EU Risk Management Plan (Version 1.1)

Global Patient Safety
Signatory information is available on request.
EU Risk Management Plan electronically approved by Lilly on date provided below.

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EU Risk Management Plan for Lasmiditan

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Summary of significant changes in this RMP: Pharmacovigilance plan updated to include a descriptive interim analysis in the study design and interim report date in the milestones of Study B006.

Other RMP versions under evaluation

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Lasmiditan hemisuccinate
Pharmacotherapeutic group(s) (ATC Code)	Not available
Marketing Authorisation Applicant	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	RAYVOW
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** 5-HT_{1F} receptor agonist
	Summary of mode of action: Lasmiditan is a low molecular weight 5-HT_{1F} receptor agonist with a nonvascular, primarily neural mechanism of action. It has high affinity for the human 5-HT_{1F} receptor and >440-fold selectivity for the human 5-HT_{1F} receptor relative to the 5-HT_{1B} receptor.
	Important information about its composition: The drug product is composed of lasmiditan hemisuccinate and the inactive ingredients croscarmellose sodium, magnesium stearate (nonbovine), microcrystalline cellulose, purified water, sodium lauryl sulphate, starch.
Hyperlink to the Product Information	See eCTD Module 1.3.1
Indication(s) in the EEA	**Current:** Lasmiditan is indicated for the acute treatment of the headache phase of migraine attacks, with or without aura in adults.
	Proposed: Not applicable
Dosage in the EEA	**Current:** In general, the recommended initial dose in adults is 100 mg lasmiditan for acute treatment of migraine attacks. If necessary, the dose can be increased to 200 mg for greater efficacy or can be decreased to 50 mg for greater tolerability. If the migraine headache recurs within 24 hours of an initial response after taking 50- or 100-mg lasmiditan, a second dose of the same strength may be taken. The second dose should not be taken within 2 hours of the initial dose. No more than 200 mg should be taken in 24 hours.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** RAYVOW 50 mg film-coated tablets, RAYVOW 100 mg film-coated tablets, and RAYVOW 200 mg film-coated tablets.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: 5-HT = 5-hydroxytryptamine (serotonin); ATC = Anatomical Therapeutic Chemical; EU = European Union; INN = International Nonproprietary Names; RMP = risk management plan.

Part II: Safety Specification

Module SI - Epidemiology of the Indication(s) and Target Population(s)

SI.1 Migraine

Migraine has 2 main categories based on headache days per month. Episodic migraine (EM) is characterised by <15 headache days per month and chronic migraine (CM) is characterised by ≥15 headache days per month (Adams et al. 2015). Of the 2 types, EM occurs most frequently and represents ≥90% of the migraine population (Lipton et al. 2017; Buse et al. 2010). When available, the epidemiology data will focus on the more common episodic type.

SI.1.1 Incidence

The incidence of migraine varies by geographic region. In an abstract describing a systematic review of migraine in Europe, authors reported an estimated 77 million people with migraine, with an incidence of up to 39.2/1000 person years (pys) (Benhaddi et al. 2018). In Denmark, the average annual incidence of any migraine from 1994 to 2002 was 17.6 per 1000 pys in adults aged 20 to 49 years (23.4 per 1000 pys in women and 11.2 per 1000 pys in men); the average annual incidence of migraine without aura, 12.0 per 1000 pys, was greater than that of migraine with aura, 5.6 per 1000 pys (Le et al. 2012). A lower incidence was observed in a UK database study (1994 to 2001) where the estimated incidence rate was 3.69 cases per 1000 pys for a first diagnosis of migraine in those aged ≤79 years. The incidence rate was highest in those aged 10 to 19 years (6.43 per 1000 pys), relatively stable in those aged 20 to 49 years (approximately 4.5 per 1000 pys), and lowest in older patients aged 70 to 79 years (1.32 per 1000 pys). Incidence across all ages is greater in women than men, 5.21 and 2.13 per 1000 pys, respectively (Becker et al. 2008a). The cumulative migraine incidence as determined in the American Migraine Prevalence and Prevention study (AMPP) by Stewart et al. (2008) was 21% in females and 7.5% in males. The median age of onset was 23.2 years for females and 25.5 years for males. The AMPP data was used to model age-standardized incidence rates; the peak incidence was 18.2/1000 in females aged 20 to 24 years and 6.2/1000 in males aged 15 to 19 years (Stewart et al. 2008).

SI.1.2 Prevalence

The 2010 Global Burden of Diseases Study reports a global prevalence of 14.7% (10.68% in males and 18.79% in females) for migraine in the all ages combined population (Vos et al. 2012). Estimates of migraine prevalence in the global adult population is estimated to be 11% to 11.5% (Stovner et al. 2007; Merikangas 2013). A recent systematic review and meta-analysis of community-based and observational studies (n=302 studies involving 6 216 995 participants) reports a global migraine prevalence of 11.6% (6.9% of males and 13.8% of females) and European prevalence of 11.4% (Woldeamanuel and Cowan 2017). Prevalence of EM from the International Burden of Migraine Study (IBMS) and the AMPP study ranges from 11% to 17.1% in females and 5% to 8% in males (Katsarava et al. 2012; Payne et al. 2011). A review article of epidemiology studies using the International Classification of Headache Disorders second edition criteria reports the weighted average 12-month prevalence of CM to be 0.5% (range: 0.2% to

2.7%) and of migraine with aura to be 4.4% (range: 1.2% to 5.8%) (Merikangas 2013). Given that the 12-month prevalence weighted average of definite or probable migraine was 18.5% across these studies, migraine with aura represents approximately one-quarter of adult patients with migraine (Merikangas 2013).

The frequency of EM in the IBMS study ranged from 5.6% in Australia to 12.3% in the UK to 17.1% in France (Blumenfeld et al. 2011). In a review of headache prevalence studies conducted in European countries, the mean prevalence of current migraine in adults was reported as 14.7% (8% in males and 17.6% in females) (Stovner and Andree 2010). Prevalence ranged from 4.8% to 18.1% among individual country studies (Korolainen et al. 2019; Hagen et al. 2018). The lowest prevalence was observed in a retrospective register study that included migraineurs using occupational health care in Finland, where the point prevalence of migraine was 4.8% (7.4% versus 2.1% in men) among 369 383 individuals in the cohort (Korolainen et al. 2019). In a questionnaire given to a representative sample of the Greek general population (N=10 008), the 1-year prevalence of migraine that reduced activity was 8.2% (Mitsikostas et al. 2018). Similarly, in a nationally representative cross-sectional survey (European Health Survey) in Spain, the overall 1-year prevalence of migraine among 22 842 individuals was 8% (95% confidence interval [CI]: 8, 9) (Roy et al. 2019). In a Swedish study, the 1-year prevalence of migraine among 1668 randomly selected individuals was higher at 13.2% (±1.9%) (Dahlöf and Linde 2001). The 1-year prevalence of definite migraine was highest in the smaller fourth wave of the Nord-Trondelag Health Survey in Norway (n=232 subjects interviewed) at 18.1% (95% CI: 13.1, 23.1) (Hagen et al. 2018).

SI.1.3 Demographics of the Population and Risk Factors for the Disease

The male to female sex ratio for lifetime migraine remains stable at 1:2 to 1:3 and is generally consistent across countries (Merikangas 2013). When stratified by migraine type, the male to female gender ratio for EM is higher, with a range spanning approximately 1:3 to 1:4 (Buse and Lipton 2013; Adams et al. 2015). Patients with migraine are predominantly female (approximately 3:1) with a higher prevalence from 18 to 49 years (Buse et al. 2013).

The most common age of onset of migraine is in the second and third decades of life (Jensen and Stovner 2008). In the Eurolight study, migraine prevalence peaked at 33.5% in the age range 30 to 40 years for males; in females, there was a prevalence plateau at 37% to 40% in the age range of 20 to 60 years. After age 60 years, prevalence fell in both genders (males: 12.2%; females: 22.3%) (Steiner et al. 2014). Similar results were seen in a large US health care database where the frequency of migraine (any evidence) by age group was: 0 to 9 years (1%), 10 to 19 years (10%), 20 to 29 years (17%), 30 to 39 years (21%), 40 to 49 years (21%), 50 to 59 years (16%), 60 to 69 years (9%), 70 to 79 years (3%), 80+ years (1%) (Pressman et al. 2016).

Several risk factors for migraine are reported in the literature; these include female sex, younger age (teenagers and younger adults aged less than 50 years have the highest incidence and prevalence), and a family history of migraine (Stewart et al. 2006; Merikangas 2013; Dzoljic et al. 2014). For some migraine comorbidities, such as asthma (Becker et al. 2008b; Martin et al. 2016) and depression (Patten et al. 2008; Modgill et al. 2012), a bidirectional association has

been found; people with migraine are more likely to have asthma or depression, and people with asthma or depression are more likely to have migraine. Strong inference of the aetiology is limited as treatment-seeking for these primary disorders may increase the opportunity to detect migraine, or vice versa. Obesity has been associated with more frequent and more disabling migraine headache (Bigal et al. 2007); and in the EM population, depression is associated with an increased risk of transitioning to CM (Ashina et al. 2012).

SI.1.4 Main Existing Treatment Options

Triptans are commonly recommended for acute treatment of migraine (NICE 2015; Sarchielli et al. 2012; Swedish Headache Society 2018; Lantéri-Minet et al. 2014). Seven triptans are currently approved for the acute treatment of migraine in the US, Canada, and Europe (See Table SI.1). Labelling for the triptans includes a class labelling, which contraindicates their use in patients with ischaemic coronary artery disease (CAD), coronary artery vasospasm, Wolff–Parkinson–White syndrome, peripheral vascular disease, uncontrolled hypertension, and a history of stroke, and recommends cautious use in patients with and without relevant cardiovascular (CV) history because myocardial ischaemia, myocardial infarction, Prinzmetal's angina, life-threatening arrhythmias, cerebrovascular events, and sensations of pain, tightness, and pressure in the chest, neck, throat, and jaw have been reported (Imigran Tablets 50 mg summary of product characteristics; Maxalt 5 mg Tablets summary of product characteristics; Zomig Tablets 2.5 mg summary of product characteristics; Naramig Tablets 2.5 mg summary of product characteristics).

Table SI.1 summarises acute migraine therapies (Evers et al. 2009; Sarchielli et al. 2012; Worthington et al. 2013).

Table SI.1. Summary of Current Commonly Recommended Migraine Acute Therapies

Substance	Drug/Daily Dose
Triptans	Almotriptan 12.5 mg Eletriptan 20 mg or 40 mg Frovatriptan 2.5 mg Naratriptan 2.5 mg Rizatriptan 5 mg or 10 mg Sumatriptan 25 mg, 50 mg, or 100 mg Zolmitriptan 2.5 mg or 5 mg
NSAIDs	Diclofenac 50 mg to 100 mg Ibuprofen 200 mg to 1200 mg Naproxen 500 mg to 1500 mg Aspirin 500 mg to 1000 mg

Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.
Source: Evers et al. 2009; Sarchielli et al. 2012; Worthington et al. 2013.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics, including combination analgesics, are often recommended for mild to moderate attacks, or when triptans are contraindicated or ineffective. Nonsteroidal anti-inflammatory drugs may be less effective for the

treatment of moderate to severe headaches than many available triptans (Cameron et al. 2015; Xu et al. 2016). The National Institute for Health Care Excellence (NICE) recommends that NSAIDs or paracetamol should be taken in combination with triptans (NICE 2015). Nonsteroidal anti-inflammatory drugs may have side effects involving the gastrointestinal system and may include warnings concerning CV disease (Naproxen 500 mg Tablets summary of product characteristics; Coxib and traditional NSAID Trialists' Collaboration [CNT] et al. 2013).

Recommendations for the use of ergot derivatives vary, ranging from advising that they should be avoided to advising that use should be restricted to low frequency, severe migraine attacks that are unresponsive to other treatment options (Sarchielli et al. 2012; NICE 2015). Opiates and barbiturates are not recommended for the treatment of migraine headaches and should be avoided (Sarchielli et al. 2012; NICE 2015; Lantéri-Minet et al. 2014).

Gepants (CGRP antagonists) are a new class of drug for acute treatment of migraine. Two gepants, ubrogepant and rimegepant, have been approved by the US Food and Drug Administration (FDA) for the acute treatment of migraine, but none are currently approved in the EU (Tepper 2020).

SI.1.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Natural History

Migraine is a serious, chronic, disabling neurological disease characterised by severe headache attacks. These headaches typically last from 4 to 72 hours if left untreated, are generally unilateral in nature, and frequently include throbbing or pulsating pain, often with associated symptoms such as nausea, vomiting, and sensitivity to light, sound, or movement. The natural history of migraine is worse in women. Women experience more frequent, longer lasting, and more severe headaches compared with men and have a greater risk of transition from EM to CM than men (odds ratio [OR] = 2.9, 95% CI = 1.2, 6.9), even after adjusting data for triptan use and headache frequency (Finocchi and Strada 2014).

Migraine can be a progressive disease; in some patients, the condition can transform from EM to CM. An analysis in the AMPP study estimated that this transition from EM to CM occurs at a rate of about 2.5% per year and is associated with increased migraine frequency and use of barbiturates and opioids (Bigal et al. 2008; Lipton 2009). Chronic migraine can also remit to EM, with 1 study reporting a 2-year transition rate of 26% of CM patients to EM patients (Katsarava et al. 2012).

Mortality

Although serious and disabling, migraine by itself is not immediately life-threatening or fatal. An Icelandic study determined that the hazard ratio (HR) of all-cause mortality in adult patients with migraine was slightly increased when compared with patients without migraine in adjusted analyses (HR = 1.15, 95% CI = 1.08, 1.23) (Gudmundsson et al. 2010). An increased risk of mortality from cardiovascular disease (CVD) was reported in patients with migraine (HR = 1.22, 95% CI = 1.10, 1.36) (Gudmundsson et al. 2010).

Morbidity

Cardiovascular: Migraine is associated with an increased risk of a number of CV events, which are in turn associated with increased morbidity. These associations were more significant in patients with migraine with aura (Bigal et al. 2010). Meta-analyses of observational studies identified an increased relative risk (RR) of stroke as 2.16 (migraine with aura, RR = 2.88; migraine without aura, RR = 1.56) (Etminan et al. 2005).

Spector et al. (2010) conducted a meta-analysis of 21 observational studies that examined the risk of ischaemic stroke in patients with migraine and reported an overall pooled effect estimate of 2.04 (95% CI 1.72, 2.43) (Spector et al. 2010). In a nationwide, population-based study of Danish hospitals and outpatient clinics from 1995 to 2013 (n=51 032 migraine patients; n=510 320 general population) that evaluated incident CV events, after adjustment for the covariables, migraine was associated with myocardial infarction (adjusted HR 1.49, 95% CI: 1.36, 1.64), ischaemic stroke (2.26, 95% CI: 2.11, 2.41), and haemorrhagic stroke (1.94, 95% CI: 1.68, 2.23), as well as venous thromboembolism (1.59, 95% CI: 1.45, 1.74) and atrial fibrillation or atrial flutter (1.25, 95% CI: 1.16, 1.36) (Adelborg et al. 2018). In another Danish study including 46 418 twins in Denmark, any CVD (composite) was increased in those with migraine compared to those without migraine (14.3% versus 10%; OR: 1.51; 95% CI: 1.33, 1.71; p<.001) (Le et al. 2011). Another Danish study that captured incident migraine from 2005 through 2013 (N=97 431 migraine patients) reported that at baseline 24.3% of patients took CV medication, 1.7% had cerebrovascular disease, 0.6% had CAD, and 0.2% had peripheral vascular disease (Thomsen et al. 2019).

Psychiatric: Suicidal ideation (Ratcliffe et al. 2008) and suicidal attempt (Ratcliffe et al. 2008; Breslau et al. 2012) have been reported to be increased in patients with migraine compared with those without migraine. Limited data are available on suicide in European patients with migraine. Breslau et al. (2012) reported a baseline prevalence of suicide attempt of 9.1% among adult patients aged 25 to 55 years in the US with migraine (n=496). The 2-year cumulative incidence of suicide attempt was 8.7% compared with 1.3% in controls (Breslau et al. 2012). When adjusted for other confounders, suicide attempt was increased 4-fold (OR = 4.43, 95% CI = 1.93, 10.2) among patients with migraine (Breslau et al. 2012).

In a large systematic review of migraine and psychiatric comorbidity, a bidirectional association of major depression and panic disorder was observed with migraine (Dresler et al. 2019). The prevalence of major depression varied by country, from 6.1% to 73.7%, while the prevalence odds ratios varied from 0.8 to 5.8. The risk of suicide attempts is particularly increased in migraine subjects with comorbid anxiety and depressive symptoms (Dresler et al. 2019). Anxiety was more prevalent than depression in all migraine studies reported here. In a cross-sectional survey of adults in 10 EU countries (Eurolight), depression was prevalent in 6.9% and anxiety was present in 19.1% of migraine subjects. Migraine was associated with depression in males (OR: 2.1; 95% CI: 1.3, 3.4; p=.002) and females (OR: 1.8; 95% CI: 1.1, 3.1; p=.030) and also with anxiety in males (OR: 4.2; 95% CI: 2.8, 6.3; p<.0001) and females (OR: 2.4; 95% CI: 1.7, 3.4; p<.0001) (Lampl et al. 2016). In a retrospective, cross-sectional analysis conducted using data captured through the Migraine Buddy app among individuals with migraine in 17 European

countries, 40.9% of those with EM experiencing 8 to 14 migraine days per month and 34.7% of those experiencing 4 to 7 migraine days per month reported anxiety and/or depression symptoms during migraine attacks (Vo et al. 2018). In a nationally representative cross-sectional survey (European Health Survey) in Spain, among 1902 individuals with migraine in the past 1 year, 28% of females and 17% of males reported chronic anxiety. Among females, 20%, 27%, 31%, and 34% reported mild, moderate, moderately severe, and severe depression, respectively, while 11%, 12%, 14%, and 21% of men reported these symptoms (Roy et al. 2019). In a retrospective register study of patients with migraine using occupational healthcare in Finland (n=17 623) compared with age and gender matched controls (n=17 623) a depressive episode was observed in 13.0% of participants with migraine and 7.1% of controls, a recurrent depressive disorder was reported in 4.8% and 2.5%, respectively, and other anxiety disorders were reported in 14.1% and 7.9%, respectively (Korolainen et al. 2020). In a nationwide population-based postal survey in France, among subjects who had migraine attacks during the last 3 months (n=1957) 50.6% were anxious and/or depressive (28.0% anxiety alone, 3.5% depression alone, 19.1% both) (Lantéri-Minet 2005).

SI.1.6 Important Co-morbidities

Table SI.2. Important Comorbidity Prevalence in Adult Migraine Population by Disease Category

Category	
Psychiatric	
Anxiety*	9.9%-59.1% (Breslau and Davis 1993; Becker et al. 2008a; Breslau et al. 2012; Chen et al. 2012; Goulart et al. 2014)
Depression*	7.1%-48.2% (Breslau and Davis 1993; Becker et al. 2008a; Breslau et al. 2012; Chen et al. 2012; Goulart et al. 2014)
Panic Disorder*	0.6%-10.9% (Breslau and Davis 1993; Chen et al. 2012; Goulart et al. 2014)
Suicide Ideation	3.3%-12.5% (Ratcliffe et al. 2008). Adjusted OR compared to participants without migraine:1.31; 95% CI: 1.10, 1.55 (Friedman et al. 2017).
Suicide Attempt*	0.4%-9.1% (Breslau and Davis 1993; Ratcliffe et al. 2008; Breslau et al. 2012)
Suicide Behaviours*	Adjusted OR compared to participants without migraine: 2.07 (95% CI: 1.96, 2.19) (Friedman et al. 2018)
Cardiovascular Conditions	
Any CVD	14.3% (Le et al. 2011)
Heart Disease	6.7%-8.4% (Chen et al. 2012)
Myocardial infarction*	4.1% (Bigal et al. 2010)
Stroke*	1.0%-2.8% (Becker et al. 2008a; Bigal et al. 2010; Chen et al. 2012)

Abbreviations: CI = confidence interval; CVD = cardiovascular disease; OR = odds ratio.
*Comorbidities shown to be higher in migraine patients compared to matched controls in at least 1 published study.

Co-Medications:

Co-prescribed medications reported among patients with migraine (n=51 688) (before migraine diagnosis) in a population-based study in the UK were nonsteroidal anti-inflammatory drugs (2.0%), paracetamol (10.9%), oral contraceptives (10.2%), and oestrogens/hormone replacement

therapy (6.4%) (Becker et al. 2008a). Patients in the US with migraine reported prescription medications for hypertension (not diuretic [19% to 20%]); diuretic for hypertension (13% to 15%); medication for high cholesterol (13 to 16%), and medication for diabetes (7.3% to 7.5%) (Buse et al. 2013).

In the IBMS study, within the EM population 9.7% used antidepressants, 5.6% used antiepileptics, and 10.8% used CV drugs (Stokes et al. 2011). A pharmacy claims database reported medications in the acute migraine population as any psychotropic (17%), anxiolytics (10%), new generation hypnotics (8%), antipsychotics (0.3%), mood stabilizers (0.1%), and stimulants (0.6%) (Muzina et al. 2011).

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Key issues from the toxicology studies are described in terms of target organ systems.

CNS Findings

Lasmiditan is a central nervous system (CNS)-active drug, and treatment of mice, rats, and dogs was associated with CNS-related clinical signs including tremors, ataxia, hypoactivity, head shaking, clonic movements, and convulsions. These signs progressed in severity as dose (and thus, maximum observed drug concentration [C_{max}] exposures) increased and generally occurred 1 to 2 hours post dose. Convulsions and/or mortality occurred only at oral or intravenous (IV) doses associated with high C_{max} values (>10-fold that at the clinical dose of 200 mg). The lowest no-observed-adverse-effect-level (NOAEL) for CNS signs in the dog, the most sensitive species for these effects, was 30 mg/kg (Week 39 C_{max} and area under the concentration versus time curve [AUC] exposures >8-fold the clinical exposure at the 200-mg dose).

In repeat-dose studies in rats, lasmiditan treatment was associated with pigmentary inclusions in the cytoplasm of large motor neurons in the brain stem and spinal cord. These findings, which were observed histologically in the 26-week chronic toxicity study and the carcinogenicity study, were considered to represent increased autophagocytosis in lasmiditan-treated rats when compared with controls. The intracellular neuronal inclusions were rat-specific (that is, not evident in the morphologic pathology findings from studies in mice or dogs dosed at a maximum tolerated dose for as long as 39 weeks) and were associated with prolonged exposure (that is, present in 26-week and lifetime carcinogenicity studies and not in studies of ≤13-week duration). The inclusions were not considered adverse as there was no evidence of a corollary adverse morphologic effect (for example, inflammation, necrosis). The neuronal inclusions observed in rats are not considered predictive of risk in humans based on the rat-specific nature of the finding.

Cardiovascular System

The in vitro human ether-a-go-go-related gene (hERG) half maximal inhibitory concentration (IC_{50}) for lasmiditan is approximately 10-fold higher than the human plasma unbound lasmiditan concentrations ($C_{max,u}$) at the 200-mg dose. In the in vivo CV safety pharmacology study in conscious dogs using surgically implanted telemetry devices, there were no important effects on CV function or haemodynamics after single IV doses up to 6 mg/kg (C_{max} approximately 1277 ng/mL, approximately 5-fold higher than human exposure at the 200-mg dose). Increases in QRS, QT, and QTc intervals were reported in a 39-week toxicity study in dogs (electrocardiograms [ECGs] collected using surface electrodes) at the high dose of 50 mg/kg (reduced to 40 mg/kg based on the nature of multiple adverse clinical signs). The C_{max} and AUC exposures for these findings were >10-fold human exposure at 200 mg clinical dose. Given these large exposure multiples, the findings are not considered to have clinical significance, particularly in light of the negative findings in a Phase 1 thorough QT (TQT) study.

Vasoconstriction: In multiple assays, which included a positive control (sumatriptan), lasmiditan showed no vasoconstrictive effects. Lasmiditan did not contract rabbit saphenous vein rings ex vivo, a model that correlates highly with human coronary artery constriction (Nelson et al. 2010). Furthermore, in in vitro pharmacology studies, lasmiditan did not induce constriction of the human internal mammary artery, human proximal coronary artery, or human distal coronary artery ex vivo. Finally, lasmiditan did not change coronary or carotid artery diameter in anesthetized beagle dogs. Sumatriptan, the positive control, showed vasoconstrictive effects in all of these experiments. These data are consistent with a lack of evidence for vasoconstriction in clinical experience (Krege et al. 2019).

Renal System

Lasmiditan treatment was associated with changes in the kidney characterised in studies with rats of ≤13 weeks in duration. The changes were manifested as altered renal function with associated histopathologic changes, including renal medullary tubule degeneration and regeneration. The NOAEL in the 13-week rat study was 30 mg/kg corresponding to exposures >6-fold greater than human exposure at a 200-mg dose. Exacerbation of chronic progressive nephropathy was also observed in the 13-week and 6-month studies and was attributed to an age-related, spontaneously occurring condition in rats. No treatment-related histopathologic effects on the kidneys were observed in dogs treated for up to 39 weeks, and there were no renal safety concerns observed from the integrated clinical data. As a result, the rat findings are not considered to be of relevance to human use.

Reproductive/Developmental Toxicity

Lasmiditan treatment was not associated with effects on male or female fertility in a rat study of fertility and early embryonic development.

In embryofoetal development studies with rats and rabbits, there were no test article–related increases in external, visceral, or skeletal malformations. Developmental effects (decreased foetal body weights and associated skeletal variations) occurred at maternally toxic doses (250 mg/kg, rats and 115 mg/kg, rabbit) corresponding to exposures which were approximately 50- and 2.4-fold higher in rats and rabbits, respectively, than exposures at a clinical dose of 200 mg (maternal toxicity included clinical signs, decreased body weight or body weight gain, decreased food consumption; in rabbits, these effects led to the moribund sacrifice of 1 doe [75 mg/kg] and 1 doe which aborted [115 mg/kg]). Exposures at the NOAEL doses (175 mg/kg, rats and 75 mg/kg, rabbits) were approximately 30- and 1.2-fold higher, respectively, than exposures at a clinical dose of 200 mg. In the rabbit only, a slight increase in postimplantation loss and a low incidence of foetal CV (ventricular septal) defects (2 foetuses from 2 separate litters) were also observed at 115 mg/kg. Through the course of development, 2 additional embryofoetal development studies were conducted in rabbits (1 via the IV route and another with oral doses similar to those in the definitive oral study); the increased postimplantation loss and CV defects were not observed in either of these studies.

In the rat pre/postnatal study, prolonged gestation and parturition were observed and the number of stillborn pups and the frequency of postnatal death was increased; however, effects occurred

at a maternally toxic dose of 225 mg/kg which corresponded to exposures estimated to be greater than 40-fold higher than human exposure at 200 mg; the NOAEL of 150 mg/kg/day corresponded to exposures greater than 30-fold higher than human exposure at the 200-mg dose.

Genotoxicity and Carcinogenicity

Lasmiditan was not genotoxic or carcinogenic in rats or transgenic mice.

Drug Abuse Liability

In rats, lasmiditan was not associated with physical dependence and did not generalize to the benzodiazepine, lorazepam. Lasmiditan was weakly self-reinforcing in a self-administration study in heroin-maintained rats (see Module SVI.1).

SII.2 Safety Pharmacology

Other than the findings already discussed above, no significant effects related to Safety Pharmacology were observed.

SII.3 Other Toxicity-Related Information or Data

To support clinical trials with paediatric patients, a juvenile toxicology study was conducted in male and female rats treated with lasmiditan from postnatal day 21 to 77. As for adult rats (in the 13-week study), adverse findings of renal tubule and collecting duct degeneration and regeneration occurred in males in the 50- and 150-mg/kg group. There were no significant lasmiditan-related effects on sexual maturity, neurobehavioral function, or reproduction. Based on renal toxicity in males, the NOAEL was the lowest dose of 15 mg/kg.
There were no other significant effects observed in the nonclinical studies.

Conclusion

Based on the findings from the nonclinical studies and relatively limited experience on use in pregnancy in humans, adverse pregnancy outcomes will be classified as an important potential risk for lasmiditan.

Module SIII - Clinical Trial Exposure

The initial randomized placebo-controlled studies were single dose studies; therefore, the data in Table SIII.1 only reflect the subset of patients from the completed open-label extension long-term study (COL MIG-305/H8H-CD-LAHL [305/LAHL]) who treated 2 or more migraine attacks per month on average in the time period of interest. Given the as needed (PRN) use of lasmiditan for acute treatment of migraine, exposure to the drug in person-time is only possible for the long-term study (Table SIII.1) and is not calculated for exposure based on placebo-controlled single dose studies (Table SIII.2, Table SIII.3, and Table SIII.4). It should be noted that person time is calculated using the time between the dates of the first and last dose, even though the drug is only taken as needed for migraine attacks.

Table SIII.2 and Table SIII.4 show the distribution of patients across all oral Phase 2 and Phase 3 studies by age and by gender (Table SIII.2) or ethnic origin (Table SIII.4). Patients are only counted once if they rolled over from a placebo-controlled study into the open-label extension.

Table SIII.3 shows exposure data by dose across the Phase 2 and Phase 3 clinical development programme based on exposures from individual studies. Patients are counted in both feeder and the open-label long-term study if they participated in both.

Cumulatively, more than 6500 adult subjects/patients have received lasmiditan in the clinical development programme, including 777 in completed Phase 1 studies and 5916 in completed or ongoing Phase 2 and Phase 3 studies. The programme has included more than 30,000 migraine attacks treated with lasmiditan.

Table SIII.1. Duration of Exposure in Patients who Treated ≥2 Migraine Attacks per Month on Average in the Time Period of Interest in Study 305/LAHL

Acute Treatment of Migraine		
Duration of Exposure	**Patients**	**Person time (years)**
≥3 Months	731	509.4
≥6 Months	365	309.4
≥12 Months	186	175.0
Total person time	2030	934.7

Source: Output Location: prd/ly573144/h8h_cd_lahl/final/output/shared/tfl/t14_01_08_01_exp.rtf.

Table SIII.2. Exposure by Age Group and Gender

Acute Treatment of Migraine		
Gender	**Patients**	**Person time[a]**
Male	929	-
Female	4987	-
Total	5916	-
Age Group 1 (Years)	**Patients**	**Person time[a]**
<65	5713	-
≥65 and <75	184	-
≥75 and <85	19	-
≥85	0	-
Total	5916	-
Age Group 2 (Years)		
<75	5897	-
≥75	19	-
Total	5916	-
Age Group 3 (Years)		
<85	5916	-
≥85	0	-
Total	5916	-

Source: Output Location: /lillyce/prd/ly573144/idb_lasmi/idb eu rst/output/shared/tfl_css/fqdemcrev1.rtf.

Note: Data from the oral Phase 2 and Phase 3 studies (COL MIG-202/H8H-CD-LAHO [202/LAHO], H8H-JE-LAIH [LAIH], COL MIG-301/H8H-CD-LAHJ [301/LAHJ], COL MIG-302/H8H-CD-LAHK [302/LAHK], H8H-MC-LAIJ [LAIJ] double-blind, 305/LAHL, and LAIJ open label extension) are included in this table.

[a] This table includes data from single attack studies; therefore, no person time data is provided.

Table SIII.3. Exposure by Dose

Acute Treatment of Migraine		
Dose of exposure[a,b]	**Patients**	**Person time[c]**
Lasmiditan ≤45 mg[d]	88	-
Lasmiditan 50 mg	824	-
Lasmiditan 100 mg	3432	-
Lasmiditan 200 mg	3036	-
Lasmiditan 400 mg	70	-
All Oral Lasmiditan	7362	-
All IV Lasmiditan	88	-
Total	7450	-

Source: Output Location: /lillyce/prd/ly573144/idb_lasmi/idb eu rst/output/shared/tfl_css/fqexpt1.rtf.

Abbreviations: IV = intravenous.

Note: Data from the Phase 2 and Phase 3 studies (COL MIG-201/H8H-CD-LAHM [201/LAHM], 202/LAHO, LAIH, 301/LAHJ, 302/LAHK, LAIJ [double-blind], 305/LAHL, and LAIJ [open label extension]) are included in this table.

[a] The treatment group is categorized based on the first dose, regardless of whether a patient took a second dose.

[b] A patient is counted in both the feeder study and the long-term follow up study if the patient was treated in both studies.

[c] This table includes data from single attack studies; therefore, no person time data is provided.

[d] Lasmiditan dose arms in the 201/LAHM study are 2.5 mg, 5 mg, 10 mg, 30 mg, and 45 mg administered IV.

Table SIII.4. Exposure by Ethnic Origin

Acute Treatment of Migraine		
Race	**Patients**	**Person time[a]**
American Indian or Alaska Native	97	-
Asian	692	-
Black or African American	700	-
Native Hawaiian or Other Pacific Islander	13	-
Caucasian	4297	-
Multiple[b]	42	-
Other/Missing[b]	75	-
Total	5916	-
Ethnic Origin		
Hispanic or Latino	814	-
Not Hispanic or Latino	4162	-
Missing[c]	940	-
Total	5916	-

Source: Output Location: /lillyce/prd/ly573144/idb_lasmi/idb_eu_rst/output/shared/tfl_css/fqdemcrev1.rtf

Note: Data from the oral Phase 2 and Phase 3 studies (202/LAHO, LAIH, 301/LAHJ, 302/LAHK, LAIJ [double-blind], 305/LAHL, and LAIJ [open label extension]) are included in this table.

[a] This table includes data from single attack studies; therefore, no person time data is provided.

[b] In Study LAIJ, mixed-race patients were included in the “Multiple” race category and patients who did not select a racial category were included in the “Other/Missing” race category.

[c] For Study LAIH, patients are included in the 'Missing' category because ethnicity was not collected.

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criterion: Patients <18 years of age

Reason for exclusion: The safety and efficacy for patients <18 years of age has not yet been established; paediatric trials are ongoing. The efficacy and safety of this molecule in Phase 3 clinical trials were first studied and established in adults.

Is it considered to be included as missing information? No

Rationale: While the clinical development programme did not include children and adolescents, given the pharmacology and known safety profile of lasmiditan, the likely safety profile in patients <18 years is not expected to be different from adult patients. In addition, data from a pharmacokinetic study in children with migraine showed pharmacokinetic findings (in patients >40 kg) similar to those in adults with adverse events consistent with the known safety profile of lasmiditan. Early data from the ongoing Phase 3 studies (double-blind placebo-controlled H8H-MC-LAHV [LAHV] and open-label H8H-MC-LAHW [LAHW]), suggest similar tolerability and safety profile in children and adolescents, with no new patterns or trends observed in the adverse events reported.

Criterion: Women who are pregnant

Reason for exclusion: This is a standard exclusion criterion in clinical development. Nonclinical studies using pregnant rats and rabbits demonstrated adverse effects on the embryos, foetuses, and offspring in association with maternal toxicity. However, there is insufficient information on the effects of lasmiditan on human maternal and foetal health. Women of childbearing potential are expected to comprise a significant proportion of the target migraine population. Through 12 June 2020, there were 26 pregnancies in maternal exposure (total female exposure N=4987) and 1 pregnancy from paternal exposure reported during the clinical development programme. Of the 26 pregnancies reported, 16 were exposed to lasmiditan during the first trimester of their pregnancy. There were no patients exposed to lasmiditan beyond the first trimester. The remaining 10 pregnancies were not temporally related to lasmiditan dosing. Outcomes from the 16 pregnancies that were exposed to lasmiditan included 5 normal births, 3 spontaneous abortions, 1 elective termination, and 1 premature birth. Additionally, 3 cases are awaiting follow-up information regarding the birth and delivery and 3 cases were lost to follow-up.

Is it considered to be included as missing information? No

Rationale: While pregnant women were excluded from clinical trials, given the pharmacology and known safety profile of lasmiditan, the likely safety profile in pregnant women is not expected to be different from other adult patients. In addition, data from use of lasmiditan in pregnant women will also be available from planned safety studies in this population to assess adverse pregnancy outcomes.

Criterion: Patients with CVD

Phase 2 studies excluded patients with history or evidence of CAD, ischaemic or haemorrhagic stroke, controlled or uncontrolled historical or current hypertension and those with use of hemodynamically active CV drugs. The first Phase 3 study (COL MIG-301/H8H-CD-LAHJ [301/LAHJ]) limited the exclusion to those with a known history or evidence of CAD, clinically relevant arrhythmia, and uncontrolled hypertension. The Phase 3 studies, COL MIG-302/H8H-CD-LAHK (302/LAHK) and H8H-MC-LAIJ (LAIJ) did not exclude these patients.

Reason for exclusion: Patients with CV conditions were excluded in earlier studies to avoid exposing such patients to an investigational drug whose safety profile was not fully established.

The exclusion criteria were then removed from Studies 302/LAHK and LAIJ in order to specifically assess the safety of lasmiditan in this population as the mode of action of lasmiditan was not predicted to have adverse ischaemic CV effects. The CVD noted at baseline in oral placebo-controlled Phase 2 and 3 studies (by SMQ) included 63 patients with ischaemic heart disease, 136 patients with cardiac arrhythmias, 30 patients with cardiomyopathy, and 48 patients with ischaemic CNS vascular conditions.

Is it considered to be included as missing information? No

Rationale: The Phase 2/3 clinical development programme for lasmiditan included a well-balanced population across lasmiditan- and placebo-treated patients in the placebo-controlled studies (COL MIG-202/H8H-CD-LAHO [202/LAHO], H8H-JE-LAIH [LAIH], 301/LAHJ, 302/LAHK, LAIJ) with respect to the presence of baseline CVD (16.3% of lasmiditan-treated patients and 16.9% of placebo-treated patients) and 1 or more CV risk factors (CVRFs) (lasmiditan-treated patients 62.4% with ≥1, 23.2% with ≥2, and 4.6% with ≥3 CVRFs; placebo-treated patients: 61.5% with ≥1, 23.5% with ≥2, and 4.9% with ≥3 CVRFs) in addition to their migraine history. The rates of risk factors appear to be generally representative of the overall migraine population. In the oral placebo-controlled trials 16.3% of patients on lasmiditan reported CVD at baseline, with hypertension (and related conditions) reported most frequently (n=642, 13.1%). The CVDs noted at baseline (by SMQ) included 63 patients with ischaemic heart disease, 136 patients with cardiac arrhythmias, 30 patients with cardiomyopathy, and 48 patients with ischaemic CNS vascular conditions when combined across placebo and lasmiditan treatment groups. These numbers, although relatively lower compared with self-reported CV events in the AMPP study (Buse et al. 2017), are reflective of the migraine population that were included based on inclusion criteria.

Safety in patients with CVD or CVRFs is not expected to be different from in those patients without CVD or CVRFs.

Criterion: Patients with significant hepatic and renal impairment.

Reason for exclusion: To avoid exposing a patient with an acute or known serious hepatic and/or renal condition to an investigational drug whose safety profile is not fully established.

Is it considered to be included as missing information? No

Rationale: Lasmiditan undergoes hepatic and extrahepatic metabolism primarily by non-cytochrome P450 (CYP) enzymes, with ketone reduction to the alcohol S-M8 representing the major pathway. Renal excretion is a very minor route of lasmiditan clearance. Recovery of unchanged lasmiditan in urine was low, with approximately 2% of the dose recovered by 24 hours post dose and was consistent for all dose levels. Given that the target population for migraine is predominantly young adults, the proportion of these patients with pre-existing renal and/or hepatic conditions will likely be limited. Further, in 2 separate studies of lasmiditan in patients with impaired hepatic function (Study COL MIG-114/H8H-CD-LAHF [114/LAHF]; mild hepatic impairment n=8 and moderate hepatic impairment n=8) and impaired renal function (Study COL MIG-113/H8H-CD-LAHN [113/LAHN]; severe renal impairment n=8), lasmiditan was generally safe and well-tolerated by subjects with normal hepatic/renal function and by subjects with mild-to-moderate hepatic/severe renal impairment.

Overall, during the clinical development programme, there has been no pattern or trend observed for renal or hepatic adverse events.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure because lasmiditan is developed for acute treatment of migraine with PRN use and most Phase 2 and 3 placebo-controlled studies were based on treatment of a single migraine attack.

The size of the lasmiditan-exposed patient group in migraine oral placebo-controlled clinical trials (N=4861) means that detection of adverse drug events with a 95% level of certainty is limited to those which occur at a frequency of greater than 1 in 1620 patients (0.06%).

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Since lasmiditan is developed for acute treatment of migraine with PRN use and most Phase 2 and 3 placebo-controlled studies were based on treatment of single migraine attack, calculation of exposures in person-time was not feasible for typically under-represented populations.

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Pregnancy was an exclusion criterion in the clinical development programme; however, pregnancies in women exposed to lasmiditan have been reported in Phase 3 clinical trials but with limited information on outcomes (26 total pregnancy cases: 2 from Study 302/LAHK, 20 from Study 305/LAHL, and 4 from Study LAIJ as of 12 June 2020. Female exposure = 4987).
Breastfeeding women	Not included in the clinical trial development programme.
Patients with relevant comorbidities:	
Patients with hepatic impairment (Study 114/LAHF)	Mild hepatic impairment Number of patients: 8 Moderate hepatic impairment Number of patients: 8
Patients with renal impairment	Severe Renal Impairment: N=8 patients from Study 113/LAHN; additionally, 3 patients from double-blind placebo-controlled Phase 2/3 studies had renal failure, 2 patients had renal impairment, 1 patient had renal disorder, and 1 patient had renal tubular acidosis at baseline.

Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Patients with cardiovascular impairment	In Phase 2/3 placebo controlled studies, lasmiditan-treated patients with at least 1 or more cardiovascular risk factors (age >40, hypertension or SPB ≥140 mmHg, diabetes, total cholesterol ≥240 mg/dl) (based on the ACC/AHA criteria, Goff et al. 2014, and the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001) included: n= 3031 (62.4%) with ≥1 n= 1128 (23.2%) with ≥2 n= 224 (4.6%) with ≥3 CVRFs In addition to their migraine history, 16.3% (n=798) of all lasmiditan-treated patients had a history or pre-existing cardiovascular disease (SMQ narrow terms of cardiac arrhythmias, ischaemic heart disease, hypertension, cardiac failure, cardiomyopathy, CNS vascular disorders, embolic and thrombotic events, pulmonary hypertension, and Torsade de pointes/QT prolongation).
Immunocompromised patients	Lasmiditan has not been specifically studied in immunocompromised patients.
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical development programme included a representative population of patients with varying disease severity across acute migraine.
Population with relevant different ethnic origin	The oral Phase 2 and Phase 3 studies included participants with the following ethnic origins: n= 97 American Indian or Alaska Native n= 692 Asian n= 700 Black or African American n= 13 Native Hawaiian or Other Pacific Islander n=4297 Caucasian n= 42 Multiple
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; CNS = central nervous system; CVRFs = cardiovascular risk factors; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; SBP = systolic blood pressure; SMQ = Standardised MedDRA Query.

Module SV - Post-Authorisation Experience

Lasmiditan was first approved in the US (first global approval) on 11 October 2019 by the FDA (FDA 2019). However, marketing authorization was not granted until the final recommendation of the Drug Enforcement Administration to place lasmiditan (REYVOW) in Schedule V of the Controlled Substance Act (DEA 2020). This occurred on 31 January 2020 and lasmiditan has only been available by prescription since that date.

As of 31 July 2020, 11 140 800 mg of lasmiditan have been sold in the postmarketing environment. All sales as of 31 July 2020 have occurred in the US. The number of patients cannot be adequately estimated at this time due to small volume sales and limited period of market availability.

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

Results from the human abuse potential study (H8H-MC-LAHB [LAHB]) showed higher drug liking for lasmiditan compared with placebo in recreational poly drug users. At a supratherapeutic dose of 400 mg lasmiditan, this effect was not significantly different from that seen with alprazolam. However, there is no evidence indicating that lasmiditan produces any physical dependence based on a lack of withdrawal symptoms observed in a multiple-ascending dose study where healthy subjects took a daily dose of study drug for 7 consecutive days (Study H8H-MC-LAHE [LAHE]).

Additionally, in the oral Phase 2 and Phase 3 studies (202/LAHO, LAIH, 301/LAHJ, 302/LAHK, LAIJ [double-blind and open label extension], and 305/LAHL), lasmiditan (N=5916) was associated with treatment-emergent adverse events ([TEAEs] defined as an adverse event [AE] that has its onset or worsens in severity within 48 hours of a lasmiditan dose) that are considered to be potentially associated with abuse liability (key AL terms) such as ‘feeling abnormal’ (n=79, 1.3%), ‘euphoric mood’ (n=35, 0.6%), ‘abnormal dreams’ (n=27, 0.5%), ‘hallucination, visual’ (n=14, 0.2%), ‘feeling drunk’ (n=13, 0.2%), ‘hallucination’(n=11, 0.2%), ‘dysphoria’ (n=5, 0.1%), ‘mental impairment’ (n=5, 0.1%), ‘depersonalisation/derealisation disorder’ (n=4, 0.1%), ‘hallucination, auditory’ (n=2, 0.0%), ‘apathy’ (n=1, 0.0%) and illusion (n=1, 0.0%). These key abuse liability (AL) TEAEs that are more specific for the assessment of AL occurred uncommonly, but the majority were reported numerically more frequently for lasmiditan-treated patients than for placebo-treated patients. In the Phase 2/3 placebo-controlled trials (Studies 202/LAHO, LAIH, 301/LAHJ, 302/LAHK, and LAIJ) key AL TEAEs of feeling abnormal ($p<.001$), euphoric mood ($p=.022$), and hallucination, visual ($p=.040$) were reported with a significantly higher frequency in the lasmiditan-treated group than in the placebo-treated group. Drug misuse/abuse will be classified as an important potential risk in the Risk Management Plan (RMP).

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

- Injuries secondary to neurological adverse drug reactions (ADRs):

  Although neurological ADRs (dizziness, somnolence, paraesthesia, fatigue, hypoesthesia, and incoordination) are commonly reported AEs with lasmiditan exposure, the majority of these AEs were not associated with serious outcomes such as injuries or accidents in the clinical development programme. Of the 2388 patients (from the oral Phase 2 and Phase 3 studies) with at least 1 reported CNS TEAE, 9 patients had accidents and or injuries that were noted to be in temporal proximity to the treatment-emergent nervous system AEs. On review, none of these were determined to be a consequence of the neurological AEs. Neurological events, although frequently observed with lasmiditan treatment, have not been associated with serious injuries/accidents or other adverse consequences that could lead to individual or public health risks and thus, are not considered important safety concerns at this point.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

- Serotonin syndrome:

  Serotonin syndrome has been identified as an ADR with lasmiditan and may occur with lasmiditan alone or when used concomitantly with other drugs known to increase serotonin levels. While the impact of a serious serotonin syndrome may be high for an individual requiring medical intervention and discontinuation of lasmiditan, given that the use of lasmiditan is as a PRN drug and the rarity of severe/serious events, the risk for serotonin syndrome is considered minimal from a public health perspective and for the benefit-risk profile of lasmiditan at large. The adverse reaction of serotonin syndrome is thus not considered an important safety concern at this point.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (for example, actions being part of standard clinical practice in each EU Member state where the product is authorised)

- None

Known risks that do not impact the risk-benefit profile

- Adverse reactions such as dizziness, somnolence, fatigue, anxiety, visual impairment, paraesthesia and muscle weakness are known to occur but do not impact the risk-benefit profile of lasmiditan.

Other reasons for considering the risks not important

- None

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk 1: CNS effects and impaired ability to drive and use machines

Risk-Benefit Impact:

A simulated driving study (COL-MIG-106/H8H-CD-LAHG [106/LAHG]) demonstrated a dose-dependent impact of lasmiditan on simulated driving as measured by standard deviation of lateral position (SDLP), lane exceedance, speed deviation, and other measures of driving safety. Effects on attention were also measured 90 minutes after a single oral dose of lasmiditan and at the approximate time of peak concentration of lasmiditan. For SDLP, 73% to 96% of subjects exceeded the impairment threshold of 4.4 cm (comparable to 0.05% blood alcohol concentration, the most common equivalent of legal alcohol limit for driving globally) across all 3 doses of lasmiditan (50 mg, 100 mg, and 200 mg). The increase in SDLP with the 200 mg dose was similar to a 1 mg dose of alprazolam. Although there were subjects who did not report TEAEs, they still demonstrated impairment in the simulated driving tests. In addition, although the majority of subjects said they felt safe to drive prior to the driving simulator assessment (80% of the subjects following the 50 mg dose of lasmiditan and 55% of subjects at the 200 mg dose), >50% showed driving impairment.

A second study (H8H-MC-LAIF [LAIF]) conducted with 100 mg and 200 mg lasmiditan demonstrated that clinically meaningful impairment had resolved by 8 hours after dosing.

Although a definitive association between lasmiditan use and road traffic accidents in the Phase 2 and Phase 3 clinical trial population has not been seen, the ability to detect infrequent events such as road traffic accidents is limited in clinical trials, and it is possible that minor events were incompletely ascertained. Despite common reports of TEAEs that may impair mental ability in lasmiditan-treated patients in the Phase 2 and Phase 3 programs, no clear association was observed with road traffic accidents, impaired ability to use machinery, or other accidents and the occurrence of those TEAEs. Whilst a clear association between the observed effects and significant adverse outcomes has not been demonstrated in clinical trials, impairment of driving or use of machinery after exposure to lasmiditan can have serious consequences for both the patient as a driver and also for others (passengers, drivers of other vehicles involved in the accident, or pedestrians) in the real world. As a result, the risk of CNS effects and impaired ability to drive and use machines is considered an important identified risk based on its likely impact on the overall benefit-risk of lasmiditan exposure in the context of migraine treatment.

Important Potential Risk 1: Adverse pregnancy outcomes

Risk-Benefit Impact: In embryofoetal development studies with rats and rabbits, decreased foetal body weights and skeletal variations occurred concomitant with maternal toxicity in both rats and rabbits following exposure to lasmiditan. At the maternally toxic dose (115 mg/kg) in rabbits only, there was a slight increase in postimplantation loss, and foetal CV (ventricular septal) defects occurred at a low incidence. In a rat pre- and postnatal study, prolonged gestation and parturition and an increased number of stillborn pups and increased frequency of postnatal death occurred in conjunction with maternal toxicity (225 mg/kg).

There have been 26 pregnancies in the completed and ongoing Phase 2 and 3 studies with limited information on outcomes. As such, the current data are too limited to draw conclusions about the effect of lasmiditan exposure during pregnancy in humans.

The nonclinical effects observed following lasmiditan treatment of pregnant animals occurred at exposures associated with maternal toxicity and which were at higher doses than would be used in humans, and no adverse outcomes have been demonstrated to date. As a result, there is no current impact on benefit-risk in human use. However, women of childbearing potential will constitute a significant proportion of the target patient population in the treatment of migraine, so if further human experience on use in pregnancy provides consistent evidence of significant adverse pregnancy outcomes effects, this risk, when balanced against the potential benefit for a nonlife-threatening condition like migraine, will impact the benefit-risk of lasmiditan.

Important Potential Risk 2: Drug misuse/abuse

Risk-Benefit Impact: Based upon the findings from a human abuse potential study in recreational drug users (Study LAHB), lasmiditan 100 and 200 mg doses demonstrated higher drug liking compared with placebo based on Drug Liking scores. The supra-therapeutic dose of lasmiditan (400 mg) was not significantly different from alprazolam, indicating a potential for abuse in recreational drug users.

From the Phase 2 and 3 studies in patients treated with lasmiditan, there have been reports of euphoric mood, feeling drunk, feeling abnormal, and hallucinations that could be associated with AL.

Patients with recent or current evidence of abuse of any drug, prescription or illicit, or alcohol were excluded from the clinical studies; however, it is possible that those with such history and/or risk factors (including comorbidities that predispose patients to drug abuse such as depression, anxiety, and posttraumatic stress disorder) may misuse and/or abuse lasmiditan when prescribed in real-world practice (Back and Brady 2008; Peterlin et al. 2011). Given the adverse consequences (including psychological, behavioural, and social changes) related to drug misuse/abuse, if this risk was confirmed in every day clinical practice and in more extensive patient exposures than included in clinical development to date, the benefit-risk of lasmiditan would be adversely impacted.

Missing Information 1: Long-term intermittent use

Risk-Benefit Impact: The maximum treatment exposure duration was 12 months in the migraine clinical development programme. During this period, patients were exposed to varying frequency of doses based on the frequency of their migraine attacks. Although the current data do not pose any concern related to use of lasmiditan for 1 year, migraine is a chronic condition, and it is anticipated that acute intermittent treatment will continue for long periods of time. Long-term use is considered to be missing information worthy of further study to collect more data on outcomes in a larger population and for longer periods of time than occurred in clinical development. If the data demonstrate that long-term use is associated with clinically meaningful adverse outcomes or morbidity, this could impact the benefit-risk in the context of acute treatment of a nonlife-threatening condition such as migraine.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the initial RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: CNS effects and impaired ability to drive and use machines

Potential mechanisms:

As a centrally penetrant selective $5HT_{1F}$ receptor agonist, the most common adverse effects observed with lasmiditan are of neurological nature, including dizziness and somnolence. It is plausible that these adverse effects may contribute to or cause impaired driving and the use of machinery.

Evidence source(s) and strength of evidence:

A simulated driving study in healthy volunteers demonstrated a dose-dependent impact of lasmiditan on driving, as observed by a number of different measures of driving safety. Adverse effects on attention were also observed 90 minutes after a single oral dose of lasmiditan and at the approximate time of peak concentration of lasmiditan. In this driving study, 73% to 96% of subjects who received any of the 3 doses of lasmiditan (50 mg, 100 mg, or 200 mg) showed impairment greater than the legal alcohol limit for driving (0.05% blood alcohol content). The majority of subjects felt safe to drive prior to the simulated driving assessment, but >50% showed driving impairment.

A second study conducted with 100 mg and 200 mg lasmiditan demonstrated that clinically meaningful driving impairment had resolved by 8 hours after dosing.

Despite common reports of TEAEs that may impair mental ability in lasmiditan-treated patients, in the Phase 2 and Phase 3 programs, no clear association was observed with road traffic accidents, impaired ability to use machinery, or other accidents and the occurrence of those TEAEs. However, the role of the CNS effects in contributing to an impairment in driving or in using machinery cannot be excluded.

Characterisation of the risk:

- Frequency in the simulated driving study (106/LAHG):
  - Total collisions represent the sum of collisions with other vehicles and off-road crashes in a 100 km highway simulated driving test. These counts also include the number of times that a lane deviation exceeded 4 feet (that is, a crash-likely event). The mean number of total collisions[a] with lasmiditan were:
    - 1.3 (50 mg)
    - 2.3 (100 mg)
    - 4.4 (200 mg)

[a]Nearly all collisions in the total collision score were due to off-road collisions.

- In the integrated clinical trial database (as of 12 June 2020)
  - There were 4 AEs of driving-related accidents reported in the oral placebo-controlled Phase 2/3 studies.
  - In all oral lasmiditan studies (including uncontrolled studies), a total of 12 unique driving accidents were identified, 10 of which were AEs. In the 2 accidents reported as TEAEs (1 considered a TEAE because of imputed dosing and the other event occurring 2 days after the last dose), the patient was the driver at the time of the accident; both were nonserious and of mild and moderate severity. One of these TEAEs reported a related injury of 'contusion'.
  - Three additional driving-related incidents of relevance were identified from Studies LAIJ and LAIH based on the 'Assessment of Driving Accidents and Violations' questionnaire. Of these, 2 were in patients on lasmiditan and 1 in a patient on placebo. In the 2 lasmiditan patients (both drivers at the time of the incident), 1 incident occurred 3 hours postdosing with 200 mg and 1 at 10 hours postdosing with 100 mg. The incidents were not reported as TEAEs (no severity noted), and 1 of these presented with TEAE of paraesthesia and fatigue at the time of the incident.
- No driving/machinery use related accidents have been reported from postmarketing use of lasmiditan through 12 June 2020.

Risk factors and risk groups:

No specific risk factors and/or risk groups that have a risk higher than the overall population have been identified.

Preventability:

There are currently no data on the predictability of this risk or factors that would increase the risk, and no information that would indicate that this risk can be detected at an early stage in order to mitigate serious outcomes. Although a dose-dependent impact on various driving related parameters was observed in the simulated driving study, overall, the majority of subjects at all

doses had driving impairment. Furthermore, on self-reported measures indicating the extent to which subjects were aware of CNS sedative effects, only 20% and 44.7% of the subjects reported not feeling safe to drive following the 50 mg and 200 mg dose of lasmiditan respectively, in spite of clear evidence of driving impairment. The Reference Safety Information, and hence local labels, will reflect relevant data and include a cautionary statement for prescribers emphasizing the risk and the importance of adhering to the period of driving restriction (8 hours post dose) to mitigate/minimise the risk. A similar statement will also be included in the outer packaging of the drug carton.

Impact on the risk-benefit balance of the product:

Driving impairment/use of machinery can have serious consequences for both the patient as a driver/user and others (passengers or drivers of other vehicles involved in the accident). As a result, if this risk is not adequately managed, then benefit-risk overall will be impacted in the context of migraine treatment.

Public health impact:

Given that serious injury/accidents secondary to driving impairment/use of machinery following lasmiditan use may involve other individuals as well as the patient, if this risk is realised it could potentially have a significant public health impact.

Important Potential Risk: Adverse pregnancy outcomes

Potential mechanisms:

The potential mechanisms by which lasmiditan may cause impaired embryo foetal development and/or adverse pregnancy outcomes have not been identified.

Evidence source(s) and strength of evidence:

In nonclinical studies in which pregnant rats and rabbits were dosed with lasmiditan, the offspring had decreased body weights and skeletal variations were observed. In rabbits only, there was a small increase in post implantation loss (miscarriage) and in the number of foetal CV defects. An increased number of stillborn pups and an increase in the frequency of postnatal death occurred in rats. All effects occurred in circumstances of maternal toxicity (that is, where there were significant reductions in maternal body weight and food consumption, and at exposures higher than would be used in patients).

Characterisation of the risk:

There have been 26 pregnancies in the completed Phase 2 and 3 studies with limited information on outcomes (female lasmiditan exposure n=4987). Of the 26 pregnancies reported, 16 patients were exposed to lasmiditan during the pregnancy. Outcomes of these 16 pregnancies included 5 normal births (0.10%), 3 spontaneous abortions (0.06%), 1 elective termination (0.02%), and 1 premature birth (0.02%). Additionally, 3 of these cases are awaiting follow-up information (0.06%) regarding the birth and delivery and 3 were lost to follow-up (0.06%). As such, the

current data are too limited to draw conclusions on the characterisation of this risk in humans.

No pregnancies have been reported from postmarketing use of lasmiditan.

Risk factors and risk groups:

Women of childbearing potential who become pregnant during treatment with lasmiditan are the at risk population, but no specific risk factors for abnormal foetal outcomes have been identified.

Preventability:

The Reference Safety Information and local labels will reflect that there are insufficient human data to establish the safety of lasmiditan during pregnancy. It will also clearly state that lasmiditan should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. However, it is likely that women exposed to lasmiditan will become pregnant in routine clinical practice, as the indicated population is predominantly women of childbearing potential. Therefore, it is unlikely that this risk will be entirely preventable in everyday clinical practice.

Impact on the risk-benefit balance of the product:

The findings from the nonclinical developmental and reproductive toxicity studies and their potential implications on use in human pregnancy exposure have been classified as an important potential risk, as the current data are too limited to draw any definitive conclusions or refute any similar adverse effects in pregnant women. In addition, the potential for other adverse effects of lasmiditan on human foetal development is not known.

If data from further systematic study or other data sources demonstrate that use in pregnant women with migraine is associated with adverse outcomes to the mother, foetus, or baby, there could be an impact on the benefit-risk in the context of migraine treatment, depending on the clinical significance of the findings from these studies.

Public health impact:

Although nonclinical effects were observed at higher doses associated with maternal toxicity and with daily dosing during gestation and lactation in toxicology studies, the impact on human exposure is unknown. The existing data on pregnancy outcomes in pregnant women treated with lasmiditan is very limited, with no evidence to date of medically significant abnormalities in the foetus or offspring. Therefore, the population-level impact is not readily quantifiable, but overall is expected to be low.

Important Potential Risk: Drug misuse/abuse

Potential mechanisms:

Although it is primarily a CNS active substance, the potential mechanism by which lasmiditan may cause drug misuse or abuse has not been identified.

Evidence source(s) and strength of evidence:

The findings from nonclinical studies with lasmiditan were either not indicative of or inconclusive with respect to any misuse or abuse potential. The main evidence source came from a clinical human abuse potential study in users of multiple recreational drugs (Study LAHB). This study demonstrated that the possibility for lasmiditan to have a higher AL than placebo could not be excluded. The mean Drug Liking scores with lasmiditan were shown to increase with increasing doses up to 400 mg and, at this highest dose, were seen at a similar rate to that observed following administration of the positive control, alprazolam. The subjects in the study considered that the effects of lasmiditan were most similar to those of benzodiazepines. In addition, there was a clear dose-related trend in the incidence of AEs reported in this study that could indicate abuse potential of lasmiditan, especially somnolence, euphoric mood, and a feeling of relaxation. In the Phase 2/3 placebo-controlled studies, the number of lasmiditan-treated patients reporting feeling abnormal; hallucination, visual; or euphoric mood was statistically significantly greater than in placebo-treated patients.

Characterisation of the risk:

In the Lilly Search Category (LSC) for Abuse Liability Terms, 1759 (36.4%) lasmiditan-treated patients reported at least 1 AL TEAE compared with 177 (8.4%) placebo-treated patients in the Phase 2/3 placebo-controlled studies (202/LAHO, LAIH, 301/LAHJ, 302/LAHK, LAIJ). The most frequently reported (≥2%) AL TEAEs (lasmiditan vs. placebo) were dizziness (n=960, 19.9% vs. n=68, 3.2%), somnolence (n=350, 7.2% vs. n=47, 2.3%), paraesthesia (n=306, 6.4% vs. n=30, 1.4%), fatigue (n=258, 5.3% vs. n=20, 1.0%), and asthenia (n=122, 2.5% vs. n=4, 0.2%), which do not, by themselves, signify abuse potential, but rather are common TEAEs within the lasmiditan clinical programme. Therefore, several key terms from the LSC list are considered more specific to abuse potential and capture events that may represent either of the following were used to better characterise AL

- rewarding effects (for example, euphoric mood), which could lead to abuse in humans, or
- effects which could reduce or offset the likelihood of abuse (for example, dysphoria)

The frequency of the occurrence of TEAEs for these key terms in the oral placebo-control Phase 2 and Phase 3 studies are summarised in Table SVII.1.

Table SVII.1. Frequency of Key Abuse Liability TEAEs by Preferred Term

SMQ/LSC Potential Abuse Liability Preferred Terms	Placebo (N=2061) n (%)	All lasmiditan (N=4861) n (%)
Feeling abnormal	1 (0.1%)	54 (1.1%)
Euphoric mood	1 (0.0%)	18 (0.4%)
Abnormal dreams	1 (0.0%)	12 (0.3%)
Hallucination, visual	0 (0.0%)	9 (0.2%)
Feeling drunk	0 (0.0%)	6 (0.1%)
Depersonalisation/derealisation disorder	0 (0.0%)	3 (0.1%)
Mental impairment	0 (0.0%)	3 (0.1%)

Hallucination	0 (0.0%)	2 (0.0%)
Apathy	1 (0.0%)	1 (0.0%)
Dysphoria	0 (0.0%)	1 (0.0%)

Source: /lillyce/prd/ly573144/idb_lasmi/idb_eu_rst/output/shared/tfl_css/fqteaealpa1.rtf
Abbreviations: LSC = Lilly Search Category; N = total number of patients in this category; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients reporting TEAE; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.
Note: This table includes the oral placebo-controlled Phase 2 and Phase 3 studies (202/LAHO, LAIH, 301/LAHJ, 302/LAHK, and LAIJ).

In the integrated database through 12 June 2020, there have been reports of key AL TEAEs (based on all oral integrated lasmiditan exposure across studies). Events reported in ≥10 patients included: feeling abnormal (n=79, 1.3%); euphoric mood (n=35, 0.6%); abnormal dreams (n=27, 0.5%); hallucination, visual (n=14, 0.2%); feeling drunk (n=13, 0.2%); and hallucination (n=11, 0.2%).

No definitive patterns of abuse of lasmiditan were reported or identified during the Phase 2 and Phase 3 clinical trials based on medical review of the data.

No events of abuse or misuse of lasmiditan have been reported from postmarketing data through 12 June 2020.

Risk factors and risk groups:

No specific risk factors or risk groups have been identified from the clinical trial programme in patients. However, based on a clinical human abuse potential study, it is possible that certain patient groups could be more likely to misuse and/or abuse lasmiditan when it is prescribed. These could include patients with recent or current evidence of abuse of any drug (including prescription medicines, illicit drugs, or alcohol), or those with other conditions that might predispose them to drug abuse such as depression, anxiety, and posttraumatic stress disorder (Back and Brady 2008; Peterlin et al. 2011).

Preventability:

The Reference Safety Information, and hence local labels, will reflect relevant data and include a cautionary statement for prescribers to assess patients for history of risk factors and/or abuse as well as evaluate for any signs of lasmiditan abuse.

However, the extent to which this effect is preventable is unknown at this stage.

Impact on the risk-benefit balance of the product:

Given the adverse consequences (including psychological, behavioural, and social changes) related to drug misuse/abuse, if this risk was observed in every day clinical practice and in more extensive patient exposures than included in clinical development to date, the benefit-risk of lasmiditan would be adversely impacted.

Public health impact:

Although the adverse consequences (including psychological, behavioural, and social changes) related to drug misuse/abuse may impact the benefit-risk of lasmiditan at an individual patient level, the likelihood of a public health impact is low.

SVII.3.2 Presentation of the Missing Information

Missing Information: Long-term intermittent use

Evidence source:

The long-term safety of lasmiditan beyond 1 year of intermittent use has not been established through the clinical trial programme. As migraine is a chronic condition, long-term intermittent

use is anticipated in routine clinical practice, although assessment of utilisation patterns for triptans suggests that the majority of patients discontinue the prescribed treatment within 1 year (Lombard et al. 2018). If lasmiditan use patterns are similar to triptan use patterns, then there may be a small population of patients that utilise lasmiditan for more than 1 year, which will need to be identified to study safety concerns in that subgroup.

Anticipated risk/consequence of the missing information:

It could be anticipated that with long-term use, adverse effects that are infrequent and/or have a longer latency period could occur. Therefore, further evaluation of adverse events with a low frequency and/or long latency is warranted.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	CNS effects and impaired ability to drive and use machines
Important potential risks	Adverse pregnancy outcomes Drug misuse/abuse
Missing information	Long-term intermittent use

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

None

Other forms of routine pharmacovigilance activities:

The safety concerns identified for lasmiditan will be included in routine and regular safety signal detection and management activities.

III.2 Additional Pharmacovigilance Activities

Lasmiditan Exposure and Driving

Study Short Name and Title: Study H8H-MC-B006: Lasmiditan Use and Motor Vehicle Accidents in Real-World Settings in the US

Rationale and Study Objectives:

A driving simulation study (106/LAHG) has demonstrated a dose-dependent impact of lasmiditan on simulated driving and on an embedded divided attention test measured at 90 minutes after taking a single oral dose of lasmiditan. Study LAIF, which was conducted to determine the duration of effect of 100 mg and 200 mg lasmiditan compared with placebo on simulated driving performance at 8, 12, and 24 hours after dosing, demonstrated that clinically meaningful impairment was resolved by 8 hours after dosing. The clinical trial data on use of lasmiditan in patients and any association with road traffic accidents was limited and inconclusive. In the Phase 2/3 studies, despite a higher frequency of TEAEs that may represent impairment in mental ability in lasmiditan-treated patients compared to placebo-treated patients, there were no associations between those TEAEs and driving accidents.

A post marketing observational study is proposed to investigate lasmiditan use and motor vehicle accidents in real-world settings. Specifically, the primary study objective is the following

- To evaluate the potential relationship between real-world lasmiditan use and motor vehicle accidents in the US.

Study Design:

An observational study is proposed in a real-world setting to establish a background rate of motor vehicle accidents for patients prescribed lasmiditan, patients prescribed other antimigraine medications, and/or migraine patients without any antimigraine prescriptions. The observational study will evaluate the association between lasmiditan and driving impairments, adjusting for

confounding factors, if a sufficient number of lasmiditan-treated patients will accrue during the study period.

This study will recruit experienced drivers and will administer patient baseline and follow-up surveys on a monthly basis over a 12-month period to collect data on medication use, driving behaviors and any accident information. Patient survey data will be linked with data from the US Department of Motor Vehicles (DMV) for car accident validation in Connecticut, North Carolina, Florida and Washington to validate details on reported motor vehicle accidents and to obtain additional details on these events. A descriptive interim analysis is planned to provide baseline assessment of lasmiditan-treated patients.

Study Population:

The study population of interest includes patients with migraine exposed to lasmiditan, other antimigraine prescriptions, and untreated patients.

Milestones:

The proposed milestones are as follows:

Milestone	Anticipated Due Date*
Start of data collection	Estimated for 31 December 2021
Interim report submission	31 March 2026
Final study report submission	31 December 2027

*These timelines are currently under discussion with the vendor and are subject to change.

Lasmiditan Exposure During Pregnancy and Adverse Pregnancy Outcomes

Study Short Name and Title: Study H8H-MC-B002: Observational Cohort Study of Exposure to Lasmiditan During Pregnancy

Rationale and Study Objectives:

Pregnant women were not included in the clinical development programme; however, the indicated population for migraine is predominantly women, many of whom are of childbearing age. For risk management purposes, this represents missing information and adverse outcomes in pregnancy could impact the benefit-risk. Adverse effects, including abnormal embryo-foetal development and reproductive toxicity, were observed in rats and rabbits exposed to maternally toxic doses of lasmiditan during nonclinical development. Although it is uncertain how well the findings in the animal studies can predict the effects in humans, the potential for adverse pregnancy outcomes in pregnant women treated with lasmiditan are safety concerns that warrant further investigation.

A postmarketing pregnancy study is planned to describe exposure to lasmiditan before or during pregnancy and to investigate any association between maternal exposure of lasmiditan before or during pregnancy and adverse outcomes including major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births. This study plans to compare the incidence of adverse pregnancy outcomes in women with lasmiditan exposure

during pregnancy to the incidence of adverse pregnancy outcomes in unexposed comparator groups.

The objectives are

- To estimate the prevalence of major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in pregnant women with migraine exposed to lasmiditan and pregnant women not exposed to lasmiditan.
- To compare the prevalence of major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in pregnant women with migraine exposed to lasmiditan to pregnant women not exposed to lasmiditan.

Study Design:

This is a comparative safety study conducted among pregnant women using electronic claims data. The comparative analysis will assess pregnancy, maternal, and infant outcomes, comparing pregnant women exposed to lasmiditan to pregnant women not exposed to lasmiditan. Utilisation among patients treated with lasmiditan and other acute migraine medications (such as triptans) will also be described. Medical record review will be used to obtain additional information on outcomes and confounders where feasible.

Study Population:

The source population for this study will include pregnant women with a migraine diagnosis exposed to lasmiditan compared to unexposed pregnant woman in the US.

Milestones:

The proposed milestones and anticipated due dates are as follows:

Milestone	Anticipated Due Date*
Start of data collection	Within 2 months of FDA endorsement/approval
Final study report submission	31 December 2028

*These timelines are currently under discussion with the vendor and are subject to change.

Drug Utilisation Study

Study Short Name and Title: Study H8H-MC-B005: Real-World Observational Study to Assess Drug Utilisation Patterns in the US Among Migraine Patients Treated with Lasmiditan

Rationale and Study Objectives:
Drug abuse/misuse is an important potential risk based on drug liking data observed in recreational drug users treated with lasmiditan. Real-world use of lasmiditan will be studied by accessing a healthcare database in order to evaluate use patterns (abuse/misuse) after approval as well as duration of use.

Study objectives are

- to assess drug utilisation patterns for lasmiditan prescriptions over a period of up to 2 years after market availability in order to identify potential patterns of drug misuse or abuse
- to identify patients treated for longer than 1 year and describe treatment patterns
- to assess off-label treatment with lasmiditan among paediatric and adolescent migraine patients, and
- to describe characteristics of lasmiditan treated patients, including patients treated beyond 1-year.

Study Design:

Cohort study using a US electronic claims database to assess drug utilisation patterns. The potential for abuse and misuse will be assessed by evaluating irregular prescription refill behaviours over a period of 2 years. Treatment patterns will be described and, where possible, diagnosis information will confirm indication for use.

Study Population:

Migraine patients initiating treatment with lasmiditan.

Milestones:

The proposed milestones are as follows:

Milestone	Anticipated Due Date*
Start of data collection	Estimated for 31 December 2021
Final study report submission	31 December 2023

*These timelines are currently under discussion and are subject to change.

Long-Term Safety Study

Study Short Name and Title: Study H8H-MC-B010: Real-World Observational Study to Assess Safety Outcomes in the US among Migraine Patients Treated with Lasmiditan Long-Term.

Rationale and Study Objectives:
Migraine is a chronic condition; therefore, long-term lasmiditan use beyond 1 year is reasonably anticipated in routine clinical practice. Adverse effects that are infrequent, have a longer latency period, and/or are infrequent among migraine patients could occur.

Given the clinical study designs, specifically the respective inclusion/exclusion criteria and the duration of studies, use of lasmiditan over a longer (>1 year) duration of time have not been adequately studied. Treatment patterns for patients treated with lasmiditan and safety outcomes among these patients will be studied by accessing a healthcare database. Among patients treated beyond 1 year, incidence rates for safety outcomes such as CV, malignancies, and other rare events will be described.

Study objectives are

- to assess safety outcomes among patients treated with lasmiditan for longer than 1 year, and
- to describe characteristics of lasmiditan treated patients treated long-term, beyond 1 year.

Study Design:

Cohort study using a US electronic claims database to assess safety outcomes among patients treated with lasmiditan for longer than 1 year. Treatment patterns among patients treated for longer than 1 year will be described and, where possible, diagnosis information will confirm indication for use. To evaluate long-term safety, this study will assess safety outcomes for long-term users, patients treated with lasmiditan beyond 1 year. Safety outcomes will include known and emergent outcomes using electronic claims data for patients identified as long-term intermittent users.

Patient duration of exposure cannot be accurately estimated at this time, and limitations in patient follow-up exist in real-world data sources, such as patients switching between treatment providers. It is intended to initiate patient follow-up from start of exposure until the patient discontinues therapy, the patient is lost to follow-up, or occurrence of an event, at which point they will be censored.

Study Population:

Migraine patients treated with lasmiditan for longer than 1 year.

Milestones:

The proposed milestones are as follows:

Milestone	Anticipated Due Date*
Start of data collection	Estimated for 31 December 2023
Final study report submission	31 December 2026

*These timelines are currently under discussion and are subject to change.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Anticipated Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Lasmiditan Exposure and Driving (Study H8H-MC-B006: Lasmiditan Use and Motor Vehicle Accidents in Real-World Settings in the US) (Planned)	• To evaluate the potential relationship between real-world lasmiditan use and motor vehicle accidents in the US.	CNS effects and impaired ability to drive and use machines (important identified risk)	Start of Data Collection	Estimated for 31 December 2021
			Interim Report Submission	31 March 2026
			Final Report	31 December 2027
Lasmiditan Exposure During Pregnancy and Adverse Pregnancy Outcomes (Study H8H-MC-B002: Observational Cohort Study of Exposure to Lasmiditan During Pregnancy) (Planned)	• To estimate the prevalence of major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in pregnant women with migraine exposed to lasmiditan and pregnant women not exposed to lasmiditan. • To compare the prevalence of major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in pregnant women with migraine exposed to lasmiditan to pregnant women not exposed to lasmiditan.	Adverse pregnancy outcomes (important potential risk)	Start of Data Collection	Within 2 months of FDA endorsement/ approval
			Final Report	31 December 2028
Drug Utilisation Study (Study H8H-MC-B005: Real-World Observational Study to Assess Drug Utilisation Patterns in the US Among Migraine Patients Treated with Lasmiditan) (Planned)	Study objectives are • to assess drug utilisation patterns for lasmiditan prescriptions over a period of up to 2 years after market availability in order to identify potential patterns of drug misuse or abuse • to identify patients treated for longer than 1 year and describe treatment patterns	Drug misuse/abuse (important potential risk) Long-term intermittent use (missing information)	Start of Data Collection	Estimated for 31 December 2021

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Anticipated Due Dates
	• to assess off-label treatment with lasmiditan among paediatric and adolescent migraine patients, and • to describe characteristics of lasmiditan-treated patients, including patients treated for longer than 1 year.		Final Report	31 December 2023
Long-Term Safety Study (Study H8H-MC-B010: Real-World Observational Study to Assess Safety Outcomes in the US Among Migraine Patients Treated with Lasmiditan Long-Term) (Planned)	Study objectives are • to assess safety outcomes among patients treated with Lasmiditan for longer than 1 year, and • to describe characteristics of lasmiditan treated patients treated long-term, beyond 1 year.	Long-term intermittent use (missing information)	Start of Data Collection	Estimated for 31 December 2023
			Final Report	31 December 2026

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Table Part IV.1. Planned and Ongoing Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
Not applicable				
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
CNS effects and impaired ability to drive and use machines	Routine risk communication • SmPC Sections 4.4 and 4.7 • Instructions on outer and inner packaging Routine risk minimisation activities recommending specific clinical measures to address the risk • SmPC sections 4.4 and 4.7 advise that patients should not drive or engage in other activities requiring heightened attention until at least 8 hours after taking each dose of lasmiditan, even if they feel well enough to do so. • The outer packaging (carton) advises patients not to drive or operate machinery until at least 8 hours after dosing with lasmiditan. Other routine risk minimisation measures beyond the Product Information • Pack size: Not applicable. • Legal status: Not applicable.
Adverse pregnancy outcomes	Routine risk communication • SmPC Section 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk • SmPC Section 4.6 advises that lasmiditan should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Other routine risk minimisation measures beyond the Product Information • Pack size: Not applicable. • Legal status: Not applicable.
Drug misuse/abuse	Routine risk communication • SmPC Section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk • SmPC Section 4.4 advises that patients should be evaluated for risk of drug abuse and observed for signs of lasmiditan misuse or abuse. Other routine risk minimisation measures beyond the Product Information • Pack size: Not applicable. • Legal status: Not applicable.

Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine Risk Minimisation Activities
Long-term intermittent use	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Not applicable • Pack size: Not applicable. • Legal status: Not applicable.

Abbreviation: SmPC = Summary of Product Characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
CNS effects and impaired ability to drive and use machines	Routine risk minimisation measures • SmPC Sections 4.4 and 4.7 • Instructions on inner and outer packaging: The outer packaging (carton) advises patients not to drive or operate machinery until at least 8 hours after dosing with lasmiditan Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B006 Lasmiditan Use and Motor Vehicle Accidents in Real-World Settings in the US
Adverse pregnancy outcomes	Routine risk minimisation measures • SmPC Section 4.6 Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B002 Observational Cohort Study of Exposure to Lasmiditan During Pregnancy

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Drug misuse/abuse	Routine risk minimisation measures • SmPC Section 4.4 Additional risk minimisation measures • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B005 Real-World Observational Study to Assess Drug Utilisation Patterns in the US Among Migraine Patients Treated with Lasmiditan

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term intermittent use	No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B010 Real-World Observational Study to Assess the Safety Outcomes in the US Among Migraine Patients Treated with Lasmiditan Long-Term

Abbreviation: SmPC = Summary of Product Characteristics.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for RAYVOW (lasmiditan hemisuccinate)

This is a summary of the risk management plan (RMP) for RAYVOW. The RMP details important risks of RAYVOW, how these risks can be minimised, and how more information will be obtained about RAYVOW's risks and uncertainties (missing information).

RAYVOW's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how RAYVOW should be used.

This summary of the RMP for RAYVOW should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of RAYVOW's RMP.

I - The Medicine and What It is Used for

RAYVOW is authorised for the acute treatment of migraine with or without aura in adults (see SmPC for the full indication). It contains lasmiditan hemisuccinate as the active substance and it is given by tablet.

Further information about the evaluation of RAYVOW's benefits can be found in RAYVOW's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (link to the EPAR summary landing page).

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of RAYVOW, together with measures to minimise such risks and the proposed studies for learning more about RAYVOW's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (for example, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including the periodic safety update report assessment, so that immediate

action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of RAYVOW is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of RAYVOW are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of RAYVOW. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (for example, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	CNS effects and impaired ability to drive and use machines
Important potential risks	Adverse pregnancy outcomes Drug misuse/abuse
Missing information	Long-term intermittent use

II.B Summary of Important Risks

Important Identified Risk: CNS effects and impaired ability to drive and use machines	
Evidence for linking the risk to the medicine	A simulated driving study in healthy volunteers demonstrated a dose-dependent impact of lasmiditan on driving, as observed by a number of different measures of driving safety. Adverse effects on attention were also observed 90 minutes after a single oral dose of lasmiditan and at the approximate time of peak concentration of lasmiditan. In this driving study, 73% to 96% of subjects who received any of the 3 doses of lasmiditan (50 mg, 100 mg, or 200 mg), showed impairment greater than the legal alcohol limit for driving (0.05% blood alcohol content). The majority of subjects felt safe to drive prior to the simulated driving assessment, but >50% showed driving impairment. A second study conducted with 100 mg and 200 mg lasmiditan demonstrated that clinically meaningful driving impairment had resolved by 8 hours after dosing. Despite common reports of TEAEs that may impair mental ability in lasmiditan-treated patients in the Phase 2 and Phase 3 programs, no clear association was observed with road traffic accidents, impaired ability to use machinery, or other accidents and the occurrence of those TEAEs. However, the role of the CNS effects in contributing to an impairment in driving or in using machinery cannot be excluded.
Risk factors and risk groups	No specific risk factors and/or risk groups that have a risk higher than the overall population have been identified.
Risk minimisation measures	Routine risk minimisation measures • SmPC Sections 4.4 and 4.7 • Instructions on inner and outer packaging: The outer packaging (carton) advises patients not to drive or operate machinery until at least 8 hours after dosing with lasmiditan. Additional risk minimisation measures • None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B006: Lasmiditan Use and Motor Vehicle Accidents in Real-World Settings in the US See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: AE = adverse event; SmPC = Summary of Product Characteristics.

Important potential risk: adverse pregnancy outcomes	
Evidence for linking the risk to the medicine	In nonclinical studies in which pregnant rats and rabbits were dosed with lasmiditan, the offspring had decreased body weights and skeletal variations were observed. In rabbits only, there was a small increase in post implantation loss (miscarriage) and in the number of foetal CV defects. An increased number of stillborn pups and an increase in the frequency of postnatal death occurred in rats. All effects occurred in circumstances of maternal toxicity (that is, where there were significant reductions in maternal body weight and food consumption, and at exposures higher than would be used in patients).
Risk factors and risk groups	Women of childbearing potential who become pregnant during treatment with lasmiditan are the at risk population, but no specific risk factors for abnormal foetal outcomes have been identified.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.6 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B002: Observational Cohort Study of Exposure to Lasmiditan During Pregnancy See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: CV = cardiovascular; SmPC = Summary of Product Characteristics.

Important potential risk: drug misuse/abuse	
Evidence for linking the risk to the medicine	The findings from nonclinical studies with lasmiditan were either not indicative of or inconclusive with respect to any misuse or abuse potential. The main evidence source came from a clinical human abuse potential study in users of multiple recreational drugs (Study LAHB). This study demonstrated that the possibility for lasmiditan to have a higher AL than placebo could not be excluded. The mean Drug Liking scores with lasmiditan were shown to increase with increasing doses up to 400 mg and, at this highest dose, were seen at a similar rate to that observed following administration of the positive control, alprazolam. The subjects in the study considered that the effects of lasmiditan were most similar to those of benzodiazepines. In addition, there was a clear dose-related trend in the incidence of AEs reported in this study that could indicate abuse potential of lasmiditan, especially somnolence, euphoric mood, and a feeling of relaxation. In the Phase 2/3 placebo-controlled studies, the number of lasmiditan-treated patients reporting feeling abnormal; hallucination, visual; or euphoric mood was statistically significantly greater than in placebo-treated patients.
Risk factors and risk groups	No specific risk factors or risk groups have been identified from the clinical trial programme in patients. However, based on a clinical human abuse potential study, it is possible that certain patient groups could be more likely to misuse and/or abuse lasmiditan when it is prescribed. These could include patients with recent or current evidence of abuse of any drug (including prescription medicines, illicit drugs, or alcohol), or those with other conditions that might predispose them to drug abuse such as depression, anxiety, and posttraumatic stress disorder (Back and Brady 2008; Peterlin et al. 2011).
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4 Additional risk minimisation measures • None
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B005: Real-World Observational Study to Assess Drug Utilisation Patterns in the US Among Migraine Patients Treated with Lasmiditan See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: AE = adverse event; AL = abuse liability; SmPC = Summary of Product Characteristics.

Missing information: long-term intermittent use	
Risk minimisation measures	No risk minimisation measures.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Planned study: Study H8H-MC-B005: Real-World Observational Study to Assess Drug Utilisation Patterns in the US among Migraine Patients Treated with Lasmiditan • Planned study: Study H8H-MC-B010: Real-World Observational Study to Assess Safety Outcomes in the US among Migraine Patients Treated with Lasmiditan Long-Term

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of RAYVOW.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: Study H8H-MC-B006: Lasmiditan Use and Motor Vehicle Accidents in Real-World Settings in the US

Purpose of the study: A driving simulation study (106/LAHG) has demonstrated a dose-dependent impact of lasmiditan on simulated driving and on an embedded divided attention test measured at 90 minutes after taking a single oral dose of lasmiditan. Study LAIF, which was conducted to determine the duration of effect of 100 mg and 200 mg lasmiditan compared with placebo on simulated driving performance at 8, 12, and 24 hours after dosing, demonstrated that clinically meaningful impairment was resolved by 8 hours after dosing. The clinical trial data on use of lasmiditan in patients and any association with road traffic accidents was limited and inconclusive. In the Phase 2/3 studies, despite a higher frequency of TEAEs that may represent impairment in mental ability in lasmiditan-treated patients compared to placebo-treated patients, there were no associations between those TEAEs and driving accidents.

A post marketing observational study is proposed to investigate lasmiditan use and motor vehicle accidents in real-world settings. Specifically, the primary study objective is the following

- To evaluate the potential relationship between real-world lasmiditan use and motor vehicle accidents in the US.

Study short name: Study H8H-MC-B002: Observational Cohort Study of Exposure to Lasmiditan During Pregnancy

Purpose of the study: Pregnant women were not included in the clinical development programme; however, the indicated population for migraine is predominantly women, many of whom are of childbearing age. For risk management purposes, this represents missing information and adverse outcomes in pregnancy could impact the benefit-risk. Adverse effects, including abnormal embryo-foetal development and reproductive toxicity, were observed in rats and rabbits exposed to maternally toxic doses of lasmiditan during nonclinical development. Although it is uncertain how well the findings in the animal studies can predict the effects in humans, the potential for adverse pregnancy outcomes in pregnant women treated with lasmiditan are safety concerns that warrant further investigation.

A postmarketing pregnancy study is planned to describe exposure to lasmiditan before or during pregnancy and to investigate any association between maternal exposure of lasmiditan before or during pregnancy and adverse outcomes including major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births. This study plans to compare the incidence of adverse pregnancy outcomes in women with lasmiditan exposure

during pregnancy to the incidence of adverse pregnancy outcomes in unexposed comparator groups.

The objectives are

- To estimate the prevalence of major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in pregnant women with migraine exposed to lasmiditan and pregnant women not exposed to lasmiditan.
- To compare the prevalence of major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in pregnant women with migraine exposed to lasmiditan to pregnant women not exposed to lasmiditan.

Study short name: Study H8H-MC-B005: Real-World Observational Study to Assess Drug Utilisation Patterns in the US Among Migraine Patients Treated with Lasmiditan

Purpose of the study: Drug abuse/misuse is an important potential risk based on drug liking data observed in recreational drug users treated with lasmiditan. The use of lasmiditan will be studied by accessing a healthcare database in order to evaluate use patterns (abuse/misuse) after approval.

Study objectives are

- to assess drug utilisation patterns for lasmiditan prescriptions over a period of up to 2 years after market availability in order to identify potential patterns of drug misuse or abuse
- to identify patients treated for longer than 1 year and describe treatment patterns
- to assess off-label treatment with lasmiditan among paediatric and adolescent migraine patients, and
- to describe characteristics of lasmiditan-treated patients, including patients treated beyond 1-year.

Study short name: Study H8H-MC-B010: Real-World Observational Study to Assess Safety Outcomes in the US among Migraine Patients Treated with Lasmiditan Long-Term

Purpose of the study: Migraine is a chronic condition; therefore, long-term lasmiditan use beyond 1 year is reasonably anticipated in routine clinical practice. Adverse effects that are infrequent, have a longer latency period, and/or are infrequent among migraine patients could occur.

Given the clinical study designs, specifically the respective inclusion/exclusion criteria and the duration of studies, use of lasmiditan over a longer (>1 year) duration of time have not been adequately studied. Treatment patterns for patients treated with lasmiditan and safety outcomes among these patients will be studied by accessing a healthcare database. Among patients treated beyond 1 year, incidence rates for safety outcomes such as CV, malignancies, and other rare events will be described.

Study objectives are

- to assess safety outcomes among patients treated with lasmiditan for longer than 1 year, and
- to describe characteristics of lasmiditan-treated patients treated long-term, beyond 1 year.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities

Not applicable.