Protocol H8H-MC-B006

Observational Cohort Study of Lasmiditan Exposure and Motor Vehicle Accidents in the United States

Confidential Information

Protocol Electronically Signed and Approved by Eli Lilly: approval date provided below.

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Post-Authorisation Safety Study (PASS) Information

Title	Observational Cohort Study of Lasmiditan Exposure and Motor Vehicle Accidents in the United States
Study identifier	Protocol H8H-MC-B006
Version identifier	Version 1.0
Date of last version	N/A
EU PAS Register No	EUPAS1000000347
Active substance	Lasmiditan Succinate (ATC code: NO2CC08)
Medicinal product(s)	Lasmiditan tablets 50 mg, 100 mg, 200 mg
Product reference	LY573144
Procedure number	Not applicable
Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	A review of published literature has not identified any available data regarding the risk of motor vehicle accident (MVAs) among users of lasmiditan in a real-world setting. It is, therefore, important to conduct a real-world study to characterise the risk of MVAs among participants who have used lasmiditan to treat acute attacks of migraine. Primary objective: • To describe baseline participant characteristics, and to compare the hazards of self-reported MVAs for which the participant was the driver, between 3 treatment strategies: 1) use of lasmiditan exclusively or in conjunction with other acute anti-migraine migraine medication for up to one year (Lasmiditan Group); 2) use of any non-lasmiditan prescribed acute anti-migraine medication (see Annex 3) for up to one year (Other Acute Medication Group); and 3) no use of any prescribed acute anti-migraine medication for up to one year (No Acute Medication Group). Secondary objectives: • To describe migraine experience and reported use of prescribed anti-migraine medication among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group) at baseline and during the follow-up period. • To describe the circumstances of MVAs, including migraine status at the time of MVA, self-reported use of prescribed anti-migraine medication up to 24 hours prior to MVA, preceding symptoms, as well as severity of the accident and related injuries, among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group).

	• To contextualise incidence rates of MVAs observed among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group) using the rates in the US general population as a frame of reference. • To describe the concordance between self-reported use of prescribed anti-migraine medication (acute and preventive) and prescription claims records among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group).
Country of study	United States
Author	PPD PhD, Epidemiologist, Agile Analytics, IQVIA

Abbreviations: ATC = Anatomical Therapeutic Chemical; EU = European Union; MVA = motor vehicle accident; PAS = post-authorisation study; PASS = post-authorisation safety study; US = United States.

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285
MAH contact person	Eli Lilly Global Patient Safety Pharmacoepidemiologist

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2. List of Abbreviations

Term	Definition
5-HT	serotonin
AE	adverse event
ASMD	absolute standardised mean difference
ATC	Anatomical Therapeutic Chemical Classification System
CGRP	calcitonin gene-related peptide
CI	confidence interval
DtP	direct-to-participant
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	ethical review board
EU	European Union
FDA	Food and Drug Administration
FMV	fair market value
GPP	Good Pharmacoepidemiology Practice
HCP	healthcare practitioner
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	hazard ratio
HRS	Health Research Space
ICD	International Classification of Diseases
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IRN	IQVIA Research Network
ISPOR	Professional Society for Health Economics and Outcomes Research
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MVA	motor vehicle accident
OTC	over-the-counter
PAS	post-authorisation study
PASS	post-authorisation safety study
PHI	protected health information
PI	principal investigator
PIRS	Primary Intelligence Research Service
Q	quartile

Term	Definition
QR	quick response
RUCA	Rural-Urban Commuting Area
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SD	standard deviation
TLAC	The Lilly Answers Center
US	United States
WHO	World Health Organization

3. Responsible Parties

Principal Investigator

PPD

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4. Abstract

Title

Observational Cohort Study of Lasmiditan Exposure and Motor Vehicle Accidents in the United States

Rationale and Background

Migraine is a common type of primary headache disorder which occurs in 12%-15% of the United States (US) population. Migraine is a debilitating chronic neurologic disease characterised by severe, intermittent headaches with associated symptoms including nausea, vomiting, phonophobia, and photophobia that can be severe, chronic, and disabling. Migraine is described as "chronic" when attacks occur on at least 15 days per month, and "episodic" when attacks are less frequent. A third of migraines are accompanied by aura that is characterised by visual, sensory, or speech/language disturbances.

Literature on the effect of migraine on driving performance is limited. A few reports suggest that having a diagnosis of migraine is associated with greater risk for injury from motor vehicle accidents (MVAs) but these studies suffer from a number of limitations. When exploring the commonly experienced symptoms of a migraine attack, many have the potential to negatively influence driving performance.

Lasmiditan is a serotonin (5-HT)1F receptor agonist approved by the Food and Drug Administration (FDA) for acute treatment of migraine with or without aura in adults. In a computer-based simulated driving study, driving impairment was observed with all doses of lasmiditan at 90 minutes after administration, and was resolved at 8 hours. Patients are advised not to drive or operate machinery until at least 8 hours after taking each dose of lasmiditan. Patients who cannot follow this advice should not take lasmiditan for that particular migraine attack.

Research Question and Objectives

A review of published literature has not identified any available data regarding the risk of MVAs among users of lasmiditan in a real-world setting. It is therefore important to conduct a real-world study to characterise the risk of MVAs among participants who have used lasmiditan to treat acute attacks of migraine, particularly in comparison to other participants diagnosed with migraine who have not used lasmiditan (i.e., have recently used other prescription medications, or not using any prescription medication). Additionally, insight into the risk of MVAs among participants treated with lasmiditan can be gained by contextualising the findings using the rates in the US general population as a frame of reference.

The study aims to address the following objectives:

Primary objectives:

- To describe baseline participant characteristics, and to compare the hazards of self-reported MVA for which the participant was the driver between 3 treatment strategies: 1) use of lasmiditan exclusively or in conjunction with other acute anti-migraine migraine medication for up to one year (Lasmiditan Group); 2) use of any non-lasmiditan prescribed acute anti-migraine medication (see Annex 3) for up to one year (Other Acute Medication

Group); and 3) no use of any prescribed acute anti-migraine medication for up to one year (No Acute Medication Group).

Secondary objectives:

- To describe migraine experience and reported use of prescribed anti-migraine medication among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group) at baseline and during the follow-up period.
- To describe the circumstances of MVAs, including migraine status at the time of MVA, self-reported use of prescribed anti-migraine medication up to 24 hours prior to MVA, preceding symptoms, as well as severity of the accident and related injuries, among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group).
- To contextualise incidence rates of MVAs observed among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group) using the rates in the US general population as a frame of reference.
- To describe the concordance between self-reported use of prescribed anti-migraine medication (acute and preventive) and prescription claims records among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group).

Study Design

This is an observational cohort study, aiming to compare the one-year risk of MVA associated with three treatment strategies of interest in patients with migraine (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group) in the US.

Self-reported use of prescribed acute anti-migraine medication will be utilised to assign treatment exposure category. The treatment strategies of interest are: 1) use of lasmiditan exclusively or in conjunction with other acute anti-migraine migraine medication for up to one year (Lasmiditan Group); 2) use of any non-lasmiditan prescribed acute anti-migraine medication for up to one year (Other Acute Medication Group); and 3) no use of any prescribed acute anti-migraine medication for up to one year (No Acute Medication Group). The outcome of interest is the first occurrence of self-reported MVA since enrolment, for which the participant was the driver. Participants will be followed-up from the time they meet all eligibility criteria (baseline) until the earliest of the following: outcome event, loss to follow-up (e.g., non-response of two consecutive surveys), participant withdrawal, deviation from assigned treatment strategy (e.g., treatment change), loss of eligibility or administrative end of study (one-year of follow-up).

Participants will be recruited through healthcare practitioner (HCP) referrals, leveraging the IQVIA Primary Intelligence Research Service (PIRS).

The study comprises 2 phases: Phase 1 includes development activities for the survey to be administered during Phase 2, and Phase 2 includes enrolment and prospective follow-up of study participants as well as validation of self-reported prescription medication data for a subset of participants in each treatment group.

Interested and potentially eligible participants will be provided a web-link to enrol in the study by their HCP. For Phase 1, participants will complete online screening and informed consent and schedule an interview through the IQVIA PIRS team. For Phase 2, all participants are sent into the IQVIA Health Research Space (HRS) study platform for their screening and subsequent enrolment. Both links to the online survey platform (Phase 1) and IQVIA HRS study platform (Phase 2) can be accessed on personal devices with internet connection such as phone, tablet or computer via secure web-link.

Phase 1: Survey development interviews

In Phase 1, 9 participants with migraine will be recruited to participate in one-on-one interviews to ensure both baseline and follow-up survey questions are relevant, easily understood, and can provide reliable and accurate results. Individuals who participate in Phase 1 are not eligible to participate in Phase 2. Phase 1 participants will be able to view the surveys interactively in the same format as they would appear in HRS, without creating an account or completing a profile. An institutional review board- (IRB-) approved standardised interview guide will be used to conduct the 60-90-minute interviews. Qualitative feedback will be solicited for each question and the questions that receive comments indicating they are not well understood or may not collect the intended type of responses will be modified based on the feedback.

Phase 2: Prospective surveys

Participants enrolled into Phase 2 of the study will create an HRS profile and complete a baseline survey assessing events in the past year and follow-up surveys are planned to subsequently be administered once every 30 days for 12 months.

Participants will be classified into study treatment groups based on their self-reported use of prescribed acute anti-migraine medication in the 30-day period before enrolment, independently of the self-reported use of prescribed preventive anti-migraine medication.

Data collected in the baseline surveys, will include demographics, migraine experience, use of prescribed anti-migraine medication, medical history, driving characteristics and self-reported MVAs history (for which the participant was the driver) in the past year.

Data collected every 30 days in follow-up surveys, will include any change in self-reported use of prescribed anti-migraine medication (acute and preventive) and concomitant medication potentially associated with MVA risk, recent migraine experience, self-reported MVAs (for which the participant was the driver) in the last 30-day period, circumstances of these MVAs (including migraine status, use of prescribed anti-migraine medication up to 24 hours prior the accident, symptoms immediately preceding the MVA and details on environmental factors including weather), severity and impact of the accident (including property damages, injuries and hospitalisation). Each time the monthly follow-up survey is administered to a given participant, the participant will be allotted a 7-day window to complete it.

For Phase 2, a validation of migraine diagnosis will be completed by the referring HCP.

Data agreement:

Approximately 60% of a targeted 1000 participants will be randomly selected in each treatment group (up to 600 in each treatment group) to describe the agreement between self-reported data on prescription migraine medication use (acute and preventive) and prescription claims data. Self-reported survey data on the use of prescription medication (acute and preventive) will be compared against pharmacy data obtained via linkage with ExamOne ScriptCheck. The data agreement will be assessed at two time points: once at baseline, and once at the end of the online survey data collection period described above.

Population

This study follows participants with migraine in the US. Detailed eligibility criteria are listed below.

Inclusion Criteria

The following criteria must be met to take part in the survey development interviews (Phase 1) and prospective surveys (Phase 2):

1. Participant must be at least 18 years old and younger than 75 years old at enrolment;
2. Participant must have a valid driver's licence that they received ≥1 year before enrolment†;
3. Participant must have access to a vehicle at the time of enrolment†, and confirm that they anticipate having access to a vehicle for the following 12 months;
4. Participant must confirm they have driven at least once during the 6 months prior to enrolment†;
5. Participant must provide informed consent to participate in this study;
6. Participant must be able to read and understand English;
7. Participant must currently reside in the US†;
8. Participant must self-report a migraine diagnosis with or without aura (for Phase 2, migraine diagnosis will be confirmed by the participant's health care practitioner); and
9. Participant must have access to a personal device with internet connection (such as phone, tablet, laptop or computer)

†These criteria must be met throughout follow-up as well.

In order to participate in the prospective study surveys (Phase 2), the following additional inclusion criteria must be met:

10. Participant must be willing to complete an online survey on driving and migraine experience, taking approximately 20 minutes to complete, once every 30 days for 12 months after the baseline survey; and
11. Participant must be willing to provide consent to access their anti-migraine medication prescription claims data from ExamOne ScriptCheck and allow HCP to confirm migraine diagnosis, completing the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Authorisation/Medical release Form.

Exclusion Criteria

Participants meeting the following criteria will be excluded from Phase 1 (survey development interviews):

1. Participants who report use of lasmiditan in the past 12 months.

Participants meeting the following criteria will be excluded from Phase 2 (enrolment and prospective study surveys):

2. Participants who participated in the interviews for the survey development qualitative study (Phase 1).

Variables

At participant screening for Phase 2, data related to participant eligibility and consent/HIPAA authorisation will be assessed and collected.

Participants enrolled into the Phase 2 study will complete a baseline survey assessing baseline characteristics via self-report as part of the primary study objective. The baseline assessment include participant demographics, medical history and migraine experience (e.g., comorbidities and history of anti-migraine medication use within the last year and in the past 30 days), driving characteristics, as well as self-reported MVAs for which the participant was the driver within the last 30 days and the last 12 months (including details such as perceived level of fault, time of the day, injuries and property damages) and circumstances of MVAs (e.g., migraine status at the time of MVA, use of anti-migraine medication and/or concomitant medication carrying a risk of MVA within 24 hours prior to MVA and preceding symptoms). The participant's HCP will confirm the diagnosis of migraine after baseline survey completion.

Additional variables will be collected via self-report using follow-up surveys administered every 30-days, for analysis of both the primary and secondary objectives. This includes recent migraine experience and use of anti-migraine medication in the past 30 days, driving characteristics, occurrence of MVAs for which the participant was the driver in the past 30 days, as well as circumstances of MVA, severity and related injuries.

Data Sources

Qualitative Survey Development Interviews

Nine participants with migraine, who do not report use of lasmiditan in the 12 months prior to enrolment will be recruited to participate in cognitive debriefing interviews, in which participants will be asked to read, complete, and provide their feedback on a series of survey questions, in order to identify the relevance and potential issues of the questions and/or their content. Interviews will be approximately 60 minutes in duration via video call and will be moderated by an IQVIA interviewer experienced in qualitative interviews. IQVIA will use secure teleconferencing capabilities to conduct and record the interview. Feedback from the survey development interviews will be used to inform the structure and wording of the Phase 2 baseline and prospective surveys, and to refine the tool as needed.

Direct-to-Participant Online Surveys

The primary data source for the study will be participant profiles and direct-to-participant online survey responses to baseline and follow-up surveys on participant health history (particularly migraine), driving characteristics, MVA occurrences and circumstances of MVAs (e.g., medication use prior to MVA, migraine status and preceding symptoms) collected electronically using IQVIA's HRS platform. To validate self-reported data on anti-migraine medication use (acute and preventive), ExamOne ScriptCheck prescription data extraction will operationally be performed twice: following the recruitment of the last participant and following the completion of the last survey by the last study participant.

ExamOne ScriptCheck Prescription Claims

ExamOne ScriptCheck is a data retrieval service utilised to verify participant pharmacy prescriptions and prescribed drug and dosage by providing the participant's last name, first name, sex, date of birth, phone number and residential address. ExamOne ScriptCheck prescription claims data on anti-migraine medications (preventive and acute) will be extracted for approximately 60% of participants in each treatment group (up to 600 participants in each treatment group) and will be linked to study data. These prescription claims will be compared to self-reported anti-migraine medication use. For each randomly selected participant, the data agreement will be assessed at two time points: once at baseline, and once at the end of the online survey data collection period.

HCP Validation of Migraine Diagnosis

For participants in Phase 2 of the study, self-reported diagnosis of migraine will be validated by contacting the referring HCP after participants complete a HIPAA authorisation/Medical Release Form. HCPs will be contacted by virtual site staff and asked to confirm whether the participant has a diagnosis of migraine.

Benchmark Comparison

Data on national MVA rates will be accessed via the National Highway Traffic Safety Administration's annual Traffic Safety Facts report to contextualise incidence rates of MVAs observed among study participants using the rates in the US general population as a frame of reference. The report from the same year of study enrolment or the closest year available at the time of data analysis will be used.

Study Size

Assuming that the incidence of MVAs in the general population (3%) can be expected in any of the comparison groups, a sample of 793 participants per treatment group would provide 80% power at 5% level of significance for detection of a hazard ratio (HR) of 2.0. Given this is a safety study, no alpha correction method will be used. In order to achieve this sample size, an additional 20% will be targeted for enrolment in anticipation of participant dropout (992 per treatment group). Thus, a number of 1000 participants per treatment group, is targeted to be enrolled into the study. Due to a limited source population of lasmiditan-treated patients, challenges are anticipated for the recruitment of participants in the Lasmiditan Group. The number of enrolled participants exposed to lasmiditan in both the 12-months and 30-days periods prior to enrolment will inform on the

feasibility of conducting the planned comparative analysis using the available sample size and observing the above-listed effect sizes.

Data Analysis

An interim descriptive analysis will provide a baseline assessment of participants treated with lasmiditan, in the 12 months and 30 days pre-baseline periods, including treatment patterns, driving patterns and self-reported MVAs experience. All variables collected for screening and at baseline will be summarised for each treatment group (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group) based on the self-reported use of prescribed acute anti-migraine medication in 12 months and 30 days pre-baseline periods. This interim descriptive analysis will summarise demographic characteristics, medical history and migraine experience, driving characteristics, and the number of accidents before enrolment and their circumstances, including migraine status, anti-migraine medication use in the 24-hour prior period and symptoms preceding MVAs.

The relative hazard of self-reported MVAs during follow-up will be assessed in the final analysis, comparing Lasmiditan Group to Other Acute Medication Group and to No Acute Medication Group, if the required sample size is achieved. Additionally, for self-reported MVAs in the observational period, descriptive statistics will be performed to summarise participants' driving characteristics, severity of the MVA and related injuries, as well as circumstances of the MVA (e.g., migraine status at the time of MVA, use of prescribed anti-migraine medication within 24 hours prior, preceding symptoms, concomitant medication use carrying a risk of MVA, environmental factors) and will be presented per treatment group.

Pharmacy claims records will be reviewed for approximately 60% of enrolled participants (up to 600 participants randomly selected in each treatment group), and the consistency with self-reported anti-migraine medication use will be descriptively reported with relevant agreement statistics, such as percentage of agreement, percentage of disagreement and Kappa statistics. Further details of the planned analyses will be documented in the statistical analysis plan (SAP).

Categorical data will be summarised as frequency counts and percentages (%). Continuous data will be summarised using the mean, standard deviations (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of non-missing and missing observations.

Missing data will be mitigated by design by requiring answers on all survey questions prior to each participants' submission.

Milestones – Start of data collection (March 2025), interim report submission (March 2026), and final study report submission (December 2027).

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned date
Registration in the EU PAS register	17 October 2024
Start of data collection	04 March 2025
Interim report submission	31 March 2026
End of data collection	04 September 2026
Final report of study results submission	31 December 2027

Abbreviations: EU = European Union; PAS = post-authorisation study; TBD = to be determined.

7. Rationale and Background

Migraine is a common type of primary headache disorder which occurs in 12%-15% of the United States (US) population (Burch et al. 2019). Global estimates are generally higher and it ranks fourth among the world's causes of disability, and second among young women according to findings from the Global Burden of Disease 2021 (Steiner et al. 2024). Migraine is a debilitating chronic neurologic disease characterised by severe, intermittent headaches with associated symptoms including nausea, vomiting, phonophobia, and photophobia that can be severe, chronic, and disabling. Migraine is described as "chronic" when attacks occur on at least 15 days per month, and "episodic" when attacks are less frequent.

The migraine attack phase usually lasts between 4–72 hours. A postdromal phase follows and usually lasts less than 12 hours with symptoms including asthenia, fatigue, somnolence, difficulty with concentration, photophobia, and irritability. A third of migraines are accompanied by aura that is characterised by visual, sensory, or speech/language disturbances. Vestibular migraine, occurring in a small subset of patients, is associated with moderate or severe vestibular symptoms including spontaneous, positional, and head motion- or visually-induced vertigo.

Literature on the effect of migraine on driving performance is limited. Findings from two population studies in New Zealand (Norton et al. 1997) and Canada (Vingilis and Wilk 2012) suggest that having a diagnosis of migraine vs not having a diagnosis of migraine is associated with a 50%-60% greater risk for injury from motor vehicle accidents (MVAs). Another study of older drivers (aged 65-79 years) found that individuals newly diagnosed with migraine had more than three times the odds of an MVA during the first year after diagnosis, but found no association between prevalent migraine and risk of MVA (DiGuiseppi et al. 2024). Nevertheless, published studies on the topic are scarce, suffer from a number of limitations, and do not provide MVA incidence rates among people with migraine (Tepper et al. 2020).

Lasmiditan is a serotonin (5-HT)1F receptor agonist indicated for the acute treatment of migraine with or without aura in adults, and approved on 11 October 2019 by the Food and Drug Administration (FDA), as randomised clinical trials (NCT02439320; NCT02605174) have demonstrated its efficacy for acute treatment of migraine. (Goadsby et al. 2019; Kuca et al. 2018) The recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed. In a computer-based simulated driving study, administration of single 50 mg, 100 mg, or 200 mg doses of lasmiditan was associated with impairment in simulated driving performance at 90 minutes after administration and was resolved at 8 hours. (Pearlman et al. 2020) Therefore, patients are advised not to drive or operate machinery until at least 8 hours after taking each dose of lasmiditan. Patients who cannot follow this guidance are advised not to take lasmiditan for that particular migraine attack; patients may not be able to assess their own driving competence and the degree of impairment caused by lasmiditan. (FDA 2019).

8. Research Question and Objectives

A review of published literature has not identified any available data regarding the risk of MVAs among users of lasmiditan in a real-world setting. As a result, conducting a real-world study to characterise the risk of MVAs among participants who have used lasmiditan to treat acute attacks of migraine, particularly in comparison to other participants diagnosed with migraine who have not used lasmiditan, will provide valuable information for patients and prescribers. Additionally, insight into the risk of MVAs among participants treated with lasmiditan can be gained by contextualising the findings using the rates in the US general population as a frame of reference.

This study aims to address the following objectives:

Primary objectives:

- To describe baseline participant characteristics and to compare the hazards of self-reported MVA for which the participant was the driver between 3 treatment strategies: 1) Use of lasmiditan exclusively or in conjunction with other acute anti-migraine migraine medication for up to one year (Lasmiditan Group); 2) Use of any non-lasmiditan prescribed acute anti-migraine medication (see Annex 3) for up to one year (Other Acute Medication Group); and 3) No use of any prescribed acute anti-migraine medication for up to one year (No Acute Medication Group).

Secondary objectives:

- To describe migraine experience and reported use of prescribed anti-migraine medication among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group) at baseline and during the follow-up period.
- To describe the circumstances of MVAs, including migraine status at the time of MVA, self-reported use of prescribed anti-migraine medication up to 24 hours prior to MVA, preceding symptoms, as well as severity of the accident and related injuries, among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group).
- To contextualise incidence rates of MVAs observed among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group) using the rates in the US general population as a frame of reference.
- To describe the concordance between self-reported use of prescribed anti-migraine medication (acute and preventive) and prescription claims records among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group).

9. Research Methods

9.1 Study Design

This is an observational cohort study, aiming to compare the one-year risk of MVA associated with three treatment strategies of interest, in patients with migraine in the US. The comparative treatment strategies of interest, as well as other core elements of the study design, are described in Table 1. No visits, examinations, laboratory tests, or procedures are mandated or recommended as part of this study.

Table 1. Core Study Elements for The Primary Analysis using a 'Nested Trial' Approach

Eligibility Criteria	• Participant age is 18 to 74 years old at enrolment; • Participant has a valid driver's licence that they received ≥1 year before enrolment; • Participant has access to a vehicle at the time of enrolment and anticipates having access to a vehicle for the next 12 months (at enrolment); • Participant must confirm having driven at least once during the 6 months prior to enrolment; • Participant must provide informed consent to participate in this study; • Participant must be able to read and understand English; • Participant must currently reside in the US; • Participant must self-report a migraine diagnosis with or without aura at enrolment; • Participant must have access to a personal device with internet connection; • Willing to complete study surveys once every 30 days for 12 months at enrolment; and • Participant must be willing to provide consent to access their anti-migraine medication prescription claims data from ExamOne ScriptCheck and allow HCP to confirm migraine diagnosis, completing the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Authorisation/Medical release Form.
Treatment strategies	1. Use of lasmiditan exclusively or in conjunction with other acute anti-migraine migraine medication for up to one year; 2. Use of any non-lasmiditan prescribed acute anti-migraine medication (see medications list in Annex 3) for up to one year; and 3. No use of any prescribed acute anti-migraine medication for up to one year. Self-reported use of prescribed acute anti-migraine medications will be utilised to assign treatment exposure category. The self-reported use of prescribed preventive anti-migraine medication will not be considered for treatment group classification

Outcome	Self-reported first occurrence of MVA for which the participant was the driver since study enrolment.
Follow-up	Start: Date(s)[a] participant meets all eligibility criteria (baseline survey) End: Earliest of the following events: • Outcome event, • Loss to follow-up (e.g., non-response of two consecutive surveys)[b], • Participant withdrawal, • Deviation from assigned treatment strategy (e.g., treatment change), • Loss of eligibility, and • Administrative end of study (one-year of follow-up).

Abbreviations: HCP = Healthcare Practitioner; HIPAA = Health Insurance Portability and Accountability Act; MVA = motor vehicle accident

[a] Participants may meet eligibility criteria at numerous calendar dates. The study design permits participants to enter the analytic cohort repeatedly (i.e., at each calendar date that participant is study-eligible) during the participant enrolment period (see Section 9.1 for a detailed description).

[b] Participants who are lost to follow-up will be censored at 67 days following the opening of their last survey (as participants are allotted 7 days to answer each monthly survey).

Data on potential confounders, treatments received, and occurrence of the outcome event over follow-up will be ascertained with a series of monthly surveys administered sequentially over the 12 months following enrolment (see Section 9.3.4). The initial (baseline) survey will collect additional information on potential confounders and treatments in the year prior to enrolment (see Section 9.3.3). To align with the primary research objective, only the first occurrence of MVA since study enrolment will serve as the outcome of interest for primary analysis.

Given that patients may be eligible for study entry at multiple calendar times, and that their eligibility may fluctuate over the course of the study (e.g., due to loss of access to a vehicle or driving privilege for one or more months), a 'nested trial' approach will be implemented (Danaei et al. 2013; Danaei et al. 2018). In this approach, the raw survey data collected from participants will be transformed into an analytic dataset as follows:

1. Select participants who are study-eligible on the first calendar day of study recruitment and assign their analytic 'time zero' to this day.

2. Assign each participant to one of the three treatment strategies of interest (see Table 1) based on their self-reported use of prescribed anti-migraine medications in the prior 30 days: participants who used lasmiditan at least once (Lasmiditan Group), participants who used another prescribed acute anti-migraine medication (includes, but is not limited to, triptans, ubrogepant [Ubrelvy], rimegepant [Nurtec], zavegepant [Zavzpret]; see Annex 3 for the complete list) at least once and did not use lasmiditan (Other Acute Medications Group), and participants who did not use any prescribed acute anti-migraine medication

(No Acute Medication Group). The self-reported use of prescribed preventive anti-migraine medication will not be considered for treatment group classification.

3. Collect and record each participant's self-reported and calculated confounder history prior to their analytic 'time zero' (see Section 9.7 for potential confounders of interest).

4. Define follow-up for each participant from analytic 'time zero' until the earliest of the following: outcome event, loss to follow-up (day 67 of non-response, corresponding to non-response on two consecutive surveys), participant withdrawal, deviation from assigned treatment strategy (e.g., treatment switch), loss of eligibility, or administrative end of study (one-year of follow-up).

5. Generate a counting-process formatted dataset for this 'nested trial' derived from longitudinal treatment, outcome, and confounder information assessed in Steps 1-4 (see Section 9.7.2.2.2.1 for example data structure).

6. Repeat Steps 1-5 above for each sequential calendar day in which participants will be recruited into the survey study.

7. Bind all datasets produced in Step 5 by row. This will serve as the analytic dataset for the primary analysis (see Section 9.7.2.2.2.1 for example data structure).

The 'nested trial' approach has several distinctive advantages. First, it permits greater statistical power by leveraging information following treatment changes in participants over follow-up. For example, if a participant switches treatment strategy from lasmiditan to other prescribed acute anti-migraine medication, that participant will contribute person-time to two separate 'trials' (each associated with a single treatment strategy), provided they remain study-eligible. Second, the approach allows the investigator to specify precise and dynamic treatment strategies of interest for comparison, while accounting for potential confounders that have changed since baseline enrolment in the survey study. Third, seasonality of MVA can be accounted for as data within each 'nested trial' is aggregated by calendar time. Fourth, time-varying and time-dependent factors can be accounted for easily with the data structure generated by this approach, including dynamic study eligibility and evolving confounder histories.

Self-reported survey data on prescription migraine medication use (acute and preventive) will be compared with pharmacy data (including prescribed drug and dosage), obtained via linkage with ExamOne ScriptCheck (additional information in Section 9.4.3) to describe concordance.

Participants for this study will be recruited through healthcare practitioner (HCP) referrals. This study will utilise IQVIA Primary Intelligence Research Service (PIRS) to identify and recruit HCPs providing care to the population of interest into a network of referring providers. The HCPs who opt into the study will be able to refer potentially eligible and interested participants with migraine.

The study comprises 2 phases: Phase 1 includes development activities for surveys planned to be administered during Phase 2; while Phase 2 includes prospective follow-up of study participants as well as validation of self-reported prescription medication data for a subset of participants in each treatment group. The study will be administered by one central virtual site managed by IQVIA and a central principal investigator (PI). Using a central PI delivery model is designed to leverage

one PI to provide oversight on the participants' rights, safety, and welfare, and ensure data quality and integrity. Additional details are described below.

Interested and potentially eligible participants will be provided a link to enrol in the study by their HCP. Screening will be conducted for both phases of the study. For Phase 1, patients will follow the link to an online Institutional Review Board- (IRB-) approved screener programmed through Confirmit to complete screening and enrol in the study. For Phase 2, all patients are sent into the IQVIA Health Research Space (HRS) study platform to enrol and upon successful screening, participants will continue through to the baseline survey. Both the link to the online screener platform (Phase 1) and IQVIA HRS study platform (Phase 2) can be accessed on personal devices with internet connection such as phone, tablet or computer via secure web-link. During the screening, the participants will be asked to confirm their eligibility based on the eligibility criteria outlined in Sections 9.2.1 and 9.2.2. After confirming eligibility via screening, participants will provide informed consent for the study via an online consent form (Phase 1) or directly in the HRS study platform (Phase 2).

9.1.1 Phase 1: Survey Development Interviews

In Phase 1, 9 patients with migraine will be recruited to participate in one-on-one interviews to ensure both baseline and follow-up survey questions are relevant, easily understood, and can provide reliable and accurate results. After completing screening and enrolling in the study Phase 1 as described previously, participants will use an online scheduler to choose an interview slot, which will be confirmed by the PIRS team via email. On the date of the interview, participants will be interviewed using a virtual interview platform. Interviews will be transcribed and results combined for all participants. Assuming that the literacy of eligible participants would not differ according to anti-migraine medication exposure, potential participants reporting use of lasmiditan in the preceding year will be referred to Phase 2 and will not be included in the survey development phase of this study.

In particular, the purposes of the survey development interviews are to capture how participants understand the questions, their understanding and context for the options and language, how they align them with their own experience of living with migraines and to assess the feasibility of recalling events over a period of time (e.g., recall of MVAs). Phase 1 participants will be able to view the surveys interactively in the same format as they would appear in HRS, without creating an account or completing a profile. An IRB-approved standardised interview guide will be used to conduct the 60-90-minute interviews. The interview approach is in line with recommended guidelines provided by Professional Society for Health Economics and Outcomes Research (ISPOR) Good Research Practices Task Force.

Qualitative feedback will be solicited for each question and the questions that receive comments indicating they are not well understood or may not collect the intended type of responses will be modified based on the feedback. This may include changes such as rephrasing the question or available responses, removing available options to be more concise, or adding available options. Responses from participants will be summarised and the sponsor will be consulted to review and confirm IQVIA’s recommended changes to the survey design.

The survey development interviews will be conducted among 2 waves of participants to allow revision of the survey based on the first set of interviews, as needed, and then to confirm the changes with the second set of interviews. The changes made in the survey between the two sets

of interviews will be documented, and feedback from both waves will be incorporated in the baseline and prospective follow-up surveys used in Phase 2. Individuals who participate in Phase 1 are not eligible to participate in Phase 2.

Additional details of the data collected in the survey development interview phase are provided in Section 9.4.1.

9.1.2 Phase 2: Prospective Surveys

Participants enrolled into Phase 2 of the study will create an HRS profile and complete a baseline survey assessing events in the past year and follow-up surveys are planned to subsequently be administered once every 30 days for 12 months.

Data collected in the baseline surveys will include demographics, migraine experience (including age at diagnosis, presence of aura, impact on daily life and average number of migraine attacks by month), use of prescribed anti-migraine medication, medical history (including use of concomitant medication potentially associated with MVA risk and comorbidities), driving characteristics and self-reported MVAs history (for which the participant was the driver) in the past year, as presented in Section 9.3.3. A validation of migraine diagnosis will be completed by the referring HCP after the baseline survey is completed by the participant.

Data collected every 30 days in follow-up surveys, will include any change in self-reported use of prescribed anti-migraine medication (acute and preventive) and concomitant medication potentially associated with MVA risk, recent migraine experience, self-reported MVAs (for which the participant was the driver) in the last 30-day period, circumstances of these MVAs (including not exclusively migraine status, use of prescribed anti-migraine medication 24 hours prior the accident, symptoms immediately preceding the MVA, details on environmental factors including weather), severity and impact of the accident (including property damages, injuries and hospitalisation), as presented in Section 9.3.4. Each time the monthly follow-up survey is administered to a given participant, the participant will be allotted a 7-day window to complete it.

Approximately 60% of participants will be randomly selected in each treatment group (up to 600 in each treatment group) to describe the agreement between self-reported data on prescription migraine medication use (acute and preventive) and prescription claims data.

Self-reported survey data on prescription migraine medication use (acute and preventive) will be compared with pharmacy data (including prescribed drug and dosage), obtained via linkage with ExamOne ScriptCheck (additional information in Section 9.4.3). For each randomly selected participant, the data agreement will be assessed at 2 time points: once at baseline, and once at the end of the online survey data collection period described above.

In addition to providing consent for the linkage, completion of a Health Insurance Portability and Accountability Act of 1996 (HIPAA) Authorisation/Medical Release Form is required.

9.2 Setting

9.2.1 Inclusion Criteria

The following criteria must be met to take part in the survey development interviews (Phase 1) and enrolment in the study and prospective surveys (Phase 2):

1. Participant must be at least 18 years old and younger than 75 years old at enrolment;
2. Participant must have a valid driver's licence that they received ≥1 year before enrolment†;
3. Participant must have access to a vehicle at the time of enrolment†, and confirm that they anticipate having access to a vehicle for the following 12 months;
4. Participant must confirm they have driven at least once during the 6 months prior to enrolment†;
5. Participant must provide informed consent to participate in this study;
6. Participant must be able to read and understand English;
7. Participant must currently reside in the US†;
8. Participant must self-report a migraine diagnosis with or without aura (for Phase 2, migraine diagnosis will be confirmed by the participant's HCP); and
9. Participant must have access to a personal device with internet connection (such as phone, tablet, laptop, or computer).

† These criteria must be met throughout follow-up as well. If participants become ineligible during follow-up in ways that may be temporary, such as not having access to a car for a period of time, this change in eligibility will be captured and accounted for in the primary analysis, but the participant will remain in the study on the presumption that this condition could reverse again during the remainder of their study enrolment period.

In order to participate in the baseline and prospective follow-up surveys (Phase 2), the following additional inclusion criteria must be met:

10. Participant must be willing to complete an online survey on driving and migraine experience, taking approximately 20 minutes to complete, once every 30 days for 12 months after the baseline survey; and
11. Participant must be willing to provide consent to access their anti-migraine medication prescription claims data from ExamOne ScriptCheck and allow HCP to confirm migraine diagnosis, completing the HIPAA Authorisation/Medical release Form.

9.2.2 Exclusion Criteria

Participants meeting the following criteria will be excluded from Phase 1 (survey development interviews):

1. Participants who report use of lasmiditan in the past 12 months.

Participants meeting the following criteria will be excluded from Phase 2 (prospective surveys):

2. Participants who participated in the interviews for the survey development qualitative study (Phase 1).

9.2.3 Rationale for Inclusion/Exclusion Criteria

Older drivers (aged 75 years or older) will not be recruited as they have been reported being at higher crash death rates than middle-aged drivers (aged 35 to 54). (Cicchino 2015) Age-related declines in vision and cognitive functioning as well as physical changes might also affect both their driving abilities (TRB 2004) and their ability to accurately complete the survey questions.

All participants will be required to have been issued their driver's licence at least 1 year before enrolment in order to capture baseline driving history. Additionally, this criterion will exclude novice drivers, who are known to be at higher risk of accidents (Ivers et al. 2009).

To be representative of the targeted populations, no exclusion will be made based on the number of accidents a participant has had prior to enrolment to the study, the number of miles a participant drove the year prior to enrolment, or the class of driver's licence possessed by the participants. Given these characteristics would potentially be associated with the risk of accidents, this information will be collected and incorporated into the statistical analysis.

For feasibility reasons and in order to ensure the representativeness of the targeted population, participants using preventive migraine medication will not be excluded. Nevertheless, self-reported use of preventive migraine medication will be collected and the data agreement with linked prescription data will be assessed at baseline and at the ed of follow-up period. Self-reported use of preventive migraine medication will be taken into account as a potential confounding factor in the main analysis (see Section 9.7.2.2) and subgroups descriptive analyses will be performed to describe participants' baseline characteristics and circumstances of MVAs. Assuming that over-the-counter (OTC) medications used to treat migraine attacks do not carry an excess risk of accident, and considering that it is not possible to assess the concordance between self-reported use of OTC medications and prescription data, no information regarding the use of non-prescribed anti-migraine medication will be collected and no exclusion is considered. Nevertheless, self-reported use of concomitant medication carrying a risk of MVA (including some OTC drugs) will be collected at baseline and at each follow-up survey (see Section 9.3.3 and Section 9.3.4).

Assuming that the literacy of eligible participants would not differ according to anti-migraine medication exposure and for feasibility reasons, any potential participants reporting in the Phase 1 screening having ever used lasmiditan in the past 12 months will be excluded from the survey development Phase 1. The HCPs will be invited to refer these potential participants after study Phase 1 is completed, as they may be eligible for Phase 2.

9.2.4 Recruitment Methods and Study Duration

9.2.4.1 Recruitment Methods

Participants for this study will be recruited through HCP referrals. This study will utilise IQVIA PIRS to recruit HCPs providing care to the population of interest into a network of referring providers. These HCPs can come from group practices, individual practices, academic hospitals, or community hospitals across the US. The HCPs who opt into the study will be able to refer

potentially eligible and interested participants with migraine. HCPs are administered a communication plan, which is designed to keep the HCP interested in participating and inform the HCP of study progress. The communication plan includes training for all HCPs, informing them of best practices to identify and refer patients. HCPs are provided with many options to refer patients including quick response (QR) codes, patient flyers or handouts, emails with a link, and a short-link into the landing page.

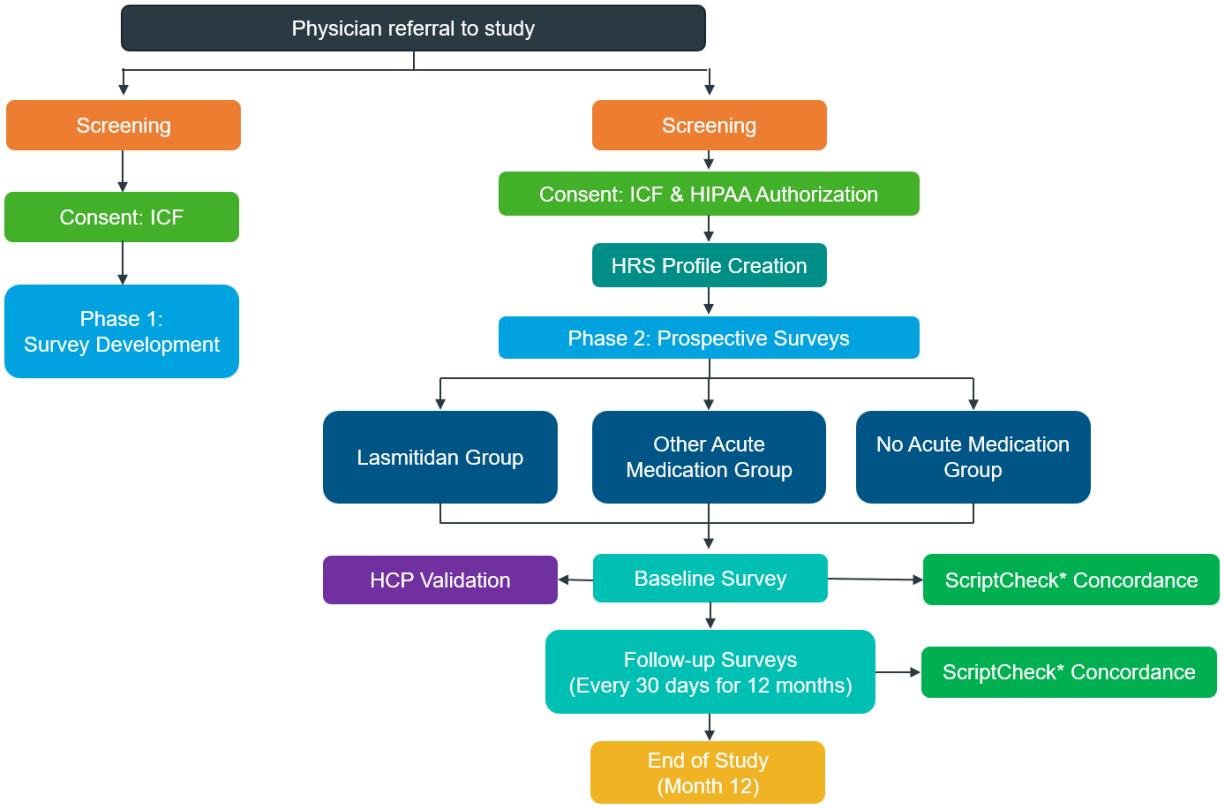
Recruitment of HCPs by PIRS will leverage the IQVIA Research Network (IRN), a primary research panel consisting of almost 200,000 US HCPs that will be used to identify nurse practitioners, physician assistants, and medical doctors specialising in primary care and neurology to refer patients with migraine for enrolment in this study. Using a proprietary algorithm based on the IQVIA CORE to target HCPs, potential panelists will be contacted and enrolled via direct and social media marketing initiatives. The panel, which supports both commercial and clinical research projects, is demographically and geographically representative and can be evaluated on over 200 data reference points. Potential referring HCPs will be provided with an opt-in survey used to quantify patient population and express interest in referring patients, training on the study among those HCPs interested, and a platform to refer patients. HCPs may choose to share study information with interested and potentially eligible participants in accordance with the communication plan. Upon being provided the study information by their HCP, patients may choose to complete screening for participation in the study. For Phase 1, patients will complete online screening and consent and schedule an interview through the IQVIA PIRS team. For Phase 2, all patients are sent into the IQVIA HRS study platform for their screening and subsequent enrolment which can be accessed on personal devices with internet connection such as phone, tablet, laptop, or computer via secure web-link.

9.2.4.2 Study Screening

Figure 1 provides a high-level overview of the enrolment procedure. Potential participants will be notified about the study opportunity according to the recruitment methods outlined above. Patients interested in participating in the study will undergo a screening process which includes a list of questions to determine their eligibility.

After following a link provided by their referring HCP, patients in Phase 1 will complete their study screening via an online IRB-approved screener programmed through Confirmit. If determined to be eligible for participation, patients will continue on to provide informed consent. Patients enrolling into Phase 2 will be provided a link from their referring HCP to the study landing page on the IQVIA HRS platform where they will be presented with an overview of the study and where they will complete their screening process.

For both phases, participants will be asked to complete a screening questionnaire that assesses domains for inclusion and exclusion and categorised as ineligible for the study or eligible for further assessment. Potential participants can complete the screening questionnaire, and all online surveys, using a personal device with internet connection such as phone, tablet, laptop, or computer. If determined to be eligible for further consideration for entry into the study based on answers to the screening questionnaire, potential participants in both study phases will continue on to provide informed consent and register for the study.



HIPAA = Health Insurance Portability and Accountability Act of 1996; ICF = informed consent form.

* ExamOne ScriptCheck Concordance will be done at baseline and after 12 months of follow-up for up to 600 participants from each treatment group (approximate proportion 60%). This extraction will operationally be performed twice: following the recruitment of the last participant and following the completion of the last survey by the last study participant.

Figure 1. Overall study flow diagram.

9.2.4.3 Informed Consent and HIPAA Authorisation/Medical Release Form

As part of study registration, informed consent will be obtained from patients prior to enrolment for both Phase 1 and Phase 2. For Phase 1, patients informed consent will be obtained via an IRB-approved online informed consent form (ICF). For Phase 2, informed consent will be obtained via the IQVIA HRS platform using an IRB-approved ICF. The ICF will detail that participation in the study is voluntary and that it is being conducted to better understand the driving characteristics of participants with migraine. Separate ICFs will be prepared for participation in the survey development interview (Phase 1) or for enrolment in the study and prospective surveys (Phase 2).

ICF information will include the study purpose, eligibility requirements, involvement from the participants, expected duration of the study, and a contact email and phone number for more information.

Participants will also be informed of how their personal information will be secured and that all analyses will be conducted on Coded Study Data. To allow collection of pharmacy claims records and HCP verification of migraine diagnosis, Phase 2 participants will be asked to provide authorisation to allow use and disclosure of personal health information in compliance with the US HIPAA. Participants will be able to revoke this authorisation during the study period by contacting IQVIA but will no longer be able to participate in the study without this authorisation if it is declined or revoked. Beginning on the date participants withdraw consent and authorisation, no new Protected Health Information (PHI) will be used for research. However, researchers may continue to use the PHI that was provided before they withdrew consent or authorisation.

Participants must be able to complete the e-consent process themselves; a legally authorised representative cannot consent the participant into the study.

Once participants complete the consent process, an electronic copy of the ICF and HIPAA Authorisation/Medical Release Form will be available for access and download on HRS platform. ICF and HIPAA Authorisation/Medical Release Form are required to be completed in order to participate in the study Phase 2.

9.2.4.4 Study Steps

After completing the screening questionnaire and providing informed consent and HIPAA authorisation/Medical Release Form, Phase 2 participants will be requested to complete the baseline survey. After completing the baseline survey, the referring HCP will be notified to complete a validation of migraine diagnosis. Throughout the 12-month follow-up period, participants will be asked to complete surveys every 30 days, collecting information on their driving history over the past 30 days, occurrence and circumstances of any MVAs, medication use and migraine experience, and anti-migraine medication use, as presented in Section 9.3.4.

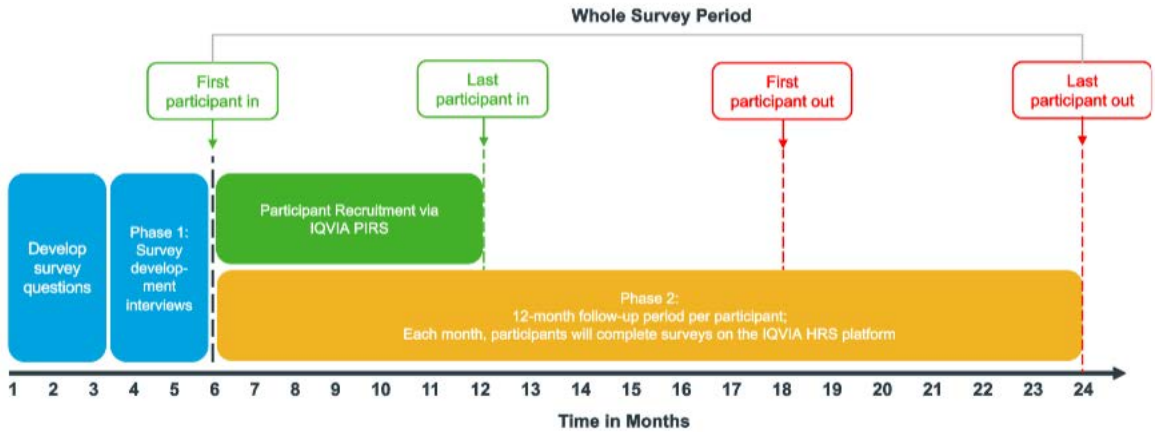
A participant will be considered as lost to follow-up in case of non-response on two consecutive follow-up surveys. Participants who are lost to follow-up will be censored at 67 days following the opening of their last survey (as participants are allotted 7 days to answer each monthly survey). Missing data arising from non-response will be addressed using *last observation carried forward*, (See Section 9.7.2.2.2.3). Participants may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment.

Participants will be compensated for study participation with an honorarium at fair market value (FMV). Participants will be compensated for completing all baseline surveys and then receive additional compensation for each 30-day survey completed.

9.2.4.5 Study Duration

The study preparatory period is estimated to last about 6 months, consisting of initial survey development, followed by survey development interviews (Phase 1) to develop, refine and validate the survey questions among 9 participants, and implement any changes based on survey feedback from Phase 1. Subsequently, participants of the prospective study (Phase 2) will be recruited during a 6-month enrolment period, from the date of first participant being enrolled. Data will be collected for a 12-month follow-up from baseline (see Figure 2).

The extraction of prescription claims data for linkage will operationally be performed twice: following the recruitment of the last participant and following the completion of the last survey by the last study participant.



Abbreviations: HRS = Health Research Space; PIRS = Primary Intelligence Research Service.

Figure 2. Study duration.

9.3 Variables

The data collection schedule (Table 2) describes the sources of the data and whether data will be collected for screening, for the online survey at baseline or during follow-up. Details of the definition of each of the variables in Table 2 are provided in the following sections.

Table 2. Data Collection Schedule – Phase 2

Schedule of data collection	Screening/ Consent	Participant profile	Baseline	Follow-up surveys (every 30 days) [a]
Participant characteristics				
Capacity to provide informed consent	x			
Informed consent	x			
HIPAA Authorisation/Medical Release Form	x			
Duration of holding a valid driver's licence	x			
Vehicle access and recent driving experience	x			
Willingness to complete study surveys	x			
English language literacy and comprehension	x			
Demographics	x[b]	x		
Alternative contact		x		
Migraine experience and medication use				
Migraine diagnosis	x		x[c]	
Migraine history and characteristics			x	x
Acute anti-migraine medication – prescribed	x[d]		x[e]	x[e]
Preventive anti-migraine medication – prescribed			x[e]	x[e]
Other medical history				
Concomitant medications			x	x
Comorbidities			x	x
Driving and MVA characteristics				
Licence classification			x	
Driving characteristics			x	x
Self-reported accidents for which the participant was the driver			x	x
Circumstances and characteristics of reported accidents [f]			x	x

Abbreviations: HCP = healthcare practitioner; HIPAA = Health Insurance Portability and Accountability Act of 1996; MVA = motor vehicle accident.

[a] Follow-up surveys to be completed once every 30 days after baseline, up to 12 times (12-month follow-up period).

[b] At screening, only age will be queried.

[c] HCP validation of migraine diagnosis will be performed after the participant has completed the baseline survey.

[d] At screening, only use of lasmiditan within past 12 months will be collected.

[e] For approximately 60% of participants, self-reported anti-migraine medication will be evaluated for concordance with prescription records in ExamOne ScriptCheck at baseline and at the end of follow-up.

[f] Migraine status, symptoms, anti-migraine medication use, influence of drugs or alcohol, road conditions, etc.

9.3.1 Participant Screening

The following information will be required to identify eligible participants for both Phase 1 and Phase 2, who would subsequently be invited to provide consent:

- Age,
- Possession of and time since acquiring an active driver's licence,

- Motor vehicle access and driving characteristics: access to a motor vehicle at the time of enrolment and anticipated access for the subsequent 12 months; one or more driving occasions in the past 6 months,
- English language literacy and comprehension,
- Currently resides in the US,
- Self-report of migraine diagnosis with or without aura,
- Willingness to complete baseline and follow-up online surveys, taking approximately 20 minutes to complete, once every 30 days for 12 months after baseline (for Phase 2 screening),
- Willingness to provide informed consent to participate in the study,
- Willingness to provide HIPAA authorisation/Medical Release Form to access their anti-migraine medication data from ExamOne ScriptCheck and to allow HCP to confirm migraine diagnosis (for Phase 2 screening only), and
- Use of lasmiditan within the past 12 months (for Phase 1 screening only).

Missing data are not permitted; all questions must be answered in order to be screened for the study.

9.3.2 Participant Profile Creation

In order to participate in Phase 2 of the study, a profile must be created to access the HRS study platform and register into this study. The following variables are required for the HRS profile:

- Sex and gender,
- Race and ethnicity, and
- ZIP code of residency (to classify urbanisation of area of residence using Rural-Urban Commuting Area (RUCA) Codes published by the US Department of Agriculture Economic Research Service).

Participant name, date of birth, phone number and residential address, as well as alternative contact information (name, relation, email, phone number) will be collected for operational purposes but will not be used as study variables.

9.3.3 Variables Collected at Baseline

In addition to the variables collected to identify eligible participants, and to create HRS profile, the following variables collected at baseline will be used to describe the recruited population as part of the primary study objective:

Participant characteristics

- Highest level of education, and
- Current employment status.

Migraine experience and use of anti-migraine medication

- Age at migraine diagnosis (calculated from self-reported date of migraine diagnosis),

- Migraine experience (i.e., over the past 12 months: presence of aura, average number of attacks per month, impact of migraine on daily life; over the past 30 days: number of attacks, impact of migraine on daily life),
- Use of acute and preventive prescribed anti-migraine medications over the past 12 months (medications names and dosage for lasmiditan), and
- Use of acute and preventive prescribed anti-migraine medications over the past 30 days (medications names and dosage for lasmiditan).

Medical history & concomitant medication use

- Relevant comorbidities at baseline (including hypertension, hypotension, musculoskeletal diseases, ophthalmological diseases, insomnia, anxiety, diabetes, depression, other psychiatric disease, chronic insomnia, chronic fatigue syndrome, seizure disorders), and
- Use of concomitant medications potentially associated with MVA risk (including antihistamines, antidepressants, benzodiazepines, beta-blockers, opioids, anti-seizure medications, antipsychotics, sleeping pills including sedatives and hypnotics) within the past 12 months and the past 30 days.

Driving characteristics and experience of MVAs for which the participant was the driver

- Type of active driver's licence,
- Approximate number of miles driven within the last year and in the past 30 days, and
- Self-reported MVAs for which the participant was the driver within the last 30 days and the last 12 months, details on the accident (including location of the accident, speed, perceived level of fault, time of the day, other vehicle(s) and/or persons involved, injuries, severity of the accident approximated by motor vehicle and property damages) and circumstances of these MVAs (details provided below).

Circumstances of self-reported MVAs for which the participant was the driver

- Migraine status at the time of MVA,
- Use of prescribed anti-migraine medication up to 24 hours prior to the accident (preventive and acute) (medications names, dose and time since medication administration relative to the occurrence of MVA for lasmiditan),
- Symptoms immediately preceding (right before) the MVA, including but not limited to aura, headache, fatigue, nausea, dizziness, somnolence, palpitations, vertigo, visual impairment, chest discomfort, muscle weakness, paresthesia, incoordination, lethargy, restlessness, and anxiety,
- Use of concomitant medications potentially associated with MVA risk within 24 hours of the accident (including antihistamines, antidepressants, benzodiazepines, beta-blockers, opioids, anti-seizure medications, antipsychotics, sleeping pills including sedatives and hypnotics), and
- Influence of alcohol or drugs at the time of the MVA.

After the participant completes the baseline survey, the participant's referral HCP will be contacted to confirm the self-reported migraine diagnosis. No participant will be withdrawn if the diagnosis of migraine is not confirmed by the referring HCP, but the information will be included in the concordance analyses (see Section 9.7.5).

9.3.4 Follow-up Variables

The following additional variables will be collected every 30 days during a 12-month period of follow-up for analysis of the primary and secondary objectives:

Dynamic eligibility variables

- Possession of an active driver's licence over the past 30 days,
- Access to a motor vehicle over the past 30 days,
- Have driven at least once in the previous 30 days, and
- Resides in the US over the past 30 days.

Medication use, migraine experience, and the use of anti-migraine medication in the past 30 days

- Migraine experience over the past 30 days: number of migraine attacks, impact of migraine on daily life),
- Use of acute and preventive anti-migraine medications over the past 30 days (medications names, dose for lasmiditan),
- Use of concomitant medications potentially associated with MVA risk (including antihistamines, antidepressants, benzodiazepines, beta-blockers, opioids, anti-seizure medications, antipsychotics, sleeping pills including sedatives and hypnotics) within the last 30 days, and
- New comorbidities declared in the last 30 days (including hypertension, hypotension, musculoskeletal diseases, ophthalmological diseases, insomnia, anxiety, diabetes, depression, other psychiatric disease, chronic insomnia, chronic fatigue syndrome, seizure disorders).

Driving characteristics and experience of MVAs for which the participant was the driver

- Change of ZIP code of residency,
- Approximate number of miles driven in the past 30 days, and
- Number and dates of self-reported MVAs for which the participant was the driver occurring during the past 30 days, details and circumstances of these MVAs (details provided below).

Details on self-reported MVAs for which the participant was the driver in the last 30 days

- Location of MVA,
- Severity of the accident (approximated by the extent of motor vehicle and property damages),
- Speed of the motor vehicle driven by the participant,
- Other vehicle(s) and/or persons involved (i.e., pedestrian, cyclist, motorcyclist, car, other vehicle),

- Perceived fault and reasoning for the accident,
- Seriousness of related injuries for any persons involved in the MVA:
    - Slightly injured: minor character of injury not requiring medical treatment such as a sprain (including neck whiplash injury), bruise or cut which are not judged to be severe, or slight shock requiring roadside attention, and
    - Seriously injured: fractures, concussion, internal injuries, crushings, burns (excluding friction burns), severe cuts, severe general shock requiring medical treatment or death), hospitalisation for the driver.

Circumstances of self-reported MVAs for which the participant was the driver in the last 30 days

- Migraine status at the time and within 24 hours of MVA,
- Use of prescribed anti-migraine medication up to 24 hours prior to the accident (preventive and acute) (medications names, dose and time since medication administration relative to the occurrence of MVA for lasmiditan),
- Symptoms immediately preceding (right before) the accident, including but not limited to aura, headache, fatigue, nausea, dizziness, somnolence, palpitations, vertigo, visual impairment, chest discomfort, muscle weakness, paresthesia, incoordination, lethargy, restlessness and anxiety,
- Use of concomitant medications potentially associated with MVA risk within 24 hours of the accident (including antihistamines, antidepressants, benzodiazepines, beta-blockers, opioids, anti-seizure medications, antipsychotics, sleeping pills including sedatives and hypnotics),
- Influence of alcohol or drugs at the time of the MVA, and
- Time of day, weather, visibility and lighting conditions at time of the accident.

9.3.5 Additional Contact

In the event that participants do not respond to two consecutive survey invitations, the alternative contact provided as part of profile creation may be contacted. The following information will be solicited from the alternative contact:

- Vital status of the study participant,
- (If deceased) Cause of death for the study participant, including whether it was related to an MVA, and
- Hospitalisation or serious injury related to MVA for the driver.

9.4 Data Sources

Data will be collected from the following sources, described in greater detail in the following sections:

- Qualitative survey development interviews (Phase 1),
- Direct-to-participant online surveys via IQVIA HRS platform (Phase 2), including
    - Participant profile, including additional contact information,

  - Baseline survey,
  - Follow-up surveys,

- ExamOne ScriptCheck prescription claims (Phase 2),
- HCP validation of migraine diagnosis (Phase 2), and
- Publicly available MVA statistics for the US (Phase 2).

No visits, examinations, laboratory tests, or procedures are mandated or recommended as part of this study.

9.4.1 Qualitative Survey Development Interviews

Nine patients with migraine, who do not report use of lasmiditan in the 12 months prior to enrolment will be recruited to participate in cognitive debriefing interviews, in which participants will be asked to read, complete, and provide their feedback on a series of questions in order to identify the relevance and potential issues of the questions and/or their content. A process requiring participants to "think aloud" will be used in which they will be asked to verbalise the thought process involved in responding to each item of the survey and their experiences.

Prior to the interview process, IQVIA will prepare a semi-structured guide to help the interviewer conduct the interviews smoothly while ensuring all topics of interest are well covered. Interviews will be approximately 60 minutes in duration via video call and will be moderated by an IQVIA interviewer experienced in qualitative interviews. Feedback from the survey development interviews will be used to inform the structure and wording of the Phase 2 baseline and prospective surveys, and to refine the tool as needed.

IQVIA will use secure teleconferencing capabilities to conduct and record the interview. Participants will be compensated with an honorarium at FMV.

9.4.2 Direct-to-Participant Online Surveys

The primary data source for the study will be participant profiles and direct-to-participant (DtP) online survey responses to baseline and follow-up surveys on participant's health history (particularly migraine), MVA occurrences and circumstances of MVAs (including medication use prior to MVA, migraine status and preceding symptoms), and driving characteristics, collected electronically from recruited participants using IQVIA HRS' dynamic web-based platform. Participant profile will include identifying information (name, date of birth, phone number and residential address), sex, gender, race, ethnicity, and a designated alternative contact in the event the participant cannot be contacted.

The online survey will include built-in logics module and custom logic segments to: 1) reduce the time spent by participants filling in information; and 2) minimise clean-up activities needed by coding and quality checks. The online survey system provides access to standardised operational reports on study progress and study data extracts for data management and analysis teams.

The online survey will consist of multiple-choice questions (i.e., a list of possible responses among which participants will be instructed to select the one(s) that best described what they had

experienced in the past 30 days) and is estimated to take up to 20 minutes to complete. Surveys will be completed at baseline and every 30 days of follow-up for a total of up to 12 surveys.

9.4.3 ExamOne ScriptCheck Prescription Claims

ExamOne ScriptCheck is a data retrieval service utilised to verify participant pharmacy prescriptions and prescribed drug and dosage by providing the participant's last name, first name, sex, date of birth, phone number and residential address. Data is drawn from some of the largest pharmacy benefits management companies in the US, as well as self-pay data sources, and is anticipated to yield prescription claims data on the majority of study participants. ExamOne database covers about 93% of the US population and, when matches are obtained based on patient identifiers described above, has a match accuracy >99.8%.

ExamOne ScriptCheck prescription claims data on anti-migraine medications (preventive and acute) will be extracted for up to 60% of participants randomly selected in each treatment group (up to 600 participants in each treatment group) and will be linked to study data (see Annex 3). These prescription claims will be compared to self-reported anti-migraine medication use as described in Section 9.7.4. For each randomly selected participant, the data agreement will be assessed at 2 time points: once at baseline, and once at the end of the online survey data collection period described above.

The data extraction and linkage will operationally be performed twice: following the recruitment of the last participant and following the completion of the last survey by the last study participant. Self-reported use of prescribed acute anti-migraine medication will be utilised to assign treatment exposure category. No treatment strategy re-classification is planned after ScriptCheck concordance is assessed. The data concordance agreement aims to answer secondary objective to describe the concordance between self-reported use of prescribed anti-migraine medication (acute and preventive) and prescription claims records among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group and No Acute Medication Group).

9.4.4 HCP Validation of Migraine Diagnosis

For participants in Phase 2 of the study, self-reported diagnosis of migraine will be validated by contacting the referring HCP after participants complete a HIPAA authorisation/Medical Release Form. HCPs will be contacted by virtual site staff and asked to confirm whether the participant has a diagnosis of migraine. The HCP's response, based on review of the participant's medical records, will be compared to the self-reported diagnosis of migraine and the agreement reported. No participant will be withdrawn if the diagnosis of migraine is not confirmed by the referring HCP, but the information will be included in the concordance analyses (see Section 9.7.5).

9.4.5 Benchmark Comparison

Data will be downloaded from the National Highway Traffic Safety Administration's annual Traffic Safety Facts report to contextualise incidence rates of MVAs observed among study participants using the rates in the US general population as a frame of reference. The report from the same year of study enrolment or the closest year available at the time of data analysis will be used.

9.5 Study Size

According to the US Department of Transportation data through 2021 (US DOT [WWW]), approximately 3% of licenced drivers in the US have motor vehicle crashes during a year; therefore, approximately 3% of participants are expected to have an accident during the 12 months follow-up. This incidence rate is restricted to crashes involving either the car insurance or the police and might be slightly different than the incidence of MVAs self-reported by drivers.

Due to the lack of clear evidence for elevated incidence of MVAs in individuals with migraine compared to the general population, it is assumed that the incidence of MVAs in the general population can be expected in any of the comparison groups (3% per year). A sample of 793 participants per treatment group would provide 80% power at 5% level of significance for detection of a hazard ratio (HR) of 2.0. Given this is a safety study, no alpha correction method will be used. In order to achieve this sample size, an additional 20% will be targeted for enrolment in anticipation of participant dropout (992 per treatment group). A HR of 3.0 could be detected with a minimum of 397 participant after attrition, assuming an MVA rate of 3% in the lower risk group. Thus, a number of 1000 participants per treatment group, is targeted to be enrolled into the study. Due to a limited source population of lasmiditan-treated patients, challenges are anticipated for the recruitment of participants in the Lasmiditan Group.

If a sufficient number of participants treated with lasmiditan is enrolled, prospective follow-up and a comparative analysis will be executed as part of the final analysis (See Section 9.7.2.2).

If the required sample size is not achieved in the Lasmiditan Group and/or the number of incident MVA in the study period is insufficient to provide meaningful comparison between Lasmiditan Group and comparator groups (Other Acute Medication Group and No Acute Medication Group), unadjusted incidence rates of MVAs in each treatment group with precision estimates will be provided as primary analysis (see Section 9.7.2.2.2.2) and descriptive statistics will summarise participants characteristics, treatment patterns, driving patterns and self-reported MVAs experience through the 12-months of follow-up period.

Precision estimates as a function of sample size and one-year risk of MVA are shown in Table 3, under the assumption of no confounding and no modeled covariates. By way of example, if only 500 participants are recruited into each treatment group and the hazard ratio of MVA over the study period is 2.0, the confidence interval will be (1.07 – 3.72), which will trend narrower with greater sample sizes and wider with hazard ratios closer to the null.

Table 3. Sample Sizes for Two-Sided Confidence Interval Formula

N (Per Group)	Risk Rate		Hazard Ratio	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Confidence Limit Width (Difference)
	Lasmiditan Group	Comparator Group				
1000	5.9%	3.0%	2.00	1.29	3.10	1.81
750	5.9%	3.0%	2.00	1.20	3.32	2.12
500	5.9%	3.0%	2.00	1.07	3.72	2.65
250	5.9%	3.0%	2.00	0.83	4.82	3.99
1000	4.5%	3.0%	1.50	1.26	3.17	1.91
750	4.5%	3.0%	1.50	1.17	3.41	2.24
500	4.5%	3.0%	1.50	1.04	3.84	2.80
250	4.5%	3.0%	1.50	0.79	5.04	4.25

The number of enrolled participants exposed to lasmiditan in both the 12-month and 30-day periods prior to enrolment will inform on the feasibility of conducting the planned comparative analysis using the available sample size and observing the above-listed effect sizes.

9.6 Data Management

For Phase 1, all participants' data will be collected on a virtual communication platform and transcribed into an Excel spreadsheet. Data will be stored in a secure electronic document management system. For Phase 2, all participants' survey responses will be collected and recorded on the IQVIA HRS electronic platform. This platform will be securely accessed via a personal device such as phone, tablet or computer via a secure web-link. It allows for easy integration of survey data completed by participants to be directly reported in a database. Participants may access the surveys via the dashboard in the HRS platform. After receiving prescription claims data from ExamOne ScriptCheck data will be store within the IQVIA HRS database as ingested data tables. HCP confirmation of migraine diagnosis will be stored within the HRS platform.

IQVIA's Data Management team will maintain participants' data per US local regulations. Study documentation may include information defined as "source data" including completed e-Consent forms, enrolment, and study entry assessment information. IQVIA study personnel are responsible for the integrity of the data (i.e., accuracy, completeness, legibility, and timeliness) reported to Eli Lilly and Company.

IQVIA will assure that the data collection tool for the online survey is tested prior to use. A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and monitoring. Datasets and analytic programs will be kept on a secure server and archived per IQVIA record retention procedures.

To enable evaluations and/or audits from regulatory authorities or the study sponsor, IQVIA agrees to keep records, including the identity of all participating patients, all original signed consent to release information, data from all electronic surveys, serious adverse event (SAE) forms, source documents, and adequate documentation of relevant correspondence. The records should be

retained by the virtual site according to local regulations or as specified in the study-specific site contract, whichever is longer.

All copies of all documentation and records relating to the conduct of the study will be retained in compliance with all applicable legal and regulatory requirements. Participants' data will be handled in compliance with all applicable confidentiality and privacy laws.

9.6.1 Data Security and Confidentiality

All identifiable information about participants, their medical conditions, and other study data will be secured by IQVIA in accordance with all local and state laws, regulations, and IRB policies regarding collection and distribution of participants' information. IQVIA's Data Management will ensure that data are pseudonymised and will not have access to original files with identifiable information (e.g., email addresses, cell phone numbers).

Pharmacy claims records will be sent from ExamOne ScriptCheck to IQVIA HRS using a secure data transfer method. These files will also be integrated and stored in the IQVIA HRS database.

Personally identifiable information is only accessible to a restricted set of individuals at IQVIA and is only used to distribute study material and for participant support and compensation purposes. Coded Study Data from surveys will be transferred to Eli Lilly at the end of the study.

9.6.2 Missing Data

Data fields in the online survey will be designed to reduce ineligible answers. The online surveys will be configured such that enrolled participants can choose all responses that apply when relevant only. Participants will be required to complete all questions in the online survey, thereby minimising missing data for required items. Where appropriate, questions will include a 'prefer not to answer' option to ensure choice (e.g., racial identity, level of education). Select items may not be applicable to all participants and will be recorded appropriately in the study platform.

9.6.3 Participant Withdrawal

Participants may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a participant is withdrawn prior to completing the study follow-up period, any known reason for withdrawal (if volunteered) should be documented in the database. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the participants. (Note: once a participant withdraws consent, Eli Lilly cannot use any data beyond the date of withdrawal; thus, no information should be collected from participants after withdrawal.)

9.6.4 Study Compliance and Lost to Follow-up Participants

Virtual site staff will monitor whether participants are completing the online surveys. Participants who do not complete the study steps (e.g., the baseline online survey, the follow-up online surveys) will be contacted by phone call and/or text message with reminders to complete tasks within a time window that is appropriate to the specific task; participants will remain in the study sample regardless of whether they submit data in a timely manner.

Participants who begin the enrolment registration process will remain active and able to complete their enrolment until recruitment targets are reached, at which point they will be notified the study is no longer actively recruiting.

For follow-up online surveys sent every 30 days after the baseline survey, participants will be sent an automated reminder to complete their online survey, which be available for completion for 1 week. Additional automated reminders will be sent as needed, and study staff will contact the participant via phone 1-2 days before the survey window expires to address any barriers to completing the survey. After 1 week passes, access to that follow-up online survey will close. An invitation for the subsequent follow-up survey will be sent according to the schedule determined at baseline.

If a participant does not respond to two consecutive online survey invitations, IQVIA will make no more than five additional attempts, including outbound calls and other means of communication as appropriate, to contact the participant and encouraging to respond to the most recent survey invitation, and/or the alternative contact provided at enrolment. If there is no response to the fifth attempt, the participants will be considered lost to follow-up. All available information in the participants' file through the date of last contact or survey completion will be recorded for the lost to follow-up participants. The statistical analysis plan (SAP) will specify how such participants will be considered for purposes of endpoint assessment.

9.7 Data Analysis

Categorical data will be summarised as frequency counts and percentages (%). Percentages will not include the missing category and will be calculated over the number of subjects with available (non-missing) data. The count of missing observations will be provided in all tables. Continuous data will be summarised using the mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum, maximum, and the number of non-missing and missing observations.

Computed percentages will be presented with one decimal place. Percentages equal to 100 will be presented as 100% and no percentage will be presented for zero frequencies. In case of presenting confidence intervals for categorical/qualitative data, exact methods for deriving these intervals will be used in case of descriptive statistics. For continuous variables, mean, median, Q1 and Q3 will be presented with one more decimal than the raw data, the minimum and maximum will be presented with the same number of decimals as for the original measurement. The SD will be presented with 2 more decimals as the raw data. Where appropriate, a log transformation of continuous variables will be applied to handle skewness (back-transformed prior to reporting). Continuous variables may be categorised into tertiles/quartiles as required.

The distribution of each variable will be examined graphically using boxplots, symmetry plots, normal quantile plots and normal probability plots.

Variables will be summarised for all follow-ups in which the variable is assessed. No missing and invalid survey responses will be imputed, and missing observations will be tabulated as separate categories. The calculation of proportions will not include the missing/invalid category, unless specified otherwise in the SAP.

Complete details of the planned analyses will be documented in the SAP. Changes from the analyses planned in the SAP may result in amendments to the protocol and to the SAP. Aspects of the analysis that are specific to each phase of the study are described below.

9.7.1 Phase 1: Analysis of Survey Development Interviews

Descriptive data from the participants-reported demographics (participant description) and screening documents will be tabulated to characterise the participant sample.

For each of the items (including questions, recall period, response scales, and instructions) of the survey and for each individual participant, responses to the relevance, appropriateness, understandability, and comprehensiveness will be reported. Feedback from the survey development interviews will be used to inform the structure and wording of the prospective surveys.

Qualitative feedback will be solicited for each question and the questions that receive comments indicating they are not well understood or may not collect the intended type of responses will be modified based on the feedback. This may include changes such as rephrasing the question or available responses, removing available options to be more concise, or adding available options. Responses from participants will be summarised and the sponsor will be consulted to review and confirm IQVIA's recommended changes to the survey design. The survey development interviews will be conducted among 2 waves of participants to allow revisions based on the first set of interviews to be confirmed among the second set of interviews.

9.7.2 Phase 2: Analyses of Prospective Surveys

Analyses for Phase 2 will include an interim analysis and a final analysis. The interim analysis will be conducted using information collected at baseline for each participant, on baseline participant characteristics and the 12-months of data prior to enrolment. The final analysis, consisting of the primary analysis and additional descriptive analysis, will include all available study data, including data from follow-up surveys administered every 30 days.

Table 4 presents collected data and assessment periods that will be used in each planned analysis.

9.7.2.1 Interim Analysis

The interim analysis will be conducted using baseline data collected during the first 6 months of enrolment for Phase 2 (data collected from screening survey, baseline survey, participant HRS platform profile, and prescription claims data from baseline linkage).

It will provide a baseline assessment of participants treated with lasmiditan in the 12-month and 30-day baseline periods, including treatment patterns, driving patterns and self-reported MVA experience. In addition, the interim descriptive analysis will empirically evaluate enrolment for survey participation and inform on the feasibility of conducting the planned comparative analysis using the available sample size. Findings from the interim descriptive analysis results will be subject to an interim report submission.

9.7.2.1.1 Interim Analysis Population

An interim descriptive analysis will be performed on all participants who have given informed consent for Phase 2 and completed the baseline online survey.

To summarise information collected at baseline, all Phase 2 enrolled participants will be classified into treatment groups according to their self-reported prescribed anti-migraine medication use; firstly within the 12-month period prior to enrolment, and secondly within the 30-day period prior to enrolment (see Section 9.3.3):

1) Participants who used lasmiditan at least once (Lasmiditan Group),

2) Participants who used another prescribed acute anti-migraine medication at least once (see Annex 3) and did not use lasmiditan (Other Acute Medication Group), and

3) Participants who did not use any prescribed acute anti-migraine medication (No Acute Medication Group).

If a participant is eligible for both Lasmiditan Group and Other Acute Medication Group (having ever used lasmiditan and other prescribed acute migraine medications in the last 12 months), participants using lasmiditan at any time during the lookback period will be classified into the Lasmiditan Group, regardless of other medication use.

The self-reported use of prescribed preventive anti-migraine medication will not be considered for group classification but will be summarised in subgroup descriptive analysis.

No participant will be withdrawn if the diagnosis of migraine is not confirmed by the referring HCP, but the information will be included in the concordance analyses.

9.7.2.1.2 Interim Statistical Analysis

The interim descriptive analysis will descriptively summarise information collected for all enrolled participants on the 12-month and 30-day periods prior to enrolment (see Table 4). This includes demographics, medical and migraine history (including migraine experience, use of acute and preventive prescribed anti-migraine medication, comorbidities, and use of concomitant medications carrying a risk of MVA), as well as driving characteristics (type and duration of holding an active driver's licence, ZIP code of residency to classify urbanisation of area of residence, and approximate number of miles driven) and occurrence of MVAs for which the participant was the driver in the past 12 months and in the past 30 days. The number of participants in each treatment group at baseline will also be reported to inform on the feasibility of conducting the planned comparative analysis according to the sample size calculations presented in Section 9.5.

Details and circumstances of MVAs for which the participant was the driver will be descriptively summarised among the subgroups of participants who reported: 1) at least one MVA during the 12-month period prior to enrolment, 2) at least one MVA during the 30-day period prior to enrolment and according to each treatment group (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group).

Subgroup descriptive analyses to characterise circumstances of MVAs will be conducted by demographics and driving characteristics (type and duration of holding an active driver's licence, ZIP code of residency to classify urbanisation of area of residence and approximate number of miles driven), number of self-reported MVAs, perceived level of fault, severity of the accident (approximated by the extent of motor vehicle and/or property damages), other vehicles and persons involved and related injuries.

Subgroup analyses will use common descriptive statistics to summarise migraine attack at the time of MVA, use of prescribed anti-migraine medication up to 24 hours prior (acute and/or preventive, drug class, lasmiditan dosage and timing of administration in relation to the MVA), symptoms immediately preceding the accident, as well as potential mitigating factors (such as use of concomitant medication carrying a risk of MVA up to 24 hours prior, influence of alcohol or drugs, and time of the day) (details in Section 9.3.4).

In addition, circumstances and details of MVAs will be described among subgroups of participants 1) self-reporting at least one MVA and treated with lasmiditan in the 12 months prior to enrolment, 2) self-reporting at least one MVA and treated with lasmiditan in the 30 days prior to enrolment, 3) treated with lasmiditan in the 24-hour period prior to a self-reported MVA (in the 12 months and in the 30 days prior to enrolment).

Complete details of the planned analyses will be documented in the SAP.

Table 4. Use of Collected Data and Assessment Periods in Each Planned Analysis (Excluding Eligibility Criteria)

	Interim analysis	**Primary analysis (nested 'trial' approach)**		**Additional analysis[#]**
	Baseline data	**Baseline data**	**Follow-up (every 30 days)[a]**	**Follow-up (every 30 days)[a]**
General and driving characteristics				
Demographics[b]	x	x		x
Type of active driver's licence	x	x		x
Duration of holding a valid driver's licence	x	x		x
ZIP code of residency[c]	x	x	x	x
Approximate number of miles driven	*Past year and past 30 days*	*Past year and past 30 days*	*Past 30 days*	*Past 30 days*
Migraine experience	***Past year and past 30 days***	***Past year and past 30 days***	***Past 30 days***	***Past year and past 30 days***
Age at first migraine diagnosis	x	x		
Presence of aura	x	x		
Number of migraine attacks by month	x	x	x	
Impact of migraine on daily life	x	x	x	
Use of prescribed anti-migraine medications	***Past year and past 30 days***	***Past year and past 30 days***	***Past 30 days***	***Up to 24h before the MVA***
Acute anti-migraine medication	x	x	x	x
- Dosage of lasmiditan	x			x
- Time since administration of lasmiditan, relative to the MVA	x			x
Preventive anti-migraine medication	x	x	x	x
Other medical history	***Past year and past 30 days***	***Past year and past 30 days***	***Past 30 days***	***Up to 24h before the MVA***
Use of concomitant medications[d]	x	x	x	x
Comorbidities	x	x	x	
Self-reported MVAs for which the participant was the driver	***Past year and past 30 days***	***Past year and past 30 days***	***Past 30 days***	***Past 30 days***
Occurrence of self-reported MVA	x	x	x	x
Severity of MVA[e]	x			x
Migraine attack at the time of the MVA	x			x
Symptoms immediately preceding the MVA	x			x
Influence of alcohol and/or drugs	x			x
Perceived level of fault	x			x

	Interim analysis	Primary analysis (nested 'trial' approach)		Additional analysis[#]
	Baseline data	Baseline data	Follow-up (every 30 days)[a]	Follow-up (every 30 days)[a]
Other persons involved	x			x
Related injuries[f]	x			x
Time of the day	x			x
Additional details on environmental factors[g]				x

Abbreviations: MVA = motor vehicle accident.

[#] Additional analysis will describe circumstances of MVAs occurring during the study period and will use the same baseline information as for primary analysis.

[a] Follow-up surveys administered once every 30 days after baseline, up to 12 times (12-month follow-up period).

[b] Demographics include age, sex, gender, race, ethnicity, highest level of education and current employment status.

[c] ZIP codes will be used to classify urbanisation of area of residence using Rural-Urban Commuting Area (RUCA) Codes published by the US Department of Agriculture Economic Research Service.

[d] Use of concomitant medications carrying a risk of MVAs.

[e] Severity of the MVAs will be approximated by the extent of motor vehicle and property damages, and injuries will be described separately.

[f] Related injuries include seriousness of injuries for any person involved in the MVA and hospitalisation for the driver.

[g] Additional details on environmental factors include weather, visibility and lighting conditions and are intended to characterise more precisely the circumstances of the reported MVA in secondary analysis, considering the potential memory bias.

9.7.2.2 Primary Analysis

The number of participants in each treatment group and total amount of follow-up time per treatment group will be reported and compared to enrolment targets (1000 participants per group). If a sufficient number of participants treated with lasmiditan is enrolled, a comparative analysis will be executed as part of the final analysis (See 9.7.2.3 for Additional Analyses).

If the required sample size is not achieved to provide meaningful comparison between Lasmiditan Group and comparator groups (Other Acute Medication Group and No Acute Medication Group), unadjusted incidence rates of MVAs in each treatment group with precision estimates will be provided as primary analysis (see Sections 9.5 and 9.7.2.2.2.2) and descriptive statistics will summarise participant characteristics, treatment patterns, driving patterns, and self-reported MVA experience through the 12-months of the follow-up period.

9.7.2.2.1 Primary Analysis Population

Unless otherwise stated, analyses will be performed on all participants who have given informed concent and completed at least the baseline online survey and the first follow-up online survey 30 days after baseline. To align with the primary research objective, the first occurrence of MVA since study enrolment will serve as the outcome of interest for primary analysis.

9.7.2.2.2 Primary Statistical Analysis

9.7.2.2.2.1 Data Structure and Notation

The data structure generated from the procedure illustrated in Section 9.1 will take on the general form shown in Table 5. As illustrated, each row of the data will represent an observation of a given participant at the k^{th} interval of follow-up for the m^{th} 'trial.' The treatment indicator A_k will take on one of three values corresponding to the treatment strategies of interest (see Section 9.1) and will be constant for a given participant within a given m^{th} trial. Treatment history, denoted A_{k-1}, is the treatment the participant received in the prior (k-1) interval. A vector of baseline covariates, denoted L_0, will take on fixed values across all 'k' intervals of a given participant's 'participation' in an m^{th} trial. A vector of time-varying covariates, denoted L_k, will take on their recorded values at time 'k' in a given participant-trial. The event indicator, denoted D_{k+1}, will take on a value of one if the event occurred in the subsequent (k+1) interval, or a value of 0 otherwise (e.g., censoring).

In the data structure, the number of rows for each participant in a given m^{th} trial will correspond to the length of follow-up. For example, in Table 5, Participant 3 participated in nested trial 7 and nested trial 9. This participant was followed-up for four intervals in trial 9 and experienced the outcome event in the 4^{th} interval of follow-up. Notably, treatment information recorded in the 4^{th} interval of follow-up is discarded because it is unknown whether treatment was administered before or after the outcome event within that interval. This is because the surveys only collect information and treatment data at the 30-day level.

Table 5. Generalised Longitudinal Data Structure for the Final Analysis

Participant ID	Trial No. (m)	Follow-up (k)	Treatment (A_k)	Treat Hx (A_{k-1})	Baseline Covariate (L_0)	Time-Varying Covariate (L_k)	Outcome (D_{m+k+1})	Censor (C_{m+k+1})
1	45	0	0	0	0	0	0	0
1	45	1	0	0	0	1	0	0
1	45	2	0	0	0	0	0	1
2	34	0	2	2	1	0	0	0
2	34	1	2	2	1	1	1	0
3	8	0	1	1	0	1	0	0
3	8	1	1	1	0	0	0	1
3	9	0	0	1	1	0	0	0
3	9	1	0	0	1	0	0	0
3	9	2	0	0	1	1	1	0

9.7.2.2.2.2 Statistical Models

The crude (unadjusted) estimates of the number of incident MVAs, total person-time, and incidence rate of first occurrence of MVA since study enrolment under each treatment strategy will be presented. These figures will be calculated using the person-time-trial level analytic data set described in Section 9.7.2.2.2.1.

A marginal structural pooled logistic regression model will be fit to the data structure described in Section 9.7.2.2.2.1 to estimate the relative hazard of MVA between the Lasmiditan Group and the Other Acute Medication Group, as well as between the Lasmiditan Group and the No Acute Medication Group. Using the notation in Section 9.7.2.2.2.1, the model will take on the following form:

$$logit\left[pr\left(D_{m+k+1}=1\middle|A_k,\ L_0,\overline{D}_{m+k}=0,\ \overline{C}_{m+k+1}=0\right)\right]=\beta_{0,m+k}+{\beta_1}^T A_k+\ {\beta_2}^T L_0$$

where $\beta_{0,m+k}$ is a time-varying intercept (i.e., a parametric estimation of the baseline hazard) that will include a spline or other polynomial function of follow-up interval ‘k' and trial number ‘m’; β_1 is a vector of the log hazard ratios of interest (comparing a reference treatment strategy to the remaining strategies); β_2 is a vector of coefficients of the baseline covariates. Under the rare disease assumption, the exponentiated β_1 coefficients will approximate a hazard ratio, provided the event rate within each ‘k’ time interval is <8%. This will be verified at the time of the analysis.

To adjust for potential confounding, stabilised time-varying inverse probability of treatment to weights will be estimated as follows:

$$SW_{m+t}^{A}=\prod_{k=m}^{m+t}\frac{f(A_k|\bar{A}_{k-1},\ L_0,\ \overline{D}_{k-1}=0)}{f(A_k|\bar{A}_{k-1},\ L_0,\ \bar{L}_{k-1},\overline{D}_{k-1}=0)}$$

Given that there are three comparator treatment strategies, the density in the numerator and denominator of this stabilised weights will be estimated using a multinomial regression model. Informally, the numerator of the weight is the probability of receiving the treatment that the participant actually received at time 'k,' conditional on treatment and baseline covariate histories and the denominator of the weight is the probability of receiving the treatment that the participant actually received at time 'k' conditional on treatment, baseline covariate, and time-varying covariate histories.

Because participants are censored when they deviate from their assigned treatment strategies, selection bias may result. To account for this, inverse probability of censoring weights will be estimated as follows:

$$SW_{m+t}^{C} = \prod_{k=m}^{m+t} \frac{f(C_{k+1} = 0 | \bar{A}_k,\ \bar{C}_k = 0)}{f(C_{k+1} = 0 | \bar{A}_k, L_0, \bar{L}_k, \bar{C}_k = 0)}$$

The density in the numerator and denominator of this weight will be estimated using a logistic regression model. Informally, the numerator of the weight is the probability of being uncensored in the next interval conditional on treatment history and the denominator of the weight is the probability of being uncensored in the next interval conditional on treatment, baseline covariate, and time-varying covariate histories.

Observations in the marginal structural pooled logistic model specified above will be weighted by the joint density of the two weights as follows:

$$SW_{m+t}^{A,C} = SW_{m+t}^{A} \times SW_{m+t}^{C}$$

Observations in this analysis are not independent due to the use of weighting and allowance of repeated entry into the analytic cohort (i.e., through participation in more than one nested trial). To account for this lack of independence, nonparametric bootstrap will be used to estimate standard errors and confidence intervals.

A weighted and unweighted table of baseline characteristics will be generated using the person-time-trial level data set described in Section 9.7.2.2.2.1. Absolute standardised mean differences (ASMD) will be used to evaluate imbalances in these characteristics between participants assigned to the lasmiditan treatment strategy vs. the remaining two treatment strategies. ASMDs of the <0.1 will be considered imbalanced.

Contingencies**:**

1. The joint density of the inverse probability weights $SW_{m+t}^{A,C}$ may contain extreme values if there are few patients in the study sample that possess a particular combination of characteristics within each level of treatment strategy and time interval. If this occurs, weights will be incrementally truncated at upper and lower P^{th} percentile (e.g., 99.9th, 99.8th, 99.7th percentiles, etc.) until there are no longer extreme weights.

2. It may not be possible to achieve balance between all potential confounders across treatment groups (i.e., ASMD<0.1). Imbalances in baseline characteristics will be addressed with a re-specification of inverse probability weights (e.g., Changing the functional form of the variable or including interaction terms). However, if imbalances remain these will be described along with their potential impact on the outcome estimate(s).

3. It may not be possible to model all collected covariates due to sparsity, collinearity, or other factors that can preclude convergence of statistical models. For this reason, the final variables and functional forms of the baseline (L_0) and time-varying ($\bar{L}_k$) covariate vectors described in the models above will be determined at the time of analysis.

4. The time interval of the analysis, denoted 'k', directly influences the dimensionality of the dataset, and concequent computational intensity of the analysis. Particularly, choosing a time interval of one day will greatly increase the number of rows in the analytic data set and, concequently, increase the computation time of nonparametric bootstrap algorithms for standard error estimation. Therefore, if computation times are too great then the time interval of the analysis may be expanded accordingly (e.g., to one week or one month).

9.7.2.2.2.3 Missing Data

Missing data may arise from participants who skip a single survey only, or who are lost to follow-up (defined as non-responce on two concecutive follow-up surveys). Participants who are lost to follow-up will be censored at 67 days following the opening of their last survey (as participants are allotted 7 days to answer each 30-day survey). Missing data arising from non-response will be addressed using *last observation carried forward*, where the most recent survey responses are "carried forward" under the assumption that participants' treatment and confounder histories did not change during the time spanning from the participant's final response through the period of non-response.

9.7.2.3 Additional Analyses

Additional analyses aiming to address secondary objectives will be conducted as part of the final analysis: 1) to describe migraine experience and reported use of prescribed anti-migraine medication among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group) at baseline and during the follow-up period, and 2) to describe the circumstances of all MVAs self-reported during the study period, including migraine status, reported use of prescribed anti-migraine medication prior to MVA, preceding symptoms, and influence of alcohol or drugs at the time of the MVA, as well as severity of the accident and related injuries, among study treatment groups' participants (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group).

Descriptive statistics will be used to summarise information collected for all enrolled participant at baseline and during the 12-months follow-up period and characterise migraine experience (age at first diagnosis, presence of aura, number of migraine attacks by month and impact on daily life) and reported use of prescribed anti-migraine medication (names of acute and preventive anti-migraine medications, dosage for lasmiditan) among the three treatment groups, and according to demographics subgroups and other medical history.

Details and circumstances of MVAs for which the participant was the driver will be descriptively summarised among the subgroup of participants who reported at least one MVA during the 12-month follow-up period and according to each treatment group (Lasmiditan Group, Other Acute Medication Group, and No Acute Medication Group).

Subgroup descriptive analyses to characterise circumstances of MVAs will be conducted by demographics and driving characteristics (type and duration of holding an active driver's licence, ZIP code of residency to classify urbanisation of area of residence, and approximate number of miles driven), number of self-reported MVAs during the observational period, perceived level of fault, severity of the accident (approximated by the extent of motor vehicle and/or property damages), speed of the motor vehicle driven by the participant, other vehicles and persons involved, and related injuries.

Subgroup analyses will use common descriptive statistics to summarise migraine attack at the time of MVA, use of prescribed anti-migraine medication up to 24 hours prior (acute and/or preventive, drug class, lasmiditan dosage and timing of administration in relation to the MVA), symptoms immediately preceding the accident, as well as potential mitigating factors (such as use of concomitant medication carrying a risk of MVA up to 24 hours prior, use of alcohol or drugs, environmental factors [i.e., time of the day, weather, visibility and lighting conditions]) (details in Section 9.3.4).

In addition, circumstances and details of MVAs will be described among subgroups of participants 1) having experienced at least one MVA during the study period and treated with lasmiditan in the 12-month study period, 2) treated with lasmiditan in the 30-day period prior to a self-reported MVA, 3) treated with lasmiditan in the 24-hour period prior to a self-reported MVA.

Complete details of the planned analyses will be documented in the SAP.

9.7.3 Benchmark Comparison

To our knowledge, no hazard ratio or incidence rate of MVA among migraine patients have been previously published in the literature. An unadjusted descriptive comparison of the annual incidence of self-reported MVAs in each of the study groups (among participants in Phase 2) relative to the rate observed for the general population will be provided, drawing on statistics from the National Highway Traffic Safety Administration including the annual Traffic Safety Facts report from where the annual national MVA rate will be extracted for the same or soonest year of study enrolment. The description will be presented by subgroups where possible, including by age group and sex.

9.7.4 Validation of Self-Reported Anti-Migraine Medication Use

Approximately 60% of participants will be randomly selected in each group (up to 600 in each treatment group) to describe the agreement between self-reported anti-migraine medication use and pharmacy claims records for all acute and preventive prescription anti-migraine medications at baseline and after 12 months of follow-up.

Pharmacy claims records will be reviewed and the consistency with self-reported medication use reported descriptively with relevant agreement statistics such as percentage of agreement, percentage of disagreement, Kappa statistics (Cohen, Fleiss or Weighted depending on the distribution of the class variable).

9.7.5 Validation of Self-Reported Diagnosis of Migraine

For participants enrolled in Phase 2 of the study, referring HCPs will confirm self-reported diagnosis of migraine. The agreement between self-reported migraine diagnosis and review of the medical records by referral HCPs will be assessed and reported descriptively with relevant agreement statistics such as percentage of agreement, percentage of disagreement, Kappa statistics (Cohen, Fleiss or Weighted depending on the distribution of the class variable). No participant will be withdrawn if the diagnosis of migraine is not confirmed by the referring HCP, but the information will be included in the concordance analyses and discussed as potential limitation.

9.8 Quality Control

A data management plan (see further details in Section 9.6) will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, validation, and monitoring. Changes to data collection on the HRS data platform will require documentation of the reason for each change.

HRS will configure and test the survey functions and logic as part of the end-to-end participant experience of the platform. The platform configuration and development must be complete and tested following software development lifecycle processes before starting to enrol participants via the HRS platform for each of the three participant groups. HRS platform software development lifecycle process includes proctored user acceptance testing activities in addition to thorough software testing at all stages of platform configuration.

Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data and will prompt the participants to re-enter a valid response. Data fields in the online survey will be limited to reduce ineligible answers and there will be a very limited number of open data fields to maximise data quality. The online survey will also prevent multiple survey entries from the same participants. Participants will be required to complete all questions in the online survey. To reduce the opportunity for bias, online survey participants will not be contacted to clarify or revise their responses.

As the online survey invitations will be sent for 12 months for each participant, IQVIA will ensure the appropriate follow-up to maintain proper participant engagement and share status updates to Eli Lilly raising potential issues/concerns with appropriate mitigations.

9.9 Limitations of the Research Methods

9.9.1 Participant Recruitment

As with many online studies, participants' eligibility will be predominantly self-reported. Given the relatively high number of participants the study aims to recruit, this approach is preferred to requiring participants to give evidence of their condition and medication as part of study inclusion, which would be substantially more operationally complex and would likely reduce recruitment numbers. Prescriptions will be verified via ExamOne ScriptCheck in a data validation procedure for approximately 60% of participants randomly selected in each group (up to 600 in each group) to describe the consistency between this self-reported prescription data and pharmacy claims records. According to data shared by ScriptCheck, ScriptCheck covers most of the US population (around 93%) with a match accuracy of 99.8%. However, pharmacy claims records represent only

medication dispensed, not medication actually taken by an individual. Additionally, participants will be referred by their HCP, who will confirm the participant's self-reported diagnosis of migraine.

9.9.2 Information Bias

As with all collection of self-reported data, there is the possibility that participants may give inaccurate responses. For prescription anti-migraine medication, agreement between self-report and pharmaceutical claims data was notably higher when participants were asked to report 'current' use (kappa statistic 0.66, 95% confidence interval [CI] 0.23-1.00) relative to the results for a recall period of the past year (kappa statistic 0.36, 95% confidence interval [CI] 0.00-0.72). (Lacasse et al. 2016) Validation with pharmacy claims data will assess the internal data validity of self-reported prescription medication.

Sensitive data regarding MVAs are being collected in the study, including whether the accident was reported, the use of medications, drugs, or alcohol prior to the accident, and/or distracted driving, which could predispose participants to not answer truthfully due to the fear of judgment or embarrassment. For MVAs, there is evidence that self-reported data has poor test re-test reliability. (af Wåhlberg and Dorn 2015) The risk of social desirability bias may be mitigated by use of an anonymised online survey, combined with assurance on data privacy, compared to interview-based methods. This will be emphasised in the survey instructions to encourage accurate and truthful responses from participants. Moreover, participants will not be able to change answers once they are submitted and will not be contacted to clarify or revise responses at any point. If a participant reports illegal activities (i.e., taking illegal drugs or taking medications that are not allowed before driving), he will be aware that no action will be taken.

The survey will ask participants to consider their driving and migraine experience within the last 30 days and within the last 12 months at baseline; while the primary analysis depends on the relatively recent 30-day period, there remains the potential for recall bias, particularly for self-reported data within the last 12 months. In case of a collision, the longer the time elapsed since the collision, the more difficult it will be for the participants to recall. This may have an impact on their ability to accurately report circumstances and events occurring the hours proceeding the accident (e.g., accurately recall the timing of any accidents relative to when medications were last taken). To minimise recall bias in this study, participants will be administered follow-up surveys every 30 days, will be instructed to complete a survey in one sitting and guided to answer the questions in sequence. The questionnaires have been designed to collect only the information required for the analytic objectives to minimise recall burden. At baseline, a limited set of key variables will be collected for MVAs within the past 12 months to limit the burden on participants and improve response accuracy, and results for the 12-month period will be interpreted cautiously.

Because treatment and outcome variables are ascertained at the 30-day level, temporality between treatments and outcomes reported in the same interval cannot be established. For this reason, the primary statistical analysis is designed to estimate the hazard of experiencing a MVA in the *subsequent time interval* given treatment history *in the time interval prior* to the MVA. If a participant had in fact ceased using the treatment reported in the interval prior to the MVA, or begun an alternate treatment in the interval in which the accident was reported, then the participant's treatment status maybe misclassified. However, this misclassification bias is likely to be non-directional, resulting in a similar bias on the effect estimation between treatment groups.

Secondary objectives were specified to investigate the extent of treatment misclassification for this cause providing additional information on circumstances of MVA, including use of anti-migraine medication in the 24 hours prior to the accident.

9.9.3 Generalisability

Conducting research online could bias findings toward participants who are more familiar with electronic devices and browsing the internet and are more able, meaning that participants unfamiliar or less confident with electronic devices or browsing the internet may be under-represented.

The selection of the cohort for analysis for the primary objective based on the lasmiditan therapy use could potentially result in a small population, and therefore could be underpowered if the sample size falls below that required to detect the HR of interest.

It is assumed in all the analyses that all prescribed drugs are prescribed and then taken by patients in a compliant manner. Non-compliance would result in misclassification of exposure and could cause an underestimation of the association between exposure and outcome.

9.9.4 Confounding

As with other non-randomised studies, one limitation could be that participants' characteristics are imbalanced between the different treatment groups, and some groups may therefore have higher risk of MVA due to these differences in participants' characteristics. Given most of these participants' characteristics will be self-reported, this information might be partly available or less accurate as it would have been if assessed with objective and verifiable data sources. Subgroup analysis for the calculation of MVA incidence rates will be considered and restricted to subgroups of participants with specific characteristics (described in Section 9.7.2.3). Causal inference methods are planned for the management of potential confounders and are further described in Section 9.7.2.2.2.

9.9.5 Missing Data and/or Dropout

Missing items will not be permitted by the online survey and so intermittent missingness is not expected. Anticipated missing data could be due to participants exiting the questionnaire before completion and as for any longitudinal study, attrition and loss-to-follow-up may occur. However, participants may not complete all surveys included as part of the study design (e.g., every 30 days for 12 months).

It could also happen that a participant has a very serious/severe accident and due to injuries or death, information will not be known/reported for the study, which could lead to underestimation of MVA incidence. This will be mitigated by requiring participants to designate an alternative contact who can confirm information if the participant is unable to be reached (see Section 9.3.5 for details of what may be requested from the alternative contact) Missing data arising from non-response will be addressed using *last observation carried forward*, (See Section 9.7.2.2.2.3).

10. Protection of Human Subjects

This study will be submitted to at least one ethical review board (ERB) for review and to confirm that the study is considered non-interventional. Regulatory authorities will be notified and approval sought as required by local laws and regulations. This observational study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki (WMA 2013), the ICH guideline E6R1 (International Council for Harmonisation 1996) and the Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISP 2015) and the applicable legislation on non-interventional studies and/or observational studies.

11. Management and Reporting of Adverse Events/Adverse Reactions

11.1 Primary Data Collection

The centralised study team will collect via electronic data capture system all protocol-defined adverse events (AEs), including all associated fatal outcomes, occurring in temporal association with Eli Lilly product(s) and comparator product(s) that are under evaluation as defined in this protocol. The protocol-defined AEs include:

- MVA for which the participant was the driver,
- Non-serious injuries for the driver,
- Migraine attacks at the time of MVA,
- Aura, headache, light sensitivity, sound sensitivity, fatigue, nausea, vomiting, visual impairment, and
- Dizziness, somnolence, palpitations, vertigo, chest discomfort, muscle weakness, paraesthesia, lack of coordination, lethargy, restlessness, anxiety.

All other AEs will not be actively collected due to lack of relevance to the study objectives or outcomes.

Protocol-defined AEs collected will be summarised in the interim safety report and in the final study report.

Study personnel are requested to report any Suspected Adverse Reactions (SARs) with Eli Lilly products not under evaluation in this protocol or SARs with non-Eli Lilly products to the appropriate party (for example, regulators or the marketing authorisation holder [MAH]) as they would in normal practice.

Study personnel are not obligated to actively collect AEs or serious adverse events (SAEs) in participants once they have discontinued from the study. However, if the study personnel learn of any SAE, including death, at any time after the participant has discontinued from the study and the event is considered reasonably possibly related to the Eli Lilly product under evaluation, the study personnel must notify Eli Lilly within the timeframes specified in Sections 11.1.1 and 11.1.2.

With respect to spontaneous AE reports, any voluntary reports of AEs provided during the interviews for survey development (Phase 1) or through the HRS platform (i.e., by email or phone, or by the free-text field in the survey question regarding symptoms immediately preceding the MVA) will be reported to Eli Lilly via The Lilly Answers Center (TLAC; 1-800-545-5979) to report all AEs and/or product complaints within 24 hours of awareness. Similarly, Study personnel are requested to report any SARs with Eli Lilly products not under evaluation in this protocol or SARs with non-Eli Lilly products to the appropriate party (for example, regulators or the MAH) as they would in normal practice, through The Lilly Answers Center listed above.

11.1.1 Serious Adverse Events (SAEs)

The study personnel will report to Eli Lilly or its designee any protocol-defined SAE arising in temporal association with the Eli Lilly product(s) under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. A protocol-defined SAE is any AE from this study that results in one of the following outcomes:

- Death,
- Initial or prolonged participants hospitalisation,
- MVAs resulting in the driver hospitalisation,
- Serious injuries for the driver,
- A life-threatening experience (that is, immediate risk of dying),
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, and
- Or is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participants or may require intervention to prevent one of the other outcomes listed above.

11.1.2 Nonserious Adverse Events

The study personnel will record any nonserious protocol-defined AE arising in temporal association with the Eli Lilly product(s) under evaluation within 30 days of awareness of the event via electronic data capture system.

11.2 Product Complaints

Eli Lilly collects product complaints on marketed Eli Lilly products such as drugs, drug/device combinations, medical devices, software as medical device (e.g., mobile medical applications), and comparator product(s) used in post-marketing medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

For Eli Lilly products under evaluation and/or Eli Lilly products not under evaluation but discovered in the course of the study, study personnel are instructed to report product complaints as they would for products in the marketplace.

For non-Eli Lilly products, such as comparator drugs or medical devices, or concomitant drugs or medical devices, study personnel are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

An interim report and the final study report will be submitted to regulatory agencies. The study, including the final report, will also be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Registry. The study findings may be submitted to a scientific congress and/or to a peer reviewed journal.

13. References

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Annex 1. List of Standalone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

Study title: Observational Cohort Study of Lasmiditan Exposure and Motor Vehicle Accidents in the United States

EU PAS Register® number: EUPAS1000000347

Study reference number (if applicable): Protocol H8H-MC-B006

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒			6.
1.1.2 End of data collection[2]	☒			6.
1.1.3 Progress report(s)			☒	
1.1.4 Interim report(s)	☒			6.
1.1.5 Registration in the EU PAS Register®	☒			6.
1.1.6 Final report of study results.	☒			6.

Comments:

Section 2: Research question	Yes	No	N/A	Section number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒			7.
2.1.2 The objective(s) of the study?	☒			8.
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒			8.
2.1.4 Which hypothesis(-es) is (are) to be tested?			☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?			☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	Yes	No	N/A	Section number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒			9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒			9.1
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒			8. and 9.7.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒			9.7.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒			11.

Comments:

This study is descriptive and does not investigate association.

Section 4: Source and study populations	Yes	No	N/A	Section number
4.1 Is the source population described?	☒			9.2.4.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒			9.2.4
4.2.2 Age and sex	☒			9.2
4.2.3 Country of origin	☒			9.2
4.2.4 Disease/indication	☒			9.2
4.2.5 Duration of follow-up	☒			9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒			9.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒			9.3.3; 9.3.4

5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒			9.4
5.3 Is exposure categorized according to time windows?		☒		
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒			9.3.3; 9.3.4
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?			☒	
5.6 Is (are) (an) appropriate comparator(s) identified?			☒	

Comments:

This study does not have comparators as it is a descriptive study.

Section 6: Outcome definition and measurement	Yes	No	N/A	Section number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒			9.3.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒			9.3.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒			9.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)		☒		

Comments:

A survey development qualitative study consisting in one-on-one interviews to document the driving characteristics of participants eligible for the different treatment groups will be conducted to ensure the survey questions are relevant, easily understood, and can provide reliable and accurate results.
Information on migraine experience (i.e. over the past 30 days: number of attacks, number of days with migraine attacks, impact of migraine on daily life) constitutes relevant information for HTA.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒			9.7.2.2, 9.7.2.3, 9.7.5
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒			9.9

7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒			9.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒			9.7.2.2, 9.7.2.3

Comments:

This descriptive study will have subgroup analyses that will allow assessing confounding and potential effect modification.

Section 9: Data sources	Yes	No	N/A	Section number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒			9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, participants interview including scales and questionnaires, vital statistics)	☒			9.4
9.1.3 Covariates and other characteristics?	☒			9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒			9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple events, severity measures related to event)	☒			9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒			9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)		☒		
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))		☒		
9.3.3 Covariates and other characteristics?		☒		
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒			9.4.3; 9.7.4

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section number
10.1 Are the statistical methods and the reason for their choice described?	☒			9.7
10.2 Is study size and/or statistical precision estimated?	☒			9.5
10.3 Are descriptive analyses included?	☒			9.7.1; 9.7.2
10.4 Are stratified analyses included?	☒			9.7.2.3
10.5 Does the plan describe methods for analytical control of confounding?	☒			9.7.2
10.6 Does the plan describe methods for analytical control of outcome misclassification?		☒		
10.7 Does the plan describe methods for handling missing data?	☒			9.7
10.8 Are relevant sensitivity analyses described?	☒			9.7.2.3

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒			9.6
11.2 Are methods of quality assurance described?	☒			9.8
11.3 Is there a system in place for independent review of study results?		☒		

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒			9.9
12.1.2 Information bias?	☒			9.9
12.1.3 Residual/unmeasured confounding?	☒			9.9
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				

12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, participants recruitment, precision of the estimates)	☒			9.2.4

Comments:

The potential impact of some selection bias on generalizability of results is addressed in Section 9.9
A survey development qualitative study consisting in one-on-one interviews to document the driving characteristics of participants eligible for the different treatment groups will be conducted to ensure the survey questions are relevant, easily understood, and can provide reliable and accurate results.

Section 13: Ethical/data protection issues	Yes	No	N/A	Section number
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?		☒		
13.2 Has any outcome of an ethical review procedure been addressed?			☒	
13.3 Have data protection requirements been described?	☒			10.

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section number
14.1 Does the protocol include a section to document amendments and deviations?	☒			5.

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒			12.
15.2 Are plans described for disseminating study results externally, including publication?	☒			12.

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

Annex 3. Additional Information

List of prescribed anti-migraine medications

Medication Name	Drug Class	Classification
Lasmiditan (Reyvow)	Ditan	Acute
Ubrogepant (Ubrelvy)	CGRP antagonist / gepant	Acute
Rimegepant (Nurtec)	CGRP antagonist / gepant	Acute*
Zavegepant (Zavzpret)	CGRP antagonist / gepant	Acute
Almotriptan (Axert)	Triptan	Acute
Eletriptan (Relpax)	Triptan	Acute
Rizatriptan (Maxalt)	Triptan	Acute
Sumatriptan Succinate (Imitrex, Sumavel, Alsuma, Zembrace)	Triptan	Acute
Frovatriptan (Frova)	Triptan	Acute
Naratriptan (Amerge)	Triptan	Acute
Zolmitriptan (Zomig, Zomig ZMT)	Triptan	Acute
Sumatriptan / Naproxen (Treximet)	Triptan / NSAID	Acute
Diclofenac (Cambia, Cataflam, Zipsor, Zorvolex)	NSAID	Acute
Galcanezumab (Emgality)	CGRP antagonist	Preventive
Erenumab (Aimovig)	CGRP antagonist	Preventive
Eptinezumab (Vypepti)	CGRP antagonist	Preventive
Fremanezumab (Ajovy)	CGRP antagonist	Preventive
Atogepant (Qulipta)	CGRP antagonist / gepant	Preventive
Topiramate (Topamax, Trokendi XR, Qudexy XR)	Antiepileptic	Preventive
Valproate sodium (Depacon)	Antiepileptic	Preventive
Divalproex sodium (Depakote, Depakote ER)	Antiepileptic	Preventive
Nortriptyline (Pamelor)	Tricyclic antidepressant	Preventive
Venlafaxine, Venlafaxine XR (Effexor, Effexor XR)	Antidepressant/SSRI/SSNRI/ TCA	Preventive
Amitriptyline	Tricyclic antidepressant	Preventive
Metoprolol (Toprol XL, Lopressor)	Beta Blocker	Preventive
Propranolol (Inderal LA, Hemangeol, InnoPran XL)	Beta Blocker	Preventive
Timolol (Blocadren)	Beta Blocker	Preventive
Atenolol (Tenormin)	Beta Blocker	Preventive
Nadolol (Corgard)	Beta Blocker	Preventive
Frovatriptan (Frova)	Triptan	Preventive
Naratriptan (Amerge)	Triptan	Preventive
Zolmitriptan (Zomig, Zomig ZMT)	Triptan	Preventive
OnabotulinumtoxinA (Botox)	Neurotoxin	Preventive
Bisoprolol (Zebeta)	Cardioselective beta blocker	Preventive
Candesartan Cilextile (Atacand)	Angiotensin II receptor blocker (ARB)	Preventive
Metoclopramide (Reglan, Maxolon, Metozolv ODT, Gimoti)	Prokinetic agent/ antiemetic	Preventive
Prochlorperazine (Compazine, Compro)	Antipsychotic/ antiemetic	Preventive

* Although rimegepant may be used for both acute treatment of migraine attacks and preventively, for this study all participants who report use of rimegepant will be classified as using acute prescription anti-migraine medication, which will allow for all potential acute use of rimegepant to be captured.