Not applicable for this study.

9.4.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable for this study.

9.4.5. Other Analyses

Analysis of C-SSRS Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (CSSRS [WWW]).

9.5. Interim Analyses

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

9.6. Data Monitoring Committee

No data monitoring committee is required for this study.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, relevant curriculum vitae, 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 or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.
- Some of the obligations of the sponsor will be assigned to a third-party organization.

10.1.2. Financial Disclosure

Investigators and subinvestigators 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 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act 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 re-consented 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 that 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. 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 (e.g., through 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 are 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.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF 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 CRU personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the CRU. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.
- To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:
    - provide instructional material to the CRUs, as appropriate.
    - provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
    - make periodic visits to the CRU.
    - be available for consultation and stay in contact with the CRU personnel through mail, telephone, or fax.

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 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 electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. 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 electronic transfers will be provided to the investigator

for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.7. 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 electronic CRF 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.

10.1.8. 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 CRU or terminate the study at any time for any reason at the sole discretion of the sponsor. CRUs will be closed upon study completion. A CRU 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 CRU by the sponsor or investigator may include but are not limited to:

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

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

10.1.9. 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.

10.1.10. Long-Term Sample Retention

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

Sample Type	Custodian	Retention Period After Last Patient Visit*
Long-term storage samples	Sponsor or Designee	15 years
PK	Sponsor or Designee	2 years
Genetics	Sponsor or Designee	15 years

*Retention periods may differ locally.

The sponsor has a right to retain a portion of submitted biopsy tissue. Archival blocks will be returned to the CRU. Slides and tissue samples collected on study will not be returned.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of this protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing

Investigators must document their review of each laboratory safety report.

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphate
Leukocytes (WBC)	Glucose (random)
Platelets	
Coagulation	
Prothrombin time (PT-INR)[a]	
Activated partial thromboplastin time (aPTT)[a]	
Differential WBC (absolute counts) of	Urea
Neutrophils	
Lymphocytes	
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
	Alkaline phosphatase (ALP)
Urinalysis[b]	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	Direct bilirubin
Protein	Creatinine
Glucose	
Ketones	
Bilirubin	
Urobilinogen	Hepatitis B surface antigen[c,d]
Blood	Hepatitis C antibody[c,d]
Nitrite	HIV[c,d]
Leukocytes	Pregnancy test (females only)
Microscopy[e]	FSH (if applicable)[c]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalization ratio; RBC = red blood cell; WBC = white blood cell.

a Performed at screening only.

b Performed at screening, follow-up and early discontinuation only.

c Performed at screening only.

d Test may be waived if previously performed within 6 months before screening, with reports available for review. Optional hepatitis C RNA testing may be performed.

e Microscopy to be performed at the local safety laboratory if clinically indicated, per investigator's discretion.

10.2.1. Blood Sampling Summary

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

Protocol H8H-MC-LAIO Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples (Part 1)	Part 1 (Dabigatran – etexilate) Total Volume (mL)	Number of Blood Samples (Part 2)	Part 2 (Rosuvastatin) Total Volume (mL)
Screening tests[a]	23.4	1	23.4	1	23.4
Clinical laboratory tests[a]	8	5	40	5	40
Pharmacokinetics – Lasmiditan	2	15[b]	30	15[b]	30
Pharmacokinetics – Dabigatran (Part 1)	2	31[b]	62	--	--
Pharmacokinetics – Rosuvastatin (Part 2)	2	--	--	33[b]	66
Blood discard for cannula patency	0.3	29	8.7	29	8.7
Pharmacogenetics	10	1	10	1	10
Transporter genotyping[c]	10	1	10	1	10
Total			184.1		188.1
Total for clinical purposes			190		190

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

[b] Includes additional 3 samples, if required. No more than 3 additional samples may be taken in the study for PK (total includes combined lasmiditan, dabigatran, and rosuvastatin PK samples).

[c] Participants for both Part 1 and Part 2 will be consented with a single consent form, and genotyping will be performed for both parts during screening. Part 2 will be prioritized to complete first. Once Part 2 has achieved last patient dosed, no further genotyping will be needed for screening.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign 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 overdoses 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 that 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:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to 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.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the

participant or may require medical or surgical intervention to prevent 1 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 the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The investigator will consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used while determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor. • 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. • The investigator or site must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible. • Additionally, the investigator or site must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed up with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

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

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the 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: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female is defined as, women with:
   - A woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed through operative note; or
   - A woman aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or
   - A woman aged 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
   - A woman aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy

* Women should not be taking medications during the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

Contraception Guidance:

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 up 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 up 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 poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from receiving the study intervention, follow the standard discontinuation process and continue directly to the follow-up phase.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 8.2.5.1 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 patient 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)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin G (quantitative)
HAV total antibody	Immunoglobulin M (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[b]	Anti-actin antibody[c]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA[b]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

[a] This is not required if anti-actin antibody is tested.
[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.
[c] This is not required if anti-smooth muscle antibody (ASMA) is tested.
[d] Assayed by investigator-designated local laboratory ONLY; no central testing is available.

Evaluation of patients with treatment-emergent abnormal hepatic biochemical tests during a clinical trial*

Test/Procedure:	Rationale	Action
Close Hepatic Monitoring		
Clinical Chemistry: Total bilirubin Direct bilirubin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST)[a] Gamma-glutamyl transferase (GGT) Creatine kinase (CK)	All: Routine follow-up CK: Muscle injury/rhabdomyolysis	Utilize a Hepatic Monitoring central laboratory collection kit and select Clinical Chemistry
Hematology Hemoglobin Hematocrit Erythrocytes (RBCs – red blood cells) Leukocytes (WBCs – white blood cells) Differential: Neutrophils, segmented Lymphocytes Monocytes Basophils Eosinophils Platelets Cell morphology (RBCs and WBCs)	Infection	Utilize a Hepatic Monitoring central laboratory collection kit and select Hematology
Medical History:[b,c] Symptoms Co-existing medical conditions Concomitant medications Dietary and nutritional supplements Exercise (excessive) Muscle injury Alcohol consumption Illicit substances	Used to evaluate/rule out: Systemic infection or sepsis Ischemic or congestive hepatic injury Gallstone disease Alcoholic liver disease Muscle injury/rhabdomyolysis Acetaminophen toxicity Drug-induced liver injury (DILI) due to another drug, herbal or dietary substances	If findings are clinically significant, report as an adverse event.
Hepatitis A Virus (HAV) Testing: HAV total antibody HAV IgM antibody	Used to evaluate/rule out: Acute Hepatitis A virus (HAV) infection	Utilize a Hepatic Monitoring central laboratory collection kit and select Hepatitis A (HAV)
Hepatis B Virus (HBV) Testing: Hepatitis B surface antigen (HBsAg) Hepatitis B surface antibody (anti-HBs) Hepatitis B core total antibody (anti-HBc) Hepatitis B core IgM antibody Hepatitis B core IgG antibody HBV DNA	Used to evaluate/rule out: Acute or exacerbation of chronic Hepatitis B virus (HBV) infection.	Utilize a Hepatic Monitoring central laboratory collection kit and select Hepatitis B

Hepatis C Virus (HCV) Testing:[d,e] HCV antibody HCV RNA	Used to evaluate/rule out: Acute or exacerbation of chronic hepatitis C virus (HCV) infection.	Utilize a Hepatic Monitoring central laboratory collection kit and select Hepatitis C
Hepatitis E Virus (HEV) Testing:[f] HEV IgG antibody HEV IgM antibody HEV RNA	Used to evaluate/rule out: Acute hepatitis E virus (HEV) infection.	Utilize a Hepatic Monitoring central laboratory collection kit and select Hepatitis E
Anti-nuclear antibody (ANA) Anti-smooth muscle antibody (ASMA) Anti-actin antibody Immunoglobulin A Immunoglobulin G Immunoglobulin M	Used to evaluate/rule out: Autoimmune hepatitis	Utilize a Hepatic Monitoring central laboratory collection kit and select only the specific test/s required.
Hepatobiliary Imaging:[b,c] Ultrasonography CT scan MRI MRCP[g] ERCP[g]	Used to evaluate/rule out: Biliary obstruction Pancreatitis Gallstones Portal-vein/hepatic vein thrombosis Hepatic metastasis	Performed locally. If findings are clinically significant, report as an adverse event.
Comprehensive Hepatic Monitoring		
Coagulation: Prothrombin time, INR (PT-INR)	Used to evaluate/rule out: Suspected liver failure, for patients with elevated total bilirubin level	Utilize a Hepatic Monitoring central laboratory collection kit
Epstein-Barr Virus (EBV) Testing: EBV antibody EBV DNA **Cytomegalovirus (CMV) Testing:** CMV antibody CMV DNA **Herpes Simplex Virus (HSV) Testing:** HSV (Types 1 and 2) antibody HSV (Types 1 and 2) DNA	Used to evaluate/rule out: Epstein-Barr virus (EBV) or Hepatic injury due to cytomegalovirus (CMV), or Herpes simplex virus (HSV) infection.	Utilize a Hepatic Monitoring central laboratory collection kit and select only the specific test/s needed.
Liver biopsy[h]	Used to evaluate/rule out: Autoimmune hepatitis (AIH)	If findings are clinically significant, report as an adverse event.
Additional Hepatic Monitoring Tests		
Alkaline phosphatase isoenzymes	Used to evaluate/differentiate: Elevated alkaline phosphatase origination from bone or liver	Utilize a Hepatic Monitoring central laboratory collection kit
Liver kidney microsomal type 1 (LMK-1) antibody	Used to evaluate: Autoimmune hepatitis	Utilize a Hepatic Monitoring central laboratory collection kit
Urine Chemistry: Ethyl glucuronide (EtG)[i] **Other Chemistry:** Phosphatidylethanol (PEth)[j]	Used to evaluate: Alcoholic liver disease	Utilize a Hepatic Monitoring central laboratory collection kit
Other Chemistry: Acetaminophen Acetaminophen protein adducts	Used to evaluate: Acetaminophen toxicity	Utilize a Hepatic Monitoring central laboratory collection kit
Ethyl Alcohol (EtOH)	Used to evaluate recent alcohol consumption	Utilize a Hepatic Monitoring central laboratory collection kit

Haptoglobin	Used to evaluate a diagnosis of hemolysis	Utilize a Hepatic Monitoring central lab collection kit
Cardiology consult[b] Electrocardiogram Echocardiogram Vital Signs: Blood pressure Pulse	Used to evaluate: Ischemic or congestive hepatic injury	Performed locally. If findings are clinically significant, report as an adverse event.
Urine Chemistry: Drug screen	Used to evaluate: Hepatotoxicity due to cocaine, opiates, and other illicit substances	Utilize a Hepatic Monitoring central laboratory collection kit
Hepatitis D Virus (HDV) Testing: HDV antibody	Used to evaluate/rule out: Acute hepatitis D virus (HDV) infection.	Utilize a Hepatic Monitoring central laboratory collection kit and only select required test needed.
Microbiology: Cultures: Blood Urine	Used to evaluate/rule out: Sepsis or systemic infection	Perform locally. If findings are clinically significant, report as an adverse event.
Slit lamp eye examination (Kayser-Fleisher rings) Genetic evaluation	Used to evaluate/rule out: Wilson's disease	Perform locally. If findings are clinically significant, report as an adverse event.
Other Chemistry: Ceruloplasmin Copper	Used to evaluate/rule out: Wilson's disease	Utilize a Hepatic Monitoring central laboratory collection kit

Abbreviations: CT = computed tomography; ERCP = endoscopic retrograde cholangio-pancreatography; INR = international normalized ratio; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; PT = prothrombin time.

[a] Serum AST typically (although not always) is higher than ALT.

[b] Extent and type of work-up may vary with patient's history, severity of liver injury, underlying disease, and geography.

[c] Based on medical history and clinical judgment.

[d] If anti-HCV positive, HCV RNA is required to confirm HCV infection.

[e] Acute hepatitis C may be anti-HCV negative but HCV RNA positive.

[f] If anti-HEV IgM positive, consider confirmation with HEV RNA by nested polymerase chain reaction.

[g] If cholestatic injury, MRCP or ERCP may be recommended.

[h] A liver biopsy is needed to confirm a diagnosis of AIH.

[i] Alcohol consumption in the past 3 to 5 days.

[j] Alcohol consumption in the past 3 weeks.

* This tool is to be used by the clinical research unit for reference during the evaluation of a patient who met hepatic monitoring criteria based on laboratory results and clinical judgment for a suspected liver injury during protocol participation.

10.7. Appendix 7: Abbreviations

Term	Definition
$5\text{-}HT_{1F}$	5-hydroxytraptamine 1F
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC(0\text{-}\infty)$	area under the concentration versus time curve from time zero to infinity
BCRP	breast cancer resistance protein
C_{max}	maximum observed drug concentration
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, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
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.
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.

FDA	Food and Drug Administration
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
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.
IRB	Institutional Review Board
OATP	organic anion-transporting polypeptide
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
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
P-gp	p-glycoprotein
PK	pharmacokinetics
SAE	serious adverse event
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.
SNP	single nucleotide polymorphism
SoA	Schedule of Activities
$t_{1/2}$	half-life associated with the terminal elimination phase
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.

t_{max}	time of maximum observed drug concentration
TOST	two 1-sided t-test
ULN	upper limit of normal

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